Critical Explorations

Research Anthology on Diagnosing and Treating Neurocognitive Disorders

Information Resources Management Association

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Bogdan, Martin / *Leipzig University, Leipzig, Germany* 473
Boukadoum, Mounir / *CoFaMic Research Centre, Department of Computer Science, UQÀM, University of Quebec, Canada* 267
Bourdon, Allen K / *University of Tennessee at Knoxville, Knoxville, USA* 427
Bourdon, Allen K. / *University of Tennessee at Knoxville, Knoxville, USA* 411
Camargo, Carlos Henrique Ferreira / *Hospital Universitário dos Campos Gerais – UEPG, Brazil* 387
Chatoui, Hicham / *Private University of Marrakech, Morocco & Cadi Ayyad University, Morocco* 59, 79
Datta, Amitava / *The University of Western Australia, Australia* 341
Della-Coletta, Marcus Vinicius / *State University of Amazonas, Brazil* 387
Devi, Debashree / *National Institute of Technology Silchar, India* 295
Dhage, Shrikant Ninaji / *Institute of Chemical Technology, India* 502
Draoui, Ahmed / *Cadi Ayyad University, Morocco* 79
Dugan, Jason L / *University of Texas at San Antonio, San Antonio, USA* 427
El Got, Abdeljalil / *Hassan 1st University, Morocco* 79

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El Kherchi, Ouassil / *Hassan 1st University, Morocco* 79
El Moudden, Ismail / *Mohammed V University, Morocco* 59
Freitas, Diamantino / *University of Porto, Portugal* 245
Freitas, Diamantino Rui / *University of Porto, Porto, Portugal* 224
Gamrani, Halima / *Cadi Ayyad University, Morocco* 59
Garg, Munish / *Maharshi Dayanand University, India* 18
Garrett, Carolina / *Hospital de São João, Porto, Portugal* 224, 245
Goswami, S. P. / *All India Institute of Speech and Hearing, India* 210
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José da Silva, Delson / *Federal University of Goias, Brazil* 387
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Lahouaoui, Hasna / *Cadi Ayyad University, Morocco* 79
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Purkayastha, Biswajit / *National Institute of Technology Silchar, India* 295
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Tang, Xiaoyu / *Liaoning Normal University, China & Okayama University, Japan* 147
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Varghese, Reuben Thomas / *All India Institute of Speech and Hearing, India* 210
Villareal, Greg / *AL Phahelix Biometrics, Inc., San Antonio, USA* 411, 427
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Wu, Fengxia / *Okayama University, Japan* 147
Wu, Jinglong / *Okayama University, Japan* 109, 147
Wu, Qiong / *Okayama University, Japan* 109
Wu, Yan / *Northeast Normal University, China* 109
Yang, Weiping / *Hubei University, China & Okayama University, Japan* 147
Yu, Yiyang / *Northeast University, China* 109
Yücel, Gökçen Firdevs / *Istanbul Aydın Unıversity, Turkey* 550
Zouhairi, Nadia / *Cadi Ayyad University, Morocco* 59, 79

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Table of Contents

Preface xiii

Section 1
Causes and Prevention

Chapter 1
Amyloid Beta: The Foremost Protagonist in Alzheimer's Disease 1
Abhinav Anand, Lovely Professional University, India
Neha Sharma, Lovely Professional University, India
Monica Gulati, Lovely Professional University, India
Navneet Khurana, Lovely Professional University, India

Chapter 2
Lewy Body Disease: Point Towards Progressive Dementia 18
Vaibhav Walia, Maharshi Dayanand University, India
Munish Garg, Maharshi Dayanand University, India

Chapter 3
Creutzfeldt-Jakob Disease: A Prion-Related Neurodegenerative Disorder 42
Sadeeq Muhammad Sheshe, COMSATS Institute of Information Technology, Pakistan

Chapter 4
Neuropathogenesis of Multiple Sclerosis and Huntington's Disease: An Overview of Environment Patterns 59
Omar El Hiba, Chouaib Doukkali University, Morocco & Cadi Ayyad University, Morocco
Nadia Zouhairi, Cadi Ayyad University, Morocco
Hicham Chatoui, Private University of Marrakech, Morocco & Cadi Ayyad University, Morocco
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Chapter 5
Environmental Aspects of Alzheimer's and Parkinson's Diseases Neuropathologies: A Focus on Heavy Metals and Pesticides 79
Nadia Zouhairi, Cadi Ayyad University, Morocco
Omar El Hiba, Chouaib Doukkali University, Morocco & Cadi Ayyad University, Morocco
Hasna Lahouaoui, Cadi Ayyad University, Morocco
Hind Benammi, Cadi Ayyad University, Morocco
Hicham Chatoui, Private University of Marrakech, Morocco & Cadi Ayyad University, Morocco
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Abdelali Bitar, Chouaib Doukkali University, Morocco
Kholoud Kahime, Cadi Ayyad University, Morocco
Ahmed Draoui, Cadi Ayyad University, Morocco
Ouassil El Kherchi, Hassan 1st University, Morocco
Wafa Ait Hmyed, Cadi Ayyad University, Morocco

Chapter 6
Dementia and Language Bilingualism Helps Ward Off Alzheimer's Disease 109
Yiyang Yu, Northeast University, China
Sihan Lu, Northeast Normal University, China
Yan Wu, Northeast Normal University, China
Qiong Wu, Okayama University, Japan
Jinglong Wu, Okayama University, Japan

Section 2
Early Detection and Diagnosis

Chapter 7
Cognitive Functions in the Geriatric Population 123
Shivani Sharma, All India Institute of Medical Sciences, India
Ashima Nehra, All India Institute of Medical Sciences, India

Chapter 8
The Early Diagnosis of Alzheimer's Disease: From Behavioral to Genetic Study 147
Yanna Ren, Okayama University, Japan
Weiping Yang, Hubei University, China & Okayama University, Japan
Xiaoyu Tang, Liaoning Normal University, China & Okayama University, Japan
Fengxia Wu, Okayama University, Japan
Satoshi Takahashi, Graduate School of Natural Science and Technology, Okayama University, Japan
Jinglong Wu, Okayama University, Japan

Chapter 9
Deep Learning in Early Detection of Alzheimer's: A Study 160
Anitha S. Pillai, Hindustan Institute of Technology and Science, India
Bindu Menon, Apollo Hospitals, India

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Chapter 10
Analysis of Biomedical Image for Alzheimer's Disease Detection 170
Rashmi Kumari, Birla Institute of Technology, India
Shashank Pushkar, Birla Institute of Technology, India

Chapter 11
Neuro-Imaging Machine Learning Techniques for Alzheimer's Disease Diagnosis 191
Gehad Ismail Sayed, Cairo University, Egypt & Scientific Research Group in Egypt (SRGE), Egypt
Aboul Ella Hassanien, Cairo University, Egypt & Scientific Research Group in Egypt (SRGE), Egypt

Chapter 12
Assessment of Cognitive-Communicative Functions in Persons With Mild Cognitive Impairment and Dementia of Alzheimer's Type 210
Reuben Thomas Varghese, All India Institute of Speech and Hearing, India
S. P. Goswami, All India Institute of Speech and Hearing, India

Chapter 13
Electroencephalogram Signal Analysis in Alzheimer's Disease Early Detection 224
Pedro Miguel Rodrigues, Department of Electrical and Computer Engineering, University of Porto, Porto, Portugal
Diamantino Rui Freitas, University of Porto, Porto, Portugal
João Paulo Teixeira, Electrical Department, Polythecnic Institute of Bragança, Bragança, Portugal
Dílio Alves, Neurophysiology Department, Hospital de São João, Porto, Portugal
Carolina Garrett, Hospital de São João, Porto, Portugal

Chapter 14
Early Detection of Electroencephalogram Temporal Events in Alzheimer's Disease 245
Pedro Miguel Rodrigues, University of Porto, Portugal
Diamantino Freitas, University of Porto, Portugal
João Paulo Teixeira, Polythecnic Institute of Bragança, Portugal
Dílio Alves, Hospital de São João – Porto, Portugal
Carolina Garrett, Hospital de São João – Porto, Portugal

Chapter 15
Dealing With Noise and Partial Volume Effects in Alzheimer Disease Brain Tissue Classification by a Fuzzy-Possibilistic Modeling Based on Fuzzy-Genetic Initialization 267
Lilia Lazli, CoFaMic Research Centre, Department of Computer Science, UQÀM, University of Quebec, Canada & Department of Electrical Engineering, ÉTS, University of Quebec, Canada
Mounir Boukadoum, CoFaMic Research Centre, Department of Computer Science, UQÀM, University of Quebec, Canada

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Chapter 16
Early Detection of Parkinson's Disease: An Intelligent Diagnostic Approach 295
Debashree Devi, National Institute of Technology Silchar, India
Saroj K. Biswas, National Institute of Technology Silchar, India
Biswajit Purkayastha, National Institute of Technology Silchar, India

Chapter 17
Soft Computing-Based Early Detection of Parkinson's Disease Using Non-Invasive Method Based on Speech Analysis 329
Chandrasekar Ravi, National Institute of Technology Puducherry, India

Chapter 18
Tremor Identification Using Machine Learning in Parkinson's Disease 341
Angana Saikia, North-Eastern Hill University Shillong, India
Vinayak Majhi, North-Eastern Hill University Shillong, India
Masaraf Hussain, North-Eastern Indira Gandhi Regional Institute of Health and Medical Sciences, India
Sudip Paul, North-Eastern Hill University Shillong, India
Amitava Datta, The University of Western Australia, Australia

Chapter 19
QSAR and QAAR Studies on Mixtures of 3-(Benzylidene)Indolin-2-One Isomers as Leads to Develop PET Radiotracers for Detection of Parkinson's Disease 366
Sagar S. Bhayye, University of Calcutta, Kolkata, India
Achintya Saha, Department of Chemical Technology, University of Calcutta, Kolkata, India

Section 3
Immunotherapy, Pharmacotherapy, and Technological Treatments

Chapter 20
Alpha-Synucleinopathies: Parkinson's Disease, Dementia With Lewy Bodies, and Multiple System Atrophy 387
Carlos Henrique Ferreira Camargo, Hospital Universitário dos Campos Gerais – UEPG, Brazil
Marcus Vinicius Della-Coletta, State University of Amazonas, Brazil
Delson José da Silva, Federal University of Goias, Brazil
Hélio A. G. Teive, Federal University of Paraná, Brazil

Chapter 21
Alzheimer's and Parkinson's Disease Novel Therapeutic Target: The Mitochondrial Pyruvate Carrier - Ligand Docking to Screen Natural Compounds Related to Classic Inhibitors 411
Allen K. Bourdon, University of Tennessee at Knoxville, Knoxville, USA
Greg Villareal, AL Phahelix Biometrics, Inc., San Antonio, USA
George Perry, University of Texas at San Antonio, San Antonio, USA
Clyde F. Phelix, University of Texas at San Antonio, San Antonio, USA

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Chapter 22
MSDC-0160 and MSDC-0602 Binding with Human Mitochondrial Pyruvate Carrier (MPC) 1 and 2 Heterodimer: PPARγ Activating and Sparing TZDs as Therapeutics 427
Clyde F. Phelix, University of Texas at San Antonio, San Antonio, USA
Allen K Bourdon, University of Tennessee at Knoxville, Knoxville, USA
Jason L Dugan, University of Texas at San Antonio, San Antonio, USA
Greg Villareal, AL Phahelix Biometrics, Inc., San Antonio, USA
George Perry, University of Texas at San Antonio, San Antonio, USA

Chapter 23
User-Independent Detection for Freezing of Gait in Parkinson's Disease Using Random Forest Classification 456
Amruta Meshram, University of Massachusetts, Dartmouth, USA
Bharatendra Rai, University of Massachusetts, Dartmouth, USA

Chapter 24
Stroke Rehabilitation and Parkinson's Disease Tremor Reduction Using BCIs Combined With FES 473
Sophie V. Adama, Leipzig University, Leipzig, Germany
Martin Bogdan, Leipzig University, Leipzig, Germany

Chapter 25
Virtual Reality Therapeutic Environments in Autism Spectrum Disorder (ASD) and Alzheimer's: Treatment, Diagnosis, and Refinement 492
David W. Sime, Online Corporate Video Production Ltd., UK

Section 4
Management, Monitoring, and Improving Quality of Life

Chapter 26
Role of Diet, Functional Foods, and Nutraceuticals in Brain Disorders 502
Vandana Bharat Patravale, Institute of Chemical Technology, India
Shivraj Vasantrao Naik, Institute of Chemical Technology, India
Shrikant Ninaji Dhage, Institute of Chemical Technology, India

Chapter 27
Dementia: A Capability Deprivation for Elderly Women in India 526
Sudeshna Mukherjee, Bangalore University, India

Chapter 28
Environmental Landscape Design for Alzheimer's 550
Gökçen Firdevs Yücel, Istanbul Aydın Unıversity, Turkey

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Chapter 29
Monitoring System for Persons With Alzheimer's Disease via Video-Object Tracking 570
Haitham Asaad Al-Anssari, Electrical and Computer Engineering, Western Michigan University, Kalamazoo, USA
Ikhlas Abdel-Qader, Electrical and Computer Engineering, Western Michigan University, Kalamazoo, USA
Maureen Mickus, Occupational Therapy, Western Michigan University, Kalamazoo, USA

Chapter 30
Assessment of Graph Metrics and Lateralization of Brain Connectivity in Progression of Alzheimer's Disease Using fMRI 589
Bhuvaneshwari Bhaskaran, Centre for Healthcare Technologies, Department of Biomedical Engineering, SSN College of Engineering, Chennai, India
Kavitha Anandan, Centre for Healthcare Technologies, Department of Biomedical Engineering, SSN College of Engineering, Chennai, India

Chapter 31
IoT in the Field of Healthcare 611
K. Govinda, VIT University, India

Chapter 32
Assessment of Gait Disorder in Parkinson's Disease 626
Divya Govindaraju, Anna University, India
Gururaj Nagarajan, Birla Institute of Technology and Science, India
Paramasivam Alagumariappan, B.S. Abdur Rahman Crescent Institute of Science and Technology, India

Chapter 33
Using Technology to Empower People With Multiple Sclerosis (MS) to Make Shared Decisions About Managing Their Own Healthcare: A UK Case Study 645
Helen King, Independent Researcher, UK
Darina M. Slattery, University of Limerick, Ireland

Index 667

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Preface

Affecting millions of individuals worldwide, neurocognitive disorders remain an unfortunate and often incurable staple of life for many. Stemming from neurodegenerative diseases that include Alzheimer's, Parkinson's, Huntington's, Lewy Body, and Multiple Sclerosis, the resulting impaired mental function and its progressive worsening over time can be terrifying for patients and heartbreaking for caregivers and family members. Resulting problems with memory, changes in behavior, and difficulty performing daily activities can lead to a decrease in the quality of life for those afflicted as they struggle to manage these diseases. Advancements in technologies, immunotherapies, and drugs must be continually explored in order to better treat these disorders and provide better comfort for patients. Moreover, with the lack of a cure, including for those suffering from Alzheimer's and Parkinson's, it's imperative that tools and methods that can detect and diagnose these diseases in their earliest stages are found, enhanced, and utilized so that symptoms can be slowed.

Thus, the *Research Anthology on Diagnosing and Treating Neurocognitive Disorders* seeks to fill the void for an all-encompassing and comprehensive reference book covering the latest and most emerging technologies, tools, concepts, and theories for the better understanding and treatment of neurocognitive disorders. This one-volume reference collection of reprinted IGI Global book chapters and journal articles that have been hand-picked by the editor and editorial team of this research anthology on this topic will empower medical practitioners, healthcare workers, medical technology professionals, students, researchers, and academicians with a strong understanding of critical issues within the management of neurocognitive disorders by providing both broad and detailed perspectives on cutting-edge developments.

Research Anthology on Diagnosing and Treating Neurocognitive Disorders is organized into four sections that provide comprehensive coverage of important topics. The sections are:

1. Causes and Prevention;
2. Early Detection and Diagnosis;
3. Immunotherapy, Pharmacotherapy, and Technological Treatments;
4. Management, Monitoring, and Improving Quality of Life.

The following paragraphs provide a summary of what to expect from this invaluable reference tool.

Section 1, "Causes and Prevention," opens this comprehensive reference work with research that introduces the major neurocognitive disorders and their causes, including the latest theories on the contribution of environmental factors, and discusses prospective prevention measures.

The first chapter in this section, "Amyloid Beta: The Foremost Protagonist in Alzheimer's Disease," by Profs. Abhinav Anand, Neha Sharma, Monica Gulati, and Navneet Khurana from Lovely Professional

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University, India, examines Amyloid Precursor Protein and its enzymatic cleavage, which leads to Alzheimer's Disease. The following chapter, "Lewy Body Disease: Point Towards Progressive Dementia," authored by Profs. Vaibhav Walia and Munish Garg of Maharshi Dayanand University, India, addresses the entire profile of Lewy Bodies, types, composition, formation, and various Lewy Body pathologies as well as diagnostic criteria and pharmacotherapy. In the next chapter, "Creutzfeldt-Jakob Disease: A Prion-Related Neurodegenerative Disorder," by Prof. Sadeeq Muhammad Sheshe from COMSATS Institute of Information Technology, Pakistan, the author explores recent development in pathogenesis, diagnosis, and treatment of Creutzfeldt-Jakob Disease. Following this chapter is "Neuropathogenesis of Multiple Sclerosis and Huntington's Disease: An Overview of Environment Patterns," by Prof. Omar El Hiba of Chouaib Doukkali University, Morocco & Cadi Ayyad University, Morocco; Prof. Nadia Zouhairi of Cadi Ayyad University, Morocco; Prof. Hicham Chatoui of Private University of Marrakech, Morocco & Cadi Ayyad University, Morocco; Prof. Tiziano Balzano from Príncipe Felipe Research Center, Spain; Prof. Hind Benammi of Cadi Ayyad University, Morocco; Prof. Faical Isbaine from Emory University, USA; Prof. Abdelali Bitar of Chouaib Doukkali University, Morocco; Profs. Hamid Rguibi Idrissi and Ismail El Moudden from Mohammed V University, Morocco; and Profs. Fatima Zahra Marhoume and Halima Gamrani of Cadi Ayyad University, Morocco. This chapter discusses the role of different metals and pesticides in the onset and progress of Multiple Sclerosis and Huntington's Disease with an overview of the possible underlying pathomechanisms. Another chapter in this section titled "Environmental Aspects of Alzheimer's and Parkinson's Diseases Neuropathologies: A Focus on Heavy Metals and Pesticides," by Prof. Nadia Zouhairi of Cadi Ayyad University, Morocco; Prof. Omar El Hiba from Chouaib Doukkali University, Morocco & Cadi Ayyad University, Morocco; Profs. Hasna Lahouaoui and Hind Benammi from Cadi Ayyad University, Morocco; Prof. Hicham Chatoui of Private University of Marrakech, Morocco & Cadi Ayyad University, Morocco; Prof. Abdeljalil El Got from Hassan 1st University, Morocco; Prof. Abdelmohcine Aimrane from Cadi Ayyad University, Morocco; Prof. Abdelali Bitar of Chouaib Doukkali University, Morocco; Profs. Kholoud Kahime and Ahmed Draoui of Cadi Ayyad University, Morocco; Prof. Ouassil El Kherchi from Hassan 1st University, Morocco; and Prof. Wafa Ait Hmyed of Cadi Ayyad University, Morocco, examines the link between heavy metals and the occurrence of Parkinson's and Alzheimer's diseases. Concluding this section is the chapter "Dementia and Language Bilingualism Helps Ward Off Alzheimer's Disease," authored by Prof. Yiyang Yu from Northeast University, China; Profs. Sihan Lu and Yan Wu of Northeast Normal University, China; and Profs. Qiong Wu and Jinglong Wu from Okayama University, Japan, which discusses the theory of whether bilingualism helps ward off dementia.

Section 2, "Early Detection and Diagnosis," presents extensive coverage of the latest technologies and tools that are being used for the early detection and diagnosis of typical neurocognitive disorders and the challenges encountered in their prognosis. The section presents an emphasis on detecting Alzheimer's and Parkinson's Diseases. The first chapter, "Cognitive Functions in the Geriatric Population," authored by Profs. Shivani Sharma and Ashima Nehra from All India Institute of Medical Sciences, India, describes how one of the challenging issues of clinical diagnosis is distinguishing between the cognitive deficits manifested in normal aging, depression, mild cognitive impairment (MCI), and dementia. The next chapter, "The Early Diagnosis of Alzheimer's Disease: From Behavioral to Genetic Study," by Prof. Yanna Ren of Okayama University, Japan; Prof. Weiping Yang from Hubei University, China & Okayama University, Japan; Prof. Xiaoyu Tang of Liaoning Normal University, China & Okayama University, Japan; and Profs. Fengxia Wu, Satoshi Takahashi, and Jinglong Wu of Okayama University, Japan, focuses on the diagnosis of Alzheimer's disease in the early stage through imaging detection via CT, MRI,

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PET, and MSR, or prediction before the disease (genetic examination). Following this chapter is "Deep Learning in Early Detection of Alzheimer's: A Study," by Prof. Anitha S. Pillai of Hindustan Institute of Technology and Science, India and Prof. Bindu Menon from Apollo Hospitals, India. This chapter provides an introduction to big data, deep learning, Alzheimer's Disease, biomarkers, and brain images and concludes by suggesting blood biomarker as an ideal solution for early detection of Alzheimer's Disease. Another chapter, "Analysis of Biomedical Image for Alzheimer's Disease Detection," written by Profs. Rashmi Kumari and Shashank Pushkar from Birla Institute of Technology, India, analyzes 3D images to detect Alzheimer's disease and compare the statistical results of the whole brain image data with standard doctor's results. In the next chapter, "Neuro-Imaging Machine Learning Techniques for Alzheimer's Disease Diagnosis," authored by Profs. Gehad Ismail Sayed and Aboul Ella Hassanien from Cairo University, Egypt & Scientific Research Group in Egypt (SRGE), Egypt, an automatic AD diagnosis system from MRI images based on using machine learning tools is proposed. The following chapter, "Assessment of Cognitive-Communicative Functions in Persons With Mild Cognitive Impairment and Dementia of Alzheimer's Type," by Profs. Reuben Thomas Varghese and S. P. Goswami of All India Institute of Speech and Hearing, India, provides an assessment that sheds light on the differential diagnosis of MCI and DAT, the clinical description of the characteristics between the two clinical groups, the prognosis for improved outcomes, recommendations for intervention and support, and referral for other professionals for assessments or services. Next, the chapter, titled "Electroencephalogram Signal Analysis in Alzheimer's Disease Early Detection," by Profs. Pedro Miguel Rodrigues and Diamantino Rui Freitas of University of Porto, Portugal; Prof. João Paulo Teixeira of the Polythecnic Institute of Bragança, Portugal; and Profs. Dílio Alves and Carolina Garrett of the Hospital de São João, Porto, Portugal, performs a classification methodology skilled with Artificial Neural Networks (ANN) to improve the discrimination accuracy amongst patients at AD different stages comparatively to the state of the art. In follow-up of this chapter, "Early Detection of Electroencephalogram Temporal Events in Alzheimer's Disease," authored by Profs. Pedro Miguel Rodrigues and Diamantino Freitas from the University of Porto, Portugal; Prof. João Paulo Teixeira of Polythecnic Institute of Bragança, Portugal; and Profs. Dílio Alves and Carolina Garrett of the Hospital de São João – Porto, Portugal, studies a new approach to detect early AD Electroencephalogram (EEG) temporal events in order to improve early AD diagnosis. The last chapter focuses on Alzheimer's Disease detection and is titled "Dealing With Noise and Partial Volume Effects in Alzheimer Disease Brain Tissue Classification by a Fuzzy-Possibilistic Modeling Based on Fuzzy-Genetic Initialization," by Profs. Lilia Lazli and Mounir Boukadoum from the University of Quebec, Canada. This chapter suggests an automatic segmentation of brain tissues for magnetic resonance and functional images of Alzheimer's patients, based on an efficient and robust genetic-fuzzy-possibilistic clustering scheme for the assessment of white matter, gray matter, and cerebrospinal fluid volumes. Switching to the detection of Parkinson's Disease, the chapter, "Early Detection of Parkinson's Disease: An Intelligent Diagnostic Approach," by Profs. Debashree Devi, Saroj K. Biswas, and Biswajit Purkayastha from National Institute of Technology Silchar, India, proposes an intelligent diagnostic system by integrating one-class SVM, extreme learning machine, and data preprocessing technique. One of the final chapters, "Soft Computing-Based Early Detection of Parkinson's Disease Using Non-Invasive Method Based on Speech Analysis," written by Prof. Chandrasekar Ravi of National Institute of Technology Puducherry, India, uses speech analysis to help identify the complications in conversation from the inception of the symptoms of Parkinson's Disease in initial phases. Another concluding chapter, "Tremor Identification Using Machine Learning in Parkinson's Disease," authored by Profs. Angana Saikia and Vinayak Majhi from North-Eastern Hill University Shillong, India; Prof.

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Masaraf Hussain of North-Eastern Indira Gandhi Regional Institute of Health and Medical Sciences, India; Prof. Sudip Paul from North-Eastern Hill University Shillong, India; and Prof. Amitava Datta from The University of Western Australia, Australia, focuses on an in-depth review on identification and classification of various Parkinsonian tremors using machine learning algorithms. The final chapter in this section, "QSAR and QAAR Studies on Mixtures of 3-(Benzylidene)Indolin-2-One Isomers as Leads to Develop PET Radiotracers for Detection of Parkinson's Disease," by Profs. Sagar S. Bhayye and Achintya Saha from the University of Calcutta, Kolkata, India, describes how the derived models postulate that conformation of molecules and presence of unsaturated hydrocarbon chains, nitro, methoxy, and amine functionalities play an important role in determining binding affinity.

Section 3, "Immunotherapy, Pharmacotherapy, and Technological Treatments," reveals the latest treatments used to support patients with neurocognitive disorders and presents new technologies that assist with disease management. The opening chapter, "Alpha-Synucleinopathies: Parkinson's Disease, Dementia With Lewy Bodies, and Multiple System Atrophy," by Prof. Carlos Henrique Ferreira Camargo of Hospital Universitário dos Campos Gerais – UEPG, Brazil; Prof. Marcus Vinicius Della-Coletta from State University of Amazonas, Brazil; Prof. Delson José da Silva of Federal University of Goias, Brazil; and Prof. Hélio A. G. Teive of Federal University of Paraná, Brazil, presents the α-synucleinopathies as well as the most recent researches about treatment of synucleinopathies based on knowledge of the pathophysiology of α-synuclein pathways. The next chapter, "Alzheimer's and Parkinson's Disease Novel Therapeutic Target: The Mitochondrial Pyruvate Carrier - Ligand Docking to Screen Natural Compounds Related to Classic Inhibitors," authored by Prof. Allen K. Bourdon of the University of Tennessee at Knoxville, USA; Prof. Greg Villareal of AL Phahelix Biometrics, Inc., USA; and Profs. George Perry and Clyde F. Phelix from the University of Texas at San Antonio, USA, investigates Thiazolidinedione (TZD) drugs (Takeda Pharmaceuticals and Metabolic Solutions Development Company) targeting inhibition of the mitochondrial pyruvate carrier (MPC), which are currently being tested in clinical trials to prevent progression into mild cognitive impairment of Alzheimer's Disease (AD) or in the pipeline to prevent neurodegeneration in Parkinson's Disease (PD). The following chapter, titled "MSDC-0160 and MSDC-0602 Binding with Human Mitochondrial Pyruvate Carrier (MPC) 1 and 2 Heterodimer: PPARγ Activating and Sparing TZDs as Therapeutics," authored by Prof. Clyde F. Phelix from the University of Texas at San Antonio, USA; Prof. Allen K. Bourdon of the University of Tennessee at Knoxville, USA; Prof. Jason L. Dugan from the University of Texas at San Antonio, USA; Prof. Greg Villareal of AL Phahelix Biometrics, Inc., USA; and Prof. George Perry from the University of Texas at San Antonio, USA, describes results for a MPC1/2 heterodimer homology model. In the next chapter, "User-Independent Detection for Freezing of Gait in Parkinson's Disease Using Random Forest Classification," by Profs. Amruta Meshram and Bharatendra Rai of the University of Massachusetts, Dartmouth, USA, a user-independent method is proposed to detect FOG events in PD patients. One of the concluding chapters, titled "Stroke Rehabilitation and Parkinson's Disease Tremor Reduction Using BCIs Combined With FES," authored by Profs. Sophie V. Adama and Martin Bogdan of Leipzig University, Germany, describes the design of a brain-computer interface system (BCI) system paired with an electrical muscle stimulation suit for stroke rehabilitation and the reduction of tremors caused by Parkinson's Disease. The final chapter, "Virtual Reality Therapeutic Environments in Autism Spectrum Disorder (ASD) and Alzheimer's: Treatment, Diagnosis, and Refinement," by Prof. David W. Sime from Online Corporate Video Production Ltd., UK, is devoted to observing and analyzing the role of virtual reality environments in the therapeutic treatment, analysis, and ongoing treatment planning of autistic spectrum disorders (ASD), Alzheimer's, and dementia.

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Section 4, "Management, Monitoring, and Improving Quality of Life," discusses leading research for the helping patients to manage and monitor their diseases, as well as the latest theories and technologies that can be used to improve their quality of life. The first chapter in this section, "Role of Diet, Functional Foods, and Nutraceuticals in Brain Disorders," by Profs. Vandana Bharat Patravale, Shivraj Vasantrao Naik, and Shrikant Ninaji Dhage of the Institute of Chemical Technology, India, presents an overview of various complementary nutritional approaches for the management of brain disorders. The next chapter, "Dementia: A Capability Deprivation for Elderly Women in India," authored by Prof. Sudeshna Mukherjee from Bangalore University, India, uses a capability approach and the concept of "disability paradox" to project dementia as a capability deprivation situation and through comparative analysis of various care models proposes a comprehensive economic care model and plan of action for a developing country like India to ensure dignified quality living for dementia patients and their caregivers. In the following chapter, "Environmental Landscape Design for Alzheimer's," by Prof. Gökçen Firdevs Yücel from Istanbul Aydın Unıversity, Turkey, the author proposes that a good environmental landscape design will have an important role to play in improving the quality of life of Alzheimer's patients. The next chapter, "Monitoring System for Persons With Alzheimer's Disease via Video-Object Tracking," by Profs. Haitham Asaad Al-Anssari, Ikhlas Abdel-Qader, and Maureen Mickus from Western Michigan University, Kalamazoo, USA, presents a framework for a food intake monitoring system intended for use with persons with Alzheimer's disease and other dementias. Another chapter within this section, "Assessment of Graph Metrics and Lateralization of Brain Connectivity in Progression of Alzheimer's Disease Using fMRI," authored by Profs. Bhuvaneshwari Bhaskaran and Kavitha Anandan from SSN College of Engineering, Chennai, India, analyzes the brain connectivity patterns and the functional topology through the progression of Alzheimer's disease using resting state fMRI. A concluding chapter, "IoT in the Field of Healthcare," written by Prof. K. Govinda from VIT University, India, focuses on IoT being used in Parkinson's disease, specifically, and how people with it can be benefitted by IoT. Following this chapter is "Assessment of Gait Disorder in Parkinson's Disease," by Prof. Divya Govindaraju from Anna University, India; Prof. Gururaj Nagarajan from Birla Institute of Technology and Science, India; and Prof. Paramasivam Alagumariappan from B.S. Abdur Rahman Crescent Institute of Science and Technology, India. This chapter investigates the assessment of gait, which plays a significant role in maintaining the balance disorders in Parkinson's disease. The concluding chapter, "Using Technology to Empower People With Multiple Sclerosis (MS) to Make Shared Decisions About Managing Their Own Healthcare: A UK Case Study," by Prof. Helen King an Independent Researcher, UK and Prof. Darina M. Slattery from University of Limerick, Ireland, presents the key findings from a mixed methods study that explored how people with MS (PwMS) access and use health digital information when trying to manage their MS.

Although the primary organization of the contents in this work is based on its four sections, offering a progression of coverage of the important concepts, methodologies, technologies, applications, social issues, and emerging trends, the reader can also identify specific contents by utilizing the extensive indexing system listed at the end. As a comprehensive collection of research on the latest findings related to using technology to providing various services, the *Research Anthology on Diagnosing and Treating Neurocognitive Disorders* provides researchers, medical professionals, medical technologists, IT specialists, neurocognitive disorder specialists, academicians, students, and all audiences with a complete understanding of the development of applications and concepts in these debilitating disorders. Given the vast number of issues concerning the diagnosis and treatment of neurocognitive disorders in countries around the world, this extensive book addresses the demand for a resource that encompasses the most

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pertinent research in technologies being employed to globally bolster the knowledge of neurodegenerative diseases.

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Section 1
Causes and Prevention

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Chapter 1
Amyloid Beta: The Foremost Protagonist in Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD), exhibiting accumulation of amyloid beta (Aβ) peptide as a foremost protagonist, is one of the top five causes of deaths. It is a neurodegenerative disorder (ND) that causes a progressive decline in memory and cognitive abilities. It is characterized by deposition of Aβ plaques and neurofibrillary tangles (NFTs) in the neurons, which in turn causes a decline in the brain acetylcholine levels. Aβ hypothesis is the most accepted hypothesis pertaining to the pathogenesis of AD. Amyloid Precursor Protein (APP) is constitutively present in brain and it is cleaved by three proteolytic enzymes (i.e., alpha, beta, and gamma secretases). Beta and gamma secretases cleave APP to form Aβ. Ubiquitin Proteasome System (UPS) is involved in the clearing of Aβ plaques. AD also involves impairment in UPS. The novel disease-modifying approaches involve inhibition of beta and gamma secretases. A number of clinical trials are going on worldwide with moieties targeting beta and gamma secretases. This chapter deals with an overview of APP and its enzymatic cleavage leading to AD.

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INTRODUCTION

Dementia is considered to be an aggregation of symptoms affecting memory, cognition, social abilities on a severe magnitude. These adverse effects affecting the daily activities result from physical changes in brain. Dementia can further be of several types depending upon the underlying pathological condition and symptoms (Anand, Khurana, Chawla, Sharma, & Khurana, 2017). Dementias are progressive in nature. The sufferers may have troubles with short-term memory in the beginning which evolves into a loss of memory altogether. While there are varied symptoms of dementia, impairment in at least two of the following mentioned core mental functions should be there for the condition to be considered as dementia. These include deficit in memory, language and communication, ability to focus, capability to reason and judge and visual perception (Alzheimer's Association, 2017c). AD is the most common form of dementia. Over 47.5 million people globally were estimated to be suffering from dementia in 2016. By 2030, the figure is expected to reach as high as 75.6 million (World Health Organization, 2016). AD generally appears in mid to late adulthood. It is associated with a progressive and rather irreversible decline in memory and various other cognitive capabilities. In AD, there is neuronal destruction and deterioration of neural connections in the cerebral cortex region of the brain along with a substantial loss of brain mass (Perl, 2010). AD is lethal within 5–10 years of its onset (Dwyer et al., 2009). Mortality usually ensues due to complications of the chronic illness.

AD is characterized by the presence of two neuropathological hallmarks i.e. extracellular Aβ plaques and intracellular NFTs. The plaques constitute chiefly of the neurotoxic peptide Aβ, which forms after the sequential cleavage of a large precursor protein i.e. APP by two enzymes, namely, β-secretase (commonly known as BACE1) and γ-secretase (involving four proteins, including presenilin). However, Aβ is not formed if APP is first acted upon and cleaved by the enzyme α-secretase instead of β-secretase. NFTs comprise mainly of the protein tau which is a microtubule associated protein (MAP) i.e. it binds microtubules in cells to facilitate the neuronal transport system. In the development of AD, Tau uncouples from microtubules and aggregates into tangles thereby inhibiting transport and resulting in microtubule disassembly. It also depends on the phosphorylation of Tau (Anand, Patience, Sharma, & Khurana, 2017; Nisbet, Polanco, Ittner, & Götz, 2015).

The actual causes at play behind the development of AD are still not well defined. However, certain factors like anomaly in the phosphorylation of tau protein, alterations in calcium metabolism, oxidative stress, neuro-inflammation, abnormal energy metabolism and protein processing i.e. undesired Aβ formation and aggregation, are considered to be important factors in the pathogenesis of AD (Butterfield et al., 2002; Habibyar, Sharma, & Khurana, 2016; J Hardy & Selkoe, 2002). In the present chapter, role of Aβ formation and aggregation as the foremost protagonist in AD is discussed with special emphasis on APP and enzymes involved in its cleavage along with involvement of UPS in amyloid hypothesis of AD.

BACKGROUND

AD was first described by a German neuropathologist Alois Alzheimer in 1906 (Editors of Encyclopædia Britannica, 2016). AD was recognized as the most prevalent form of dementia among geriatric persons by the commencement of 21st century. It is one of the top five most common causes of mortality in population of the United States (Centers for Disease Control and Prevention, 2017). In rare cases, it may appear in people in their 40s and 50s, but otherwise it is a disease of old age. Based on clinical, population-

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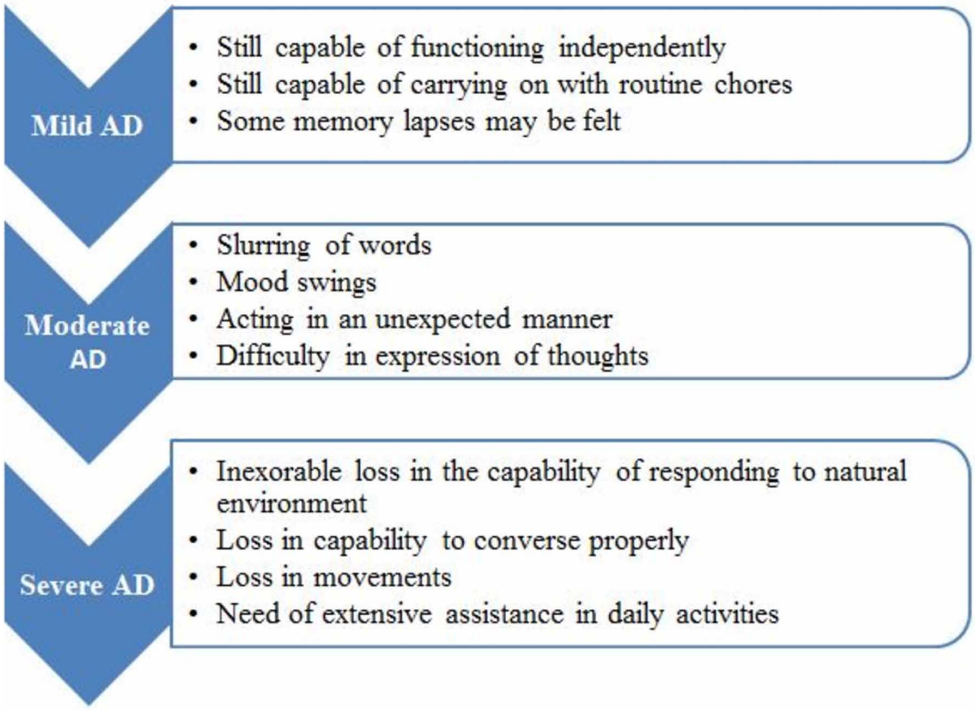
based studies, about 200,000 people under 65 years of age are suffering from AD. In contrast, around 5 million of those over 65 years of age have AD. As per speculations, a new case of AD is expected to be developed every 33 seconds, by 2050 (Alzheimer's Association, 2014).

The symptoms of AD get worse with time, although the pace at which the disease progresses is variable. Alterations in the brain related to AD commence years before any related clinical manifestations emerge. This period, spanning over a few years, is known as preclinical AD. The progression of AD occurs in three stages, namely mild AD (early-stage), moderate AD (middle-stage) and severe AD (late-stage). The symptoms associated with each stage are given in Figure 1.

Figure 1. Stages and associated symptoms of Alzheimer's disease (Alzheimer's Association, 2017a)



There are several hypotheses which have been put up by several researchers for pathogenesis of AD out of which cholinergic hypothesis (McGleenon, Dynan, & Passmore, 1999) and Aβ hypothesis (Storey & Cappai, 1999) have been subjected to extensive research. Aβ hypothesis talks more about the actual pathological hallmarks which are visible in the patients' brains during autopsy. Cholinergic hypothesis has generated several acetylcholinesterase inhibitors as therapeutic measures for AD. However, these agents provide mere symptomatic relief (Anand, Patience, et al., 2017). Researchers are foraying more and more into the potential drugs targeting the amyloid pathway as it is considered to be a disease modifying approach.

Evidence exists suggesting involvement of both cholinergic and glutamatergic neurochemical systems in the etiology of AD. Acetylcholine (ACh) is an essential neurotransmitter responsible for cognitive functions and learning. In the brains of patients suffering from AD, it is decreased both in concentra-

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tion and function. This deficit and other presynaptic cholinergic limitations, like loss of cholinergic neuronal network and reduced acetylcholinesterase activity, validate the cholinergic hypothesis of AD. Another neurochemical hypothesis for development of AD is the N-Methyl d-aspartate (NMDA) mediated glutamatergic hypothesis. Glutamate is an excitatory neurotransmitter which acts on NMDA receptors, which are pivotal in learning and memory. However, in some circumstances, over stimulation of NMDA receptors by glutamate causes neuronal damage due to excitotoxicity (Francis, 2005). A relatively recent mitochondrial dysfunction hypothesis for pathogenesis of AD proposes that AD brain mitochondrial dysfunction leads to amyloidosis, cell cycle re-entry, and tau phosphorylation (Swerdlow, Burns, & Khan, 2014).

The appearance of Aβ begins many years before the clinical manifestations of the disease appear, so it could be a reliable biomarker for AD prediction. As indicated, Aβ plays a major role in the formation of both amyloid plaques and NFTs, which gradually leads to AD. Aβ deposition leads to degeneration in synapses which leads to faulty interactions with different types of CNS receptors. Therefore, it disrupts neuronal homeostasis. Moreover, Aβ deposition along the cerebral vessels changes their tonicity and leads to some of the cerebrovascular deficits. Furthermore, its accumulation disrupts intracellular Ca^{2+} homeostasis which ultimately reduces neuronal Ca^{2+} buffering capacity. This, in turn increases excitotoxicity outcomes. Also, Aβ peptides may fold in different ways and show a prion-like pathology in the brain of AD patients (Sadigh-Eteghad et al., 2015).

An evidence base implicates Aβ in the pathogenesis of AD, leading to the formulation of the amyloid cascade hypothesis, i.e., the null hypothesis (John Hardy, 2006). The post mortem observation of the brain tissue of diseased individuals has made it quite obvious why Aβ is the primary suspect in disease pathogenesis. Aβ is the major constituent in two of the most distinctive histopathological hallmarks, namely senile plaques and cerebral amyloid angiopathy (Glenner & Wong, 1984a, 1984b).

The first and foremost argument that Aβ does not inititate AD is that deposition of Aβ into senile plaques is in no way specific to AD patients and is instead a marker of normal aging, i.e. the alternate hypothesis (Davies et al., 1988). Therefore, the strong association of Aβ in AD may simply mean an acceleration of senescence related deterioration. Support for this view can be found with the number of plaques in cognitively normal individuals against those seen in advanced disease (Mann, Jones, South, Snowden, & Neary, 1992; Schmitt et al., 2000). Furthermore, there exists only a weak correlation between the burden of Aβ and neuronal loss or cognitive impairment (Guillozet, Weintraub, Mash, & Mesulam, 2003). The alternate hypothesis is based on the notion that Aβ simply acts as a bystander or a protector rather than the causative factor of AD (H. Lee et al., 2007).

AMYLOID HYPOTHESIS OF ALZHEIMER'S DISEASE

There is an on-going debate about the Aβ hypothesis stating that the early, often initiating factor in development of AD is the imbalance between the production and clearance of Aβ42 and other related Aβ peptides. There are several hypotheses that have been suggested pertaining to the pathogenesis of AD. However, Aβ hypothesis is becoming increasingly popular amongst researchers worldwide (Alzheimer's Association, 2014). The Aβ hypothesis comes with the innate advantage of involving several molecular targets for drug development. Some important molecular targets are – APP, β- secretase 2 (BACE2), Aβ plaques. By efficiently creating structural and/or functional alterations at any of these targets, the progression of AD could be delayed or halted altogether.

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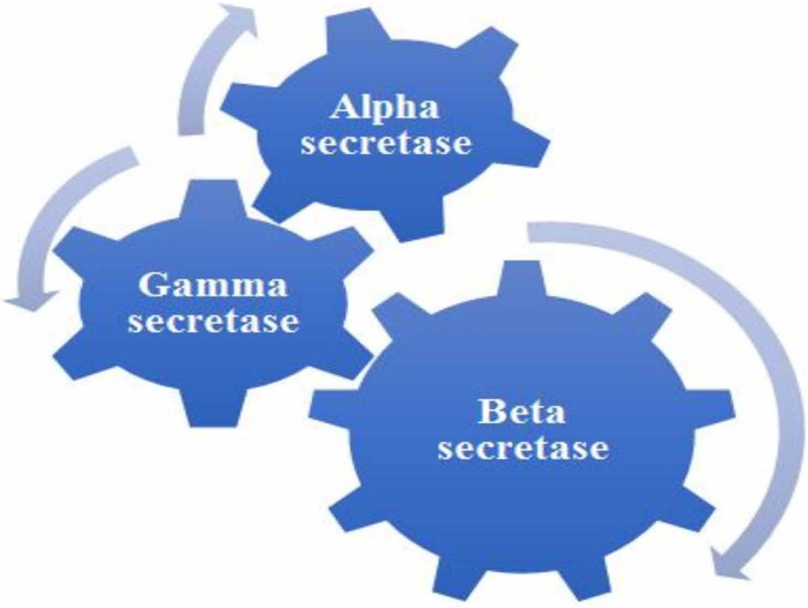
Amyloid Precursor Protein and Its Enzymatic Cleavage

APP belongs to the family of transmembrane and secreted proteins which includes the amyloid precursor-like proteins (APLP1 and APLP2) in mammals. It has several functions, which include regulation of haemostasis and mediation of neuroprotection. It is believed to stimulate neurite outgrowth and synaptogenesis. Also, it has been reported to have a role in stimulation of mitogenesis, G_0 proteins and MAP kinases for regulating cell proliferation, differentiation and survival. It seems to have a neuroprotective effect by altering cyclic guanosine monophosphate (cGMP) levels, Ca^{2+} homeostasis and activation of K^+ channels. It has also been reported to have a protective action against excitotoxicity, hypoglycemia and brain ischemia (Storey & Cappai, 1999).

The neuroprotective activity of APP has been substantiated by *in vivo* studies on mice. In one experiment, APP-transgenic mice were mated with HIV-gp120 transgenic mice and a significant protection was reported against HIV-gp 120 induced neurotoxicity (Mucke et al., 1995).

Although APP is a transmembrane protein that is present on the surface of neurons, the majority of it undergoes degradation within the secretory pathway even before it could reach the cell surface (Caporaso, Gandy, Buxbaum, & Greengard, 1992; Citron, Teplow, & Selkoe, 1995). APP is expressed in great quantities in neurons and undergoes rapid metabolism. Several alternate pathways exist for APP proteolysis. Some of these pathways lead to formation of the Aβ peptide and some of them do not (M. Lee et al., 2000). There are three enzymes which are responsible for proteolytic cleavage of APP (Figure 2).

Figure 2. Enzymes involved in proteolytic cleavage of amyloid precursor protein



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Alpha Secretase

Alpha secretase is synonymous with the metalloprotease activity that is believed to have an involvement in the prevention of underlying molecular pathways of AD pathogenesis. Increasing α-secretase associated proteolytic cleavage of APP is thought of as a therapeutic measure for AD (Lichtenthaler, 2012). Neurotoxic Aβ peptides are not formed if APP is first acted upon by α-secretase. α-secretase cleaves APP inside the Aβ sequence. This, in turn, prevents the formation neurotoxic Aβ peptides (Zhang & Saunders, 2007).

After several years of research on α-secretase, the chiefly involved enzymes have been identified as parts of a disintegrin and metalloproteinase (ADAM) family. The family comprises of three membrane proteins i.e. zinc-dependent metalloproteinases. Three members of this family i.e. ADAM 10, ADAM 17 and to some extent ADAM 9 are known to exhibit α-secretase activity. Additionally, some other membrane linked metalloproteinases may play a role in processing of APP (Postina, 2008). Several cellular signalling pathways encompassing phospholipase C (PLC), serine/threonine specific kinases (protein kinases C, MAP kinases) and phosphatidylinositol-3-kinase also contribute to expression of α-secretase. α-secretase dependent processing of APP is also known to be stimulated by direct activation of protein kinase C and activation of distinct G protein coupled receptors (Skovronsky, Moore, Milla, Doms, & Lee, 2000). Therefore, M1 muscarinic cholinergic agonists and 5-HT4/5-HT6 serotonergic agonists are being clinically evaluated for their potential in treatment of AD.

Amongst the ADAM family, ADAM 10 is the constitutive and most physiologically relevant α-secretase for shedding of APP. It partially competes with γ secretase to cleave down a C-terminal fragment generated due to β secretase (Kuhn et al., 2010). A study has reported an 81% decrease in α-secretase and 185% increase in β secretase in temporal cortex of patients of sporadic AD (Tyler, Dawbarn, Wilcock, & Allen, 2002).

α-secretase activators show a potential to become a disease modifying therapeutic approach in the coming times.

Beta Secretase and Gamma Secretase

The most widely accepted hypothesis of AD is the aggregation of Aβ peptide in neurons leading to neurodegeneration. Beta secretase (BACE) is known to be the main culprit involved in the shedding of APP to generate neurotoxic Aβ aggregates in neurons. BACE, chiefly BACE-1, cleaves APP the product of which is further acted upon by gamma secretase to generate Aβ. It was a landmark discovery when BACE-1 (memapsin-2) was identified as a novel class of type 1 transmembrane aspartic protease. BACE-2 was identified soon after but it was revealed subsequently that BACE-1 is essential for majority of neuronal Aβ aggregation (Venugopal, Demos, Rao, Pappolla, & Sambamurti, 2008). BACE-1 causes endoproteolysis of APP to liberate Aβ N-terminal fragment, APPsβ, and a C-terminal fragment, C99. Cleavage of APP by BACE1is a prerequisite for γ-secretase dependent cleavage (Figure 3) (Robert Vassar, 2004). γ-secretase is multi subunit enzyme complex which plays a great role, subsequent to BACE1, in yielding Aβ from APP. It comprises of four principle components i.e. presenilin, nicastrin, anterior pharynx defective 1 and presenilin enhancer 2. These interact in a complex of high molecular weight to execute intramembrane proteolytic cleavage on a number of membrane-bound proteins including APP and Notch (Krishnaswamy, Verdile, Groth, Kanyenda, & Martins, 2009). Notch is a transmembrane receptor that regulates the cell-fate decisions (Barten, Meredith, Zaczek, Houston, & Albright, 2006).

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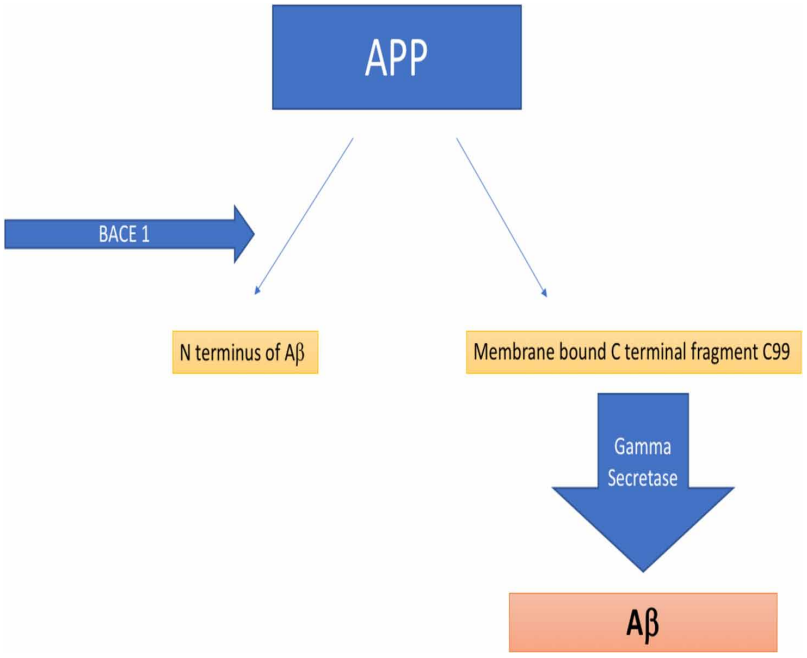
Assembly of these four subunits leads to autoproteolytic breakdown of presenilin to yield two subunits, each of which donates one aspartate to the active site of aspartyl protease. The aspartyl protease bears an initial docking site for substrate where it binds before passing between the two presenilin subunits to the internal active site. Modulators and inhibitors of γ-secretase have been in clinical assessment to evaluate therapeutic benefit in AD. The ultimate goal is to alter the function of γ secretase on APP without interfering with the processing of Notch signalling. The allosteric sites on the protease permit such selective moderation (Wolfe, 2008).

BACE 1 exists abundantly in human brain. The maximum BACE activity is seen in neural tissue while astrocytes exhibit less activity than neurons (R Vassar et al., 1999). BACE mRNA levels are low in resting glial cells. Like other members of pepsin family, BACE 1 comprises of two active site motifs and the mutation of either leads to inactivity (Bennett et al., 2000; Hussain et al., 1999). It is a type 1 membrane protease with a luminal active site which provides the optimal spatial orientation for cleavage of APP (Cole & Vassar, 2008). The gene expression of BACE1 is strictly moderated at the transcriptional level. The promoter of BACE1 comprises of a functional Sp1 response element. The gene expression of BACE gets potentiated by overexpression of transcription factor Sp1. The transcription factor Sp1 has been known to have the major involvement in modulating the BACE1 regulated cleavage of APP (Christensen et al., 2004). However, γ secretase cleavage is imprecise and yields Aβ isoforms of varying C terminus lengths. The longer isoforms are typically linked to AD (Robert Vassar, 2014).

BACE1 is the prime disease modifying therapeutic target for treatment of AD. Inhibition of BACE1 can lead to a substantial decrease in cerebral Aβ levels. Clinical development of BACE1 antagonists is being intensely researched upon. Although, BACE1 antagonism provides high hopes for prevention and treatment of AD, concerns have been rising about the mechanism based potential side effects of these agents (Yan & Vassar, 2014).

Figure 3. The interplay of BACE1 and γ secretase in processing of amyloid precursor protein to yield Aβ



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Ubiquitin-Proteasome System

Deposition of proteins is a recurring event in several NDs, including AD. Evidence is there suggesting that protein accumulation may be a consequence of an impaired UPS. Indeed, there is clear genetic and biochemical evidence of an involvement of the UPS in AD pathogenesis (Oddo, 2008) . UPS, the major intracellular protein quality control system in eukaryotes, is responsible for the clearance and degradation of Aβ (Hong, Huang, & Jiang, 2014). There is growing evidence showing that there exists a strong relationship between Aβ (Hong et al., 2014) and UPS and this relationship plays an important role in pathogenesis of AD. The disturbance in the UPS contributes to deposition of Aβ in brain. The impairment in the UPS in AD affects the degradation of Aβ and causes an abnormal aggregation of Aβ (Hong et al., 2014). Simultaneously, Aβ inhibits the proteasomal activity and subsequently causes impairment in multivesicular bodies (MVB) sorting pathway, forming an interacting relationship between Aβ and UPS. Mutant ubiquitin and ubiquitin-like ubiquilin-1 are related to Aβ accumulation (Hong et al., 2014). The proteasome is a constitutive multi-catalytic, multi-subunit protease complex which employs homopolymers of ubiquitin as a signal for targeting proteins for degradation in an ATP-dependent pathway (Baranello et al., 2015).

In mammals, the most common form is 26S proteasome comprising of a proteolytic 20S core subunit with two 19S regulatory subunits. The complex is a hollow moiety so as to provide an entrance for proteins to be takeen in and degraded (Thrower, Hoffman, Rechsteiner, & Pickart, 2000). The first event involves adenylation of ubiquitin by the ubiquitin activating enzyme E1. Then, it is transferred to the active site cysteine residue of E2- the ubiquitin conjugating enzyme. In the last event, a family of ubiquitin ligases – E3 is involved (Pappolla, Omar, Kim, & Robakis, 1992). It identifies specific targets and catalyses the transfer of ubiquitin from E2 to the target protein (Pappolla et al., 1992). A target protein has to be labelled by at least 4 ubiquitin molecules for it to be able to be recognized for proteolysis.

Despite the inhibitory action of Aβ40 on the proteasome, it does not appear to be a substrate of the UPS. The proteasome can also moderate intracellular concentrations of PS1 and PS2, both, which indirectly influence γ secretase activity (Flood et al., 2005; Perry, Friedman, Shaw, & Chau, 1987).

AMYLOID BETA AND NEUROFIBRILLARY TANGLES: THE INTERPLAY

Apart from Aβ, NFTs are also invariably found in the brains of patients suffering from AD. The first experimental evidence that relates Aβ to tau, functionally, was described in a pair of landmark papers. Together, these studies concluded that increased tau pathology due to Aβ in the absence of any demonstrable effects on Aβ is caused by excess mutant tau. Thus, Aβ was reported to function upstream of tau, albeit by pathways that remained to be defined. (Gotz, Chen, van Dorpe, & Nitsch, 2001; Lewis et al., 2001).

During the past few years, ample evidence has been reported suggesting that the soluble forms of Aβ and tau act in combination, independent of their accumulation into plaques and tangles, to take neurons from healthy state to the diseased state. Also, it has been reported that hallmark toxic properties of Aβ require tau (Bloom, 2014). The evidence that suggests that Aβ is influenced by tau, together with earlier reports that clearly demonstrated that Aβ clearly functions upstream of tau (Hurtado et al., 2010), creates the chances that Aβ triggers off a pathological feedback events with tau.

A protein that is responsible for a functional connection between Aβ and tau is fyn. It is a nonreceptor tyrosine kinase that causes positive regulation of NMDA receptor activity which was recently reported

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to be targeted to postsynaptic sites in dendrites by tau (Ittner et al., 2010) which binds fyn directly (G. Lee, Newman, Gard, Band, & Panchamoorthy, 1998). Tau is otherwise highly available in axons as compared to dendrites (Binder, Frankfurter, & Rebhun, 1985) but in response to Aβ, tau undergoes extensive redistribution into the somatodendritic compartment (Delacourte et al., 1990; H. Zempel, Thies, Mandelkow, & Mandelkow, 2010). Acute cytotoxicity is not the only tau-dependent manifestation of Aβ on cultured dissociated neurons or brain slices (Nussbaum et al., 2012; Rapoport, Dawson, Binder, Vitek, & Ferreira, 2002). Aβ oligomers have been reported to bring about tau-dependent microtubule disassembly (King et al., 2006), impaired long-term potentiation (Shipton et al., 2011), dendritic microtubule severing (Hans Zempel et al., 2013), inhibition of mitochondrial transport along microtubules (Vossel et al., 2010), and ectopic cell cycle re-entry of neurons (Seward et al., 2013), which eventually leads to massive neuronal death in AD.

NEW DEVELOPMENTS IN PHARMACOTHERAPEUTICS FOR THE MANAGEMENT OF ALZHEIMER'S DISEASE

The development of new therapeutic interventions for AD is under the threat of chasing the wrong pathology. Because of little concrete evidence base pertaining to a definite underlying pathological mechanism for development of AD, hypotheses based pharmacological interventions are being developed. Earlier, cholinergic hypothesis of development of AD emerged as a potential ground to build research upon. Several compounds were developed to target the acetylcholinesterase enzyme in order to elevate the levels of brain ACh. These agents are still in use but they provide only symptomatic relief. Also, a wide spectrum of side effects is associated with these agents. A few decades later, memantine came into picture as a protectant against glutamate excitotoxicity. However, this drug also could not yield effect better than mere symptomatic relief.

Several new chemical entities claiming to have potential benefits in AD have been developed by researchers all over the globe. However, a lot of them failed in the clinical trials due to different reasons mostly the severe adverse effects and lack of significant efficacy. A major factor that contributes to the increasing failures in development of new therapeutic measures for AD is that the current trial designs are quite nonspecific and blunt. Measure of cognitive abilities is a reductionist approach as the disease is too complex. Most of the pathobiological alterations do not manifest in alterations in cognitive processes and hence these two parameters cannot be correlated. The drug candidates targeting amyloid pathology are often employed at the later stages when Aβ related neurodegeneration has begun. This further adds to the increase in failures of new anti-AD therapeutics. This has not stopped the researchers from creating new possibilities for the treatment of AD (Anand, Patience, et al., 2017). The preclinical screening of novel entities for anti-AD effects is being carried out on a large scale worldwide. It is worth noting that no new drug (excluding nutraceutical products) has been able to obtain FDA's approval for treatment of AD in the last decade (Berk & Sabbagh, 2013). A great attrition has been found, with an overall failure rate of 99.6% (0.4% success) in the decade spanning from 2002 to 2012 in the field of anti-AD therapeutics. The trial length and magnitude for disease modifying agents is greater than those for symptomatic agents. The success rate of an entity's progression from one phase of clinical trial to the next is low. The number of entities advancing to regulatory review is among the lowest seen in any area of therapeutics (Cummings, Morstorf, & Zhong, 2014).

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Due to the limited options for the therapeutic agents, several new molecules have come in the recent years claiming to have a curative potential for AD. The existing pipeline for anti-AD drugs is quite modest in the light of the tremendous challenges associated with AD. Currently, AD is proving to be very expensive to the US economy, even more than cancer and cardiovascular diseases (Hurd, Martorell, Delavande, Mullen, & Langa, 2013).

Entities currently in clinical trials globally (as of 2017) targetting the amyloid pathological pathway of AD (Anand, Patience, et al., 2017) are given in Table 1.

Table 1. Entities currently in clinical trials for Alzheimer's disease.

Entity	C ompany	Description	Reference
AZD3293	AstraZeneca	Beta secretase inhibitor	Lilly, 2017
BACE inhibitor	Lilly	Beta secretase inhibitor	Lilly, 2017
CNP 520	Amgen	Beta secretase protein inhibitor	Amgen, 2017
E2609	Biogen	Beta secretase inhibitor	Biogen, 2017; Eisai, 2017
LY3314814	Lilly	Beta secretase inhibitor	Lilly, 2017
NGP 555	Neurogenetic Pharmaceuticals	Reported to cross blood brain barrier and effectively reducing the brain biomarkers Aβ42 and Aβ40 (in mice harbouring the human APP) by modulating the gamma secretase complex	NeuroGenetic Pharmaceuticals, 2017

FUTURE RESEARCH DIRECTIONS

Despite the exhaustive research that has happened in delineating the role of amyloid beta in AD, still certain unexplored areas remain in this amyloid hypothesis of AD. Mismatched APP cleavage by three proteolytic enzymes i.e. alpha, beta and gamma secretases, is believed to be the major reason for the production of neurotoxic Aβ peptides. The exact role of amyloid pathway of AD pathogenesis is still gray. There are several assumptions and hypotheses associated with it. An elaborate thrust on research areas intending to more clearly elucidate the intricate molecular mechanisms linked to amyloid pathway of AD pathogenesis needs to see the light of day. Recently unsuccessful antiamyloidogenic trials portray a strong need for an objective reassessment of the much talked about amyloid hypothesis of AD. The existing efforts with focus on Aβ, its deposition and accumulation, and its removal need to be supported by more intensive research in new directions. Once the exact molecular mechanisms, reaction cascades, proteolysis sequences and other associated targets are identified more clearly, effective and safe disease modifying pharmacotherapeutics can be developed.

Future research directions may be oriented thereafter towards increasing the expression of alpha secretase as its action on APP does not yield a neurotoxic product (Zhang & Saunders, 2007). Beta secretase and gamma secretase inhibitors are surely to experience an elaborate and tremendous research as they are the key enzymes that are responsible for generation of Aβ plaques which in turn cause neurodegeneration (Venugopal et al., 2008). Also, UPS stabilizers may be developed to halt or delay the impairment in the system thereby ensuring efficient clearance of formed Aβ plaques (Hong et al., 2014).

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CONCLUSION

AD being a growing health concern worldwide has received a lot of attention from researchers in the past few decades. Despite enormous research, only symptomatic relief could be provided to the sufferers of AD. Aβ hypothesis of AD is the most widely accepted hypothesis for pathogenesis of AD. It states that the beta and gamma secretase linked cleavage of APP in brain leads to the formation of neurotoxic Aβ plaques. Also, an impairment in UPS system further augments the intensity of AD as there is significantly reduced clearance of Aβ from brain. All these events contribute to the state of loss of neuronal connections in brain and eventually cause a progressive and irreversible loss in memory and cognitive abilities. From developing safer and more effective drug candidates for the existing therapeutic targets (cholinesterase, NMDA glutamate receptors) to developing moieties focusing on newer targets (Aβ, BACE, gamma secretase, α-secretase), the researchers have been contributing their efforts to bring a preventive and/or curative therapy for AD. With an in-depth understanding of the amyloid hypothesis of AD, an effective disease modifying therapy for AD can be developed in the coming years.

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Chapter 2
Lewy Body Disease:
Point Towards Progressive Dementia

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ABSTRACT

Fritz Heinrich Lewy described the intracytoplasmic inclusions found in the neurons for the very first time. In 1919 these inclusions were termed as "LBs" by Tretiakoff. LBs were found in the brain of the patients suffering from Lewy body disease (LBD). LBD is characterized by the presence of Parkinsonian symptoms in the earlier stages and dementia in the later stages of the disease. LBs were classified on the basis of the region of the brain in which they are distributed and so is the case of the LBD means the type of the LBD depends on the anatomical areas of the brain involved. LBD is not a single disorder. It is a spectrum of disorders. This chapter addresses the entire profile of LBs, types, composition, formation, and various LB pathologies as well as diagnostic criteria and pharmacotherapy.

INTRODUCTION

Lewy bodies (LBs) are the eosinophilic intracytoplasmic inclusions found in the brain of the patients of Parkinson's disease (PD) and were first described by Fritz Heinrich Lewy. These inclusions were later called "LBs" by Tretiakoff in 1919 (Wakabayashi et al, 2007). The presence of LBs in the brain of PD patients suggesting the possible involvement of LBs in the process of neurodegeneration, but the recent reports suggested that the LBs formation is a response evoked by the body to scavenge or degrade the neurotoxic substances that is responsible for neuronal degeneration (Sathiyamoorthy et al., 2014). LBs occur in context of various distinct pathologies known as Lewy body disease (LBD) characterized by the presence of the parkinsonian symptoms in earlier stages and dementia in the later stages of disease. Various symptoms of LBD include parkinsonism, hallucination, cognitive impairment, fluctuations in

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mental status, and dementia. Different types of LBD shares some common characteristics however the marked symptomatic difference found in these pathologies is mainly due to the difference in anatomical region of the brain involved (in which the LBs formation occurs) (Kosaka, 2014). Further each of these pathologies is characterized by the presence of LBs, therefore the symptoms appears very similar and sometimes overlaps making the exact pathology difficult to diagnose. Thus the exact pathology so involved sometimes remains undiagnosed and often misdiagnosed (Galvin & Balasubramaniam, 2013) which often becomes troublesome to the patients and caregivers (Galvin et al, 2010). Therefore very precise diagnostic criteria's is required to avoid the false diagnosis and the wrong prescription that may prove fatal later. The difference in diagnosis largely depends on the order of symptomatic presentation such that if only the movement deficits are present then the person is said to be suffering from PD, the development of dementia one year after the onset of the PD is referred as dementia associated with PD (PDD) and if the dementia develops before the onset of the PD or within one year of the PD then it is referred as dementia with LBs (DLB) (Galvin & Balasubramaniam, 2013). In the present chapter authors demonstrate LBD with their similar and differentiating characteristics and provides several recommendations that will prove beneficial in the diagnosis and the pharmacotherapeutics of such pathologies.

BACKGROUND

LBs are the intracytoplasmic inclusions found in the neurons of the patients suffering from LBD, however the exact type of the LBD which a patients exactly suffers from depends upon the region of brain in which the LBs were found predominantly (Kalra et al, 1996). Brainstem nuclei involvement is almost universal in the LBD while the involvement of limbic region and neocortex suggested the progression of disease (Braak et al, 2003). Further it is suggested that the brainstem is involved in the early stages of LBs pathologies whereas the different region of brain also involved when the disease progresses or in the later stages of the disease (Adler et al, 2010). LBs pathologies or the LBD represent a family of the disease that involved three distinct pathologies including PD, PDD and DLB. Before going in to the depth involved in the pathogenesis of these pathologies it remains of interest how LBs occurs and what is the reason of LBs formation. Recent reports suggested that the dopaminergic neurons isolated from the healthy individuals when implanted in the brain of the PD patients form LBs (Kordower et al, 2008; Li et al, 2008) suggesting LBs formations occurs to counteract the pathological insult. Thus LBs formation represents an epiphenomenon, or the scars of neurodegeneration (Popescu et al, 2004). In the present work authors demonstrate the different types of LBs, their formation and composition and the occurrence of LBs in various LBD.

CLASSIFICATION OF LEWY BODIES

LBs can be classified on the basis of their distribution in the different regions of brain.

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Type 1 Lewy Bodies

Type 1 LBs are also known as brainstem LBs because of the predominant involvement of the brainstem nuclei (Braak & Braak, 2000; Dickson et al, 1987; 1996; Kosaka et al, 1984). Type 1 LBs are spherical in shape containing eosinophilic cores, lamellar bands and pale halos (Campbell et al, 2001).

Type 2 Lewy Bodies

Type 2 LBs are also known as cortical LBs and characterized by the major involvement of limbic and temporal region and lesser involvement of frontal and posterior cortical region of brain (Braak & Braak, 2000; Braak et al, 2003; Kosaka, 1990; Kosaka et al, 1984). Type 2 LBs are less eosinophilic and less circumscribed (Dickson et al, 1987) and typically lack pale halos (Gomez-Tortosa et al, 2000).

COMPOSITION OF LEWY BODIES

Alpha-synuclein (α-syn) is the major component of LBs (Spillantini et al, 1997). α-syn is a small acidic protein comprises of three domains: N-terminal lipid-binding domain, responsible for the helical structure and the interaction of α-syn with the lipid membranes (Sode et al, 2007); Amyloid-binding central domain (NAC), responsible for the aggregation of α-syn (Rajagopalan & Andersen, 2001) and C-terminal acidic tail, this domain inhibit the aggregation of α-syn (Kim et al, 2004). It has been reported that the mutations in the SNCA gene increase the chances of α-syn aggregation (Minton, 2005) and the aggregation of α-syn is responsible α-synucleinopathies (Spillantini et al, 1997). Aggregation of α-syn monomers leads to the formation of oligomers (Walsh et al, 1997) responsible for neuroinflammation, and neurodegeneration (Wolozin & Behl, 2000) by disrupting proteostasis (Hinault et al, 2010); opening of "mitochondrial permeability transition pore" (mPTP) (Luth et al, 2014) and disrupting mitochondrial respiration (Nakamura, 2013). Oligomers also acts a seeds to promote seeding in which the soluble oligomers acts as the nucleus and form the large insoluble aggregates form known as amyloid fibrils (Eichner & Radford, 2011) that further promotes neuronal death (Jucker & Walker, 2011).

GENESIS OF LEWY BODIES

The precise sequence of events involved in the formation of LBs is completely not known. But it is reported that the process of LBs formation begin with the aggregation of α-syn (Campbell et al, 2001) followed by the incorporation of pale bodies (Gomez-Tortosa et al, 2000) further followed by the incorporation of ubiquitin (Engelender, 2008) and the accumulation of additional proteins (Kuusisto et al, 2003; Orosz et al, 2004). It is reported that LBs distortion often followed by the reduced immunoreactivity (Katsuse et al, 2003).

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LEWY BODY DISEASE: PARKINSON'S DISEASE, PARKINSON'S DISEASE DEMENTIA AND DEMENTIA WITH LEWY BODIES

LBD often involves three distinct pathologies including PD, PDD and DLB suggesting LBD a generic term (Figure 1). LBD can be classified into three types (Type A, Type B, and Type C) according to the regional distributional of different LBs in the different regions of brain (Kosaka et al, 1984). Type A referred as brain stem type LBD; Type B referred as transitional type LBD and Type C referred as diffuse type LBD. In brainstem type, LBs occurs in the brainstem nuclei and diencephalon, this is often seen in the PD pathologies (Braak et al, 2003). In DLBD type, LBs are found in the cerebral cortex and amygdale showing the rarely presence of LBs in brainstem and diencephalon nuclei thus the mesocortical dopaminergic system remains intact and dementia precedes parkinsonism as seen in DLBD (Kosaka et al, 1996). Further DLBD is a neurodegenerative disorder that occur either in common form (cognitive impairment followed by parkinsonism) or pure form (parkinsonism followed by dementia) (Kosaka, 2014); characterized by the symptoms including dementia, cognitive impairments, hallucinations, and parkinsonism (Zesiewicz et al, 2001). Transitional type is the transitional between brainstem type and diffuse LBD.

Figure 1. The family of the Lewy body disease

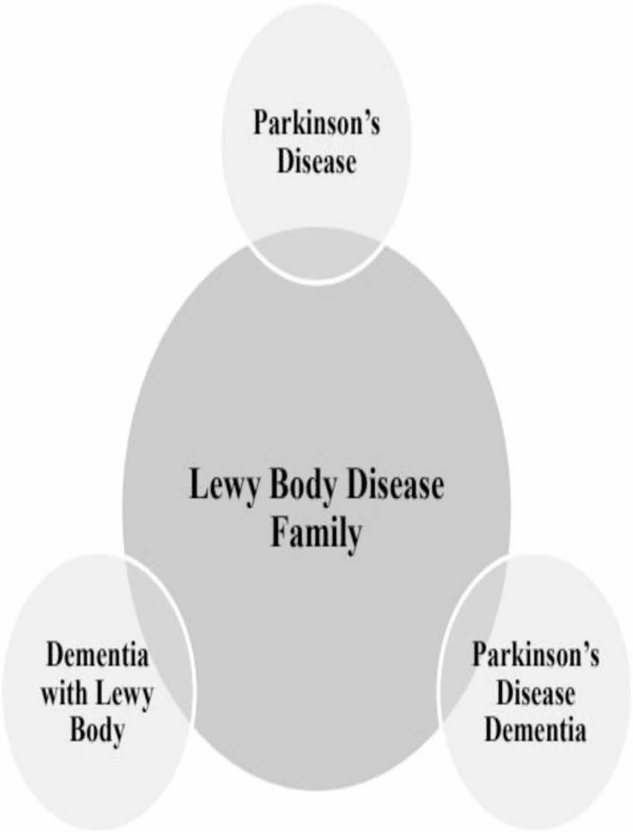

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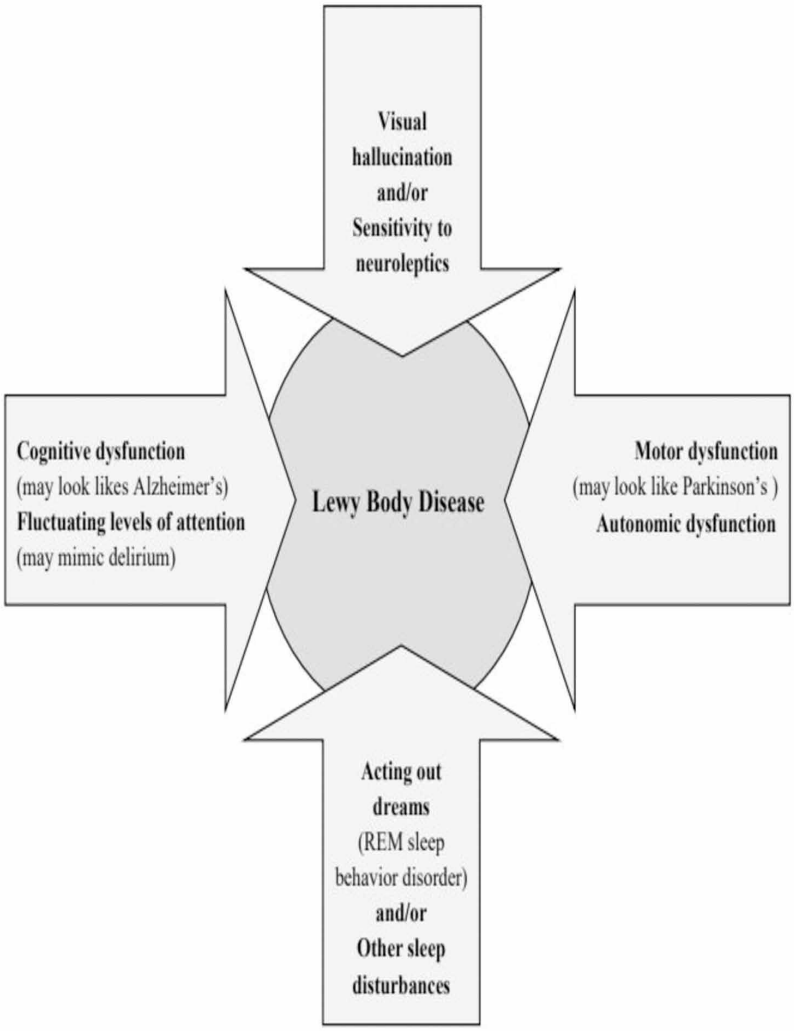
Figure 2. The spectrum of Lewy body disease



However besides these three forms of LBD there is another form of LBD which is known as incidental LBD (iLBD). LBs have been found in the patients suffering from the PD. However recent findings suggested LBs were found to be present in the brain of approx. 10% of the normal individuals above the age of 60 years, presenting a unique condition known as ILBD (Dickson et al, 2008). ILBD thus represents a condition either prior to or an early/intermediate stage leading to PD or DLB (Adler et al, 2010). Since the distribution of LBs in the brain in ILBD is similar to the PD, but the differentiating feature is that in case of ILBD there is no damage or loss of dopaminergic neurons. ILBD is thus considered as preclinical PD (Frigerio et al, 2011) but it remains to be clarified whether ILBD is pre-symptomatic PD or it is an age-related change which is unrelated to PD (Dickson et al, 2008).

LBD is not a distinct disorder but a continuum of disorders including disturbances of movement, cognition, behavior, sleep and autonomic function (Figure 2). PD, PDD and DLB, these pathologies are distinct actually but their symptoms overlap each other. In this section we describe each pathology and its characteristics in detail (Table 1).

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Table 1. Differences amid Parkinson's disease, Parkinson's disease dementia and dementia with Lewy bodies

S. No.	Parkinson's Disease	Parkinson's Disease Dementia	Dementia with Lewy Bodies
1	PD results in the motor dysfunction.	PDD results in the motor and cognitive dysfunction.	DLB results in the motor and cognitive dysfunctions
2	Dementia may or may not be present in PD.	In PDD dementia develops more than one year after the diagnosis of PD.	In DLB dementia develops before or within one year of the PD diagnosis.
3	Executive difficulties in occurs in PD.	Visuospatial functioning and semantic memory deficits occurs in PDD.	Attentional deficits, executive and visuospatial deficits occur in DLB.
6	Resting tremor and rigidity are common.	Non-tremor dominant motor symptoms are present in PDD.	Resting tremor is uncommon, facial masking and axial rigidity occur in DLB.

Parkinson's Disease

The death of the dopaminergic neurons in the substantia nigra (SN) region of brain results in the pathology known as Parkinson's disease (PD). Since PD is characterized by the degeneration or the death or the damage of the dopaminergic neurons, however what is exact reason behind the damage of these neurons in the PD still remains unknown (Walia et al., 2014). The death of the dopaminergic neurons in the SN region give rise to the deficiency of the dopamine that further results in the motor symptoms of PD. Several genes have been targeted in context of the PD and these includes SNCA gene (Chartier-Harlin et al, 2004; Forno, 1996; Kruger et al, 1998; Nishioka et al, 2006; Polymeropoulos et al, 1997; Polymeropoulos et al, 1997; Singleton et al, 2003; Zarranz et al, 2004), ubiquitin C-terminal hydrolase L1 (UCH-L1), leucine-rich kinase 2 (LRRK 2), HtrA2/Omi DJ-1, PTEN-induced putative kinase 1 (PINK1) and parkin (PRKN) (Gosal et al, 2006; Hattori & Mizuno, 2004; Hedrich et al, 2004; Hernandez et al, 2005; Maraganore et al, 2004; Marx et al, 2003; Nishikawa et al, 2003; Strauss et al, 2005). It is suggested that the mutation in the SNCA gene results in the aggregation of the α-syn, which is the main component of the LBs. LBs formation has been reported in the brain of the PD patients. It is suggested that the LBs remain confined to the brainstem nuclei in the stage 1-2, progresses to the SN region in stage 3-4 and finally reaches to neocortex in the latter stages of PD or Stages 5-6 (for detail please refer Braak et al, 2002; 2003). It is suggested that the presence of LBs in the brain of PD patients represents the sign of neuronal degeneration but do not tell anything about the exact sequence of degenerative events, however the LBs formation nowadays is considered as the response of the body to counteracts the neuronal insults (Popescu et al, 2004).

Parkinson's Disease Dementia

The development of dementia more than one year after the PD onset is known as Parkinson's disease dementia (PDD) (McKeith et al, 2006) characterized by the presence of LBs in the cortical and limbic region of the brain (Irwin et al, 2012). Thus PDD presents the condition in which the motor symptom develops one year before the cognitive impairments (Kurtz & Kaufer, 2011). The prevalence rate for PDD in the population above 65 years is about 0.2%-0.5% (Aarsland et al, 2005a; 2007), suggesting aging accelerates the development of dementia, cognitive deficits and increase the severity of motor disturbances (Levy et al, 2002). The presence of PD further increased the risk of developing dementia

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(Aarsland et al, 2003; Emre et al, 2007; Levy et al, 2002; Williams-Gray et al, 2009) and about 80% of the patients suffering from PD pathology develops dementia (Aarsland et al, 2003; Halliday et al, 2008; Hely et al, 2008). The main difference between PD and PDD is that the PD is characterized by the resting tremor greatly, while PDD is non-tremor-dominant motor subtype (Aarsland et al, 2003; Jankovic et al, 1990; Jellinger et al, 2002; Selikhova et al, 2009). Presence of the cognitive impairment often worsens the motor dysfunction associated with PD (Braak et al, 2005) and increase the disability, morbidity and mortality in the PD patients (Lo et al, 2009; Rosenthal et al, 2010). Also the patients with PDD did not represents the intrinsic core language deficit (Emre et al, 2007) but the difficulties encounters by the patients might be due to the executive dysfunctioning (Grossman et al, 2012).

Dementia With Lewy Bodies

DLB is a neurodegenerative disorder arises due to cortical and subcortical impairments that results in the development of attentional, executive and visuospatial dysfunction (Manning, 2004). The core features include dementia, parkinsonism, fluctuating cognition and hallucinations. Fluctuating cognition includes excessive daytime drowsiness, marked confusion and disorganized speech. Parkinsonism is usually bilateral, resting tremor is uncommon, while axial rigidity and facial masking is often more prominent in DLB. Visual hallucinations in DLB are often powerful, strong, bright, clear and repetitive (McKeith et al, 2005). The recurrent hallucination in DLB might be due to the burden of LBs in the anterior and temporal region of the brain (Harding et al, 2002). Rapid eye movement (REM) disturbance, a suggestive clinical feature of DLB often precedes cognitive or motor symptoms. REM sleep behavioral disturbances are characterized by the intense dreams that might harm the patients since the dream carries the destructive elements, the patients often starts screaming or fighting while sleeping that might results in the injuries (Ferman et al, 2002). Additional supportive features include repeated falls, syncope, unconsciousness, hallucinations, delusions and autonomic dysfunction (McKeith et al, 2005). In DLB, LBs formation has been noticed in the different regions of the brain including brainstem, limbic, neocortex and brain stem (Jellinger, 2009) however why limbic areas are selectively vulnerable to LBs pathology still remains unclear (Rezaie et al, 1996).

PATHOGENESIS OF LEWY BODY DISEASE

PD is disease associated with the defects in the various regions of basal ganglia (BG) resulting in movement deficits (Rubin et al, 2012). Striatum is the receptive nucleus of BG that receives afferent projections from neocortex, thalamus and SNc (Rubin et al, 2012) and sends inhibitory projection to direct pathway and indirect pathway. In direct pathway striatum send projections to globus pallidus interna (GPi)/SN which in turn send projection to thalamus and in indirect pathway striatum send projections to GPe, which then send projection to STN, which further send projection to GPi/SNr. Direct pathway of BG initiate movement and the indirect pathway of BG suppress movements (Kreitzer & Malenka, 2008). The balance between direct and indirect pathways is essential for the normal movements and functioning (Sperlagh & Vizi, 2011). Direct pathway is modulated by D_1 receptors while indirect pathway is modulated by D_2 receptors (Fuentes et al, 2010). Since PD characterized by the death of the dopaminergic neurons often resulting in the dopaminergic deficits and the alteration in the functioning of direct and indirect pathway. It is reported that in PD patients the activity of direct pathway decreases while the activity of indirect

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pathway increases (Gerfen & Surmeier, 2011; Kreitzer & Malenka, 2008) resulting in the difficulty in initiating movement and excessive inhibition of movement in PD.

The occurrence of LBs in the brainstem nuclei is the characteristic feature of PD (Braak et al, 2003). In PD, LBs has also been found in the different cranial nerve nuclei including premotor oculomotor, precerebellar and vestibular brainstem nuclei (Seidel et al, 2015). Further the presence of LBs in the cortical region is the characteristics of dementia (Duda et al, 2002; Tsuboi et al, 2007). PPN is a brainstem locomotor center, maintain balance and therefore damage to it results in the impaired gait and posture control. In PD about 50% population of the cholinergic neurons of PPN degenerate (Gai et al, 1991; Hirsch et al, 1987; Jellinger, 1988; Karachi et al, 2010; Zweig et al, 1989) resulting in the impaired postural control and gait and DA-resistant akinesia in PD (Stein, 2009).

Since PD involves the degeneration of dopaminergic neurons in the brain but Frederic Lewy first identified LBs in the nbM (Holdorff, 2006). nbM is an open nucleus of basal forebrain characterized by extensive neuronal loss in PD pathology (Arendt et al, 1983; Candy et al, 1983; Chui et al, 1986; Perry et al, 1985) suggesting cholinergic deficits results in the cognitive impairment observed in the patients of PD (Kehagia et al, 2013). This cholinergic neuronal loss even become more prominent in the presence of dementia (Candy et al, 1983; Nakano and Hirano, 1984; Rogers et al, 1985; Tagliavini et al, 1984; Whitehouse et al, 1983) suggesting a greater impairment in the PDD patients. Further the dopaminergic neuronal destruction in the PD occurs concurrently with accumulation of α-syn in the cholinergic neurons of forebrain (BF) (Braak et al, 2003). It is reported that the denervation of cholinergic neurons of forebrain is a possible marker of slowing of gait observed in the patients of PD (Bohnen et al, 2012) that might be due to the possible decrease in the cognitive processing abilities during ambulation (Woollacott & Shumway-Cook, 2002).

PDD refers to the development of dementia more than one year after the onset of PD pathology (Emre et al, 2007). The cognitive picture of PDD is commonly considered as a "subcortical" type and patients typically presents executive dysfunctions (Chui et al, 1986; Darvesh & Freedman, 1996). Both PDD and DLB involved the loss of cholinergic neurons (Klein et al, 2010; Shimada et al, 2009) resulting in the severe cortical acetylcholine deficits (Rolinski et al, 2012). LBs pathologies exist in brains of PDD and DLB (Jellinger & Attems, 2015).Approx. 78% patients suffering from PD develops dementia (Aarsland et al, 2003) which is similar to DLB (Aarsland et al, 2003; Ballard et al, 2002; Emre, 2003). Further pure DLB appear similar to PDD (Emre et al, 2007) and both of these pathologies involved narcolepsy and REM sleep behavior disorder (Kurtz and Kaufer, 2011).

DLB is the condition refers to the onset of the dementia before the onset of PD or with one year of PD onset (McKeith et al, 2006). The DLB and PDD distinguished on the basis of cognitive and motor symptoms (McKeith et al 1996). Cortical cholinergic loss is greater in DLB (Bohnen et al, 2012; Bohnen et al, 2009), while the dopaminergic neuronal loss is more severe in PDD than DLB (Tsuboi & Dickson, 2005). Thus nigrostriatal pathological changes occur in PD, subcortical pathological changes in PDD and the cortical changes occur in DLB (Petrova et al, 2015). Bilateral frontal atrophy occurs in PDD while parietal and occipital atrophy occurs in DLB (Borroni et al, 2015). Further PDD tends to affect younger patients than does DLB (Horimoto et al, 2003; Richard et al, 2002) and this might be due to its specific topography so involved (Revuelta & Lippa, 2009). These findings present the similarities and the dissimilarities in the PD, PDD and DLB.

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DIAGNOSTIC CRITERIA FOR LEWY BODY DISEASE

Diagnosis of Parkinson's Disease

The degeneration of dopaminergic neurons in the SN and the presence of LBs in the brainstem nuclei of brain are the main characteristics of PD (Lees et al, 2009; Marsden, 1994). The careful assessment of patient history is very important and therefore thorough questioning should be performed and, inquiry should be made about the presence of premotor symptoms (Massano & Bhatia, 2012). The clinician should note resting tremor, rigidity, postural instability, and akinesia and further should perform CT scan and MRI scan (Massano et al, 2008; Sitburana & Ondo, 2009) the former is used to identify the calcium deposits while the later is used to confirm degeneration (Kagi et al, 2010).

Diagnosis of Parkinson's Disease Dementia

Dementia is the primary feature of the PDD patients (Dubois et al, 2007; Emre et al, 2007). For PDD diagnosis, two core features must be present: first is the presence of PD and second is, PD developed prior to the onset of dementia. Associated clinical features of PDD include deficits in the cognition and behavioral impairments (Dubois et al, 2007; Emre et al, 2007). A patient is said to be suffering from the probable PDD if the impairment is noted in atleast two of the four cognitive domains supported by the presence of atleast one behavioral symptom. A patient is said to be suffer from the possible PDD, if dementia and PD exist together, however the associated clinical features are not considered typical (Dubois et al, 2007; Emre et al, 2007).

Diagnosis of Dementia With Lewy Bodies

According to McKeith et al. DLB is characterized by the presence of central, core, suggestive, and supportive features (McKeith et al, 2005). Like the PDD, central feature of the DLB is dementia, however the early prominent symptoms that can be seen in the patients suffering from DLB includes attention deficits, visual and executive dysfunction. Fluctuating cognition, recurrent visual hallucinations and spontaneous Parkinsonism, represent the core features, REM sleep disorder, severe neuroleptic sensitivity and low dopamine transporter uptake in BG represents the suggestive features and repeated falls, syncope, unexplained loss of consciousness; severe autonomic dysfunction, and non-visual hallucinations constitute the supportive features of DLB. Presence of one core feature with the presence of a suggestive feature suggests the probable DLB while the absence of any core features with the presence of a suggestive feature suggests possible DLB (McKeith et al, 2005).

PHARMACOTHERAPEUTICS OF LEWY BODY DISEASE

Various pharmacotherapeutics agents have been used in the symptomatic treatment of the LBD. Following section defines the selection, benefits, and restrictions of the different pharmacotherapeutics agents for the symptomatic treatment of PD.

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Treatment of Cognitive Symptoms

Cognitive symptoms of LBD should be treated with cholinesterase inhibitors (Aarsland et al, 2004; McKeith et al, 2000; Mori et al, 2012; Samuel et al, 2000; Wild et al, 2003). However cholinesterase inhibitors can exacerbate parkinsonism, and increase tremor in the prescribed patients (McKeith et al, 2000).

Treatment of Motor Symptoms

Levodopa/carbidopa might prove beneficial (Goldman et al, 2008). But the efficacy is lesser in DLB than in PD and the risk of development of psychosis increases (Lucetti et al, 2010; Molloy et al, 2005). Further the administration of oral dopamine agonists frequently increases the incidence of hallucinations, abnormal repetitive behaviors (Hassan et al, 2011) and compulsive behavior (Wesnes et al, 2005).

Treatment of Neuropsychiatric Symptoms

SSRIs and SNRIs might prove beneficial (McKeith et al, 2005). However SSRIs increased the risk of suicidality in the prescribed patients (Walia, 2017).

Treatment of Hallucinations and Delusions

Hallucinations and delusions should left untreated if possible (McKeith et al, 2000). DLB patients have increased risk of antipsychotics toxicity (Aarsland et al, 2005b) and a single dose of antipsychotics in these patients increased sedation, confusion, parkinsonism, rigidity, dysautonomia, and mortality (Aarsland et al, 2005b; Hassan et al, 2011; Rochon et al, 2005).

Treatment of Sleep Dysfunction

The presence of sleep dysfunction should be confirmed by polysomnography (Boeve et al, 2013). Treatment with caffeine is useful (Malhotra & Avidan, 2012) while the other therapeutic options may include methylphenidate, dextroamphetamine, and modafinil (Hogl et al, 2002; Seppi et al, 2011).

Treatment of Agitation and Behavioral Disturbance

Pain is often a trigger for agitation and therefore acetaminophen might prove beneficial (Husebo et al, 2011). The incidence of agitation and behavioral disturbances occurs generally in the later stages of disease (Husebo et al, 2011). Agitation and behavioral disturbance can often be treated by the simple measures that include and increased social interaction, training to the caregiver and removal of fear triggers (Rhodes-Kropf et al, 2011).

Treatment of Restless Leg Syndrome

Levodopa/carbidopa, clonazepam, and other GABA analogues might prove beneficial for the treatment of these symptoms (Hening et al, 2004).

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Treatment of Autonomic Dysfunction

Autonomic dysfunction includes constipation or diarrhea. (Jost, 1997; Lawrence et al, 2013) as a consequence of DLB (Boot et al, 2013; Postuma et al, 2013; Savica et al, 2010) treatment should include high-fiber diet, exercise, stool softeners, psyllium (Ashraf et al, 1997) and polyethylene glycol (Zangaglia et al, 2007).

ISSUES AND PROBLEMS RELATED TO LEWY BODY DISEASE

LBD are characterized by the presence of LBs in various cortical and subcortical regions (Jellinger, 2009). Presence of LBs in the cortical and limbic regions of the brain correlates dementia in patients with PD or PDD (Irwin et al, 2012). Further the pathological assessment of DLB reveals the presence of LBs primarily in limbic, and secondly in neocortical regions (Rezaie et al, 1996). The complexity of full spectrum of LBD symptoms (Galvin et al, 2008) and the similarities in clinical features, and neuropathology of LBD, make the diagnosis and management becomes so difficult (Gomperts, 2016) that sometimes clinicians made the wrong diagnosis (Zweig & Galvin, 2014). Also the clinicians view all dementias as the dementia develops due to AD pathology (Galvin et al, 2008). However there are some questions that remains still unresolved in context of LBD includes why the limbic region is more vulnerable to the LBs formation in DLB (Rezaie et al, 1996); why DLB and PDD have similar symptoms despite the fact they are distinct pathologies (Berg et al, 2014) and why the discrimination of DLB from other types of dementia is difficult (Sakamoto et al, 2014).

FUTURE RESEARCH DIRECTIONS

LBD imposed a great burden worldwide. The major limitation is that, till now the complete pathophysiology and the mechanism implicated in the pathogenesis of the LBD is not known completely. Further LBD is often misdiagnosed or underdiagnosed (Zweig & Galvin, 2014) resulting either in the delay in the pharmacotherapeutics of the disease or the wrong prescription that may prove fatal. Epidemiological studies should be done to provide the better understanding and prevalence of LBD (Galvin et al, 2008). Further the development of mouse models and an appropriate biomarker for LBD might prove beneficial in the area of the drug development for LBD (Galvin et al, 2008). Also newer diagnostic techniques and methods should be developed to avoid the incidence of misdiagnosis and under diagnosis that further worsens the conditions of patients (Zweig & Galvin, 2014).

CONCLUSION

It is concluded that the LBD put a great burden worldwide and is responsible for the disability. The greatest problem is that the symptoms are very similar and often led to wrong diagnosis. Therefore a great care should be taken while diagnosing and treating LBD because wrong treatment may further worsens the condition. Since the key step involved in the formation of LBs is the aggregation of α-syn. Therefore the interventional strategy might include the agents that interfere with α-syn aggregation. Further the interfering in either the process of α-syn secretion or neuronal uptake of α-syn might prove beneficial.

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Chapter 3
Creutzfeldt–Jakob Disease: A Prion-Related Neurodegenerative Disorder

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ABSTRACT

Creutzfeldt-Jakob disease (CJD) is a rare disease associated with neurodegeneration mostly characterized by damage to the neurons. CJD is caused by aggregation of misfolded proteins known as prions; thus, CJD is said to be a prion-related illness. CJD and other prion-related illnesses such as Kuru and Gerstmann-Sträussler-Scheinker disease (GSS) have been reported to have complex mechanisms due to their association with the brain and the nervous system in general. A lot of questions have been raised about the mechanism, diagnosis, and pathogenesis of this disease. The complexity of prion proteins themselves have contributed to more questions about the complications of CJD, whether misfolding of the prions are responsible for neurodegeneration or the misfolding are mere symptoms of the disease. This chapter attempts to explore some details about CJD and answers most related questions about the disease's mechanism. The author finally attempts to explore recent development in pathogenesis, diagnosis, and treatment of CJD.

INTRODUCTION

Human NDs have been one of the most deadly disorders with complex mechanisms and complicated treatment processes (Montie & Durcan, 2013).Particularly, thehumanprion diseases are one of the most rare human neurodegenerative diseases widely studied. These are associated with misfolding of proteins which accumulated and cause destruction of cells of the system (Friedman-Levi *et al.*, 2011). These proteins otherwise called prions, are misfolded leading to their aggregation into opaque amyloid structures. The pathogenesis of these diseases are mostly related to accumulation of the amyloid aggregates which in most cases, is associated with neural damage (Holman *et al.,* 2010). Prion diseases are therefore a group of progressive but fatal neurodegenerative disorders affecting both humans and

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animals, they are otherwise referred to as transmissible spongiform encephalopathies (TSEs) (Jackson & Krost, 2014). Some of these prion diseases including CJD, Alzheimer's disease (AD), and Huntington's disease (HD) are having rare occurrence with complicated pathogenesis (Kovacs & Budka, 2008). CJD is a prion related illness characterized by aggregation of misfolded proteins or prions. It belongs to a family of human diseases associated to and or characterized by neurodegenerative conditions and they include; Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia etc. These diseases are thought to be having similar characteristics with animals spongiform encephalopathies such as ''cow madness" also known as bovine spongiform encephalopathies (BSEs) (Lang, Heckmann, & Neundörfer, 1998). These could have both sporadic or spontaneous occurrence or could be genetical depending on occurring cases. As such as in BSEs, prions could also be transmitted resulting in the spreading of the disease (States *et al.,* 2005). Most researches in this area are focusing towards establishing a link between variant phenotypes of CJD and with the molecular features studied in wide ranges of CJD conditions.

This chapter attempts to explore details on CJD including the basic description of disease, its pathogenesis, classification, diagnosis, and epidemiology. The author objectively attempts to explain different perspectives of the current researches on Creutzfeldt-Jakob and a future sight as well recommendation on the treatment of the disease.

BACKGROUND

Neurons being the major cells of the nervous system could be damaged progressively by one cause or another leading to neurodegeneration and consequently diseases, such diseases are known as NDs (Aguzzi & Zhu, 2012). NDs are diseases associated with damage in structure and functions of the neurons, one of the important cells of the nervous system (Aguzzi & Zhu, 2012). In neurobiology, neurons form the complex network of communication around the central nervous system. Damage to neurons due to a number of factors has been reported to be lethal and associated with a number of diseases and disorders (Murray & Davis, 2003).

CJD was discovered by the German neurologist, Hans Gerhard Creutzfeldt and Alfons Maria Jakob in 1921 (Cordery *et al.,* 2003). Creutzfeldt was the first to describe the disease characterized with neurodegeneration and Jakob proposed the disease to be associated with prions (Holman *et al.,* 2010). However some of descriptions of the disease made by Jakob and Creutzfeldt did not match the current description of the disease (Creutzfeldt, 2002). This including being transmissible as well as currently being observed to be part of a class of both human and animal diseases called TSEs.

CJD as a TSE is associated with and mostly caused by diseased or misfolded prions (Aguzzi & Zhu, 2012). Prions are proteins that often misfold into amyloid structures and can possibly infect other proteins resulting into spreading or transmission (Jackson & Krost, 2014). In other words, prion proteins affect other neighboring proteins converting them into misfolded prion proteins and initiate the pathogenesis of TSEs including CJD (Lang, Heckmann, & Neundörfer). Spongiform refers to the characteristic appearance of infected brains, which become filled with holes until they resemble sponges under a microscope (Aguzzi & Zhu, 2012) . Transmission of the prion proteins in CJD was not initially established (Belay, 2004). The idea that prion proteins can be transmitted in CJD was established in 1986 after the London epidermic (Garske & Ghani, 2010). The incidence of the epidermic has stimulated interest in study of CJD with major aspects on the molecular mechanisms of its pathogenesis (Wilesmith *et al.,* 1988). Studies on prion proteins in fungi has already established the transmissible property of normal prions in the

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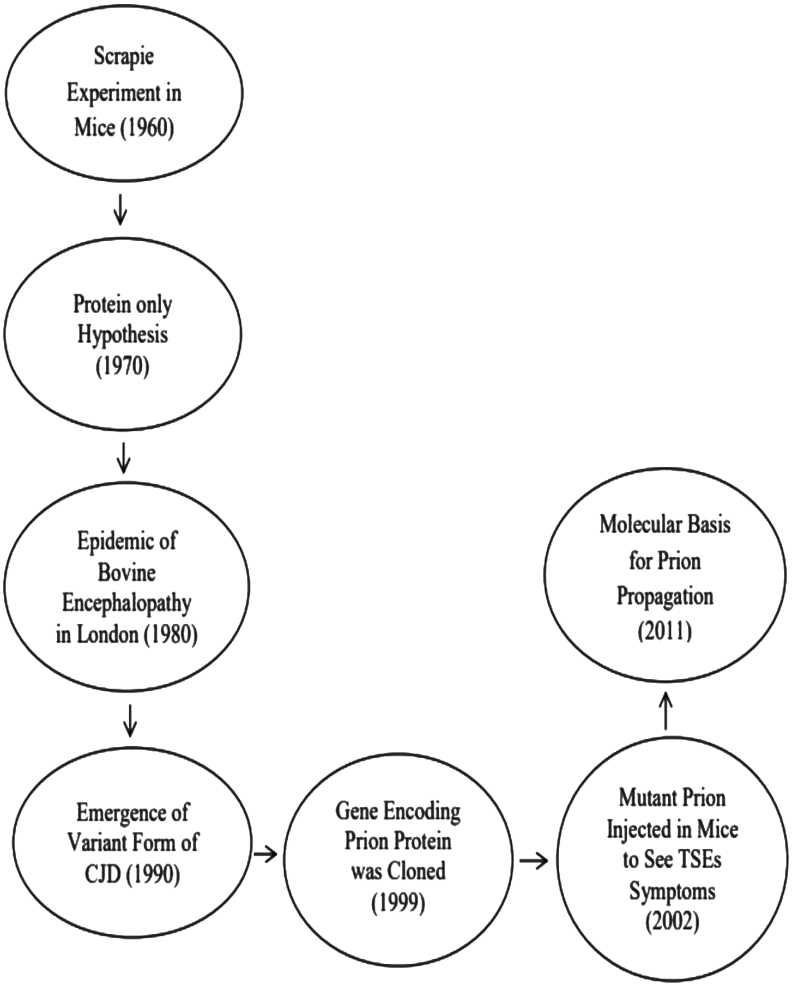
cell (Anderson *et al.,* 1996). Similar prion studies on vCJD was carried on human patients sample which confirmed the spreading ability of misfolded prions in CJD (Griffith, 1967). Protein only hypothesis was established and served as a model for supporting transmissibility of prion proteins (Soto, 2011). Consequently, studies were on to provide experimental basis for the hypothesis. Particularly, transgenic animals expressing mutant prion protein that develop clinical and pathological signs of TSE, were produced (Soto, 2004). Figure1 shows a brief timeline of the major occurrences and findings related to TSEs.

Figure 1. Timeline of experimental events during the discovery of prions



MISFOLDED PROTEINS' AGGREGATION AND THEIR ROLES IN PROTEINOPATHIES

Misfolded proteins existing together with unfolded proteins in the cell are re-folded by molecular chaperones (Kim, *et al.,* 2013). Proteins that refused to fold properly are immediately degraded however in pathologic cases, this protein resist degradation and accumulate (Halasi *et al.,* 2017). The ability to resist

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degradation has been attributed to folding into specific abnormal forms which are the infectious prion forms (Currais *et al.,* 2017). During biosynthesis cells continuously form stream of misfolded proteins and are refolded, degraded, or sequestered into specified cellular compartments such as aggresomes (Hartl, Bracher, & Hayer-Hartl, 2011). Many of such proteins have been seen to be misfolded and consequently aggregates to form insoluble structures in the cell (Stefani, 2004). These faulty or abnormally aggregates of proteins have been seen in many neurodegenerative diseases. Table 1 shows a brief summary of the misfolded proteins in some NDs. Molecular chaperones are proteins that bind assist in protein folding and remaining infolded form. They bind nascent polypeptides as they emerge from ribosomes and participate in every step in the handling of misfolded proteins. These proteins play crucial roles by monitoring the quality of the folded chains and like highlighted earliar, refold misfolded proteins *(*Kim *et al.,* 2013). Chaperones also target the misfolded proteins that couldn't be refolded/repaird for degradation.

Table 1. Some proteins Misfolded and the consequencing proteinopathies

Proteinopathy	Aggregating Protein(s)
Spongiform Encephalopathies	Prion protein
Parkinson's Disease	α-Synuclein
Cerebral β-amyloid angiopathy	Amyloid β peptide
Frontotemporal lobar degeneration	TAR DNA-binding protein 43 (TDP-43)
Alzheimer's disease	Tau protein
Huntington's disease	Huntingtin protein
Amyotrophic lateral sclerosis	Superoxide dismutase 1
Multiple tauopathies	Tau protein (microtubule associated)
Alexander's disease	Glial fibrillary acidic protein
Enfuvirtide amyloidosis	Enfuvirtide protein

PRION MISFOLDING AND CREUTZFELDT-JAKOB DISEASE

Prions are thought to be found all over the body with yet to be known function (Friedman-Levi *et al.,* 2011). In TSEs, when a prion enters a healthy organism, it induces an healthy protein to misfold into anonymous abnormal form through a chain of unknown processes (Aguzzi & Zhu, 2012). Certain proteins in cells of both lower and higher organisms such as bacteria and humans, promote or assist folding of proteins into various forms and conformations, these are known as chaperons. Thus as a prion promote misfolding of a normal protein into its own prion form, it results into spread of the prion protein which consequently form amyloid aggregate forms or plagues (Fania *et al.,* 2017). The amyloid form refers to an aggregate of misfolded or prion proteins with characteristic opaque sheets (Jackson & Krost, 2014).

Prion aggregates or amyloids are characteristically stable and show resistant to denaturation processes caused by temperature and chemical changes and as such stay for prolonged periods in the infected cell consequently resulting into its death (Kovacs & Budka, 2008). One question that is yet to be answered is, "misfolding of the prions causes the damage to the cell or other external damages to the cell causes the initiation of the misfolding resulting into the prion aggregation'' (Kovacs & Budka, 2008). However

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some scientists believed mutations in some genes initiated prion development in HD, a prion related disease (Mercado *et al.,* 2015). However in most TSE, infection of a prion resulted into transmission and spreading of neighboring prions resulting into their misfolding and aggregation into amyloid prion forms (Jackson & Krost, 2014).

The ability of misfolded prions (mostly from bovine encephalopathies) to infect neighboring normal prions was initially a not accepted (Murray & Davis, 2003). With the ability to infect prion to cause disease upon incubation, it resembles the commonly accepted processes of pathogenesis in microbes including bacteria, viruses and fungi (Nuvolone *et al.,* 2017). Critics of infectious prion pathogenesis argued that bacteria and viruses, major causative agents of diseases are mostly living organisms with delicate and distinct structures (Whalley, 2017). These organisms either secret toxins that temper normal cellular processes and or insert their genomes into the host cell thereby destroying the hosting cells and continue to spread and transmit to other cells by similar mechanism (Jackson & Krost, 2014). According to these critics, a protein would not be able to be transmitted in a similar fashion. However researches in various prion-related illnesses including CJD described the mechanism of prion transmission especially in TSEs *(*States *et al.,* 2005). Normal prion proteins being found all over the cell can be infected by an infectious prion mostly coming from contaminated food (e.g meat from cattle suffering from BSEs, also known as cow madness). These infectious agents infect the normal prion by facilitating the folding its into a similar abnormal form hence becoming a potential infectious prion. The infected prion infects another and the process continues all over the neighboring prions consequently aggregating into amyloid forms (Nuvolone *et al.,* 2017). However it is not exactly known how it facilitates the misfolding process, some hypothesized that by acting in a similar way as molecular chaperons (Whalley, 2017). In Figure 2, the underlying mechanism of prion misfolding is mentioned.

In CJD, aggregation of misfolded prions has been thought as the cause of neurodegeneration due to increased destruction of neuronal cells (Lang et al., 1998). However the actual mechanism by which these aggregates cause cell damage has not been clearly established and appears to be variable within each of the disease (Montie & Durcan, 2013). Some scholars hypothesized that misfolded disease proteins appear to act primarily by toxic gain-of-function and/or dominant-negative effects, although loss-of-function effects have also been observed (Whalley, 2017).

Although most misfolding events might be associated with toxicity leading to disease but not all events are responsible for toxicity (Valastyan, 2014). In the fungal organism, *Saccharomyces cerevisiae*, the presence and availability of prions are regulated and most of these prions utilized for various adaptive purposes (Chernova, Wilkinson, & Chernoff, 2014). Prion proteins in CJD are infectious and are associated with progressive neural damage hence dementia and other symptoms and conditions of neurodegeneration (Kovacs & Budka, 2008).

CLASSES OF CREUTZFELDT-JAKOB DISEASE

Different studies have suggested variety of classification of CJD. Some of the classifications were made based on the neuropathology of the disease (Hill *et al.,* 2003). However, based on the occurrence and cause of CJD, the disease can be classified into two main groups.

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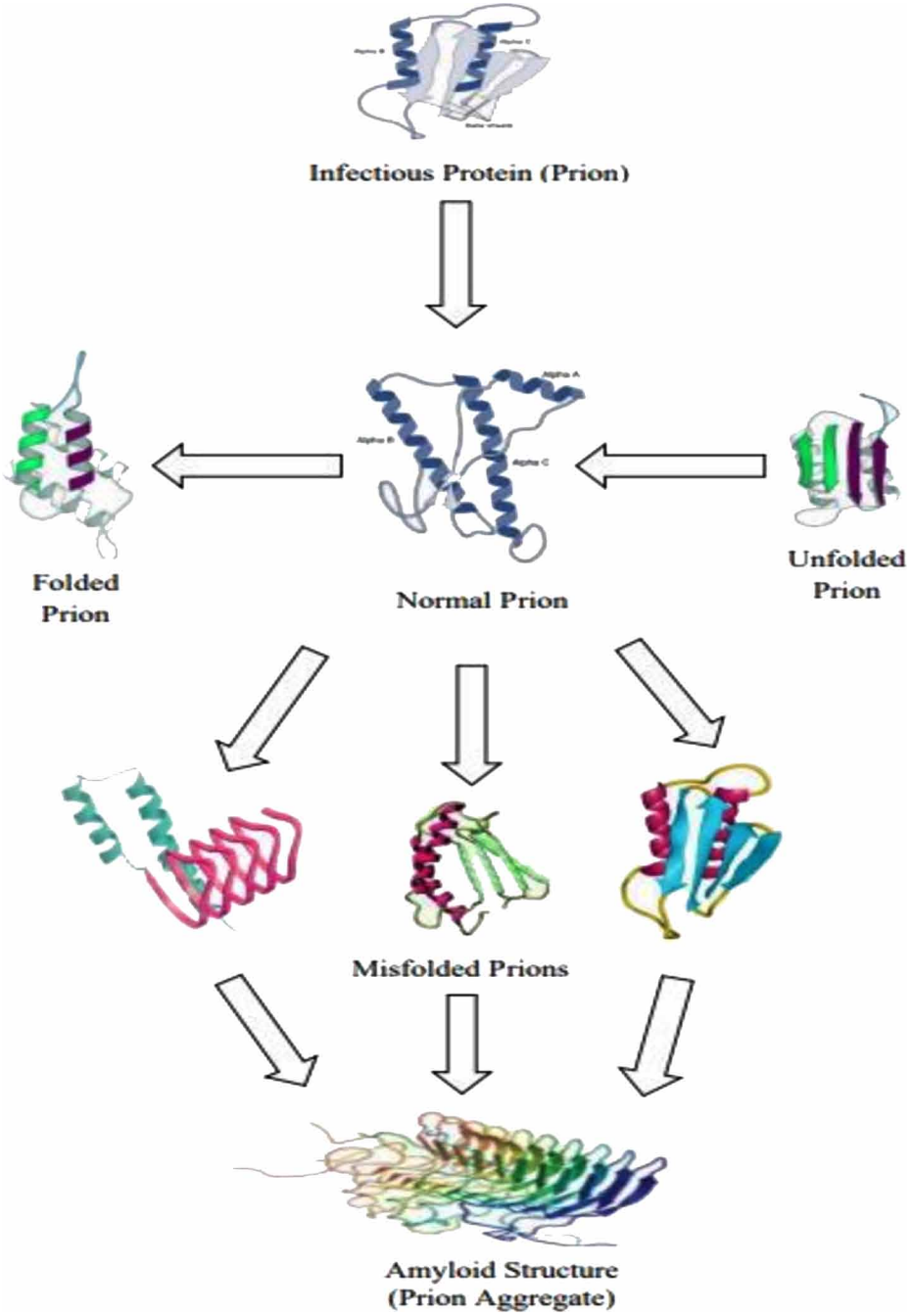
Figure 2. The mechanism of prion misfolding



Sporadic Creutzfeldt-Jakob Disease

Sporadic CJD (sCJD) refers to the rarest yet the most common form of the disease. Its major cause has been established to be genetically associated (Brandt, 2003). sCJD is reported to possess variability in

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its clinical and neuropathological phenotype (Mead *et al.,* 2013). However, It remains to be seen whether the variability might be related to variations in the causative TSE agent strains, or to the influence of the methionine/valine polymorphism at codon 129 of the *PRNP* gene. The polymorphism on the PRNP gene encoding either methionine or valine remain the major susceptibility factor of sCJD with mutant methionine prototype dominating in most cases than valine (Rubenstein, Petersen, & Wisniewski, 2016). The germline mutation in the *PRNP* gene can be inherited in an autosomal dominant fashion leading to harboring a homozygous allele (Mead *et al.,* 2001). Key phenomenon in the molecular mechanism of sCJD is the conversion of PrP^{C} (normal prion) to the pathological PrP^{Sc} (diseased Prion) which is the pathological form associated with the disease. However the conversion is caused initially by mutation as earlier described (Bilheude *et al.,* 2008).

sCJD constitute about 85% of all recognized prion diseases in humans (Safar *et al.,* 2005). It has been reported that 1 person in every million of people suffers from sCJD every year (Chen & Dong, 2016). It usally affects people between the ages of 40-60 and mostly takes upto 6-8 weeks while taking upto a year in some minority (Mastrianni, 2010). Similarly Brown et al. (1984) reported that about 10% of cases of sCJD have prolonged clinical course with the duration of the disease taking upto 2 years. Major symptoms associated but peculiar to sCJD are less pronounced and are mostly seen in other forms of the disease, however, a significant percentage of sCJD has been associated with cerebellar ataxia (Cooper *et al.,* 2006). Other symptoms including fatigue, weight loss, immediate loss of coordination, and Hallucination. Later stage symptoms include depression and sensory disturbances are common in sCJD that consequently progress to profound dementia (Geschwind *et al.,* 2013).

Variant Creutzfeldt-Jakob Disease

Variant CJD is the most widely known form of CJD as it can be transmitted between individuals via blood transfusion and can be acquired through ingestion of food contaminated with the agent of BSE (Maheshwari *et al.,* 2015). BSE is a TSEs in cattle and bovine family (Creutzfeldt, 2002). Consumption of a meat of cattle infected with BSE results into infection and transmission of infectious into the body of the healthy consuming individual resulting into infection of normal prions in the individual (Friedman-Levi *et al.,* 2011) The mechanism of conversion or transmission of a normal prion to an infectious one has been argued (Jackson & Collinge, 2001). However certain researchers have described key mechanisms involved. A Normal prion ($PrP^{C)}$ is converted to an infected or diseased prion (PrP^{Sc}) during a post-translation modification process involving structural modifications of the protein and resulting in a higher β-sheet content (Riesner, 2003). PrP^{C} is completely degraded after controlled digestion with proteinase K (PK) in the presence of detergents. PrP^{Sc} is N-terminally truncated under such conditions, resulting in a PK resistant core, termed PrP^{RES} (States *et al.,* 2005) . Most symptoms associated with the vCJD are similar to vCJD. However, in vCJD cognitive disorders appeared at much earliar stages than sCJD with severe behavioural disturbances (Mastrianni, 2010).

EPIDEMIOLOGY OF CREUTZFELDT-JAKOB DISEASE

Before the identification of vCJD in 1996, only three forms of CJD were thought to be existing and represent the most common prion related illness in humans. The three forms include:

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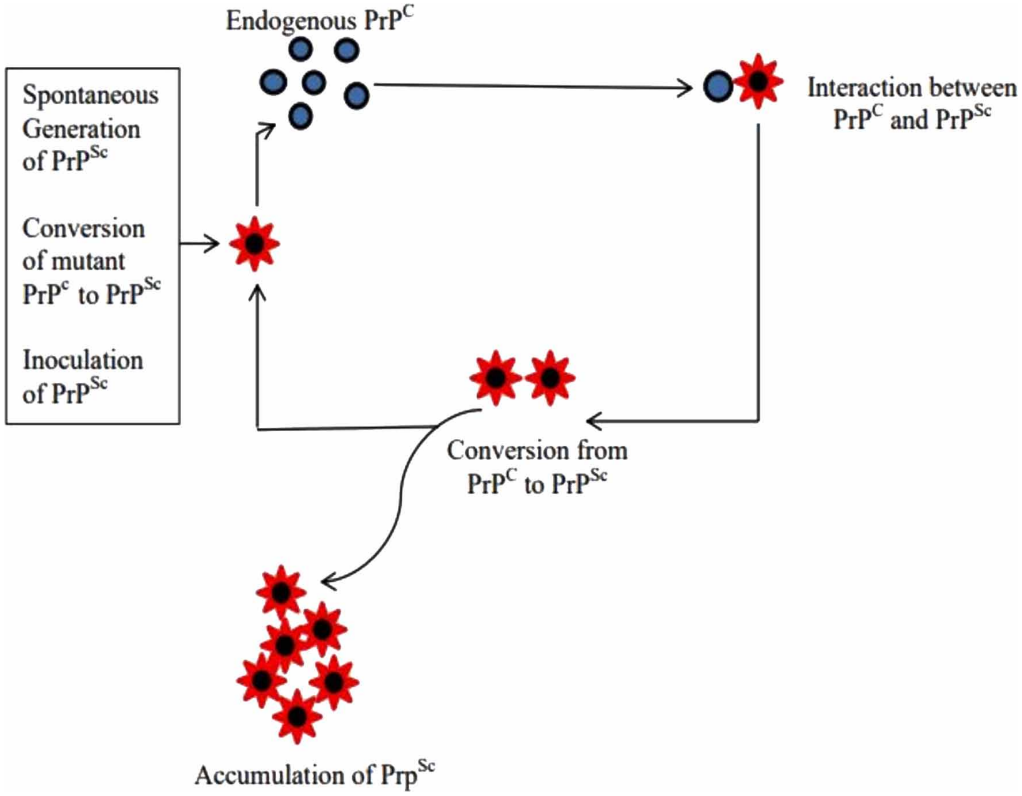
- Familial CJD, comprising of about 5-15% of CJD cases. It has been found to be with one or more mutations on the *PRNP* gene (Babi *et al.,* 2016, WHO, 2010).
- Iatrogenic CJD, representing about 5% of CJD cases and mostly occurs as result of contamination from used surgical equipment (WHO, 2010).
- Sporadic CJD, most common form of CJD consisting of about 85% of CJD cases of CJD. It is also associated with mutation of the *PRNP* gene and was reported to occur throughout the world at the rate of about one per million people (Bonda *et al.,* 2016, WHO, 2010).

CJD occurs world and among every population with an average of 1.5-2.5 cases in every million per years (Brandel *et al.,* 2015). According to the centers for disease control and prevention (2017), the average case occurrence of CJD is 285.19 from 1979-2015 with the cases increasing with time progress.

Figure 3. The pathogenesis of Creutzfeldt-Jakob disease



PATHOGENESIS OF CREUTZFELDT-JAKOB DISEASE

Destruction of neurons due to an accumulation of these proteins consequently resulted in neurodegeneration (Whalley, 2017). A major characteristic of CJD and by extension most TSEs is formation of sponge-like appearance in the brain (Acevedo-Morantes & Wille, 2014). The conversion of the normal prion protein PrP^C to PrP^{Sc} initiates the pathogenesis of the disease (Riesner, 2003). Normal

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PrP^{C} is a membraned surfaced protein of whose clear function has been unknown. Structurally, it has a predominantly α-helical structure that is highly conserved between species (Trevitt & Singh, 2003). The pathogenic prion form, PrP^{Sc} is formed by posttranslational modification of the normal PrP^{C} form without the alteration of the primary structure of the normal protein. PrP^{Sc} is characterized by highly β-plated structures and being protease resistant (Kovacs & Budka, 2008). In vCJD, prion infection is caused eating meat or any contaminated food from cattle with ‘’cow madness’’ also known as bovine spongiform ESEs (Billette de Villemeur *et al.,* 1996). The infected prion facilitates the misfolding of the normal prion PrP^{C} into the pathogenic prion PrP^{Sc} (Figure 3). Most biochemical evidences have shown that both BSE and vCJD were caused by invariably similar prion strain (Riesner, 2003). Distinct prion related diseases or illnesses can be differentiated by their biological properties including incubation periods and patterns of neuropathology (Trevitt & Singh, 2003).

Major symptoms of associated generally with CJD include loss of memory, coordination, sight and dementia. At early stage symptoms include memory failure and behavioral changes. As the disease progress, individual suffer from involuntary movements, loss of sight and even coma (World Health Organization [WHO], 2010).

DIAGNOSIS OF CREUTZFELDT-JAKOB DISEASE

Clinical symptoms associated with CJD are more are less similar in most neurological impairment (Van Everbroeck *et al.,* 2004). Neurological signs characterizing CJD include;lack of coordination, difficulty in walking and involuntary movements. These signs progress with each developmental stage of the illness as it progresses and, by the time of death, patients become completely immobile and mute (Poser *et al.,* 2000). In diagnosis of CJD, disorders with similarl features with CJD can be ruled out using several tests, one of which is biopsy test. Brain biopsy is the most accurate test in CJD diagnosis. It involves a procedure where a small piece of brain tissue is removed for study (Heinemann *et al.*, 2008). However, any brain surgery carries risk of damage to the brain and a tissue might be removed from a non-infected area thus will likely show an inaccurate representation of the disease (Creutzfeldt, 2002). In such case, the biopsy cannot be a reliable test to confirm or rule out the diagnosis. Similarly, autopsies on the whole brain can be used in given cases of CJD diagnosis. Autopsy is the study carried out on dead bodies to analyse different systems of the body (Heinemann *et al.,* 2008). It also is useful for research. Other tests commonly used for CJD diagnosis include:

- A brain magnetic resonance imaging (MRI) which uses magnetic and radio waves to capture a detailed image of the whole or portion of the brain in other to have a detailed picture and observe defects in the brain peculiar to CJD (Morgan *et al*., 2009) present
- A brain computed tomography (CT) scan, which provides much more details on the structural components of the brain tissues and can be used to observe patient’s symptoms related to stroke or brain tumor (Rubenstein *et al*., 2016).
- A blood and fluid test, where different techniques can be used on blood of patients’ sample to rule out other forms of dementia that may be treated (Zerr *et al.,* 1998). Cerebrospinal fluid tests such as 14-3-3 protein test, are particularly carried out to see if proteins such as the 14-3-3 protein that is associated with dementia or CJD are present (Zanusso *et al.,* 2016).

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TREATMENT OF CREUTZFELDT-JAKOB DISEASE

In general, there is no treatment available to cure CJD. Treatment of prion diseases remains supportive; no specific therapy has been shown to stop the progression of these diseases (Belcastro *et al.,* 2010). Treatments are mostly done to alleviate the symptoms and to make the patient as comfortable as possible (Pocchiari & Ladogana, 2015). However for patients with CJD at initial stages, therapeutic measures can be take via use of many some drugs such as amantadine and acyclovir that target misfolding of a normal prion (Appleby & Lyketsos, 2011). Similarly, some pentosan polysulfate were used to target protease resistance of the diseased or misfolded prions and thus increasing their susceptibility to protease attack (Zuber, Ludewigs, & Weiss, 2007). Another target initial accumulation of the misfolded prions into an amyloid structure and promotes its clearance (Gauczynski *et al.*, 2006). Although some of the drugs have been successfully used for those purposes, their use has not been consistent in subsequent CJD patients (Vetrugno *et al.,* 2015). Researchers are now targeting protein regions on the misfolded proteins and designing specific antibodies to target them for destruction (Panegyres & Armari, 2013).

Due to the circumstances associated with treatment of CJD, the World Health Organization and other supporting agencies set up measures to alert the public about CJD (WHO, 2008). Some measures are taken to protect public health include:

- As researches established links between vCJD and BSE, governments through Health departments enlist CJD as a major health concern for the public. Example government of the United Kingdom made CJD a notifiable disease in 1988 (Ponte, 2006).
- The UK government similarly placed a ban on individuals that have lived in countries with high risk of BSE as a means to prevent a possible spread of infections to patients (Food and Drug Administration, 2002).

World Health Organization's Recommendations

The World Health Organization in its effort to provide measures that could decrease spread of BSEs and TSEs including CJD, made the following recommendations:

- WHO recommended that countries should ban use of ruminant tissues in food supplement preparation of domestic animals particularly members of the bovine family. All tissues potentially containing BSE agent, nor part or product of any animal which has shown signs of a TSE should be prevented from entering the (human or animal) food chain. (Centers for Disease Control and Prevention, 1996).
- WHO also recommended ban on pharmaceutical industries on the use of materials and product from the bovine family in which TSEs naturally occur. Id such materials are to be necessary be used, they should be important from countries with 0% reported cases of BSEs (WHO, 2003).
- The guidelines on tissue infectivity distribution in TSEs in 2006 provide information and assist national regulatory authorities in conducting risk assessments of vCJD. The tables on tissue infected were later updated in 2010 with the aim of providing current knowledge of tissue infectivity providing information on the possible transmissions in TSEs (WHO, 2010).

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FUTURE RESEARCH DIRECTIONS

Previously researchers have been towards understanding mainly the pathogenesis and spread of the disease as being transmissible (Kovacs & Budka, 2008). Current and future researches focus on elucidation of the process of prion proteins associated with CJD (Aguzzi & Zhu, 2012). Targeting abnormal prions is crucial in treatment of CJD (Pocchiari & Ladogana, 2015). Recent development of techniques in immunotherapy and proteomics are used to understand structural organization of prion proteins and how they aggregate to amyloid plaques (Biasini *et al.,* 2012). Other researches focus on stimulating physiological processes to eliminate prion aggregates (Karapetyan *et al.,* 2013). For example astemizole is an antihistamine drug which has been found to stimulate autophagy through its action of being an antagonist of H1 receptor, leading to generation of reactive oxygen species and activation of autophagy (Jakhar *et al.,* 2017). Prion-based screening assays have been used in model organisms such as yeast to identify infectious prions and allowed identification of drugs active against mammalian prions (Voisset *et al.,* 2009). Similarly researches are also focusing on ways to develop agents that will block transmission of infectious prions as ways to provide cure to CJD. Future researches should stress the following:

- With the progress made in immunotherapy, directing immune cells towards recognizing specifically abnormal prions and destroying them should be a focal research area to be exploited.
- Similarly designing specific agents that target molecular chaperones that aid abnormal folding of prions can similarly be exploited.
- Different types of chaperones are associated with re-folding of abnormal prions back into normal prions. Researches should focus on these chaperones as a potential target in therapy.
- Although biopsy has been used for period in treatment of CJD, advanced technique in radiotherapy can be used to target and eliminate aggregates of misfolded proteins. Researches can be focus in neuroimaging to study the structures of these aggregates. This will ensure success of the radiotherapy.

CONCLUSION

CJD is a major concern as most researchers believed neurodegeneration progressively becomes irreversible and the disease could not be cured. The chapter described the pathogenesis of different types of CJD and their distribution. It also revealed how a number of drugs have been unsuccessfully used in treatment of CJD. As the use of most therapeutic agents has proven to be consistently unsuccessful, there is a need to change focus towards the studies to find a possible cure to the disease. Studies are now focused more towards the molecular mechanisms underlying the development and spread of the different types of the disease. With advanced techniques currently in used, it is believed that a final cure for any type of CJD will be developed.

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Chapter 4
Neuropathogenesis of Multiple Sclerosis and Huntington's Disease:
An Overview of Environment Patterns

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ABSTRACT

Substantial epidemiological studies have established a link between environmental factors and prevalence of neurodegenerative diseases. Increasingly, some studies report a direct cause-and-effect relation between environmental agents such as heavy metals and pesticides, and some neurodegenerative disorders including multiple sclerosis (MS) and Huntington's disease (HD). Interestingly, high blood level of heavy metals and pesticides has been shown in patients with MS and HD. Those agents could be involved directly or indirectly in the pathogenesis of MS and HD. The underlying mechanisms may imply an immune breaking of self-tolerance or neurodegeneration onset of several neurotransmission systems. The chapter will discuss the role of different metals and pesticides in the onset and progress of MS and HD with an overview of the possible underlying pathomechanisms.

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INTRODUCTION

Multiple sclerosis (MS) and Huntington disease (HD) are two different neurodegenerative disorders, however, in spite of being pathologically distinguished, quite similarities between the two disorders exist including several cognitive functions that have been shown to be altered similarly including: reading, interpretation of metaphors and proverbs, sequential finger tapping (motor speed), motor praxis, Trails errors, and orientation (Caine, Bamford, Schiffer, Shoulson & Levy, 1986).

MS is known as a neurological disease with chronic autoimmune and neuroinflammatory features (Calabresi, 2004; Fauci, Braunwald, Kasper & Hauser, 2008). Pathologicallay, MS is primarily characterized by attack of the myelinated axons of the central nervous system (CNS), leading to a progressive destruction of the myelin and consequently axons (Weinshenker, 1996).

Neurologically, MS patients show episodes of reversible neurological deficits, generally followed by progressive and irreversible neurological deterioration. Statistics in U.S, affirm that 250,000 to 350,000 patients are suffering from MS with more incidence in men compared to women (Singh, Mehrotra & Agarwal, 1999), while 50% of those patients need help walking within 15 years after the onset of the disease (Navikas & Link, 1996). While HD, firstly named as Huntington chorea, is a neurodegenerative disorder generally of a genetic origin with onset in middle age. HD is characterized by abnormal choreatic movements, as well as several behavioral and psychiatric disturbances and even dementia (Bruyn, 1968). Its old appellation (H chorea) was maintained during several decades until 1990s, when light have been shed on the extensive non-motor symptoms of the disease, hence, H chorea was changed to H disease (Hunington's disease collaborative research group, 1993). Increased body of evidence support the involvement of environmental factors in the pathogenesis of MS and HD. Indeed, numerous environmental exposures such as heavy metals, organic solvents, ultraviolet radiation, infection, and diet have been investigated as possible etiologic factors which could interact directly with responsible genes and my precipitate symptoms onset and progress of the disease. (Aminzadeh & Etminan, 2007; Ascherio & Munger, 2007; Ascherio, Munger & Simon, 2010; Irvine, Schiefer & Hader, 1988; Ketelaar, Hofstra & Hayden, 2012; Lauer & Firnhaber, 1985; Landtblom, Flodin, Söderfeldt, Wolfson & Axelson, 1996; Marrie, 2004; Moszczynski, 2011).

In the present chapter, we will discuss the role of environmental exposures, with a focus on heavy metals and pesticides, both as a risk factors for MS and HD pathogenesis and progress with the underlying pathomechanisms in order to delineate the role of the environmental part as piece of puzzle of neurodegenerative disorders.

CLINICAL FEATURES AND PHYSIOPATHOLOGY OF MS

Symptomatology of MS

The history of MS dates back to the 14th century when anatomoclinical methods made the first time a correlation between the clinical features of the disease and the post-mortem neuropathological characteristics (Lublin, 2005). The recognition of MS as a distinct disease was quite a feat for the time. Since, many diseases in the early 19th century that would now be categorized as either neurological or psychiatric would have been classified as "nervous disorders" without separation between individual conditions (Murray, 2009). Such an attempt at the classification of neurological diseases had not been

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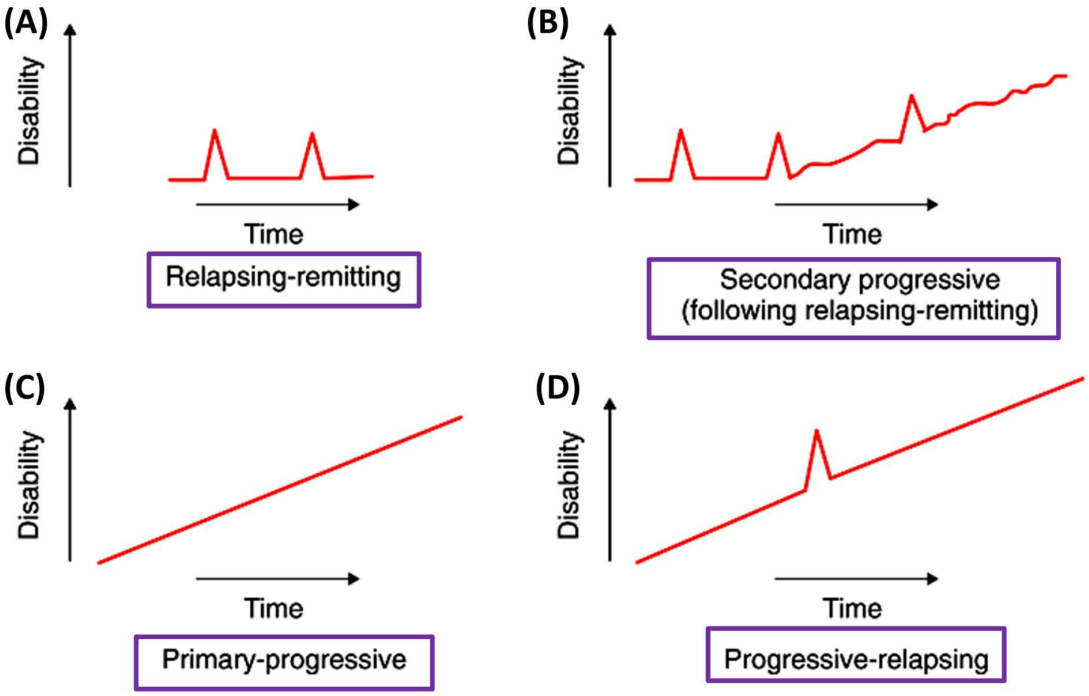
undertaken prior to Charcot (Tollis, 1996). Only a small group of illnesses such as epilepsy, paraplegia, and neurosyphilis were differentiated at the time (Murray, 2009).

On the basis of the neurological features of MS, neurologists agreed about grouping patients into 4 major categories depending on the development of the disease (Figure 1) (Fauci, Braunwald, Kasper & Hauser, 2008).

Figure 1. Classification of the different forms of MS. A: Relapsing-remitting MS, B: secondary progressive MS, C: primary progressive MS, D: progressive-relapsing MS



Physiopathology of MS

Pathology Basis of MS

The hallmark of MS is the presence of plaques of inflammatory demyelination, CNS injury and axonal loss (Figure 2) (Frohman, Racke & Raine, 2006). Plaques are present in the brain as well as in the spinal cord, preferentially within the white matter surrounding the ventricles, the optic nerve and tracts, the corpus callosum, cerebellar peduncles, the brainstem, and also in the gray matter (Compston & Coles, 2008).

At the beginning of relapsing remitting stage, a pronounced demyelination appears with axonal loss and reactive gliosis (Van Der Valk & De Groot, 2000), while patients show focal inflammatory plaques containing demyelinated axons, reduced number of oligodendrocytes, astrocyte proliferation with subsequent gliosis, transected axons, and perivenular as well as parenchymal infiltrates of lymphocytes and macrophages. At the advanced stages, a diffuse gray and white matter atrophy is usually noticed which

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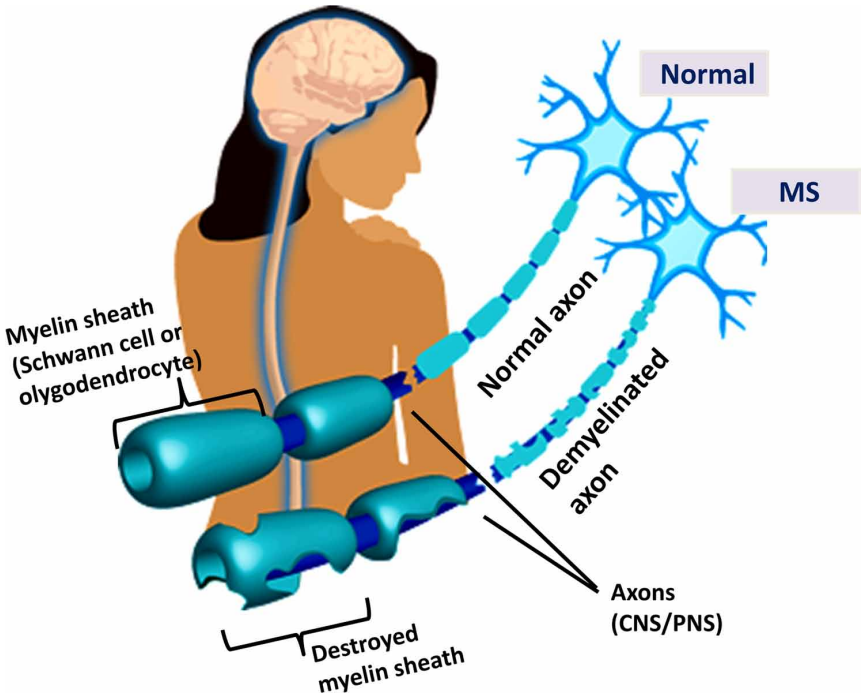
Figure 2. Normal and destroyed myelin of Schwann cells and oligodendrocytes in MS



is featured by low-grade inflammation and microglial activation at the plaque borders concomitant with diffuse injury of the normal-appearing white matter outside the plaque (Figure 3) (Mahad, Trapp & Lassmann, 2015).

In the burnt-out stage the presence of iron in the brain in the absence of additional oxidative burst from microglia does not lead to further neurodegeneration, although patients may become affected by concomitant diseases such as stroke or Alzheimer's disease (figure 3).

Involvement of Heavy Metals in the Pathogenesis of MS

Beside the genetic etiology of MS, the influence of environment is well sustained by cumulative evidences that environmental agents can drive a T-cell-mediated chronic inflammatory response to myelin proteins in genetically predisposed individuals (Napier et al., 2016).

Role of Lead

The theory of Pb as an etiology of MS is very old and its originator was Putnam (1887a, b) who discovered the presence of Pb in the urine of a small number of patients with MS and all of whom had been exposed to Pb during occupation.

Several years later, Cone et al. (1934), confirmed the presence of Pb in CSF, urine, and faeces of 6 patients with the disease.

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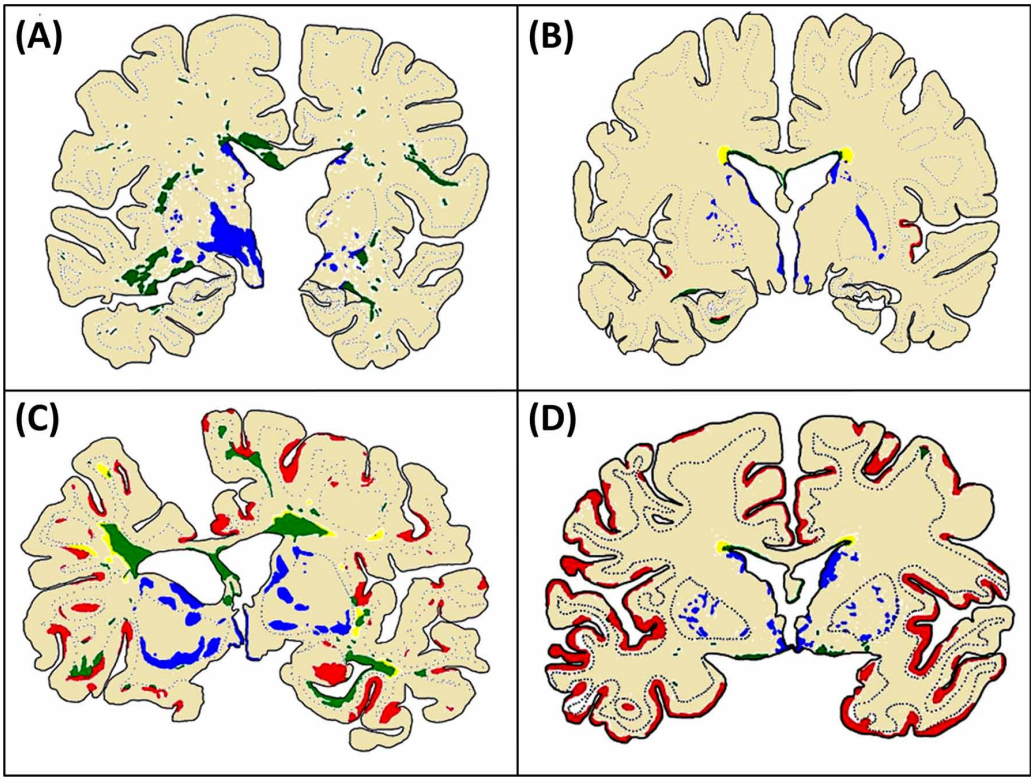
Figure 3. Kinetic evolution of MS patterns pathology in cortical, white matter and deep grey matter demyelination. Acute MS (A), Relapsing-remitting MS (B), Secondary Progressive MS (C) and Primary Progressive MS (D). Green color refers to white matter demyelination, yellow color refers to white matter remyelination, the blue refers to deep gray matter lesion and the red one refers to cortical lesion (modified Haider et al., 2014).



A recent study performed by Aliomrani et al., (2016), in 69 patients with relapsing-remitting MS compared to 74 age/gender-matched healthy individuals resident in Tehran as most polluted city in Iran, authors measured the level of Pb in blood of males and females of the studied population, they showed an increased Pb level in MS male patients particularly, while female MS patients didn't showed any difference compared to healthy controls (Aliomrani et al., 2016).

In addition, a low-to-moderate level of Pb exposure is able to trigger several functional alterations in T-lymphocytes and macrophages, and consequently increased hypersensitivity together with impaired cytokine production, which increases risk of inflammation-associated to tissue damage (Dietert & Piepenbrink, 2006).

Support of the view that Pb is mainly involved in the pathophysiology of MS, is provided by this interesting investigation published in Sciences, 1970 (Sauer, Zook & Garner, 1970) where authors investigated Pb poisoning in four primates, they showed by histological examination, a focal, symmetrical demyelination of subcortical white matter, which has been associated with degenerative and proliferative vascular lesions. In addition, wet liver and kidney tissue contained lead in concentrations of 110 and 120 PPM, respectively.

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Role of Mercury

Mercury as well, can be considered as one of the heavy metals that can be associated to MS. Indeed, a comparison between circulating blood Pb in MS subjects with removed dental amalgams to MS subjects with amalgams, showed decreased erythrocytes density, hemoglobin and hematocrit levels in MS patients. Other parameters were changed including thyroxine levels which were lower in the MS amalgam subjects with significantly lower total T Lymphocytes and T-8 (CD8) suppressor cells number. Similarly, MS amalgam patients exhibited significantly increased blood urea nitrogen and lower serum IgG, while in hair, mercury level was largely increased in MS patients compared controls (non-MS) (Siblerud & Kienholz, 1994).

Indeed, in humans and animals, cell accumulation of mercury as well as Pb has been widely associated with the development of autoantibodies against different neuronal components such as: cytoskeletal proteins, neurofilaments, and myelin basic protein (El-Fawal, Waterman, De Feo & Shamy, 1999; Stejskal & Stejskal, 1999; Hansson et al., 2005). Whereas, excessive exposure to those metals has been shown to be highly neurotoxic, especially for motor neurons (Callaghan, Feldman, Gruis & Feldman, 2011). Otherwise, in non-predisposed animals, exposure to inorganic mercury is able to trigger prior autoimmune disease (Via et al., 2003), while in genetically susceptible animals, the metal, even at low doses, can precipitate autoimmune diseases leading to impaired cytokine production (Hansson et al., 2005).

Role Cadmium

Cadmium is one of the most important neurotoxic metals that have been associated to the pathogenesis of MS. Indeed, Aliomrani et al. (2016), have assessed blood cadmium levels in 69 patients with relapsing-remitting MS resident in Tehran; they have found an increased Cd level in MS patients particularly men while compared to controls. (Aliomrani et al., 2016).

Different routes by which Cd can reach the body including respiratory and digestive tracts. Once in the body, Cd can bind to metallothionein forming a complex: Cd-MT. However, the precise underlying mechanisms of Cd neurotoxicity is not yet fully understood. It has been suggested that Cd indirectly enhances the free radical generation and participates in oxidative stress via Fenton reaction (Jomova & Valko, 2011).

Role of Pesticides

Likewise, pesticides are also another environment agent able de drive MS. Several findings support such view, indeed, a correlation between exposure levels to pesticides and MS prevalence in a Spanish population, indicates that the prevalence and risk of MS is greater in populations living in areas of high pesticide use (indicating a higher exposure potential) relative to those of low pesticide use (Table 1 and 2). Otherwise, females showed an increased risk for MS in areas of high pesticide exposure compared to males (Parrón Requena, Hernández & Alarcón, 2011).

The sex differences in the prevalence of MS between men and women may involve the physiological differences between both sexes. Indeed, taken into account the involvement of heavy metals in the pathogenesis of MS, it has been shown that, estrogen causes enhanced copper absorption and extends its half-life (Johnson, Milne & Lykken, 1992). During adolescence, females have a high Zn requirement while, Cu excessively absorbed Cu interacts with Zn metabolism by reducing its absorption. Otherwise, the brain production of melatonin which is required for Zn absorption is highly reduced adolescence.

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Table 1. Representation of the MS prevalence (100,000 inhabitants), sex differences, odds ratio (OR) and 95% confidence interval (95% CI) for a number of MS in the population living in high exposure areas relative to that resided in low exposure areas (according to Parrón, Requena, Hernández & Alarcón, 2011)

		Prevalence rate		OR	95% CI	P value
		High Exposure	Low Exposure			
Total population		41.62	33.88	1.23	1.05–1.43	0.007
Males		28.21	26.89	1.05	0.81-1.35	0.007
Females		55.08	40.79	1.35	1.11-1.64	0.001

Consequently, a gradual depletion of Zn occurs. Otherwise, Zn is necessary for the zinc fingers of the protein TPO-1 involved in myelin synthesis in the oligodendrocyte (Krueger et al., 1997).

In addition, most of the damage in MS is due to peroxinitrite which results from excessive superoxide, due to deficient CuZn SOD affinity for Zn (Kesel et al., 1999). Also, Cu inhibits the synthesis of uric acid by Xanthine oxidase (Konstantinova, Russanova & Russanov, 1991), explaining the abnormally low levels of uric acid in the CSF during MS

Physiopathology of HD

Pathology Basis of HD

HD is a rare neuropsychiatric disorder genetically caused by dominant autosomal mutations. Clinically HD is characterized by movement disorders and cognitive decline. The cardinal features of the disease are motor defects including chorea and loss of coordination. Whereas, other psychiatric symptoms are also common to HD such as depression, psychosis, and obsessive–compulsive disorder (Rosenblatt. 2007). The prevalence of HD is 4-10 cases/100,000 in populations of Western European origin. Neurologically, HD patients manifest a general shrinkage of the brain and degeneration of the striatum especially efferent medium spiny neurons (Reiner et al., 1988). Although, specific thinning of the brain cortex was also observed in patients with HD (Rosas et al., 2002). Cortical degeneration extends from posterior to the anterior parts during the disease progression, which may be behind the heterogeneity the clinical features of HD. Genetically, HD is caused by a mutations in the gene encoding for huntingtin (HTT gene) which is an ubiquitously expressed protein of 350 kDa (figure 4) (Huntington's Disease Collaborative Research Group, 1993) with several functions including early embryonic development and neurogenesis,

Table 2. Representation of differences in the mean age for the medical conditions at the time of the first hospital discharge after diagnosis (according to the Andalusian Minimum Dataset) between high exposure and low exposure areas in the study population and after stratifying by gender. (according to Parrón, Requena, Hernández & Alarcón, 2011)

Exposure	Mean Age (Total Population)	P Value	Mean Age (Males)	P Value	Mean Age (Females)	P Value
High dose **Low dose**	39.44 42.78	<0.05	41.33 44.16	<0.10	38.47 41.84	<0.05

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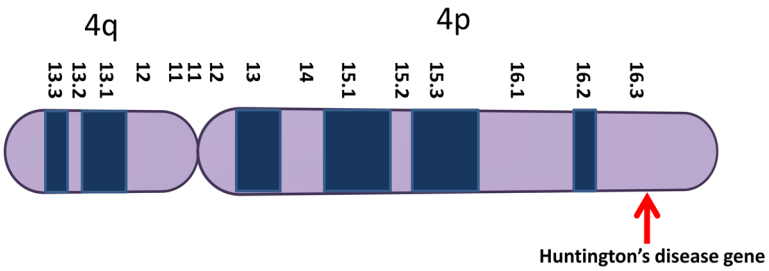
us knockout mice show embryonic lethality around day 8.5, before the emergence of the nervous system (Nasir et al. 1995; Zeitlin, Liu, Chapman, Papaioannou & Efstratiadis, 1995). Huntingtin is a scaffolding protein which interacts with b-tubulin and binds to microtubules (Hoffner, Kahlem & Djian. 2002). It may be considered also as a transcriptional factor; us the nuclear localization confers huntingtin a role in transcriptional regulation (Kegel et al. 2002) as well as synaptic connectivity (Di Figlia et al. 1995)

The mutant gene of HTT contains a polyglutamine tract encoded by uninterrupted CAG trinucleotide repeats (more then 36) while the wild type up to 35 CAG repeats (Rubinsztein et al.,1996). A particular aspect of HD is phenomenon of anticipation. In successive generations, the onset age of the disease become earlier resulting from cumulative mutations of the HTT gene due to the unstable nature of the CAG repeats which increase in size, particularly when passed through the male germline (Trottier, Biancalana & Mandel, 1994).

Figure 4. Localization of the HD gene in band 4p16.3 of chromosome 4 (Adapted from Gusella, MacDonald, Ambrose & Duyao, 1994)



The different pathomechanisms suggested for HD are summarized in the Figure 5.

1. The mutant HTT protein (polyglutamine expansion) is cleaved in fragments with toxicity ptotential arising from the oligomeric soluble parts or from the insoluble inclusions (aggregates) that scavenge essential proteins (Jimenez-Sanchez, Licitra, Underwood & Rubinsztein, 2017).
2. Transcription of essential genes such as BDNF and chromatin modifications is also altered during HD.
3. During HD, a possible dysfunction of proteasome could be another pathomechanism as well as impaired autophagic breakdown due to cargo sequestration or autophagosome transport leading to alteration of proteins homeostasis.
4. Defective Ca2+ homeostasis leads to a mitochondrial dysfunction especially of protein import, impaired mitochondrial dynamics (increased fragmentation), oxidative stress onset and decreased ATP genesis.
5. Synaptic plasticity could be also altered during HD;a possible excitotoxicity could arise from alteration of postsynaptic NMDAR, from glutamate uptake, or from impaired synaptic vesicle trafficking.
6. Impairment of synaptic transport of organelle (mitochondria, autophagosomes, synaptic vesicles) and neurotransmitters

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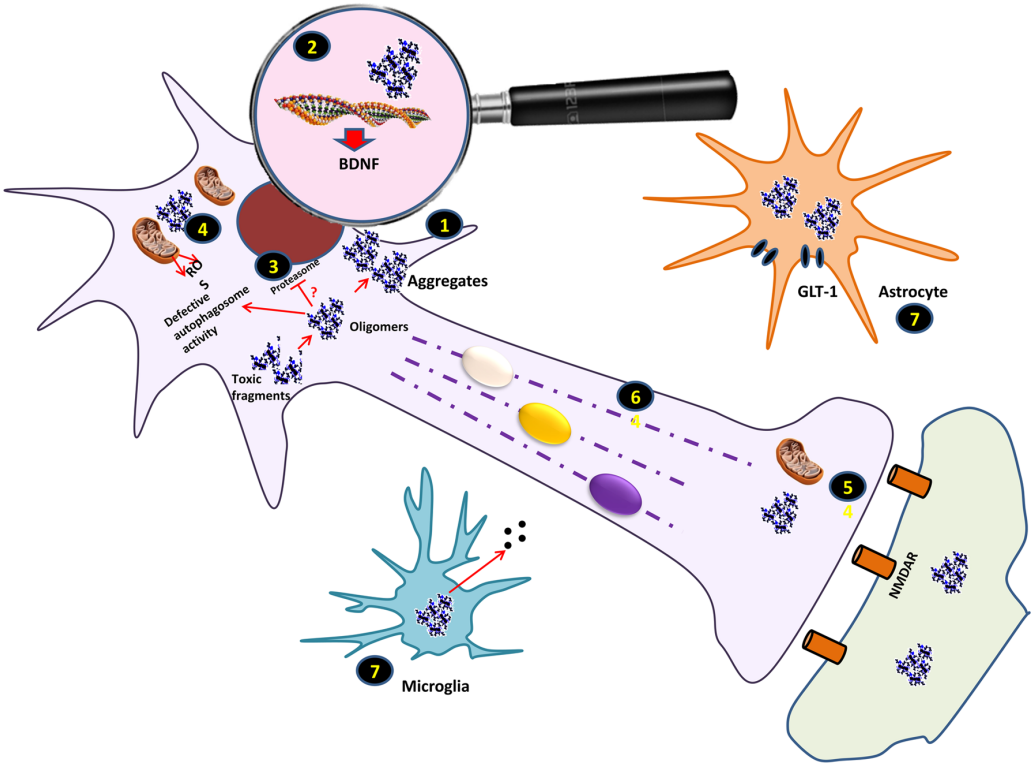
7. Neuroglia dysfunction: beyond neurons, astrocytes and microglia are involved as well. Secretion of pro-inflammatory cytokines and chemokines originating from microglia and alteration of astrocytic glutamate uptake.

Figure 5. Schematic representation of the different pathophysiological mechanisms of HD



BDNF (Brain-derivedneurotrophicfactor), ROS (reactive oxygen species), NMDAR (N-methyl-D-aspartate receptor). GLT-1 (glutamate transporter 1). (modified Jimenez-Sanchez, Licitra, Underwood & Rubinsztein, 2017)

Macroscopical Noticeable Brain Lesions in HD Patients

Gross examination of postmortem brains of HD shows a remarkable and characteristic bilateral atrophy of the striatum (Vonsattel & DiFiglia, 1998). Chronologically, brain atrophy and neurodegeneration adopt a topographical distribution: the tail and body of the caudate nucleus show more degeneration than the head in the very early stages of the degenerative process. Degeneration in the caudate nucleus and the putamen occurs earlier in the tail and progress to the head and body (Vonsattel & DiFiglia, 1998). Other brain areas are also touched such as the cerebral cortex and the centrum semi-ovale which show features of sever atrophy.

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Involvement of Heavy Metals in the Pathogenesis of HD

It well established that not all HD patients with similar polyQ tract length develop the disease at the same age (Rosenblatt et al., 2001). Such observation leads to suppose the effect of environment on the progress of the disease. Whereas, the lack of correlation between phenotype and genotype in some cases of HD, especially monozygotic twins, may provide clues to the role of environment on the onset/progress of monogenic diseases (Ketelaar, Hofstra & Hayden, 2012) as well as other polyglutamine disorders such as spinocerebellar ataxias (Anderson et al., 2002; Durr, 2010).

In a relatively recent report, correlation between substance abuse and HD showed that individuals with histories of alcohol or drug abuse had a significantly lower age of onset of the disease (Byars et al., 2012).

Involvement of heavy metals in basal ganglia disorders is very well established, hence, such association may involve those metals in the pathogenesis of HD as an environmental rather than genetic cause of the disease.

Due to its particularity as a highly metabolizing organ and the detoxification function against reactive oxygen species, the brain solicits the presence of high concentrations of the biologically essential heavy metal ions (Fe, Mn, Cu, Zn) which are important cofactors for enzymes that regulate these processes. However, accumulation of metal ion leads to oxidative stress onset, and cellular damages (mitochondrial dysfunction, protein aggregation, and apoptosis).

Similarities between metals (especially heavy metals) neurotoxicity and neurodegenerative diseases (Gaeta & Hider, 2005; Jomova, Vondrakova, Lawson & Valko, 2010; Molina-Holgado, Hider, Gaeta, Williams & Francis, 2007) support the view of a possible involvement of those metals in the pathophysiology of HD as a neurodegenerative disorder.

Role of Manganese (Mn)

An over view of literature shows that Mn exposure at high levels is associated to neurotoxicity with preference to some brain regions such as the globus pallidus, striatum, substantia nigra and the subthalamic nucleus (Olanow, 2004; Pal, Samii & Calne, 1999).

A comparison of striatal proteomes of wild-type and HD (YAC128Q) mice by two-dimensional differential gel electrophoresis (DIGE) identified 16 proteins whose expression was altered on exposure to Mn in case of HD mice (Wegrzynowicz, Holt, Friedman, & Bowman, 2012). Most of these proteins were associated with cytoskeletal mobility, glutamatergic neurotransmission and energy metabolism. Such finding lead to suggest that exposure to Mn induces toxicity in HD mice by altering the interaction of the mutant huntingtin (128Q) with these proteins, thus affecting various cellular processes.

In addition, Mn is associated with alterations in integrity of DAergic striatal neurons and DA neurochemistry, including decreased DA transport function and/or striatal DA levels (Aschner, Guilarte, Schneider & Zheng, 2007; Perl & Olanow, 2007). The medium spiny neurons (MSN) are the target of the dopaminergic innervation of the striatum, comprising more than 90% of striatal neurons (Deutch, Colbran & Winder, 2007). MSN have radially projecting dendrites that are densely studded with spines, synapsing with dopamine and glutamate axons and providing the site of integration of several key inputs and outputs of the striatum (Day et al., 2006). A relevant study showed following quantitative morphometric analyses of Golgi-impregnated striatal sections from mice exposed to single or three Mn injections, a progressive spine degeneration and dendritic damage of medium spiny neurons (MSNs) (Milatovic, Zaja-Milatovic, Gupta, Yu & Aschner, 2009). Consequently, alterations in dendritic length

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and dendritic spine number may destabilize the structural basis of synaptic communication and thus compromise MSN function.

Whereas, an increase in brain Mn levels is also known to cause motor dysfunction in humans, non-human primates and rodents (Aschner, 2000; Autissier et al., 1982; Calne, Chu, Huang, Lu & Olanow, 1994; Gianutsos & Murray, 1982; Guilarte et al., 2006; Gwiazda, Lee, Sheridan & Smith, 2002; Kontur & Fechter, 1988; Milatovic, Zaja-Milatovic, Gupta, Yu & Aschner, 2009; Olanow et al., 1996; Pal, Samii & Calne, 1999; Olanow, 2004; Reaney, Bench, & Smith, 2006; Struve, McManus, Wong, & Dorman, 2007; Vezer et al., 2005; Vidal et al., 2005). Since the basal ganglia, including striatum are a common target for both HD neuropathology and Mn accumulation, this provides the opportunity to observe a disease-toxicant interaction.

Role of Copper

Previous findings support an accumulation of copper in the striatum of post-mortem HD human brain (Dexter et al., 1991). Preferentially, such accumulation occurs within basal ganglia. Support of this view is provided by observation in patients with Wilson's disease; a genetic disorder in which copper builds up in the body involving the brain and liver axis, in which 40% of cases present with neurologic symptoms related to copper-mediated striatal degeneration (Kitzberger, Madl & Ferenci, 2005). Such data suggest a possible involvement of copper induced disorders of basal ganglia and the neuropathogenesis of HD. *In vitro* studies have shown that Cu is able to accelerate the fibrillation and aggregation of purified recombinant Htt exon1 with polyQ tract (Hands, Mason, Sajjad, Giorgini & Wyttenbach, 2010), whereas, it has been also reported that the fragment containing the first 171 amino acids of human wild-type Htt and its glutamine-expanded mutant form can directly interact with copper (Fox et al. 2007). An experimental study in transgenic mice of HD; CAG140 knock-in with a CAG expansion within one of the endogenous full-length huntingtin alleles and R6/2 expressing human huntingtin exon-1 containing a glutamine coding CAG representing respectively the preclinical and the late stage of HD, Cu levels was increased significantly by 26% and 51% in the striatum and the cortex respectively (Figure 6) (Fox et al. 2007).

Pesticides and HD

Pesticides as well, have been linked to the pathogenesis of HD as environmental agents. Indeed, the complex II inhibitor, 3-nitropropionic acid (3-NP), on the aggregation profile of mutant huntingtin has been studied. In fact, exposure to 3-NP, a fungal-derived neurotoxin, has been reported to cause HD-like symptoms in Drosophila, rats and mice (Beal et al., 1993; Ludolph, He, Spencer, Hammerstad & Sabri, 1991; McConoughey et al., 2010). 3-NP is a mitochondrial complex II inhibitor and is increasingly being used to generate HD animal models (McConoughey et al., 2010; Túnez et al., 2006).

Beal et al. (1993), have assessed intrastriatal administration of 3-NP in rat, they have shown that 3-NP produced dose-dependent striatal lesions. Whereas, neurochemical and histological evaluation showed that markers of both spiny projection neurons were affected. While subacute systemic administration of 3-NP produced age-dependent bilateral striatal lesions with a similar neurochemical profile. As well, chronic administration showed growth-related proliferative changes in dendrites of spiny neurons similar to changes in Huntington's disease (HD) (Beal et al., 1993).

Other researchers have studied the effect of mitochondrial complex I inhibitors, by means of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and rotenone, and complex II inhibitor using 3- nitropropionic acid, on the aggregation of the mutant huntingtin (mthtt) protein whose misfolding and aggregation is known

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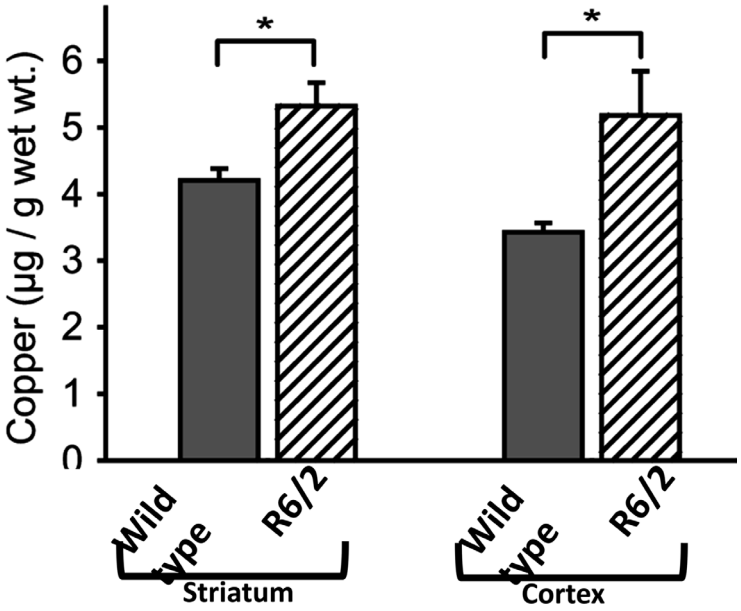
*Figure 6. Copper level in brains of 12-week-old R6/2 HD mice (late-stage HD) as measured by ICP spectroscopy. p-values: *<0.05 (modified Fox et al. 2007)*



to result in cellular abnormalities which characterize HD. Data showed that all these inhibitors accelerate the aggregation of mthtt in vitro with differences in the amount of aggregates formed depending on the agent used (Deshmukh, Chaudhary & Roy, 2012).

CONCLUSION

Neurodegenerative diseases including MS and HD are often highly debilitating to both mental and physical functioning. MS and HD have been considered for long time as an exclusive genetic CNS disorders. However, recent data of experimental and clinical investigations seem to revolutionize our comprehension of those pathologies, since, heavy metals and pesticides seem to be a new key factors that underlie, in some cases, the earlier onset and/or the aggravation of the disease progression.

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Chapter 5
Environmental Aspects of Alzheimer's and Parkinson's Diseases Neuropathologies:
A Focus on Heavy Metals and Pesticides

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ABSTRACT

This chapter presents a literature review on the effect of environmental changes factors exposure in the etiology of Alzheimer's and Parkinson's diseases. The use of pesticides is more intense and somehow erratic as it aims to face climate change consequences like drought and water scarcity. The rural population is getting to be more vulnerable to have these neurodegenerative diseases. However, intense food

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production and economic models mean also the use of heavy metals in many stages as well during the production and the consumption processes and practices. Evidence from experimental studies shows that such heavy metals may also be a factor for the occurrence of Parkinson's and Alzheimer's diseases. At least, the environmental lifestyle and, likely, genetic factors, individually and collectively, play a significant role in the etiology of the diseases.

INTRODUCTION

In human history, adaptation to environmental challenges has been always a key criterion for development and survival in challenging periods. This adaptation implies natural and cognitive responses to the environmental challenges through science and technology improving human health and survival rates.

Since the industrial age, the quality of life as a concept has gained much importance in people's life. In the last decades, health has been considered as one of the major standards to measure human well-being and life quality by the major international rating organizations. Therefore, human health is becoming a priority for the policymakers in the majority of national, regional and international organizations. Climate change is an example where this understanding is becoming urgent. Humans are obliged as never before to adapt to their changing environment, due to the raising concerns and scientific evidence of health issues caused directly or indirectly by climate change.

Although the human body has the capability to avoid many of the climate change negative effects, the costs remain obviously hazardous spreading worldwide to a great extent. For that reason, and from an ethical concern, it is crucial to mobilize the efforts in order to spare the risk of affection from future generations. This awareness may furthermore be fundamental for short-term protection and long-term alleviation of health consequences.

Food production is usually correlated with pesticides and synthetic fertilizers use. These products to increase crops yields to meet the population needs in these countries are usually a response to climate change consequences such as the lack of rainfall and drought. In such situations, farmers are also using sewage, which is harmful to population health.

Many countries in the world such the United States have seen an increased prevalence of neurological diseases and deficits (Steenland, MacNeil, Vega, &Levey, 2009). The onsets of diseases like Alzheimer (AD) and Parkinson (PD) disease is occurring at earlier ages across the population. Environmental factors are supposed to be responsible for both the onset and severity of these diseases. However, there is a gap in the understanding of this role, especially in relation to genetics, aging, and other factors. (Bronstein et al., 2009). Despite the fact that changes in neurological health are likely due to the aging of a large portion of the population, learning disabilities that affect children also are on the rise. There is also evidence that environmental factors may be involved including changes in climate that may exacerbate factors affecting the rates and severity (Altevogt, Hanson, & Leshner, 2008)of neurological conditions. Neurological conditions related to AD and PD generally carry high costs in terms of quality of life for both the patient and the caregiver and increases healthcare stresses on the financial charges and the workforce. The presence of these factors may affect an extended portion of a population and have significant impacts on productivity.

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PARKINSON AND ALZHEIMER DISEASES AS NEURODEGENERATIVE DISORDERS: ETIOLOGY AND HISTORY

Health care improvements have contributed to people living longer leading to an increasing life expectancy in the last decades. However, the cases of AD and PD increased as well. Parkinson's diseases are among the most common neurodegenerative disorder after AD, and overall incidence rates for all age groups have been reported to range from 1.5 to 22 per 100,000 person-years. Other reports estimate the prevalence range of PD from 167 to 5703 per 100,000 with preference in men (Wirdefeldt, Adami, Cole, Trichopoulos, & Mandel, 2011)and these diseases are increasingly raising big international concerns in last decades due to their high incidence. Etiology of AD and PD still little understood and genetic and environmental factors may contribute to the onset and/or development of these illnesses, which highlights the need to broaden the research scope by identifying the environmental risk factors that predispose to the development of AD and PD. It is known that the etiology of neurodegenerative diseases is multifactorial, and there is evidence that external factors like lifestyle and chemical exposures are linked with the risks of onset of these diseases (Campdelacreu, 2014).The vast majority of AD and PD cases are observed among elderly persons. As the exposure to risk factors occur many years before the diagnosis, the assessment of these chronic exposures are difficult to perform in retrospective studies to associate them with the onset/development of AD and PD.

Pre-and post-natal exposures to environmental factors are also proved to predispose to the onset of AD and PD in later life. Neurotoxic, pesticides and metal-based nanoparticles have been involved in AD by increasing beta-amyloid (Ab) peptide and the phosphorylation of Tau protein (P-Tau), causing senile/amyloid plaques and neurofibrillary tangles (NFTs) specific of AD. Lead, manganese, solvents and some pesticides have been linked to some forms PD like the mitochondrial dysfunction, alterations in metal homeostasis and aggregation of proteins such as a-synuclein (a-syn), which is the main constituent of Lewy bodies (LB), a crucial factor in PD pathogenesis. There is evidence that environmental pollutants may increase Ab, P-Tau, a-syn and neuronal death have been reported, including the oxidative stress mainly involved in the increase of Ab and a-syn, and the reduced activity/protein levels of Ab degrading enzyme (IDE) such as neprilysin or insulin IDE. Furthermore, epigenetic mechanisms by maternal nutrient supplementation and exposure to heavy metals and pesticides have been addressed to cause phenotypic diversity and susceptibility to neurodegenerative diseases in the offspring.

AD and PD are correlated with the amyloid fibrils formation in the brain from b-amyloid and a-synuclein proteins. Oligomericfibrillization may intermediates (protofibrils), rather than the fibrils themselves, are pathogenic. However, the mechanisms responsible for neuronal death remain unknown. Mutant amyloid proteins linked to familial AD and PD form morphologically indistinguishable annular protofibrils similar to a class of pore-forming bacterial toxins. This suggests that abnormal membrane permeabilization might be the cause of cell disorder and death in amyloid diseases.

Since the 1980s, interest in the relationship between pesticides and PD was increased after the discovery of the dangerous effect of exposure to1-methyl-4-phenyl-1, 2, 3, 6,-tetrahydropyridine (MPTP), a substance structurally similar to the herbicide paraquat to humans, as it resulted in chronic Parkinsonism and degeneration of dopaminergic neurons in humans (Langston & Ballard, 1983). There is more and more evidence of a biological plausibility about an association between pesticide exposure and PD. In addition to MPTP and paraquat, animal studies have revealed that pesticides with related properties such as rotenone, maneb, dieldrin, heptachlor and atrazine are responsible fora-synuclein accumulation and to dopaminergic cell degeneration and apoptosis (Betarbet et al., 2000; Caudle, Richardson, Wang, &

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Miller, 2005; Cicchetti et al., 2005; Costa, Giordano, Guizzetti, & Vitalone, 2008; Dinis-Oliveira et al., 2006; Filipov, Stewart, Carr, & Sistrunk, 2007; Hatcher, Pennell, & Miller, 2008; Kanthasamy, Kitazawa, Kanthasamy, & Anantharam, 2005; Meredith, Halliday, & Totterdell, 2004; Moretto & Colosio, 2011). Exposure to a combination of agents affecting dopaminergic systems at multiple endpoints was also pointed as responsible for neuropathological changes beyond those caused by each individual agent (Thiruchelvam, Richfield, Goodman, Baggs, & Cory-Slechta, 2002).

Proposed mechanisms to highlight the role of pesticides in PD concern c oxidative stress, interference with dopamine transporters, mitochondrial dysfunction, promotion of a-synuclein fibrillation, and inflammation (Brown, Rumsby, Capleton, Rushton, & Levy, 2006). Furthermore, Berry, La Vecchia, & Nicotera, (2010)suggested the involvement of selected mechanisms in neuronal activities at different endpoints, leading synaptic, dendritic, and axonal damage. However, little toxicological data exists for many specific pesticides (Brown et al., 2006; Costa et al., 2008).

Familial susceptibility to PD was suggested to be mediated by genetic variability in enzymes involved in the detoxification of neurotoxins (Barbeau et al., 1985). Therefore polymorphic variations in xenobiotic metabolizing enzymes, such as glutathione transferase and paraoxonase, are supposed to influence PD occurrence risk by affecting the antioxidative defensive potential against pesticides and other putative neurotoxins (Franco, Li, Rodriguez-Rocha, Burns, & Panayiotidis, 2010; Lopez et al., 2007; Manthripragada, Costello, Cockburn, Bronstein, & Ritz, 2010).In the regard, the present chapter will discuss the possible involvement of environmental contamination with heavy metals and pesticides, in the pathogenesis of Parkinson's and Alzheimer diseases.

Clinical Features and Epidemiology of Parkinson's Disease

PD is considered as the common movement disorder and represents the second most common degenerative disease of the central nervous system. Generally it is admitted that the prevalence of PD is generally ranged from 1 to 2 / 1000 in unselected populations with high variability worldwide depending on the ethnicity and socio-economical status (Figure 1) (von Campenhausen et al., 2005), as well, the disease may affect 1% of the population older than -(de Lau & Breteler, 2006). While it is rare before the age of 50 and may reach a prevalence of 4% in the highest age groups (de Rijk et al., 1995, 2000).

Pathologically, PD is known by depletion of dopaminergic DA cell bodies in the substantianigra pars compacta with subsequent loss of DA in the nigrostriatal system (Barlow, Coryslechta, Richfield, & Thiruchelvam, 2007).The cardinal features of the syndrome are related to motor dysfunction including resting tremor, rigidity, akinesia (or bradykinesia), and postural instability. The motor symptoms appear when at least 60% of dopaminergic neurons are lost and approximately 80–85% of dopamine content in the striatum is depleted (Figure 2) (Jankovic, 2008; Wirdefeldt et al., 2011). PD pathology is not restricted to the DA system, however progressively involving noradrenergic and serotoninergic neurons within the locus ceruleus and Raphe nucleus. Degeneration in these and other structures induces non-motor symptoms but associated with the disease such as (including) autonomic sexual and sleepy disease which may lead to cognitive, psychiatric, autonomic and sensory disturbances (DeMaagd & Philip, 2015; Emre et al., 2004; Lim, Fox, & Lang, 2009). Neuronal death mechanisms in PD pathogenesis may include defective protein handling, mitochondrial dysfunction, oxidative stress, and inflammation. Furthermore, environmental factors might trigger a cascade of dopaminergic nigral neuron degeneration in genetically susceptible individuals (Hatcher et al., 2008; Manning-BoǴ & Langston, 2007). In addition, pesticides, and factors related to pesticide exposure have been pointed as potential risk factors for PD (Kontakos

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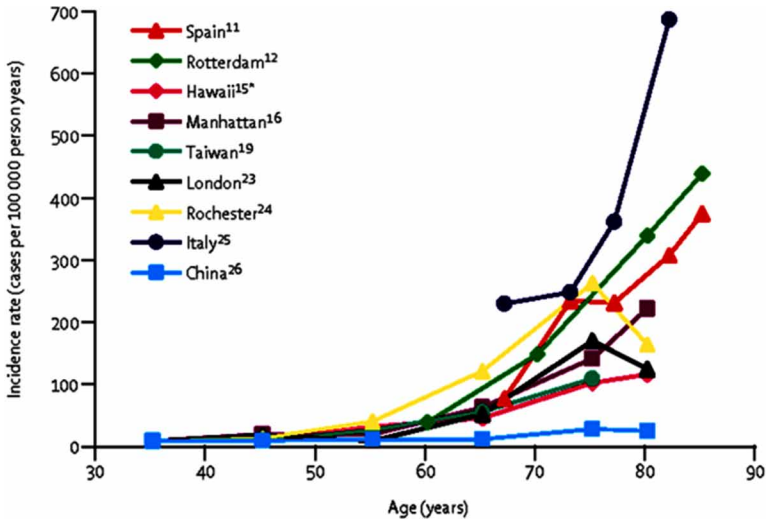
Figure 1. Comparison of PD prevalence in different populations (for review see Kasten, Chade, & Tanner, 2007)



& Stokes, 1999; Li et al., 2005; Anumeet Priyadarshi, Khuder, Schaub, & Priyadarshi, 2001).As an environmental cause, pesticide exposure is said to be linked to over 90% of PD is (Hatcher et al., 2008).

Physiopathology of Parkinson Disease: Involvement of Environmental Toxins

Pesticides Exposure

The etiology of PD is not fully understood. It is possible to involve both environmental and genetic factors (Schapira, 2009; Warner & Schapira, 2003). Several genes involved in PD pathogenesis have been identified. Alpha-synuclein and parkin are implicated in familial PD, autosomal dominant and recessive PD, respectively. In addition to other genes, including Omi/ HtrA2, PINK-1, DJ-1 and dardarin, their function has been the subject of intense studies unveiling nested gene pathways. Nevertheless, as 90% of PD cases are sporadic, genetic factors can't be the unique cause, which suggests that PD have a multifactorial etiology(Goldman, 2014). Findings from Epidemiological research suggests that the exposure to environmental toxicants, mainly pesticides, metals, and solvents may increase the risk of developing PD (Gao & Hong, 2011; Hatcher et al., 2008). A study of male twins has confirmed that genetic heritability is not a basis of sporadic PD with onset over the age of 50 (Tanner, Ottman, Goldman, Ellenberg, Chan, Mayeux, & Langston, 1999).Although it has been suggested that PD may be caused by a single toxic environmental exposure (Langston, Ballard, Tetrud, & Irwin, 1983),findings have suggested that the main PD cases may result from interactions between genetic and environmental exposures to certain toxins (Greenamyre, Betarbet, & Sherer, 2003);these findings led to the hypothesis that PD may be initiated or precipitated by environmental or endogenous toxins in genetically-predisposed individuals (Corrigan, Wienburg, Shore, Daniel, & Mann, 2000; Matsubara et al., 1995). Many epidemiological studies related the increased risk for developing PD to pesticides exposure including paraquat and rotenone and other environmental factors (table 1) (i.e. farming, well-water drinking, and rural living) (Brown et al.,

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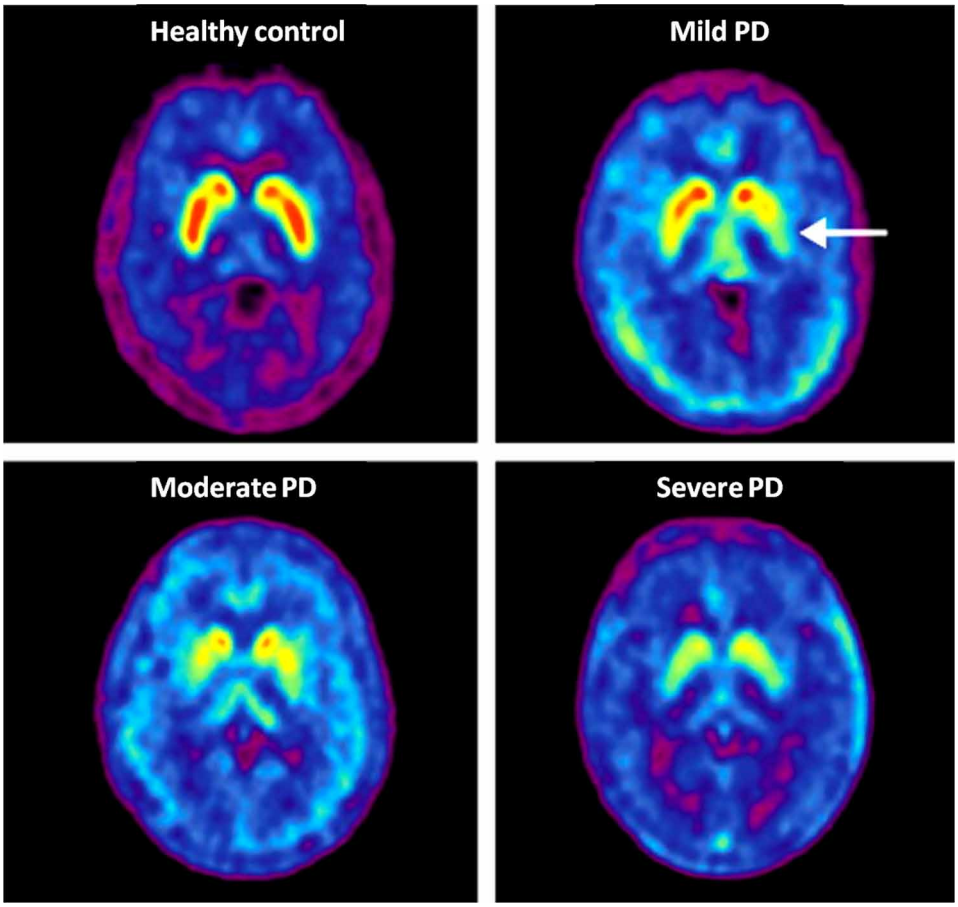
Figure 2. 18F-dopa PET scans of basal ganglia showing innervations of the striatum in different stages of PD: mild (early), moderate and severe, compared to healthy control, The color scale represents the maximum of 18F-dopa uptake in red and minimum uptake in dark blue (see Lang & Obeso, 2004)



2006; Dick, 2006; Le Couteur, McLean, Taylor, Woodham, & Board, 1999; Li et al., 2005; Priyadarshi, Khuder, Schaub, & Shrivastava, 2000).

The hypothesis that pesticide exposures may be related to PD development was prompted by the discovery that intravenous injection of the pre-toxin 1-methyl-4pheny l-1, 2, 3, 6-tetrahydropyridine (MPTP). This substance was proven as a chemical contaminant of synthetic heroin that causes an acute parkinsonian syndrome in humans and in mice similar to idiopathic PD (Langston et al., 1983; Duvoisin, 1986; Freyaldenhoven, Ali, & Hart, 1995).MPTP was also proven to selectively damaged dopaminergic neurons in the substantianigra (Langston, Forno, Rebert, & Irwin, 1984; Langston & Ballard 1983). Once in the brain, MPTP is transformed to 1-methyl-4-phenyl-4-phenylpyridinium ion (MPP+) by monoamine oxidase B (Fahn, 1988). MPP+ is then stocked into the dopaminergic neurons by the high-affinity DA uptake system (Frederickson, 1989). Biochemically, MPTP administration causes damage to the nigrostriatal system, with subsequent DA depletion similar to that seen in PD (Hallman, Lange, Olson, Strömberg, & Jonsson, 1985),and therefore, it is possible that compounds similar to MPTP may cause PD. Since then, environmental factors with similar toxicological profiles have received attention as potential risk factors for PD.

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Table 1. Literature summary of epidemiological studies of PD related to pesticides exposure (Rotenone and Paraquat)

Study	Design	Method of assessing pesticide use	No. enrolled (cases, controls)	Finding	OR (95% CI) or p-value	Exposed *n*
Paraquat						
Sanchez-Ramos et al. 1987	Case report	Medicalhistory	1 case	Symptoms "comparable to PD" in a 32-yearold farmer after 15 years of paraquat use	NA	1 case
Hertzman et al. 1990	Case–control	Specific question re: paraquat use	57 cases 122 controls	Association with PD	p = 0.0* [a]	4 cases 0 controls
Semchuk et al. 1992	Case–control	General questions re: pesticide use	130 cases 260 cases	One case with early-onset PD (< age 40 years) reported using paraquat (ages 26–31 years)	NA	1 case
Hertzman et al. 1994	Case–control	Specific question re: paraquat use	127 cases 245 controls	No association with PD	1.11 (0.32–3.87)	6 cases 5 controls
Firestone et al. 2010	Case–control	Checklist [c]	404 incident cases 526 controls	Added subjects to 2005 interim population No association with PD in reanalysis	0.9 (0.14–5.43)	2 cases 3controls
Rotenone						
Kamel et al. 2007	Case–control	Specific question re: rotenone use in a supplementary questionnaire	83 prevalent cases 79,557 controls 78 incident cases 55,931 controls	Association of PD with ever use Could not determine	1.7 (0.6–4.7)	4 prevalent 671 controls 1 incident 565 controls
Tanner et al. 2009	Case–control	Specific question re: occupational rotenone use	519 cases 511 controls	No association with PD	0.82 (0.05–13.34)	1 case 1 control

Paraquat (1,1'-dimethyl-4, 4'-bipyridinium dichloride) is a highly toxic quaternary nitrogen largely used herbicide. Because of its low cost, rapid action, it is widely used in agricultural and other settings. Due to its structural resemblance with MPP (the active metabolite of MPTP), it was thought to be toxic to dopaminergic neurons and thus might be related to PD.

Paraquat toxicity is due to its ability to redox cycle, accepting an electron from an appropriate donor with subsequent reduction in oxygen to produce superoxide anion while also regenerating the parent compound (Bus & Gibson, 1984).

In vivo research has shown that repeated administration of paraquat in mice or rats produces weak or moderate decreases in the number of dopaminergic neurons of the substantianigra, striatal levels of dopamine and its metabolites, expression and activity of tyrosine hydroxylase, and immunoreactivity of the dopamine transporter (McCormack et al., 2002; Thiruchelvam, Richfield, Baggs, Tank, & Cory-Slechta, 2000).These results suggest that chronic poisoning of rodent with paraquat may increasingly set off cellular mechanism similar to those operating in PD. There is evidence that paraquat causes selec-

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tive degeneration of dopaminergic neurons in the substantianigra pars compacta (SNpc), reproducing a characteristic feature of PD (Fei, McCormack, Di Monte, & Ethell, 2008). In addition, regions of high paraquat use overlap with regions of high PD incidence (Lanska, 1997; Ritz & Yu, 2000; Shimizu et al., 2003).Because of its use in agriculture, paraquat exposure may increase the risk of developing PD in the human population. Liou, Tsai, Chen, Jeng, Chang, Chen, & Chen, (1997)reported the possible link between paraquat and PD observed in PD patients in Taiwan, in which the pesticide use was associated with an increased risk of developing PD, being higher for those individuals using paraquat(Liou et al., 1997). Also, Tanner, Kamel, Ross, Hoppin, Goldman, Korell, M., … Langston, (2011) reported acorrelation between PD and the use of oxidative pesticides, including paraquat (Tanner et al., 2011). Other epidemiological studies have also linked the exposure to paraquat with PD (Ascherio et al., 2006; Hertzman, Wiens, Bowering, Snow, & Calne, 1990; Kamel et al., 2006; Wang et al., 2011).

Paraquat is conducted to dopaminergic terminals by the dopamine transport and organic cation transporter (Rappold et al., 2011), and causes cellular toxicity (figure 3) by oxidative stress through the cellular redox cycling generating superoxide radical by the oxidation of NADPH, which in turn impairs the restoration of GSH levels and thus the activity of several antioxidant systems (Berry et al., 2010; Franco et al., 2010). Observations from repeated administrations of paraquat to adult mice and rats (5–10 mg/Kg/ week/at least 3 weeks, i.p.) increases ROS levels in the striatal homogenate, causes a dose-dependent decrease in dopaminergic neurons from the substantianigra, and decreases thestriatal dopamine nerve terminal density, and neurobehavioral syndrome characterized by reduced ambulatory activity (Brooks, Chadwick, Gelbard, Cory-Slechta, & Federoff, 1999; Kuter, Nowak, Gołembiowska,& Ossowska, 2010; McCormack et al., 2002). Paraquat belongs to a class of redox cycling compounds capable of inducing mitochondrial damage, increases reactive oxygen species(ROS) production and oxidative stress (Castello, Drechsel, & Patel, 2007; Jenner, 2003)which is considered to be a key indicator (foundation) of neurotoxicity. Experiments indicate that paraquat targets mitochondria of brain cells and the damage to the latter cells is the main source of ROS. In-vitro assays paraquat have been proved to disturb the mitochondria isolated from mouse brains and from differentiated human neuroblastoma cells (McCarthy, Somayajulu, Sikorska, Borowy-Borowski, & Pandey, 2004).Also, Fukushima, Yamada, Isobe, Shiwaku, & Yamane,(1993)showed that paraquat may generate ROS by accepting electrons from purified Complex I of the mitochondrial respiratory chain (Fukushima, et al., 1993), with the subsequent inhibition of this mitochondrial complex; suggesting the importance of the interaction of paraquat with mitochondria in its toxicity. Many neurodegenerative diseases have been linked to mitochondrial dysfunction (Lin & Beal, 2006; Schon & Manfredi, 2003). Abnormal mitochondrial electron transfer mechanism has been detected in Alzheimer, Parkinson, and Huntington disease (Franco et al., 2010; Hanagasi, Ayribas, Baysal, &Emre, 2005).

Heavy Metals Exposure

An increased risk of developing PD has been associated with exposure to heavy metals such as iron, Pb and Mn and their combinations. Heavy metals may accumulate in the substantianigra and cause oxidative stress. As a heavy metal, iron is an essential element transported into the brain through the transferrin receptor and divalent metal transporter1 (DMT1) (Zheng, & Monnot (2012). Postmortem and in vitro studies confirmed links between iron accumulation and the cardinal pathological features of PD, the loss of dopamine neurons in the substantianigra (SN) pars compacta (Dexter, Wells, Agid, Agid, Lees, Jenner, & Marsden, 1987) and the presence of a-synuclein-rich Lewy bodies (Hashimoto,

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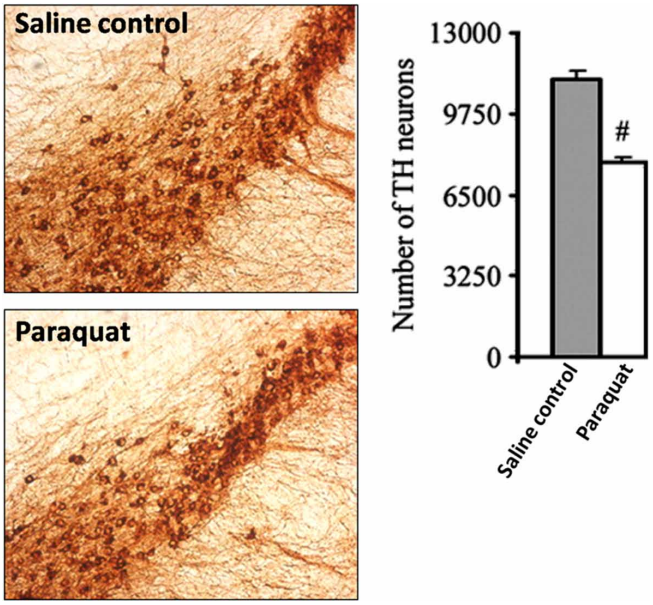
Figure 3. Photomicrographs of frontal sections through midbrain substantianigracompacta (SNpc) stained with anti-Tyrosine hydroxylase in saline control and Paraquat treated rat at 12 months of age with statistical analysis of TH immunoreactivity. Note a drastic loss of TH-immunopositive neurons in Paraquat treated group (modified according to Peng, Peng, Stevenson, Doctrow, & Andersen, 2007)



Hsu, Xia, Takeda, Sisk, Sundsmo, & Masliah, 1999). Iron has also been linked to risk of PD in some epidemiological studies without strong evidence (Abbott et al., 2012; Logroscino, Gao, Chen, Wing, & Ascherio, 2008; Miyake et al., 2011; Rybicki, Johnson, Uman, & Gorell, 1993).Nevertheless, iron and its deregulated homeostasis have been suggested to play a role in the pathogenesis of PD because of its prooxidants characteristics that may lead to ROS generation via Fenton and Haber–Weiss reactions (Sian-Hülsmann, Mandel, Youdim, & Riederer, 2011; Stohs & Bagchi, 1995). The substantianigra has the highest levels of iron in the human brain, which may be caused by the presence of neuromelanin in pigmented SNpc dopaminergic neurons known for their high chelating capacity for metals, and iron in particular. However, this may increase their vulnerability since iron may react with ROS produced from dopamine metabolism and promote the further generation of highly toxic radicals (Zecca et al., 2002; Zecca, Youdim, Riederer, Connor, & Crichton, 2004). Dexter et al.,(1987) found that free ferrous iron (Fe2+) acts as a catalyst in a reaction with hydrogen peroxide (Fenton reaction), producing highly toxic reactive oxygen species and ferric iron (Fe3+) that lead to oxidative-stress-related damage to cellular components including proteins, lipids, and DNA. To relieve potential toxicity, excess ferrous iron within deep brain nuclei is accumulated and transported into the core of apoferritin molecules where it is oxidized and safely stored in high concentrations in the ferric state (Haacke et al., 2005). As ferritin (iron-containing apoferritin) is highly paramagnetic and indeed one of the only non-haem iron molecules present in a sufficient quantity to cause local field inhomogeneities (Haacke et al., 2005; Schenck & Zimmerman, 2004).

The epidemiological proof of Pb association with PD is more accurate as the accumulative lifetime exposure can be estimated through Pb concentration in bone that has a half-life of years to decades. Ini-

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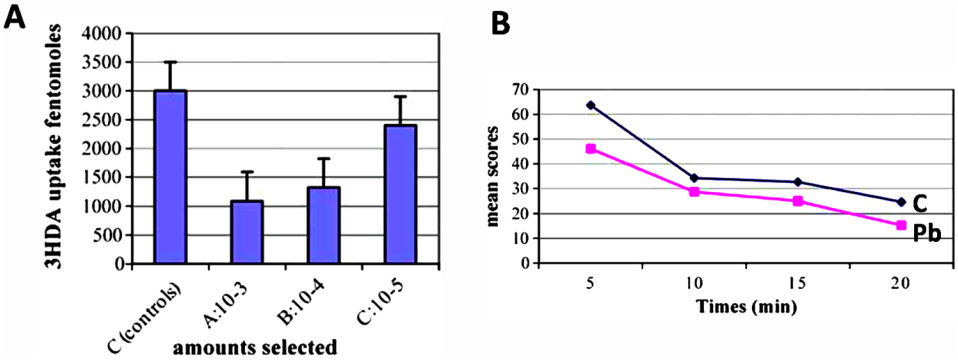
tially, Kuhn, Winkel, Woitalla, Meves, Przuntek, & Muller, (1998) reported that 7 out of 9 postal workers exposed to lead sulfate batteries for up to 30 years developed parkinsonian symptoms, concluding that Pb intoxication may be a cause of these symptoms (Kuhn et al., 1998).

As well, experimental studies showed that acute and chronic, in vivo and in vitro, exposures to lead may trigger a potent neurotoxic effect on the midbrain SNpcdopaminergic neurons. NourEddine, Miloud, & Abdelkader, (2005) have shown a clear dose-dependent inhibition of 3H-DA uptake in presence of lead which was associated with a deficit in locomotor behavior (Figure 4), leading to suggest a possible involvement of such heavy metal in the pathogenesis of PD (NourEddine, et al., 2005).

Figure 4. (A): Effect of lead acetate on ^{3}H-DA uptake rates in synaptosomes isolated from the brain in vitro of controls and Pb treated (amounts selected of lead acetate from 10-3 M to10-5M). (B): Effect of lead acetate on locomotor activity in controls (C) and lead-exposed rats (Pb) (modified NourEddine, Miloud, & Abdelkader, 2005)



As a heavy metal, manganese is an essential element with important physiological functions for cellular homeostasis. The epidemiologic evidence does not provide sufficient proof for an association between Mn exposure and PD risk (Mortimer, Borenstein, & Nelson, 2012; Wirdefeldt et al., 2011). Only one case-control study (144 cases vs. 464 controls) in a population from the metropolitan Detroit area reported an increase of PD risk when the exposure to Mn was over 20 years (OR = 10.63, 95% CI, 1.07–105.99) (Gorell, Peterson, Rybicki, & Johnson, 2004). However, occupational or environmental exposures to Mn have been associated with a neurological syndrome that includes cognitive deficits, neuropsychological abnormalities and Parkinsonism (Guilarte, 2013).

Clinical Features and Epidemiology of Alzheimer Disease

AD is the most common and age-related neurodegenerative disorder and affects approximately 47 million people worldwide (Prince et al., 2015) with heterogeneity of prevalence rate between nations, depending on race and the socioeconomic status (Figure 5). Almost 50% of cases of AD are found in individuals older than 85 years. Few cases are due to genetic mutations and the majority is occurring without known familial genetic mutation (Ceccom et al., 2012). Typical symptoms of AD patients are early memory loss, personality and behavioral changes and deficits in sensory and motor functions. The brain of AD patients presents synaptic and neuronal loss resulting in brain atrophy, affecting regions including the

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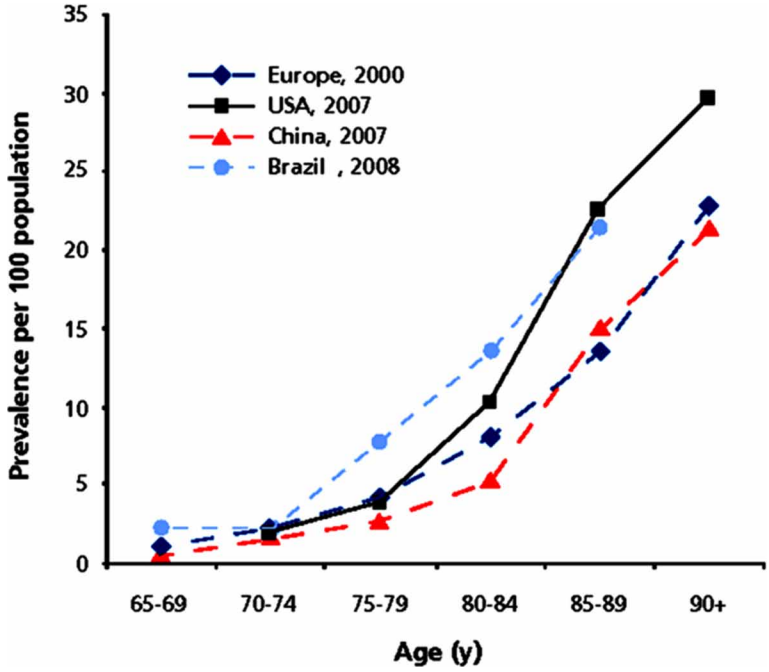
entorhinal cortex, hippocampus (figure 6), basal forebrain and amygdala (Bertram, Lill, & Tanzi, 2010; Ittner & Götz, 2011). Clinical symptoms of AD are characterized by a progressive deterioration of higher mental functions and cognitive functions, ending in severe dementia (Nunomura, Moreira, Castellani, Lee, Zhu, Smith, & Perry, 2012). The neuropathology is characterized by the accumulation of two types of fibrous material in the brain: the Aß-amyloid extracellular peptide deposited in senile plaques and intraneuronal neurofibrillary tangles (NFT) composed mainly of abnormal and hyperphosphorylated forms of the microtubule-bound tau protein. A large number of reactive astrocytes is also observed as-signs of neuroinflammation, metal dyshomeostasis, and oxidative stress (Nunomura et al., 2012; Reddy, 2006). The formation of NTFs and the resulting degeneration first appear in the hippocampus, especially pyramidal neurons in CA1 and layer II of the entorhinal cortex and the neocortex (Kepp, 2012).

Figure 5. Age-specific prevalence of Alzheimer's disease (per 100 populations) across continents and countries (Qiu, Kivipelto, & von Strauss, 2009)



Environmental factors such as diet (fat-rich), heavy metals, biogenic metals, and pesticides have been involved in AD development due to their ability to disrupt metabolic pathways involved in the homeo-stasis of (amyloid betaAb). However, factors such as lifestyle (antioxidants and exercise) can prevent AD development (Paillard, Rolland, & de Souto Barreto, 2015).

Many of these environmental factors are oxidative agents acting through different mechanisms. The brain is particularly vulnerable to oxidative stress due to its high glucose-based metabolic rate, low levels of antioxidants, high levels of polyunsaturated fatty acids, and high enzymatic activities related to transition metals that catalyze the formation of free radicals (Halliwell, 1992).

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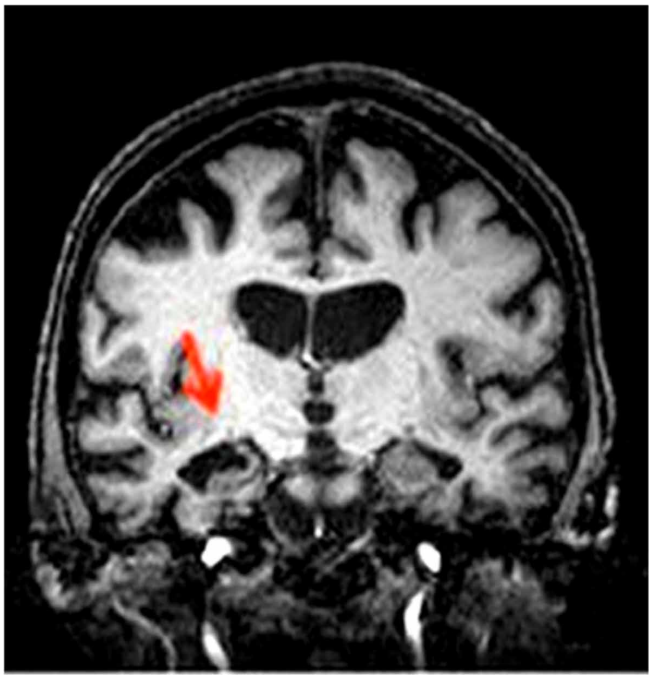
Figure 6. T1-weighted MRI image of a patient with Alzheimer's disease, the arrow pointing at right hippocampal atrophy (Bonifacio & Zamboni, 2016)



Etiology of Alzheimer Disease

The etiology of AD still unclear. AD may be caused by a multifactorial process involving both a genetic predisposition and exposure to environmental factors modulated by the biological aging process (Gauvreau, 1987).

AD is a progressive neurodegenerative disorder characterized by extracellular Aß plaques and intracellular neurofibrillary tangles (NFTs) with high synaptic defects (Correia et al., 2012). In 2010, around 36 million people were affected by AD in the world with projections to elevate to 66 million by 2030 and 115 million by 2050 (Honjo, Black, & Verhoeff, 2012).

Oxidative stress and inflammatory mechanisms are the main factors responsible for AD progression and targeting these mechanisms may be the best way in its treatment. Oxidative stress is an early feature of AD pathogenesis that contributes to Aß generation and NFTs formation (Cai, Zhao, & Ratka, 2011; Kalra, Kumar, Majeed, & Prakash, 2016). The inflammatory reactions involving cytokines such as IL-1, IL-6, NF-κß, COX-2, and TNF-a, contribute dramatically to AD progression (Bronzuoli, Iacomino, Steardo, & Scuderi, 2016). Moreover, neuroinflammatory cytokines have been detected at high levels in post-mortem brains of AD patients. Findings reported that aspirin and non-steroidal anti-inflammatory drug treatment (NSAID) could reduce the incidence of AD (Hung et al., 2016; Su et al., 2016).

AD is the fourth leading cause of death in the elderly (McDowell, Hill, Lindsay, Helliwell,Costa, Beattie, ... & Parboosingh, 1994). AD is a neurodegenerative disease defined by specific neuropathological and neurochemical features. The main lesions observed in the brain of AD cases are senile plaques (Duyckaerts et al., 1986) and neurofibrillary tangles (NFT) (Ball, 1977). Some studies identified a major

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decrease of choline acetyltransferase and acetylcholinesterase (AchE) in AD cases (Davies& Maloney, 1976; Perry, Perry, Blessed, & Tomlinson, 1977). Others reported oxidative stress by free radicals (FR) as a risk factor for AD (Frölich & Riederer, 1995).Ikeda, Toda, Wang, & Nakazawa, (1994) observed that FR are highly toxic and can initiate lipid peroxidation specifically because of the increase of NFT.

However, the genetic components account is known for only few cases of AD (Van Broeckhoven, 1995), suggesting that other genes or risk factors, such as environmental exposure, may be implicated in the etiology AD. Epidemiological studies revealed a higher prevalence of AD in rural environments than in urban settings (Jean et al., 1996; Shibayama, Kasahara, & Kobayashi, 1986). For many decades, pesticides have been used more intensively in rural than in urban areas and their use has been increasing with the growth of productivity and the specialization of cultures (Brundtland, 1989). Many pesticides have been known to have neurotoxic properties (Corriveau & Lajoie, 1987). Toxicological studies showed that some pesticide families (carbamates, organophosphates, organochlorines, bipyridyls) may be responsible for serious damage to the nervous system (Blain, 1990).

The organophosphorus compounds like parathion and fenitrothion and carbamates such as aldicarb are known inhibitors of AchE (Bardin, 1994; Fukuto, 1990). Bipyridyls such as paraquat can generate FR that is able to cross the blood-brain barrier and inflict irreversible damage to neurons (Corasaniti, Defilippo, Rodinò, Nappi, & Nisticò, 1991; Elroy-Stein, Bernstein, & Groner, 1986). Organochlorines such as DDT and dieldrin can disturb the functioning of the mitochondrial system and produce FR (Kimbrough, Gaines, & Linder, 1971). Thus, exposure to pesticides may contribute to the cholinergic system deficiency and the production of FR observed in AD. Epidemiological studies in the workplace have identified some damage to the central nervous system and neuropsychological disorders due to pesticide exposure (Boyd, Weiler, & Porter, 1990).Others have shown significant relationships between exposure to pesticides and neurodegenerative diseases such as PD(Barbeau, Roy, Cloutier, Plasse, & Paris, 1987; Fleming, Mann, Bean, Briggle, & Sanchez-Ramos, 1994) and AD (Cannas, Costa, Tacconi, Pinna, & Fiaschi, 1992; McDowell, Hill, Lindsay, Helliwell, Costa, Beattie, ... &Parboosingh, 1994). The Canadian Study of Health and Aging has estimated an odds ratio (OR) of 2.17 (95% CI, 1.18-3.99) associated to AD with respect to occupational exposure to pesticides (Pasture & Onkia, 1994)

However, the scope of this result is limited because the study did not long-term environmental exposure to pesticides. In addition, occupational exposure to pesticides was established from answers provided by contacts to a simple binary question on whether the subjects were exposed or not exposed. This does not permit the quantification of exposure. Finally, the Canadian study of Health and Aging (1994) (Pasture & Onkia, 1994) did not consider potential confounding factors such as age, sex, education level, occupation, and genetic factors that might influence the relationship between pesticides and AD.

Physiopathology of Alzheimer Disease Involving Environmental Neurotoxicity

Role of Heavy Metals

As neurodegenerative disorders progenitor, heavy metals play a role in the precipitation of abnormal ß-amyloid protein and hyperphosphorylated tau, which are the main hallmarks of AD.

Environmental heavy metals affect brain development. There is evidence of a link between heavy metals and neurodegenerative disorders such as AD and PD(Brown, Lockwood, & Sonawane, 2005; Nallagouni & Pratap, 2017). Aluminum is known as one of the heavy metals causing neurodegenerative diseases. It upregulates the expression of pathogenic genes that are implicated in AD such as APP,

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IL-1ß, IL-6, TNF-a, AChE and MAO (Cao, Wang, Xiu, Zhang, & Li, 2017; Lukiw, Percy, & Kruck, 2005). Further studies have suggested that the interaction of metal ions such as iron and aluminum with Ab, and also copper and zinc, could play a crucial role in the release of reactive oxygen species (ROS) that contribute to neurodegenerative damage (House et al., 2004; Khan, Dobson, & Exley, 2006; Smith, Richey Harris, Sayre, Beckman, & Perry, 1997).

Other heavy metals like cadmium and fluoride enhance neurotoxicity by several mechanisms including free radical generation and lipid peroxidation in the hippocampus (Blaylock, 2004; B. Wang & Du, 2013). Transition metals such as Cu or Fe, together with Zn, cause oxidative stress as well as to the aggregation and precipitation of amyloid- peptides in the AD brain (Bush, 2003; Bush et al., 1994). Influence of Transgenic Metallothionein-1 on Gliosis, CA1 Neuronal Loss, and Brain Metal Levels of theTg2576 Mouse Model of AD.

Transition metals, particularly iron (Fe) zin (Zn) and copper (Cu) have been studied in AD etiology. These metals bind to amyloid ßpeptide (Aß) accelerate (Aß) aggregation and consequently promote neurotoxic plaque formation. Fe and Cu are also likely to be responsible for causing oxidative stress and neuroinflammatory changes in the AD brain (Choo, Alukaidey, White, & Grubman, 2013; Praticò, 2008; Sayre, Perry, & Smith, 2008). In addition, cognitive decline in AD has been associated with the interference of the processing and function of the amyloid-ß precursor protein (APP) and the phosphorylation and aggregation of the microtubule-associated protein (MAP), tau both of which are associated with altered metal homeostasis (Crouch et al., 2009).

Lead (Pb) is a heavy metal characterized by its neurological toxic effects, even if a direct effect on AD development has not been reported. Pb affects cognitive abilities, intelligence, memory, speed processing and motor functions in children (Mason, Harp, & Han, 2014). However, studies in the elderly are still limited. A cohort study reported that bone Pb levels were associated with poor cognitive performance scores in old workers, suggesting that past Pb exposure can lead to late cognitive deterioration (Dorsey, Lee, Bolla, Weaver, Lee, Lee, … Schwartz, 2006).

However, a recent study reported no evidence on the role of serum Pb levels in AD (Park, Lee, Park, & Joung, 2014). Experimental studies are showing more solid evidence compared to epidemiological studies related to the link between Pb exposure with AD. Mercury (Hg) is known as a heavy metal with a high potential to cause neurotoxicity. Studies about Minamata and Iraq disasters helped to understand the neurotoxicity of this metal. There is a large consensus that Hg disrupts the brain development and produces cognitive and motor disabilities (Johansson et al., 2007), and in adults, Hg exposure causes memory loss and cognitive alterations (Chang et al., 2008; Wojcik, Godfrey, Christie, & Haley, 2006). An early study suggested a relation between Hg exposure and AD. Authors reported increased levels of Hg (in microsomes) and bromide (in the whole brain), and lower levels of rubidium (in the whole brain, microsomes, and nuclei), selenium (Se; in microsomes) and zinc (Zn; in nuclei) in AD brains compared with controls (Wenstrup, Ehman, & Markesbery, 1990). Cadmium is another toxic heavy metal associated with neurological alterations including memory loss and mental retardation (Wang & Du, 2013). Another study found an increase of plasma levels of various metals including Cadmium, aluminum, mercury, and selenium in 24 AD patients compared with 28 healthy volunteers (Basun, Forssell, Wetterberg, & Winblad, 1991).

Aluminum (Al) is the most used neurotoxic metal, widely bioavailable to humans and involved in the etiology of neurodegenerative diseases such as AD. It is known to accumulate at higher concentrations in brain regions that are selectively affected in AD, including the entorhinal cortex (an area that shows the earliest pathological changes in AD), hippocampus, and the amygdala (McDermott, Smith, Iqbal, &

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Wisniewski,1979; Walton, 2009b, 2009a). Pyramidal cells in the hippocampus and cortex, basal forebrain cholinergic neurons, and upper brainstem catecholaminergic neurons are the most affected neuronal populations in AD and also, the most susceptible to Al-induced neurofibrillary degeneration (Bertholf & Gambetti, 1987;Kowall, Pendlebury, Kessler, Perl, & Beal, 1989; Matyja, 2000; Walton, 2006).

The incident of Al pollution in Cornwall, UK (1998) after a discharge of 20 tonnes of aluminum sulfate into the drinking water, gave evidence of Al potential neurotoxicity. Another brain pathological characteristic found in AD patients were observed in subjects exposed to Al in this region (Exley & Esiri, 2006), as well as damage in cerebral functions (Altmann et al., 1999). A Chinese study reported that high concentrations of iron and copper in the soil might be associated with the high AD annual mortality. However, no association between Al levels in soil and the mortality caused by AD (Shen, Yu, Zhang, Xie, & Jiang, 2014)was reported.

Role of Pesticides

Epidemiological studies revealed a higher prevalence of AD in rural environments compared to urban settings (Jean et al., 1996; Hiroto Shibayama et al., 1986). Pesticides have been used more intensively in rural than in urban areas and their use has been increasing with the growth of productivity and the specialization of cultures (Brundtland, 1989). Many pesticides have shown neurotoxic properties (Corriveau & Lajoie, 1987). Toxicological studies revealed that some pesticide families (carbamates, organophosphates, organochlorines, bipyridyls) can cause serious damage to the nervous system (Blain, 1990).

The organophosphorus compounds such as parathion and fenitrothion and carbamates including aldicarb are known inhibitors of AchE (Bardin, 1994; Fukuto, 1990). Bipyridyls such as paraquat can generate free radicals (FR) that is able to cross the blood-brain barrier and cause irreversible damage to neurons (Corasaniti et al.,1991; Elroy-Stein et al., 1986). Organochlorines such as DDT and dieldrin can disturb the functioning of the mitochondrial system and produce FR(Fleming et al., 1994; Kimbrough et al., 1971).Thus, exposure to pesticides may contribute to the cholinergic system deficiency and the production of FR observed in AD. Epidemiological studies in the workplace have identified some damage to the central nervous system and neuropsychological disorders due to pesticide exposure (Boyd et al., 1990; Stephens, Spurgeon, Calvert, Beach, Levy, Harrington, & Berry, 1995). Others have shown significant correlation between exposure to pesticides and neurodegenerative diseases such as PD(Butterfield, Valanis, Spencer, Lindeman, & Nutt, 1993; Fleming et al., 1994) and AD (Cannas et al., 1992; McDowell, Hill, Lindsay, Helliwell, Costa, Beattie, ... &Parboosingh, 1994). Studies in the workplace have identified some damage to the central nervous system and neuropsychological disorders due to pesticide exposure (Boyd et al., 1990; Stephens et al., 1995).

Paraquat is a commonly used herbicide that has been supposed to be involved in AD development. A recent study showed that treatment of wild-type and β-amyloid precursor protein (APP) transgenic mice with PQ produced a significant increase in β-amyloid(Aβ) levels in transgenic mice that was associated with mitochondrial oxidative damage in cerebral cortex causing mitochondrial dysfunction which induces an impairment of learning and memory (Chen, Yoo, Na, Liu, & Ran, 2012). This result demonstrates that mitochondrial damage is a key mechanism underlying cognitive impairment and elevated amyloido genesis induced by paraquat, suggesting that pro-oxidant xenobiotics like PQ can cause AD.

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CONCLUSION

A variety of environmental and occupational exposures have been implicated in the etiology of PD and AD. These include exposure to well water, pesticides, herbicides, rural living, and certain heavy metals. Chronic low-level exposure to pesticide and heavy metals may potentiate the neurodegeneration caused by aging (Bolin, Basha, Cox, Zawia, Maloney, Lahiri, & Cardozo-Pelaez, 2006; Peng et al., 2007), these pollutants present similar mechanisms of toxicity, which lead to a generalized mechanism based on the generation of oxidative stress causing common hallmarks of both neurodegenerative disorders.

More studies are needed to clarify the mechanisms involved in the early lifetime exposure to neurotoxic pesticide residues and other possible drinking water contaminants effects on AD and PD disorders in humans. This knowledge would be crucial for improving the life quality of elderly people and would significantly help the health authorities to develop global prevention programs against neurodegenerative diseases.

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Chapter 6
Dementia and Language Bilingualism Helps Ward Off Alzheimer's Disease

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ABSTRACT

There has been extensive discussion with regard to whether bilingualism helps ward off dementia. However, there is still debate over bilingualism's effects. Researchers have determined that bilinguals have a greater advantage in delaying dementia than monolinguals. Researchers have used cognitive reserve to explain their views. However, recently, some researchers have arrived at a different conclusion, stating that bilinguals have no advantage compared with monolinguals in delaying dementia. In this review, we summarize a review of studies on bilingualism and dementia, supporting the viewpoint that bilinguals have an advantage in delaying dementia compared with monolinguals.

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INTRODUCTION

As technology leads to advancements in medical treatment, life expectancy continues to increase, thus increasing the proportion of the elderly population. Adverse effects of brain diseases on the health of the elderly, particularly dementia, have become increasingly prominent. According to the report from the World Health Organization and the International Alzheimer's Association titled "Dementia: A public health priority" (World Health Organization, Alzheimer's Disease International, 2012), there were 35.6 million patients with dementia patient worldwide in 2012; this number is expected to increase to 65.7 million by 2030 and to 115.4 million by 2050. Moreover, $604 billion was spent on nursing care in 2012 alone. To benefit the health of mankind and save the resources of human society, it is imminent to find a way to resist dementia. Recently, resistance to dementia has received significant attention in society, and many efforts have been focused on this field, with some achievements. Many researchers focus on the study of dementia and language. Alzheimer's disease directly affects the patient's language skills. Researchers have found that different subtypes of dementia have different effects on the language ability of patients; for example, the language skills of patients with Alzheimer's disease will be reflected in the phoneme (Whitaker 1976, Balyes 1982), syntax, (Schwarts 1979, Obler 1983), semantics (Barker 1968, Bayles 1982, Nicholas 1985, Schwartz 1979, Bayles & Tomeda 1983, Gewirth 1984, Robinson 1996), discourse and pragmatic aspects (Nicholas 1985, Ripich 1988). Therefore, do language skills, particularly the number of language acquisitions, have effects on resisting dementia?

BACKGROUND

Classification of Dementia

The word 'Dementia' is derived from Latin, *de-men-tia*. *De* means away from, *men* means the mind, and *tia* is to the state. Dementia is a type of brain disease that results in memory and cognitive problems in patients; it is also characterized by degenerating functions of patient emotion, language and behavior. It can result in degeneration of the personal life, but the individual can still be physically maintained.

Sixty-five years old is used as the disease onset time boundary. If onset occurs before 65 years old, it is referred to as presenile dementia; if the onset occurs after 65 years old (including 65), it is referred to as senile dementia. Most patients have dementia in the senile stage. Smith (2013) believes that dementia is characterized by persistent changes in senile mental changes.

Current studies show that brain damage, aging and disease are the causes of dementia, which results in mental function degrading at a faster than typical rate at that age. Dementia is not one disease but rather a group of similar clinical manifestations of disease clusters.

Dementia can be divided into three types based on its cause: degenerative dementia, vascular dementia and post-traumatic dementia. Degenerative dementia includes Alzheimer's disease, front temporal dementia and Lewy body dementia. Vascular dementia is caused by cerebral vascular disease, and traumatic dementia is caused by a head trauma.

According to lesion location, dementia can be divided into cortical dementia and subcortical dementia. In cortical dementia (Corsellis, 1962), including Alzheimer's disease, the lesion is detected in the cerebral cortex. In subcortical dementia (Albert, 1974), the lesion area is detected in the cortex of the

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brain, such as in Parkinson's disease and Huntington's disease. In limbic dementia, the lesion area is detected in the limbic system (Gascon, 1973).

According to the possibility of cure, dementia can be divided into reversible and irreversible dementia. Some types of dementia can be cured, for example, when dementia is caused by a lack of vitamins or cancer. However, only approximately 5% of patients have reversible dementia. Most patients have irreversible dementia, which can only be prevented and relieved.

Diagnosis Tools of Dementia

Currently, people mainly use the CDR MMSE scale to diagnose dementia. In addition, brain science technology also plays an increasingly important role in the diagnosis of dementia.

Clinical Dementia Rating (CDR)

CDR is a clinical dementia rating scale that includes six dimensions: memory, orientation, judgment and problem-solving skills, work and social skills, family and personal preference and the ability to live independently. Each dimension has five levels corresponding to a different point value as follows: health (CDR = 0), suspected dementia (CDR = 0.5), mild dementia (CDR = 1), moderate dementia (CDR = 2) and severe dementia (CDR = 3). Doctors obtain assessment scores through communication with patients and their relatives.

When the patient receives a CDR score of 0 and does not display obvious symptoms, the patient is in a healthy state. A CDR score of 0.5 indicates that the patient is essentially normal, with only minor damage. A CDR score of 1 indicates that the patient has more obvious symptoms and cannot complete complex tasks. A CDR score of 2 indicates that the patient's cognitive ability is greatly affected and that they can complete only simple tasks; the patient must be taken care of. A CDR score of 3 indicates that the patient's cognitive ability is severely damaged and that the patient cannot perform independent activities.

Mini Mental Status Examination (MMSE)

The MMSE is a simple psychological scale, also known as the Folstein Test (Folstein, 1975); this test was originally designed for intellectual impairment evaluation and was only later used to diagnose dementia. It is currently used to diagnose Alzheimer's disease in clinical situations. The diagnosis includes time and place orientation, language, mental arithmetic, short-term memory, graphics imitation and other projects. A correct answer receives one point, and the test has scores ranging from 0-30. A score above 24 represents a normal score. A score of 18-24 indicates mild dementia, a score of 16-17 indicates moderate dementia, and a score of 15 or less indicates severe dementia.

Other Diagnostic Tools

The DRS scale was designed by Mattis (1976). It contains five dimensions: attention, boot protection, concept formation, structure and memory. Compared with the MMSE scale, the DRS scale has more content. However, according to the Stuss (1996) survey, the DRS does not have a significant advantage compared with the MMSE scale in the diagnosis of dementia. The ADAS, CERAD, ADL and other tools are also used in the diagnosis of dementia.

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Structural brain imaging includes MRI and CT. Brain imaging technology can identify degradations of the patient's brain. Additionally, we can explore the relationship between the degrees of brain atrophy in patients with individual differences. MRI is better than CT for the technical analysis of dementia.

Functional brain imaging includes positron emission tomography (PET) and single photon emission computed tomography (SPECT). The PET technique is more sensitive than SPECT technology in the diagnosis of early stage Alzheimer's. In recent years, functional magnetic resonance imaging (FMRI) has increasingly been used in the diagnosis of dementia. FMRI and PET diagnostic results are similar. However, the advantage of FMRI is that it can conduct brain function tests while the patient is performing cognitive tests.

Electroencephalography (EEG) has low costs, and it can be frequently repeated. The test results of the elderly differ significantly from those of normal young people. According to Berger (1937), the brain waves of elderly people are similar those of young people with brain disease. However, as Alzheimer's disease progresses, EGG changes will become more apparent.

It is possible to diagnose Alzheimer's disease by neuropsychological indicators (Wu 2012), in addition to using a variety of scales to diagnose Alzheimer's disease. Researchers have made successful diagnosis through visual, auditory, tactile and multisensory integration. (Wu 2012) In clinical diagnosis, neuropsychological testing has the following advantages:

First, wide range of applications. Scale diagnostic requests subjects have knowledge and language background. Neuropsychological indicators diagnosis according to visual auditory and tactile, which has good adaptability for subjects.

Second, cost saving. Current neuroimaging method for diagnosing Alzheimer's costs more. Therefore, taking neuropsychological screening in advance is necessary, and then do further examination to the patients who have a high risk on Alzheimer's disease.

Third, high accuracy. Neuropsychological index can test the subject's visual, auditory and tactile cognitive abilities, rather than indirectly inferred through questionnaires.

However, this experimental method also has disadvantages, such as survey conditions are difficult to unify and the operation is too complex. To solve this problem, researchers invented a tactile testing equipment which can improve the efficiency and accuracy of neuropsychological examination, and reduce the difficulty of surveying at the same time (Yang, 2012, 2015). This equipment diagnoses MCI by subject's ability that can distinguish different tactile stimuli.

DEMENTIA LANGUAGE PERFORMANCE

Language Performance with Alzheimer's Disease

The cause of Alzheimer's disease is brain degeneration, which occurs at a much faster rate than the normal rate of aging. Although the pathology of Alzheimer's disease is different from that of aphasia, the symptoms of Alzheimer's disease in different stages are similar to the different types of aphasia; thus, we can learn from the research experience of aphasia. Currently, the disease cannot be cured (Selkoe, 2012), but it can be intervened through drugs. Researchers have discovered factors that influence the age of onset and have identified a series of cognitive training methods: a non-drug treatment for this disease prevention intervention, in which foreign language training is one of the most important cognitive training methods.

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Alzheimer's disease is not equivalent to dementia; however, it is the most common type of dementia. Currently, many researchers are focusing on Alzheimer's disease because the proportion of patients with Alzheimer's disease accounts for approximately 70% of the total patients with dementia. Moreover, Alzheimer's disease is caused by brain degeneration, and this type of dynamic process of change has more research value.

Alzheimer's disease seriously affects the patient's language skills in the late stages of illness. Outsiders do not easily perceive the patient's condition in early illness, but patients themselves have a feeling and will use certain strategies to avoid the loss of verbal communication function (Bayles 1982). As the disease progresses, the patient will have more obvious language problems, such as naming obstacles. The main impaired language ability problem of patients with mid-term Alzheimer's is expressing one's intended meaning. Fluency, pronunciation, and grammar are not problems, but the ability of description is damaged. Late in the illness, the patient's language is completely meaningless.

Language Performance in Patients with Other Sub-Types

Pick's disease is another multiple sub-type of presenile dementia. Researchers have found that the language performance of patients with Pick's disease is different from that of patients with Alzheimer's disease. Language skills are greatly impacted in early illness (Holland, 1985). In late illness, patients with Alzheimer's disease will have the same performance as patients in the early stage of Pick's disease. The effect of sub-cortical dementia on language ability, such as in Parkinson's disease, does not have as much of an effect as that of cortical dementia (Bayles, 1982; Luo 2001).

COGNITIVE DIFFERENCES OF BILINGUALS AND MONOLINGUALS

A bilingual person is someone who can communicate in two languages. According to the mastery of the language, they can be divided into balanced and unbalanced bilinguals. Balanced bilinguals can maintain and master two languages at a similar level. Unbalanced bilinguals can master two languages, but one of the languages is more dominant. Prior studies have shown that bilinguals differ from monolinguals in cognitive ability. Researchers compared bilinguals and monolinguals and found that both bilinguals and monolinguals have advantages and disadvantages in cognitive ability.

Language Cognitive Differences

Some researchers believe that bilinguals have disadvantages in language ability. Since the 1960s, many studies have supported this view (Hakuta, 1986; Gollan, Montoya 2002; Lvanova 2008). For example, bilinguals cannot keep up with monolinguals on the following aspects: speed and fluency in picture naming, language fluency, word recall, and other aspects of the development of child language ability.

Li (2012) stated that compared with monolinguals, bilinguals have the following disadvantages: first, second language learners have a slower learning speed. Researchers found that this condition exists only in early child bilinguals and that the situation will be improved after attending school; however, they are still at a disadvantage in language examinations. Second, in terms of vocabulary, bilinguals are limited compared with monolinguals. (Páez Tabors & López 2007; Colier 1995, French & Llorente 2008). In

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both adults and children, bilinguals' vocabulary is smaller than that of monolinguals (Bialystok, E. Barac, R. Blaye, A. & Poulin-Dubois, D., 2010).

Conversely, some researchers believe that second language learners have no disadvantages in language ability. Petitto (2009) believes that bilingual children do not differ from monolingual children regarding language learning speed. Moreover, some researchers believe that adults' disadvantages in the vocabulary of their second language will gradually disappear (Hamers & Blanc, 2000).

However, some research shows that bilinguals have advantages in language ability. The studies of Blumenfeld (2011), Bosch (2001), Costa (2004), and Kaushanskaya (2009) have validated this view. These researchers found that bilinguals received better results in the following tasks: bilingual discrimination, language switching, and new word learning. In addition, bilinguals were more dominant in meta-language capability (Bialystok, 2003; Baker, 2001).

Both bilinguals and monolinguals display different performances in cognitive ability. For tasks involving only one language, monolinguals have an advantage over bilinguals. If the task involves cross-language, language learning, or meta-language capability, bilinguals are more dominant.

Central Executive Functions of Bilinguals

Central executive function is responsible for the processing mechanisms that occur when humans process various types of information. It is responsible for attention and the inhibition of the conversion of control (Baddeley, 2010). Bilinguals have more obvious advantages in nonverbal cognitive tasks, particularly in terms of attention selection and cognitive control (He, 2011).

Specifically speaking, there are three aspects to the advantages of bilinguals (Li, 2011). First, it is easier for bilinguals to concentrate and inhibit other irrelevant interferences. This advantage is shown in both verbal tasks and non-verbal tasks (Bialystok 2010; Morereno, Bialystok, Wodniecka, & Alain, 2010). Second, bilinguals have advantages in attention allocation, such as in task switching (Prior & Mac Whinnry, 2010). Third, bilinguals' short-term memory capacity is greater than that of monolinguals (Michael & Gollan, 2009).

A study has indicated that Broca's area, which exists in the prefrontal cortex, has executive control function regarding language function (Bialystok, 2005). Moreover, there are interactions between these two functions. In addition, Bialystok found that in conflict control tasks, bilinguals are dominant and activate more brain regions. Diamond believes that when using one language, bilinguals must inhibit the activation of the other language, which indicates that bilinguals are engaged in control suppression training throughout their lives (Jared, 2010). Under brain training, bilinguals will have better central executive function. As bilinguals continue to use both languages, the cognitive ability and processing modes of the brain will become exercised and improved.

THE EFFECT OF BILINGUAL EXPERIENCE ON DEMENTIA

In a study that strictly controlled occupation, gender, immigrant experience, language level and other factors, the average onset age of dementia in bilinguals was postponed by four years; in addition, the onset age in Alzheimer's patients was postponed for five years (Bialystok, 2007, 2010). A researcher from India (Suvarna, 2013) classified different sub-types of dementia and then observed the effects of bilingual experience on dementia. He found that Alzheimer's disease, vascular dementia and frontotem-

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poral dementia are delayed in onset as a result of bilingual experience. Even illiterate patients benefited from their bilingual experience with postponed onset. The question becomes: how can the bilingual experience resist dementia?

Researchers found that cognitive abilities are not affected in approximately 25% of the elderly (Esiri, 2001) in whom brain physiological degeneration has reached the clinical criteria for Alzheimer's disease. This indicates that some people have stronger resistance to brain degradation. Stern proposed a hypothesis called cognitive reserve (Stern, 2002). If dementia patients receive more training before onset, this training will slow down the speed of the onset.

We can assume that when using language, bilinguals' brains receive more training than monolinguals; thus, their central control is enhanced. More training results in more reserves in the brain. Consequently, bilinguals who have better control and more brain reserves have an advantage over monolinguals.

However, recently, researchers have doubted the bilingual effect against dementia. Researchers found that the bilingual experience of Spanish users cannot combat dementia (Zahodne, 2014).

FUTURE RESEARCH DIRECTIONS

Research on bilingualism and dementia has continued in recent years, but controversy remains in the following areas.

At present, researchers believe that the bilingual experience does not play a significant role in defense against dementia. If we can obtain a more detailed distinction of the language level of bilinguals, we will have more accurate answers. Gollan found that the higher language levels of bilinguals resulted in lower possibilities of suffering from dementia (Gollan, 2011). Previous studies have shown that balanced bilinguals have more obvious advantages than unbalanced bilinguals in cognitive ability. Thus, in terms of resistance to dementia, do balanced bilinguals still have advantages? Additionally, which level must unbalanced bilinguals reach to effectively resist Alzheimer's disease?

Because it is possible that bilingual experience can resist dementia, is it possible to reduce the risk of suffering dementia by learning a foreign language? Research has shown that cognitive training can resist dementia. As a type of cognitive training, foreign language learning can be effective for the prevention of dementia. However, further study is necessary to determine whether the time-period, the type of language, and the language level are factors that will affect resistance to dementia. Questions remain regarding which aspects of second language ability play a significant role in resisting dementia. Indian researchers found that some respondents who are illiterate still have the ability to resist dementia, similar to bilinguals who are literate.

Is there a possibility that the more languages people can master, the greater the ability of people to resist dementia? This issue remains a controversy. Chertkow's (2010) study shows that each additional language can delay the onset of Alzheimer's. However, Suvarna (2013) found that in terms of resisting dementia, multilinguals do not have a significant advantage compared with bilinguals. This issue is meaningful because in non-English speaking countries, students currently spend a significant amount of time learning English; thus, they can be considered unbalanced bilinguals. If people who can master two or more foreign languages have a greater ability to resist dementia, learning a new foreign language is significant because those people can more effectively resist dementia. If there is no evidence to support this view, then there is no need to learn a new foreign language to reduce the risk of dementia.

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CONCLUSION

Currently, language studies on dementia are still being conducted. Researchers in every field are working on this subject. Researchers have found that bilinguals and monolinguals display differences in many cognitive aspects throughout life. There is an even greater need for bilingual word-guessing activities that cause speculation in the case of incomplete information; however, this can lead to the degeneration of the brain and missing information, and this lack of knowledge will result in incomplete information. There are many strengths and weaknesses in the different cognitive abilities of bilinguals and monolinguals. The brains of bilinguals and monolinguals function differently. The cognitive ability and brain differences appear to be caused by learning language. Language learning is a type of cognitive training. A number of studies have shown that cognitive training can reduce the risk of Alzheimer's; therefore, people who learn a second language should have this ability. However, some researchers have questioned whether bilingualism can reduce the risk of dementia; thus, a more detailed study is necessary.

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KEY TERMS AND DEFINITIONS

Alzheimer's Disease: An onset of dementia that results in memory, thinking and behavioral problems. Alzheimer's disease develops slowly and becomes worse as time goes on, becoming severe enough to interfere with daily life. Alzheimer's is the most common form of dementia, accounting for 60 to 80 percent of dementia cases. Although the most important risk factor for Alzheimer's is age and most people who suffer from Alzheimer's disease are 65 years old or older, this disease is an abnormal result of aging. However, old age is not the only factor that results in Alzheimer's disease. Approximately 5 percent of people with this disease have early-onset Alzheimer's disease (presenile dementia), which often occurs by age 40 or 50. Alzheimer's disease is a progressive disease that causes deterioration over several years. In the early stages of Alzheimer's disease, memory loss is mild, but in the last stage of Alzheimer's disease, individuals lose their ability to respond to the environment. Alzheimer's disease is the sixth leading cause death in the US. When a patient has had Alzheimer's disease for eight years, their symptoms become obvious to others, but the patient can survive for 4 to 20 years with the disease. There is no cure for Alzheimer's disease, but we can continue to research the symptoms to alleviate the worsening of dementia symptoms and improve the quality of life for those with Alzheimer's disease. However, there is an ongoing effort to find a better way to treat Alzheimer's disease (Wiki.org *Alzheimer's disease* https://en.wikipedia.org/wiki/Alzheimer%27s_disease).

Bilingual / Multilingual: The use of two or more languages, by an individual speaker or a speaker community. Bilingualism / multilingualism is the ability of a bilingual / multilingual. There are more multi-language speakers than monolingual speakers in the world. Multilingualism is becoming increasingly common because of the development of the Internet, which promotes the ease of access to spread information. The frequency of people who use more than one language has increased, thus promoting the necessity to master other languages (by Wiki.org *Multilingualism* https://en.wikipedia.org/wiki/Multilingualism).

Cognitive Reserve: Describes the ability to resist damage to the brain using the mind. There are two models that can be used to explore the concept of "reserve": brain reserve and cognitive reserve; these terms are often used interchangeably in the literature. Using a computer analogy, brain reserve and cognitive reserve can be thought of as hardware and software respectively. At present, all of these factors are thought to contribute to global reserves. Cognitive reserve is usually used to refer to the brain and cognitive reserve in the literature. (Wiki.org *Cognitive reserve* https://en.wikipedia.org/wiki/Cognitive_reserve).

Dementia: A cluster of diseases that interfere with daily life because a person's mental abilities decline. Dementia is not a specific disease; it is a general term that describes a wide range of use in thinking skills severe enough to interfere with a person's ability. Dementia symptoms can vary widely, but at least two of the following core mental functions must be significantly impaired to be diagnosed with dementia: Memory, Communication and language, Ability to focus and pay attention, Reasoning and judgment, and Visual perception. There are many areas of the brain that are responsible for different

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functions. When a particular area is destroyed, the function of that area cannot be implemented properly. The cause of dementia is brain cell damage. This damage can affect how brain cells communicate. When brain cells cannot communicate properly, mind, behavior and emotion are all affected (Alz.org *what is dementia* http://www.alz.org/what-is-dementia.asp).

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Section 2

Early Detection and Diagnosis

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Chapter 7
Cognitive Functions in the Geriatric Population

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ABSTRACT

This chapter describes how one of the challenging issues of clinical diagnosis is distinguishing between the cognitive deficits manifested in normal aging, depression, mild cognitive impairment (MCI) and dementia. The diagnostic challenge is that there is a great deal of overlap in the symptom constellations of these conditions. It is thus important to establish conceptual and clinical criteria with sufficient predictive validity to accurately identify differences and similarities in cognitive states to justify initiation of appropriate treatments.

INTRODUCTION

The world population continues to grow older rapidly as fertility rates have fallen to very low levels in most world regions and people tend to live longer. When the global population reached 7 billion in 2012, 8% were aged 65 and over. In 2015, 3 years later, the older population rose by 55 million and the proportion of the older population reached 8.5 percent of the total population (He, Goodkind & Kowal, 2016). Old age makes one susceptible to a gamut of diseases and disorders. While some of them affect the physical functioning, others affect mood and cognitive functioning, casting a serious impact on quality of life, daily functioning and independence. Changes in cognition with aging are not universal and there is considerable variability. With increase in age, decline in cognitive ability becomes more and more pronounced. Age related decline of abilities of memory, attention and executive function have been most widely investigated. More pronounced deficits in these and other cognitive domains have been reported

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in mild cognitive impairment, depression and dementia. However, there is a great deal of overlap in the symptoms of the stated conditions, making it difficult to differentiate between them (see Table 1).

Further, these cognitive abilities (especially executive functioning) are directly related to independence of performing activities of daily living. Thus, reiterating the need to maintain proficiency of the same. However, literature has revealed impairment in the same, thus pointing to dependence on others. However, a common misconception is that loss of abilities like memory, attention, and other mental facilities that help us to think clearly and maintain social relationships, decline inevitably, and become untreatable as we age. Increasing number of studies suggest that the brain is malleable even in later life (Kueider & Rebok, 2014). Thus, the authors propose to write a chapter on the similarities and differences in cognitive functioning of the geriatric population with respect to normal aging, mild cognitive impairment, depression, and dementia. A clear distinction between these is pivotal not only in terms of creating awareness but also from the perspective of diagnosis and rehabilitation.

Table 1. Comparison of cognitive deficits in normal aging, mild cognitive impairment, depression and dementia

Cognitive Domain	Normal Aging	Mild Cognitive Impairment	Depression	Dementia
Memory	x	x	x	x
Attention	x	x	x	x
Language		x	x	x
Executive Function	x	x	x	x
Visuospatial Ability	x	x	x	x
Psychomotor Ability		x	x	x

BACKGROUND

Cognitive change as a normal process of aging has been well documented in the scientific literature. Mental abilities change throughout life, first as a result of brain maturation and later with aging of brain cells. Some cognitive abilities, such as vocabulary, are resilient to brain aging and may even improve with age. Other abilities, such as conceptual reasoning, memory, and processing speed, decline gradually over time. There is also significant variation among older adults in the rate of decline in some of these abilities, such as measures of perceptual reasoning and processing speed (Harada, Love & Triebel, 2013). Although differences between the young and elderly can be shown in some cognitive areas, declining ability does not translate into impairment of daily activities. These changes are subtle. However, these changes can be noted on cognitive testing in terms of severity of impairment (Example: On cognitive testing, when scored based on age and education matched norms, an individual with MCI is more likely to score below the normal performance of ± 1 standard deviation. Further, the differences are sometimes so subtle that that some MCI patients may reveal an overall 'normal' score, however, reflecting certain affected sub domains of cognitive functioning). MCI definitions can be broadly classified as amnestic and non-amnestic. Amnestic MCI is characterized by a primary memory disorder with less-impaired function in other neurocognitive domains (Lopez et al., 2003). Non-amnestic MCI, on the other hand,

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is characterized by impairment in 1 or more neurocognitive domains other than memory, including language, executive function, and visuospatial skills (Petersen, 2004). While most studies indicate that amnestic MCI progresses to Alzheimer disease (AD), non-amnestic MCI is more likely to progress to dementias other than AD (Steffens et al., 2008).

Depression is a disorder of mood that produces sad feelings, negative thoughts, and disruptions of sleep, appetite, thinking, and energy level. Although most clinicians diagnose depression based on a categorical approach like that in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Revision (DSM-V) (APA, 2013), it is important to recognize that any depressive symptoms that impair cognition or activities of daily living (ADLs) are clinically significant (Potter & Steffens, 2007).One problem with understanding the relationship of depression to MCI is that depression has often been excluded from the definition of this condition. Although this exclusion initially occurred because depression was viewed as a "pseudo-dementia" that confounds the detection of "true" impairment, research now indicates a high rate of co-occurrence between depression and MCI that raises the risk for persistent cognitive impairment and dementia (Potter & Steffens, 2007). Dementia refers to an outcome of changes in the brain that produce dysfunction in memory, thinking, communication, and praxis that impairs an individual's ability to function in daily life. Different types of Dementia are characterized by cognitive impairment in different domains (Table 1). Although research has not yet resolved whether depression is more accurately characterized as a risk or prodrome of dementia, the important clinical issue is that the 2 conditions are frequently linked; thus, the presence of depression, particularly of late onset, raises attention to screening for cognitive impairment as part of a long-term approach to care. One of the challenging issues of clinical diagnosis is distinguishing between individuals with normal aging, depression, MCI and dementia. The diagnostic challenge is that there is a great deal of symptom overlap between these conditions. For instance, the symptom constellation of decreased concentration and processing speed, irritability, sleep loss, fatigue, and anhedonia that occur in depression are similar to the constellation of memory loss, agitation, sleep-wake disturbance, and apathy that often occur in dementia (Potter & Steffens, 2007). Despite similarities between these conditions, careful attention to clinical history and presentation can help distinguish between them.

In the sections to follow, the authors attempt to provide an outline of the neuropsychological functioning (definitions in Table 2) and impairment as a result of normal aging, mild cognitive impairment, depression and dementia.

NORMAL AGING

Intelligence

Crystallized intelligence is less subject to decay as a result of rehearsal, practice and use of knowledge. These abilities remain relatively stable and may even gradually improve in the later decades of life as they are a product of the accumulated knowledge (Zillmer, Spiers & Culbertson, 2007). In contrast, fluid abilities (table) which involve novel reasoning and efficiency in solving new problems have been found to peak around the third decade of life and decline thereafter (Harada et al., 2013). It has been found that executive function, processing speed, memory and psychomotor ability fall under this broad domain (Harada et al., 2013).

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Language

It is a complex cognitive domain composed of crystallized and fluid cognitive abilities. This ability remains stable over time with even an increase in vocabulary with age (Hayden & Welsh-Bohmer, 2011; Singh-Manoux et al., 2012). However, an exception to this general trend of stability is naming (ability to see a common object and name it) and verbal fluency (ability to generate or perform words for a certain category) (Singh-Manouxet al., 2012; Salthouse, 2010).

Memory

The most common complaint among older adults is that of change in memory. Like attention, memory is not a unitary construct; some kinds of memory remain relatively intact with age while others show significant declines (Glisky, 2007). Age related decline in this domain may also be a function of decline in processing speed, cognitive control or use of mnemonic devices. Unlike declarative memory, non-declarative memory remains unchanged in the later decades of life (Harada et al., 2013). Episodic memory has been found to be the most susceptible to the aging brain and most affected my normal aging (Glisky, 2007). Although many older adults believe that their memories for remote events are better than their memories for recent events, it is likely that older memories have become more gist like, retaining the general core information but lacking other details. More problematic for older adults is remembering context or source information: where or when something was heard or read, or even whether something actually happened or was just thought about. Semantic memory however, has been found be intact and even enhanced in older adults. Autobiographical memory which involves memory of one's past personal experiences is both episodic and semantic in nature. Literature revels that this ability is largely preserved in older adults (Rubin, 2000).

In general, older adults show normal acquisition of procedural skills in both motor and cognitive domains and retain them across the lifespan. With high levels of expertise, there is often little slowing of skilled performance with age, although some individual components of the skill may decline (Salthouse, 1984). Older adults do quite well on Prospective memory daily tasks, using a variety of external aids such as calendars and appointment books to remind themselves of these activities (West, Herndon, & Covell, 2003).Prospective memory may also rely on some aspect of working memory to maintain future intentions over time and likely also involves divided attention, both functions that show age-related deficits (Glisky, 2007).Memory can also be understood through the stages of encoding, storage and retrieval. While encoding (rate of acquisition of new information) and retrieval (ability to recall learnt information) declines with age, retention of information that is successfully encoded (storage), remains relatively stable in older adults.

Executive Functions

Executive Functions are an umbrella term for the three core EFs as agreed upon by different researchers: Inhibition (inhibitory control, which includes self-control (behavioural inhibition) and interference control (selective attention and cognitive inhibition)), working memory (WM), and cognitive flexibility (also called set shifting, mental flexibility, or mental set shifting) (Diamond, 2012). From these, higher order EFs of reasoning, problem-solving and planning are built (Collins & Koechlin, 2012; Lunt et al., 2012). These functions make it possible to play with mentally with ideas, take time to think and act,

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Table 2. Definitions and examples of cognitive domains

Cognitive Domain	Sub Domain/ Ability	Definition	Example
Intelligence	Fluid Intelligence	Novel reasoning and efficiency of problem solving or responding to abstract ideas	Coming up with a new approach to solve a problem at hand
	Crystallized Intelligence	Stored knowledge and habitual ways of acting or solving problems built up over a lifetime	Knowing the answer to the first prime minister of India
Language	Expressive Language	Ability to produce language	Giving a string of comprehendible instructions
	Receptive Language	Understanding or recognition of linguistic information	Understanding a string of instructions
Memory	Declarative (explicit) • Semantic • Episodic (Autobiographical)	Conscious recollection of facts and events • General world knowledge accumulated throughout life • Memory for personally experienced events that occurred in a particular place and time	• Knowing the year in which India got Independence • Remembering how one celebrated their 18th birthday
	Non- Declarative (implicit) • Procedural • Prospective	Memory for how to do things • Knowledge of skills and procedures • Remembering to perform intended actions in the future	• Remembering how to ride a bicycle • Remembering to take medicine after meals
Executive Functions		Group of highly interrelated functions that include planning, initiation, and regulation of behavior, working memory, response inhibition, and task switching	Planning a complex multi staged activity and carrying it out successfully
Working Memory		Active memory system on which information is manipulated and assembled to help us comprehend language, make decisions and solve problems	Spelling a word backwards
Visouspatial abilities/ Construction		Object perception, the ability to recognize familiar objects and spatial perception, the ability to appreciate the physical location of objects either alone or in relation to other objects/ ability to put together individual parts to make a coherent whole	Navigating through a map in an unfamiliar location
Attention	Selective Attention	Ability to attend to some stimuli while disregarding others that are irrelevant to the task at hand	Focusing on reading a book in a noisy coffee house
	Divided Attention	Processing of two or more sources of information at the same time	Talking on the phone while driving
	Sustained Attention	Ability to maintain concentration on a task over an extended period of time	Concentrating throughout a 3 hour lecture

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meet unanticipated and novel challenges, resist temptations and stay focused. These skills are essential for our mental and physical health, success in life and in our social, cognitive and psychological aspects of development. Numerous studies have implied a decline in these abilities as a result of aging (Apfelbaum, Krendl & Ambady, 2010).

Working Memory

Working memory is a multidimensional cognitive construct which is an active memory system on which information is manipulated and assembled to help us comprehend language, make decisions and solve problems. This has been hypothesized as the fundamental source of age-related deficits in a variety of cognitive tasks, including long-term memory, language, problem solving, and decision making. In fact, the majority of theories of cognitive aging seem to implicate working memory (Baddeley, 2000). Older adults exhibit significant deficits in tasks that involve active manipulation, reorganization, or integration of the contents of working memory. Although the mechanisms underlying these age-related deficits are as yet poorly understood, the effects of such deficits are far-reaching.

Attention and Processing Speed

Processing speed is the speed with which cognitive activities are performed. Decline in this ability in the later years of life affects the above stated cognitive functions as well (Salthouse, 2010; Salthouse, Fristoe, Lineweaver, & Coon, 1995; Carlson, Hasher, Connelly & Zacks, 1995). Some form of attention is involved in virtually all other cognitive domains, except when task is habitual. Declines in attention can therefore have broad-reaching effects on one's ability to function adequately and efficiently in everyday life. Selective attention refers to the ability to attend to some stimuli while disregarding others that are irrelevant to the task at hand. Deficits found in many of selective attention tasks can be largely attributed to a general slowing of information processing in older adults rather than to selective attention deficits per se (Glisky, 2007). Divided attention tasks require the processing of two or more sources of information or the performance of two or more tasks at the same time. It has usually been associated with significant age-related declines in performance, particularly when tasks are complex.

Visuospatial Ability/ Construction

This group of cognitive functions involves the ability to understand space in two and three dimensions. Literature reveals impairment in tasks that require visual construction abilities. However, visuospatial abilities are believed to remain intact (Howieson, Holm, Kaye, Oken & Howieson, 1993).

MILD COGNITIVE IMPAIRMENT

MCI has been described as a cognitive disturbance representing the transitional or prodromal phase between normal aging and Dementia (Rivas-Vazquez, Mendez, Rey & Carrazana, 2004). Based on criteria by Petersen et al. (1999), Rivas-Vazquez et al. (2004) have devised a mnemonic device (SOUND) for the same:

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- **S**ubjective memory complaints.
- **O**bjective memory deficit.
- **U**naffected overall cognition.
- **N**ormal capacity to perform Activities of Daily Living.
- **D**ementia criteria not met.

With the above-mentioned factors adjusted for age and education (Diniz, Pinto & Forlenza, 2008). A Meta-analysis carried out recently reported that, patients with MCI evolve to Dementia at approximately 10% per year (Bruscoli & Lovestone, 2004). Petersen reported that, after approximately 6 years, 80% of the MCI progress to dementia (Peterson et al., 2001). Although the original criteria of MCI focussed on memory complaints the recent classification has been expanded to encompass other cognitive domains like executive function, attention, language etc. Resulting in the following sub-types of MCI: MCI single domain- memory type, MCI single domain – non-memory type, multi domain including memory impairment and multi domain without memory impairment (Winbald et al., 2004). Due to the variation in neuropsychological profiles and aetiology of the stated sub types, it is believed that their progression over time can result in different outcomes (Petersen et al., 2001). For example: Single domain amnestic MCI may be a pre-dementia stage for AD however, single domain non-amnestic MCI may be a found in transitional phases to frontotemporal dementia, dementia with lewy bodies, vascular dementia or depressive disorders (Bennett et al., 2002). The following section delineates the neuropsychological functioning in MCI.

Memory

Memory deficits form the core problem in MCI. It is however difficult to derive a standard equation of these memory problems given the diversity in memory-related functions. Conceptually, for encoding of any form of memory, attention is the most important prerequisite. It is being increasingly recognized that attention deficits are prevalent in MCI (Yanhong, Chandra &Venkatesh, 2013). Studies have reported reduction in episodic memory as the most prevalent in MCI (Petersen, 2004). Decline in prospective memory (ability to remember and perform an intended action at an appropriate point in the future) can also serve as an early sign in of memory failure (Spíndola & Brucki, 2011). This type of memory is relevant for social functioning, adherence to treatment, and carrying out instrumental activities of daily living (Chasteen Park & Schwarz, 2001; Smith, Del Sala, Logie & Maylor, 2000). Additionally, both familiarity based memory and recollection have been found to be impaired in MCI (Wolk, Mancuso, Kliot, Arnold & Dickerson, 2013; Algarabel González et al., 2012). Studies have also shown that MCI patients have difficulties in all the stages of verbal memory processing including acquisition, consolidation, and recall stages (Hutchens et al., 2013). These memory deficits are not limited to the amnestic MCI, but are also present in non-amnestic MCI, albeit at lower intensities (Yanhong et al., 2013). However, subjects with MCI are often aware of their memory deficits (Seelye, Schmitter-Edgecombe & Flores, 2010). Thus, this meta-memory skill can be utilized to design interventions involving compensatory strategies for daily issues related to memory deficits.

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Executive Functions

Executive functions are a group of highly interrelated functions that include planning, initiation, and regulation of behaviour, working memory, response inhibition, and task switching (Miyake et al., 2000). In contrast to the well-established finding of memory deficits in MCI, the executive function tests have revealed no-deficits on some studies to global impairments of EFs in others (Zheng et al., 2012). Analysis of day-to-day application of executive functions in MCI patients revealed impairments in episodic memory, executive function, semantic knowledge and arithmetic. At the same time, control and MCI groups performed significantly better than patients with AD on financial capacity and cognitive measures (Griffith et al., 2003).

Other Impairments

Other amnestic cognitive deficits in MCI include impairment in fluid intelligence, working memory and attention processing (Saunders & Summers, 2010, Kramer et al., 2006). Further subjects with MCI also exhibit deficits in visual personal familiarity and recognition of facial emotional expression (Jurjanzet al., 2011; Varjassyovaet al., 2013). Such deficits lead to impaired social cognition and may adversely impact the patients' efficacy in handling complex situations and tasks.

DEPRESSION

Depression is not a normal part of aging (Flint, 1994). It is a medical condition that affects many older adults and can often be successfully treated. Symptoms of depression include: low mood, loss of interest or pleasure in activities, disturbed sleep, fluctuation in weight, lack of energy, feeling of worthlessness, difficulty with concentration or decision making, noticeable restlessness or slow movement and frequent thoughts of suicide or an attempt of suicide (Palazzolo, 2015).The World Health Organization Global Burden of Disease Study ranked depression as the most burdensome disease in the world in terms of total disability-adjusted years among people in the middle years of life (Murray & Lopez 1996).It has been found that the combination of depression and cognitive impairment is present in roughly 25% of older adults and this is expected to double every 5 years after the age of 70 (Arve, Tilvis, Lehtonen, Valvanne & Sairanen, 1999). In some cases, these conditions may be related to the same underlying disorder while in others they may be relatively independent (Morimoto, Kanellopoulos & Alexopoulos, 2014). Results of a meta-analysis reveal that a history of depression doubles the risk of developing dementia later on in life (Ownby, Crocco, Acevedo, John & Loewenstein, 2006). Depression has been found to be highly prevalent in MCI and most dementias. It may be a risk factor for the subsequent development of Dementia or in some conditions, a prodromal symptom (Potter & Steffens, 2007). Some studies have shown that these patients report depression well before they report cognitive difficulties, raising the possibility that depression was a risk factor for dementia. Meta-analyses of the world literature suggested that history of depression was a risk factor for dementia (Jorm, 2001). However, studies that examine the temporal sequence reveal that although depressive symptoms preceded the onset of dementia, depression appear to be a prodrome rather than an independent predictor of dementia (Chen, Ganguli, Mulsant & DeKosky, 1999). Thus, depression might be a prodromal or early sign of dementia rather than a separate condition or risk factor for dementia. Impairment in attention, concentration and thinking ability are one of

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the key diagnostic criteria of depression. Meta-analysis on the neurocognitive deficits in depression has found impairment in domains in executive function, memory, processing speed to name a few (Veiel, 1997, Zakzanis, Leach & Kaplan, 1998). Studies reveal 33-50% of depressed individuals have cognitive impairment (Butters et al., 2004; Reischies & Neu, 2000).

Memory

Memory has been the most assessed function for evaluation of cognitive differences between depression and dementia. Evidence suggests deficits in episodic memory, learning and explicit verbal and visual memory in depression patients. However, other memory functions appear to be spared (Danion, Kauffmann-Muller, Grange, Zimmermann & Greth, 1995; Bazin, Perruchet, De Bonis & Feline, 1994). It is imperative to note here that these memory deficits are significantly mild when compared with dementia (Kang et al., 2014). Taking this comparison forward depressed patients show relatively mild impairment on recognition memory, encoding, forgetting and psychomotor speed (Hart & Kwentus, 1987; Miller & Lewis, 1977). Literature reveals that most common memory deficits being those related to tasks of recall or remembering. However, the sample sizes of these studies have been relatively small and the methodologies varied. Additionally, these memory deficits in spite of being significantly worse than normal individuals are comparably better than those associated with dementia. Most researchers have suggested that such differences represent general cognitive inefficiency and attention problems rather than a fundamental lack of ability. This can be seen in the differences between depression and dementia patients as well as in the temporariness of these deficits in the clinical picture of depression (Kang et al., 2014).

Executive Functions

Executive function impairment in depression have been studied widely. It has been found that deficits in planning, organizing, set shifting etc. have predicted low antidepressant response and functional disability. Further, such deficits occur at a rate of 20-30% in such patients (McIntyreet al., 2013). In general, significant EF impairments have been observed in subjects with more severe depression (Raskin, Friedman & DiMascio, 1982; Friedman, 1964). Processing speed impairment is another important executive function deficit observed in depression. It has been found that such impairments partially mediate the effect of depression on functioning. A more clinical outcome of this processing speed impairment is psychomotor slowing, which is almost universally found in the depressed patients, irrespective of the number of episodes (Brown et al., 2013). However, differences between normal and depressed patients on executive functioning are sufficiently subtle to not significantly influence scores on standard cognitive screening instruments (Bieliauskas, Costello & Terpenning, 1991; Bieliauskas, Boczar & Lamberty, 1991).

Speech and Language

Small numbers of studies have specifically examined speech-language function in elderly depressed patients. While most of the tasks used to measure cognitive abilities in above-mentioned studies have obvious receptive and expressive language components, it has been found that depressed patients perform better than patients with dementia on naming, repetition, general reading skill, syntax, and auditory verbal comprehension. At the same time, normal individuals tend to show better language performance

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than depressed patients overall, though these differences were considerably less obvious than those noted between depressed and AD patients (Gray, Rattan & Dean, 1986).

PSEUDO-DEMENTIA AND DELIRIUM

Pseudo-dementia is defined as cognitive impairment that mimics dementia however diminishes upon remission of depression (Morimoto et al., 2014). These patients have been found to have severe, however late onset of depression but mild dementia. Over decades of practice, clinicians have observed that findings of neuropsychological tests may not precisely match subjective complaints in MCI. In contrast, dementia patients are unconcerned about memory problems but reflect poor performance on testing. More differences between these patients have been recorded in order to aid the process the diagnosis (Table 3). Further, studies that examined depressed cognitively impaired patients over time, found that a significant proportion continued to experience progressive cognitive decline even after remission of depression (Reifler, 2000). Thus suggesting that the impairment recorded during depression was not 'pseudo' but a warning signal for more permanent cognitive decline in the future. Another condition that if often confused in dementia is *delirium* which is a state of severe confusion and rapid changes in brain function. However, it is important to differentiate between their key characteristics (Table 4).

Table 3. Difference between Dementia and Pseudo- dementia

No.	Dementia	Pseudodementia
1.	Forgetful behavior usually reported by family member	Detailed account of cognitive impairment provided
	Unconcerned about memory problems	Prominent subjective memory loss
2.	Emphasis on achievements	Emphasis on disability
3.	Unconcerned appearance	Communication of distress
4.	Usually liable affect	Severe depression
5.	Errors on examination after genuine attempts	Frequent "don't know" answers
6.	Recent memory impaired	Recent memory not impaired
7.	Confabulation may be present	Confabulation is rare
8.	Consistently poor performance on cognitive testing	Variability in performance on cognitive testing
9.	History of depression uncommon	History of manic/ depressive episodes may be present
10.	Aphasia, apraxia, agnosia are common	Language, recognition and motor skills are intact however, reduced psychomotor speed, sustained attention and executive function deficits are noted on neuropsychological testing

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Table 4. Difference between Dementia and Delirium

No.	Dementia	Delirium
1.	Gradual onset (months to years)	Acute onset (hours to days)
2.	Chronic progression	Fluctuating course
3.	Clear consciousness	Impaired consciousness
4.	Impaired attention	Fluctuating impairment in attention
5.	Recent and remote memory impaired	Recent and immediate memory impaired
6.	Depressed mood, apathy	Fluctuating moods- anger, fear
7.	Difficulty in abstraction, judgment impaired	Fragmented and disorganized thinking
8.	Misperceptions present	More misperceptions, illusions, delusions and hallucinations than Dementia
9.	Withdrawn, agitated psychomotor activity	Hypo or hyper kinetic psychomotor activity

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DEMENTIA

Dementia does not describe a specific disease, but rather describes a clinical syndrome characterized by a loss of previously acquired cognitive functions that adversely affect an individual's ability to complete day to day activities (Schoenberg & Scott, 2011). The decline in cognitive functioning is greater than what occurs during the normal aging, depression and mild cognitive impairment. The most common types of dementia are: Alzheimer's disease, vascular dementia, Dementia with Lewy Bodies, fronto temporal dementia and Parkinson's disease with dementia. Some of these degenerative conditions have neuropathological signs that differentiate them from other conditions (e.g., tau mutations in AD), while others are a secondary result of multiple illnesses that have a primary central nervous system deterioration (e.g., hypertension and diabetes in vascular dementia). Dementias can be caused by a variety of medical (e.g., cerebrovascular, metabolic) and psychiatric illnesses (e.g., substance abuse) (Schoenberg &Scott, 2011). The cognitive deficits in dementia are not confined to memory and may include impairment in language, praxis, organisational skills, attention and judgement. Significant cognitive impairment results in loss of social functioning. Behavioural changes also occur that can be particularly troublesome to the family (Gifford & Jones, 2009). Different forms of dementia have characteristic presentations and patterns of cognitive change (Table 5).

A detailed history of symptom onset and the course of its progression can be very valuable in the differential diagnosis of dementia.

ISSUES, CONTROVERSIES, AND PROBLEMS

Thus, there is little knowledge and awareness about the subtle differences between normal aging and mild cognitive impairment as most elderly give into their fate of old age and believe the experienced level of decline and impairment is inevitable. Further, there is ongoing debate about whether depression is a risk factor for dementia or a prodrome of this condition. Additional uncertainty exists as depression in elderly

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Table 5. Cognitive deficits in sub types of Dementia

Domains	Dementia				
	Alzheimer's Disease	**Vascular Dementia**	**Dementia With Lewy Bodies**	**Fronto-Temporal Dementia**	**Parkinson's Disease With Dementia**
Behavioral Observations	Irritability, social withdrawal	Symptoms of depression and apathy are common	Visual hallucinations and other psychiatric symptoms may be present	Prominent personality changes	Apathy and depression are common
Attention	Simple Attention intact Complex Attention Impaired	Often both impaired	Gross Impairment	Simple Attention intact Complex Attention Impaired	Simple Attention intact Complex Attention Impaired
Learning/ Memory	Prominent and progressive impairment especially for recent events	Severe impairment. Consolidation, free recall impaired Recognition intact	Learning impaired Visual, immediate and delayed memory impaired	Late impairment in immediate free recall	Slowed learning Encoding impaired
Language	Impaired fluency, naming, reading, comprehension Vocabulary intact	Variable degree of impairment	Verbal fluency and naming impaired	Varied impairment Fluency, naming, comprehension impaired	Impaired with dysarthria, hypophonia and micrographia Verbal fluency and naming impaired Repetition and comprehension intact
Visuo-perpectual/ visuo-constructional Ability	Impaired and worsens as disease progresses	Variable degree of impairment, if at all present	Severe impairment as disease progresses	Late impairment	Impairment worsened by motor deficits
Executive Function	Progressive difficulty in handling complex reasoning based tasks	Varied severity of impairment	Moderate to severe impairment may be present	Severe perseveration	Mild to moderate impairment present
Sensory/ Motor Ability	Olfaction may be impaired Dyspraxia common	Gait instability and rigidity	Simultaneous or late development of parkinsonian features	Poor motor programming may be present	Parkinsonian features before development of Dementia

Dysarthria: Slurred or slow speech which can be difficult to understand; Hypophonia: Soft speech, especially resulting from a lack of coordination in the vocal musculature.

Micrographia: Abnormally small, cramped handwriting, or the progression to continually smaller handwriting.

Dyspraxia: Difficulty in activities requiring coordination and movement.

(Adapted from Schoenberg and Scott, 2011 (Permission Pending); Gifford & Jones, 2009)

causes cognitive impairment in its own right (Butters et al., 2000). Depression could result from a number of factors. It could be a psychological response to an individual self-awareness of cognitive deficits,

misinterpretation by others of a natural response to withdraw from previously enjoyed activities of dementia patients who find them hard and effortful, response to a prospect of having an incurable progressive disease (Ganguli, 2009). Thus, pointing to the need to draw up a detailed medical, psychiatric and psycho-social history of patients.

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SOLUTIONS AND RECOMMENDATIONS

Due to lack of insight in patients, patients and informants (such as family members) may report conflicting views regarding the presence and severity of symptoms (thus implying the importance of being cognizant of early signs, Table 6) (Nehra & Bajpai, 2015). A history of cognitive changes over time, validated by knowledgeable informants, is therefore important for identifying the first diagnostic criterion. Critical features that may clarify a cause are onset, trajectory, time-course, and nature of the cognitive symptoms. Very rapid cognitive decline (e.g., weeks to months) is not typical of MCI due to AD, and should raise concerns for other causes, such metabolic disorders (McCarten, 2013; Holsinger, Deveau, Boustani & Williams, 2007). Thus, as mentioned above, cognitive impairment as a result of MCI can affect virtually all cognitive domains (Table 5). Estimated conversion rates from MCI to dementia range from 2-31%, with a mean annual conversion of 10.2% (Bruscoli & Lovestone, 2004) with some individuals also displaying persistent MCI without converting to dementia (Schonknecht, 2011). Although, cognitive impairment associated with MCI does not hamper independent functioning in activities of daily living, research suggests that it has a significant impact on psychological wellbeing and Quality of Life (Teng, Tassniyom & Lu, 2012). Reviews also reveal the presence of neuropsychiatric symptoms (such as depression, anxiety, agitation, irritability, sleep disturbance, fatigue) in such patients (Bombois, Derambure, Pasquier & Monaca, 2010). Thus, overall impacting daily functioning in terms of financial management, driving and scheduling to name a few (Gold, 2012) more debilitating results have been found in patients with dementia. Further, as mentioned above, depression can impair an older adult's ability to function and enjoy life and can contribute to poor health outcomes. Compared to older adults without depression, those with depression often need greater assistance with self-care and daily living activities and often recover more slowly from physical disorders. Without appropriate treatment, symptoms of depression can limit an older adult's ability to achieve successful aging (Palazzolo, 2015). Thus, detection of cognitive impairment is critical and deficits that are validated by neuropsychological testing should not be ignored or considered normal manifestation of aging (Ritchie, Artero & Touchon, 2001). In order to combat these issues, cognitive rehabilitation interventions along with cognitive behavior therapy can be used increase to frequency of engaging in positive lifestyle behaviors which can be thought of as protective factors which contribute to reduced risk of impairment.

Evidence from RCTs and clinical trials suggest that aerobic exercises, mental activities and social engagement have beneficial effects on cognitive functioning (Lin, O'Connor, Rossom, Perdue & Eckstrom, 2013). These factors contribute to the 'cognitive reserve capacity' of individuals. It is a hypothetical construct used to explain how individuals vary in severity of cognitive decline when neurodegenerative changes occur (Whalley, Deary, Appleton & Starr, 2004). Further, since it is not fixed, there are opportunities for modification and enhancement of the same through above stated factors and those of education and occupational achievement. Cognitive retraining activities can be of two types: (a) Restorative cognitive retraining activities directly target cognitive compromise by restoring abilities through neuroplasticity mechanisms like repeated practice on structured tasks of specific cognitive domains (Huckans et al., 2013; Bajpai, Tripathi, Dey & Nehra, In Press) and (b) Compensatory cognitive retraining activities directly target functional deficits by teaching skills and strategies to compensate for cognitive impairments so that the impact of these deficits on daily function and QOL can be reduced. Compensatory strategies can include internal strategies (e.g., using mnemonic devices compensate for memory difficulties), external strategies (e.g., time tables and navigation devices), or environmental strategies (e.g., eliminating distracting stimuli at work) (Huckans et al., 2013; Bajpai, Tripathi & Nehra, 2015).

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Table 6. Strub and black Neuropsychological test battery components and corresponding neuropsychological tests

S.No.	Component	Description	Most Popular Tests
1.	History	Developmental, educational, social and vocational	Proforma based on clinical condition
2.	Behaviour	Attention, cooperation, level of effort, mood, rapport	Digit Symbol Substitution Test (DSST), Digit Span Test, Brief Test of Attention (BTA)
3.	Intelligence	General, verbal and non- verbal	Ravens Progressive Matrices (RPM) and Wechsler Adult Intelligence Scale (WAIS)
4.	Language	Auditory discrimination, single word and sentence comprehension, repetition	Boston Naming Test (BNT), Controlled Oral Word Association Test (COWA), Indian Aphasia Battery (IAB) and Verbal Adult Intelligence Scale (VAIS)
5.	Memory	Verbal and non- verbal memory, acquisition, immediate recall, recent and remote memory, incidental memory and recognition	California Verbal Learning Test (CVLT), PGI Memory Scale (PGIMS) and Wechsler Memory Scale (WMS)
6.	Abstract reasoning and Executive Functions	Verbal and non- verbal reasoning, problem solving, conceptual shifting	Trail Making Test (TMT), Stroop Test, Wisconsin Card Sorting Test (WCST), Iowa Gambling Test (IGT), Tower of London Test (TOL)
7.	Spatial Analysis and Constructional Ability	Paper and pencil reproduction, three dimensional constructions, reproduction from memory, visual analysis	Bender Visual Motor Gestalt Test (BVMGT), Rey Osterrieth Complex Figure Test (ROCF)
8.	Sensory Perceptual Ability	Visual, auditory and tactile perception	Same as above
9.	Geographic Orientation	Awareness of place and person	Mini Mental Status Examination (MMSE), Galveston Orientation and Amnesia Test (GOAT)
10.	Time Orientation	Awareness of time	Same as above
11.	Reading and Writing	Achievement in reading, spelling and calculation	Same as Language Tests
12.	Perceptual Motor Speed	Planning ability and concept manipulation	Finger Tapping Test (FTT), Digit Symbol Substitution Test (DSST), Bender Visual Motor Gestalt Test (BVMGT), Grooved Pegboard Test
13.	Strength	Motor strength and coordination	Same as above
14.	Personality	Focal signs	Rorschach Inkblot Test, 16 Personality Factor Questionnaire (16PF), Thematic Apperception Test (TAT), Myers-Briggs Type Indicator (MBTI)
15.	Social Functioning	Social adaptive functioning	Disease specific

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The efficacy of these activities in rehabilitating cognitive functions has been seen in older adults, patients with MCI and Dementia. However, another set of mentally stimulating activities (such as reading, playing music) that increase an individual's active participation in their day to day life and draw from their hobbies and interests have also shown promising results (Kelly et al., 2014). The importance of and encouragement to engage in these types of activities communicated is through psycho-education

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Table 7. Signs to look out for

Cognitive Domain	Early Signs
Attention	• Poor concentration • Easily distracted • Cannot hold phone number in mind • Taking too long to complete tasks
Memory	• Poor recall of recent events • Repeating self • Needs reminders
Language	• Difficulty in keeping up with conversations • Word finding difficulty • Use of vague generic terms • Comprehension difficulty
Praxis, Somatosensory and Motor Functions	• Difficulty in use of familiar tools • Difficulty with sequencing of actions
Visuospatial Functions	Difficulty navigating familiar environment
Executive Functions	• Poor task persistence • Avoidance of multi stage activities

(Morimoto, Kanellopoulos & Alexopoulos, 2014)

programs. These interventions come under the umbrella of lifestyle interventions that target modifiable risk and protective factors by directly engaging individuals in healthy lifestyle practices (such as regular exercise, nutrition) (Huckans et al., 2013).Another set on interventions known as psychotherapeutic interventions directly target neuropsychiatric symptoms like depression and anxiety through techniques like Cognitive Behavior Therapy (CBT) and traditional relaxation and mindfulness (Huckans et al., 2013) Cognitive Behavior Therapy (CBT) is a structured, short term collaborative process between the client and therapist which is directed towards solving current problems and modifying dysfunctional (problematic) thinking and behavior. The therapist adopts a variety of methods of bring about a change in the clients thought process and belief system. However, the client is not passive in this process, the interaction is structured yet collaborative. The basic idea behind CBT is that when an individual realizes that there is a more productive and adaptive way of thinking, they change their thinking which further leads to improvement in their emotional states and behavior. Vast number of studies supports the effectiveness of CBT in treating depression symptoms in elderly. Studies have also shown continued effect of the same even after 1 year of follow up (Laidlaw et al., 2008). Further, aside from counselling patients on how to deal with their symptoms, dissemination of facts and statistics can also be comforting. For example, it can be revealed that only a minority of patients will progress to dementia annually. Further, many patients with MCI (40-70%) may not even progress to dementia even after 10 years.74 Importantly, some MCI patients (15-20%) have been found to have improved cognition1-2 years later, although the latter group may still remain at increased risk of future cognitive decline (Koepsell & Monsell, 2012; Plassman et al., 2008).

Thus, holistic history taking, longitudinal follow-up and serial cognitive assessments are useful since they allow a clearer assessment of patient's true baseline and trajectory of cognitive function over time, and decrease the risk that poor performance on a single assessment due to anxiety, fatigue, or acute illness leading to a false positive diagnosis (Langa & Levine, 2014).

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FUTURE RESEARCH DIRECTIONS

Limited studies are available that point to the subtle differences between the overlapping cognitive deficits in the stated conditions. For instance, consistent findings have shown that episodic memory and executive functioning are the most sensitive measures in detecting individuals who may eventually develop Dementia (Chen et al., 2001). Further, investigators have also concluded that performance on fine and complex measures of psychomotor functioning may be as useful as traditional cognitive tests for detecting MCI, and should be incorporated in screening batteries (Rivas-Vazquez et al., 2004). However, there is still a dearth of such studies that can aid the process of differentiating between these conditions from a neuropsychological perspective (Nehra & Bajpai, 2013). Additionally, there is a dire need to investigate and standardize protocols for assessment with exhaustive history taking. Although it is not always necessary to evaluate exhaustively every aspect of mental functioning, certain critical functions should be assessed in every patient. These include level of consciousness, physical appearance, emotional status, attention, expressive and receptive language, memory, constructional ability and executive function.

History taking (Table 7) should be directed towards 4 major areas of clinical concern

- The presence or absence of the classic behavioural changes indicative of organic dysfunction (memory impairment or language disorder) must be established
- The possibility of functional psychiatric disorders must be considered
- Establish patients pre-morbid behaviour and level of functioning
- Evaluation of general medical status

CONCLUSION

Thus, the above stated conditions, namely, normal aging, mild cognitive impairment, depression, and dementia are linked closely to one another. As explained, the differences between normal aging and MCI are very subtle. Thus, in order to make the correct diagnosis, it is important to divulge more into these surface level differences and explore and evaluate sub domain differences through detailed neuropsychological assessment. However, there is a clear contrast between the cognitive functioning seen in MCI and Dementia which can most-importantly be differentiated through independence in performing activities of daily living. Further, depression is related to dementia and cognitive impairment in several ways (Ganguli, 2009):

- Both can occur together, independent from each other.
- Both can be manifestations of the same brain disease.
- Knowledge of presence of cognitive impairment can led to depression.
- Early onset of depression can be increase the probability for future development of dementia.

Although antidepressant medication is an important approach to treating depression, not all individuals respond to pharmacologic therapy, and some may experience adverse effects (Lyketsos et al., 2002). One useful approach in the context of cognitive impairment is to apply interventions that compensate for the compromised abilities. These interventions aim to reduce the symptoms, delay or prevent progression to dementia or increase the rate of conversion to normal cognition (Huckans et al., 2013).Similar ap-

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proaches to cognitive-behavioural therapy and support groups have been helpful in facilitating problem solving and reducing negative affect among individuals with early dementia (Kasl-Godley &Gatz, 2000). Thus, developing guidelines for specific type of activities, defining degree of ability reflective of intact functioning would enhance sensitivity and specificity to diagnosis and holistic assessment.

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KEY TERMS AND DEFINITIONS

Attention: It is the concentration of awareness on some phenomenon to the exclusion of other stimuli in the environment.

Cognition: Cognition is a term referring to the mental processes involved in gaining knowledge and comprehension. These processes include thinking, knowing, remembering, judging and problem-solving.

Delirium: It is a state of severe confusion and rapid changes in brain function. However, it is differentiated from Dementia by acute onset, fluctuating course and impaired consciousness.

Executive Function: Executive functions are a set of cognitive processes that are necessary for the cognitive control of behavior: selecting and successfully monitoring behaviors that facilitate the attainment of chosen goals. Executive functions include basic cognitive processes such as attentional control, cognitive inhibition, inhibitory control, working memory, and cognitive flexibility. Higher order executive functions require the simultaneous use of multiple basic executive functions and include planning and fluid intelligence.

Impairment: A state of diminished or weakened ability especially in a specified faculty/ domain

Language: Language is a formal system of communication which involves the combination of words and/or symbols, whether written or spoken, as well as some rules that govern them.

Memory: Memory is the faculty of the mind by which information is encoded, stored and retrieved.

Neuropsychological Rehabilitation: Neuropsychological rehabilitation can be defined as teaching or retraining activities aimed at improving and alleviating symptoms associated with brain damage or brain dysfunction

Processing Speed: It is the speed with which various cognitive activities are performed.

Pseudo-Dementia: It is defined as cognitive impairment that mimics dementia however diminishes upon remission of depression. Further, it is marked by detailed account of cognitive impairment, subjective memory loss and frequent "don't know" answers.

Visuospatial Ability: It is the capacity to identify visual and spatial relationships among objects. Visuospatial ability is measured in terms of the ability to imagine objects, to make global shapes by locating small components.

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Chapter 8
The Early Diagnosis of Alzheimer's Disease:
From Behavioral to Genetic Study

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ABSTRACT

Alzheimer's disease, a common form of dementia, is a type of neurodegenerative disease that affects more than 30% of the population older than 85. Clinically, it is characterized as memory loss and cognitive decline. Pathologically, its symptoms include cerebral atrophy, amyloid plaques and NFTs. Generally, the life expectancy is no more than nine years after the definite diagnosis, and life expectancy exceeds 14 years in only 3% of patients. Presently, there is no effective treatment to stop the process; the only measures we can take are to ease or improve symptoms temporarily. Therefore, it is necessary to diagnosis the disease in the early stage, such as through imaging detection via CT, MRI, PET and MSR, or prediction before the disease (genetic examination). However, literature data have supported the notion that Alzheimer's disease patients show cognitive reserve abilities to some degree. In the future, research perspectives may focus on the cognitive training paradigms in compensatory and restorative strategies.

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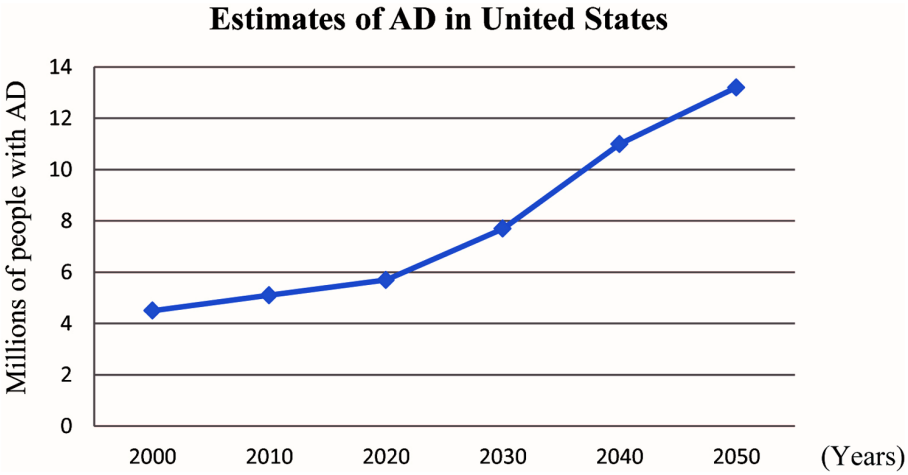
INTRODUCTION

Alzheimer's disease (AD), also known as just Alzheimer's, is the sixth leading cause of death in the United States and is the fifth leading cause of death in Americans aged 65 or older (Association, 2011). Alzheimer's disease, which is a chronic neurodegenerative disease, accounts for 60 to 70% of dementia cases. It often begins in people over 65 years of age and is an aging-related neurodegenerative disorder (Palop et al., 2003). According to Hebert, in next 40 years, the number of individuals with Alzheimer's disease in the United States will increase dramatically (Hebert et al., 2013). There were approximately 4.5 million people with Alzheimer's disease in 2000, and this number has since reached 5.1 million. This number is expected to reach 5.7 million by 2020, 7.7 million by 2030, 11.0 million by 2040, and 13.2 million by 2050 (Figure 1).

Figure 1. Estimated number of people aged 65 and over with AD in the United States



The exact causes that lead to Alzheimer's disease are not yet known. However, many experts have now reached an agreement that, similar to other chronic diseases, Alzheimer's disease likely develops as a result of multiple factors. Changes in the brain include the accumulation of the protein β amyloid outside of the neuron and the accumulation of the protein tau in the neuron (Hebert et al., 2013). In addition, approximately 70% of the risk is believed to be genetic, with many genes usually involved, such as apolipoprotein E- ε4 (APOE ε4). The APOE gene has three common forms, APOE ε2, APOE ε3 and APOE ε4; this gene provides a blueprint for one type of transmitter protein that carries cholesterol in the bloodstream. Every individual inherits one form from each of his or her parents. If an individual inherits APOE ε4, their risk of developing Alzheimer's disease is increased. Moreover, those individuals have an increased risk of developing it at an earlier age than those who inherit the APOE ε2 or APOE ε3 genes from their parents. However, those who inherit two APOE ε4 genes have a higher risk. Other risk factors include a history of head injuries, depression, or hypertension (Hebert et al., 2013).

Clinically, in the early stage, the most common symptom is short-term memory problems, which mainly present as the inability to remember recent events. As the disease advances, symptoms can include problems with language, disorientation (including easily getting lost), mood swings, not managing self-

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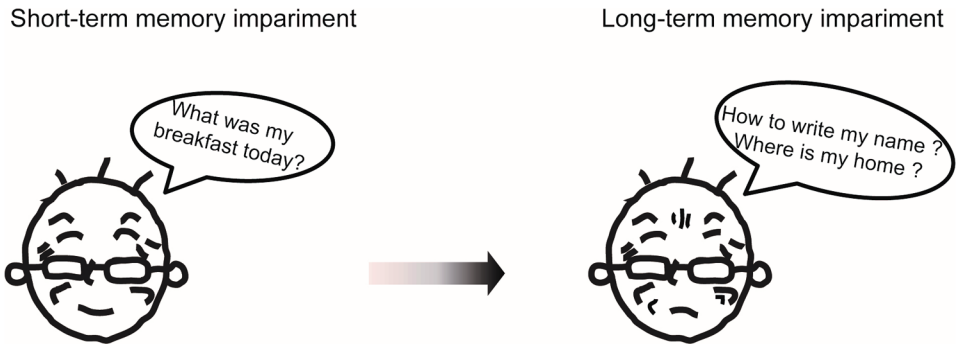
care, and behavioral issues. Generally, during long-term memory deficits, episodic memory is the most vulnerable, followed by semantic memory and, finally, procedural memory (Figure 2).

Pathologically, the main characteristics include the following: loss of neurons, neuritic plaques, granular-vacuolar degeneration, abundant amyloid plaques, neurofibrillary tangles (NFTs), and dystrophic neurites containing hyperphosphorylated tau. All of these neuropathological characteristics can be used as diagnostic markers of AD (Crews & Masliah, 2010).

Figure 2. The sequence of memory impairment in AD



No treatments stop or reverse the progression of AD, although some may temporarily improve symptoms. However, the present neuroscience investigations show that the cognitive deficits of Alzheimer's disease can produce significant functional impairments. Although memory deficits are typically most prominent, impairments in attention, visuospatial functioning, language, reasoning, and executive functioning are common, along with personality changes and behavioral disturbances (Sitzer et al., 2006). The most important measure is early diagnosis and consequent intervention. Recently, with the development of investigative techniques for the diagnosis of Alzheimer's disease, neuroimaging, biological markers and genetic examinations increase the probability of the early diagnosis of Alzheimer's disease.

DIAGNOSIS

Alzheimer's disease is a progressive degenerative disorder of insidious onset, characterized by memory loss, confusion, and a variety of cognitive dysfunctions. There is no effective treatment; therefore, the current plan of action is to ensure an accurate diagnosis and delay further development of Alzheimer's disease.

Behavioral Test

The diagnosis of Alzheimer's disease is based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV-TR) (Association, 2000), and the National Institute of Neurological Disorders and Stroke (NINDS), Alzheimer Disease and Related Disorders (NINCDS-CADRDA) working group (McKhann et al., 1984a). These accepted criteria include two steps. The first step involves

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a diagnostic process in which there is an initial identification of a dementia syndrome (DSM-IV-TR); the second step involves the application of criteria based on the clinical features of the Alzheimer's disease phenotype. The publication of NINCDS-CADRDA criteria greatly advanced our understanding of the biological basis of Alzheimer's disease in 1984 by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984b). After the detection of the above two steps, the exclusion of dementia caused by other factors is necessary.

In addition, some other methods are currently being developed for the diagnosis of Alzheimer's disease. In 2012, Wu et al. used audiovisual facilitation to compare the differences between healthy participants and patients with Alzheimer's disease; they found that patients with Alzheimer's disease exhibited adequate audiovisual integration and a greater peak and broader temporal window of multisensory enhancement (Gomez-Ramirez & Wu, 2014). Moreover, there are also techniques to study Alzheimer's disease. In the future, such techniques may provide evidence for the early diagnosis of Alzheimer's disease(Ren et al., 2014).

Neurological Imaging Detection

In the last few decades, we have witnessed major advances in research technology in Neuroscience, including Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), and Electroencephalography (EEG). Compared with diagnostic markers, neuropil threads, abundant amyloid plaques, neurofibrillary tangles (NFTs), and dystrophic neurites containing hyperphosphorylated tau neuroimaging methods maybe provide more precise measures for the diagnosis of Alzheimer's disease.

Computed Tomography, CT

CT was introduced in 1983 and has been an extremely important medical tool for the structural imaging of neurological damage without invasion in living people. The key principle underlying CT is that the density of biological material varies and that the absorption of X-ray radiation is correlated with tissue density. The absorption capacity of neural tissue lies between these extremes. Thus, the software for making CT scans actually provides an image of the differential absorption of the intervening tissue. The typical spatial resolution for CT scanners is approximately 0.5 to 1.0 cm in all directions. Each point on the image reflects an average density of that point and the surrounding 1.0 mm of tissue. Thus, it is impossible to discriminate two objects that are closer than approximately 5 mm.

The initial criteria for a CT scan diagnosis of Alzheimer's disease is the presence of diffuse cerebral atrophy with increased ventricles and enlarged cortical sulci. Several studies have indicated that cerebral atrophy is significantly greater in patients with Alzheimer's disease than in aging adults without Alzheimer's disease. However, this concept was soon challenged because cerebral atrophy can be present in elderly healthy persons, and some patients with dementia may have no cerebral atrophy, particularly in the early stages of Alzheimer's disease. The extent of cerebral atrophy was determined using linear measurements; in particular, the bi-frontal and bi-caudate diameters and the diameters of the third and lateral ventricles. Various measurements were adjusted according to the diameter of the skull to account for normal variation.

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To make up for this modification, volumetric investigations of the ventricles were performed. Despite these efforts, it is still difficult to distinguish between findings in a healthy elderly patient and those in a patient with dementia (Bird et al., 1986). Moreover, some clinical studies have indicated that CT results for cerebral atrophy cannot provide sufficient evidence for the diagnosis of Alzheimer's disease alone.

Recent studies have found that the rate of atrophy progression may be an important factor in diagnosing Alzheimer's disease (Jagust et al., 1987). The third and lateral ventricles are significantly larger in patients with Alzheimer's disease than in healthy older subjects (Luxenberg et al., 1987). In addition, the hippocampal sulcus, known as the hippocampal fissure, is a sulcus that separates the dentate gyrus from the subiculum and the CA1 field in the hippocampus. Numerous studies have reported that hippocampal degeneration has a close relationship with Alzheimer's disease and that there is AD-type alteration in the hippocampus. In 1989, researchers examined 175 individuals using a medical and neuropsychological investigation protocol consistent with the US consensus criteria for the clinical assessment of Alzheimer's disease. They found that CT hippocampal fissure dilatation appears to correlate well with post-mortem hippocampal degeneration and that the hippocampal fissure may be a useful radiologic marker for the early stage diagnosis of Alzheimer's disease. Moreover, studies have showed that although the specificity of hippocampal atrophy has not been established, the predictive accuracy of hippocampal degeneration can reach 81% with a specificity of 67% (Bastos-Leite et al., 2006).

Magnetic Resonance Imaging, MRI

In contrast to CT, MRI exploits the magnetic properties of organic tissue. MRI creates a powerful magnetic field, measured in Tesla units. When a person is placed within the magnetic field of the MRI machine, a significant proportion of the protons become oriented in the direction parallel to the magnetic force. Radio waves then pass through the magnetized regions, and as the protons absorb the energy in these waves, their orientation is perturbed in a predictable direction. When the radio waves are turned off, the absorbed energy is dissipated, and the protons rebound toward the orientation of the magnetic field. This synchronized rebound produces energy signals that are picked up by detectors surrounding the head. MRI scans provide a much clearer image of the brain than is possible with CT scans.

Structural MRI can be considered the preferred neuroimaging examination for Alzheimer's disease because it allows the accurate measurement of the three-dimensional (3D) volume of brain structures, particularly the size of the hippocampus and related regions. Studies have shown that hippocampal atrophy detected by structural MRI is a sensitive feature of early Alzheimer's disease (Laakso et al., 1996). Together with CT, structural MRI is the most common method used to diagnose Alzheimer's disease clinically in the cranial capacity (Frisoni et al., 2010).

However, the structural alterations that are always present in the middle and later stages of Alzheimer's disease may not be useful for the diagnosis of early stage disease. According to an AD-related study, the function of the brain begins to decline before cerebral atrophy. Therefore, it is meaningful to make use of functional magnetic resonance imaging (fMRI) for the diagnosis of Alzheimer's disease in the early stage (Gomez-Ramirez & Wu, 2014). fMRI can not only detect the activation of the brain, it can also evaluate the regions and the level of the activation. fMRI is a functional neuroimaging procedure that uses MRI technology to measure the activity of the brain by detecting alterations associated with blood flow (Matthews & Jezzard, 2004). This technique depends on the foundation that cerebral blood flow and neuronal activation are coupled. When an area of the brain is in use, the blood flow to that brain region also increases. According to blood-oxygen-level dependent (BOLD) contrast, the function of the

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detected region can be evaluated (Logothetis, 2008). Studies have indicated that decreased connectivity between the hippocampus and the visual cortices may indicate reduced integrity of hippocampus-related cortical networks in AD (Wang et al., 2006). Currently, fMRI has been widely used clinically to map functional areas of the brain by checking left-right hemispherical asymmetry in language and memory regions (such as the hippocampus). In addition, a recent study showed that resting-state functional Magnetic Resonance Imaging (rs-MRI) can provide useful evidence for the early diagnosis of Alzheimer's disease (Yamaguchi Shuhei, 2014). rs-MRI is a method of functional brain imaging that can be used to evaluate regional interactions that occur when a subject is not conducting an explicit task (Wang et al., 2006; Onoda & Yamaguchi, 2013).

Positron Emission Tomography, PET

Positron emission tomography is a functional imaging technique that is based on nuclear medicine. Using small amounts of radioactive materials (radiotracers), a camera, and a computer, it can evaluate the function of an organ and tissue at the cellular level (Valk, 2003). The system detects pairs of gamma rays emitted indirectly by the radiotracers, which are introduced into the body by being injected, inhaled or swallowed depending on which organ or tissue is being studied by the PET scan. 3D images of the tracer concentration within the body are then constructed by computer analysis.

Alzheimer's disease is characterized by progressive loss of cognitive function with β-amyloid (Aβ) (Southwick et al., 1996), neurofibrillary tangles (NFTs) and senile plaques (SPs) serving as the pathological hallmarks of this disease (Vickers et al., 2000;Jin et al., 2011). PET in Alzheimer's disease patients has indicated that in the early stage of Alzheimer's disease, the metabolism of the limbic system declines. PET has a sensitivity of 84% and a specificity of 93% for the diagnosis of Alzheimer's disease. In particular, when the biologically active molecule is 18F-fluorodeoxyglucose (18F-FDG), the detection of Alzheimer's disease is based on changes in the glucose metabolic rate; for example, studies have found that the glucose metabolic rates in the temporal and parietal lobes are reduced (Small et al., 2006). Moreover, the abnormal levels of β-amyloid and the tau protein in cerebrospinal fluid (CSF) provide important evidence for the diagnosis of Alzheimer's disease in the early stage. Recently, researchers have used a new compound to diagnose Alzheimer's disease; this compound is known as 18F-FDDNP, and it is bound to the plaques and tangles within the brain that are the characteristic features of Alzheimer's disease. In addition, tracer Pittsburgh Compound-B (PIB) can selectively combine with amyloid β-protein (Zhang et al., 2005). Therefore, positron emission tomography is helpful for the diagnosis of Alzheimer's disease in the early stage.

In 2011, Behrooz and his colleagues reported that a novel series of 11C-labeled imidazo[2,1-b]benzothiazoles (IBTs) were used as tracers for the imaging of cerebral β-amyloid (Aβ) deposits in Alzheimer's disease patients using positron emission tomography (PET); they found that the IBTs were useful PET imaging agents for high-sensitivity detection of Aβ plaques (Yousefi et al., 2011). Additionally, on a limited basis, many other radioactive tracers are used in PET to image the tissue concentrations of other types of molecules of interest. However, one of the disadvantages of PET scanners is their operating cost.

PET scans measure functions of the body, such as oxygen use, blood flow, and sugar (glucose) metabolism. These results can help doctors evaluate the present function of certain organs or tissues. CT imaging uses special x-ray equipment, and in some cases, a contrast material, to produce multiple images of the inside of the body. Then, these images are interpreted by a radiologist on a computer monitor to provide anatomic information for other doctors. Presently, a combination of PET and CT scanners

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is commonly used. Combined PET/CT scans provide images that pinpoint the anatomic location of abnormal metabolic activity within the body. These combined scans have been shown to provide more accurate diagnosis evidence than the scans separately.

Magnetic Resonance Spectroscopy (^{1}H-MRS)

Magnetic resonance spectroscopy is a non-invasive technique that has been used to measure the concentration of low molecular weight metabolites in-vivo, with a detection threshold of approximately 1 mmol/L (mM) from a volume of interest typically between 1 to 8 cm^3 (Gujar et al., 2005). Detectable brain metabolites, including glutamine (Gln), glutamate (Glu), creatine compounds (Cr), N-acetylaspartate (NAA), choline-containing compounds (Cho) and myo-inositol (mI), have a typical concentration between 1 and 10 mM (Gujar et al., 2005). Although MRS can theoretically be performed in almost any tissue of the human body, the main area of focus has been the brain.

Reduced N-acetylaspartate has been found in Alzheimer's disease, and alterations in the level of N-acetylaspartate or N-acetylaspartate/Cr are the most common findings in patients with Alzheimer's disease (Chantal et al., 2002). Therefore, the use of magnetic resonance spectroscopy in the early diagnosis of Alzheimer's disease has been reported in many studies. N-acetylaspartate has been reported to have poor clinical specificity for Alzheimer's disease, and the ratio of N-acetylaspartate to myo-inositol is significantly different between Alzheimer's disease patients and healthy age-matched controls. The ratio of N-acetylaspartate to myo-inositol in Alzheimer's disease patients is much lower than that in control groups (Killiany et al., 2000).

Genetic Examination

All of the above described neuronal imaging biomarkers are based on pathological changes. However, it will be advantageous if Alzheimer's disease can be predicted before these pathological changes occur. The development of genetic investigations regarding Alzheimer's disease makes this possible. Some Alzheimer's related genes come directly from kindreds, such as the Aβ42 risk factors for Alzheimer's disease. Moreover, it is well known that those who have Down's syndrome, are APOE ε4 allele homozygotes, or who are either amyloid precursor protein (APP) or presenilin (PSEN) mutation carriers have an extremely high risk of developing Alzheimer's disease (Hampel et al., 2010). Previous studies have indicated that in the cerebrospinal fluid (CSF), the concentration of β-amyloid protein decreases, whereas the concentrations of the Tau protein and the phosphorylated Tau protein increase. In addition, genetic examinations are available for individuals who have family members with early onset familial Alzheimer's disease. These genetic screens include testing for PSEN1, PSEN2, APP and APOE mutations (Schellenberg et al., 1992).

MEDICATIONS FOR TREATING ALZHEIMER'S DISEASE

Presently, there is no effective treatment to stop the progression of Alzheimer's disease; however, there are some medicines that can reserve or improve clinical symptoms (Tariot et al., 2004).

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Cholinesterase Inhibitors

Since the introduction of the first cholinesterase inhibitor (ChEI) in 1997 (McGleenon et al., 1999), many researchers have begun developing cholinesterase inhibitor drugs. Currently, clinical trials in Japan, Europe, and the USA are evaluating approximately 10 cholinesterase inhibitor drugs, and most of these drugs have already advanced to clinical phases III and IV (Giacobini, 2000). The cholinesterase inhibitors that are currently used in the clinic include Aricept, rivastigmine, Galantamine, and Huperzine. All of these drugs are used to improve the choline system. These drugs have slightly different pharmacological properties; however, all of them work by inhibiting the breakdown of acetylcholine. Acetylcholine is an important neurotransmitter that is associated with memory by blocking the enzyme acetylcholinesterase (Larner, 2010).

N-Methyl-D-Aspartate (NMDA) Receptor Antagonists

N-methyl-D-aspartate (NMDA) receptor antagonists, such as Namenda, help block the activity of the neurotransmitter glutamate by binding to N-methyl-D-aspartate (NMDA) receptors on the surface of brain cells (Olivares et al., 2012). Glutamate plays an important role in learning and memory. If the level of glutamate is too low, cognitive problems develop. If the level is too high, glutamate overstimulates nerve cells, leading to cell death. Moreover, selective NMDA receptor antagonists completely block Aβ1–42 uptake or internalization and the subsequent up-regulation of cathepsin D and activation of microglia in organotypic hippocampal cultures (Danysz & Parsons, 2012).

Additionally, there are some other types of medicine that can improve the symptoms of Alzheimer's disease, such as fibroblast repair factor (bFGF).

REHABILITATION

Patients with Alzheimer's disease may derive some cognitive and functional benefits from cognitive training. In 1996, Hofmann and colleagues used a computer-based cognitive training experiment to evaluate the effect of training on patients with Alzheimer's disease. Their results showed that after three weeks of training (three to four sessions a week), the patients required less help in performing the programs, they became faster, and eight out of ten patients made fewer mistakes (Hofmann et al., 1996). This study suggested that it is possible to improve the cognitive function in patients with Alzheimer's disease.

Presently, there are two main categories of cognitive training strategies: compensatory and restorative strategies (Sitzer et al., 2006). Compensatory strategies mainly teach new ways to perform cognitive tasks by working around cognitive deficit regions (Bäckman, 1996; Bellack et al., 1999; Spaulding et al., 1999; De Vreese et al., 2001; Mahendra, 2001). Compensatory interventions, as described above, may use internal strategies, for example, organizing information by visualizing or categorizing information to be remembered (Bäckman, 1996; Hofmann et al., 1996); focusing on a single task and asking questions and paraphrasing during learning (Mahendra, 2001; Tang et al., 2016); procedural training to teach complex, higher-order cognitively mediated behaviors, such as balancing a checkbook; or external strategies, such as environmental cues, memory notebooks, and calendars (Sitzer et al., 2006).

Restorative strategies attempt to improve functioning in specific domains, with the ultimate goal of returning functioning in those domains to premorbid levels. In actuality, there are many examples in our

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life. Restorative techniques include drills in which patients engage in repeated attention and memory tasks; errorless learning, which involves preventing mistakes during recall trials (Bäckman, 1996; Mahendra, 2001); spaced retrieval, which requires patients to recall information over longer periods of time; and reminiscence therapy, in which patients discuss remote events to place one's life in perspective (Woods et al., 1992).

CONCLUSION AND FUTURE DIRECTIONS

Because there are not effective measures to stop the symptoms of Alzheimer's disease, the key to combatting this disease is to develop effective prediction or early diagnosis methods. For early diagnosis, the combination of the present imaging techniques may provide a more sensitive biomarker. In addition, to improve the quality of life of patients with Alzheimer's disease, cognitive intervention is necessary.

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KEY TERMS AND DEFINITIONS

Amyloid β (Aβ): Aggregation-prone peptide derived from the amyloid precursor protein. The 42 amino acid isoform of the peptide is the main component of plaques in Alzheimer's disease (Hampel et al., 2010).

Amyloid Plaques: The accumulation of amyloid plaques between nerve cells, or neurons in the brain. In the normal brain, such fragments of protein can be broken down, but in patients with Alzheimer's disease, protein fragments accumulate to form hard plaques.

Neurofibrillary Tangles (NFTs): Aggregates of filamentous tau polymers that comprise a portion of the fibrillar pathologies in Alzheimer's disease (AD). Other elements include the neuropil threads and the dystrophic neurites that invade a subset of amyloid plaques (neuritic plaques) (Binder et al., 2005).

Tau Protein: A microtubule-associated protein located in the neuronal axons. Hyperphosphorylated tau is the main component of neurofibrillary tangles in Alzheimer's disease (Hampel et al., 2010).

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Chapter 9
Deep Learning in Early Detection of Alzheimer's: A Study

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ABSTRACT

Advancement in technology has paved the way for the growth of big data. We are able to exploit this data to a great extent as the costs of collecting, storing, and analyzing a large volume of data have plummeted considerably. There is an exponential increase in the amount of health-related data being generated by smart devices. Requisite for proper mining of the data for knowledge discovery and therapeutic product development is very essential. The expanding field of big data analytics is playing a vital role in health-care practices and research. A large number of people are being affected by Alzheimer's Disease (AD), and as a result, it becomes very challenging for the family members to handle these individuals. The objective of this chapter is to highlight how deep learning can be used for the early diagnosis of AD and present the outcomes of research studies of both neurologists and computer scientists. The chapter gives introduction to big data, deep learning, AD, biomarkers, and brain images and concludes by suggesting blood biomarker as an ideal solution for early detection of AD.

INTRODUCTION

The huge amount of data being generated by healthcare industry has great future to support a variety of healthcare and medical functions. The digitization of this voluminous data generated by the healthcare industry is the Big Medical data. This data includes physicians' prescription, laboratory test data, X-ray, scan reports, pharmacy data, patient data in Electronic Health records, sensor data, social media posts

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which includes tweets, Facebook messages and status updates, news feeds, newspaper, magazines and medical journals.

The digitization of medical data, the field of genomics and use of wearable sensors to monitor patient health are some of the factors that have contributed to the growth of Big Data in Health Care/Biomedicine (Mathew & Pillai, 2016).

Big Medical Data can be used by researchers to identify patterns which can be used for predictions. For example, in the case of Alzheimer's, disease (AD) by analyzing the MRI images of the brain certain patterns can be identified. This knowledge can be used in identifying the ones who are at the greatest risk of getting this disease.

Big data analytics has helped in medical research as we have the necessary software and algorithms capable of analysing cognitive functions and help doctors to easily identify such patients. Lumosity is a brain game platform wherein user score data is used for early detection of Alzheimer's before a permanent neuronal loss occurs (Krishnan, 2018). High-dimensionality research in the future is likely to create intelligent analytical systems that are capable of generating effective disease diagnostic and drug development deliverables. Biomedical datasets are growing daily and a plethora of high-dimensionality datasets are now freely accessible for neurodegenerative diseases, such as AD (Maudsley, Devanarayan, Martin & Geerts, 2018). The convergence of advanced computing and numerous Big Data technological options has paved the way to attain high performance and scalability at a relatively low cost. Big data solutions usually come with a set of innovative data management solutions and analytical tools, and when effectively implemented can transform the healthcare outcomes (Mathew & Pillai, 2015).

Deep Learning

Deep learning is an artificial intelligence function in machine learning that enables computers to learn from experience and understand the world in terms of a hierarchy of concepts. Deep Learning (DL) is a subfield of machine learning concerned with algorithms inspired by the structure and function of the brain called artificial neural networks (Browniee, 2016). In Deep learning neural network composed of several layers are used. The node combines input from the data with an associated weight or coefficient. The product of input and weight are summed and sent to the activation function. Depending on the value of the summation, the signal progresses further through the network to identify the final outcome. The earlier versions of Neural Networks had one input, one output, and one hidden layer. In deep learning, there is more than one hidden layer and each layer of nodes is trained on a different set of features based on the previous layer's output. One main benefit of deep learning is as there are several layers, and as we go deep into the network, nodes will be capable of identifying complex features as they aggregate and recombine features from the previous layer.

Supervised learning algorithms used are:

- Logistic Regression
- Multilayer perceptron
- Deep Convolutional Network

Semi-Supervised / Unsupervised Learning algorithms are:

- Auto Encoders

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- Restricted Boltzmann Machines
- Deep Belief Networks

DL can be applied to Biology and medicine as they are rich in data that are complex and difficult to understand. DL is used for the diagnosis of a number of diseases including Cancer and Alzheimer's. Literature survey reveals that some of the challenges faced by DL researchers in applying to Medical / Biomedical studies is the unavailability of the Biomedical dataset, privacy issues, guidance from medical experts etc. Though deep learning based application has provided good results, however, due to the sensitivity of healthcare data and challenges, more sophisticated deep learning methods that can deal complex healthcare data efficiently is required. Most researchers believe that within few years, deep learning based applications will take over human and not only most of the diagnosis will be performed by intelligent machines but will also help to predict disease, prescribe medicine and guide in treatment (Razzak, Nazb & Zaib, 2017).

Alzheimer's Disease

Alzheimer's disease is a progressive neurological disorder which causes cognitive decline involving memory loss and behavioural changes due to the death of brain cells. It is the most common type of dementia, accounting for 60 to 80 percent of cases of dementia in the United States and In 2013, 6.8 million people in the U.S. had been diagnosed with dementia (MacGill, 2018) also according to MacGill (2018), Of these, 5 million had a diagnosis of Alzheimer's and according to the author By 2050, the numbers are expected to double. Alzheimer's is a neurodegenerative disease with mild symptoms at the beginning and progresses over the years.

Fast facts on Alzheimer's disease (MacGill, 2018)

- Alzheimer's disease is the most common type of dementia.
- AD usually occurs when plaques containing beta- amyloid form in the brain.
- As time progresses symptoms also worsen and becomes difficult for AD subjects to remember recent events, to recognize people they know, use appropriate words/spellings.
- Mostly, a person with AD will need full-time assistance to carry out their day to day activities.

Biomarkers

The term "biomarker" or "biological marker", are a set of medical signs – which are medical states observed from outside the patient – which can be measured accurately. Some examples of biomarkers include pulse and blood pressure through basic chemistries to more complex laboratory tests of blood and other tissues (Strimbu & Tavel, 2010). According to the WHO, biomarkers includes "almost any measurement reflecting an interaction between a biological system and a potential hazard, which may be chemical, physical, or biological. Biomarkers can be classified based on different parameters, including their characteristics, such as imaging biomarkers (computed tomography, positron emission tomography, magnetic resonance imaging) or molecular biomarkers (Huss, 2015).

According to Ralf Huss (2015), Molecular biomarkers have biophysical properties, which permit them to be measured in biological samples, and include nucleic acid–based biomarkers such as gene

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mutations or polymorphisms and quantitative gene expression analysis, peptides, proteins, lipids metabolites, and other small molecules.

Brain Imaging / Neuroimaging

One of the most encouraging areas of research focused on prompt detection of AD is Neuroimaging. Structural imaging with MRI or computed tomography (CT) is usually used to detect tumours, small or large strokes, damage from severe head trauma or a fluid in the brain.

The following are taken from https://www.alz.org/research/science/earlier_alzheimers_diagnosis.asp

- Studies related to Structural imaging has shown that the brains of people with Alzheimer's shrink considerably as the disease advances and shrinkage in some specific brain regions such as the hippocampus may be an initial sign of Alzheimer's. But standardized values for brain volume has not been identified so as to conclude the presence of AD.
- Using Functional imaging with positron emission tomography (PET) and other methods it has been noticed that patients with AD typically have less brain cell activity in certain regions. Lessening of glucose in areas of the brain which are important in memory, learning and problem solving is also associated with AD.
- Another active area of research namely Molecular imaging helps in detecting biological clues specifying Alzheimer's is underway even before the disease alters the brain's structure or function.
- Pittsburgh compound B (PIB) was the first radiotracer capable of highlighting deposits of beta-amyloid—one identifier of AD.
- Florbetaben (Neuraceq®), Florbetapir (Amyvid®) and Flutemetamol (Vizamyl®) also help in identifying beta-amyloid in the brain.

Cerebrospinal fluid (CSF) biomarkers (Aβ peptides and tau proteins). *Amyloid-β precursor protein* (*AβPP*), *presenilin 1* (*PSEN1*), and *presenilin 2* (*PSEN2*) genes are strongly involved in early-onset Alzheimer's disease (EOAD).

Late-onset Alzheimer's disease (LOAD) has been linked with other genes including *apolipoprotein E-ε4* (*APOEε4*), *bridging integrator 1* (*BIN1*) region, *clusterin* (*CLU*), *phosphatidylinositol clathrin assembly lymphoid-myeloid* (*PICALM*), and *complement receptor 1*, mostly identified through genome-wide association studies (GWAS).

LITERATURE REVIEW

Korolev et al. (2017) proposed deep 3D convolutional neural network architectures for classification of brain Magnetic Resonance Imaging (MRI) scans. Their study compared the performance of the residual and plain convolutional neural networks with their proposed model based on the Alzheimer's Disease National Initiative (ADNI) dataset with Alzheimer's disease and normal controls. The comparative study revealed that their proposed model performed better in comparison with the earlier methods and one advantage of the model according to the authors was ease of use and no need for handcrafted feature generation. Authors used label propagation and classified MRI images in a manifold-based semi-supervised learning framework and used voxel morphometry analysis to extract some of the most

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critical AD-related features of brain images from the original MRI volumes and also grey matter (GM) segmentation volumes. Their main focus was to identify the features that differentiate between a healthy and Alzheimer-affected brain. Next dimension reduction of the extracted features was done using Principal Component Analysis (PCA) for faster and accurate analysis. Using the subset of labelled training data and using the label propagation method the labels of the remaining images were predicted and classified into two groups namely mild Alzheimer's and normal condition. According to the authors, the accuracy of the classification using their proposed method is 93.86% for the Open Access Series of Imaging Studies (OASIS) database of MRI brain images which when compared to the best existing methods, provided a 3% lower error rate (Korolev et al., 2017).

Using data from healthy people getting scopolamine, Simpraga et al. (2017) developed an index of the muscarinic acetylcholine receptor antagonist (mAChR) consisting of 14 EEG biomarkers. Authors reported that the mAChR index developed produced higher classification performance than any single EEG biomarker with precision ranging from 88–92%. Their research reported that the mAChR index also helped to differentiate between healthy elderly from patients with Alzheimer's disease (AD). Their study further stated the importance of integrating multiple EEG biomarkers to improve the accuracy of identifying disease or drug interventions, which was important for clinical trials.

Lu et al. (2018) proposed a novel deep neural network to identify individuals at risk of developing Alzheimer's disease. Their multi-scale and multi-modal deep neural network (MMDNN) was designed to integrate different scales of information from various regions of the brain taken from several modalities. Initially, the authors demonstrated the efficiency of the proposed MMDNN approach by comparing with the existing methods in differentiating between stable MCI and progressive MCI individuals. Later the classifier was trained to distinguish subjects of a probable AD. Authors observed that MMDNN had the overall classification accuracy of 82.4% in identifying the individuals with mild cognitive impairment (MCI) who will convert to AD at 3 years prior to conversion, a 94.23% sensitivity in classifying individuals with clinical diagnosis of probable AD, and a 86.3% specificity in classifying non-demented controls (Lu et al., 2018). By performing this study, the authors suggest that deep neural network classifiers have a great potential for providing evidence in support of the clinical diagnosis of a probable AD.

Li et al. (2017) presented a deep ordinal ranking model for classifying AD's different stages using structural imaging data focusing on the hippocampus, built on CNNs and ordinal ranking techniques. Then on comparison with the traditional multi-category classification methods based on the ADNI dataset authors demonstrated that their method could achieve better classification performance by utilising inherent ordinal severity of brain degeneration associated with AD's different stages. The study also pointed out that the deep learning features of the hippocampus outdid hand-crafted imaging features, like shape. Authors suggested that the performance of the flexible architecture of proposed deep model could be further improved if multimodality information is taken into account, e.g., PET imaging and cerebrospinal fluid (CSF) biomarkers.

3D convolutional neural networks (3D-CNNs) to learn the multi-level imaging features for classification of AD using PET brain images was done by Cheng and Liu (2017). Initially, they constructed multiple deep 3D-CNNs on different local image patches to transform the local image into more compact high-level features and then a deep 3D CNNs was trained to learn the high-level features for final classification. According to the authors, the proposed method could automatically learn the generic features from PET imaging data for classification. The proposed method was evaluated on the PET images from 193 people which consisted of 93 AD patients and 100 normal controls (NC) taken from Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Results of the experiment indicated that the proposed

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method achieved an accuracy of 92.2% for the classification of AD versus NC, establishing a very promising classification performance (Cheng & Liu, 2017).

A study to show the importance of deep learning techniques for the classification of CT brain images, using a convolutional neural network (CNN), for providing information on the early diagnosis of Alzheimer's disease was conducted by Gao, X. W., & Hui, R, 2016. CT images (N=285) are clustered into three groups namely, AD, Lesion (e.g. tumour) and Normal ageing. In order to handle images with a larger thickness along the direction of depth (z) (∼3-5mm), an advanced CNN architecture was used integrating both 2D and 3D CNN networks. According to Gao and Hui (2016), the classification accuracy rates obtained by this CNN architecture are 85.2%, 80% and 95.3% for classes of AD, Lesion and Normal respectively with an average of 87.6%.

A deep learning method using 8-layer 3D Convolutional Network (3D ConvNet) was used for automatic feature learning and Alzheimer's disease classification by Backstrom et al (2018). The study was performed on the ADNI dataset containing 1198 MRI brain scans from 199 AD patients and 141 NC subjects. Authors claim that by using the random data partitioning strategy, the proposed scheme yielded 98.74% accuracy on the test dataset, with 100% for AD detection with false alarm 2.4%.

According to LeWitt, Li, Lu, et al. (2017) Biomarkers in the blood and cerebrospinal fluid (CSF) of patients with Parkinson's disease (PD) show strong correlations to disease progression, according to a report in the February 8 online issue of *Neurology*. Le Witt PA et.al, reports that as on date, neurologists rely on clinical rating scales or radioisotope neuroimaging results and, no additional biological indicators have emerged that can help in predicting how a patient will do over time, or whether an experimental treatment is neuroprotective. They also suggested that biomarkers could provide information about subtypes of PD and would aid in assessing the effectiveness of neuroprotective treatments.

According to Buckley, Schultz, Hedden et al. (2017) Among healthy adults, those with the lowest default mode network (DMN) connectivity — the network of interacting brain regions — and a positive amyloid scan shown via the PET radiotracer scan, Pittsburgh compound PiB, had poorer cognitive outcomes and were more likely to progress from preclinical Alzheimer's disease to the symptomatic phase of the disease. The authors predicted that in healthy older adults who had lower functional brain connectivity and presence of amyloid as per the scan reports were prone to cognitive decline within three years.

Fluorodeoxyglucose (FDG) positron emission tomography (PET) measures the decline in the regional cerebral metabolic rate for glucose, offering a reliable metabolic biomarker even on presymptomatic Alzheimer's disease (AD) patients (Singh et al., 2017). This model made use of probabilistic principal component analysis on max-pooled data and mean-pooled data for dimensionality reduction, and to perform binary classification multilayer feed forward neural network was used. According to the authors, 186 cognitively unimpaired (CU) subjects, 336 mild cognitive impairment (MCI) subjects with 158 Late MCI and 178 Early MCI, and 146 AD patients from Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset was used for this study and the study reported that deep model-based research as an effective imaging biomarker of AD in comparison with FDG-PET.

Various researchers are working on blood, cerebrospinal fluid and brain images to detect Alzheimer's as early as possible. A team of researchers from the University of Bari in Italy used an algorithm based on Artificial Intelligence (AI) that can spot tiny structural changes in the brain caused by the disease a decade before symptoms even appear (Moon, 2017). They made use of 67 MRI scans ie 38 from Alzheimer's patients and 29 from healthy controls to train their AI. Initially the researchers divided the scans into small regions and had their AI analyze the neuronal connectivity. After training, the algorithm

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was tested with 148 brain scans from 148 people. According to Moon (2017) AI was able to diagnose Alzheimer's 86 percent of the time and detect mild cognitive impairment 84 percent of the time.

Rachmadi, Hernández, Agan, Perri, and Komura (2018) proved the effectiveness of the 2D CNN scheme by comparing its performance against those obtained from another deep learning approach like Deep Boltzmann Machine (DBM), two conventional machine learning approaches: Support Vector Machine (SVM) and Random Forest (RF), and a public toolbox: Lesion Segmentation Tool (LST) and concluded that Deep learning algorithms perform much better than the traditional machine learning algorithms.

According to Xiaonan Liu, Kewei Chen, Teresa Wu, David Weidman, Fleming Lure, Jing Li, (2018), most of the studies concentrate only on building classifiers that used multi-modality imaging and non-imaging data to predict MCI conversion to AD and obtained accuracy which was generally below or barely above 80%. They suggested that in order to monitor the progression of the disease, a binary classification was not sufficient and a multi-class model was the need of the hour. Xiaonan et.al also felt that machine learning algorithms are mostly used in the existing studies and DL-based algorithms have not been used for early AD diagnosis though DL is very popular in other areas of computer vision.

CASE STUDIES

Studies have shown that many people with mild cognitive impairment go on to develop Alzheimer's, which is much more severe. People with this condition forget words, spellings, stop recognizing close relatives, lose basic self-care skills and eventually become entirely dependent on caregivers. But not all people with mild cognitive impairment develop AD. So, it would be really great if AD can be detected at an early stage and treated, and one way of doing it is by studying positron emission tomography (PET) scans of the brain. Alzheimer's is generally characterized by the unwanted growth of protein clumps called amyloid plaques and slow brain metabolism which is usually measured by the rate at which the brain uses glucose. Certain types of PET scans can reveal signs of both these conditions and can, therefore, be used to identify people with mild cognitive impairment who are most at risk of developing Alzheimer's (Choi & Jin, 2018). Choi and Jin (2018) developed a deep-learning neural network to train brain images of people with and without Alzheimer's to recognize the difference between them. The data set had brain images of 182 people in their 70s with normal brains and brain images of 139 people of roughly the same age who have been diagnosed with AD. With conventional training, the machine was taught to differentiate between normal brain images and the ones diagnosed with AD with an accuracy of almost 90 percent. The authors then used their deep learning machine on a different dataset which had brain images of 181 people in their 70s with mild cognitive impairment of which 79 developed AD within three years and wanted their network to identify those 79 people. According to Choi and Jin (2018), their neural network identified those at risk of developing AD with an accuracy of 81 percentage. That according to them was significantly higher than what was done manually. Their study results proved that deep learning could be used as a tool for predicting disease outcome using brain images and the network was useful in spotting people at risk of developing Alzheimer's and those who could benefit by early diagnosis and treatment.

A question that has been in existence for a long time is how best to use brain morphometric and genetic data to distinguish AD patients from cognitively normal (CN) subjects and how to predict those who will progress from MCI to AD (Ning, Chen, Sun, Hobel, Zhao, Matloff, & Toga, 2018). Ning et al. (2018) used a Neural Network (NN) on both structural brain measures and genetic data to address

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this question. They tested the effectiveness of neural networks in classifying and predicting AD. Data used for the study was from ADNI which included baseline structural MRI data and single nucleotide polymorphism (SNP) data for 138 AD patients, 225 CN subjects, and 358 MCI patients. NN models with both brain and SNP feature as predictors perform significantly better than models with either alone in classifying AD and CN subjects, (Ning et al., 2018). Their work also proved that NN models to not only classify and predict AD occurrence but can also be used to identify important AD risk factors.

CONCLUSION

From the literature review it is very clear that many researchers have used Deep Learning for early prediction of AD. Though some of them have received good results there is still a long way to go in early prediction of the disease. We should be able to develop a good biomarker. A biomarker for the biological diagnosis of AD needs to have sensitivity and specificity especially form differentiating from other neurodegenerative disorders. MRI can assess a sequential and regional imaging of the brain for anatomical details. However, this tool of assessment can be vague with less precision. The diagnostic accuracy needs to be high for continued clinical utility and for further research for newer drug discoveries. A blood biomarker would be an ideal scenario however as the concentration of CSF analytes are less in peripheral blood due to its inability to pierce the blood-brain barrier, this method remains a challenge. The pathology of AD is predominantly extracellular deposition of beta amyloid-Aβ and intracellular accumulation of tau protein. A good biomarker would be non-invasive detection of these pathological biomarkers. Imaging brain amyloid in the brain is probably the best imaging diagnostic tool.

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Chapter 10
Analysis of Biomedical Image for Alzheimer's Disease Detection

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ABSTRACT

Image analysis is giving a huge breakthrough in every field of science and technology. The image is just a collection of pixels and light intensity. The image capturing was done in two ways: (1) by using infrared sensors and (2) by using radiography. The normal images are captured by using the infrared sensors. Radiography uses the various forms of a light family, such as x-ray, gamma rays, etc., to capture the image. The study of neuroimaging is one of the challenging research topics in the field of biomedical image processing. So, from this note, the motivation for this work is to analyze 3D images to detect Alzheimer's disease and compare the statistical results of the whole brain image data with standard doctor's results. The authors also provide a very short implementation for brain slicing and feature extraction using Freesurfer and OpenNeuro dataset.

INTRODUCTION

The most common neurodegenerative disease is Alzheimer's (AD). It also goes a major health care issue of the future. During the next four decades, it has been estimated that the occurrence of AD will quadrivial the population of affected people from 27 million to 106 million vide Brookmeyer et al. (2007). According to Koenders et al. (2016), the count of Alzheimer patient has increased to 1 in 85 persons across the world. Any delay in detection and taking preventing step on Alzheimer disease lead to serious damage to brain cells. Intervention at an early stage of Alzheimer disease help in slowing down the process of

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mental disorder. In the initial stage, mild cognitive impairment (MCI) is found in the patient. It is a heterogeneous syndrome but it is not necessary that all MCI subjects develop into Alzheimer patients.

GENETIC FACTOR BEHIND ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a common form of neurodegenerative disease. Individuals who are impacted by this disease are aware of causes of dementia. The clinical characterization of Alzheimer's involves progressive loss of memory deficits in thinking, problem-solving and it has an impact on language abilities. Neuropathlogically AD can be characterized as progressive cortical atrophy due to neural loss and characteristic intracellular and extracellular deposits as insoluble tau and amyloid beta proteins vide Cauwenberghe et al. (2015), this is typically the process in which the disease manifests itself. Study of this disease based on genetically classification provides some important insights. Patients can be divided into two groups one is early onset and the other is late onset. For early onset, studies represent that there is a small set of genes that can be responsible for early onset of the disease but early-onset cases are fraction around five to 10 percent of total observed cases of these patients of early onset 2 to 10 percentage first display symptoms their 20s or their 30s. But the late onset of Alzheimer's tends to manifest itself after the age of 65. Late onset is pretty complex and is multifactorial, which means multiple genes could be involved and contributing to the disease and it has been found there is a pretty strong genetic predisposition. We have seen that about 30 to 48 percent of patients with Alzheimer's tend to have a first degree relatives that are also affected. So in trying to pinpoint which genetic risk are contributing to the disease, a number of Genome-wide association studies (GWAS) have been conducted GWAS helped in identifying as a community of 20 plus genetic risk loci, but these loci have small odds ratio. Hence none of them are really clear contenders to contribute to the disease. These loci include both common functional variants, and also rare and structural variants in that makeup. These are shown in Figure 1.

Genetics is a very important and interesting factor. Every individual is born with a particular set of genes and the assortment of genes that we have determined the number of things that might happen to us during life. Alzheimer's disease is no exception and there are different types of genetic effects on people's risk of developing Alzheimer's disease. Some of these can be very extreme or strongly predictive. These are associated with rather rare families who are at risk for developing early onset of Alzheimer's disease in a familial fashion. In this case, multiple people within a family will be affected. The age of onset is usually under the age of 50 and very often in the 30s as well as 40s. So, in these families, the fact is that a mutation in a gene really causes Alzheimer's disease. There are three genes that were identified in the 1990s that are responsible for early-onset familial Alzheimer's disease Cauwenberghe et al. (2015) and Brookmeyer et al. (2007).

BIOLOGICAL BEHAVIOUR OF ALZHEIMER'S DISEASE

A centurial, German doctor, Alois Alzheimer's spotted anomalies in brain sections from patients with dementia. Since then people have been studying the strange plaques and tangles in the hope that we could one day understand and cure Alzheimer's disease. Inside Alzheimer's disease plaques is insoluble deposit the peptide of the tangles called amyloid beta or Abeta. They are formed when a protein called amyloid precursor protein is sequentially separated by two enzymes beta as well as gamma-secretase.

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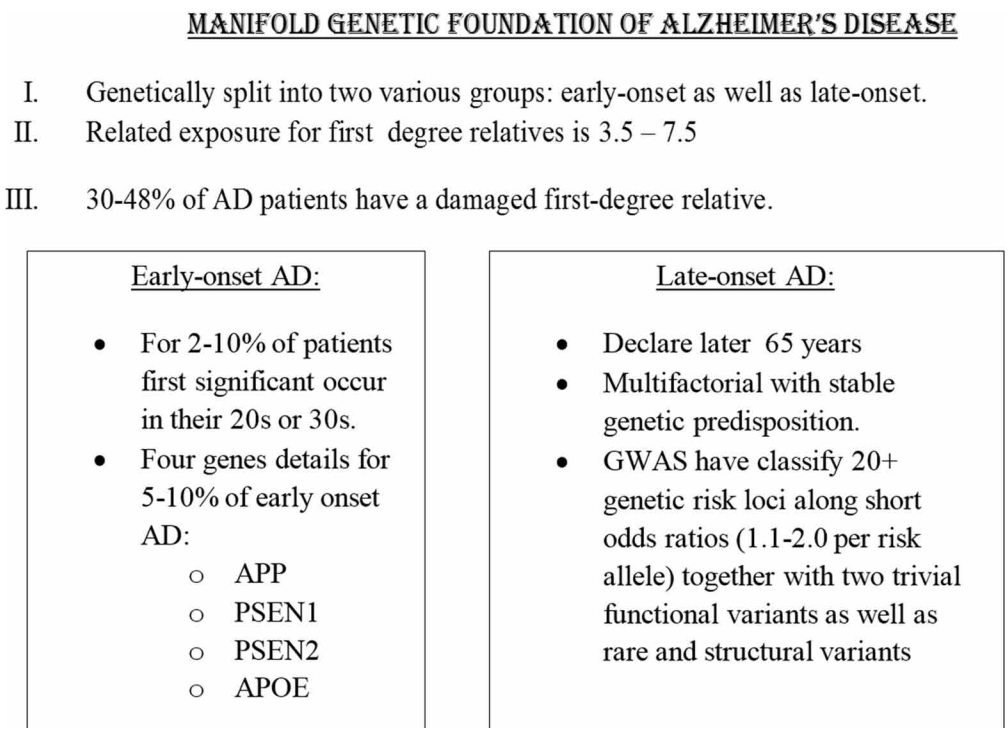
Figure 1. Complex genetic makeup of AD



Other molecules are generated by this cleavage and may show an act in the disease but Abeta is the main culprit. Abeta tends to misfold and become sticky eventually clumping together to form soluble oligomers. Some of these aggregates into large fibrils that deposited in the brain as plaques vide Tobin (1987). The oligomers come in several forms or species. We do not know which species are toxic, but research shows that they weaken communication and plasticity at synapses. This could stop the brain from forming or retrieving memories. Neurons are not only cells affected in Alzheimer's disease, astrocytes and microglia also play a role. Microglia are immune cells that clear our waste and prune synapses during development. Microglia take up Abeta but they also get activated by it triggering the release of inflammatory cytokines that can damage neurons. The microglia also start to remove synapses by phagocytosis. As synapses start to misfunction and neuron die, an abnormal pattern of activity emerge and eventually the brain cannot process and store information properly. Another key feature of Alzheimer's disease is neurodegeneration. In this neuron death is triggered by Abeta, but some time Abeta's effects seem to be mediated by another protein like Tau component. A healthy neuron, molecules are carried along the axon on a series of tracks made by microtubules and established by Tau. But in Alzheimer's disease, Tau is modified, causing it to dissociate from the microtubules, adopt an abnormal shape and move from the axon to the cell body. Like Abeta, Tau comes in a variety of forms and we do not know which one contribute to what type of disease. According to a neurologist, Tau will remain soluble, or stick together and make a tangled structure in the brain. Eventually, these processes kill the neuron. Another problem seen in animal models is that misfolded Tau protein can spread, across synapses into healthy neurons. There they make healthy Tau proteins which start to misfold as well, spreading the pathology across the brain. The pattern of spreading through the different brain regions matching the

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changing symptoms from early to late stage of Alzheimer's disease. This pattern also reflects how certain neurons are more vulnerable than other dying neurons. Despite these advances in our understanding of Alzheimer's disease, no cure of AD exists. While drugs are being developed to target Amyloid Beta or Tau, it is unclear whether they will eventually be successful in treating the disease. There is only one certainty: continued support for basic and clinical research will enable us one day to diagnose and treat this devastating condition.

EVOLUTION OF ALZHEIMER'S DISEASE

Curing of Alzheimer's disease (AD) is one of the most challenging tasks. Researchers are trying to understand the main mechanism of the brain. The brain plasticity is a very important mechanism in the brain hippocampus. This mechanism is really elaborate on learning as well as memory functions. The question arises: what are the mechanisms that initiate experience the gradual transition of physiology to pathology? Most of them are unknown. Alzheimer's disease (AD) is the biggest frequent and common form of Dementia. In the last 10 years, unfortunately, all the clinical trials fail. Doctors are trying to understand why it happens, and if you are looking through the research during the last 50 years, it is clear that Alzheimer's disease (AD) is uncommon of the serious problems for every individual vide Ng et al. (2007). So, Pharmacist tried to design drugs which help to reduce the plaques in the brain. But it didn't work out and if you reckon current research it clearly shows the dysfunction of synapses. According to Ming et al. (2005), the neurons in the brain are really the primary cause of the disease. The reduction of synapse inside the brain will be caused by the cognitive decline in remembering things. Hence the question is arises: What will initiate the synaptic loss? Loss of synaptic integrity is combined with the pathogenesis of Alzheimer's disease (AD). However, it also correlates with cognitive decline in amyotrophic lateral sclerosis (ALS). Synaptic loss is the strongest pathological cognitive decline in the frontal cortex and it can predict whether or not someone would have a cognitive problem as well as the motor problem in ALS. According to the neurologist, it is found that people who had cognitive problems, as well as their motor symptoms, did have significantly lower synapse density in BA9 which is frontal cortex than people who only had the motor symptoms. This support the hypothesis of synapse and generation of multiple neurodegenerative diseases. The brain consists of amyloid beta peptide that can be produced by different lenses short like 42 amino acids. During the last 20 years, many patients are suffering from Alzheimer's disease due to mutations which are given by the ancestor. The increase in production of toxic amyloid beta 42 has a high tendency of Alzheimer. So, the amyloid beta peptide can be the monomeric form which can be reduced by eating the legume in the daily diet. The novel studies view that higher levels of soluble oligomers can cause the end of the synaptic depression to vide Ng et al. (2007). So, reduction in synaptic activity and brain activity will end the memory decline. The huge progress has been done during the last 20 years in biochemistry related to Alzheimer's disease. Causes of Synaptic dysfunction are still not known. In fact, there are several key questions to be answered. In upcoming years we have to gather more information about ancestor based Alzheimer's disease (AD). The ratio of Alzheimer's disease patients is increasing every day. We have to find how the synaptic depression was caused and how the molecular mechanism is working for the synaptic change. The overall study of Alzheimer diseases (AD) is described in Figure 2.

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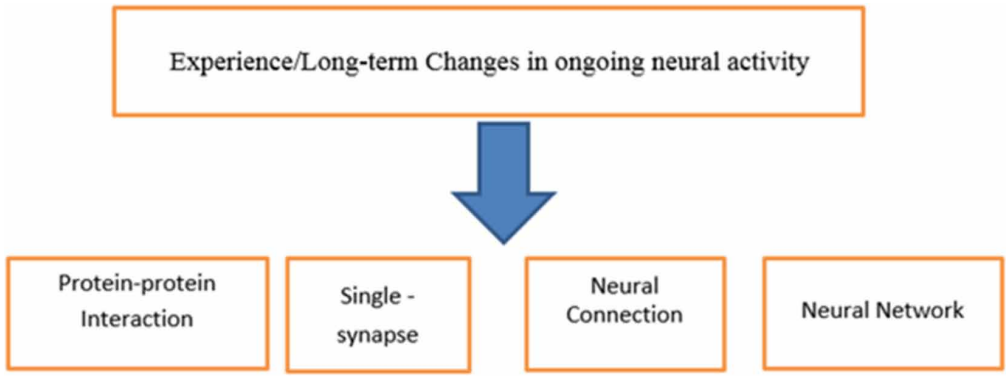
Figure 2. Method of study



COMPUTER SCIENCE SUPPORT IN ALZHEIMER'S DISEASE DIAGNOSIS

Biomedical image processing is used for the interpretation of Alzheimer's disease (AD). The ability of an earlier diagnosis of any disease is achieved by using different techniques of computer science. Various breakthroughs and researches have been done to increase the ability for diagnosis of Alzheimer's disease. Whereas doctors are used in doing brain slicing to examine the different blocks of the brain at the microscopic level. But using the Advance imaging tools will also provide the visualization of brain parts in 2D and 3D forms. We can see the amyloid image which is responsible for Alzheimer. There are various tools present to analyze the spinal fluid. Traditional techniques like lupuncture used a small needle to obtain the spinal fluid sample. A critical way to measure in spinal fluid defines whether the patient is anguish from Alzheimer's disease (AD) or not.

According to Reisberg et al. (1982), scale vide the Global Deterioration Scale for assessment of primary degenerative dementia Alzheimer is divided into seven stages which are shown in Figure 3.

Stage 1: No Impairment: In this stage, memory and cognitive abilities are normal. If there are any impairments, they might only be slightly apparent to the patient themselves.

Stage 2: Very mild cognitive decline: In this stage, we can see some trouble in remembering the recent events or information, but it could be a more subtle thing like forgetting a word or misplacing things. Friend, family and medical workers cannot detect these lapses and change in thoughts. The reasons is that half of peoples over the age of 65 experience the loss of concentration and difficulty in recalling names or words.

Stage 3: Mild Cognitive Impairment: According to Gauthier et al. (2006), it is a point where subtle difficulties can start to impact their daily life. The patients might consciously or even subconsciously try to hide these issues. They might remember what was just said or read and planning and organizing, which can all start to affect life at home or at work. It could be still difficult though, to diagnose Alzheimer's at this very early stage.

Stage 4: Mild Alzheimer's disease: This stage lasts about two years, and during these two years things like financials and math start to become very challenging. And the ability to remember recent events and what was just learned become increasingly difficult. The patient might have trouble carrying out tasks especially if there are specific sequences, like cooking and driving. But the patients are

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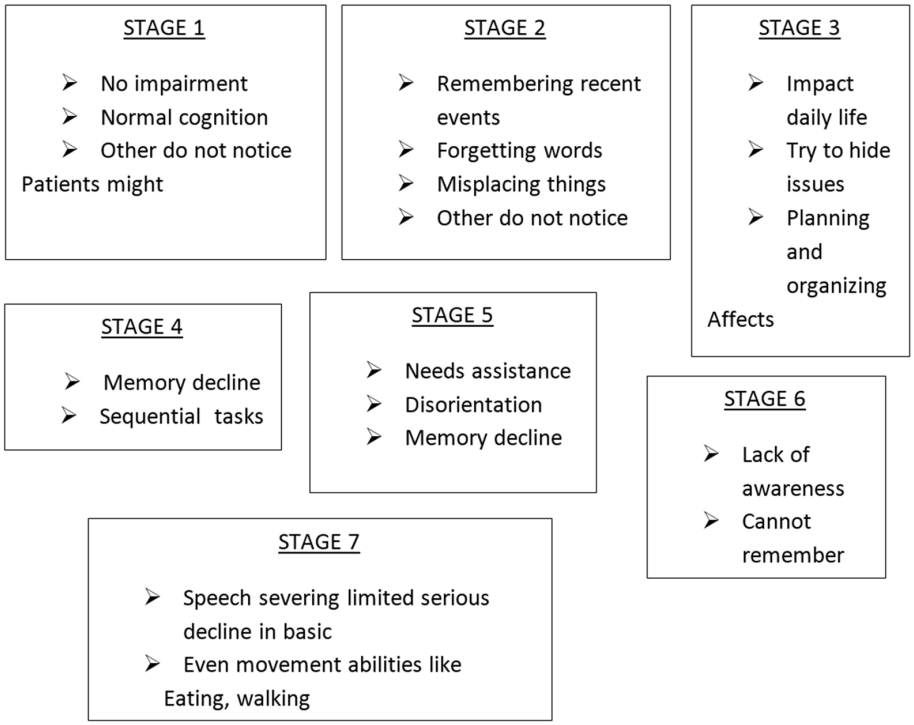
still usually able to recognize their family and friends although a diagnosis at this stage is usually accurate.

Stage 5: Moderate Alzheimer's disease: More drastic and the patients require some assistance. They will probably have trouble remembering things like an address or phone number and can be disoriented very easily regarding the time or place. This stage can last an average of about 1.5 years.

Stage 6: Moderately Severe Alzheimer's Disease: In this stage, there is a significant lack of awareness of current measures as well as the inability to remember the past and carry on the conversation; they will likely need help with essential regular functions like getting dressed, eating, as well as going to the bathroom. The patients will likely be unable to recall the names of family members yet will likely notice they are familiar. This stage lasts about 2.5 years

Stage 7: Severe Alzheimer's disease: Speech becomes severely limited, and there is a serious decline in basic abilities. Even movement abilities like eating, walking, sitting or standing up all start to fade as the disease starts to spread to more areas of the brain. Patients need extensive assistance in eating and drinking as they can lose the ability to discern when they are thirsty or hungry. Therefore they need total assistance and care around the clock for all functions of daily life. Due to these inabilities, they become much more susceptible to secondary complications such as diseases and infections especially pneumonia and falls. This final stage can last from one to two and a half years. But again it is very important to stress the flexibility in the timeline in these stages. Not all patients with Alzheimer's will experience this exact progression, some may deviate significantly from the expected duration with each stage and the disease itself.

Figure 3. Stages of Alzheimer Diseases



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BACKGROUND

Biology of Alzheimer's Disease

Alzheimer's disease (AD) is a continuous neurodegenerative disease in which dementia symptoms deliberately damage your past memories Tiraboschi et al. (2004), is written in the paper that Alzheimer disease is evolving by a collection of β-amyloid plaques as-well-as tau tangles. Luchsinger et al. (2019), hold that actual treatment is not available at present for preventing or reversing the disease. Social connections and regular mental activate can lower the risk of AD. But the reason behind these facts are not known to vide Stern et al. (2006) and Szekely et al. (2007), and Paradise et al. (2009) established that the neurogenesis arises from subventricular zone of the lateral ventricle as well as the subgranular zone of the hippocampus and progresses throughout life vide Ming and H. Song et al. (2005), Balu and Lucki et al. (2009). In the SGZ region, new cells are differentiated into both neurons and glial cells, as well as the new-born neurons, incorporate to the granule cell layer of the dentate gyrus vide Lledo et al. (2006), a growing body of clue hold the contribution of new born neurons to hippocampus-dependent memories vide Shors et al. (2001), Saxe et al. (2006). However, conflicting results have also been reported. For example, ablation of hippocampal neurogenesis has no effect on tasks including contextual fear memory and Morris water maze vide Shors et al. (2002), Snyder et al. (2005).

Classification Feature Extraction Approach

Classification feature extraction approach can be categorized by voxel method, vertex method and ROI method vide Zheng, et al. (2015). In the mid-1990s, Wright et al. (1995), started the study of the gray matter and the white matter voxel assessment. He used statistical methods. Voxel-based methods usually use statistics of voxel diffusion on large scale of brain tissues vide Vemuri et al. (2008), and Davatzikos et al. (2008), Fan et al. (2008), Kloeppel et al. (2008), Magnin et al. (2008), Leo Z et al., J Ye (2008), calculate the voxel importance histogram in large scale anatomical regions, which could be accessed by each of two image segmentation. Fan et al. (2007), Davatzikos C et al. (2007), Misra et al. (2009), proposed an additive parcellation method. In this method, the image space is apart into the better discriminative regions. Liu et al. (2015), suggested voxel-based morphometry (VBM). Currently, Liu et al. (2015), proposed a simulation method to predict the longitudinal brain morphological mutation in degenerative brains placed on VBM. Clinical experiments lead to the conclusion that if we want to differentiate between MCI, NC, AD we require a volume of anatomical regions, as well as their vertex atrophy, vide Desikan RS et al. (2009), Querbes et al. (2009), Direct index of atrophy caused by dementia is defined by cortica thickness. Cortical thickness is measured by an elegant method given by Querbes et al. (2009), cortical thickness measurement helps in the cortical atrophy. Lerch et al. (2005), suggested a link between cortical atrophy and the changes examined by a microscope which observes the appearance of diseased cells in biological tissues. Desikan et al. (2006), divided the brain into parcels viz. neocortical and non-neocortical ROIs. He used the mean thickness and volume of each ROI as features. Methods based on ROI determine image features in major brain components e.g. corpus callosum, cingulum, fasciculus, and hippocampi. Neurodegeneration in AD starts in the medial temporal lobe and affects entorhinal cortex, hippocampi and limbic system. It extends to neocortical areas vide Braak et al. (1995), National Institutes of Health (NIH) (2005). Most of the researchers in this area hold the view

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that medical temporal atrophy is a sensitive AD biomarker vide Frisoni et al. (2010), CR et al. (2010). This is why in most of the studies use hippocampi as a marker of early AD vide Cuingnet et al. (2011).

CASE STUDY 1: AUTOMATED IMAGING MODALITIES OF DIAGNOSIS OF BIOMEDICAL ANALYSIS IN 3D IMAGES

Magnetic Resonance Imaging (MRI) is not an invasive test. It requires a powerful magnetic field as well as radio frequency pulses.

Brain MRI Mapping

The procedure is very simple, the patients to lay flat inside the MRI suite. And is provided with a cushion for your knees which will help in to take some pressure off from the back. The test is a bit noisy so patients are provided with some hearing protection gear. In this case, earplugs are given, there is also a call button facility which is required in case patient need to stop the test or want to talk with the technician. MRI is used to collect the brain image and therefore head is placed inside a head coil. The coil is nothing but a fancy antenna which uses to collect the MRI data. The table-like platform is raised and the head is placed in the center of the machine. Now, the rest of the body is still outside the MRI scanner. As per the Doctor's permission, the test proceeds, and contrast injection is injected. This procedure will normally take about half an hour and during this time the technologist will keep tracking your all date. Once the MRI is completed the technologists will re-enter the room and slide the table out of the machine, it will lower the table and take the head out from the coil. This is the whole scenario for the MRI scanning procedure.

Diagnosing Alzheimer's Disease

According to Cummings et al. (2007), diagnosis of Alzheimer diseases (AD) is conducted by the MRI. The magnetic field, as well as Radio Frequency Pulses, are used to build the virtual structure of all the internal parts of the brain. The soft tissues and detailed pictures of organs are used to predict the irregularity in brain condition which is associated with MCI to AD. In the prodromal stage of Alzheimer, the MRI examination of the brain is found to be normal. Basically, it affects the temporal and parietal lobes of the brain. The size of different areas of the brain may show a decrease during MRI scanning. Whether a person has Alzheimer's disease or not can be determined in a single test. According to Petersen et al. (2001), symptoms of Dementia help in the diagnosis of the disease. The Medical evaluation is conducted by using the medical history of the patient, mental status, physical and neurological exam, blood test and brain imaging. In the late '70s, most of the people develop a mild memory loss. According to neuroradiologist, it is a normal part of aging. A sign of dementia is the inability to recognize a person or the patient recognizes after some time. According to the Alzheimer's Association, 5.7 million Americans are suffering from Alzheimer's (AD). By 2050 this number is calculated to increase by nearly 14 million. More and more are people looking for the doctors for diagnosis? The doctors can only provide immediate reliefs while checking the MRI images. The neurologists cannot ensure that the patient is not suffering from cerebral infarction, stroke, old trauma, and unexpected brain tumor. But using advanced software for comparing the brain volume with a large database for predictions including gender and age

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for matching. The comparison can help doctors to know whether memory loss is related to Alzheimer's or not. Currently, the tremendous amount of research is going on in a country like the US, UK, India, etc. for the analysis of Alzheimer's (AD). Different medications are being developed to slow down the process of Alzheimer but there is no accurate diagnosis available to help the patient.

Advantages and Disadvantages of MRI

As with any form of medical measure, there are also a few "Pros" as well as "Cons" such as MRI is not an invasive imaging technique and doesn't involve exposure to ionizing radiation. The contrast material in some MRI has less probability to produce an allergic reaction when compared to the material based on iodine. However certain metal used in MRI examination cause problem. If a coil malfunction during the scan it causes serious damage to brain cells which cannot be recovered

fMRI (FUNCTIONAL MAGNETIC RESONANCE)

For a long period of time, we have not known anything about the brain. That's because it is extremely dense to measure the changes in electric signals during brain activity. In the year 1992, the invention of Functional magnetic resonance imaging (fMRI) done by a group of scientists in order to observe brain activity. Functional magnetic resonance (fMRI) imaging is also not an invasive approach to examining brain activity or in short it allows us to learn about what every single brain block.

Working Principle of fMRI

The fMRI is a magnetic field based imaging machine which is used to scan the brain block. It is a very powerful magnet, 10000 times stronger than the earth magnetic field. The brain is made up of neurons and these communicate with each other using electrical signals. Now a brain area becomes more progressive when the neurons inside that the brain area start sending more signals than before. For example, if you want to move your arm, the fMRI view that which brain area is lights up or become active so that you can know which brain area is mainly responsible for your arm movement. But it is not possible to measure electric signals directly from the scalp. To find the exact origin of the signal in the brain area by measuring the signal by overlaying signals that you actually want to measure. Now fMRI can solve the problem but it also involves three things:

- **Blood Neurons**: These have a pretty nifty trick after sleep. When they become active they need more oxygen which they get from red blood cells (RBC). So, what they do is that they actually widen the blood vessels surrounding them in order to attract more oxygenated blood. That means that a neuron becomes more active with oxygen concentration.
- **Water and Spins**: Our bodies are mainly made up of water and each water molecules has a spin orientation of hydrogen atom. The magnetic property is generated by the spin orientation of the molecules. Now we all know that how the compass always points to the north because it always aligns with Earth magnetic field. The same thing is done with water molecules but you need a much stronger magnet like fMRI machine. Our bodies are mainly made up of water. Each water molecule has something called a spin which gives its magnetic property. For example, the compass

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always points to the north because it wants to realign with the earth's magnetic field. The same thing holds for the water molecules but it needed a much stronger magnet like fMRI machine. Suppose, you want to align the water molecules in your strong magnetic field on same position and direction then you add a little bit of energy in the form of radio waves. You can actually force them for the alignment. If you want to stop sending radio waves all the molecules regained their original position. It shows that radio waves can add up small energy to strong signal for the alignment.

- **Magnetic Field Disturbances**: Small interference in the magnetic field cause a serious problem for the patient. Suppose that a magnetic field has a small disturbance that causes water molecules to desynchronize faster. For example, two coins are spinning on your desk and one of them constantly bumping into other objects then one will stop spinning earlier. Similarly, for water molecules also it turns out that deoxygenated blood causes such disturbances while oxygenated blood doesn't. Now we can put everything together, a brain area becomes more active, causes the blood vessels riding meaning more oxygenated blood flowing towards it. It means less magnetic field disturbances. The spins synchronizing for a longer period of time and the signal that we want to measure staying for a long duration of instant. In other words, what fMRI is doing is that it looks at a particular brain area and repeatedly measures how long the signals stay and when that signal start staying longer. We know there is more oxygen and we know that the brain area is becoming more active

Just twenty year ago we hardly knew anything about the brain but with fMRI, we are able to learn so many things. Every single brain area is responsible for movement in the body. The scientists are already looking at the next frontier and brain research. Now the current work is going on:

- How the brain areas are connected to each other?
- How they work together depending on the task goal?

The network of connections inside the brain would have tremendous value. One day one will be able to diagnose depression by just looking at how the brain map of patients differs from a healthy people's brain map. It could also help to explain how a tiny brain is capable of so many amazing things. Computer and Brain scientists are already working together to build new powerful computers that mimic the human brain. All these advancements and many more were largely made possible by fMRI (Functional Magnetic Resonance Imaging).

Advantages and Disadvantages of fMRI

See table 2.

Table 1. Pros and cons

Modality	Advantages	Disadvantages
fMRI	• Spatial resolution is good • Not invasive • Easily available	• Almost low temporal resolution • It cannot trace neurotransmission-related PET

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PET (Positron Emission Tomography)

Positron emission tomography (PET) is used to represent images of diminutive changes in the body's Meta. The procedure for scanning is as follows: a PET scan will have restrictions on what a patient can eat or drink before the start of the procedure. Detailed information on diet is especially given by the technologist. Another precaution taken by the doctor does not bring any children or pregnant women inside the room. The technologist first checks the blood sugar and then the radioactive tracer called FDG is injected. The radiotracer is circulated with blood for about 45 minutes. After that, the PET scan is taken. After the examination, you will not feel anything. You have to body drink plenty of fluids to flush the radiotracer. A radiologist will review the report sent to the physician for thorough evaluation. The computed tomography images are used to allow the physicians to identify the correct locus size as well as the shape of the tissue or else tumor. PET scans are often used in to detect the cancer cell. Whereas, PET scan of the brain is used to evaluate the patients suffering from memory loss, seizure problems, or brain tumors. PET scans of the heart are used to check the blood flow inside the heart muscle and it also helps to evaluate the signs of the heart disease.

Workflow of PET Scan

A PET scan uses a radioactive tracer to make 3D images of the body. The radioactive tracers are administered to the body of the patient through intravenous injection. The tracer consist of molecules that are lightly bounded to an isotope. The molecules can interact with specific protein-sugar in the body. If a doctor suspect's the sign of cancer or wants to know cancer's cell growth. Then the molecule is FDG which is a modified form of glucose. When tissues absorb a lot of glucose it indicates a cancerous tumor. The isotope produces small particles called positrons. Positrons interact with surrounding electrons resulting in the complete annihilation of both particles which release two photons. The detectors in the PET scanner measures theses photons movements. It is used for creating an image.

Advantages and Disadvantages of PET

Advantages

- To study bodily function in biomedical processes, PET scan is able to detect disease easily before any sign and symptoms show through the biomedical process. Hence PET scan is more effective as compared to another medical imaging test.
- PET scan can easily find metabolic function and can also easily determine how far the disease has spread when compared to biopsy and other exploratory surgeries.
- PET scan is an effective biomedical tool that can help in to minimize the number of unnecessary surgeries.
- PET scan are very effective tools for easy detection of Alzheimer's, epilepsy and other mental illnesses.
- PET scan is exposed relatively very low radiation dosage as compared to other forms of CT scan.
- Through the infection from a medical procedure, people are scared. PET scan is the best options for analysis of the body.

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Disadvantages

- PET scan is not very good especially to pregnant ladies because of the radioactive elements used in the scanning process.
- PET is an expensive treatment compared to another form of medical imaging. The PET instrument (cyclotron) are attached to it which emits radioactive rays.
- To create radio-isotopes for radioactive rays is not good as well as a radioactive component at the time of scan are not long lasting. That's Why PET imaging is required a number of times again and again.

Table 2. Comparison between MRI and PET

	MRI	PET
Patient Advantages Drawbacks	• The non – invasive method • Free Radiation combine with imaging • Consist of two possibly anatomical as well as biochemical information from MR spectroscopy. • Smaller patient bore due to the claustrophobia • Interior body contraindicated in patients for loose metal foreign bodies.	• Using PET scanners used for both anatomical as well as functional information • High acquisition scan • Direction by intervenes injection related to radiopharmaceutical compounds
Imaging Advantages Drawbacks	• Among good spatial resolution major soft tissue imaging. • Any oblique plane is the correct multiplanar capability to image • Distortion in MR image • Being dosimetry due to lack of electron density information • To make DDR (digitally reconstructed radiographs) due to lack of cortical bone information.	• Both functional as well as biological information. • Either conventional imaging may have diagnostic value. • Major increase asses locoreginal lymph node correctly than CT • Finite spatial resolution • Lesion detectability • Large interobserver variability • The variable result of thresholds
Machine Advantages Drawbacks	• Strength as well as positioning for RT, easier patient access for open MRI system • Shorter bore than CT(50cm) • Twisted table top	• Comparative high bore (70cm) • Smooth table top • Protecting to escape radiation risk

CASE STUDY 2: APPLICATION OF MACHINE LEARNING IN BIOMEDICAL IMAGE PROCESSING

Machine Learning Used in Medical Image Analysis

Analysis of medical image is being widely used in the modern system of disease diagnosis. With the increase of patient's data, we face new challenges and get a new opportunity for a different stage of the clinical routine. Use of machine learning helps in automatic analysis of patient's data. Modern techniques of Machine learning are used for automatic measurement of anatomy and anomalies. It can monitor disease progression semantic navigation and visualization. It can also develop a natural user interface for Doctor's, computer-aided diagnosis and personalized medicine. Here, we will talk about the analysis of radiological images which is used in medical science. But in many cases, patients undergo medical scans

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such as CT scans, Magnetic Resonance Scans (MRI) which is used for looking inside of your body. PET is another type of scan which uses the ultrasound for scanning. There are many ways of acquiring medical images. Applying modern machine learning technique to the automatic analysis of medical scans like CT scan of the patient it helps for computed tomography. With a patients scan image, you can see the different horizontal views and different side views of the patient. First of all, we want to automatically identify the spine parts of the patients. After that, it is important to identify as well as analyze whether there are broken vertebrae. Because the spine is a natural coordinate system for the patients. So, it is very helpful. They already have a good idea of where the spine is and not only have that you have an exact name for each of the vertebrae. So, any trained radiologist will able to identify the location. Using the machine learning technique we use the labeled data of patients. Using some machine learning algorithms is used to learn the model by using the labeled data of the patients. Three-dimensional (3D) and four-dimensional (4D) imaging play an important role in computer-aided diagnosis treatment. At the same time progress in (Supervised and unsupervised), machine learning techniques lead to the solution many old problems by computer-vision based machine learning.

Artificial Intelligence in Medical Image Classification

What is Artificial intelligence (AI)?

Artificial intelligence can be defined as vision, hope, and threat to the world. With the help of Artificial Intelligence image-based data analysis is used to extract more information for the diagnostic process. It also provides a way of treatment and decision support for any patient data. Artificial Intelligence can be used to detect various diseases. Using a simple body scan can provide enough data to detect any diseases. Doctors are trained for many years to do this type of diagnosis but the error rate is still higher. Artificial intelligence (AI) can diagnose disease better than any human being provided the datasets is correctly trained. This will lead to a considerable reduction in the rate of patient's death. Artificial intelligence thus is a powerful tool for the diagnosis of any disease. In the current scenario, artificial intelligence start-ups are growing very fast in the field of healthcare. The radiologist regular disagree on their respective interpretation of medical images but artificial intelligence can do many things. It is estimated that the results are 10% more accurate than any average radiologist. The accuracy gap will only be increased by using more computing power. It also gets cheaper and applied in many countless subfields. Doctors also have to understand the patients' medical records and it can be a very complex task. A Natural Language Processing is a sub-branch of artificial intelligence that helps in to understand human language. It used for evaluation of thousands of medical records in optimal time. The objective of artificial intelligence is the diagnosis of patients without any preconceived socio-economic notions which can produce disparities in care. Today Computer's algorithms are performing the unbelievable task with a high degree of exactness using superhuman intelligence. This intelligence of computer is known as Artificial Intelligence (AI). AI will make a profound impact on human lives in the future. In spite of this, we have to phase big challenges in detecting and diagnosing, many fractal diseases such as cancer as well as other bacterial, viral and genetic diseases. The only way to save their lives is to make only the detection and diagnosis of diseases. If a person is suspecting the above types of diseases. Some expensive medical test like CTs, MRIs, fluorescent imaging is necessary. After the collecting of images, another expert physician analyses those images and talks to the patient. Thus the process requires several resources viz expert physician, medical imaging technologies. This expensive process is not suitable for developing country like India. It is better to solve this problem by using new techniques of Artificial

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Intelligence (AI).In traditional Artificial Intelligence (AI) approaches we require tens of thousands of very expensive medical images which are sent to the expert physician for the analyses. Using these two information's one can train the system using a deep neural network. In the new approach of Artificial Intelligence (AI) we start with a single medical image. From this image one figure out a very clever way to extract billions of information packet. Thus one convert one image into billions of training data points viz colors, pixels, geometry, etc. One starts with standard white light photograph acquired either from a DSL camera or a mobile phone for the patient. Then one overlay the billions of information packets mentioned above. One to this image creating something called composite image. This one requires only fifty composite images to train one's algorithm to high efficiencies. We can see that in this new process. We can provide a diagnosis using a white light photograph from the patient instead of expensive medical imaging technology. Traditional Artificial Intelligence was reached in data but poor in application

CASE STUDY 3: AUTOMATED 3D TOOLS USED IN BIO-MEDICAL ANALYSIS

Case Study Cannabis User and Controls

In this paper, the author uses the Freesurfer software. It is an open source software suitable for processing and analyzing (human) brain MRI images. The 3D features extraction packages like Neuroimaging analysis software package. It fully characterizes the anatomy of cortex thickness, folding patterns, ROIs, subcortical structure boundaries and longitudinal. The Surface extraction like Inter-subject Registration and Multi-modal integration like fMRI (task, rest, and retinotopy) and DTI tractography.

Working of Freesurfer

Freesurfer is an analysis suite for brain image segmentation vide Muschelli et al. (2018), the vast majority of our work is on MRI and brain imaging. Freesurfer is a fully automated pipeline tool to characterize the anatomy of brain blocks. Each block is well labeled by using the Freesurfer. Every macroscopically visible piece of brain block is generated by using a reasonably good input image. To measures the brain anatomy the input data is very reasonable in quality. The procedure is pretty much automated. Sometimes it also faces the failure modes. So, for the precaution, we always advise to look through their data and make sure that the results are what they except. If you are doing some type of group study and you find an effective interest in the analysis. Here, we use Freesurfer to analyze the different models for brain cortex. The brain is divided into two parts functional organization and structural organization. The cortex is just like sheet whose thickness is half a millimeter. However, voxel has a certain issue such as one single voxel can encompass information from two anatomically distinct areas. For example, if a single voxel encompasses two distinct gyri, this can make localization of fMRI activation much less accurate. The voxels and volumetric data are much harder to estimate structural properties such as gray matter thickness and gray matter volume to address this problem. We are going to use Freesurfer a program that reconstructs the cortical surface from the 3D volume. The reconstruction process converts this volume from 3D voxels to 2D triangles. The points of the triangle are called vertices and the lines connecting them are called edges. Each vertex contains a number indicating gray matter volume, thickness, areas, curvature as well as another surface of the brain.

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Datasets Description

We are using Freesurfer to analyze a dataset from open source (fmri.org). Dataset consists of both cannabis users and control subject. The datasets are collected from the website openneuro.org. According to L. Koenders et al. (2016), Data comprises of Heavy cannabis users (N = 20, age baseline M = 20.5, SD = 2.1) as well as non-cannabis working healthy controls (N = 22, age baseline M = 21.6, SD = 2.45) endured a full psychological valuation and a T1- structural MRI scan at baseline as well as 3-years follow-up. Entire structural MRI scans were collected by 3T MRI scanner (Intera, Philips Healthcare, Best, and The Netherlands) through a phased array SENSE eight-channel receiver head coil. For all participant, a T1-weighted structural MRI image was attained (T1 turbo field echo, TR 9.6 s, TE 4.6 s, 182 slices, slice thickness 1.2 mm, FOV 256x256 mm, in-plane resolution 256x256 mm, flip angle 8°).

Procedure

Here we are going to discuss a single subject data out of 42 samples data size. We use a single virtual machine to find out the whole brain reconstruction process. The correlation analysis is used for comparison between two individuals. The separate time point is baseline and a follow-up session is used for longitudinal analysis of brain. Since it contains one of two different groups which can be compared to individual difference measures which can be used for correlation analyses, and three two separate time point a baseline and a follow-up session this can be used for longitudinal. Let's take a look at the directory structure in Figure 4. Each subject directory contains a baseline anatomical and a follow-up anatomical for this analysis. We have compared baseline anatomical scans of the cannabis users with the baseline anatomical scans for the control subjects. Freesurfer analyzes individual subjects or several subjects simultaneously (represented in Figure 5). Here, we have to cover the batch mode and custom options.

Figure 4. Representation of sample data

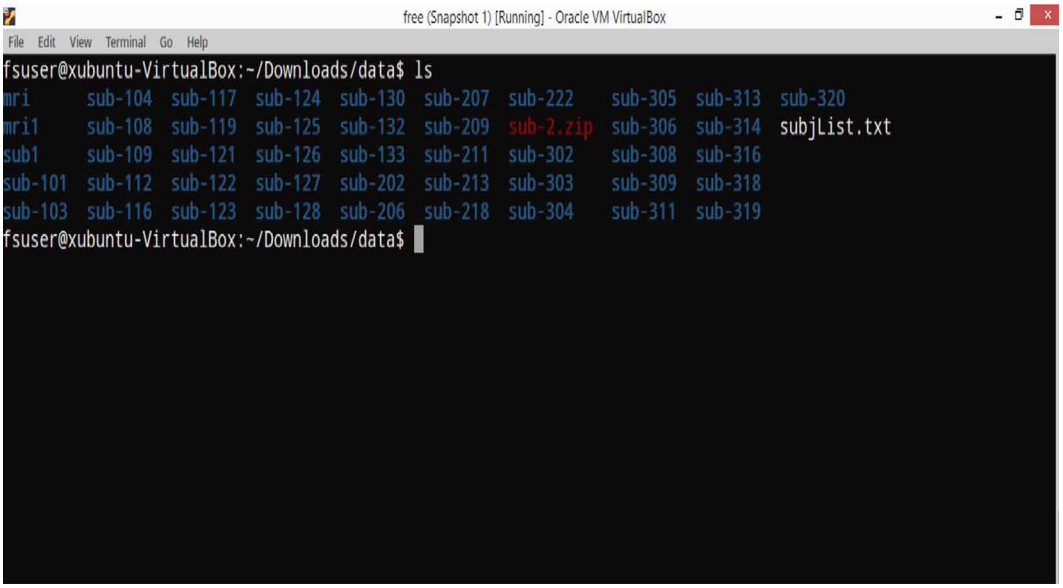

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Figure 5. Representation of single set data

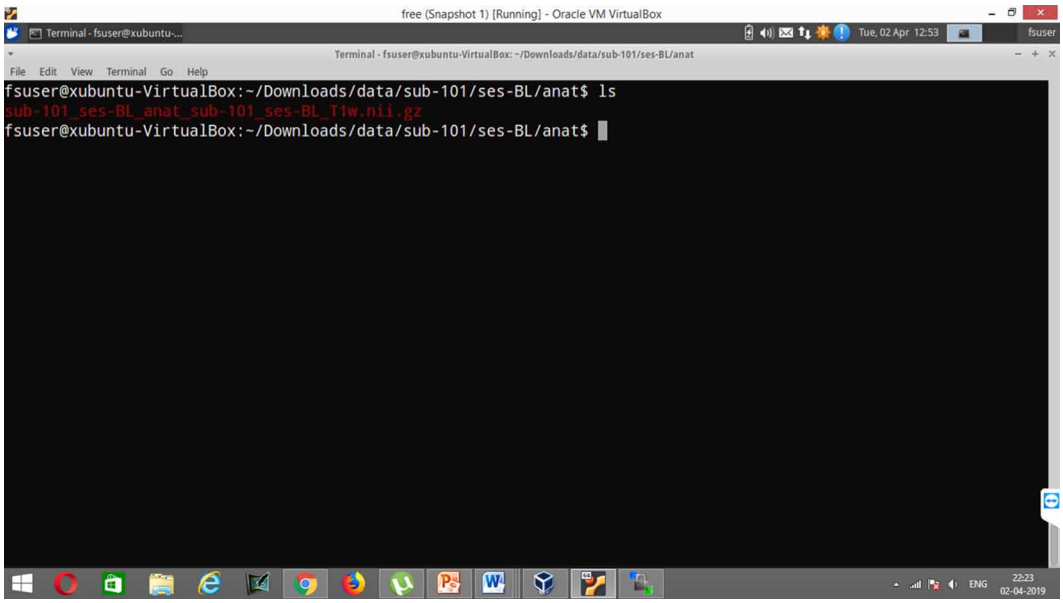

Figure 6, represents the individual difference within the data. Each subject directory contains a baseline directory anatomical and a follow-up anatomical. For this analysis, we compare the baseline anatomical scans of the cannabis users with baseline anatomical scans for the control subjects. Freesurfer can analyze individual subjects or several subjects simultaneously. Here, we first create a text file of subject_list.txt by using the grep command. we then redirect to subject_list .txt, run the script to prepare the data for surf. Each subjects anatomical folder in the baseline session and then runs a recon-all command which is shown in Figure 6 and Figure 7. Here, 30 different reconstruction brain processing outputs are done if you notice that Freesurfer has not failed at any stage for reconstruction. For again the reconstruction of the result, you can go back and run a subset of those steps to save time. Note that all flag is omitted which will only convert the anatomical data set to (.mgz) format and then create subfolders for the Freesurfer analysis without any further pre-processing.

Here, we have implemented the segmentation process for one data sample. The same process is done for 42 different samples using Freesurfer 3D automated tool for reconstruction of the whole brain. The performance of Freesurfer is increased by using the high performance computing machine) or remote server. One major disadvantage regarding Freesurfer is its high computing time if using a single machine. It takes so long to analyse a single subject as shown above figure 6 and figure 7, that it might take 6 to 24 hours for single subject analysis. In the case of several subjects, processing can take weeks. This disadvantage can, however, be overcome using high performance computing machine.

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Figure 6. Reconstruction of brain 1

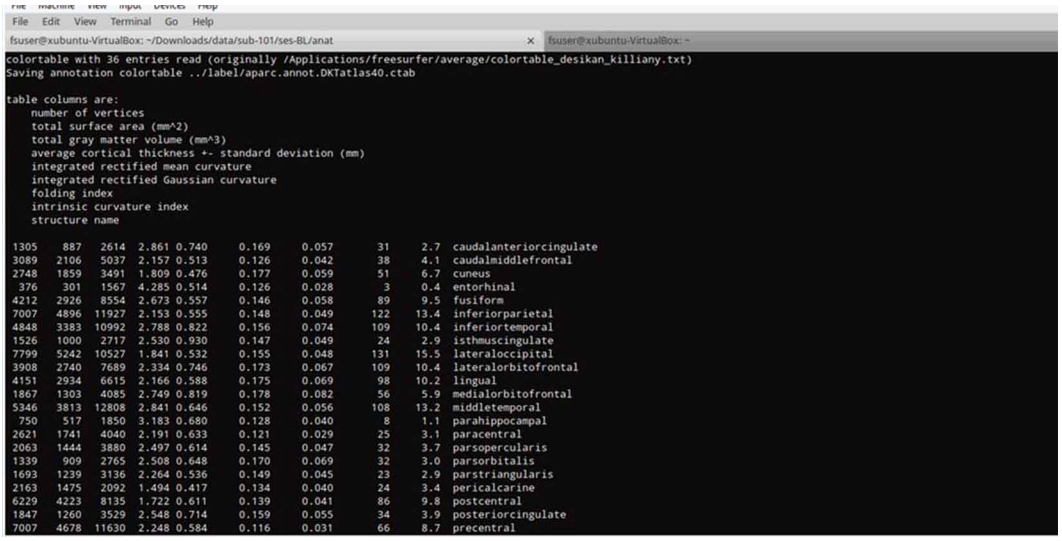
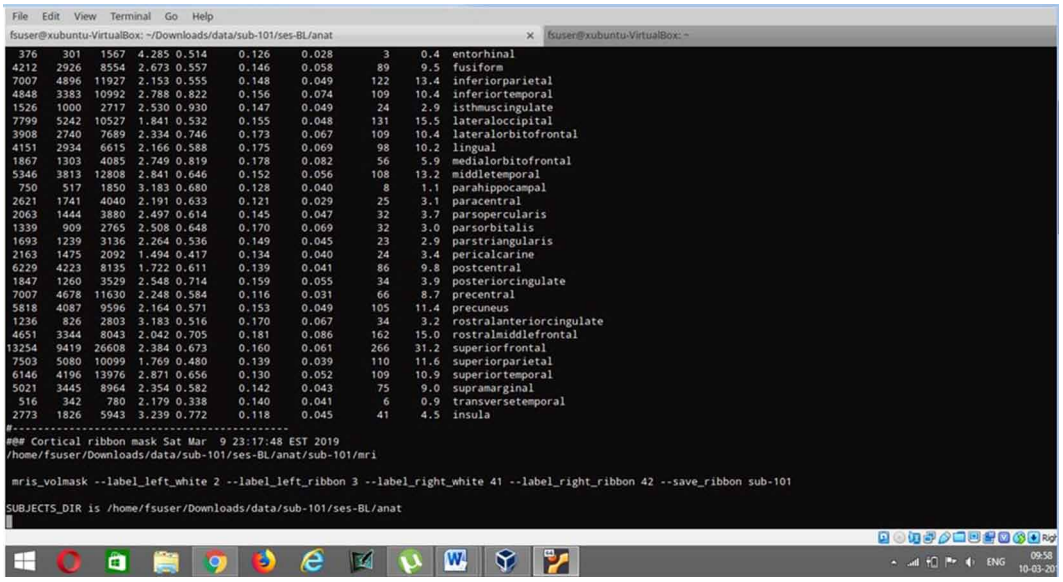


Figure 7. Reconstruction of brain 2



CONCLUSION

A brief introduction to Alzheimer's disease and its diagnosis by biomedical imaging has been presented. The last two sections aimed to provide the solutions and uses of biomedical imaging in the diagnosis of Alzheimer Diseases. The solutions are exhibited through three case studies. It evolves the machine learning technique to meet the challenges of modern health care system. Foremost diagnosis using biomedical imaging technology is a better track for prediction. The methods are used to quantify the value of care and it also evolves a shift from fee-for-service care to value-based care.

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Chapter 11
Neuro-Imaging Machine Learning Techniques for Alzheimer's Disease Diagnosis

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ABSTRACT

Alzheimer's disease (AD) is considered one of the most common dementia's forms affecting senior's age staring from 65 and over. The standard method for identifying AD are usually based on behavioral, neuropsychological and cognitive tests and sometimes followed by a brain scan. Advanced medical imagining modalities such as MRI and pattern recognition techniques are became good tools for predicting AD. In this chapter, an automatic AD diagnosis system from MRI images based on using machine learning tools is proposed. A bench mark dataset is used to evaluate the performance of the proposed system. The adopted dataset consists of 20 patients for each diagnosis case including cognitive impairment, Alzheimer's disease and normal. Several evaluation measurements are used to evaluate the robustness of the proposed diagnosis system. The experimental results reveal the good performance of the proposed system.

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia which affecting seniors age staring from 65 and over. AD progression has raised a great medical research interest recently in the United States. The main symptoms of AD are tissue brain loss and nerve cell death which resulted in shrinking brain tissue and reduces larger ventricles. Advanced medical imaging modalities such as magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), computed tomography (CT),

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positron emission tomography (PET) are used in excluding other subtypes of dementia or cerebral pathology (Schroeter, Stein, Maslowski, & Neumann, 2009). Moreover, they can predict conversion from mild cognitive impairment (prodromal stages) to Alzheimer's disease (Schroeter et al., 2009), which is considered the most critical stage affecting the senior population.

Machine learning techniques and medical image processing tools can help neurologists for predicting whether the patient is developing the Alzheimer disease. In earlier AD stages, usually patients are having an amnestic Mild Cognitive Impairment (MCI). The standard criteria for detecting AD from affected subjects are usually based on neuropsychological assessment and cognitive tests and often followed by a brain scan (Schroeter et al., 2009). This procedure is tedious and time consuming. Also it is reported that the early detection of AD is the most effective way to treat it (Solomon & Murphyb, 2008).

The main contribution of the chapter is (1) to aid physicians in detecting AD through proving an automated system for AD detection and (2) to compare two different anatomical views of the brain and identify the best representative view of AD. In this paper, five bio-inspired algorithms including Grey Wolf Optimizer (GWO), Moth Flame Optimization (MFO), flower pollination algorithm (FPA), whale optimization algorithm (WOA) and Genetic Algorithm (GA) are presented and compared with each other.

The proposed system first read the original MRI image without extracting specific regions, then the original is enhanced through applying median filter and removing the background of the image, then a set of features from different categories are extracted from the extracted ROI image including statistical, texture, energy and fractal features, then different features selector algorithms are adopted in order to extract the best representative features subset, and finally these features are used to feed Support Vector Machine (SVM) in order to be classified to AD or MCI or Normal. 7-fold cross validation algorithm is used to proof the robustness of the proposed system.

BACKGROUND

Several machine learning systems for AD diagnosis are developed and proposed in literature. The proposed system in (Davatzikos, Fan, Wu, Shen, & Resnick, 2008), starts from segmenting the MRI image into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) regions, then using Pearson correlation coefficient and a leave-one-out procedure in order to discriminate normal and MCI images. A watershed clustering algorithm is used to determine brain regions.

In the other hand, the proposed system in (Magnin et al., 2009), first cluster the image into multiple regions by using anatomically labeled brain template to get probability of GM, WM, and CSF, then SVM is used to classify the subjects and statistical procedures based on using bootstrap resampling method into AD and control subjects (CS). Likewise, the proposed system in (Robinson, Hammers, Ericsson, Edwards, & Rueckert, 2010), it uses the principal component analysis (PCA) and maximum uncertainty linear discriminant analysis followed by classifier fusion in order to classify.

Moreover, Zhang et al. in (Zhang, Wang, Zhou, Yuan, & Shen, 2011) extracted different bio-markers modality to accurately distinguish between AD or MCI and healthy subject controls. The authors use a kernel combination method and atlas warping algorithm. Moreover they apply SVM to evaluate the classification accuracy, using a 10-fold cross-validation. In (Cuingnet et al., 2011), An automatic classification system used to distinguish between patients with MCI or AD and elderly controls (CN) from structural T1-weighted MRI and it has compared with 10 methods based on ADNI database.

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THE PROPOSED ALZHEIMER'S DISEASE DIAGNOSIS SYSTEM

The proposed Alzheimer's disease diagnosis system is comprised of four main phases: preprocessing, features extraction, features selection and finally classification phase. These phases are described in detail in the following section along with the steps involved with the characteristics feature for each phase. The overall architecture of the proposed system is described in Figure 1.

Preprocessing Phase

Noise is always undesirable. It is a kind of degradations which can be a random variation of brightness or color information in images (Sakthive & Prabhu, 2014). Removing this kind of noise with preserving edges plays a vital role in image processing field. Median filter is one of the simplest and most popular systems for removing noise like salt and pepper noise. In this paper, MRI image will be first resized to 150*150 in order to reduce computation time, then, median filter with window size 3*3 is applied, and finally the image background from brain region is removed by using threshold with value equal to 0.4 (trial and error), then the columns and rows having value = 0 are removed.

Features Extraction Phase

In this phase, four different types of features (Statistical, Texture, Gabor and fractal features) are extracted from enhanced MRI image obtained from previous phase (Sayed, 2016). The total number of extracted features is 134. These features are first six moments, median, mean, skewness and standard deviation (Zulpe & Pawar, 2012), 22 haralick texture features extracted from gray level co-occurrence matrix (GLCM) including (energy, entropy, correlation,...etc) (Galloway, 1975), 20 features of grey run length matrix (GLRLM) (Sheethal, Kannan, Varghese, & Sobha, 2013), 40 absolute Gabor coefficient features were extracted from the Gabor wavelet with the number of the direction and the frequencies equals 8 and 4, respectively (Malviya & Joshi, 2014) and finally 20 features extracted from fractal theory (Iftekharuddin, Zheng, Islam, & Ogg, 2009). The overall features types are summarized in Figure 2.

Features Selection Phase

Features selection is an important task before classification phase. A large number of extracted features are usually resulted in irrelevant, relevant and redundant features. These large numbers of features known as "the curse of dimensionality" can reduce the classification performance. However, Feature selection algorithms can solve this problem through selecting only relevant features. This can be done by removing or eliminating irrelevant and redundant features. Moreover, they could reduce the training computational time and simplify the learned classifier (Gheyas & Smith, 2010).

Feature selection algorithms can be classified into two systems: filter (Liu & Yu, 2005) and wrapper (Jayaram, Karegowda, & Manjunath, 2010) systems. The wrapper system depends on the classification or clustering algorithm in the evaluation procedure, while the filter system is independent of such algorithms (Sayed, Soliman, & Hassanien, 2016). The search mechanism of filter systems is done through ranking individual features or nested subset of features using statistical tests. While, the search space of wrapper system is done by search for all features subset, evaluate each and assign score based on model accuracy (Sayed, Hassanien, & Schaefer, 2016).

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Figure 1. The overall architecture of the proposed system

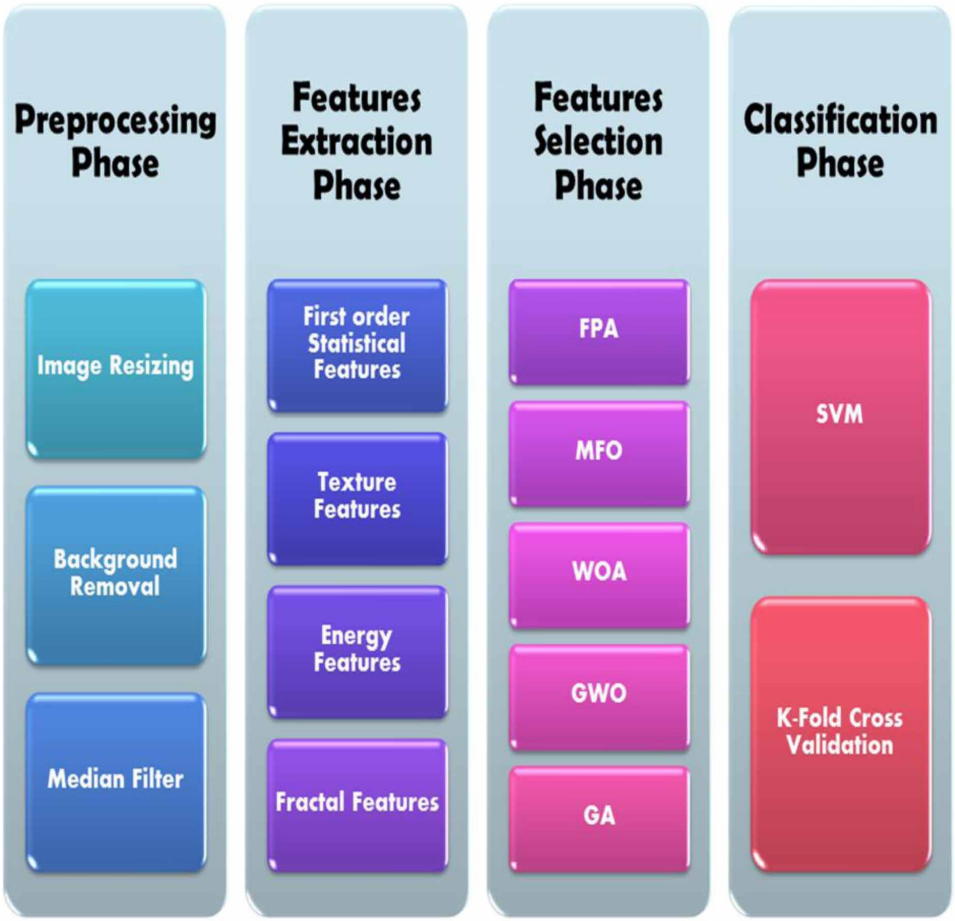
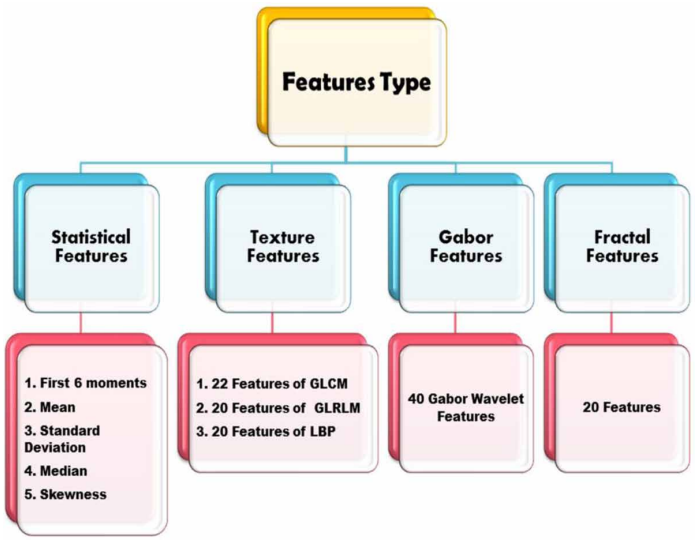


Figure 2. Features types



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Filter system is argued to be computationally less expensive and more general; however it may fail to select the most representative features. On the other hand, wrapper system can achieve better results (Kohavi & John, 1997). However, it requires always an intelligent search algorithm as part of the evaluation function.

In this chapter, various features selection algorithms have been proposed and compared with each other. These algorithms are used to choose a suitable combination of features in wrapper mode for maximizing classification performance and minimizing the data dimensionality. All these algorithms are population based. Only two main parts are changed in these algorithms to able to be used as features selectors. The rest of the algorithms steps are same. These parts are population initialization and the adopted fitness function. Figure 3 describes the main steps of any bio-inspired algorithm. However, the way that the position of search agent updated is differ for each algorithm.

Table 1. Parameters settings of all bio-inspired algorithms

Parameter	FPA	WOA	GWO	MFO	GA
Number of Search Agents (Population)	50	50	50	50	50
Lower Bound	1	1	1	1	1
Upper Bound	134	134	134	134	134
Number of Iterations (Generation)	10	10	10	10	10
Dimension	134	134	134	134	134
Switch Probability	0.7	-	-	-	-
Selection Rate	0.7	-	-	-	0.6
Crossover Rate	0.7	-	-	-	0.6
Mutation Rate	0.7	-	-	-	0.6

Table 1 shows the parameters setting for all adopted bio-inspired algorithms. As it can be seen, the common parameters for all adopted bio-inspired algorithms are initialized identically. Also the used fitness function is same too. Through this, it can be made a fair comparison of the performance of each bio-inspired algorithm. A brief description of each adopted algorithm is provided below.

- **Grey Wolf Optimization (GWO):** Grey Wolf Optimizer is natural inspired algorithm proposed by Mirjalili in 2014 (S. M. Mirjalili & Lewis, 2014). It mimics the leadership hierarchy and hunting mechanism of grey wolves in nature. Grey wolves are considered as apex predators, which they are at the top of the food chain. Grey wolves prefer to live in a group (pack), each group contains 5-12 members on average. All the members in the group have a very strict social dominant hierarchy. Four types of grey wolves such as alpha, beta, delta, and omega are employed for simulating the leadership hierarchy. In addition, there are three main steps of hunting, searching for prey, encircling prey, and attacking prey (Sayed & Hassanien, 2015).
- **Moth Flame Optimization (MFO):** Another nature-inspired optimization is called Moth-Flame Optimization (MFO) algorithm inspired by Mirjalili (S. M. Mirjalili, 2015). The main inspiration of moth is their special navigation methods in night. They used to y in night using the moon light

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which called transverse orientation. A moth flies to the moon by using a fixed angle regarding to the moon. The same kind of navigation method can be done by humans. Moths are tricked by artificial lights and show such behaviors. When the light source is very far, moths are moving in straight line using a similar angle (Yamany, Fawzy, Tharwat, & Hassanien, 2015).

- **Flower Pollination Algorithm (FPA):** Flower pollination algorithm (FPA) is a meta-heuristic algorithm which developed by Xin-She Yang (Yang, 2012). It simulates pollination process of flowering plants. The main characteristics of flower constancy, pollination process and Pollinator behavior are summarized at; (1) Biotic and cross-pollination is considered as global pollination process with pollen carrying pollinators performing levy flights, (2) Self-pollination and abiotic are considered as local pollination, (3) Flower constancy can be considered as the reproduction probability is proportional to the similarity of two flowers involved, (4) Local pollination and global pollination is controlled by a switch probability. Due to the physical proximity and other factors such as wind, local pollination can have a significant fraction in the overall pollination activities. FPA has been applied to solve practical problems in solar parameter estimation, engineering...etc.
- **Whale Optimization Algorithm (WOA):** The Whale Optimization Algorithm is another version of swarm which developed recently by Mirjalili (S. Mirjalili & Lewisa, 2016). It mimics the humpback whales social behavior. It is inspired by the bubble-net hunting strategy. Whales are one of the biggest mammals in the world. There are seven different main mammal species such as Minke, killer, humpback, Sei, finback, blue and right. Whales are predators, where breathing from the oceans 'surface so that they never sleep. Whales and spindle cells of human have similar cells in certain areas of their brains. These spindle cells are responsible for judgment, social behaviors and emotions in the humans. However, whales have twice number of adult human 'spindle cells that is why the main reason of whales 'smartness.
- **Genetic Algorithm (GA):** Genetic algorithm is a search heuristic which developed by Prof. Holland and his students during the 1960s and 1970(Darrell, 1994). It mimics the process of natural selection. GA belong to evolutionary algorithms (EA), which generate solutions to the optimization problems using algorithms inspired by natural evolution, such as mutation, crossover, inheritance and selection, navigation method in nature which called transverse orientation, through maintaining a fixed angle respect to the moon, moths y in night. It's an effective mechanism for travelling in a straight line for long distances (Soliman, Hassanien, & Onsi, 2015).

In this paper, the population initialization mechanism for all adopted algorithms is same. Where each agent position including ants, wolves, whale...etc. is represents a feature subset (solution). Each subset has different size with different features combination. This combination is randomly initialized within range between 1 and 134.

Fitness function is a measure that used to determine the goodness or quality of a search agent or solution. In each iteration every search agent (such as wolf, ant, moth... etc.) is evaluated for fitness value. The search agent's quality is evaluated by its ability to obtain highest accuracy results. In this chapter, classification accuracy is the adopted fitness function. K-Nearest Neighbor is the used classier which used to evaluate the performance of each solution. The classification accuracy obtained on average from 7-fold cross validation method. It is calculated for each agent position using Equation (1), where Fn is defined as the fitness function at iteration i.

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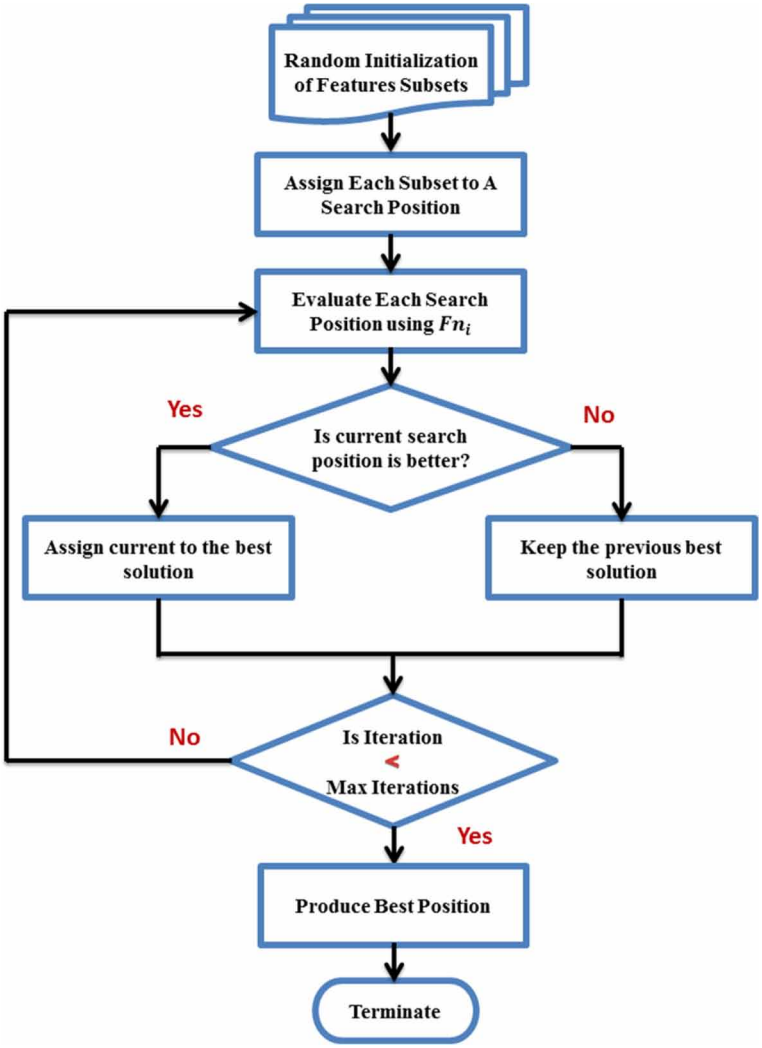
Figure 3. General bio-inspired steps



$$Fn_i = Classification\ Accurracy(\upsilon(\mathrm{i})) \tag{1}$$

The main objective Q of the used optimization algorithms this fitness function is maximized the fitness function as defined at Equation (2). The best position is the subset which gives highest classification accuracy.

$$Q = \max(Fn) \tag{2}$$

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Table 2. Dataset description

No. of Patients	60
Coronal View	21 slice for each patient from each case (normal, AD, MCI)
Axial View	21 slice for each patient from each case (normal, AD, MCI)

Classification Phase

The selected features obtained from previous phase are used to feed SVM. SVM is a supervised learning method that transforms input data to high-dimensional feature space using several kernel functions (i.e. polynomial, RBF and Linear) where the transformed input data becomes more separable (Tharwat et al, 2014). It used to solve linear and non-linear classification problem through finding an optimal hyper plane with maximal margin. Also, it found that it successfully deals with high dimensional datasets (Xu, Caramanis, & Mannor, 2009). Moreover, in order to evaluate the robustness of the proposed approach one of cross validation methods used. 7-fold is the adopted cross validation method. In k-fold, the original datset is partitioned randomly into k equal sized sub-samples. Each sub-sample is used for testing the proposed and the remaining k 1 sub-samples are used as training data. This process is repeated k times (the folds).

EXPERIMENTAL RESULTS AND DISCUSSION

Dataset Description and Measurements

Dataset Description We used benchmark dataset consist of 20 patients for each case (Alzheimer's disease, Normal and Cognitive Impairment). We originally uses MRI dicom files 3D-T1. It was made with 1.5 Telsa MRI systems with head surface coi. The scan parameter was adapted for every patient to fulfill the best spatial resolution for the image (TR450, TR450 and TE 20). The dataset are extracted from the National Alzheimer's Coordinating Center (NACC) (Beekly, Ramos, & Lee, 2007), in this work, we used total of 60 subjects. The description of the used dataset is presented at Table 2.

Figure 4 shows some sample of used dataset, where first row for axial view and second row for coronal cut view, (a) denotes normal patients slice images, (b) denotes AD patients slice images and (c) denotes MCI patients slice images.

Measurements

Several measurements are used to evaluate the performance of the proposed features selector algorithms. These measurements are Accuracy, Precision, Recall and F-Score. They are defined mathematically at Equation (3), (4), (5) and (6) respectively (Geyer & DeWald, 1973). Using multi-level confusion matrix, each measure calculated for each class, and then the overall obtained value calculated on average of three classes (Normal, Ad and MCI).

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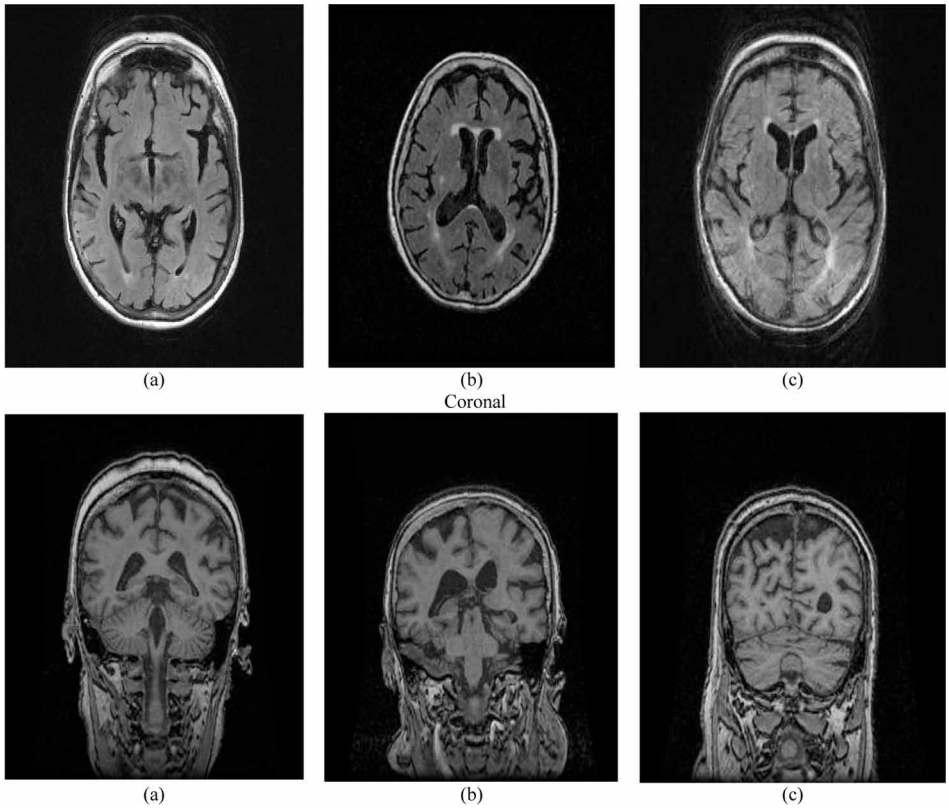
Figure 4. Samples of MRI Alzheimer dataset images; (a) Samples of normal patients, (b) Samples of AD patients and (c) Samples of MCI patients



$$Accurracy = \frac{FP + FN}{TP + TN + FP + FN} \tag{3}$$

$$Precision = \frac{TP}{TP + FP} \tag{4}$$

$$Recall = \frac{TP}{TP + FN} \tag{5}$$

$$F - Score = \frac{2 \times (Precision \times Recall)}{(Precision + Recall)} \tag{6}$$

TP denotes true positives, TN denotes true negative, FP denotes false positive and FN denotes false negative.

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RESULTS AND DISCUSSION

The proposed Alzheimer's disease diagnosis system was programmed in MATLAB-R 2007 on a computer having Intel Core I3 and 2 GB of memory.

Three experiments are proposed and evaluated. Each experiment uses different brain view including (1) coronal view, (2) axial view and (3) coronal and axial view. Moreover different features selectors are evaluated and compared too.

Figure 5 shows the obtained results from preprocessing phase; (a) shows the original MRI image where first row is axial view image and second row is coronal cut view image, (b) shows the original image after applying median filter with window size 3*3, (c) shows the image after converting the image to binary using ostu' trhresholding applying open morphology to remove small objects and (d) shows final extracted ROI image after removing rows columns with zero values.

Figure 6 compares the obtained results produced after using features selectors algorithm and before using any of them (All Features) for coronal view in terms of Accuracy, Recall, Precision and F-Score. As it can be observed, the best obtained results produced from linear kernel function. It obtains overall Accuracy 39.90%, Precision 46.74%, Recall 44.48% and F-Score 43.95%. However, using GA, it enhances the results. It obtains overall Accuracy 53.85%, Precision 53.99%, Recall 54.01% and F-Score 54.00%. This result is highest achieved results which produced from polynomial kernel function. Using MFO, it obtains Accuracy 59.48%, Precision 62.70%, Recall 59.49% and F-Score 61.05%. Also polynomial is the best kernel function too. Using FPA with polynomial kernel obtains Accuracy 45.30%, Precision 45.61%, Recall 44.93% and F-Score 45.73%. Moreover, using WOA, it obtains Accuracy 51.30%, Precision 57.61%, Recall 51.15% and F-Score 54.19% using polynomial kernel function. For GWO, it obtains using polynomial kernel Accuracy 48.28%, Precision 51.26%, Recall 47.98% and F-Score 49.57%. From these results, MFO is the best algorithm which obtains highest results. Also polynomial kernel function is the best kernel function.

Figure 7 compares the obtained results produced after using features selectors algorithm and before using any of them (All Features) for axial view in terms of Accuracy, Recall, Precision and F-Score. As it can be observed, the best obtained results produced from polynomial kernel function. It obtains overall Accuracy 62.37%, Precision 61.55%, Recall 61.54% and F-Score 61.50%. Using GA, it obtains using polynomial Accuracy 57.28%, Precision 58.45%, Recall 57.67% and F-Score 58.06%. For MFO, It obtains using polynomial overall Accuracy 78.33%, Precision 78.32%, Recall 78.33% and F-Score 78.33%. For FPA, it obtains using polynomial overall Accuracy 63.60%, Precision 63.79%, Recall 63.69% and F-Score 63.73%. For MFO, It obtains using polynomial overall Accuracy 78.33%, Precision 78.32%, Recall 78.33% and F-Score 78.33%. For FPA, it obtains using polynomial overall Accuracy 63.60%, Precision 63.79%, Recall 63.69% and F-Score 63.73%.

For WOA, it obtains using polynomial over- all Accuracy 71.79%, Precision 71.71%, Recall 71.86% and F-Score 71.79%. And finally for GWO, it obtains using polynomial overall Accuracy 48.28%, Precision 51.26%, Recall 47.98% and F-Score 49.57%. From these results, MFO is best algorithm which produced best representative features subset. Also polynomial is proved to be the best kernel function.

Figure 8 compares the obtained results produced after using features selectors algorithm and before using any of them (All Features) for both coronal and axial views in terms of Accuracy, Recall, Precision and F-Score. As it can be observed, the best obtained results produced from polynomial kernel function. It obtains overall Accuracy 60.02%, Precision 54.41%, Recall 52.63% and F-Score 53.51%. For GA, it obtains overall using polynomial Accuracy 63.55%, Precision 57.85%, Recall 55.21% and

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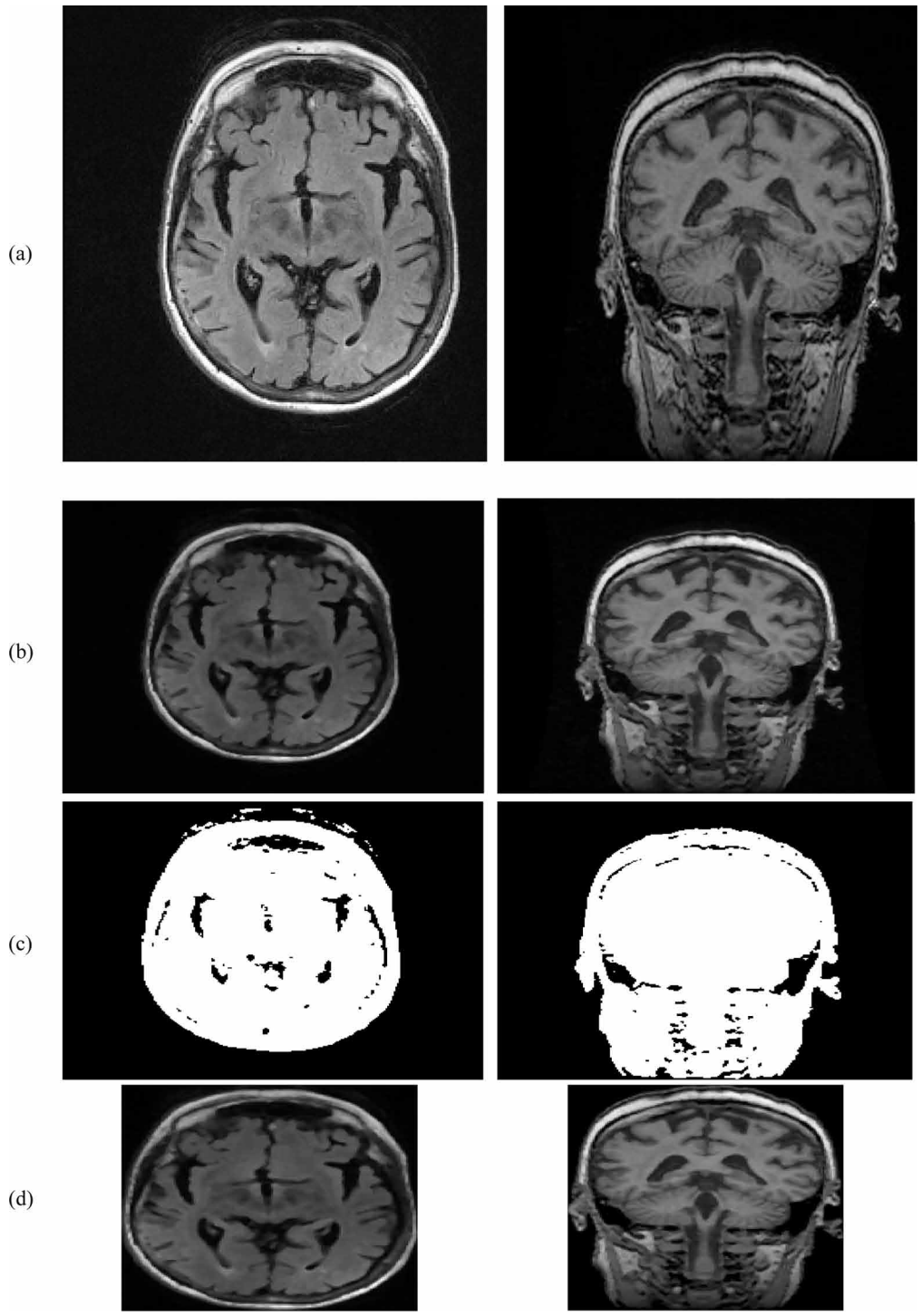
Figure 5. Preprocessing phase results; (a) Original image, (b) Median filter result, (c) Image after converted to binary and (d) Extracted ROI



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F-Score 56.50%. For MFO, it obtains overall using polynomial Accuracy 61.36%, Precision 54.82%, Recall 50.14% and F-Score 52.45%. For FPA, it obtains overall using polynomial Accuracy 59.68%, Precision 54.85%, Recall 51.85% and F-Score 53.31%. For WOA, it obtains overall using polynomial Accuracy 65.91%, Precision 61.83%, Recall 58.75% and F-Score 60.25%. For GWO, it obtains overall using polynomial Accuracy 62.93%, Precision 63.05%, Recall 62.57% and F-Score 62.81%.

A comparison of the elapsed time taken for MFO, GA, WOA, GWO and FPA are presented at Figure (9). As it can be seen, FPA takes the minimum time for all three experiments. Also it can be observed that MFO and WOA are close to each other.

From these results, WOA is best algorithm which produced best representative feature for both coronal and axial views. Moreover, polynomial is best kernel function too. As it can be seen from the previous three figures, polynomial kernel function is best kernel for all three experiments. MFO is best features selector algorithm for axial view and coronal view. However, WOA is the best features selector algorithm for both coronal and axial views. Also axial view is the best brain view to identify AD.

FUTURE RESEARCH DIRECTIONS

In the future, there is a research direction of increasing the MRI slice images dataset used in order to test the reliability of the proposed CAD system. Also, more enhancements could be provided to the system by using modified versions of different swarms algorithms. The modifications aim to reduce number of swarm parameters in order to limit user interaction with the automatic system.

CONCLUSION

Optimal features selection is to find the best representative features subset from original feature set that can represent the whole dataset. In this paper, a fully automatic CAD system which uses seven bio-inspired algorithms as features selection algorithm has been presented. An application of Alzheimer's disease diagnosis from MRI images has been chosen and the scheme have been applied to see their ability and accuracy to detect AD from MRI images Support Vector Machine with its kernel functions was adopted to classify MRI images into Normal or AD or MCI. In addition to, two different anatomical views of the brain including coronal cut and axial have been compared. The experimental results show that the SVM-polynomial kernel function is best one which gives highest results in terms of accuracy, precision, recall and f-score for all proposed bio-inspired algorithms. Moreover, it shows that MFO is the best features selector algorithm for axial view and coronal view coronas it obtains highest accuracy, precision, recall and f-score. However, WOA is the best features selector algorithm for both coronal and axial views. Also it has been observed that axial view is the best brain view to identify AD.

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Figure 6. Comparison between different features selectors algorithms and without using them for (coronal cut view) in terms of accuracy, precision, recall and f-score

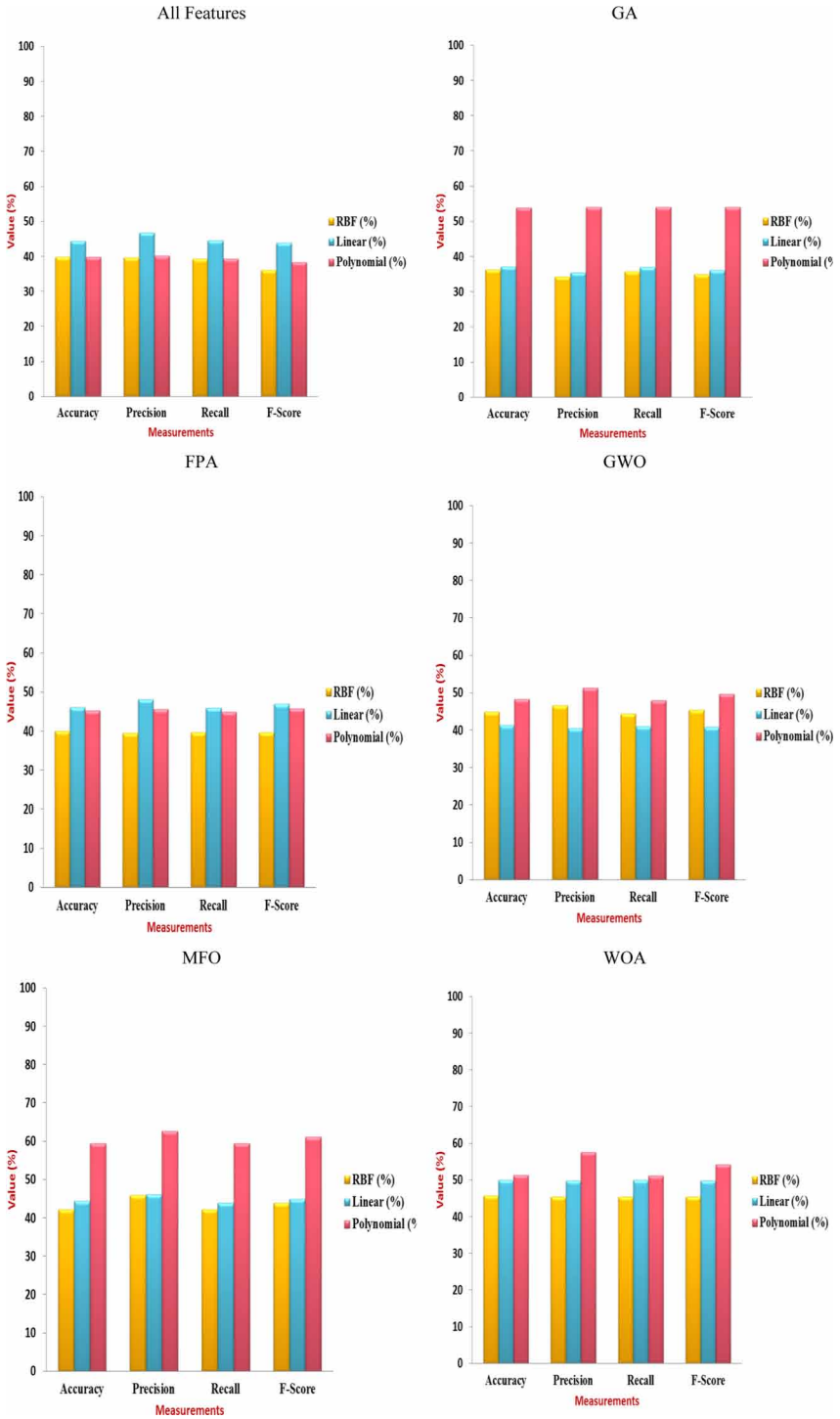

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Figure 7. Comparison between different features selectors algorithms and without using them for (axial view) in terms of accuracy, precision, recall and f-score

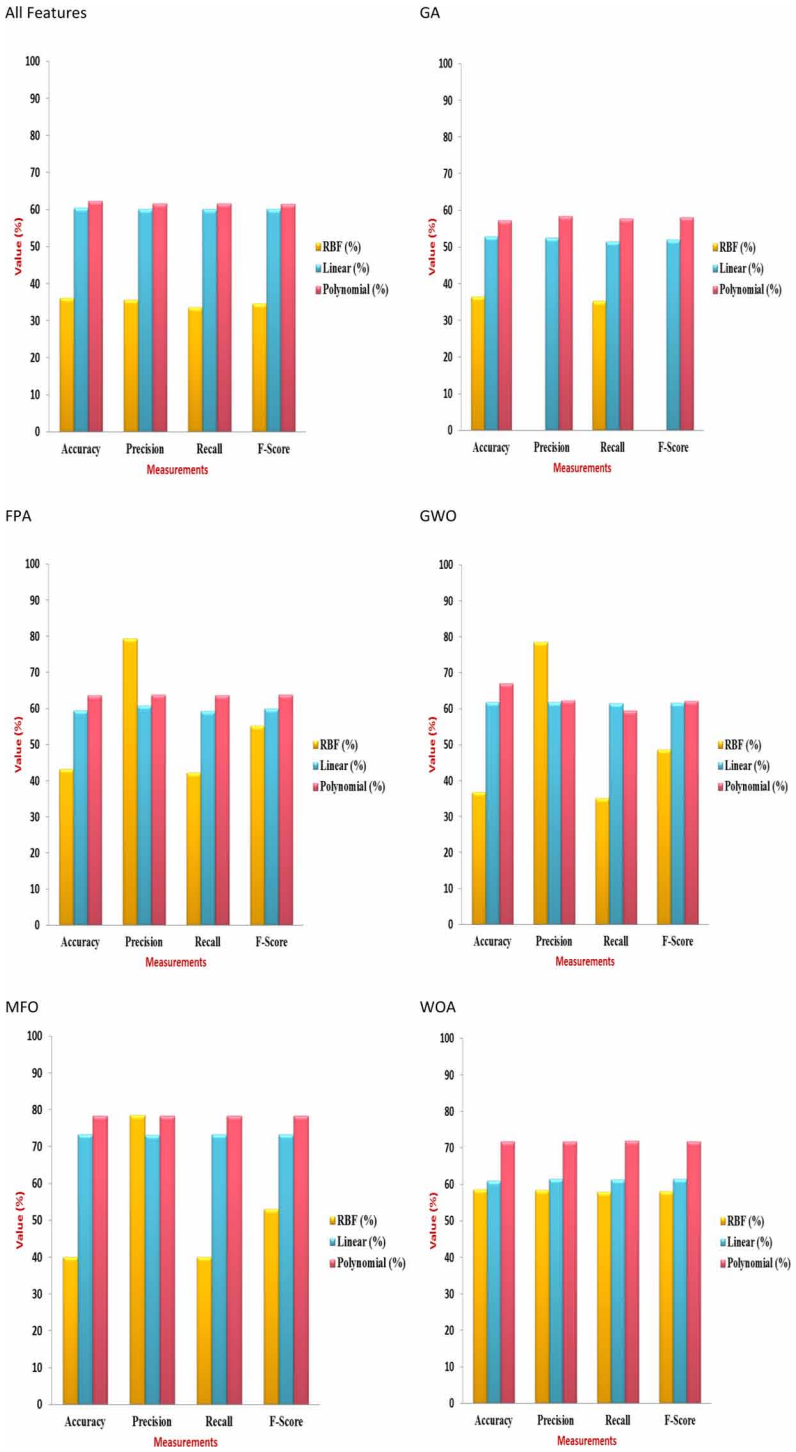

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Figure 8. Comparison between different features selectors algorithms and without using them for (coronal cut and axial view) in terms of accuracy, precision, recall and f-score

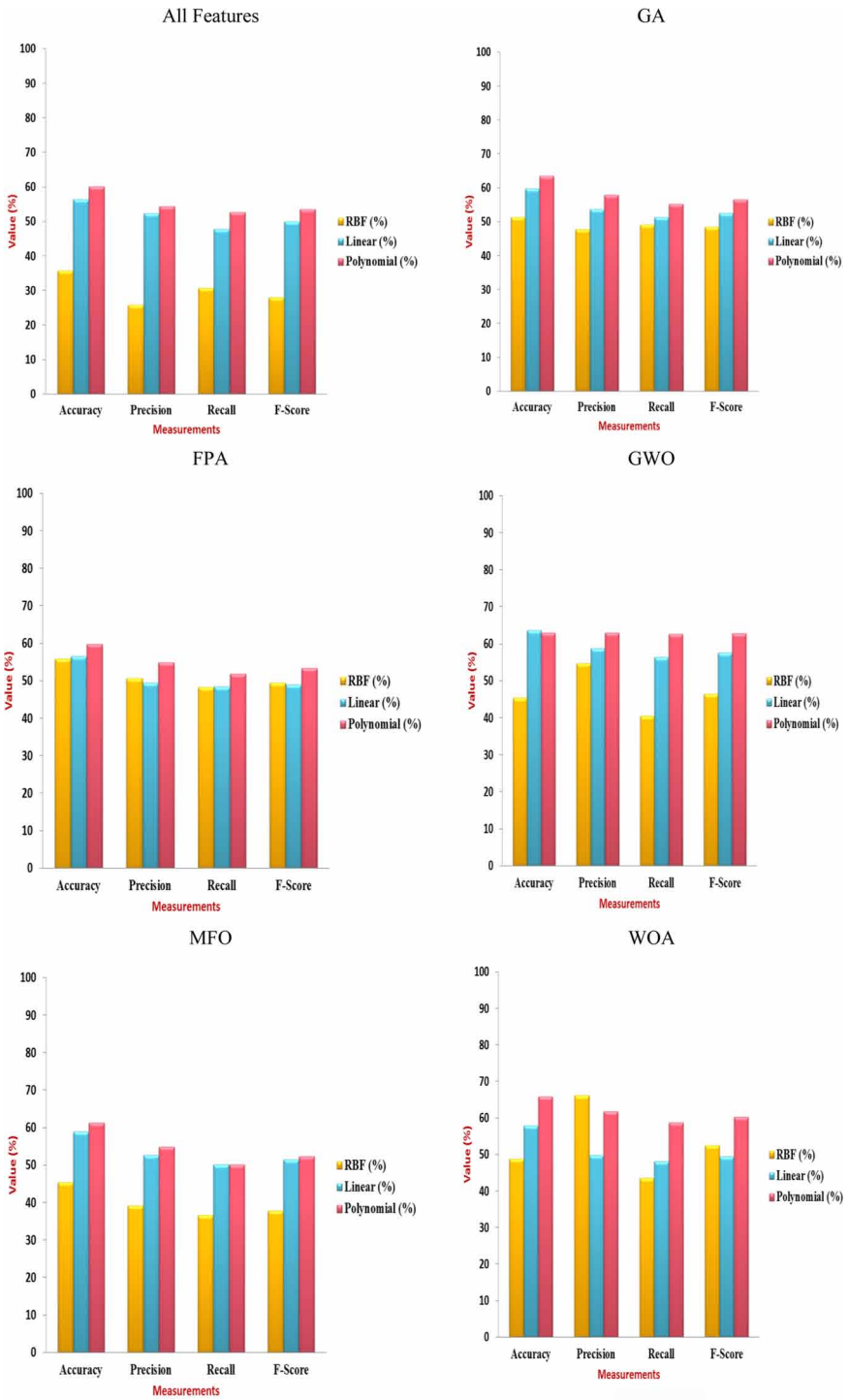

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Figure 9. Comparison between different features selectors algorithms in terms of elapsed time in seconds

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Chapter 12
Assessment of Cognitive-Communicative Functions in Persons With Mild Cognitive Impairment and Dementia of Alzheimer's Type

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ABSTRACT

According to world population prospects data report, older individuals, especially those aged 60 years and above, have increased substantially over the recent year, which is going to accelerate in the coming decades. The most common problems the aging population faces are dementia of the Alzheimer's type (DAT) and mild cognitive impairment (MCI). Assessment of cognitive-communicative markers is essential for persons with MCI and DAT. Furthermore, it can help in the differential diagnosis of DAT and MCI. Proper assessment by speech-language pathologists is warranted in this area as it will throw light on the differential diagnosis of MCI and DAT, the clinical description of the characteristics between the two clinical groups, the prognosis for improved outcomes, recommendations for intervention and support, and referral for other professionals for assessments or services.

INTRODUCTION

According to world population prospects data report (DESA, 2015), older individuals especially those aged who are 60 years and above have increased substantially over the recent year, which is going to accelerate in the coming decades. The number of people in the world aged sixty years or over is expected

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to increase by 56 percent between the years 2015 and 2030. The recent advancement in health care facilities and better living conditions has resulted in the longevity of human life. Due to this change, it is indeed time to pay more focus to the problems that the aging population faces, one of the most common amongst them is dementia. Persons having Dementia of Alzheimer's type (DAT) is one of the fastest growing clinical populations. Prince et al. (2013) reported that by the year 2030, around 65.7 million people will be affected and 115.4 million will be affected by 2050 by Dementia. Speech-Language Pathologists (SLPs) form one of the core team members who are qualified to treat the cognitive-communicative disorders associated with dementia. Early identification of dementia along with Mild Cognitive Impairment-which constitutes the earliest manifestation of clinical symptoms of dementia, has become a matter of research recently.

MILD COGNITIVE IMPAIRMENT (MCI)

According to the Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition (DSM-IV) American Psychiatric Association (1994), Mild Cognitive Impairment (MCI) is defined as an intermediary stage between the cognitive stages of normal elderly aging and the mild degree of dementia. Petersen et al. (2001a) reported that persons with MCI have more risk of progressing to clinically probable DAT.

Sub-Types of MCI

According to Petersen et al. (2001b), based on cognitive features MCI can be divided into

1. **Amnestic MCI:** These individuals have impairment predominantly in memory.
2. **Multiple Domain MCI:** These individuals have impairments noticed in more than one cognitive domain which can include memory.
3. **Single Domain Non-Amnestic MCI:** These individuals have impairment in any one cognitive domain apart from memory.

Dementia

Dementia describes a group of brain disorders which can progressively lead to brain damage, and subsequently lead to gradual deterioration of a person's functional capacity and socio-cultural relations. The term dementia is originally derived from Latin word 'de mens' meaning a decline in mental abilities. Cummings, Benson, and LoVerme (1980) reported that at least three out of the following five areas-memory, language, visuospatial skills, emotional skills, personality and cognition must be disrupted in persons with dementia. The definition according to Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition (DSM-IV) (1994) states that the most prominent feature among dementia is the impairments in both short-term (STM) and long-term memories (LTM). These memory deficits may also be associated with one or more concomitant features like agnosia, aphasia, apraxia, impairment in abstract thinking, and personality changes. The salient features for diagnosis of dementia are

1. Impairment in both short term and long-term memory.
2. Impairment in abstract thinking and judgment.

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3. Personality changes.
4. Specific organic factor.
5. The absence of a non-organic factor as a reason for the symptoms like depression.

DEMENTIA OF ALZHEIMER'S TYPE (DAT)

It is reported as the most common cause of DAT. The classic DAT symptoms involve initial memory deficits due to dysfunction of the medial temporal lobe structures -particularly the hippocampus and entorhinal cortex. However, as the disease progresses the person also exhibits deficits in the parietal and frontal regions, thus affecting language, executive functions, personality and visuospatial systems. Other than disturbances in cognitive abilities, there are often neuropsychiatric and behavioural symptoms which includes depression, anxiety, irritability, agitation, hallucinations, impulsivity, insensitivity and sleep problems. While the predominant presentation of DAT is an amnestic one (typical DAT) where the individual has poor recent memory and better remote memory events, there also exist non-amnestic DAT which exhibits language, visuospatial and executive dysfunction deficits. Thus, the above symptoms for persons with DAT can lead to problems in their quality of life, activities of daily living and self-care. As older persons tend to live well, beyond 70 years due to better healthcare advancements, the prevalence of DAT is anticipated to rise 2-3 fold in the coming decades. The major risk factors of developing DAT are older age (above 65 years); family history of DAT, vascular risk factors (diabetes, hypertension, dyslipidemia, stroke), repeated brain trauma and low cognitive reserve, Down's syndrome and genetic factors mainly apolipoprotein-E (APOE).

Diagnostic Criteria for MCI and DAT

According to McKhann et al. (2011), the four neurobehavioral criteria that define MCI are

1. **Concern Regarding Change in Cognitive Level Compared With Prior Level:** This can be elicited by the patient, caregiver, informant or clinician.
2. **Impairment in One or More Cognitive Skills:** It can be noticed that for persons with MCI, there will be impairment in one or more cognitive domains like attention, memory, language abilities, executive function and visuospatial skills that is much lower than the client's age and socio-economic background.
3. **Preservation of Independence in Performing Functional Abilities:** It can be noticed that although persons with MCI maintain their ability to manage their daily living activities, they are less efficient doing so and require more time for completion of the task.
4. **Not Demented:** In persons with MCI, the cognitive and behavioral changes are significantly mild to affect social and occupational functioning.

Procedure for Clinical Diagnosis of DAT

Diagnosing dementia and determining what type it is can be challenging. There is no single procedure to diagnose dementia; the professionals use a test battery to diagnose. First and foremost the clinician will obtain an accurate case history. The clinician may interview both the caregiver as well as the client to

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get a better picture. Along with cognitive impairments, depression is also screened as well as neuropsychiatric symptoms such as disinhibition, irritation, apathy etc. are also noted by the clinician. Physical examination by a physician is also done to identify co-morbid conditions such as atrial fibrillation, heart disease or pulmonary problems. Cognitive & Neuropsychological assessment is also carried. Neurological evaluation is carried out by a neurologist where cranial nerve examination, focal weakness and gait are assessed. Cerebro-spinal fluid (CSF) evaluation, as well as neuroimaging techniques like Computed Tomography scan (CT), magnetic resonance imaging (MRI) and Positron emission tomography (PET) etc. are useful in providing clinical diagnosis of dementia.

Cognitive Deficits in Persons With DAT

Numerous studies report that persons with DAT exhibit cognitive deficits which vary with the different subtypes (Brandt et al., 2009; Saunders & Summers, 2010; Bozoki, Giordani, Heidebrink, Berent, & Foster, 2001; Hodges, Erzinclioglu, & Patterson, 2006). Since various cognitive processes such as attention, memory, perception, speed of processing and various executive functions play an important role in language functions there exist a strong correlation between language and cognitive domains. Cognitive deficits in Persons with DAT are discussed.

Memory Deficits

Memory problems are exhibited as the major sign of cognitive decline in persons with dementia. Working memory (WM) deficits are seen in persons with dementia due to the poor executive control system. There are also studies that have reported reduced memory span and short-term memory (STM) capacities in persons with dementia (Morries, 1986). Belleville, Peretz and Malenfant (1996) investigated the verbal and attention components of working memory in patients with DAT, normal elderly, and healthy young adults. It was also noticed that Persons with DAT showed a reduced attention span but were sensitive to word length.

Deficits in Executive Function (EF)

Voss and Bullock (2004) explored the role of executive control function (ECF) within DAT and Vascular Dementia. The results indicated that DAT performed more poorly than Vascular Dementia on most of the cognitive tests.

Attention and Concentration Deficits

Perry and Hodges (1999) reported that Persons with DAT have more difficulty in performing complex tasks which require divided attention such as listening for the target word in a list. While simple tasks like selecting and sustaining are not typically impaired in early stages of dementia (Assal & Cummings, 2003).

Abstraction and Problem Solving Deficits

Cummings and Benson (1992) reported that impaired abstract thinking and problem-solving abilities are often prominent clinical features of dementia. These problems differ across the stages of dementia

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and are more prominent in the middle stage of the disease. Freedman and Oscar-Berman (1986) investigated the problem-solving impairment in persons with dementia using a tactile discrimination test. The impaired performance in these people was a result of the impaired cognitive flexibility that is required to alternate responses and shift mental set.

Linguistic Deficits in Dementia

The presence of memory impairment deficits in persons with dementia will also interfere with their linguistic abilities and will vary over the course of the illness. Early cognitive linguistic changes in discourse might be helpful for the preclinical identification of dementia.

Syntactic Comprehension Deficits

Bickel, Pantel, Eysenbach, and Schroder (2000) investigated the syntactic comprehension abilities of German speakers with dementia. The authors used semantically reversible sentences using a sentence-picture matching paradigm. Syntactic complexity was in the range from simple active voice sentences to complex sentences. Persons with dementia showed deficits in all the categories. However, syntactic comprehension is only mildly affected in the early stages of DAT.

Word Finding Difficulties

Ash et al. (2006) investigated the discourse abilities in persons with progressive non-fluent aphasia (PNFA), non-aphasic persons with a social disorder and persons with semantic dementia (SemD). The authors reported significant discourse impairments in all three groups of individuals. Persons with PNFA had the least verbal output, producing few narratives per minute. Persons with SemD had difficulty retrieving words while aphasics' persons with a disorder of social comportment and executive functioning had profound difficulty in organizing and expressing their narratives.

Discourse Abilities in Persons With Dementia

Impairment in discourse abilities of persons with dementia has become the area of recent research. Studies have reported that persons with mild to moderate dementia show relatively preserved phonologic, syntactic and lexical knowledge, while semantic and pragmatic knowledge is affected (Appell, Kertesz, & Fisman, 1982). Gracia and Joanette (1997) investigated the topic shifts in the spontaneous speaking abilities of persons with dementia of Alzheimer's type. Persons with dementia of Alzheimer's type demonstrated impaired topics shifts than healthy elderly which were due to failure to continue and repetition of ideas.

Cognitive-Linguistic Deficits in MCI

The cognitive –linguistic deficits in MCI are found to be similar to those found in DAT. These include deficits in category fluency and confrontation naming including Reaction time for language comprehension. Persons with MCI also tend to exhibit impairments in syntactic reasoning (Collie et al., 2002) and as well as naming rhyming words (Dwolatzky et al., 2003). Picture-description task, such as the Cookie Theft Picture, is less likely to reveal alterations in MCI or mild DAT (Bschor et al., 2001). Thus, it ap-

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pears that linguistic impairments in MCI are most likely located at the semantic level which is exhibited in early DAT. It is reported that timed tests are especially sensitive to the declines seen in MCI. Massoud et al. (2002) reported that word-reading threshold may be useful in discriminating MCIs from DAT; Similarly lexical decision tasks (Taler & Jarema, 2006) and Event-related potentials (ERPs; Olichney et al., 2002) studies have shown to distinguish well between MCI and healthy controls and early DAT .

Neuroimaging Techniques in Dementia Assessment

Neuroimaging has become a vital fundamental part of a routine dementia assessment to find the causes of cognitive impairment, and also to support early, accurate dementia subtype diagnosis. Neuroimaging techniques used in the assessment of dementia can be mainly classified into three types-Structural, Functional, and Molecular.

Structural imaging basically includes computed tomography (CT) and magnetic resonance imaging (MRI). The images produced by these techniques allow one to visualize the anatomical 'structure' of cerebral tissue.

Functional imaging consists of Tc-HMPAO single positron emission CT scan (HMPAO-SPECT), F-FDG positron emission tomography (FDG-PET) and DaTscan, which uses radioactive tracer elements to give an indication of the functioning of the brain tissues. HMPAO-SPECT scan uses a lipophilic tracer element that crosses the blood-brain barrier and moves into brain tissue by diffusion technique, the resulting SPECT image shows the degree of cerebral blood perfusion. FDG-PET uses a glucose analogue to show the degree of cerebral glucose metabolism. Thus, in practice, these two imaging modalities give similar information and are used to identify impaired brain physiology prior to the onset of obvious atrophy. Finally, Molecular imaging use radioactive traces that helps to bind specific molecules of interest is an emerging field.

Team Approach in the Assessment of Dementia

The trans-disciplinary team approach is essential for the diagnosis of dementia. This inter-professional team consist of speech-language pathologists, neurologists, physicians, nurses, social workers, psychologists, health educators, other allied health professionals and support staff. An excellent trans-disciplinary approach allows shared commitment for better quality care and strong communication skills among team members.

Role of the Speech-Language Pathologist in the Assessment of MCI and DAT

According to American Speech Language Hearing Association (ASHA), the primary aim of a speech-language pathologist (SLP) is to evaluate cognitive-communication deficits in persons with dementia and to identify socio-cultural factors that delay functioning. During the evaluation, the SLP determines the appropriate assessment protocol to be used based on the severity of dementia as well as the client's communication needs. Furthermore, while selecting screening and other comprehensive tests, the speech pathologists must also consider the socio-economic factors. SLP's also play an important role while planning treatment, especially when working with persons with DAT; is to make sure that communication and cognitive goals are based on the client's skill. The primary focus of SLPs is working on the patient's strengths, rather than their weaknesses. In due course of time, as a patient's condition progresses, SLPs

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need to spot appropriate compensatory strategies and educate family members and caregivers to improve the quality of life in persons with DAT and MCI.

Factors to Consider Prior to Screening in Older Individuals

Before screening for cognitive-communication functions associated with dementia/MCI, it is essential to consider the impact of sensory issues, depression, and effect of current medications on cognitive skills.

Hearing Loss

Since hearing loss is prevalent in older adults it is mandatory to conduct an audiological evaluation prior to the screening of cognitive-communicative deficits. Traditional behavioral hearing tests like pure tone audiometry and speech audiometry are helpful in the initial stages of dementia/MCI with the help of certain modifications such as reiterating/paraphrasing instructions, slowing presentation of speech stimuli, using pulse tones and by providing constant reminders to the client to respond. During the later stages, more objective tests like Auditory Steady State response (ASSR) and Otoacoustic emissions can be used. If the Person with Dementia fails in the hearing screening, a referral has to be made to an audiologist for further evaluation. If the client is diagnosed as having hearing loss, it is necessary that the clinician make sure that client wears hearing aids during testing. If clients hearing status cannot be determined, the clinician can administer speech discrimination test present in the Arizona Battery of Communication Disorders of Dementia (ABCD).

Visual Impairment

Since visual acuity decreases with age, it is necessary to check the visual abilities of the client prior to cognitive-communication screening. If vision is corrected, eyeglasses have to be worn by the client while screening and adequate lighting must be present in the testing environment. The clinician can check for the presence of visual field deficits by administering a simple letter cancellation task present in Arizona Battery of Communication Disorders of Dementia (ABCD).

Depression

Depression is very common among older individuals and can be mistaken for dementia as it can significantly affect test scores. The cognitive changes associated with depression can be similar to the cognitive changes due to dementia which is referred as pseudo-dementia. If depression symptoms are present, the client should be referred to a clinical psychologist for further evaluation.

Effect of Medications

Older individuals take many medications like sedatives and antidepressants to manage diseases related to aging. Furthermore, these medications can exacerbate the cognitive-communicative functions due to drug interactions. Thus, before the screening, the clinician should consider the effects of drugs on cognitive-communicative functions.

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Screening Tests for MCI and Dementia

Few of the screening tests for MCI and dementia are listed below.

1. **Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975):** The Mini-Mental State Examination (MMSE) is commonly used by SLPs and neuropsychologists. MMSE evaluates the client in terms of - orientation to place, person, time, memory, knowledge skills, communication and copying. The total score is 30, while scores less than 24 are indicative of dementia by most clinicians (Desmond, 2002). Bayles, Tomoeda, Montgomery, Cruz, and Azuma (2000) have reported that early dementia or MCI can be reported in clients having scores of 25 to 26. In another study by Monsch et al. (1995), the authors have reported that a score of less than 26 in MMSE is indicative of cognitive impairment.
2. **Montreal Cognitive Assessment (Rossetti, Lacriz, Cullum, & Weiner, 2011):** The Montreal Cognitive Assessment was designed as a quick screening tool for mild cognitive impairment to assess attention, concentration, executive functions, memory, language, visuospatial construction, conceptual thinking, calculation and orientation. The maximum score that person can get is 30, while scores of 26 and higher are considered normal; scores less than 25 indicating of cognitive impairment. Rossetti, Lacriz, Cullum, and Weiner (2011) have reported that MoCA was sensitive to detecting 90% of clients diagnosed with MCI, while MMSE was able to detect only 18% diagnosed with MCI.
3. **Mini-Cog (Borson, Scanlan, Brush, Vitaliano, & Dokmak, 2000):** This test was given by Mini-Cog uses a clock- drawing test with a simple un-cued three item word recall task. Clients are instructed to listen to and repeat three unrelated words, then draw a clock and finally recall the three previously presented words. The time taken to administer this test is four minutes. The cut-off score of less than three is indicative of dementia.
4. **Memory Impairment Screen (Buschke, Kuslansky, & Katz, 1999):** The Memory Impairment Screen (MIS) is a test that uses four item delayed free and cued recall tasks. The client is asked to read the word aloud (e.g., 'potato') and associate it with its semantic category cue (e.g. vegetable). The patient is engaged in a distractor task (counting from 1-20 forward and backward). After that the client is asked to freely recall the 4 items (free recall). Category cues are provided only if the item is not retrieved during the free recall (cued recall). MIS score is calculated as (2x [Free- recall]+(Cued -recall). The maximum score is eight. Scores of four or less are considered indicative of cognitive impairment.

Comprehensive Tests for Assessment of Dementia

Comprehensive evaluation of cognitive-communicative functions should provide information about the client's mental status, language comprehension and expression, memory, orientation and visuospatial skills.

Two of the most commonly used comprehensive tests for dementia are listed below:

1. **Arizona Battery for Communication Disorders of Dementia (Bayles & Tomoeda, 1993):** The ABCD consists of 14 subtests that evaluate mental status, verbal memory, language comprehension and expression and visuospatial memory. This test also contains four screening measures including speech discrimination, visual perception and literacy, visual field and visual agnosia. The subtests

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of ABCD can be used individually or administered as a full battery. There are 5 constructs and 14 subtests. Language comprehension constructs consists of the following subtests (i) following commands (ii) comparative questions (iii) repetition (iv) reading comprehension. Language expression construct consists of the following subtests (i) object description (ii) generative naming (iii) confrontation naming (iv) concept definition. Verbal memory constructs consists of the following subtests (i) story retelling-immediate (ii) story retelling-delayed (iii) Word learning. Visuospatial skill construct consists of the following subtests (i) generative drawing (ii) figure copying. Mental status constructs consists of mental status subtest of ABCD. The full ABCD requires 90 minutes to complete. Total overall Score less than 18 is indicative of cognitive impairment.

2. **Functional Linguistic Communication Inventory (Bayles & Tomoeda, 1994):** FLCI evolved from longitudinal studies of individuals with DAT. FLCI tests the following skills Naming and greeting, Answering questions, Participation in a conversation, Comprehending signs and matching objects to pictures, Reading and comprehending words, Following commands, Reminiscing, Gesturing, Pantomiming, and writing. It takes approximately thirty minutes to administer this test. The advantage of FLCI is that it allows clinicians to compare the performance of the client with normative. The client's intact communication functions can be charted and predictions of communicative skills vulnerable to dementia can be charted. The test results are useful in the preparation of functional maintenance programs and caregiver counselling.

Indian Assessment Tests for Dementia

1. **Dementia Assessment Battery:** Sunil and Shyamala (2009) aimed at developing a diagnostic test battery in Kannada to assess persons with dementia. The test battery consists of four major domains such as memory, linguistic expression, linguistic comprehension, and visuospatial construction skills. The battery was administered on a control group (90 normal participants; 30 each into three groups). The groups consisted of young adults in the age range of 20-40 years; older adults in the age range of 40-60 years and geriatrics above 60 years. The experimental group consisted of 30 persons with dementia (10 in each severity group). The performance of persons with mild dementia was near normal in most of the subtests which included, spontaneous speech, reading comprehension, following commands, etc. Persons with moderate dementia exhibited difficulty in tasks related to memory – working memory, episodic memory, picture naming, generative naming, and generative drawing. Persons with severe dementia failed to elicit responses to any of the tasks due to the poor spontaneous speech output. The limitations of the study were less number of participants in the dementia group. The participants with dementia had different pathologies like Parkinsonism, Multi-infarct dementia, Alzheimer's etc.
2. **Comprehensive Cognitive Assessment Protocol for Persons with Dementia in Malayalam (CCAP-M; Malayalam):** Anjana and Shanbal (2010) aimed at developing a comprehensive cognitive Assessment Protocol in Malayalam (CCAP-M) for persons with Dementia to help Speech Language Pathologists to get in-depth knowledge of impairments. The other aim was to differentially diagnose Persons with Dementia from a normal elderly population. The test consisted of 6 domains mainly Memory, Linguistic comprehension, Linguistic expression, Visuospatial construction and Problem solving and Organization. Persons with Dementia performed poorly on the following tasks like generative naming, delayed recall, picture naming, categorization abilities, problem-solving etc. compared to other domains.

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Role of Family in Dementia Care

Family can assist persons with dementia in dealing with the physical and psychological consequences of dementia. DAT impacts the client's ability to live independently and perform activities of daily living. Family members should provide emotional support, financial aid and personal care assistance to persons with DAT. Establishing a good working relationship with doctors and other team members helps in ensuring good care and ongoing support to persons with dementia. Many families provide care for a person with dementia at home. While this very rewarding experience, on the other hand, it can be stressful also. Caring for persons with dementia is more stressful than caring for someone with a physical impairment. It is also essential that caregivers take sometime to care for themselves both physically and emotionally so that caregiver burden can be avoided. It is necessary that family members take help from friends, other family members or community agencies so that they can continue to provide good care to persons with dementia without becoming exhausted, frustrated or simply burned out.

Assessment of Swallowing

A swallowing assessment should also be performed in persons with Dementia and MCI. However, assessment regarding swallowing issues is overlooked by SLPs. Studies have reported that forty-five percent of individuals with dementia who were residing in an institutional set up had dysphagia (Easterling & Robbins, 2008), which was more prevalent in patients with Dementia of Alzheimer's type (DAT) compared to normal elderly persons (Horner, Alberts, Dawson, & Cook, 1994).

Swallowing assessment with individuals with dementia involves evaluation of

1. The oro-motor examination
2. The client's ability to comprehend along with using compensatory strategies
3. The client's oral preparatory, oral, pharyngeal, and esophageal phases
4. The client's recognition of food and utensils;
5. Environmental factors like the appearance of the food, lighting, and distractions;
6. Food and liquid with a variation in textures, tastes etc
7. The effect of the persons prescribed medications on swallowing function;
8. The effect of cognitive factors on swallowing.

An instrumental evaluation is performed to determine safety as well as to identify effective treatment techniques. The instrumental evaluation may also give additional information about the oral and pharyngeal bolus transit time, airway protection reflux, the impact of bolus texture and size, and appropriate pacing (Easterling & Robbins, 2008).

CONCLUSION

Assessment of cognitive-communicative markers is essential for persons with MCI and DAT. Furthermore, it can help in the differential diagnosis of DAT and MCI. Proper assessment by SLPs is warranted in this area as it will throw light on the differential diagnosis of MCI and DAT, the clinical description of the

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characteristics between the two clinical groups, the prognosis for improved outcomes, recommendations for intervention and support; and referral for other professionals for assessments or services.

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KEY TERMS AND DEFINITIONS

Communication: It is the act of the imparting or exchanging information by means of speaking, writing, or using some other medium.

Dementia of Alzheimer's Type (DAT): It is the most common cause of dementia, affecting memory, language, thinking, and behavior of an individual in middle or older age groups. The pathological conditions reveal plaque formations and tangles which progressively affects the individual's daily living activities.

Diagnosis: It is the identification of the nature and cause of a certain phenomenon.

Executive Function: It is a set of mental skills that help you get things done. These skills are controlled by an area of the brain called the frontal lobe.

Memory: It is defined as the power or process of reproducing or recalling what has been learned and retained especially through associative mechanisms.

Mild Cognitive Impairment (MCI): It is a condition characterized by significant cognitive impairment in the absence of dementia. It primarily affects memory, but it might cause changes in daily function in subtle ways. MCI is different from Alzheimer's disease or other dementias. It does not typically affect a person's ability to complete daily tasks or cause general confusion.

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Chapter 13
Electroencephalogram Signal Analysis in Alzheimer's Disease Early Detection

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ABSTRACT

The World's health systems are now facing a global problem known as Alzheimer's disease (AD) that mainly affects the elderly. The goal of this work is to perform a classification methodology skilled with Artificial Neural Networks (ANN) to improve the discrimination accuracy amongst patients at AD different stages comparatively to the state-of-art. For that, several study features that characterized the Electroencephalogram (EEG) signals "slow-down" were extracted and presented to the ANN entries in order to classify the dataset. The classification results achieved in the present work are promising concerning AD early diagnosis and they show that EEG can be a good tool for AD detection (Controls (C) vs AD: accuracy 95%; C vs Mild-cognitive Impairment (MCI): accuracy 77%; MCI vs AD: accuracy 83%; All vs All: accuracy 90%).

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INTRODUCTION

The age structure of the world population has changed dramatically in recent decades especially in developed countries, and this reality is mainly due to the fertility decline and the longevity increase (Ballard, et al., 2011; Machado, 2002). Therefore, the aging population has become a fact of scientific interest because the elderly is most vulnerable to the onset of certain degenerative diseases (Jonker, Launer, Hooijer, & Lindeboom, 1996). Alzheimer's disease (AD) is a progressive neurodegenerative brain disorder and is currently the most common cause of dementia in the elderly (Ballard, et al., 2011). It destroys memory and several mental functions, and it causes a progressive and irreversible deterioration of several cognitive functions leading to a situation of complete dependence. AD represents 60% of elderly diseases and in 2010 AD reached more than 35,6 million affected people around the world (Prince, et al., 2015). As it is a cortical and progressive brain disorder, gradually, over time, most parts of the brain will suffer damage, and AD symptoms will severely increase (Blennow, Leon, & Zetterberg, 2006). AD origin remains unknown, and there is not a prospect of a cure shortly despite the efforts made by several researchers in this regard (Prince, et al., 2015).

AD progression can be classified into four different stages. The first stage or the pre-dementia stage is known as Mild Cognitive Impairment (MCI). The MCI is known as a transitional stage between natural aging and AD (Nestor, Scheltens, & Hodges, 2004). It corresponds to a variety of symptoms: difficulty in remembering recent events, subtle changes in behavior, discrete loss of autonomy in daily life activities, disorientation in time and space and personality changes (Nestor, Scheltens, & Hodges, 2004). Even though the MCI confers an increased risk of developing AD, at this stage only between 6% and 25% of people develop AD (Shimokawa, et al., 2001). The Mild and Moderate AD stages are characterized by increasing cognitive deficits and dependence on caregivers (Gwyther, 2001). In the Advanced stage, monitoring becomes constant and strictly necessary because patients are unable to perform any tasks and so assistance is inevitable (Mesulam, 2000). Senile plaques and neurofibrillary tangles in the medial temporal lobe and cortical areas are two pathological hallmarks of brains ravaged by AD (Blennow, 2005; Mattson, 2004). These two abnormal structures are responsible for damaging and killing nerve cells (Cummings, 2004). Parts of the brain start to shrink because the brain's nerve cells die. In the last stage of AD, the damage is generalized, and the brain tissue has decreased significantly in volume (Blennow & Zetterberg, 2010). In fact, amyloid plaques and neurofibrillary tangles are clearly visible by microscopy in brains of patients with AD (Tiraboschi, Hansen, Thal, & Corey-Bloom, 2004).

It is not yet known why the brain cells deteriorate as AD progresses and many risk factors are associated to AD development. Thus, aging is considered the principal factor given that the disease mainly affects people over 65 years. Family history is another factor pointed out because people who have a close relative who developed AD have a slightly higher risk to develop the disease themselves (Blennow, 2005). However, other factors beyond genetics are pointed out in the course and development of AD, for example, heart disease, diabetes, obesity, stress, smoking and lower educational qualifications. Most people with Down syndrome develop AD as well as people who had severe head injuries (Blennow, Leon, & Zetterberg, 2006; Lahiri, Farlow, Greig, & Sambamurti, 2002).

The development of methods that can assist in AD diagnosis may lead to the reduction of high costs associated with this illness (Lahiri, Farlow, Greig, & Sambamurti, 2002; Ferri, et al., 2005). AD represents a public health problem and a challenge to the scientific community to find solutions to minimize its socio-economic effects (Machado, 2002). Although the progress in better understanding the AD stages, the researchers have not yet discovered a good treatment for this complex and stressful disease

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and neither have found a reliable method to make an accurate AD diagnosis (Ballard, et al., 2011). The early diagnosis accuracy is low, and there is not a biomarker able to detect AD without invasive tests. It is often difficult to diagnose AD, and the diagnosis is made by excluding other possible causes of dementia symptoms (Porth & Matfin, 2009). A brain biopsy or autopsy is the effective way to make a correct and definitive diagnosis. An effective diagnosis can provide opportunities for AD patients to get involved in clinical trials and to get the best treatment (Ballard, et al., 2011).

Several tools and methods may be used to diagnose AD. In the beginning, AD presents subtle symptoms that may be confounded to others presented by people with a normal aging (Waldemar, 2007). The most common neuropsychological test for AD screening is the Mini-Mental State Examination (MMSE) that evaluates skills such as reading, writing, orientation and short-term memory. However, diagnosis is also made through personal history, Biomarkers, EEG, Magnetoencephalogram (MEG) and several techniques of brain imaging that are used to show brain changes, namely: Magnetic Resonance Imaging (MIR), Positron Emission Tomography(PET) and Computed Tomography (CT) (Weiner, 2009; Prichep, 2007).

The EEG played an important role as regards dementia diagnosis for several decades. Therefore, it may be an important tool to assist in AD diagnosis. The EEG can record the electromagnetic fields produced by brain activity with good temporal resolution. This non-invasive and cost-effective technique that presents no side effects is widely extended in clinical settings (Sanei & Chambers, 2007; Jeong, 2004; Stam, 2005). EEG is typically divided into different conventional frequency bands, such as delta (δ, 1-4 Hz), theta (θ, 4-8 Hz), alpha (α, 8-13Hz), beta (β, 13-30 Hz), and gamma (γ, 30-40 Hz). AD seems to affect the signal power in those different bands. The major effect is known as the EEG "slowing", that means a power decrease in higher frequency bands such as alpha, beta and gamma and a power increase in low-frequency bands such as delta and theta. The cholinergic synapses destruction in the Meynet nucleus where transferase responsible for the acetylcholine synthesis is produced is related to these changes (Gawel, Szmidt-Salkowska, & Kowalski, 2009). A lack of acetylcholine is, in turn, responsible for the synchronization of synaptic potentials, and then, pathological activity reveals itself in the form of EEG slow waves (Gawel, Szmidt-Salkowska, & Kowalski, 2009). The EEG can fit into the AD study because it is a sensitive diagnostic test that allows studying the changes in the bioelectric activity of the brain and the monitoring of this neurological disease evolution (Gawel, Szmidt-Salkowska, & Kowalski, 2009). Therefore, the EEG records study can provide a better understanding of the AD neuropathology.

In this study, the authors intend to develop a classification methodology that allows distinguishing between AD patients in Mild/Moderate and advanced stages, MCI Patients and Control Subjects. The aim of this methodology is to get as far as possible a more reliable AD diagnosis in early stages. For that, an Artificial Neural Network with leave-one-out-cross-validation (L1CV) and with *10-fold-cross-validation* (10FCV) will be used to classify all versus (vs.) all and between pairs of groups. The Wavelet Transform (*WT*) was applied to extract several EEG features, and genetics algorithms were used to search the best features combinations. The paper is organized as follows: In Materials and Methods - the Materials are introduced together with the EEG processing and statistical analysis. In the Classification Methodology - the methodology for EEG classification is described; Future Research Directions indicate the future research lines of this work; and finally, in the Conclusion - the results are discussed, and the paper concludes emphasizing its main contributions.

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Table 1. The dataset

Dataset				
	Control Subjects	**MCI Patients**	**ADM Patients**	**ADA Patients**
#	11	8	11	8
Age average	74	80	79	79
MMSE average	28,68	26,29	18,89	11,50

MATERIALS AND METHODS

Selection of Study Participants and EEG Recording

A set of 38 subjects participated in this study: 11 as Controls (C), 8 with MCI, 11 with moderate AD (ADM) and 8 with advanced AD (ADA). EEGs were recorded from the 19 scalp loci of the International 10-20 configuration using a digital electroencephalograph and recorded with the eyes closed in "Hospital de São João - Porto", Portugal (check Table 1 for more information). The sampling frequency was 256 Hz, and all recordings were digitally filtered with a band-pass filter with cut-off frequencies at 1-40Hz. In Table 1, additional information is provided regarding the participants in each group including the average age and Mini-Mental State Examination (MMSE) average. All EEG were organized in segments of 5s (1280 epochs). All participants gave their informed consent prior to their participation in this study, and the study protocol was approved by the local Ethics Committee.

EEG Time-Frequency Representations

The EEG signals, in general, tend to have rapid oscillations in short intervals or slow variations in long intervals (Sanei & Chambers, 2007). The Fast Fourier Transform (FFT) which was introduced in 1965, remains the spectral EEG signal processing most commonly used until today (Rodrigues & Teixeira, 2013). However, FFT is not able to provide information both about the time and frequency of signal characteristics, directly. The spectral components do not reflect changes over time, being a problem to analyze non-stationary signals, as it is the EEG (Haykin & Veen, 2003). As a result, it is convenient to use a transformation that provides a variable resolution time-frequency plane. That is the case of the *WT*, which provides a good time resolution for the high frequencies and good frequency resolution for low frequencies (Kaiser, 1994; Rioul & Vetterli, 1992). The EEG discrete signal is represented as $x(n) = x(n \cdot T_s)$, $n = 0,..,N\text{-}1$, sampled to sampling frequency F_s samples/s ($F_s = 1/T_s$) with N samples. The *WT* is an optimal tool for data analysis when time and frequency resolution are critical (Schiff & Milton, 1993). Equation 1 represents the calculation of *WT* per scale, sometimes called child *WT* ($\psi(t)_{\tau,a}$) (Kaiser, 1994; Rioul & Vetterli, 1992):

$$\psi(t)_{\{\tau,a\}} = \frac{1}{\sqrt{\{|a|\}}} \cdot \psi\left(\frac{t-\tau}{a}\right) \quad (1)$$

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where τ is the translational parameter, t represents the bins in the time domain, $\psi(t)$ is the Wavelet Mother, and a represents the basis function range that acts as an enlargement factor if $a > 1$ or as a compression factor if $a < 1$.

The Discrete Wavelet Transform (*DWT*) uses a multiresolution analysis that consists in obtaining increasingly smaller signal resolution versions by successive filtering. The *DWT* uses one set of two functions: a scale function ($\varphi[n]$) and a Wavelet function ($\psi[n]$):

$$\varphi[n] = \sum_k h[k] \cdot \phi[2 \cdot n - k] \tag{2}$$

$$\psi[n] = \sum_k g[k] \cdot \phi[2 \cdot n - k] \tag{3}$$

where k is the discrete translation parameter, and $h[k]$ and $g[k]$ respectively are the impulse responses of the low-pass and high-pass filters used in the *WT* analysis. The signal decomposition in different frequency bands is achieved by successive low-pass filters and high-pass filters in time, followed by subsampling by a factor of two until the maximum level of decomposition ($log_2(N)$) as is illustrated in the following Equations 4 and 5:

$$DWT_A^{\varphi}[j,k] = \sum_{n=0}^{\frac{N}{2^{(j-1)}}} DWT_A^{\varphi}[j-1,n] \cdot h[2 \cdot k - n] \tag{4}$$

$$DWT_D^{\psi}[j,k] = \sum_{n=0}^{\frac{N}{2^{(j-1)}}} DWT_A^{\psi}[j-1,n] \cdot g[2 \cdot k - n] \tag{5}$$

where, $k = 0, ..., N/2^j$; $j = 0, ..., log_2(N)$; A represents the *DWT* approximated coefficients; D the *DWT* detail coefficients and N the signal length. The Power Spectral Density (*PSD*) functions showed the variations strength of Power as a function of frequency. The Wavelet Packet Transform (*WPT*) spectrum was obtained by extracting the *WPT* coefficients corresponding to the terminal nodes. The *WPT* function was defined as (Rodrigues & Teixeira, 2011; Rodrigues & Teixeira, 2013):

$$X_{\varphi,\psi}[j,m,k] = \sum_{n=0}^{\frac{N}{2^j-1}} WP^{\varphi,\psi}[j,m,n] \cdot w_{j,m,k}[n]$$

$$w_{j,m,k}[n] = 2^{-\frac{j}{2}} \cdot w_m[2^{-j} \cdot n - k]$$

$$j = 1,\ldots,J; m = 0,1,\ldots,2^j - 1; k = 1,\ldots,2^{J-j} \tag{6}$$

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where $J=log_2(n)$, j represented the level of *WPT*. To estimate the *PSD* of *WT*, we used the *WPT* periodogram based on the observations of length $N=2^j-1$:

$$S_{x,\varphi,\psi}\left[m,k\right]=\left[\sum_{j=1}^{J}X_{\varphi,\psi}\left[m,k\right]\right]^2;m=0,1,\ldots,2^j-1;k=1,\ldots,2^{J-j} \tag{7}$$

To obtain the frequency spacing of *PSD* of *WT* of each level of decomposition we used the range:

$$\left[\frac{F_s}{2^{j+1}},\frac{F_s}{2^{j+1-1}}\right],j=1,\ldots,log_2(N) \tag{8}$$

Summarizing, the absolute value of the coefficients was taken, and the Wavelet coefficients were ordered by frequency. The *PSD* was normalized (PSD_n) as below (Rodrigues & Teixeira, 2013):

$$PSD_n\left[m,k\right]=\frac{S_{x,\varphi,\psi}[n]}{\sum_{n=k_1}^{k_2}S_{x,\varphi,\psi}[n]},\ m=0,...,2^j-1 \tag{9}$$

Feature Extraction

Several features were extracted in each frequency band (δ, θ, α, β and γ) of the EEG signal. These features characterize the waveform, in terms of faster, slower, greater or smaller variability that is required to observe the "*shift-to-the-left*" phenomenon. It can be described by the values of maxima (*NMax*) and minima (*NMin*), the zero-crossing rate (*Zcr*), the Relative Power (*RP*) and the spectrum energy deceleration represented by the spectral ratios (r). The extracted features were:

- ***NMax* and *NMin*:** Accounting and calculation of all signal maxima and minima, respectively, by the variation of the signal waveform derivative (view Figure 1);
- ***Zcr*:** The zero-crossing rate was calculated as (Chen, 1988):

$$Zcr_i=\frac{1}{N-1}\sum_{n=1}^{N-1}\mathbb{I}\left\{s_i\left(n\right)s_i\left(n-1\right)<0\right\} \tag{10}$$

where $i=\{\delta,\theta,\alpha,\beta,\gamma\}$, s is a *DWT* coefficient signal of length N and II the indicator function. If the II value, at a certain position, is equal to 1 a signal zero crossing is found:

- ***RP*:** It was calculated as the sum of the components of the PSD_n in the conventional frequency bands: delta (1-4 Hz), theta (4-8 Hz), alpha (8-13Hz), beta1 (13-19Hz, $\beta 1$), beta2 (19-30 Hz, $\beta 2$) and gamma (30-40 Hz):

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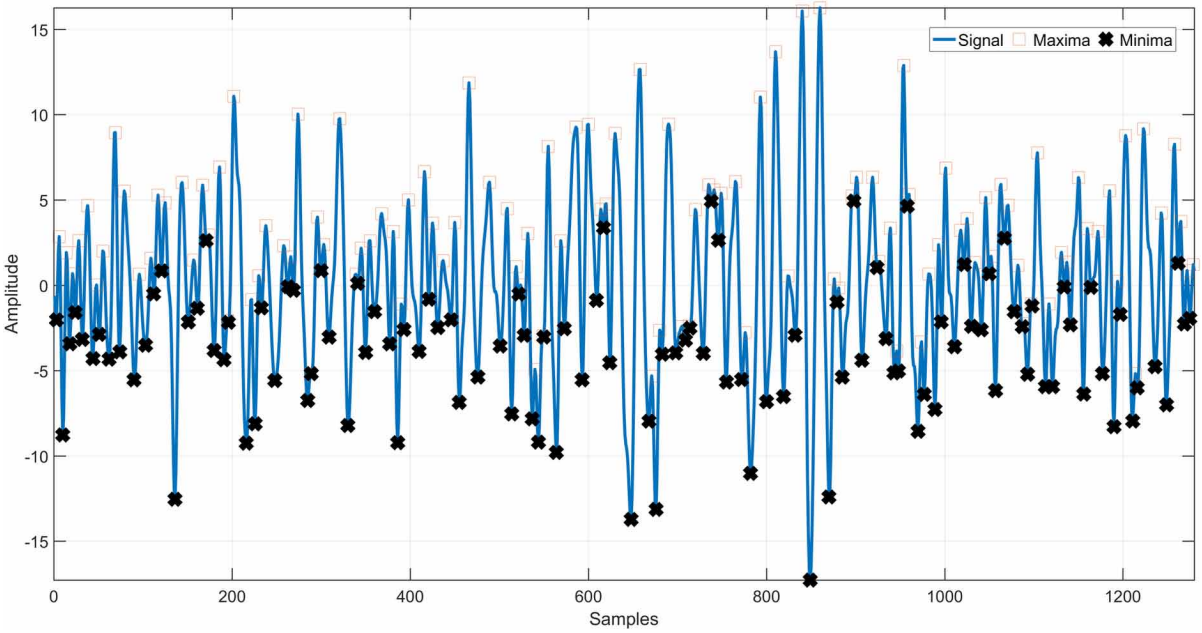
Figure 1. Signal, maxima and minima, example



$$RP(\delta) = \sum_{f=1Hz}^{4Hz} PSD_n(f) \tag{11}$$

$$RP(\theta) = \sum_{f=4Hz}^{8Hz} PSD_n(f) \tag{12}$$

$$RP(\alpha) = \sum_{f=8Hz}^{13Hz} PSD_n(f) \tag{13}$$

$$RP(\beta 1) = \sum_{f=13Hz}^{19Hz} PSD_n(f) \tag{14}$$

$$RP(\beta 2) = \sum_{f=19Hz}^{30Hz} PSD_n(f) \tag{15}$$

$$RP(\gamma) = \sum_{f=30Hz}^{40Hz} PSD_n(f) \tag{16}$$

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- ***r*:** Four spectral ratios were used to summarize the deceleration of the EEG spectrum of AD patients; r_1 is a spectral ratio that enabled us to detect changes when a slight slowdown in the EEG spectrum appears. The r_2 index summarizes the EEG slowing down globally. r_3 computes the relationship between high-frequency bands ($\beta 1$ and $\beta 2$) and the lowest frequency band (δ). r_4 is similar to r_3, but with a narrower high-frequency band (only $\beta 2$). (Rodrigues & Teixeira, 2013):

$$r_1 = \frac{RP(\alpha)}{RP(\theta)} \tag{17}$$

$$r_2 = \frac{RP(\alpha) + RP(\beta 1) + RP(\beta 2) + RP(\gamma)}{RP(\delta) + RP(\theta)} \tag{18}$$

$$r_3 = \frac{RP(\beta 1) + RP(\beta 2)}{RP(\delta)} \tag{19}$$

$$r_4 = \frac{RP(\beta 2)}{RP(\delta)} \tag{20}$$

All feature vectors were normalized as:

$$CDidx(i) = \frac{CDidx(i) - med}{std} \tag{21}$$

where:

$$std = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}\left(CDidx(i) - med\right)^2} \tag{22}$$

and:

$$med = \frac{\sum_{i=1}^{N} CDidx(i)}{N} \tag{23}$$

std means the sample standard deviation; *med* represents the mean value of the features vector *CDidx* and *N* the number of Vector *CDidx* samples.

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Statistical Analysis, Features Selection and Classification

The parameters' normality was assessed with Kolmogorov test and the homoscedasticity with Levene's test. The parameters do not meet the assumption of the parametric test hypothesis (Marôco, 2014). Moreover, the Kruskal-Wallis non-parametric-test was used to check the differences between the study groups (see Tables 2 and 3). In Table 2 and 3, it can be seen that $RP(\beta 1)$ showed the lowest p-value achieved in the statistical analysis ($p = 0{,}001$). However, there were more parameters that presented good results; the spectral ratios (r_1, r_2, r_3 and r_4), the RP in δ and θ bands and finally $Nmax$, $Nmin$ and Zcr mainly in α, β and γ bands. Those features where calculated from the average signals achieved by an overall average process per channel and subject (1 signal of 5s - 1280 epochs per study participant).

Table 2. Statistical analysis (p-value) of Nmax, Nmin, Zcr and Mdif parameters

Band (i)	Parameters (p-Value)		
	$Nmax_i$	$Nmin_i$	Zcr_i
δ	*N.S.*	*N.S.*	*N.S.*
θ	*N.S.*	*N.S.*	*N.S.*
α	**0,0219**	**0,0219**	*N.S.*
β	**0,0037**	**0,0035**	**0,0113**
γ	*N.S.*	*N.S.*	**0,0058**

Table 3. Statistical analysis (p-value) of RP bands and spectral ratios parameters

Parameter	RP(δ)	RP(θ)	RP(α)	RP(β1)	RP(β2)	RP(γ)	r_1	r_2	r_3	r_4
p-value	**0,0333**	**0,0120**	*N.S.*	**0,0010**	*N.S.*	*N.S.*	**0,0071**	**0,0051**	**0,0104**	**0,0293**

N.S. not statistically significant.

The selected features of Tables 2 and 3, with bold p, were analyzed at the sensor level and the differences ($p < 0.05$ using the Spearman correction (Zimmerman & Williams, 1997)) in spatial scalp distributions for each pair of groups and all groups vs. all. Results are shown in Figure 2. In this figure, the darker areas have lower p and higher power of discrimination.

The spatial analysis of scalp showed significant differences in all group comparison (all vs. all) mainly in parietal and right frontotemporal regions. It can also be seen that the AD progression comes from the frontal region to the occipital region (ALL vs. ALL, C vs. ADM and C vs. ADA). In the critical phase of AD progression (C vs. MCI) the methodology found channels with highly significant differences between the compared groups in frontal-temporal regions, that is very satisfying ($RP(\beta 1)$, Zcr_γ and $NMax_\beta$). Finally, the temporal region was the most affected region in all evaluations made. Previous studies have revealed that this region is a large deposit of beta-amyloid plaques, one of the main anomalies associated to AD (Sperling, et al., 2011). Moreover, in MCI vs. ADM and MCI vs. ADA, there were found significant channels in frontal, temporoparietal and occipital regions. State of the art studies identified the occipital and temporoparietal regions as great deposits of neurofibrillary tangles in AD patients comparing them with MCI

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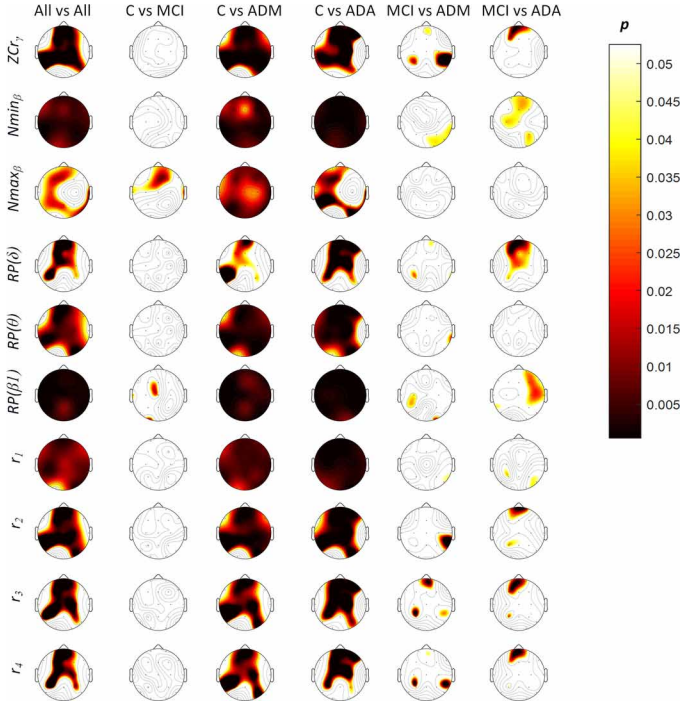
Figure 2. Topographic maps at sensor level for selected features that provided the best p-values in previous statically analysis, in all versus (vs) all, controls and MCI subjects (C vs MCI), controls and AD patients in Mild and Moderate stages (C vs ADM), and controls and AD patients in Advanced stages (C versus ADA), MCI subjects and AD patients in Mild and Moderate stages (MCI vs ADM), and MCI subjects and AD patients in Advanced stages (MCI versus ADA) comparisons. Dots indicate sensors are showing statistically significant differences (p<0.05 using the Spearman correction for multiple comparisons).



patients (Mufson, et al., 2012). In addition to the previous statistical results, a two-class Receiver Operating Characteristic (ROC) analysis with a leave-one-out cross-validation procedure and Kruskal-Wallis analysis ($p < 0.05$) were carried out to analyze the classification performance of the previously selected features to discriminate between pairs of groups. The ROC curves method summarizes the performance of a two-class classifier across the range of possible thresholds. It is a graphical representation of the trade-off between sensitivity and specificity. Sensitivity (S) measures the proportion of positives that are correctly identified, specificity (E) is the proportion of negatives that are correctly identified and Accuracy (A) is the percentage of the study participants correctly recognized. The Area Under the ROC Curve (AUC) is a single number that summarizes the diagnostic robustness of the parameter (Williams, Lee, Fisher, & Dickerman, 1999).

Checking Table 4, it can be seen that the highest classification rates were found comparing Controls and ADA patients, respectively, with AUC values of 0.977 and 94,7% accuracy using *RP*(β1). This parameter revealed a better diagnostic accuracy than achieved in previous works (Rodrigues & Teixeira, 2011; Rodrigues P. M., 2011; Rodrigues & Teixeira, 2013) comparing the discriminant power of 1 feature (0.89 vs. 0.977 achieved in the present study). Despite that, the comparison should be carefully established because the authors used a different dataset in those previous works. No significant parameters were found in the comparisons C vs. MCI and MCI vs. ADM. However, the features combination in the next steps methodology would probably increase the classification results.

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Table 4. Distributions comparison regarding accuracies, AUC and p-values for the best significant parameters previously achieved

Parameter	C vs MCI					C vs ADM					C vs ADA					MCI vs ADM					MCI vs ADA				
	S (%)	E (%)	A (%)	AUC	*p*	S (%)	E (%)	A (%)	AUC	*p*	S (%)	E (%)	A (%)	AUC	*p*	S (%)	E (%)	A (%)	AUC	*p*	S (%)	E (%)	A (%)	AUC	*p*
Zcr_{γ}	72,7	75,0	73,7	0,580	*N.S*	81,8	100,0	90,5	0,882	0,002	62,5	100,0	84,2	0,864	0,008	70,0	75,0	72,2	0,725	*N.S*	100,0	50,0	75,0	0,766	*N.S*
$NMax_{\beta}$	50,0	100,0	78,9	0,761	*N.S*	90,0	81,8	85,7	0,864	0,005	75,0	81,8	78,9	0,818	0,021	90,0	37,5	66,7	0,600	*N.S*	75,0	50,0	62,5	0,547	*N.S*
$NMax_{\beta}$	72,7	75,0	73,7	0,602	*N.S*	80,0	100,0	90,5	0,882	0,003	75,0	100,0	89,5	0,920	0,002	100,0	50,0	77,8	0,750	*N.S*	**100,0**	**62,5**	**81,3**	**0,797**	**0,046**
RP(δ)	61,8	75,0	68,4	0,523	*N.S*	60,0	100,0	81,0	0,773	0,035	75,0	90,9	84,2	0,841	0,013	90,0	50,0	72,2	0,713	*N.S*	**62,5**	**100,0**	**75,0**	**0,797**	**0,046**
RP(θ)	72,7	75,0	73,7	0,614	*N.S*	80,0	100,0	90,5	0,873	0,004	75,0	100,0	89,5	0,898	0,004	80,0	75,0	77,8	0,675	*N.S*	75,0	75,0	75,0	0,688	*N.S*
RP(β1)	75,0	72,7	73,7	0,716	*N.S*	**85,0**	**100,0**	**92,5**	**0,918**	**0,001**	**100,0**	**90,9**	**94,7**	**0,977**	**0,0005**	70,0	75,0	72,2	0,738	*N.S*	100,0	62,5	81,3	0,750	*N.S*
r_1	72,7	75,0	73,7	0,625	*N.S*	80,0	100,0	90,5	0,864	0,005	87,5	90,9	89,5	0,932	0,002	80,0	62,5	72,2	0,700	*N.S*	75,0	75,0	75,0	0,719	*N.S*
r_2	61,8	75,0	68,4	0,614	*N.S*	80,0	100,0	90,5	0,882	0,003	100,0	81,8	89,5	0,932	0,002	80,0	75,0	77,8	0,663	*N.S*	100,0	75,0	87,5	0,781	*N.S*
r_3	50,0	90,9	73,7	0,557	*N.S*	80,0	81,8	81,0	0,855	0,006	87,5	81,8	84,2	0,875	0,006	100,0	50,0	77,8	0,738	*N.S*	50,0	100,0	75,0	0,766	*N.S*
r_4	50,0	100,0	78,9	0,568	*N.S*	80,0	90,9	85,7	0,845	0,007	62,5	100,0	84,2	0,795	0,032	100,0	50,0	77,8	0,700	*N.S*	50,0	100,0	75,0	0,750	*N.S*

Table 5. Classification results for ALL vs. ALL

Type of Classification, Train Algorithm and Activation Function			The Out-of-Sample Classification Error per Number of Features (%)									Classification Results with Min. Error			
			5	6	7	8	9	10	11	12	13	S (%)	E(%)	A (%)	AUC
10FCV	LM	TS	11,35	**9,27**	11,85	13,84	14,52	12,05	14,16	14,26	12,27	86,13	93,03	89,58	0,9010
	RP	TS	**9,90**	12,13	12,25	10,11	14,26	12,62	11,58	13,91	14,84	85,50	92,40	88,95	0,8947
	SCG	TS	10,79	**9,89**	10,61	11,58	11,05	12,99	11,73	14,58	14,51	85,51	92,41	88,96	0,8948
L1CV	LM	TS	10,68	**9,63**	11,19	13,76	11,86	11,73	13,71	13,24	15,61	85,78	92,68	89,23	0,8975
	RP	TS	**10,90**	11,69	12,88	12,23	13,01	13,41	13,88	13,69	14,10	84,51	91,41	87,96	0,8848
	SCG	TS	10,89	**9,95**	12,18	12,15	13,08	13,78	10,54	14,60	15,59	85,46	92,36	88,91	0,8943
10FCV	LM	LS	9,94	**9,20**	11,42	14,00	12,48	14,41	13,44	13,85	15,73	86,21	93,11	89,66	0,9018
	RP	LS	**10,20**	11,20	12,55	12,52	11,82	13,19	12,83	14,67	13,83	92,11	92,11	92,11	0,8918
	SCG	LS	10,98	**9,80**	10,13	12,01	11,38	15,11	13,72	11,79	13,31	85,61	92,51	89,06	0,8958
L1CV	LM	LS	10,59	**8,58**	11,79	13,84	12,72	13,72	12,40	12,63	12,66	**86,83**	**93,73**	**90,28**	**0,9080**
	RP	LS	**8,94**	9,50	12,22	12,69	14,69	14,18	13,67	14,55	15,14	86,47	93,37	89,92	0,9044
	SCG	LS	10,93	**10,67**	13,15	12,02	12,40	13,88	12,66	14,69	13,03	84,91	91,81	88,36	0,8871

CLASSIFICATION METHODOLOGY

Concerning the EEG processing of this step, the leave-one-out-cross-validation and 10-fold-cross-validation process, to classify of the EEG study signals, were used. From each 5s of signal per electrode, the previously introduced features were extracted to serve as an individual classifier input vector. The features that did not provide a $p < 0.05$ in the previous section was not used at this step. Independently of the chosen cross-validation process, if in a given cross-validation iteration the test and the trained groups have, at the same time, input vectors of features from the same study subject, the classifying process automatically removes from the trained group those vectors, classifying, that way, the test group with true independent cases. A genetic algorithm with entropy criterion was used to get the best features' combinations, between 5 to 13 features, that served as input vectors for the classifier. The chosen classifier was an Artificial neural network with tangent sigmoidal - *Tansig* (TS) or logarithmic sigmoidal - *Logsig* (LS) as activation functions; Levenberg-Marquardt (LM), Resilient Propagation (RP) or Scaled-Conjugate Gradient (SCG) as the training algorithms; Mean squared error as the error function; the output layer with 4 nodes (*NCO*), input layer with different kind of nodes (*NCI*) depending on the length of features' input vectors and finally one hidden layer with a different number of nods depending of the input layer nods (*NCH*). Where $NCH=(NCI+NCO)^{0.5}+4$. The classification results can be seen in Table 5. The best classifications achieved (bold) are shown (86,83 of Sensitivity, 93,73% of Specificity, 90,28% of accuracy and 0,9080 of AUC). That was the one that produced the lowest out-of-sample classification error that is highlighted and underlined. This error value (8,58%) indicates that the classifier generalizes fairly well. The best features combination of 6 parameters was: $RP(\beta 1)$, r_2, r_1, Zcr_γ, $RP(\theta)$ and r_3.

The best architecture for ANN in all vs. all classification (Train Algorithm – LM and LS as activation function) was achieved by performing a classification between pairs of study groups. The results can be seen in Table 6, and the best classifications per pairs of study groups are bold and underlined. The lowest error achieved identifies the best classification (C vs MCI – 79,86% of Sensitivity, 75,06% of Specificity, 77,46% of Accuracy; C vs ADM – 96,14% of Sensitivity, 91,51% of Specificity, 95,01% of Accuracy; C vs ADA – 98,01% of Sensitivity, 93,34% of Specificity, 95,95% of Accuracy; MCI vs ADM – 82,40% of Sensitivity, 77,13% of Specificity, 79,77% of Accuracy; MCI vs ADA – 86,64% of Sensitivity, 85,85% of Specificity, 86,20% of Accuracy).

FUTURE RESEARCH DIRECTIONS

The future lines of research that emerged from the work we carried out include:

1. Keep collecting new EEG signals to increase the database in order to ensure results generalization;
2. Classification by range of aging groups with a view to describe the AD developing over time and to verify the diagnosis accuracy in each one of them;
3. Enlarge the EEG database to other diseases that provoke dementia like Parkinson's disease, Epilepsy, Vascular Dementia and Schizophrenia, as the EEG slowing down is not observed exclusively in AD and MCI;
4. Application of non-linear techniques based on Chaos theory to extract more EEG characteristics in order to increase the accuracy of the method, mainly between C vs. MCI (Critical phase of AD developing).

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Table 6. Classification results between pairs of study groups

		The Out-of-Sample Classification Error per Number of Features (%)									Classification Results with Min. Error			
Groups	**Classification Type**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**S (%)**	**E(%)**	**A (%)**	**AUC**
C vs MCI	**10FCV**	23,74	**23,41**	23,64	23,98	23,98	24,55	24,31	24,31	24,78	**79,86**	**75,06**	**77,46**	**0,778**
C vs. ADM		9,21	5,92	6,58	**5,92**	8,88	7,89	8,55	9,21	8,88	94,67	93,51	94,08	0,941
C vs. ADA		4,68	5,01	**4,62**	4,83	4,83	6,87	6,96	6,45	5,97	97,01	93,07	95,28	0,953
MCI vs. ADM		25,30	21,25	**20,18**	21,76	22,26	22,26	22,02	21,76	21,76	**82,40**	**77,13**	**79,77**	**0,797**
MCI vs. ADA		25,00	14,54	13,95	14,14	14,41	15,07	**13,95**	14,87	14,80	**86,64**	**85,85**	**86,20**	**0,862**
C vs MCI	**L1CV**	25,07	**23,62**	24,74	24,54	26,97	27,17	27,50	29,14	24,28	76,67	76,35	76,49	0,765
C vs. ADM		12,29	14,11	12,05	**5,02**	7,96	6,64	7,92	8,04	7,64	**96,14**	**93,51**	**95,01**	**0,950**
C vs. ADA		5,14	5,75	**3,81**	4,66	4,96	3,56	4,13	3,80	4,71	**98,01**	**93,34**	**95,95**	**0,960**
MCI vs. ADM		22,43	23,51	**21,51**	24,54	24,14	24,34	23,62	22,70	24,47	78,43	78,68	78,54	0,785
MCI vs. ADA		14,64	15,31	14,10	15,57	15,50	15,00	**14,00**	14,02	15,79	86,54	85,46	86,00	0,862

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CONCLUSION

Nowadays, the increasing urgency to find ways to diagnose and treat early the AD is the main focus of several researchers. Researchers are conducting studies in order to learn more about the biological features of AD and the early steps of this illness, so that AD may be detected years before the symptoms appear. Their findings will certainly help to make an AD early and accurate diagnosis. Early diagnosis will allow treating the AD harmful effects, as soon as the first symptoms appear and patients may maintain thinking and memory capacities longer. Early diagnosis will also provide patients' access to available treatments, while it may initiate them earlier. With early diagnoses, patients may look for support and participate in clinical trials. That is why the authors felt more and more motivated and encouraged to develop their work in order to provide a useful contribution to the AD early diagnosis. Moreover, the present study is based on EEG because the authors believe that it has several excellent characteristics and low-cost. Therefore, it appears to be a good objective to increase its value as a diagnosis tool.

The authors of this study processed the global average of each EEG signal of the AD patients and control subjects with the WT to get a reconstructed current band, from the signal. After that, several features were extracted, and significant differences were found between the features' distributions of the study groups. The best features were $RP(\beta 1)$, Zcr_{γ}, $NMax_{\beta}$, r_1 and r_2 but there are other features found that also got a $p<0.05$. This step forward to optimize and find good features that, when combined, may increase the classifier accuracy. After that, from each 5s of signal per electrode, the previously selected features with a $p<0.05$ were extracted. Then, an ANN with LCV and with 10FCV was used to classify the EEG signals. The best classification achieved was 0,934 of AUC, 86,83 of Sensitivity, 93,73% of Specificity, 90,28% of accuracy, with a low out-of-sample classification error of 8,58% which indicates that the classifier generalizes fairly well. Several studies tried to discriminate between controls and AD, AD and MCI and MCI and controls but only a few tried to discriminate between AD, MCI and control subjects. Moreover, the better accuracy achieved was 78% (Huang et al., 2000). In this study, the classifier provided a substantially higher accuracy of 90,28% (see Table 7). An increase of 12% regarding accuracy, comparing with previous works, was also found. Comparing with previous works of the authors regarding the discrimination between C and DA, an increase of 3% in accuracy was achieved. Despite that, the comparison should be carefully followed because the authors had used a different dataset during their previous works (Rodrigues & Teixeira, 2011; Rodrigues P. M., 2011; Rodrigues & Teixeira, 2013). In C vs. DA (see Table 7), Dauwels et al. in 2010, found a higher value of discriminant accuracy than the present study (98% vs. 95%).

Specifically, with regard to C vs. MCI and MCI vs. AD, the present work achieved discriminant rates in the average line of the state of art results with different EEG processing techniques. The C vs. MCI will be, in future works, the main target of authors in order to get a more and more accurate diagnostic, at this critical phase of AD development. Finally, the results should be extended to a larger population to ensure generalization.

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Table 7. Comparison between present study classification results with the state of art

Exam Type	Authors	C vs. AD			C vs. MCI			MCI vs. AD			C vs. MCI vs. AD		
		S(%)	E(%)	A(%)	S(%)	E(%)	A(%)	S(%)	E(%)	A(%)	S(%)	E(%)	A(%)
EEG	(Pritchard, et al., 1994)	-	-	85	-	-	-	-	-	-	-	-	-
	(Besthorn, et al., 1997)	-	-	86	-	-	-	-	-	-	-	-	-
	(Huang, et al., 2000)	90	75	84	-	-	-	87	68	78	87	68	78
	(Knott, et al., 2001)	-	-	75	-	-	-	-	-	-	-	-	-
	(Petrosian, et al., 2001)	80	100	90	-	-	-	-	-	-	-	-	-
	(Vialatte, et al., 2005)	-	-		-	-	93	-	-	-	-	-	-
	(Melissant, et al., 2005)	93	95	94	-	-	-	-	-	-	-	-	-
	(Buscema, et al., 2007)	-	-	-	-	-	-	89	95	92	-	-	-
	(Poil, et al., 2013)	-	-	-	-	-	-	88	82	85	-	-	-
	(Akrofi, et al., 2010)	-	-	-	-	-	-	-	-	-	-	-	77
	(Dauwels, et al., 2010)	-	-	98	-	-	83	-	-	-	-	-	-
	Previous Studies (Rodrigues & Teixeira, 2011; Rodrigues P. M., 2011; Rodrigues & Teixeira, 2013)	92	91	92	-	-	-	-	-	-	-	-	-
	Present Study	**96**	**93**	**95**	**80**	**75**	**77**	**84**	**82**	**83**	**87**	**94**	**90**
MEG	(Poza J., et al., 2008)	80	100	90	-	-	-	-	-	-	-	-	-
	(Poza, et al., 2014)	-	-	79	-	-	69	-	-	80	-	-	68
IRM	(Gupta, et al., 2013)	-	-	94	-	-	83	-	-	86	-	-	-
	(Liu, et al., 2014)	-	-	88	-	-	77	-	-	-	-	-	-
	(Batmanghelich, et al., 2009)	-	-	89	-	-	72	-	-	-	-	-	-
	(Yang, et al., 2011)	-	-	86	-	-	79	-	-	-	-	-	-
PET	(Janousova, et al., 2012)	-	-	90	-	-	87	-	-	-	-	-	-
	(Tolboom, et al., 2010)	100	85	93	-	-	-	-	-	-	-	-	-
	(Foster, et al., 2007)	86	98	90	-	-	-	-	-	-	-	-	-
Biomarkers	(Forlenza, et al., 2015)	88	78	83	-	-	-	90	65	78	-	-	-
	(Shaw, et al., 2009)	96	77	87	-	-	-	-	-	-	-	-	-
	(De Meyer, et al., 2010)	94			-	-	-	-	-	-	-	-	-
	(Hampel, et al., 2011)	80	90	85	-	-	-	-	-	-	-	-	-
	(Palmqvist, et al., 2015)	85	75	80	-	-	-	-	-	-	-	-	-
	(Colliot, et al., 2008)	84	84	84	-	-	-	-	-	-	-	-	-
	(Bartels & Murray, 2006)	80	91	86	-	-	-	-	-	-	-	-	-
	(O'Bryant, et al., 2010)	80	91	86	-	-	-	-	-	-	-	-	-
MMSE	(Knopman, et al., 2001)	81	70	76	-	-	-	-	-	-	-	-	-
	(O'Bryant, et al., 2008)	-	-	-	-	-	-	66	99	78	-	-	-

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Chapter 14
Early Detection of Electroencephalogram Temporal Events in Alzheimer's Disease

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ABSTRACT

Alzheimer's Disease (AD) is considered one of the most debilitating illness in modern societies and the leading cause of dementia. This study is a new approach to detect early AD Electroencephalogram (EEG) temporal events in order to improve early AD diagnosis. For that, Self-Organized Maps (SOM) were used, and it was found that there are sequences of EEG energy variation, characteristic of AD, that appear with high incidence in Mild Cognitive Impairment (MCI) patients. Those AD events are related to the first cognitive changes in patients that interfered with the normal EEG signal pattern. Moreover, there are significant differences concerning the propagation time of those events between the study groups($p=0.0082<0.05$), meaning that, as AD progresses the brain dynamics are progressively affected, what is expected because AD causes brain atrophy.

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INTRODUCTION

In the last decades, deep changes related to world population age structure happened with a progressive decrease of young people and a progressive increase of elderly people (Ballard, et al., 2011). The decrease of mortality and the simultaneous decrease of fertility levels have contributed to the phenomenon called overall aging of the population. The aging population has become a fact of scientific interest because the elderly are most vulnerable to the onset of certain degenerative diseases (Jonker, Launer, Hooijer, & Lindeboom, 1996). Alzheimer's disease (AD) is a degenerative, chronic, progressive and irreversible illness and is the most common cause of dementia. In 2001 AD reached more than 24.3 million affected people around the world and it has the propensity to rise significantly in the coming years (Ballard, et al., 2011). AD also represents 60% of elderly diseases and has an unknown cause. As it is a cortical and progressive brain disorder, gradually, over time, most parts of the brain will suffer damage and AD symptoms will severely increase (Blennow, Leon, & Zetterberg, 2006). The first symptoms of AD are memory loss, particularly difficulty remembering newly learned information and concentration problems (Gwyther, 2001). As the disease progresses patients manifest general cognitive problems, confusion, personality / behavioral changes and also disorientation (Bird, 2001). Finally, there is a global brain atrophy and patients acquire a complete inability (Cummings, 2004). So, permanent aids of family members or caregivers are increasingly requested (Jeong, 2004).

AD progression is gradual and usually categorized into four stages. Each one presents typical symptoms of the disease progression. The pre-dementia stage is known as Mild Cognitive Impairment (MCI). At this stage subjects present subtle symptoms, daily life activities are preserved, and cognitive impairment is restricted to memory (Nestor, Scheltens, & Hodges, 2004). MCI confers a higher risk of developing AD but only between 6% and 25% of people affected with MCI actually develops AD (Shimokawa, et al., 2001). Mild and Moderate AD are the next two stages characterized by a significant increase of cognitive impairment and a marked loss of independence (Gwyther, 2001). The last stage is Severe AD where a complete deterioration of personality occurs; patients are unable to perform any tasks and caregiving becomes fully indispensable (Mesulam, 2000).

Researchers do not know yet why the brain cells deteriorate. Senile plaques and neurofibrillary tangles in the medial temporal lobe and cortical areas are two pathological hallmarks of brains destroyed by AD (Blennow, 2005; Mattson, 2004). These two abnormal structures are responsible for damaging and killing the nerve cells (Cummings, 2004). Parts of the brain start to shrink because the brain's nerve cells die. In AD the last stage, the damage is generalized, and the brain tissue volume decreases very significantly (Blennow, 2005; Blennow & Zetterberg, 2010).

Several factors are often associated with a higher risk of developing AD. Ageing is considered the main risk factor; after the age of 65, the risk of developing the disease doubles every five years. Another factor is family history; people who have a close relative who developed Alzheimer's disease have a slightly higher risk of eventually developing the disease themselves (Blennow, 2005). Gender is considered another factor; a higher percentage of women develop AD than men do. Heart diseases (namely: high cholesterol, hypertension or poorly controlled diabetes) are considered risk factors for developing AD. Many other factors, including stress, obesity, smoking, lower educational qualifications, Down's syndrome and head injuries are associated with a possible risk of developing AD (Blennow, Leon, & Zetterberg, 2006; Lahiri, Farlow, Greig, & Sambamurti, 2002).

Despite the progress in better understanding AD stages, there remains no prospect of cure at least shortly. Therapies currently available only soften and slow the symptoms progression, that is why new

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treatments must be developed to alter the disease process itself and not just to reduce some of the common symptoms (Ballard, et al., 2011). AD has been researched for years, but researchers have not yet discovered a good treatment for this complex and stressful disease and neither have discovered a reliable method to make an accurate AD diagnosis (Ballard, et al., 2011).

AD leads to death approximately seven years after being diagnosed (Mölsä, 1986). An early and accurate diagnosis is necessary to help intervention in order to reduce the brain damage. It is often difficult to diagnose AD, and the diagnosis is made by excluding other possible causes of dementia symptoms (Porth & Matfin, 2009). Besides, a definitive AD diagnosis can only be made by necropsy (Blennow, 2005). The development of methods that can assist in AD diagnosis may lead to reducing costs associated with this illness because AD is considered a modern epidemic with a large impact on the Health Care Systems (Lahiri, Farlow, Greig, & Sambamurti, 2002; Ferri, et al., 2005). AD is a public health problem and represents a challenge to the scientific community in order to find solutions to minimize its socio-economic effects (Machado, 2002).

The Electroencephalogram (EEG) has been used for several decades as a diagnostic tool for dementia. Therefore, it can be a useful tool in AD diagnosis. The EEG is a physiological technique that records the brain electrical activity originated by the neurons with high resolution (Sanei & Chambers, 2007). It is also a non-invasive and a cost-effective technique that presents no side effects and it is widely extended in clinical settings (Jeong, 2004; Stam, 2005). Nowadays, there are equipments with up to 32 channels of EEG with electrodes connected to the scalp to conduct the electro-cortical potentials to the amplification device. This device provides quite accurate readings, and the analysis is reliable enough (Sanei & Chambers, 2007). A system consists of EEG electrodes, connecting cables, amplifiers and a microcontroller to communicate with the main computer in order to visualize the brain signals (Sanei & Chambers, 2007). The recorded EEG signals have very complex shapes, which depend on the locations of the electrodes, given a large number of interconnections that the neurons have, as well as, the fact that the brain does not have a uniform structure (Sanei & Chambers, 2007). EEG is typically divided into several frequency bands, such as delta (1-4 Hz, δ), theta (4-8 Hz, θ), alpha (8-13Hz, α), beta (13-30 Hz, β) and gamma (30-40 Hz, γ). AD seems to affect the power in those different bands. Many studies have shown that AD causes "slow down" on EEG signals (Jeong, 2004; Stam, 2005). AD is associated with an increase of power in low frequencies (delta and theta band) and a decrease of power in higher frequencies (alpha and beta) (Jeong, 2004). This phenomenon also called "shift-to-the-left" appears in advanced and intermediate states of AD and it can be seen notably in the peak occurring in the alpha range (Jeong, 2004). These changes are related to the destruction of cholinergic synapses in the Meynert nucleus where transferase is produced, responsible for the synthesis of acetylcholine (Gawel, Szmidt-Salkowska, & Kowalski, 2009). A lack of acetylcholine is, in turn, responsible for disorders of the synchronization of synaptic potentials, and then, pathological activity reveals itself in the form of EEG slower waves (Gawel, Szmidt-Salkowska, & Kowalski, 2009).

STUDY OBJECTIVE AND CHAPTER ORGANIZATION

In this study, the authors want to create a methodology to better understand AD behavior during its progression. For that propose, as it is difficult to get an accurate AD diagnoses in early stages, in this study an unsupervised learning tool (Self-Organized Maps (SOM)) was used in order to search characteristic AD events in MCI patients by using EEG signals. The Wavelet Transform (*WT*) was applied to extract

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several EEG features, and genetics algorithms were used to search the best feature combinations. The features selection process was important in order to have the best accurate EEG information to search AD temporal events with better precision by an unsupervised learning tool. The paper is organized as follows: In the section Materials and Methods - the Materials are introduced together with the EEG analysis and the unsupervised tool that leads to the development of the proposed methodology and its fundamentals; In the section Methodology - the methodology is described; section Future Research Directions indicates the future research lines of this work; and finally, in the section Discussion and Conclusions - the results are discussed and it concludes the paper emphasizing its main contributions.

MATERIALS AND METHODS

Selection of Study Participants and EEG Recording

A set of 24 subjects participated in this study (8 as Controls (C), 8 with MCI, 8 with AD). EEGs were recorded from the 19 scalp loci of the international 10-20 configuration using a digital electroencephalograph in "Hospital de São João - Porto", Portugal. The sampling frequency was 256 Hz and all recordings were digitally filtered with a band-pass filter with cut-off frequencies at 1-40Hz. In Table 1, additional information is provided regarding the participants in each group including the average age and Mini Mental State Examination (MMSE) average. All EEG were organized in segments of 5s (1280 epochs) and recorded with the eyes closed. All participants gave their informed consent prior for their participation in this study, and the study protocol was approved by the local Ethics Committee.

Table 1. The dataset

Dataset			
	Control Subjects	**MCI Patients**	**AD Patients**
#	8	8	8
Age average	75	80	78
MMSE average	28,77	26,29	20,97

EEG Time-Frequency Representations

The EEG signals, in general, tend to have rapid oscillations in short intervals or slow variations in long intervals (Sanei & Chambers, 2007). The Fast Fourier Transform (FFT) was introduced in 1965 and it remains the spectral EEG signal processing most commonly used until today (Rodrigues & Teixeira, 2013). However, FFT is not able to provide information both in the time and frequency of signal characteristics. The spectral components do not reflect changes over time, what is a problem to analyze non-stationary signals, like the EEG (Haykin & Veen, 2003). As a result, it is convenient to use a transformation that provides a variable resolution time-frequency plane. This is the case of the *WT*, which provides a good time resolution for the high frequencies and good frequency resolution for low frequencies (Kaiser, 1994; Rioul & Vetterli, 1992). The EEG discrete signal is represented as $x[n] = x(n \cdot T_s)$, $n = 0,..,N\text{-}1$, sampled

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to F_s samples/s ($F_s = 1/T_s$) with N samples. The *WT* is an optimal tool for data analysis when time and frequency resolution are critical (Schiff & Milton, 1993). The Equation 1 represents the calculation of *WT* per scale, sometimes called child *WT* ($\psi(t)_{\tau,a}$) (Kaiser, 1994; Rioul & Vetterli, 1992)

$$\psi\left(t\right)_{\{\tau,a\}} = \frac{1}{\sqrt{\left\{\left|\ a\right|\right\}}} \cdot \psi\left(\ \frac{t-\tau}{a}\right), \tag{1}$$

where τ is the translational parameter, t represents the bins in the time domain, $\psi(t)$ is the Wavelet Mother and a represents the basis functions range that acts as an enlargement factor if $a > 1$ or as a compression factor if $a < 1$.

The Discrete Wavelet Transform (*DWT*) uses a multiresolution analysis that consists in obtaining increasingly smaller signal resolution versions by successive filtering. The *DWT* uses one set of two functions: a scale function ($\varphi[n]$) and a Wavelet function ($\psi[n]$).

$$\varphi\left[n\right] = \sum_{k} h\left[k\right] \cdot \phi\left[2 \cdot n - k\right] \tag{2}$$

$$\psi\left[n\right] = \sum_{k} g\left[k\right] \cdot \phi\left[2 \cdot n - k\right] \tag{3}$$

where k is the discrete translation parameter and $h[k]$ and $g[k]$ respectively are the impulse responses of the low-pass and high-pass filters used in the *WT* analysis. The signal decomposition in different frequency bands is achieved by successive low-pass filters and high-pass filters in time, followed by subsampling by a factor of two until the maximum level of decomposition ($log_2(N)$) as is illustrated in the following equations 4 and 5.

$$DWT_A^{\varphi}\left[j,k\right] = \sum_{n=0}^{\frac{N}{2^{(j-1)}}} DWT_A^{\varphi}\left[j-1,n\right] \cdot h\left[2 \cdot k - n\right] \tag{4}$$

$$DWT_D^{\psi}\left[j,k\right] = \sum_{n=0}^{\frac{N}{2^{(j-1)}}} DWT_A^{\psi}\left[j-1,n\right] \cdot g\left[2 \cdot k - n\right] \tag{5}$$

where, $k = 0, ..., N/2j$; $j = 0, ..., log_2(N)$; A represents the *DWT* approximated coefficients; D the *DWT* detail coefficients and N the signal length. The Power Spectral Density (*PSD*) functions showed the variations strength of Power as a function of frequency. The Wavelet Packet Transform (*WPT*) spectrum was obtained by extracting the *WPT* coefficients corresponding to the terminal nodes. The *WPT* function was defined as (Rodrigues & Teixeira, 2011; Rodrigues & Teixeira, 2013):

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$$X_{\varphi,\psi}\left[j,m,k\right]=\sum_{n=0}^{\frac{N}{2^j-1}}WP^{\varphi,\psi}\left[j,m,n\right]\cdot w_{j,m,k}\left[n\right]\ ,$$

$$w_{j,m,k}\left[n\right]=2^{-\frac{j}{2}}\cdot w_m\left[2^{-j}\cdot n-k\right],$$

$$j=1,\ldots,J;m=0,1,\ldots,2^j-1;k=1,\ldots,2^{J-j} \tag{6}$$

where $J=log_2(n)$, j represented the level of *WPT*. To estimate the *PSD* of *WT*, we used the *WPT* periodogram based on the observations of length $N=2^j-1$.

$$S_{x,\varphi,\psi}\left[m,k\right]=\left[\sum_{j=1}^{J}X_{\varphi,\psi}\left[m,k\right]\right]^2;m=0,1,\ldots,2^j-1;k=1,\ldots,2^{J-j}; \tag{7}$$

To obtain the frequency spacing of *PSD* of *WT* of each level of decomposition we used the range,

$$\left[\frac{F_s}{2^{j+1}},\frac{F_s}{2^{j+1-1}}\right],\quad j=1,\ldots,log_2(N)\ , \tag{8}$$

Summarizing, the absolute value of the coefficients was taken, and the Wavelet coefficients were ordered by frequency. The *PSD* was normalized (PSD_n) as below (Rodrigues & Teixeira, 2013):

$$PSD_n\left[m,k\right]=\frac{S_{x,\varphi,\psi}[n]}{\sum_{n=k_1}^{k_2}S_{x,\varphi,\psi}[n]},\qquad m\ =\ 0,\ldots,2^j\ -\ 1 \tag{9}$$

Feature Extraction

Several features were extracted in each frequency bands (δ, θ, α, β and γ) of the EEG signal. This feature characterized the waveform in terms of faster or slower and of greater or smaller variability as it is required to observe the "shift-to-the-left" phenomenon. It can be described by the values of maxima (*NMax*) and minima (*NMin*), the zero-crossing (*Zcr*) rate, the mean derivative value at a point (*Mdif*), the Relative Power (*RP*) and the spectrum energy deceleration represented by the spectral ratios (*r*). The extracted features were:

- ***NMax*** and ***NMin*****:** Accounting and calculation of all signal maxima and minima, respectively, by the variation of the signal waveform derivative (view Figure 1).

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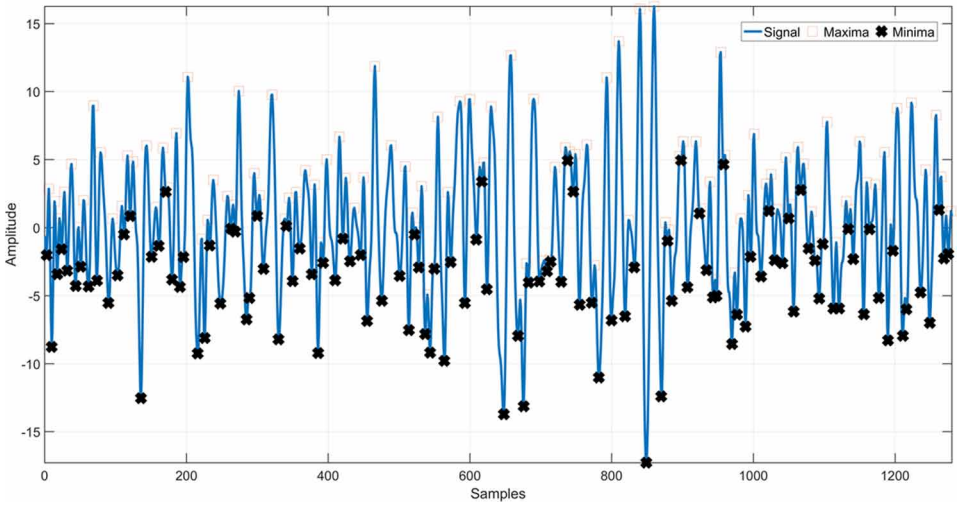
Figure 1. Signal, maxima and minima, example



- ***Zcr*:** The zero-crossing rate was calculated as (Chen, 1988):

$$Zcr_i = \frac{1}{N-1}\sum_{n=1}^{N-1}\mathbb{I}\left\{s_i\left(n\right)s_i\left(n-1\right)<0\right\}, \tag{10}$$

where $i = \{\delta,\theta,\alpha,\beta,\gamma\}$, s is a *DWT* coefficient signal of length N and II the indicator function. If the II value, in a certain position, is equal to 1 a signal zero crossing is found.

- ***Mdif*:** The mean derivative value at a point was obtained by the equation 11 (Apostol, 1988),

$$Mdif_i = \frac{1}{N-6}\cdot\sum_{n=1}^{N-6}\left(s_i\left(n\right)-\sum_{b=n}^{n+5}s_i\left(b\right)\right), \tag{11}$$

where $i = \{\delta,\theta,\alpha,\beta,\gamma\}$.

- ***RP*:** It was calculated as the sum of the components of the PSD_n in the conventional frequency bands: delta (1-4 Hz), theta (4-8 Hz), alpha (8-13Hz), beta1 (13-19Hz, $\beta 1$), beta2 (19-30 Hz, $\beta 2$) and gamma (30-40 Hz):

$$RP\left(\delta\right) = \sum_{f=1Hz}^{4Hz} PSD_n\left(f\right); \tag{12}$$

$$RP\left(\theta\right) = \sum_{f=4Hz}^{8Hz} PSD_n\left(f\right); \tag{13}$$

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$$RP\left(\alpha\right) = \sum_{f=8Hz}^{13Hz} PSD_n\left(f\right); \tag{14}$$

$$RP\left(\beta 1\right) = \sum_{f=13Hz}^{19Hz} PSD_n\left(f\right); \tag{15}$$

$$RP\left(\beta 2\right) = \sum_{f=19Hz}^{30Hz} PSD_n\left(f\right); \tag{16}$$

$$RP\left(\gamma\right) = \sum_{f=30Hz}^{40Hz} PSD_n\left(f\right); \tag{17}$$

- ***r*:** Four spectral ratios were used to summarize the deceleration of the EEG spectrum of AD patients. r_1 is a spectral ratio that enabled us to detect changes when a slight slowdown in the EEG spectrum appears. The r_2 index summarizes the EEG globally slowing down. r_3 computes the relationship between high-frequency bands ($\beta 1$ and $\beta 2$) and the lowest frequency band (δ). r_4 is similar to r_3, but with a narrower high-frequency band (only $\beta 2$). (Rodrigues & Teixeira, 2013).

$$r_1 = \frac{RP\left(\alpha\right)}{RP\left(\theta\right)}, \tag{18}$$

$$r_2 = \frac{RP\left(\alpha\right) + RP\left(\beta 1\right) + RP\left(\beta 2\right) + RP(\gamma)}{RP\left(\delta\right) + RP\left(\theta\right)}, \tag{19}$$

$$r_3 = \frac{RP\left(\beta 1\right) + RP(\beta 2)}{RP(\delta)}; \tag{20}$$

$$r_4 = \frac{RP\left(\beta 2\right)}{RP\left(\delta\right)}; \tag{21}$$

Unsupervised Classification: Self-Organized Maps

Self-Organized Maps is one example of an unsupervised neural network that reduces the dimensionality of the input data, on a map of neurons (Kohonen, 2001). It is based on competitive learning where the output neurons compete with each other, and only one is activated. This activated neuron is called the winner neuron. The winner neuron will be the one whose weights in the input connections are closer to

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the input pattern in terms of Euclidean distance. Such competition can be induced by a negative feedback system between neurons. Finally, neurons are forced to organize themselves into groups enabling a good ability to form clusters (Kohonen, 2001). The phases of SOM algorithm are:

1. **Initialization:** Randomly initialize the vectors of weight w_j.
2. **Sampling:** Build an input vector from the training set.
3. **Correspondence:** Find the winner neuron $I(x)$ witch has a weight vector most similar to the input vector.
4. **Update:** Update the weights by the function:

$$\Delta w_{ji} = \eta(t) \cdot T_{j,I(x)}(t)\left(x_j - w_{ji}\right) \tag{22}$$

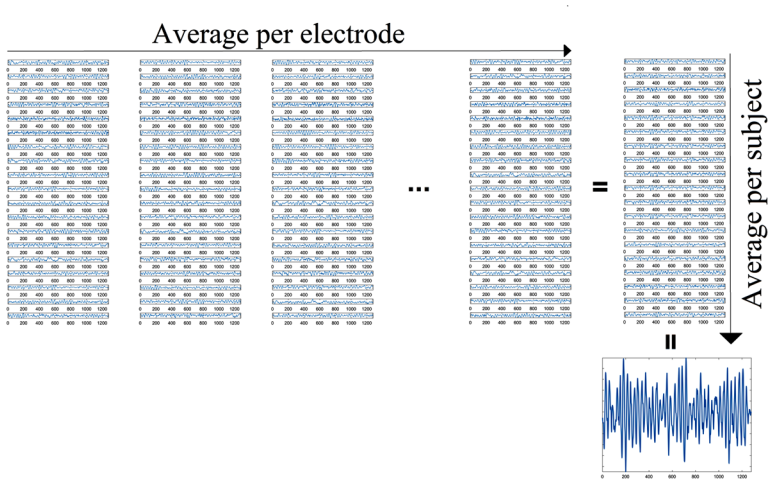
where Δw_{ji} represents the value of updating weights, η(t) is the learning rate parameter, $T_{j,I(x)}(t)$ is the neighborhood function centered around the winner neuron and w_{ji} is the current weight value.

5. **Continued:** Back to step 2 until the map of "clustering" stops changing (Haykin, 1998).

Statistical Analysis and Features Selection

Each 5 seconds (1280 epochs) of EEG signal epoch has undergone an average process per electrode and per subject in order to make a statistical analysis of the extracted features (see example of EEG signal average in Figure 2).

Figure 2. Example of signal averaging per electrode and per subject



In order to extract some information from the EEG signals of AD patients, MCI patients, and Control subjects, each signal resulting from the average process was decomposed to the level 5 by the Wavelet Biorthogonal (Bior) 3.5 *DWT.* Additionally the EEG signals were processed by Bior 3.5 *PSD* of *WT*

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technique to the level 8 of decomposition. These decomposition levels for both techniques provided the correct level of EEG signal decomposition to reach the conventional frequency bands of EEG (δ, θ, α, β and γ bands). In the case of the *PSD* of *WT* technique, the level 8 of decomposition allowed obtaining a *PSD* which ranges between 1Hz and 128Hz. Thus containing the frequency range of conventional EEG bands (1-40Hz) and in this way, the *PSD* of *WT* can be restricted to this range of frequencies. In the case of *DWT,* the level 5 of decomposition gives the detail coefficients *D*2 that corresponds to the Gamma band, *D*3 to the beta band, *D*4 to the alpha band, *D*5 to the theta band and the approximated coefficients *A*5 to the delta band. The *PSD* of *WT* and *DWT* were computed by Bior 3.5 because it proved to be a good choice in EEG previous studies (Rodrigues & Teixeira, 2011; Rodrigues & Teixeira, 2013). After this, the previously defined features were extracted from the averaged signals.

A linear classifier with a leave-one-out cross-validation procedure was performed to assess the features combination that reached the best classification performance. The classifier is intended to have the ability to discriminate AD patients from Control subjects and MCI patients. It was evaluated by using ROC curves (Williams, Lee, Fisher, & Dickerman, 1999). The ROC curve is a graphical representation of the trade-off between sensitivity and specificity. Sensitivity (Sens) measures the proportion of positives that are correctly identified, specificity (Spec) is the proportion of negatives that are correctly identified (Accu) is the percentage of the study participants correctly recognized. The Area Under the ROC Curve (AUC) is a single number that summarizes the diagnostic robustness of the parameter (Williams, Lee, Fisher, & Dickerman, 1999). The best features combinations were obtained by using genetic algorithms. After the process, the 19 features combination that achieved the best classification indexes were: r_1, r_2, $RP(\alpha)$, $Mdif_\delta$, r_4, $NMax_\gamma$, $NMin_\gamma$, $RP(\gamma)$, $NMax_\alpha$, $NMin_\alpha$, Zcr_β, Zcr_α, $RP(\theta)$, Zcr_α, $NMin_\theta$, $NMax_\theta$, r_3, $NMax_\beta$ and $NMin_\beta$.

METHODOLOGY

Each 5 seconds/1280 epochs of EEG signal epoch per electrode selected from this 24 subjects that participate in this study were split into twenty threads (each thread has 64 samples). After that, in each thread, the best-combined features that provided the best classification results for all dataset (24 subjects) it has been extracted. For that a linear classifier with leave-one-out cross-validation procedure was used, see previous section.

The EEG features extracted consisted in the set of 19 previous selected features: r_1, r_2, $RP(\alpha)$, $Mdif_\delta$, r_4, $NMax_\gamma$, $NMin_\gamma$, $RP(\gamma)$, $NMax_\alpha$, $NMin_\alpha$, Zcr_β, Zcr_α, $RP(\theta)$, Zcr_α, $NMin_\theta$, $NMax_\theta$, r_3, $NMax_\beta$ and $NMin_\beta$. In next step, as shown in Figure 3, the SOM was used to classify randomly in five groups all the twenty threads. SOM was forced to perform a logical classification in order to obtained groups. For all classifications, of twenty threads from a segment of 5 seconds length, the labels have been reordered in order to obtain a homogeneous classification (groups composed of characteristics with similar trends of values over all the classification process).

The Figure 4 represents sequentially, the SOM classification in the temporal domain, for a segment of 1280 epochs length. Depending on the threads classification, the segment threads were represented in Figure 4 with different colors. It can be observed a decrease of AD incidence degree from Group 1 to Group 5. AD patients tendentially present lower distributions of values from feature 1 and feature 2 than the healthy Controls and MCI patients. This was also observed in previous works for AD (Rodrigues P. M., 2011; Rodrigues & Teixeira, 2013; Rodrigues, Freitas, & Teixeira, 2013).

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Figure 3. Scatter plot example of the classification made with the values of two extracted features

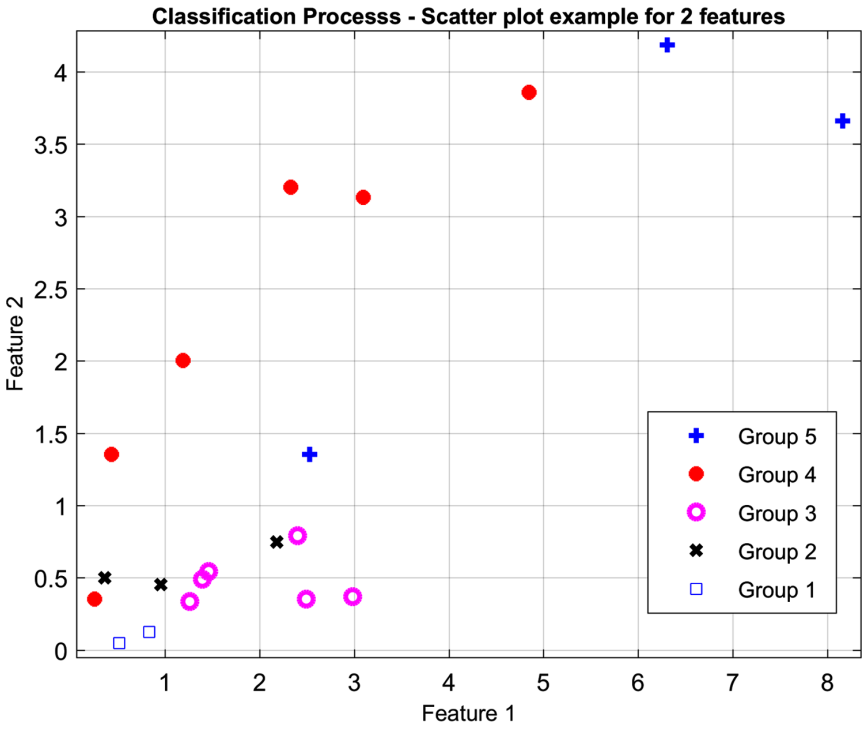
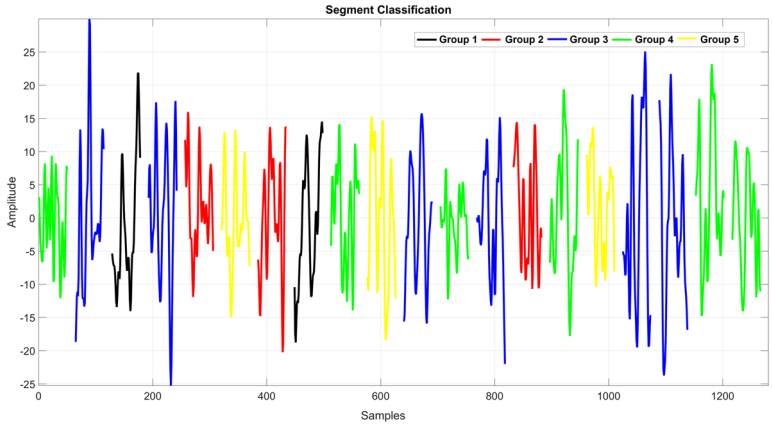


Figure 4. Example of the classification process in the temporal domain, for an EEG segment of 5s



By observing the scatter plot of Figure 3 it can be seen that from the Group 1 to the Group 5 the median values of feature 1 and features 2 in each group increases progressively. Consequently, the incidence degree of AD in EEG will decrease along the classifying groups.

After performing SOM classification for the dataset, all four combinations of five groups (SOM classification groups) were verified for AD patients, MCI patients and for Control group in any temporal SOM classification of 5s segments - 1280 epochs (see, Figure 4). In order to analyze the results, two

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tables were made (Tables 2 and 3). Table 2 provided the difference ($Diff_{ADvsC}$) between the number of temporal sequences found at AD group (Seq_{AD}) and at Control group (Seq_{C}),

$$Diff_{ADvsC} = Seq_{AD} - Seq_{C}. \quad (23)$$

and Table 3 provided the difference ($Diff_{MCIvsC}$) between the number of temporal sequences found at MCI group (Seq_{MCI}) and at Control group (Seq_{C}),

$$Diff_{MCIvsC} = Seq_{MCI} - Seq_{C} \quad (24)$$

1,2,3,4 and 5 represented the SOM classification in five groups. *Seq* represented the temporal sequences. The temporal sequences that have higher probability to appear in the EEG of AD patients and its respectively *Diff* score are shown at bold in Table 2 and Table 3.

The authors compared the sequences of four threads that appeared in Table 2 and Table 3 with a high incidence and concluded that the sequences 1133, 1311, 2255, 2555, 3112, 3214 and 4315 are the first sequences of AD that appear in early stages of the disease and constituted the denominated "AD early EEG Events". Based on the previous Events detection results, an analysis of the propagation of those events was performed. The propagation time is the time interval between the onset of the "AD early event" until its appearance/spread at other cerebral scalp zone, in another electrode, or until its demise. In Figure 5. It can be seen a boxplot; that shows that the average propagation time of the events detected in AD (approximately 850ms) is higher than in Control subjects (approximately 680 ms) and then in MCI patients (approximately 790ms), proving that the brain dynamism gets lower as the disease progresses. The statistical difference between those group relatively to the events propagation time is p=0.0082<0.05. The "AD early EEG events" detected in Control subjects results from a different kind of sources and have a different nature than the events found in AD and MCI patients, despite the EEG segments representative of those events being energetically similar to those found in AD and MCI patients.

FUTURE RESEARCH DIRECTIONS

The future lines of research that emerged from the work carried out include:

1. Modify the event detection methodology to get events with a longer time (250ms and 500ms);
2. Verify the possibility that an event appears and does not propagate by using magnetic resonance images; and
3. Results should be extended to a larger population to ensure generalization.

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Table 2. The difference between the number of temporal sequences found at AD group and Control group

Seq	Diff	Seq	Diff	Seq	Diff	Seq	Diff	Seq	Diff	Seq	Diff	Seq12	Diff	Seq	Diff	Seq1	Diff	Seq1	Diff
1111	**41**	1333	33	**2111**	**29**	**2333**	**36**	3111	12	3333	3	**4111**	**31**	4333	18	5111	13	5333	-7
1112	**27**	1334	0	2112	12	2334	-16	**3112**	**46**	3334	-47	4112	8	4334	-4	5112	14	5334	-63
1113	25	1335	15	**2113**	**32**	2335	20	**3113**	**29**	3335	-3	4113	19	4335	-6	5113	9	5335	18
1114	15	1341	15	2114	9	**2341**	**30**	3114	16	3341	11	4114	20	**4341**	**31**	5114	-12	5341	17
1115	**39**	1342	6	**2115**	**47**	2342	-2	**3115**	**31**	3342	-2	4115	8	4342	-36	5115	19	5342	3
1121	22	1343	2	2121	1	**2343**	**35**	3121	18	3343	-12	4121	12	4343	-41	5121	0	5343	-23
1122	29	1344	10	**2122**	**32**	2344	-10	3122	-2	3344	26	4122	22	4344	-30	5122	23	5344	-14
1123	21	1345	11	2123	11	2345	2	**3123**	**26**	3345	-2	4123	25	4345	0	5123	20	5345	5
1124	11	1351	20	2124	14	**2351**	**33**	3124	11	3351	-12	4124	20	4351	4	5124	-1	5351	-22
1125	14	1352	-2	2125	3	2352	-3	3125	4	3352	-77	4125	12	4352	20	5125	11	5352	-32
1131	12	1353	0	**2131**	**28**	2353	1	3131	0	3353	-15	**4131**	**39**	4353	-6	5131	23	5353	7
1132	23	1354	-13	**2132**	**27**	2354	6	3132	3	3354	-15	4132	-13	4354	-17	5132	12	5354	-46
1133	**47**	1355	-24	2133	-1	2355	25	**3133**	**27**	3355	14	4133	-9	**4355**	**28**	5133	12	5355	9
1134	22	1411	22	2134	0	2411	19	3134	-12	3411	13	4134	-15	4411	-1	5134	-1	5411	16
1135	1	**1412**	**42**	2135	18	2412	6	3135	15	3412	12	**4135**	**38**	4412	7	5135	-7	5412	-4
1141	**34**	1413	-13	2141	9	**2413**	**47**	3141	3	3413	-9	4141	18	4413	14	5141	-3	5413	-3
1142	9	**1414**	**43**	2142	21	2414	0	3142	24	**3414**	**27**	**4142**	**39**	4414	36	5142	-10	5414	-23
1143	25	1415	7	**2143**	**34**	2415	6	3143	-3	3415	17	4143	-9	4415	21	5143	7	5415	11
1144	**27**	1421	14	2144	8	2421	10	3144	14	3421	27	**4144**	**29**	4421	-27	5144	2	**5421**	**35**
1145	-4	1422	11	2145	14	**2422**	**26**	3145	8	3422	-1	4145	13	4422	12	5145	1	5422	21
1151	3	1423	-3	2151	-2	2423	-22	3151	14	**3423**	**31**	4151	20	4423	-27	5151	-4	5423	-12
1152	22	1424	-10	**2152**	**28**	2424	7	3152	-15	3424	17	4152	7	4424	-36	5152	-1	5424	-29
1153	18	1425	4	2153	17	2425	14	3153	3	3425	3	4153	-4	4425	24	5153	-15	5425	-11
1154	11	1431	14	2154	8	2431	14	3154	25	3431	0	4154	8	4431	10	5154	-25	5431	17
1155	2	**1432**	**32**	2155	21	**2432**	**34**	**3155**	**41**	3432	27	4155	6	4432	17	5155	4	5432	-13
1211	**40**	**1433**	**46**	**2211**	**47**	2433	4	3211	14	3433	-41	4211	9	4433	-3	5211	9	5433	-34

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Table 2. Continued

Seq	Diff	Seq	Diff	Seq	Diff	Seq	Diff	Seq	Diff	Seq	Diff	Seq12	Diff	Seq	Diff	Seq1	Diff	Seq1	Diff
1212	34	1434	9	2212	5	2434	15	3212	13	3434	-18	4212	-5	4434	9	**5212**	**42**	5434	-21
1213	22	1435	-4	2213	24	2435	12	3213	18	3435	11	**4213**	**32**	4435	25	5213	3	5435	-8
1214	12	**1441**	**55**	2214	19	2441	22	**3214**	**27**	3441	1	4214	23	4441	-63	5214	-19	5441	5
1215	25	1442	0	**2215**	**33**	**2442**	**32**	3215	24	3442	-1	**4215**	**30**	4442	-13	5215	17	5442	24
1221	13	1443	14	2221	-109	2443	-21	3221	8	3443	-32	4221	-4	4443	-49	5221	-47	5443	-42
1222	25	1444	2	2222	5	2444	-4	**3222**	**41**	3444	-18	4222	10	4444	-71	5222	14	5444	-4
1223	22	1445	-4	2223	-6	2445	17	3223	12	3445	14	4223	17	4445	2	5223	14	5445	-10
1224	**33**	1451	0	2224	-42	2451	23	3224	13	3451	12	4224	-9	4451	-10	5224	-13	5451	-41
1225	-34	1452	8	2225	25	2452	9	3225	24	3452	-25	4225	25	4452	-3	5225	8	5452	-14
1231	20	1453	13	**2231**	**36**	2453	-33	3231	-19	3453	-10	4231	2	4453	-40	5231	4	5453	-57
1232	11	1454	-12	2232	-2	2454	3	3232	-34	3454	-11	4232	11	4454	-31	5232	-7	5454	-88
1233	12	**1455**	**30**	**2233**	**34**	2455	8	3233	9	3455	0	4233	17	4455	-1	5233	2	5455	27
1234	**29**	1511	11	2234	-7	2511	2	3234	22	3511	-5	4234	9	4511	13	5234	-11	5511	20
1235	18	**1512**	**26**	2235	25	**2512**	**27**	3235	-1	**3512**	**30**	**4235**	**39**	4512	-7	5235	5	5512	14
1241	**33**	1513	1	2241	-13	2513	19	3241	25	3513	-7	4241	-24	4513	0	5241	-2	5513	-26
1242	25	1514	2	2242	-2	2514	6	3242	18	3514	-9	4242	9	4514	-8	5242	1	5514	-22
1243	**30**	1515	-14	**2243**	**55**	2515	14	3243	-17	3515	2	4243	-26	4515	11	5243	-20	5515	-8
1244	**30**	1521	23	2244	14	2521	-4	3244	-2	3521	7	4244	-22	**4521**	**29**	**5244**	**29**	5521	-41
1245	-8	1522	-2	2245	16	2522	-5	3245	15	3522	-16	4245	12	4522	-9	5245	5	5522	-23
1251	11	1523	22	2251	-41	2523	-41	**3251**	**54**	**3523**	**35**	4251	-24	4523	-18	5251	-47	5523	17
1252	4	1524	19	2252	8	2524	-16	3252	5	3524	-10	4252	15	4524	-30	5252	-14	5524	-46
1253	13	1525	-2	2253	-20	**2525**	**34**	3253	-5	3525	6	4253	-27	4525	10	5253	1	5525	1
1254	7	1531	-4	2254	-37	2531	-8	3254	-25	3531	-11	4254	-8	4531	24	5254	-29	5531	-12
1255	11	1532	8	**2255**	**29**	2532	20	**3255**	**40**	3532	-55	4255	-1	4532	-20	**5255**	**30**	5532	-34
1311	**42**	1533	16	2311	2	2533	1	3311	19	3533	8	4311	18	4533	-18	5311	24	5533	-3
1312	19	1534	13	2312	18	2534	-15	3312	6	3534	-43	4312	4	4534	-9	5312	13	5534	-39

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Table 2. Continued

Seq	Diff	Seq	Diff	Seq	Diff	Seq	Diff	Seq	Diff	Seq	Diff	Seq12	Diff	Seq	Diff	Seq1	Diff	Seq1	Diff
1313	9	1535	5	**2313**	**30**	2535	-1	3313	11	3535	15	4313	5	4535	0	5313	3	5535	-20
1314	-9	1541	9	**2314**	**26**	2541	-23	3314	12	3541	15	4314	-3	4541	-1	5314	-5	5541	14
1315	2	1542	17	2315	17	2542	18	3315	15	3542	-29	**4315**	**33**	4542	-25	5315	18	5542	-15
1321	**29**	1543	-14	**2321**	**31**	2543	6	3321	4	3543	10	**4321**	**38**	4543	-47	5321	-6	5543	0
1322	**28**	1544	9	2322	-13	2544	-38	3322	2	3544	-21	4322	-12	4544	-73	5322	9	5544	-7
1323	13	1545	-6	2323	-12	2545	15	3323	-3	3545	4	4323	-4	4545	3	5323	9	5545	-63
1324	-7	1551	20	2324	22	2551	-26	3324	22	3551	-26	4324	-1	4551	-23	5324	-23	5551	18
1325	**33**	1552	9	2325	-4	2552	-5	3325	20	3552	-26	**4325**	**44**	4552	-29	5325	13	5552	17
1331	**29**	**1553**	**27**	2331	-9	2553	-5	3331	13	3553	-6	4331	17	4553	-21	5331	10	5553	3
1332	6	1554	3	2332	-39	2554	-71	3332	-50	3554	-51	4332	26	4554	-40	5332	-45	5554	-23
		1555	-28			**2555**	**34**			3555	12			**4555**	**30**			5555	-14

Table 3. The difference between the number of temporal sequences found at MCI group and Control group

Seq	Diff	Seq	Diff	Seq	Diff	Seq	Diff	Seq	Diff	Seq	Diff	Seq12	Diff	Seq	Diff	Seq1	Diff	Seq1	Diff
1111	-10	1333	-2	2111	-1	2333	9	3111	-1	3333	-43	4111	0	4333	-8	5111	4	5333	-30
1112	3	1334	-7	2112	7	2334	-20	**3112**	**29**	3334	-20	4112	4	4334	-19	5112	12	5334	-52
1113	19	1335	0	2113	16	2335	8	3113	15	3335	-23	4113	-1	4335	-9	5113	-6	5335	1
1114	14	1341	14	2114	10	2341	1	3114	10	3341	-27	4114	-6	4341	-9	5114	-12	5341	-25
1115	3	1342	7	2115	14	2342	7	3115	-11	3342	-26	4115	18	4342	-28	5115	21	5342	-9
1121	0	1343	-31	2121	-1	2343	-12	3121	-11	3343	-9	4121	-23	4343	-28	5121	-15	5343	-44
1122	-8	1344	2	2122	17	2344	-27	3122	-8	3344	-10	4122	-12	4344	-33	5122	-6	5344	-37
1123	10	1345	-18	2123	12	2345	-1	3123	12	3345	8	4123	-16	4345	-9	5123	-9	5345	8
1124	4	1351	-9	2124	-14	2351	-14	3124	-38	3351	-16	4124	3	4351	2	5124	-22	5351	-8
1125	0	1352	-7	2125	-2	2352	-24	3125	-12	3352	-30	4125	8	4352	10	5125	-6	5352	-50
1131	20	1353	-2	2131	-6	2353	4	3131	6	3353	-40	4131	25	4353	-10	5131	9	5353	0

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Table 3. Continued

Seq	Diff	Seq	Diff	Seq	Diff	Seq	Diff	Seq	Diff	Seq	Diff	Seq12	Diff	Seq	Diff	Seq1	Diff	Seq1	Diff
1132	8	1354	-13	2132	1	2354	-18	3132	8	3354	-33	4132	-31	4354	-22	5132	-4	5354	-11
1133	**27**	1355	-22	2133	-18	2355	-8	3133	13	3355	-12	4133	-22	4355	-9	5133	6	5355	0
1134	7	1411	17	2134	-4	2411	-3	3134	-39	3411	-11	4134	-8	4411	-17	5134	-10	5411	-8
1135	12	1412	10	2135	16	2412	-3	3135	11	3412	-3	4135	4	4412	-7	5135	2	5412	-5
1141	8	1413	-3	2141	4	2413	3	3141	-13	3413	12	4141	9	4413	-6	5141	-16	5413	-6
1142	-3	1414	10	2142	-4	2414	-23	3142	14	3414	14	4142	0	4414	-9	5142	-24	5414	-19
1143	16	1415	14	2143	7	2415	-8	3143	-20	3415	-19	4143	-25	4415	14	5143	-8	5415	-12
1144	24	1421	-5	2144	6	2421	-9	3144	20	3421	-19	4144	25	4421	-46	5144	-7	5421	-11
1145	-20	1422	-10	2145	0	2422	13	3145	-8	3422	-14	4145	-22	4422	13	5145	7	5422	-12
1151	-12	1423	2	2151	3	2423	-25	3151	9	3423	-5	4151	20	4423	-57	5151	0	5423	-10
1152	16	1424	-20	2152	12	2424	-31	3152	-26	3424	15	4152	-7	4424	-19	5152	-34	5424	-34
1153	12	1425	8	2153	23	2425	-14	3153	-24	3425	-12	4153	-15	4425	3	5153	-28	5425	-16
1154	3	1431	12	2154	-1	2431	-8	3154	12	3431	2	4154	-1	4431	1	5154	-22	5431	-24
1155	-17	1432	8	2155	7	2432	22	3155	23	3432	-17	4155	0	4432	-30	5155	-14	5432	-32
1211	13	1433	-8	2211	20	2433	15	3211	7	3433	-46	4211	3	4433	-9	5211	-2	5433	-29
1212	12	1434	-12	2212	-18	2434	-11	3212	-8	3434	-20	4212	-25	4434	-26	5212	21	5434	3
1213	3	1435	6	**2213**	**26**	2435	-5	3213	9	3435	4	4213	0	4435	-21	5213	1	5435	-17
1214	6	1441	-8	2214	7	2441	-11	**3214**	**26**	3441	-23	4214	5	4441	-48	5214	1	5441	1
1215	2	1442	-7	2215	0	2442	-23	3215	21	3442	-24	4215	-5	4442	-12	5215	-5	5442	0
1221	**30**	1443	11	2221	-73	2443	-28	3221	4	3443	-16	4221	-40	4443	-105	5221	-31	5443	-54
1222	-24	1444	0	2222	-17	2444	-34	3222	17	3444	-25	4222	-38	4444	-62	5222	-21	5444	-26
1223	-8	1445	-19	2223	-39	2445	0	3223	-22	3445	-10	4223	-3	4445	-17	5223	10	5445	-20
1224	7	1451	-4	2224	-28	2451	0	3224	-36	3451	-8	4224	-11	4451	-27	5224	-15	5451	-54
1225	-50	1452	14	2225	-13	2452	-4	3225	18	3452	-41	4225	11	4452	-30	5225	-18	5452	-20
1231	3	1453	4	2231	-4	2453	-26	3231	-21	3453	-30	4231	-6	4453	-43	5231	24	5453	-45
1232	9	1454	-18	2232	-23	2454	-28	3232	3	3454	-21	4232	9	4454	-35	5232	-22	5454	-65

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Table 3. Continued

Seq	Diff	Seq	Diff	Seq	Diff	Seq	Diff	Seq	Diff	Seq	Diff	Seq12	Diff	Seq	Diff	Seq1	Diff	Seq1	Diff
1233	1	1455	6	2233	10	2455	-4	3233	1	3455	-3	4233	12	4455	-6	5233	-30	5455	19
1234	-1	1511	3	2234	-41	2511	-14	3234	19	3511	5	4234	-21	4511	-23	5234	-4	5511	-5
1235	-14	1512	0	2235	7	2512	4	3235	1	3512	6	4235	-14	4512	-15	5235	-12	5512	4
1241	6	1513	-7	2241	-38	2513	-21	3241	-5	3513	-15	4241	-14	4513	-12	5241	-12	5513	4
1242	-5	1514	-17	2242	-19	2514	-6	3242	-5	3514	-6	4242	-19	4514	-10	5242	7	5514	-28
1243	17	1515	-30	2243	4	2515	6	3243	-30	3515	-7	4243	-33	4515	-2	5243	-48	5515	-16
1244	2	1521	19	2244	-10	2521	-2	3244	-15	3521	3	4244	-24	4521	-3	5244	14	5521	-42
1245	-7	1522	-12	2245	-24	2522	-6	3245	-5	3522	-13	4245	-7	4522	-26	5245	4	5522	-35
1251	-7	**1523**	**30**	2251	-45	2523	-43	3251	9	3523	1	4251	-16	4523	-29	5251	-17	5523	10
1252	2	1524	23	2252	-8	2524	-15	3252	-37	3524	-15	4252	-9	4524	-16	5252	-43	5524	-31
1253	-22	1525	-10	2253	2	2525	10	3253	-10	3525	3	4253	-16	4525	-24	5253	-14	5525	-8
1254	-12	1531	-1	2254	-60	2531	-23	3254	-24	3531	-42	4254	-7	4531	21	5254	-17	5531	-2
1255	-29	1532	-21	**2255**	**31**	2532	-11	3255	-18	3532	-38	4255	7	4532	-49	5255	14	5532	-23
1311	**34**	1533	-17	2311	-34	2533	-42	3311	10	3533	-19	4311	-17	4533	-26	5311	0	5533	-25
1312	-8	1534	-8	2312	-22	2534	-35	3312	-9	3534	4	4312	-8	4534	-14	5312	22	5534	0
1313	-5	1535	-11	2313	11	2535	1	3313	20	3535	3	4313	2	4535	0	5313	-21	5535	-43
1314	-6	1541	11	2314	14	2541	-52	3314	2	3541	-12	4314	-24	4541	-9	5314	-25	5541	-21
1315	-5	1542	0	2315	1	2542	2	3315	2	3542	1	**4315**	**28**	4542	-45	5315	7	5542	-20
1321	23	1543	-29	2321	-6	2543	12	3321	7	3543	-5	4321	0	4543	-39	5321	-27	5543	-47
1322	15	1544	-2	2322	16	2544	1	3322	-1	3544	-35	4322	-19	4544	-67	5322	0	5544	-76
1323	13	1545	-24	2323	-31	2545	-8	3323	-9	3545	-9	4323	-9	4545	-9	5323	-5	5545	-3
1324	-14	1551	16	**2324**	**27**	2551	-11	3324	-27	3551	-26	4324	-12	4551	-32	5324	-34	5551	-38
1325	10	1552	-9	2325	-15	2552	-18	3325	17	3552	-20	4325	-15	4552	-24	5325	13	5552	-37
1331	2	1553	25	2331	-6	2553	-35	3331	-11	3553	-34	4331	13	4553	-31	5331	-12	5553	-30
1332	-1	1554	-21	2332	-12	2554	-63	3332	-98	3554	-28	4332	-19	4554	-40	5332	-45	5554	-52
		1555	-46			**2555**	**28**			3555	-2			4555	14			5555	1

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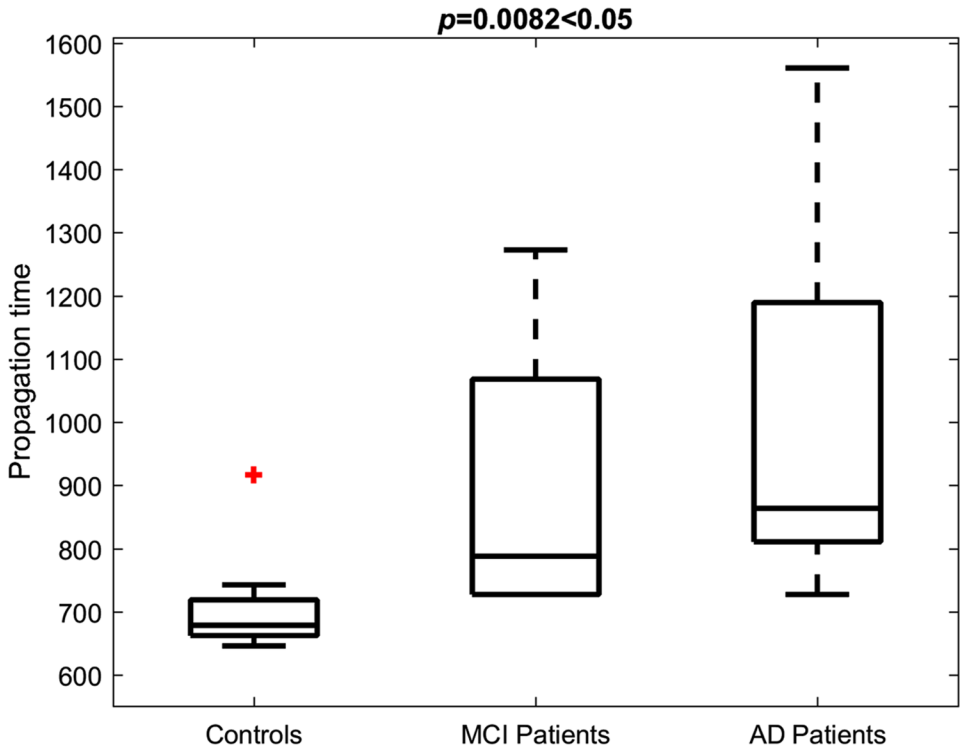
Figure 5. Time events propagation differences between Alzheimer's, MCI's and controls groups



DISCUSSION AND CONCLUSION

The future holds challenges to mankind and one of them is AD. Despite all the technological advances and decades of research, the mankind has not yet discovered the origin and the cure of AD. However, the increasing incidence of this disease is a fact more and more frequent in developed countries where the aging population has significantly raised in recent decades, and the number of AD cases grew exponentially because the probability of developing AD increases with age. It is, therefore, urgent to find new ways to early diagnose and care for the disease in the near future. Therefore, this study represents a further contribution to the search for new techniques of AD early detection based on the EEG. Most of the literature focuses primarily on the frequency analysis of the EEG signal. However, the temporal analysis should also be considered for a better diagnosis of this disease, since the episodes that show the AD in the EEG can be sporadic and not permanent. In the present study, the approach of more temporal detail was based on the good results obtained in the classification of EEG segments depending on the distribution of Power Densities in time / scale analysis provided by *WT* in previous studies (Rodrigues P. M., 2011; Rodrigues & Teixeira, 2013; Rodrigues & Teixeira, 2011).

In short, the authors of this study extracted a set of preselected features with WT tool from threads of 64 epochs obtained from a segment of 5s length for both study groups and classified them in 5 clusters by SOM. After that, the clusters that represented a thread, respectively, were evaluated in sequences of 4 over time, and a diff score was performed between AD patients/Control subjects and MCI patients/ Control subjects (Tables 2 and 3). After the analysis of Table 2 and Table 3, it can be concluded that

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there were sequences of threads that appeared with a high incidence in both Tables (Table 2 and 3), such as, 1133, 1311, 2255, 2555, 3112, 3214 and 4315 with a high positive *Diff* scores, it means that these sequences were found in MCI patients and AD patients with a higher incidence. The sequences formed by two or more threads classified in Group 1 and Group 2 were found more frequently in early AD stages (sequences with the highest positive *Diff* results). Moreover, classified threads as belonging to Group 1 and Group 2 are hypothetically indicative of AD. These sequences could be used to make an EEG temporal events model of AD at early stages in order to increase the early AD diagnosis. It should be noted that the authors analyzed the temporal classification results by combinations of 4 classified threads rather than combinations of 2 or 3 because these combinations did not show clearly AD typical early sequences. It was observed that the average events propagation time in AD is 850ms, in MCI is 790ms and in Controls 650ms. There is indeed, relevant statistical significance when comparing the values distributions of average propagation time between the three groups ($p=0.0082<0.05$).

This study allowed a better understanding of EEG temporal energy dynamics between AD patients, MCI patients, and Control subjects. The results are promising because they can help to find AD characteristic events in early stages. The authors believe that the EEG may increasingly become an accurate diagnostic method to help in AD early diagnosis. Finally, The SOM demonstrated that they might be promising tools for an unsupervised detection of AD early temporal sequences.

Despite that, in future work, the authors intend to analyze the performance, accuracy, sensibility and specificity of the SOM by cataloguing the 250ms and 500ms threads for the study participants and verify the possibility that an AD event appears and does not propagate. Results should be extended to a larger population to ensure generalization. The detected increase of EEG regularity is also not specific to AD. It appears in others dementias including Parkinson's disease (Pezard, Jech, & Ruzicka, 2001; Rodrigues & Teixeira, 2010) and schizophrenia (Fell, Röschke, & Beckmann, 1995). Therefore, this kind of studies should also be followed for future research of these diseases in order to improve their diagnosis and find the differences between them.

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KEY TERMS AND DEFINITIONS

Alzheimer's Disease: It is a neurodegenerative brain disorder. It is the most common cause of dementia among older people that causes problems with memory, thinking and behavior. There is no cure for the disease and AD has an unknown cause. Symptoms usually develop slowly and get worse over time, becoming severe enough to lead to death.

EEG Event: An Alzheimer's disease event is composed by a set of small EEG signal segments of 50ms (64 samples), characterized by a common and single dynamic energy.

EEG Early Event: An Alzheimer's disease event that it is detected in MCI patients with a high incidence.

Electroencephalogram: High resolution physiological technique that records the brain's electrical activity which originates in the neurons. It is widely used in clinical practice.

Features: Patterns that characterize a signal.

Scalp: The skin covering the top of the human head.

Shift-to-the-Left: AD EEG slowing down relatively to the control subject's EEG. It can be seen notably in Alpha band peak of Power Spectral Density.

Signal Processing: Operation or analysis of analog/digitized signals and represents time-varying or spatially varying physical quantities.

Unsupervised Classification: Type of machine learning algorithm used to draw extrapolations from datasets without labeled responses.

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Chapter 15
Dealing With Noise and Partial Volume Effects in Alzheimer Disease Brain Tissue Classification by a Fuzzy-Possibilistic Modeling Based on Fuzzy-Genetic Initialization

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ABSTRACT

Segmentation is a key step in brain imaging where clustering techniques are widely used, particularly the fuzzy approach which offers active and robust methods against noise and partial volume effect (PVE). To address those imperfections, this article suggests an automatic segmentation of brain tissues for magnetic resonance and functional images of Alzheimer's patients, based on an efficient and robust genetic-fuzzy-possibilistic clustering scheme for the assessment of white matter, gray matter and cerebrospinal fluid volumes. The proposed hybrid clustering process based on: 1) A fuzzy possibilistic c-means algorithm that models the degree of relationship between each voxel and a given tissue. 2) A fuzzy c-means algorithm to initialize the clusters centers, with subsequent optimization by a genetic algorithm. Each stage of the proposed clustering process is validated on real brain data and synthetic images of an Alzheimer's Disease Neuroimaging Initiative (ADNI) phantom. A performance comparison is made with the usual fuzzy techniques. The visual and quantitative results obtained with the proposed approach using various signal-to-noise ratios prove its effectiveness to quantify the tissue volume of images of different modalities types in the presence of noise and PVE. The effectiveness in terms of computational rate is also demonstrated.

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1. INTRODUCTION

Because of the imperfection of medical information, the field of medicine has become a very attractive domain for the application of fuzzy set theory. This is due to the large imprecision caused by the Partial Volume Effect (PVE) and the uncertainty due to noise (Behroozi & Daliri, 2012). Recently, there has been considerable interest in the use of fuzzy clustering methods for medical image segmentation, which retain more information from the original image than hard clustering methods (Vasuda & Satheesh, 2010). In hard clustering, each voxel of the image belongs to exactly one cluster or specific tissue, and a membership value of zero or one is assigned to it; in fuzzy clustering, each voxel belongs to every cluster, with its membership to each one varying between 0 and 1 (El-Melegy, Zanaty, Abd-Elhafiez & Farag, 2007). In medical images the complexity of tissue boundaries causes many voxels to contain a mixture of tissues (Links, Beach, L. Subramana et al., 1998). Fuzzy methods are better suited for this kind of situation.

In the literature on fuzzy clustering, the Fuzzy C-Means (FCM) clustering algorithm, proposed by Dunn (Dunn, 1974) and extended by Bezdek (Bezdek, J.C. 1981) is the best known and most used method. Although FCM is a useful clustering method, its membership results do not always correspond accurately to the degrees of belonging of the data, and it may be inaccurate in a noisy environment (Krishnapuram & Keller, 1993). To help address those weaknesses of FCM, methods stemming from possibilistic logic appeared.

Possibilistic logic was introduced by Zadeh (Zadeh, 1978) following its former works in fuzzy logic (Zadeh, 1965) in order to simultaneously represent imprecise and uncertain knowledge. Possibilistic logic is a weighted logic developed in the realm of artificial intelligence, with a view to develop a simple and rigorous approach to automated reasoning from uncertain or prioritized incomplete information. It enjoys properties that keep it close to classical fuzzy logic, although the introduction of weights (of different kinds) substantially increases its representation capabilities, especially for inconsistency handling (Dubois & Prade, 2004). Particularly, it has gained popularity recently in modeling and propagating uncertainty and precision in imaging applications (Pal, Pal, Keller & Bezdek, 2005).

To overcome the weakness of FCM against noise and PVE, Krishnapuram and Keller (Krishnapuram & Keller, 1993) proposed to relax the constraint of fuzziness and produce memberships that have a good explanation of the degrees of belonging for the data. They established the first Possibilistic C-Means algorithm (PCM) which used a possibilistic type of membership function to describe the degree of belonging. They showed that algorithms with possibilistic memberships are more robust to noise and outliers than FCM and its variants (Krishnapuram & Keller, 1993). However, Barni et al. (Barni, Cappellini & Mecocci, 1996) showed that the PCM algorithm is sensitive to initialization and generates coincident clusters. Timm et al. (Timm, Borgelt, Doring & Kruse, 2004) proposed then the possibilistic fuzzy clustering, and Pal et al. (Pal, Pal, Keller & Bezdek, 2005) proposed another Fuzzy Possibilistic C-Means (FPCM) that can avoid the coincident clusters of PCM while being less sensitive to noise than FCM.

Brain images are characterized by noise, intensity inhomogeneity, and weak boundaries. Therefore, the accurate segmentation of brain tissues is still challenging. The aim of this paper is to evaluate the effectiveness of fuzzy logic, especially possibilistic theory, at managing uncertainty and imprecision. The FPCM algorithm (Pal, Pal, Keller & Bezdek, 2005) was then chosen for the volumetric measurement of White Matter (WM), Gray Matter (GM), and Cerebrospinal Fluid (CSF) brain tissues, and for the computation of fuzzy tissue maps in images. The volume measurement of CSF, GM, and WM tissue plays an important role in computer aided neurosurgery, diagnosis (Yogita & Milind, 2016) and treatment of

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pathologies, and it may be of major interest in neurodegenerative disorders such as Alzheimer's Disease (AD), Parkinson's related syndromes, in WM metabolic or inflammatory disease, in congenital brain malformations or perinatal brain damage, and in post-traumatic syndrome (Saha & Bandyopadhyay, 2007).

Moreover, we propose a genetic-fuzzy process for the centers initialization of clusters. For this purpose, we use the FCM algorithm (Bezdek, 1981) to get the initial partition, and the Genetic Algorithms (GA) (Goldberg, 1996) to achieve optimization, before choosing the best score among all at the end. The integration of the genetic process allows to determine the appropriate cluster centers and the fuzzy corresponding partition matrix. This initialization process then allows to train the FPCM algorithm with the centers partition empirically obtained as opposed to randomly set, which avoids local minima and allows the clustering process to converge quickly (Lazli, Boukadoum & Aït-Mohamed, 2017).

Clustering results are reported first for several simulated T1- weighted Magnetic Resonance Images (MRI), Single Photon Emission Computed Tomography (SPECT) and (Positron Emission Tomography) PET brain images extracted from a real database (Barra & Boire, 2000a), and belonging to patients suffering from AD. Then, they are reported for MR and PET brain Alzheimer patient images extracted from the Alzheimer's Disease Neuroimaging Initiative (ADNI) phantom (Jack, Bernstein, Fox et al., 2008). The effectiveness of the proposed method is evaluated in terms of segmentation accuracy, time complexity, Tanimoto coefficient, sensitivity and specificity. The performances of indexes are experimentally evaluated and compared for several test images under noise conditions of varying degrees, showing the superiority of the proposed FCM/GA/FPCM clustering process over other conventional methods.

The paper is organized as follows: Sections 2 and 3 offer background information, including a survey of fuzzy clustering in the medical imaging field. The fuzzy and possibilistic algorithms used in our system viz. FCM, PCM and FPCM are explained in terms of mathematical and system model with their strength and limitations in section 4. Section 5 describes the principle of the hybrid clustering process used for the quantization of different tissue classes. The validation of the approach and the obtained experimental results are presented in sections 6 and 7. Finally, a discussion and conclusion are made in section 8.

2. FORMAL BACKGROUND

2.1. Image Segmentation

The goal of image segmentation is to divide an image into a set of semantically meaningful, homogeneous and no overlapping regions of similar attributes such as intensity (Despotovit, Goossens & Philips, 2015). In the case of brain images, the basic elements (voxels in 3D) are typically classified into three main tissue types: WM, GM, and CSF (Figure 1). The tissues segmentation results are further used in different applications such as the analysis of anatomical structures, surgical planning, visualization, and for studying pathological regions (Despotovit, Goossens & Philips, 2015). In our case, the interest is vested on the pathological brain regions of AD, by testing the performance of fuzzy logic-based registration algorithms, particularly those derived from the possibilistic theory.

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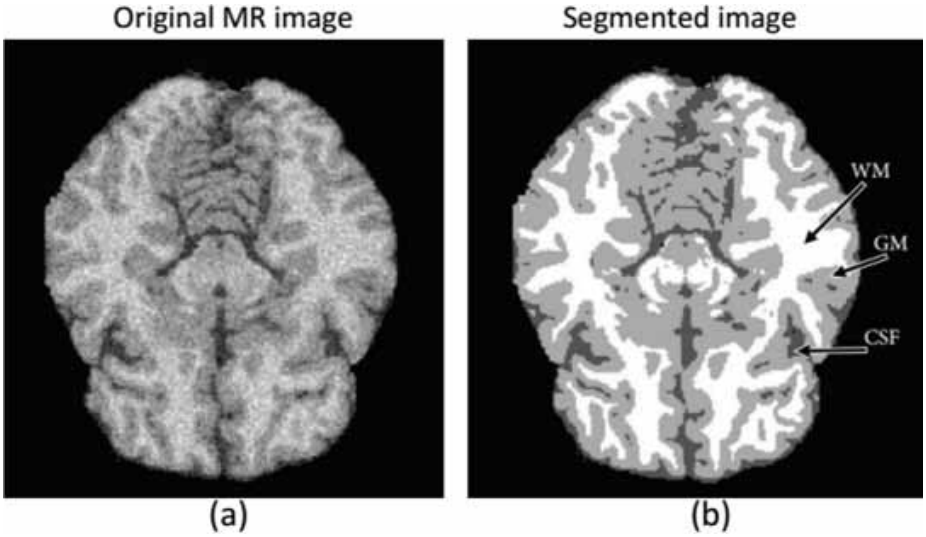
Figure 1. An example of the brain MRI segmentation with (a) an original MR image and (b) segmented image with three labels: WM, GM and CSF. Page 3 in (Despotovit, Goossens & Philips, 2015)



2.2. Fuzzy and Possibility Theories

In fuzzy logic, a fuzzy measure is a representation of uncertainty, giving for each subset F of a universe of discourse U, a coefficient in [0,1] that assesses the degree of certitude of the realization of F (Lamiche & Moussaoui, 2012).

In possibilistic logic, that fuzzy measure is modeled as a measure of possibility Π satisfying:

$$\Pi(U)=1,\ \Pi\left(\phi\right)=0, \forall F_i, \Pi\left(\bigcup_i F_i\right)=\max_i \Pi\left(F_i\right) \quad (1)$$

An event F is completely possible if $\Pi(F) = 1$ and is impossible if $\Pi(F) = 0$. Zadeh (Zadeh, 1965) showed that Π could be completely defined from the assessment of the certitude on each singleton of U. Such a definition relies on the definition of a distribution of possibility π satisfying:

$$\pi: U \rightarrow [0,1]$$

$$x \rightarrow \pi(x) \,/\, \mathrm{Max}(\pi(x)) = 1 \quad (2)$$

A fuzzy subset F of U can be represented by a distribution of possibility that is related to its membership function μ_F. More precisely, a proposition of the form "X is F," where X is a variable taking values in U, induces a possibility distribution Π_X, noted π, such that:

$$(\forall x \in X)\mu_F(x) = \pi(x) \quad (3)$$

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In other words, $\pi(x)$ assesses the compatibility of x with F. Distributions of possibility can mathematically be related to probabilities, and they moreover offer the capability to declare the ignorance about an event.

Considering such an event A (e.g., voxel v belongs to tissue T, where v is at the interface between two tissues), probabilities theory would assign $P\left(A\right) = P\left(\bar{A}\right) = 0.5$, whereas possibility theory makes the two alternatives fully possible by setting $\Pi\left(A\right) = \Pi\left(\bar{A}\right) = 1$.

2.3. Partial Volume Effect

The Partial Volume Effect (PVE) problem is one of the most common problems in brain segmentation. PVE describes the loss of small tissue regions because of the limited resolution of the anatomical/functional scanner and is seen on scans as a mix of different tissues in a single voxel. It can cause the misclassification of voxels (*mixels*) that lie in the transition between two (or more) tissues classes (Despotovit, I., Goossens, B., & Philips, W. 2015).

Several models have been proposed to describe such phenomena and to find the mixture density function. The most widely used represents the intensity of a *mixel* as follows (Choi, Haynor, & Kim, 1991; Laidlaw, Fleischer & Barr, 1998; Ruan, Jaggi, Xue, Fadili & Bloyet, 2000; Santago & Gage, 1993):

$$y_m = \sum_{k=1}^{N_t} a_k I_k + \varepsilon,\ \forall k \in \left[1, N_t\right] \tag{4}$$

where ε is white Gaussian noise with standard deviation σ_ε. N_t represents the number of tissues. I_k is related to the intensity value of the class k, and a_k its proportion which is assumed to be a uniform random variable in the interval [0,1] (Ruan, Jaggi, Xue, Fadili & Bloyet, 2000).

In the case of *mixels* of just two pure classes or clusters (k = 1, 2), the probability density function of y_m is given by (Ruan, Jaggi, Xue, Fadili & Bloyet, 2000):

$$p\left(y_m\right) = \int_0^1 \frac{1}{\sqrt{2\pi\sigma_\varepsilon}} exp \frac{-\left[y_m - \left(\left(1-a\right)I_1 + aI_2\right)\right]^2}{2\sigma_\varepsilon^2} da \tag{5}$$

3. RELATED-WORK

Several works appeared in literature to address the problem of PVE and noise, and many approaches have been proposed that rely on fuzzy clustering algorithms, especially the FCM algorithm and its extensions (Shattuck, Sandor-Leahy, Schaper, Rottenberg & Leahy, 2001). Some of those works are mentioned below.

To deal with intensity homogeneities, the authors in (Bezdek, 1981; Zexuan, Yong, Chen, Sun, Xia & Feng, 2012) proposed adaptive FCM. In this case, the centroids are multiplied by an unknown multiplier field, which represents the inhomogeneity. First and second order regularization terms are included in the cost function to make the multiplier field varying slowly and smoothly.

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In (Bezdek, Ehrlich & Full, 1984; László, Szilágyi, Benyó & Benyó, 2011), the authors used multidimensional features formed by the GLCM (Grey Level Co-occurrence Matrix) feature generation model to include spatial information into FCM. The extra dimensions make the process time consuming. So, in order to overcome this, distance metric-based compression is proposed to select the representative pixels of the groups and perform clustering on them, which resulted in fast and effective clustering.

Enhanced FCM is proposed in (Dave, 1996; Beevi, Sathik et al., 2010) to fasten the segmentation process as well as reduce the noise effect. For achieving this, a new factor which includes the pixel intensity along with mean of neighborhood pixels is calculated in advance of the segmentation process and computational complexity is condensed by considering the histogram count of the pixels into the cost function.

In (Mazouzi & Batouche, 2008), the authors presented an approach for improving range image segmentation based on fuzzy regularization of the detected edges. The segmentation process was repeated for all region boundaries in the image, using an improved version of the FCM algorithm.

A two-dimensional FCM (2DFCM) algorithm was proposed in (Yu & Wang, 2007) for molecular image segmentation. The three steps of the algorithm are: noise suppression, texture energy characterization, and introducing spatial constraints into the fuzzy clustering. The segmentation results are satisfactory for the images corrupted by noise and intensity variations.

In (Yazdi & Nasiri, 2009), the authors presented a fuzzy algorithm for image segmentation where human knowledge was used in clustering features. The results have shown that the human interaction eventuates to clarification of texture and reduction of noise in segmented images.

In (Sowmya & Sheelarani, 2009), the authors explained the task of segmenting a color image by soft computing techniques. The used techniques are FCM and PCM algorithms and a competitive neural network. A self-estimation algorithm was developed for determining the number of clusters.

A high-speed parallel FCM algorithm for brain tumor image segmentation was presented in (Murugavalli & Rajamani, 2006). Their algorithm combines the advantages of the sequential and the parallel FCM for the clustering process, and the algorithm was very fast when the image size was large.

In (Bala Ganesan & Sukanesh, 2008), the authors treat the problem of brain MRI segmentation. The distinct regions are represented by wavelet coefficients. The classification of those features was performed with the FCM algorithm. AN edge detection technique was used to detect the edges of the given images, and the silhouette method was used to find the strength of clusters.

Prior probability and fuzzy spatial information were used in ISFCM (Improved Spatial FCM), proposed in (Maulik & Bandyopadhyay, 2002) to minimize the noise effect in MR images. In that method, the cluster centers are initialized using a histogram-based FCM in the first step to achieve faster convergence and the membership updating equation was modified to use the probability obtained by the proportion of pixels belonging to the cluster with pixels in the neighborhood and spatial information.

In (Sucharitha & Geetha, 2015), the authors incorporate a method for image clustering called Reformulated Fuzzy Local information C-Means (RFLICM) clustering algorithm, which is a variant of traditional FCM that considers both spatial and gray level information. In RFLICM, the spatial distance is replaced by a local coefficient of variation in a fuzzy manner.

In (Deepali & Tarun Kumar Rawat, 2013), the comparison of three image segmentation methods based on FCM, Intuitionistic Fuzzy C-Means (IFCM), and Type-II Fuzzy C-Means (T2FCM) is presented. The algorithms are executed in two scenarios– both in the absence and in the presence of noise and on two kinds of images–: Bacteria and Computerized Tomography (CT) scan brain image.

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In (Aruna Kumar, Harish & Manjunath Aradhya, 2016), the authors presented a Picture Fuzzy Clustering (PFC) method for MR brain image segmentation. The PFC was based on the picture fuzzy set, which is the generalization of the traditional fuzzy set and intuitionistic fuzzy set.

In (Shasidhar, Sudheer Raja, & Vijay Kumar, 2011), a modified FCM algorithm for MR brain tumor detection is explored. A comprehensive feature vector space is used for the segmentation technique.

Although FCM and its variants form a very useful clustering approach, its membership results do not always correspond well to the degrees of belonging of the data, and they may be inaccurate in a noisy environment (Krishnapuram & Keller, 1993). In a sense, the FCM algorithm and its extensions create relative memberships, interpreted as degrees of sharing of the voxels between all the classes, that are unrepresentative of the true degrees of belonging.

4. POSSIBILISTIC & FUZZY ALGORITHMS-BASED CLUSTERING

For increasing the robustness against PVE and noise, and improving performance, we consider the fuzzy-possibilistic clustering algorithm, FPCM, which was exploited in our process of Alzheimer brain tissues clustering. The conventional FCM and PCM fuzzy algorithms are used for comparison. The mathematical models of these three fuzzy algorithms are as follows.

4.1. FCM Algorithm

The objective of the FCM algorithm is to establish a fuzzy partition of the representative vectors of N voxels in C clusters (classes).

The algorithm is an iterative process that relies on the search for values taken by the centroids set B of the clusters and by the membership degrees set U of the voxels set X to those clusters, minimizing the following objective function:

$$J_{FCM}\left(B,U,X\right)=\sum_{i=1}^{C}\sum_{j=1}^{N}u_{ij}^{m}d^{2}\left(x_{j},b_{i}\right) \tag{6}$$

where b_i is the center of cluster i, $m \in [1,\infty[$ is a parameter controlling the degree of fuzzification, d is the Euclidean distance from voxel x_j to the center of cluster i, and u_{ij} is the membership degrees of the j^{th} voxel to the i^{th} cluster.

The concept of fuzzy partition is defined as follows (Barra, Briandet & Boire, 2001):

$$\begin{cases}\forall i\in\left\{1..C\right\}\quad\forall j\in\left\{1..N\right\}\quad u_{ij}\in\left[0,1\right]\\ \forall i\in\left\{1..C\right\}\ 0<\sum_{j=1}^{N}u_{ij}<N\\ \forall j\in\left\{1..N\right\}\sum_{j=1}^{C}u_{ij}=1\end{cases}$$

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The updating formulas of U and B are obtained by introducing a Lagrange multiplier associated with the normalization constraint and by canceling the partial derivatives of the Lagrangian with respect to the parameters of the model. The solutions are given by:

$$u_{ij} = 1 / \sum_{k=1}^{C} \left(\frac{d^2\left(x_j, b_i\right)}{d^2\left(x_j, b_k\right)} \right)^{2/(m-1)} \tag{7}$$

$$b_i = \sum_{k=1}^{N} u_{ik}^m x_k \Big/ \sum_{k=1}^{N} u_{ik}^m \tag{8}$$

The FCM algorithm consists of iterating (7) and (8) until the stabilization of the algorithm.

FCM is the most frequently used technique in medical image applications (Dunn, J.C. 1974). Unfortunately, conventional FCM does not perform well in the presence of noise and intensity inhomogeneity.

4.2. PCM Algorithm

The PCM algorithm considers the clustering problem from the viewpoint of possibility theory and its approach is different from the FCM algorithm as the resulting u_{ij} values are interpreted as degrees of possibility or typicality of the points belonging to the classes (Krishnapuram & Keller, 1993; Correa, Valero, Barreiro, Diago & Tardaguila, 2011).

Typicality means the actual degree of belongingness of a voxel to a cluster rather than an arbitrary division of data. Krishnapuram and Keller (Krishnapuram & Keller, 1993) addressed these issues by proposing the PCM algorithm whose membership values represent the degree of typicality rather than the degree of sharing and, as consequence, constraint $\sum_{i=1}^{C} u_{ij} = 1$ is eliminated (Grover, 2014).

The fuzzy partition for PCM algorithm is defined in the following way (Barra, Briandet & Boire, 2001):

$$\begin{cases} \forall i \in \left\{1..C\right\} \quad \forall j \in \left\{1..N\right\} \quad t_{ij} \in \left[0,1\right] \\ \forall i \in \left\{1..C\right\} \; 0 < \sum_{j=1}^{N} t_{ij} < N \\ \forall j \in \left\{1..N\right\} \quad \max_i t_{ij} > 0 \end{cases}$$

The objective function for PCM is given by (Correa, Valero, Barreiro, Diago & Tardaguila, 2011):

$$J_{PCM}\left(B,T,X\right) = \sum_{i=1}^{C}\sum_{j=1}^{N} t_{ij}^m d^2\left(x_j, b_i\right) + \sum_{i=1}^{C} \eta_i \sum_{j=1}^{N} \left(1 - t_{ij}\right)^m \tag{9}$$

where T is the typicality matrix and t_{ij} is the typicality degree of voxel x_j to cluster i. η_i is a positive real number that is the square of the distance separating the center of cluster i to the set of voxels whose belonging degree to this cluster is equal to 0.5. It is defined as follows:

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$$\eta_i = K\sum_{j=1}^{N} t_{ij}^m d^2\left(x_j, b_i\right) \Big/ \sum_{j=1}^{N} t_{ij}^m \tag{10}$$

where K is most often taken as 1.

The degrees of typicality t_{ij} and the clusters centers are given as follows:

$$t_{ij} = \frac{1}{1+\left(d^2\left(x_j, b_i\right)/\eta_i\right)^{\frac{1}{m-1}}} \tag{11}$$

$$b_i = \sum_{k=1}^{N} t_{ik}^m x_k \Big/ \sum_{k=1}^{N} t_{ik}^m \tag{12}$$

The algorithm resulting from the iterated mapping of (11) and (12) constitutes the possibilistic classification algorithm.

In PCM, the updating of the membership values depends on the distance measurements. The Euclidean distance works effectively when the data set is compact or isolated, and the *Mahalanobis* distance takes into account the correlation in the data by using the inverse of the variance covariance matrix of data set (Zarandi, Zarinbal & Turksen, 2009).

The PCM algorithm is more robust in the presence of noise. It helps identify outliers (noise points) in that it results in low typicality values for them and automatically eliminates these noise points. It is efficient in finding valid clusters, and thus gives a robust estimate of the centers (Zarandi, Zarinbal & Turksen, 2009).

Unlike FCM, the value of t_{ij} in PCM only depends on the distance between voxel vector x_j to cluster i. The degrees of belonging generated by PCM are not more relative degrees or sharing, they become absolute values reflecting the force with which each vector belongs to all clusters.

Despite the previous advantages, the PCM algorithm is of limited use for certain problems: It is very sensitive to the initialization stage, and may generate coincident clusters. In addition, topicalities may be sensitive to the choice of the additional parameters needed by the PCM algorithm (Pal, Pal, Keller, & Bezdek, 2005).

4.3. FPCM Algorithm

Pal and Bezdek in (Pal, Pal, Keller & Bezdek, 2005), proposed the FPCM algorithm, which integrates the features of both FCM and PCM by using the fuzzy values of the fuzzy algorithm as well as the typicality values of the possibilistic algorithm in order to achieve a better clustering model (Correa, Valero, Barreiro, Diago & Tardaguila, 2011; Saad & Alimi, 2009). Membership and typicality are essential for the correct and precise characteristic of data substructure in the clustering model. So, FPCM uses an objective function that depends on both membership and typicality features (Saad & Alimi, 2009; Suganya & Shanthi, 2012). The objective function is given as follow (Saad & Alimi, 2009; Correa, Valero, Barreiro, Diago & Tardaguila, 2011):

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$$J_{FPCM}\left(B,U,T,X\right)=\sum_{i=1}^{C}\sum_{j=1}^{N}\left(u_{ij}^{m}+t_{ij}^{\lambda}\right)d^{2}\left(x_{j},b_{i}\right) \tag{13}$$

The FPCM algorithm obeys the following constraints (Pakhiraa, Bandyopadhyayb & Maulikc, 2005):

$$\begin{cases}\forall i\in\left\{1..C\right\}\quad\forall j\in\left\{1..N\right\};0<\sum_{j=1}^{N}u_{ij}<N;u_{ij}\in\left[0,1\right]\\ \forall j\in\left\{1..N\right\}\sum_{i=1}^{C}u_{ij}=1\\ \forall i\in\left\{1..C\right\}\sum_{j=1}^{N}t_{ij}=1\end{cases}$$

The first order necessary conditions for the extreme of $JF_{PCM}(B, U, T, X)$ in terms of Lagrange multiplier theorem can be represented as follows (Correa, Valero, Barreiro, Diago & Tardaguila, 2011):

$$u_{ij}=\frac{1}{\sum_{k=1}^{C}\left(\frac{d^{2}\left(x_{j},b_{i}\right)}{d^{2}(x_{j},b_{k}}\right)^{2/\left(m-1\right)}} \tag{14}$$

$$t_{ij}=\frac{1}{\sum_{k=1}^{C}\left(\frac{d^{2}\left(x_{j},b_{i}\right)}{d^{2}(x_{j},b_{k}}\right)^{2/\left(\lambda-1\right)}} \tag{15}$$

with $\lambda \in [3,5]$. The center updating function is:

$$b_{i}=\frac{\sum_{k=1}^{N}\left(\left(u_{ik}^{m}+t_{ik}^{\lambda}\right)x_{k}\right)}{\sum_{k=1}^{N}\left(u_{ik}^{m}+t_{ik}^{\lambda}\right)x_{k}} \tag{16}$$

The FPCM algorithm consists of iterating Equations (14), (15) and (16) until stability of the algorithm, with the stopping criterion determined by an iteration number or a predefined threshold.

5. PRINCIPLE OF THE PROPOSED CLUSTERING PROCESS

The previous fuzzy algorithms were used in our Alzheimer tissue quantization process with FCM/GA approach-based centers initialization. The clustering steps are implemented to be minimally interactive and react with a minimum of time. The different stages are as follows.

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5.1. Non-Uniformity Correction and Skull Stripping

The tissues classification problem is greatly simplified if we strip skull and scalp tissue from the brain volume, and if a non-uniformity correction is made (Shattuck, Sandor-Leahy, Schaper, Rottenberg & Leahy, 2001).

For brain extraction, we used anisotropic diffusion filtering, Marr-Hildreth edge detection, and morphological operations. To address the non-uniform intensity problem in MRI, we adapted the N3 (Non-parametric Non-uniform intensity Normalization) method (Sled & Pike, 1998), available from http://www.bic.mni.mcgill.ca/software/N3/.

5.2. Tissue Classification

We define tissue classification to be the process of assigning to each voxel in the volume a label that identifies what types of tissues are present in that voxel (Shattuck, Sandor-Leahy, Schaper, Rottenberg & Leahy, 2001).

The complexity of brain structures results in numerous voxels that contain multiple tissue types. The same thoughts proposed in (Shattuck, Sandor-Leahy, Schaper, Rottenberg & Leahy, 2001) are adapted here, and we assume that only CSF, GM, and WM remain in the image after skull stripping. Due to the finite resolution of the scanning system, we further assume that the tissue combination in each voxel is restricted to the set {CSF, GM, WM, CSF/GM, GM/WM}, where the last two classes represent partial volume voxels. We assume that CSF is sufficiently separated from WM that voxels will not contain both of these materials (Shattuck, Sandor-Leahy, Schaper, Rottenberg & Leahy, 2001).

In this section we describe our approach for labeling the tissue content of each voxel in the brain image, taking into account the noise and PVE. We propose then a three-step segmentation process:

- Centers initialization based on a hybrid FCM/GA process, and which is necessary for subsequently applying the FPCM algorithm. This initial step is proposed to select the representative centers of the clusters and perform clustering on them, which resulted in fast and effective clustering;
- Image modeling, for which the fuzzy tissue maps are created using the FPCM algorithm, and the information extracted from the images is modeled in a common theoretical frame;
- Image labeling which synthesizes the available information by creating a labeled image.

5.3. Center Initialization

Two steps are used for this initialization process: we applied the FCM algorithm to initialize the centers b_i, and GA for FCM results optimization.

5.3.1. Initialization of Centers With FCM Algorithm

We applied the FCM algorithm to determine the appropriate cluster centers b_i. The FCM algorithm is composed of the steps shown in Algorithm 1.

The stopping criterion defines the stability or the convergence of the process. In most cases, it represents the stability of the clusters centers by successively iterating the steps 2 and 3.

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Algorithm 1. FCM Steps

1. Initialize the degrees of belonging matrix $U^{(0)}$.
2. At k-step:
- Compute the belonging degrees matrix $U^{(k)}$ using Eq. (7).
- Compute the centers vectors $B^{(k)}=[b_j]$ using Eq. (8).
3. Update: $B^{(k+1)}$, $U^{(k+1)}$
4. If $J^{(k+1)} - J^{(k)} < \varepsilon$ then STOP otherwise return to step 2. ε is a termination criterion between 0 and 1, whereas *k* are the iteration steps.

5.3.2. Optimization of FCM Results With GA

The result of FCM clustering was used as initial population for GA. That allows training the GA with a population of empirically generated chromosomes and not randomly initialized.

The GA started with a population composed of the set of FCM results which represent the fuzzy corresponding partition matrix. The solutions from one population are taken and used to form a new population. This is motivated by the hope that the new population will be better than the old one. The solutions that are selected to form new solutions (offspring) are so according to their fitness - the more suitable they are, the more chances they have to reproduce (Goldberg, 1996).

The following merit function was used to assess the fitness of a chromosome (Goldberg, 1996):

$$w = \sum_{i=1}^{C} \sum_{x_j \in C_i} p_j d^2 \left(x_j, b_i\right) \tag{17}$$

where p_j is the weight of the j^{th} voxel x_j and b_i the center of gravity of cluster C_i, i referring to one of the C tissue clusters. We have:

$$b_i = \frac{1}{\left|C_i\right|} \sum_{x_j \in C_i} x_j \tag{18}$$

The crossover and mutation are the most important part of the GA. The performance is influenced mainly by these two operators. Crossover selects genes from parent chromosomes and creates a new offspring. After a crossover is performed, mutation take place. This is to prevent falling all solutions in population into a local optimum of the problem solution. Mutation randomly changes the new offspring.

The strong points of GA is that it is intrinsically parallel, easily distributed and the underlying concepts are easy to understand. Notice also that the optimization required less time, with more chances of getting the optimal solution. This initialization also avoids local minima and allows the FPCM clustering-based image modelling to converge quickly.

5.4. Image Modeling

The FPCM-based clustering gives a set of three fuzzy maps corresponding to WM, GM, and CSF tissues which are fuzzy and absolute, and allows to compute the membership degree of each voxel to

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brain tissue. Notice that each voxel is characterized by a feature vector composed of its gray levels in the different images.

FPCM associates with the feature vector of each voxel x_j a fuzzy membership degrees u_{ij} and a possibilistic typicality degree t_{ij} in each of the C clusters, representing the degree of belonging and typicality of x_j to i. Iterative optimization is used to approximate minima of a constrained objective function (Barra & Boire, 2000b).

The main steps of the FPCM algorithm used for modeling are:

1. Initialization of the membership and typicality matrices U and T;
2. Calculation of the centroids matrix B of the clusters;
3. Readjustment of the matrices U and T according to the positions of the centroids;
4. Evaluation of the minimization criterion and return to step 2 if there is no convergence of criterion.

The pseudo-code of the FPCM algorithm is shown in Algorithm 2.

Algorithm 2. FPCM Pseudo-Code

The entries
$X = [x_j]\, j = 1...N$. The vectors of voxels
C: number of clusters
$\varepsilon = 0.005$. Threshold representing the convergence error
$m \in [1.5,3]$. Degree of fuzzy
$\lambda \in [3,5]$. Degree of typicality
Step 1
Initialize the matrix of centroids B by the FCM-GA method.
Step 2
Compute the matrix of membership degrees U using Eq. (14).
Compute the matrix of typicality degrees T using Eq. (15).
Update the prototype matrix B using Eq. (16).
Compute the objective function $J_{FPCM}^{(k)}$ using Eq. (13).
Step 3
Update the matrix of membership degrees U
Update the matrix of typicality degrees T
Update objective function $J_{FPCM}^{(k+1)}$
Step 4
Repeat steps (2) and (3) until the stop criterion is met: $J_{FPCM}^{(k+1)} - J_{FPCM}^{(k)} \leq \varepsilon$
The outputs
The two matrices U, T and the center matrix of classes B.

We clustered all brain images with FCM, PCM and FPCM algorithms, with FCM-GA centers initialization. We obtained three sets of fuzzy maps: (WM_{MRI}, GM_{MRI}, CSF_{MRI}), (WM_{PET}, GM_{PET}, CSF_{PET}), and (WM_{SPECT}, GM_{SPECT}, CSF_{SPECT}). These maps are related to three distributions of possibility π_k^T, with $T \in \{CSF, GM, WM\}$ and $k \in \{1..P\}$ with P images. Where the value $\pi_k^T(v)$ is the membership of voxel v to tissue T computed from image k.

The image information is now represented in a common theoretical frame (distributions of possibility), and the result can be used in the segmentation step.

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5.5. Image Labeling

After applying fuzzy-possibilistic modeling for each image, the degrees of possibility provided will be exploited for image labeling, and a labeled image is finally computed using the three fuzzy maps obtained in the previous step. Each voxel *v* is assigned to label tissue {GM, WM, CSF} which corresponds to the highest degree of possibility in $\left\{\pi^{GM}\left(v\right),\pi^{WM}\left(v\right),\pi^{CSF}\left(v\right)\right\}$ as follow:

$$if\ \ T,T' = \left\{GM,WM,CSF\right\}\ \text{and}\ \ T' \neq T$$

$$v \in T\ \ if\ \ \pi^{T}\left(v\right) > \pi^{T'}\left(v\right) \tag{19}$$

6. EXPERIMENT ON PATIENTS WITH ALZHEIMER DISEASE

The objective of this study is to cluster registered MR, PET and SPECT brain images corresponding to patients with AD according to the neuro-psychological assessment. The experiments were performed with several real and ADNI phantom data sets.

6.1. Information on Participants

6.1.1. ADNI Phantom

The ADNI general eligibility criteria are described at www.adni-info.org (Zhang, D., & Shen, D. 2012). Briefly, subjects are between 55 and 90 years of age, having a study partner able to provide an independent evaluation of functioning.

In this paper, 95 ADNI subjects with all corresponding baseline MR and PET images are included. It contains 45 AD patients, and 50 healthy controls (HC). Table 1 lists the demographics of all these subjects.

Table 1. Participant information

	AD (n = 45)	**HC (n = 50)**
Female/male	16/29	18/32
Age	75.4 ± 7.1	75.3 ± 5.2
Education	14.9 ± 3.4	15.6 ± 3.2
MMSE (baseline)	23.8 ± 1.9	29.0 ± 1.2
MMSE (2 years)	19.3 ± 5.6	29.0 ± 1.3
ADAS-Cog (baseline)	18.3 ± 6.1	7.3 ± 3.3
ADAS-Cog (2 years)	27.3 ± 11.7	6.3 ± 3.5

MMSE = Mini-Mental State Examination, ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive subscale.

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We chose the ADNI images to test the performance of our application because they contain different levels of artifacts, the ground truth is known, and because the ADNI phantom has been widely exploited in various published studies.

6.1.2. Real Database

The real images set that is available to validate tissue quantification approaches is a protocol developed at the Gabriel Mont pied Hospital in Clermont-Ferrand. It concerns five patients (three men and two women) aged 71-86 years and suffering from AD.

It should be mentioned that in the case of real images, the performance assessment of the clustering process stages, namely skull stripping, the correction of the non-uniformity and the tissues clustering is typically difficult to achieve since the ground truth is not known.

6.2. Imaging Parameters

6.2.1. Real Images Acquisition

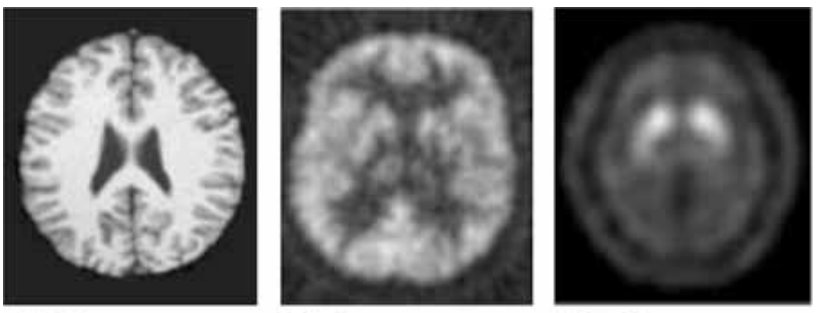
For image acquisition, the T1-weighted rapid gradient echo sequence (TR = 2600 ms and TE = 3.0 ms) was selected. The slice thickness of the images is 1 mm with no space considered between the slices. The MR volume has $256 \times 256 \times 176$ voxels which covers the whole brain with an isotropic resolution of 1.0 mm.

To obtain the PET images, each patient received two successive scans, the first is of transmission which lasted 6 minutes, and the second is of emission of 20 minutes which was started after the injection of 555 Mq of [11C]-PIB. The size of the reconstructed images is $256 \times 256 \times 207$ voxels with a voxel size of $1.2 \times 1.2 \times 1.2$ mm^3.

To obtain the SPECT images, an injection of 25 mCi (9.25 3 108 Bq) of Tc-99mHMPAO was made. The acquisition of the images was then carried out after 10 minutes on a SOPHA DSX camera using a high-resolution parallel low-energy collimator. Sixty-four projections were recorded for 30 s each. Sixty-four slices of size $64 \times 3 \times 64$ were then reconstructed using filtered back-projection with a Butterworth filter (cutoff frequency 0.25). The size of voxel was about $73 \times 7 \times 37$ mm^3 with a poor spatial resolution.

MR, PET and SPECT images corresponding to a patient from the selected patients are shown in Figure 2.

Figure 2. Example of simulated MR, PET and SPECT slice images from real database



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6.2.2. ADNI Images Acquisition

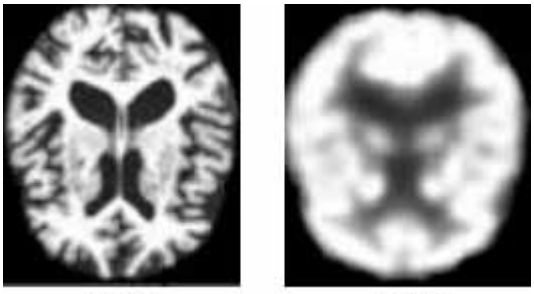
The image acquisition parameters are described in www.adni-info.org. A detailed description on acquiring MR, and PET images from ADNI as used in this paper can be found in (Zhang & Shen, 2012; Zhang, Wang et al. 2011).

MRI – All the structural MR scans used in this paper were acquired from 1.5 T scanners. Briefly, raw Digital Imaging and Communications in Medicine (DICOM) MRI scans were downloaded from the public ADNI site http://adni.loni.usc.edu/data-samples/access-data/ reviewed for quality, and automatically corrected for spatial distortion caused by gradient nonlinearity and B1 field inhomogeneity. The MR volume has $256 \times 256 \times 176$ voxels covering the whole brain and yielding a 1.0 mm isotropic resolution.

PET– all the baseline PET data was downloaded from the previous ADNI web site. A detailed description of PET protocols and acquisition can be found at www.adni-info.org. Briefly, PET images were acquired 30–60 min post-injection, averaged, spatially aligned, interpolated to a standard voxel size, intensity normalized, and smoothed to a common resolution of 8-mm full width at half maximum (Zhang & Shen, 2012). The reconstructed images had a matrix size of $256 \times 256 \times 207$ voxels with a voxel size of $1.2 \times 1.2 \times 1.2$ mm^3.

An example of MR and PET images is given in Figure 3.

Figure 3. Example of simulated MR and PET slice of ADNI images



6.3. Preprocessing

First, we developed an image of multiple regions where the gray level inside each region varies within certain limits. Then we added white Gaussian noise with different signal to noise ratio (SNR). A hybrid median filter was applied to the images. So, several variants of the same brain image were created, varying in their additive noise (11, 13 and 15%), with slice thickness ST (1 mm), and their radiofrequency (RF) inhomogeneity is 20% intensity non-uniformity.

6.4. Center Initialization

The FCM/GA clustering process is applied to a brain slices to get the cluster centers. The result of FCM clustering was used as initial population for the GA. After application of FCM, the gray level of each voxel in the volumes reflected the proportion of tissue present in that voxel. The GA-based clustering

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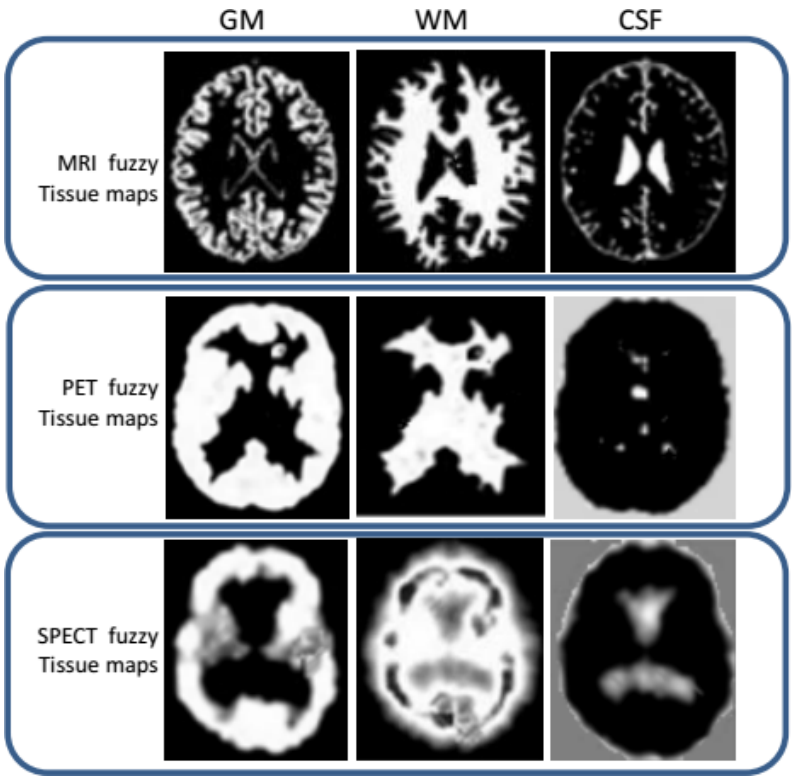
algorithm is executed for 20 generations with a fixed FCM population size of 15. The crossover and mutation probabilities are fixed as $P_c = 0.8$ and $P_m = 0.01$, respectively. These values were empirically chosen through many experiments. After convergence generation with the lowest fitness value (Goldberg, D.E. 1996), we choose the obtained centers to start the modeling by FPCM algorithm.

6.5. Tissue Possibilistic Modeling

We clustered the brain images with the FPCM algorithm for which the FCM/AG process handeld centers initialization. The result obtained of the fuzzy-possibilistic algorithm to an image $k \in \{1..P\}$ is three fuzzy maps corresponding to the tissue $T \in \{CSF, GM, WM\}$ estimated from the image. In the example of Figure 4, the WM, GM and CSF tissues are expressed by the zones with white color in each map.

Regarding parameter m which controls the degree of fuzziness of the resulting fuzzy maps, if m is close to 1, the partition generated by FPCM is almost crisp. Then, the memberships become fuzzier as m increases. When m goes to infinity, all the memberships for a given voxel are equal to $1/C$ (Barra & Boire, 2000a). There is no optimization process to compute the "best" m; it greatly depends on the nature of the data. We follow the suggestions proposed in (Barra & Boire, 2000a) and set m in [1.5, 5], which gives the "best" partition of our brain images. Then, we trained the algorithm with values in that interval and, after some experimentation, we chose on $m = 2$ with the application of a Euclidean distance, and a threshold of convergence, $\varepsilon = 0.005$.

Figure 4. Computed fuzzy tissue maps derived from an MRI, SPECT and PET images slices



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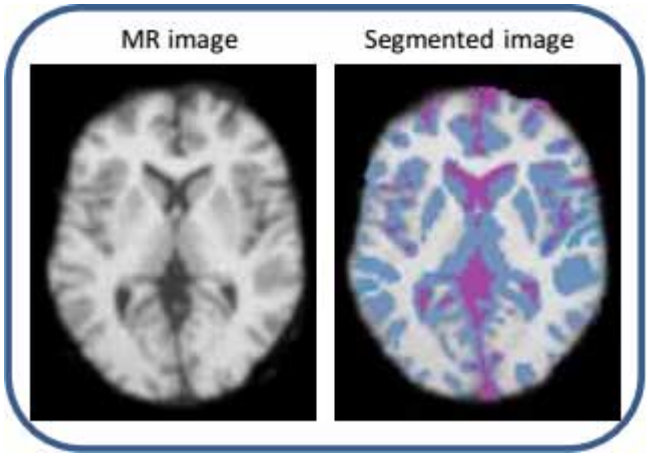
As the images information is now represented with distributions of possibility, it is expressed in a common theoretical frame, and the result can be used in the final segmentation step.

6.6. Final Segmentation

A labeled image, created by assigning each voxel to the tissue class for which it had the greatest membership (Barra & Boire, 2000a). Both reference and computed segmented images are finally presented in figure 5. The tissues are labeled WM (light grey color), GM (blue color), and CSF (purple color).

Figure 5. Example of labeled image of an MR image slice



7. PERFORMANCE EVALUATION CRITERIA

In the context of the proposed clustering process for the tissue quantization of Alzheimer's patients, FCM, PCM, and FPCM are validated by their performance on real images as well as synthetic ADNI images by using validity measures, namely the Tanimoto coefficient, sensitivity, specificity, accuracy, and time complexity. These validity measures are commonly applied to estimate the efficiency of clustering.

7.1. Validity Measures

7.1.1. Tanimoto Coefficient

The Tanimoto coefficient (TC) between two points, *a* and *b*, with *k* dimensions is calculated as (Barra, Briandet & Boire, 2001):

$$TC = \frac{\sum_{j=1}^{k} a_j \times b_j}{\sum_{j=1}^{k} a_j^2 + \sum_{j=1}^{k} b_j^2 - \sum_{j=1}^{k} a_j \times b_j} \tag{20}$$

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In the case of image segmentation, it is defined for a given tissue in computed and ground truth segmentation as the number of voxels that had a good assignment. It is close to 1 for very similar results and is near 0 on the other hand (Held, Kops, Krause et al., 1997).

7.1.2. Sensitivity

The sensitivity (SE) corresponds to the proportion of true positives (TP) compared to all of the voxels that should be segmented. It is calculated as follows (Barra, Briandet & Boire, 2001):

$$SE = \frac{TP}{TP + FN} \tag{21}$$

In our application, this indicator allows determining the percentage of voxels that are correctly identified as belonging to the tissue in question. Sensitivity tends to 1 (resp. 0) if there is little (resp. much) of false negatives (FN).

7.1.3. Specificity

The specificity (SP) corresponds to the proportion of true negatives (TN) compared to all of the voxels that should not be segmented (Barra, Briandet & Boire, 2001):

$$SP = \frac{TN}{TN + FP} \tag{22}$$

In our application, this indicator allows determining the percentage of voxels that are properly identified as belonging to complementary tissues. Specificity tends to 1 (resp. 0) if there is little (resp. a lot) of false positives (FP).

7.1.4. Accuracy

The classification accuracy index (CA) gives the performance of a method: it is defined as:

$$CA = \frac{TP + TN}{TP + FN + TN + FP} \tag{23}$$

7.2. Experimental Result

The fuzzy and other methods chosen to quantify the volume of brain tissues are tested on two types of images, namely real and synthetic images that correspond to patients suffering from AD.

To test the performance of the proposed clustering system in a noisy environment, Gaussian white noise was added with different degrees SNR = 11%, 13% and 15%, with inhomogeneity RF = 20%, and slice thickness ST = 1mm. The obtained results are visualized in Tables 2, 3, 4, 5 and 6, respectively corresponding to TC, SE, SP and CA for ADNI and real databases. The results with the fuzzy clustering

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algorithms, viz., FCM, PCM and FPCM with GA/FCM algorithm for centers initialization and without empirical initialization are reported.

Overall, the visual results and quantitative evaluation with validity measures prove the success of the fuzzy approaches in quantifying volumes of brain tissue. In particular, the FPCM fuzzy method performed well on most volumes from the real and synthetic data set, and the result tables demonstrate the robustness of this method in a highly noisy environment (15%). We can also observe that for all tissues, the proposed hybrid FCM/AG/FPCM clustering scheme produces better scores compared to that produced by the other fuzzy algorithms used in the same conditions.

We can see from tables that FCM algorithm is not stable and very sensitive to noises, and the PCM algorithm gave stable values, but it did not show a good enough performance, unlike the PFCM algorithm which gave good performance and was stable. We can even deduce from tables the following comments.

From Table 2, the Tanimoto coefficient was good for all scan images, taking into consideration the noisy condition of data preparation, but the value obtained with the FPCM approach was for all tissues better than those provided by tge PCM and FCM algorithms.

From Table 3, the proposed hybrid algorithm provides the best results in terms of sensitivity with SNR = 15%, for all scan images.

Same diagnosis is in favor of the proposed hybrid algorithm can be made with respect to the specificity results in Table 4.

Regarding Tables 5 and 6, which concern the accuracy of the fuzzy methods for real and ADNI databases respectively, for a random initialization of the centers, the results show that all the proposed fuzzy algorithms can qualify the volumes of the AD tissues provided that the initial parameters are chosen correctly. This requires time to properly select the convergence parameters. Still, the FPCM approach gave the best accuracy compared to the conventional algorithms FCM and PCM in quite noisy environments.

In comparison with the random initialization, all the fuzzy methods led to good accuracy results with the empirical initialization of the centers, and when applied on images without noise. In an highly noisy environment (15%), the FCM loses its performance and become disrupted. On the other hand, the possibilistic PCM and FPCM algorithms sill provide a good performance. Overall, it is still the FPCM algorithm that satisfies the noise constraint and which can avoid the coincident clusters.

Regarding the computation time, the proposed enhanced fuzzy-possibilistic algorithm converges very quickly because it gets its initial parameters from the already converged GA optimization-based FCM. Also, the FPCM converged more quickly compared to the PCM and FCM conventional algorithms. It only consumed 6 s compared to 8 s for the PCM and 11 s for the FCM.

8. CONCLUSION AND FUTURE WORK

In general, the information provided from medical imaging has varying degrees of perfection. The modeling of this type of information cannot be carried out by traditional techniques, but by others that manage the imperfection of the data. Techniques from artificial intelligence that manage vagueness and uncertainty are well suited for that kind of data.

In this paper, the use of fuzzy logic techniques for segmentation of Fuzzy tissue maps is motivated by the fact that the boundaries between brain tissues in the images are fuzzy rather than sharp (Barra & Boire, 2000b). Adding to this, noise, partial volume effect or anatomical and functional variations within pure tissue activities introduce uncertainty and ambiguity (Barra & Boire, 2000b).

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We thus used the FPCM hybrid method that combines a fuzzy (FCM) and possibilistic (PCM) clustering algorithms to characterizing Alzheimer's disease brain tissue from the anatomical and functional images, with the information in the images is carried out by the brain tissue distributions, revealing spatial locations in anatomical images (MRI) and distribution of a functional process in functional ones (SPECT, PET) (Barra, Briandet & Boire, 2001). The problem of fuzzy clustering has been posed as an optimization problem. So, we used GA to optimize the initial parameters of cluster centers that have been obtained by applying the FCM algorithm.

As shown from the results on simulated and real medical images, the main interest in our method arises because the uncertainties due to noise and imprecision due to the effect of partial volume are largely removed, and the imprecision at the boundaries between regions, which correspond to a lack of knowledge, is accounted for in the modelling. Moreover, considering the large amount of noise, our method outperforms a conventional FCM and PCM algorithms with fuzzy-genetic initialization.

For ongoing research, we are focusing on developing more accurate and noise-robust methods, aiming to improve the accuracy and computational speed of segmentation methods, while reducing the need for manual interaction modules. This is particularly important in real-time processing applications, especially since we are aiming for a routine diagnostic procedure in the clinical practice.

Table 2. Comparison of fuzzy tissue volumes of computed and reference labeled image with RF = 20%, ST = 1 mm and SNR = 15%, using the fuzzy clustering algorithms namely: FCM, PCM and FPCM with GA/FCM center initialization for real and ADNI databases

	TANIMOTO Coefficients									
	Real Database									
		FPCM			**PCM**			**FCM**		
Dataset	**Ref**	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**
MR	1	0.83	0.75	0.74	0.81	0.75	0.72	0.69	0.64	0.60
PET	1	0.86	0.77	0.76	0.84	0.76	0.74	0.70	0.65	0.63
SPECT	1	0.84	0.77	0.82	0.82	0.74	0.79	0.67	0.62	0.59
		ADNI Database								
		FPCM			**PCM**			**FCM**		
Dataset	**Ref**	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**
MR	1	0.85	0.88	0.82	0.87	0.84	0.79	0.75	0.70	0.66
PET	1	0.82	0.87	0.89	0.86	0.84	0.70	0.74	0.72	0.67

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Table 3. Sensitivity for WM, GM and CSF tissue with RF=20%, ST = 1 mm and SNR = 15%, using the fuzzy clustering algorithms namely: FCM, PCM and FPCM with GA/FCM centers initialization for real and ADNI databases

	SENSITIVITY								
	Real Database								
		FPCM			**PCM**			**FCM**	
Dataset		**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**
MR		0.75	0.72	0.77	0.72	0.69	0.72	0.69	0.65	0.62
PET		0.74	0.72	0.76	0.73	0.72	0.76	0.70	0.69	0.64
SPECT		0.74	0.76	0.77	0.73	0.74	0.75	0.69	0.71	0.59
	ADNI Database								
		FPCM			**PCM**			**FCM**	
Dataset		**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**
MR		0.81	0.79	0.79	0.75	0.74	0.72	0.72	0.70	0.69
PET		0.79	0.80	0.80	0.76	0.79	0.78	0.72	0.72	0.68

Table 4. Specificity for WM, GM and CSF tissue with RF = 20%, ST = 1 mm and SNR = 15%, using the fuzzy clustering algorithms namely: FCM, PCM and FPCM with GA/FCM centers initialization for real and ADNI databases

	SPECIFICITY								
	Real Database								
		FPCM			**PCM**			**FCM**	
Dataset		**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**
MR		0.85	0.80	0.85	0.82	0.76	0.80	0.68	0.64	0.68
PET		0.85	0.85	0.83	0.85	0.79	0.79	0.68	0.63	0.62
SPECT		0.89	0.89	0.89	0.86	0.75	0.75	0.70	0.69	0.59
Dataset	**ADNI Database**								
		FPCM			**PCM**			**FCM**	
		WM	**GM**	**CSF**	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**
MR		0.88	0.86	0.84	0.86	0.85	0.82	0.73	0.72	0.70
PET		0.87	0.86	0.86	0.83	0.84	0.84	0.69	0.70	0.70

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Table 5. Accuracy for real database with RF = 20%, ST = 1 mm and SNR = 11%, 13%, 15%, using the fuzzy clustering algorithms namely: FCM, PCM and FPCM with GA/FCM centers initialization and without empirical initialization

	ACCURACY								
	Real Database With FCM/GA Initialization								
	FPCM			**PCM**			**FCM**		
				SNR = 11%					
Dataset	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**
MR	0.79	0.72	0.77	0.77	0.70	0.73	0.64	0.65	0.60
PET	0.78	0.73	0.79	0.72	0.72	0.71	0.67	0.68	0.65
SPECT	0.74	0.72	0.75	0.70	0.72	0.71	0.64	0.70	0.69
				SNR = 13%					
Dataset	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**
MR	0.78	0.71	0.75	0.76	0.68	0.72	0.62	0.62	0.55
PET	0.76	0.72	0.78	0.71	0.71	0.70	0.65	0.65	0.60
SPECT	0.73	0.70	0.73	0.69	0.72	0.71	0.62	0.68	0.65
				SNR = 15%					
Dataset	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**
MR	0.76	0.70	0.74	0.75	0.68	0.71	0.59	0.59	0.52
PET	0.75	0.72	0.77	0.71	0.70	0.70	0.60	0.62	0.58
SPECT	0.73	0.70	0.73	0.68	0.72	0.70	0.54	0.65	0.60
	Real database Without FCM/GA Initialization								
	FPCM			**PCM**			**FCM**		
				SNR = 11%					
Dataset	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**
MR	0.76	0.70	0.74	0.75	0.69	0.70	0.62	0.63	0.59
PET	0.74	0.69	0.72	0.69	0.70	0.67	0.64	0.65	0.62
SPECT	0.70	0.70	0.71	0.67	0.68	0.68	0.61	0.66	0.67
				SNR = 13%					
Dataset	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**
MR	0.74	0.69	0.70	0.74	0.64	0.70	0.60	0.58	0.55
PET	0.74	0.69	0.75	0.69	0.68	0.68	0.62	0.62	0.55
SPECT	0.71	0.68	0.70	0.65	0.69	0.69	0.59	0.64	0.63
				SNR = 15%					
Dataset	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**
MR	0.73	0.68	0.70	0.73	0.64	0.68	0.57	0.56	0.50
PET	0.71	0.70	0.75	0.69	0.68	0.66	0.58	0.59	0.51
SPECT	0.71	0.70	0.71	0.66	0.68	0.69	0.56	0.61	0.58

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Table 6. Accuracy for ADNI database with RF = 20%, ST= 1 mm and SNR = 11%, 13%, 15%, using the fuzzy clustering algorithms namely: FCM, PCM and FPCM with GA/FCM centers initialization and without empirical initialization

	ACCURACY								
	ADNI Database With FCM/GA Initialization								
	FPCM			**PCM**			**FCM**		
				SNR = 11%					
Dataset	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**
MR	0.85	0.87	0.84	0.83	0.85	0.82	0.70	0.72	0.69
PET	0.86	0.85	0.85	0.83	0.83	0.83	0.75	0.70	0.71
				SNR = 13%					
Dataset	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**
MR	0.84	0.87	0.84	0.82	0.85	0.81	0.66	0.69	0.65
PET	0.85	0.85	0.84	0.83	0.82	0.82	0.72	0.67	0.69
				SNR = 15%					
Dataset	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**
MR	0.84	0.86	0.83	0.80	0.84	0.80	0.61	0.68	0.60
PET	0.84	0.84	0.83	0.81	0.81	0.81	0.65	0.63	0.64
	ADNI Database Without FCM/GA Initialization								
	FPCM			**PCM**			**FCM**		
				SNR = 11%					
Dataset	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**
MR	0.82	0.85	0.82	0.80	0.83	0.79	0.67	0.69	0.65
PET	0.83	0.83	0.82	0.80	0.80	0.80	0.73	0.68	0.69
				SNR = 13%					
Dataset	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**
MR	0.80	0.84	0.81	0.80	0.82	0.79	0.64	0.67	0.60
PET	0.83	0.83	0.81	0.80	0.80	0.79	0.68	0.62	0.66
				SNR = 15%					
Dataset	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**	**WM**	**GM**	**CSF**
MR	0.80	0.84	0.81	0.79	0.81	0.77	0.60	0.64	0.57
PET	0.81	0.82	0.80	0.79	0.79	0.78	0.65	0.58	0.63

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Chapter 16
Early Detection of Parkinson's Disease: An Intelligent Diagnostic Approach

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder that occurs due to corrosion of the substantia nigra, located in the thalamic region of the human brain, and is responsible for transmission of neural signals throughout the human body by means of a brain chemical, termed as "dopamine." Diagnosis of PD is difficult, as it is often affected by the characteristics of the medical data of the patients, which include presence of various indicators, imbalance cases of patients' data records, similar cases of healthy/affected persons, etc. Through this chapter, an intelligent diagnostic system is proposed by integrating one-class SVM, extreme learning machine, and data preprocessing technique. The proposed diagnostic model is validated with six existing techniques and four learning models. The experimental results prove the combination of proposed method with ELM learning model to be highly effective in case of early detection of Parkinson's disease, even in presence of underlying data issues.

INTRODUCTION

Parkinson's Disease (PD) is a progressive, neurodegenerative disorder that basically effects the motor system of a human being which causes physical problems such as shaking, stiffness, and difficulty in walking, balancing and coordinating movements (Parkinson's disease) (Mohamed, 2016). PD is basically

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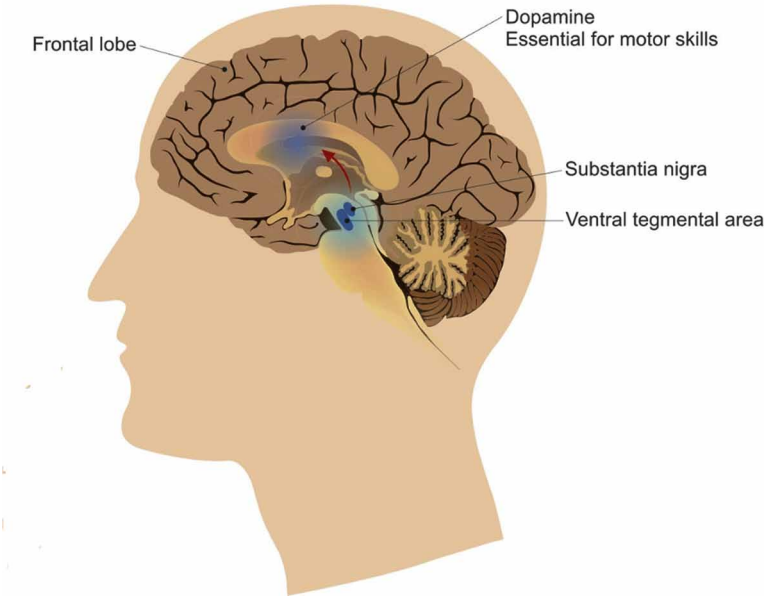
Figure 1. Location of Substantia nigra in human brain (Parkinson's disease)

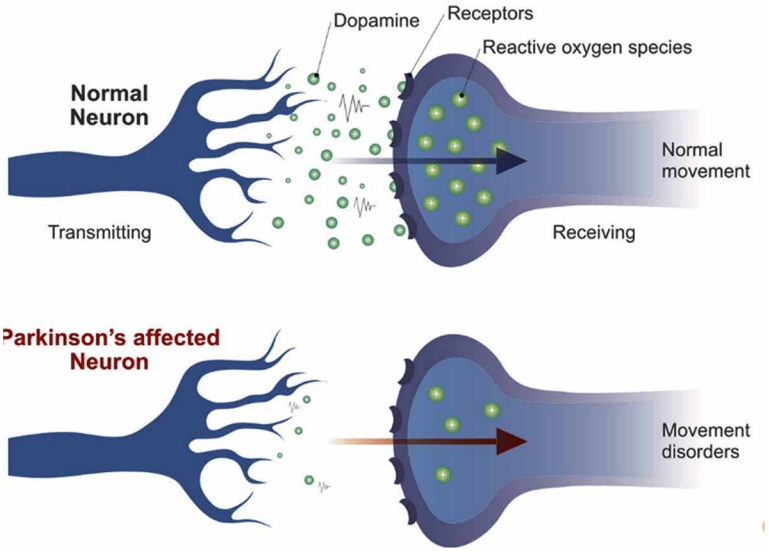


central nervous system oriented disease, occurred due to disintegration of a region called "substantia nigra" in the thalamic region of human brain (Figure 1).

This substantia nigra secretes a neurochemical named "dopamine" which is responsible for transmitting of neural signals to the different organs and parts of the human body (Figure 2).

With increase of dopamine loss in the course of time, the PD progresses gradually which ultimately leads to mental disorder such as thinking and behavioral disability, dementia, depression and anxiety,

Figure 2. Comparison of neurons of normal and PD-affected persons (Parkinson's disease)



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sleep disorder, lack of emotions etc. (Olanrewaju, Sahari, Musa, Hakiem, 2014).The various movement-difficulties experienced by PD-suffered individuals are collectively addressed by the term "Parkinsonism". It has been revealed in a recent survey in 2015 that approximately there are 7-10 million people are suffering from PD in the worldwide. The occurrence of PD is much higher in case of elderly people, typically over the age of 60 years; with a male-to-female ratio of 3:2 (Parkinson's disease) (Mohamed, 2016).

Parkinsonism is defined by "Bradykinesia", a spectrum of movement disorder, commonly known as hypokinesia. Bradykinesia refers to a situation when a person's movement or initiation of voluntary body-movement has slowed down, due to disruption in basal ganglia of human brain, with an increasing reduction of speed and range of repetitive actions (Parkinson's disease). Bradykinesia is considered to be one of the four key symptoms of PD, along with rigidity, tremor, and postural instability (Pahwa and Lyons, 2013).

There is no remedy or prevention available for PD. However, PD can be controlled if diagnosed at an early stage. Basically, in clinical diagnosis, PD is diagnosed with the presence of two or three of the four key motor-sign symptoms, namely tremor, rigidity, Bradykinesia and postural disability. The risk factor of PD tends to increase with the age of an individual. Most of the motor-sign symptoms are remained unnoticed as they are similar to the aging-sign of an elderly individual. By early detection of PD, its effect can be minimized on the affected person and proper treatment can be offered. One of the advanced and recent method of early detection of PD is using of biomarkers. Biomarker namely DaTscan, which is approved by FDA, to be used in diagnosis test of PD. The DaTscan (Ioflupane ^{123}I injection, also known as phenyltropane) is a radiopharmaceutical agent which is injected into a patient's veins in a procedure referred to as SPECT imaging (DAT-scanning) (DaTSCAN, 2011). It is used to detect the loss of nerve cells in the striatum region of human brain, specifically the cells that release dopamine. However, the use of DaTscan also carries risk of allergic reaction, especially in case of pregnant women (DaTSCAN, 2011). Hence, there is a demand for development of intelligent data mining techniques which can provide efficient and early detection and diagnosis of PD, without risking the side-effects of treatments. A number of research works have been proposed in recent years based on this idea (Olanrewaju, Sahari, Musa, Hakiem, 2014) (Alemami and Almazaydeh, 2014) (Mohamed, 2016) (Caliskan, Badem, Başturk, Yüksel, 2017) (Anita and Aruna Priya, 2016).

On application of data mining techniques to clinical diagnosis, they are more often affected by the characteristics of the underlying dataset. Clinical data are characterized by the presence of similar/overlapping cases, data imbalance and data redundancy. The similarities of the symptoms of PD with the other neurodegenerative disorders, such supranuclear palsy and multiple system atrophy (Olanrewaju, Sahari, Musa, Hakiem, 2014) (Ahmed, Santosh, Kumar, Christlet, 2009); make it difficult to precisely diagnose PD. Moreover, most of the clinical datasets have imbalanced data, which infer a scenario where cases of a specific category are found to be very high as compared to the other category. This is commonly termed as the "data imbalance" where data associated to the cases have skewed distribution which leads to produce results biased towards the majority case, when standard learning models are employed. Another issue is data redundancy, which is a common erroneous feature available in case of clinical data, as the medical history of a specific person can be recorded multiple times for diagnosis purpose. All these factors bring forward the requirement of developing an intelligent diagnostic system which can facilitate efficient and early detection of PD, from a set of clinical data even in presence issues such as overlapping cases, data imbalance, and data redundancy. The objectives of this chapter are listed as below:

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1. **Detection of Overlapping Cases**: For detection of overlapping cases, one-class SVM model is employed to extract the outliers. The outliers are defined as the case instances which are not belonging to the range of novel instances, within a definite case. One-class SVM, is commonly known as ϑ-SVM (Vlasveld, 2013) defines the parameter, ϑ which denotes the percentage of similar/ overlapping cases within a definite case.
2. **Cleaning Up of Overlapping Cases:** The concept of Tomek-link (Tomek, 1976) pair is refined to obtain the set of Abnormal Tomek- link (ATL) pairs whose significance is rare for classification purpose. The overlapping cases belong to ATL are selected for elimination. Following this, sparse neighborhood of majority overlapping cases is determined with higher misclassification probability. Cleaning up of overlapping zone is achieved by joint application of ATL and sparse neighborhood.
3. **Undersampling of the Majority Instances**: Basic Tomek-link pair (Tomek, 1976) concept, defined as Normal Tomek link (NTL) is used to detect the boundary majority instances contributing noise. The factor of data redundancy and intra-cluster significance is then incorporated with NTL to obtain a set of noisy, redundant and least significant majority instance cases. Redundancy among the instances is determined as the similarity among them while intra-cluster significance is defined as the respective distances of the majority instances to the centroid of the majority class. The detected instance cases are subjected to elimination.
4. **An Effective Data-Preprocessing Framework:** A new data processing framework is defined by incorporating the concepts of ATL, sparse neighborhood, NTL, redundancy and intra-cluster significance to compress the overlapping zone while balancing the data imbalance. The improvement of the classifier performance in the proposed scheme is evaluated with respect to Feed Forward Neural Network (FFNN), Support Vector Machine (SVM), Extreme Learning Machine (ELM), and Naive Bayes classifiers. A comparative analysis with seven state-of-the-art techniques is also carried out in this chapter.

BACKGROUND

The early detection of PD is very much crucial from adequate diagnosis point of view. The diagnosis of PD fails to detect the disease, before the patient has a significant loss of dopamine (Olanrewaju, Sahari, Musa, Hakiem, 2014). The movement-disability symptoms carry similarity with other neurological disorders, which create ambiguity during diagnosis. On discussing the PD, individuals with PD tend to lose the nerve endings that produce norepinephrine, the prime chemical messenger of the sympathetic nervous system, which controls many automatic functions of the body, such as heart rate and blood pressure (Pahwa and Lyons, 2013).The brain cells of patients affected with PD, contain Lewy bodies, which are unusual clumps of the protein alpha-synuclein. Scientists are in a mission to understand the normal and abnormal functions of alpha-synuclein and its relationship to genetic mutations that impact PD and Lewy body dementia (Pahwa and Lyons, 2013).

Although, in general the occurrence of PD in an individual appears to be hereditary, and a few can be traced to specific genetic mutations, in most of the cases the disease occurs randomly and does not seem to run in families. Many researchers have revealed the fact that PD is resultant of a combination of genetic factors and environmental factors such as exposure to toxins.

To discuss the various symptoms of PD, they can be listed down as below: (Pahwa and Lyons, 2013) (Parkinson's disease)

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Basic motor-sign symptoms:

- Tremor (trembling) in hands, arms, legs, jaw, or head.
- Stiffness of the limbs and legs
- Bradykinesia: Slowness of movement
- Postural disability i.e. impaired balance and coordination

Additional symptoms include:

- Depression
- Dementia
- Emotional breakdown or lack of emotions
- Difficulty swallowing, chewing, and speaking
- Urinary problems or constipation
- skin problems
- Sleep disruptions.
- Blood pressure variation.
- Smell dysfunction
- Fatigue.
- Sexual dysfunction.

Early symptoms of Parkinson's disease are subtle and occur gradually. For example, affected people may feel mild tremors or have difficulty getting out of a chair. It is also noticed that they speak too softly or that their handwriting is slow and looks cramped or small. Parkinsonian gait (Pahwa and Lyons, 2013) is a common body deformity gained by PD- patients that involves a tendency to lean forward, associated with small quick steps as if hurrying forward, and reduced swinging of the arms. They also may have trouble on initiating or continuing body movement.

On discussing the risk factors of PD, these include the followings (Pahwa and Lyons, 2013):

- **Age**: Age carries a big risk factor in case of PD-affected people. Generally people with age>60 or more, easily develop this disease. About 5-10% of people have "early-onset" PD, which begins before the age of 50.
- **Heredity**: Having a close relative with Parkinson's disease increases the chances of developing the disease.
- **Sex:** Men are more likely to develop Parkinson's disease than women.
- **Exposure to Toxins**: Ongoing exposure to herbicides and pesticides may slightly increase the risk of Parkinson's disease.

Treatment of Parkinson's Disease

There is no standard treatment or remedy available for Parkinson's disease. There are some medicines, surgical treatments, and other therapies which can reduce the effect of PD.

Medicines prescribed for Parkinson's disease include:

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- Drugs those increase the level of dopamine in the brain.
- Drugs those affect other brain chemicals in the body.
- Drugs those help to control motor-sign symptoms.

Alternative mode of treatments involves:

- **Deep Brain Stimulation:** For people with severe PD who has stopped responding to medications, deep brain stimulation, or **DBS,** may be an appropriate mode of treatment. DBS is a surgical procedure that surgically implants electrodes into part of the brain and connects them to a small electrical device implanted in the chest. The device and electrodes painlessly stimulate the brain in a way that helps stop many of the movement-disability of PD, such as tremor, slowness of movement, and rigidity.
- **Therapies**: A number of therapies are available which can be used for treatment of PD. These include physical, occupational, and speech therapies, which help with gait and voice disorders, tremors and rigidity, and decline in mental functions. Other supportive therapies include a healthy diet and exercises to strengthen muscles and improve balance.

DIAGNOSIS OF PARKINSON'S DISEASE

The early signs of PD are often misconceptualized as signs of aging. As a result, treatments are not sought at the early stage. The available treatments of PD are likely to be more effective when it's started in its early stage. Moreover, a number of neurological disorders have symptoms similar to those of PD. So, there are higher chances of misdiagnosis. The medical conditions with similar features to PD are listed below (Pahwa and Lyons, 2013):

- Drug-induced Parkinsonism
- Head trauma
- Encephalitis
- Stroke
- Lewy body dementia
- Corticobasal degeneration
- Multiple system atrophy
- Progressive supranuclear palsy

Since the diseases have similar features as PD but require different treatments, it is important to make an exact diagnosis as soon as possible. There are currently no blood or laboratory tests are available to diagnose non-genetic cases of PD. Diagnosis is done based on a person's medical history and a neurological examination. This way of clinical diagnosis can also be erroneous due to the presence of various indicators, similar cases of patients, data imbalance, and redundant data. In presence of data imbalance, there is a higher chance misdiagnosing a patient as the healthy one, if the cases of affected individuals create the minority class. In such scenario, it is very important to diagnose PD accurately since if a patient is misdiagnosed as healthy, his condition might worsen over the time.

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Due to all these factors, a number of researchers have adopted data mining tools and techniques for precise diagnosis of PD. Some of the research works are discussed below:

- M. S. Islam *et al*. (Islam, Parvez, Deng, Goswami, 2014) conducted a comparative analysis for effective detection on Parkinson's disease using Random tree (RT), SVM and Feed forward Back Propagation Neural Network (FBPNN).
- A. Sharma and Ram Nivas (Sharma and Giri, 2014) evaluated the performance of the model build using Artificial Neural Networks (ANN), K-Nearest Neighbor (KNN), and SVM with radial basis function.
- A. H. Hadjahamadi and T. J. Askari (Hadjahamadi and Askari, 2012) compared various classification methods (Bayesian Network, C5.1, SVM, ANN) for diagnosis of PD. They indicated that the role of computing of the variable (feature) is an important issue in many applied problems complementing variable selection by interpretation issues.
- Y. Alemami and L. Almazaydeh (Alemami and Almazaydeh, 2014) developed and validated classification algorithms based on Naïve Bayes and KNN; their results show that the automated classification algorithm, Naïve Bayes, and KNN obtained a high degree of accuracy around 93.3%.
- Olanrewaju *et al*. (Olanrewaju, Sahari, Musa, Hakiem, 2014) proposed a model in early detection and diagnosis of PD by using the Multi-Layer Feedforward Neural Network (MLFNN) with Backpropagation (BP) algorithm. The output of the network is classified into healthy or PD by using K-Means Clustering algorithm.
- Caliskan *et al*. (Caliskan, Badem, Baştürk, Yüksel, 2017) proposed a deep neural network model using stacked autoencoder and softmax classifier for diagnosis of PD.
- G. S. Mohamed (Mohamed, 2016) discussed the effect of attribute selection and discretization of PD dataset over the diagnosis of PD.
- Anita *et al.* (Anita, S. and Aruna Priya. P, 2016) have developed an ANN model for prediction of Gamma-Amino Butyric Acid (GABA) concentration level for PD and Healthy Group (HG).
- Finberg *et al*. (Finberg *et al*., 2013) has proposed an advanced technique of PD detection, by detecting of volatile molecules in exhaled breath (sensor array), and thus chances of person having PD or not.
- Chatterjee, Saxena, Vyas, and Mehra (Chatterjee, Saxena, Vyas, Mehra, 2018) have proposed cepstral feature based real-time program for detection of neurological health of a person, based on analysis of the utterance of "aah" by a person. Then, SVM classifier is used to identify the odds of PD based on various audio samples of both healthy as well as affected people.
- De Souza et al. (De Souza, Almeida, Rebouças Filho, 2017) proposed a similarity extraction approach by using structural similarity, mean squared error and peak signal-to-noise ratio measures, to evaluate the variations obtained in exam template and the handwritten trace generated by the PD patient. Each of these variations was used together with the Naive Bayes, OPF, and SVM classifiers.
- Schindlbeck and Eidelberg (Schindlbeck and Eidelberg, 2018) have proposed PD-related functional network imaging which can capture the whole brain and the responses of the patients are recorded.
- Parisi et al. (Parisi, RaviChandran, Manaog, 2018) has proposed a Multi-Layer Perceptron based feature selection technique in integration Lagrangian Support Vector Machine for classification of people, affected with PD.

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- Hariharana, Polat, and Sindhu (Hariharana, Polat, Sindhu, 2014) have proposed a hybrid intelligent system by combining feature pre-processing, feature reduction/selection and classification tasks. For feature pre-processing, Model-based clustering (Gaussian mixture model) is used. Feature selection is done by using principal component analysis (PCA), linear discriminant analysis (LDA), sequential for-ward selection (SFS) and sequential backward selection (SBS). For classification task, Least-Square Support Vector Machine (LS-SVM), Probabilistic Neural Network (PNN) and General Regression Neural Network (GRNN) are employed.
- Nilashi *et al*. (Nilashi, Ibrahim, Ahmadi, Shahmoradi, Farahmand, 2018) defined the concept of Unified Parkinson's Disease Rating Scale (UPDRS) in detection of PD, and have proposed incremental SVM based prediction system for prediction of Total- UPDRS and Motor- UPDRS.
- Chen *et al*. (Chen, Huang, Yu, Xu, Sun, Wang, Wang, 2013) have proposed Principal Component Analysis (PCA) based feature selection method for selecting the features, which are then classified by using non-linear classifier to detect the patients with PD.
- Picillo *et al*. (Picillo, Moccia, Spina, Barone, Pellecchia, 2015) have performed a comparison analysis of different biomarkers (clinical, biochemical or imaging), to retrieve the best combination of biomarkers for detection of PD in its different stages.

DIAGONOSIS OF PARKINSON'S DISEASE

Issues

The treatment of PD is generally done based on medical history of the patient and the neurological analysis. Hence, the collected medical data carries a vital role in the developing an efficient diagnostic system. Data collected for clinical diagnosis are used to be incomplete, imbalanced, and redundant, due to lack of effective data collection techniques. Moreover, the available real-life medical data are usually random data, collected from random sources. Profiling and offering treatment of a patient based on these data would carry a higher risk. Data pre-processing techniques allow mending the raw data to minimize incompleteness, imbalance and redundancy of data.

SOLUTIONS AND RECOMMENDATIONS

As a solution to the issues experienced during diagnosis of PD, the authors of this chapter have come with a concept of intelligent diagnostic system. An intelligent diagnostic system offers to deliver an efficient and rapid early detection of PD, with an aim of reduced misdiagnosis rate, even in the presence of similar/overlapping cases of patients (overlapping cases) and data imbalance. An effective data pre-processing technique is a mandatory stage for treatment of overlapping cases, data imbalance, and data redundancy. ELM classification model is considered for detection of PD, in a test individual. The motivation of an intelligent diagnostic system is to offer rapid and efficient early detection of PD, in patients in presence of different adversities.

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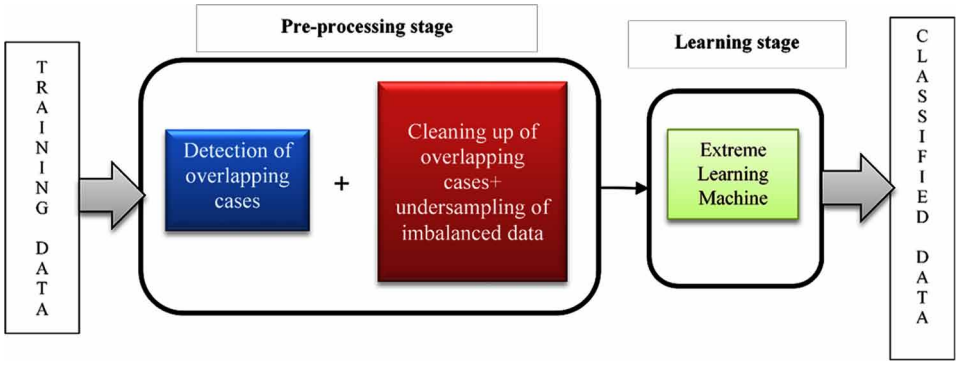
Proposed Methodology for Intelligent Diagnosis System

The proposed methodology can be categorized into two stages, namely a) *data preprocessing stage* and b) *learning stage*. The data preprocessing stage involves mining the initial training data before learning. It involves two sub-stages, namely 1) *detection of class overlapping cases*, and 2) *cleaning up of the overlapping cases and undersampling of imbalanced data.*

The initial case set is fed to one-class SVM model to detect the overlapping cases. The cases detected as outliers are extracted to generate the overlapping zone. In the next stage, cleaning up of the most insignificant overlapping cases is performed by detecting *Abnormal Tomek-Link pairs (ATL)*. The *ATL* pair concept is introduced for efficient detection of similar cases out of healthy and affected patients. Following to this, the issue of data imbalance has been treated in terms of redundancy and intra-cluster significance among the patients' cases. The refined case set is then fed to the learning stage for diagnosis/ classification of the PD (affected/ healthy). Extreme Learning Machine (ELM) learner is used for diagnosis of the disease, against a set of test cases, and then, the performance of the method is evaluated. The pictorial representation of the proposed methodology is presented in figure 3.

Figure 3. Framework of the proposed scheme



For comprehensive understanding of the proposed system, the following notations are considered. Table 1 represents corresponding description of each notation.

Data Pre-Processing Stage

This stage involves preprocessing the initial case set with aspects of class overlapping and data imbalance. One-class SVM is implemented for detection of overlapping cases. The presence of data imbalance is then treated with consent of overlapping cases in order to achieve a refined case set with balanced class distribution and a compressed overlapping zone. Figure 4 presents the block diagram of the various sub-stages in step-by-step manner. The sub-stages are discussed in details as below:

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Table 1. Notations and descriptions

Notations	Descriptions
$S_{n\times l}$	An imbalanced training dataset, with *n*- number of total instances and *l*-numberof total features
$\overrightarrow{x_a}$	$=\left(x_{a1}, x_{a2}, \cdots\cdots x_{al}\right)$; input vector of a^{th}- instance of $S_{n\times l}$, with a total of *l*-features
y_b	$=(y_1, y_2, \ldots, y_c)$= set of designated class labels for instances in $S_{n\times l}$ with a total of *c*-classes
$S_{\min}$	Set of minority class instances, where $S_{\min}$: $\{x_i \mid i=1,2,\ldots,p\}$, where *p* is the total minority-class instances
S_{maj}	Set of majority class instances, where S_{maj}: $\{x_m \mid m=1,2,\ldots,m\}$, where *q* is the total majority-class instances
NN_{maj}	Nearest neighbor from majority class
TL	Set of Tomek-link pairs
reg_{ovr}	Overlapping region
$ovr_reg_{\min}$	Overlapping region of minority class
ovr_reg_{maj}	Overlapping region of majority class
$nov_reg_{\min}$	Set of novel minority instances
nov_reg_{maj}	Set of novel majority instances
$NN_{hits}(x_m)$	K-NN hits of x_m where $class(x_m)=class(NN)$
$NN_{miss}(x_m)$	K-NN misses of x_m, where $class(x_m)\neq class(NN)$
sp_{NN}	Set of instances with sparse neighborhood
$d(x_a, x_b)$	Euclidean distance between instances x_a and x_b
d_{intra_cen}	Intra-centroid distance of x_m
cen_{maj}	Centroid of majority set, S_{maj}

Detection of Overlapping Region

One-class SVM defines a domain-based novelty detection, by setting a boundary to extract the transformed case instances with maximum margin in the feature space. The case instances not falling in the proximity of the maximum margin are termed as "outliers". In the proposed methodology, the one-class SVM model is applied to both minority and majority case sets to obtain the set of outliers from each case. These set of outliers are combined together to generate the overlapping zone, reg_{ovr} for the entire training data. Formal depiction of this stage is presented below:

***Input*:** $S_{\min}$, S_{maj}
Step 1: Apply one-class SVM to $S_{\min}$ and S_{maj}.
Step 2: Extract the outliers to obtain the overlapping instances from S_{maj} and store in the set, ovr_reg_{maj} as:

$$ovr_{regmaj} = \left\{x_m' \mid f\left(x_m'\right) < 0; x_m' \in S_{maj}\right\} \quad (1)$$

$$nov_reg_{maj} = \left\{x_m' \mid f\left(x_m'\right) > 0; x_m' \in S_{maj}\right\} \quad (2)$$

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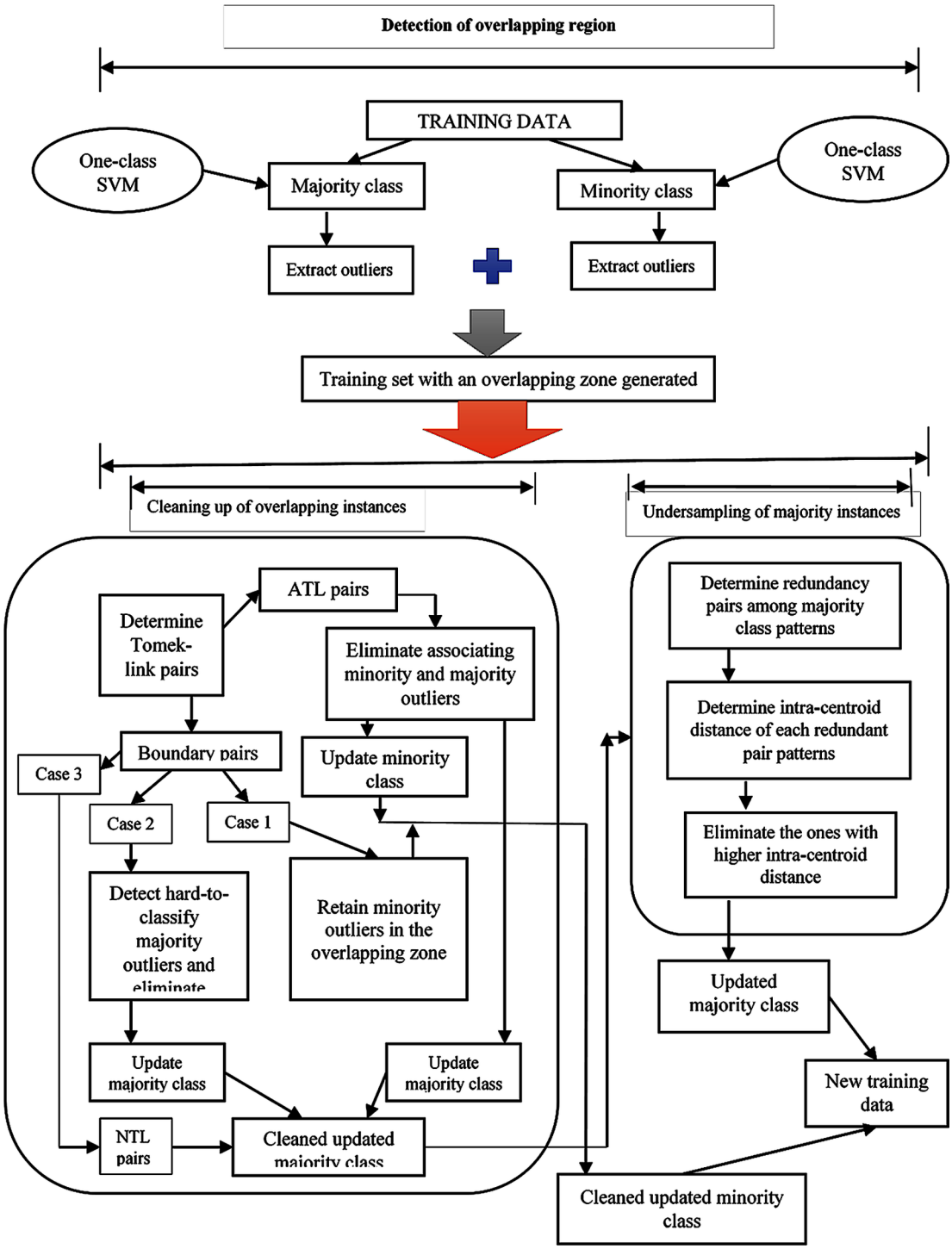
Figure 4. Step-by-step block diagram of the working of data pre-processing stage



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where $f\left(x_m^{'}\right)=\sum_{m=1}^{q}\alpha_m K\left(x_m^{'},x\right)-\rho$; for $K\left(x_m^{'},x\right)$ is the kernel function, ρ is the offset and α_m is the center of majority class region.

Step 3: Repeat step (1) and (2) for $S_{\min}$ and the resultant is

$$ovr_reg_{\min}=\left\{x_i' \mid f\left(x_i^{'}\right)<0; x_i^{'}\in S_{\min}\right\} \tag{3}$$

$$nov_reg_{\min}=\left\{x_i' \mid f\left(x_i^{'}\right)>0; x_i^{'}\in S_{\min}\right\} \tag{4}$$

where $f\left(x_i^{'}\right)=\sum_{i=1}^{p}\alpha_i K\left(x_i^{'},x\right)-\rho$; for $K\left(x_i^{'},x\right)$ is the kernel function, ρ is the offset and α_i is the center of minority class region.

Step 4: Generate overlapping zone for entire training data as:

$$reg_{ovr}=ovr_reg_{\min}+ovr_reg_{maj} \tag{5}$$

***Output*:** ovr_reg_{maj}, $ovr_reg_{\min}$, reg_{ovr}.

Algorithm 1.

Input: $S_{\min}$, S_{maj}	
1	$ovr_reg_{\min}\leftarrow one_class_SVM(S_{\min})$
2	$ovr_reg_{maj}\leftarrow one_class_SVM(S_{maj})$
3	$reg_{ovr}=ovr_reg_{\min}+ovr_reg_{maj}$
one_class_SVM	
4	For m=1…q, q is the total number of instances in S_{maj}
	a) $f\left(x_m'\right)=\sum_{m=1}^{q}\alpha_m K\left(x_m^{'},x\right)-\rho$ b) If $f\left(x_m'\right)<0$ c) $x_m'\leftarrow outlier$ d) Else e) $x_m'\leftarrow novel$ f) $ovr_reg_{maj}=\left\{x_m' \mid x_m^{'}\ is\ outlier\ ; x_m^{'}\in S_{maj}\right\}$
5	For i=1…p, p is the total number of instances in $S_{\min}$, repeat steps 4(a)-4(f).
Output: ovr_reg_{maj}, $ovr_reg_{\min}$, reg_{ovr}	

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The process of overlapping region detection is summarized in Algorithm 1.

Cleaning Up of the Overlapping Instances and Undersampling of Negative Instance

This stage involves to eliminate the trivial overlapping instances from both minority and majority case sets, in order to reduce the overlapping zone, reg_{ovr}. To accomplish the objective, the concept of Tomek-link pair is refined to retrieve Abnormal Tomek-link pair (*ATL*). The concept of Tomek-link pair basically addressed the boundary instances which promote noise along the decision boundary. However, the presence of significant borderline instances is also important to accurately define the decision boundary. In case of class overlapping, overlapping cases often occurred near the decision boundary. Random elimination of boundary instances in such cases can drift apart the decision boundary between minority and majority cases which in turn can degrade the learning process. Hence, in the proposed model, an effective way of pre-processing is defined which facilitates to eliminate only the trivial boundary cases as well as insignificant redundant majority cases without distorting the decision boundary while balancing data distribution. The behavior of instances near the decision boundary in presence of class overlapping has been deeply explored in the present study and based on the study; some inferences have been made as follows:

Tomek-Link Pairs

Tomek-link pairs, formed by instances lying in the overlapping zone may not always endorse boundary instances. But, there is a higher chance of these instances promoting noise; as it's difficult to draw a crisp decision boundary along these instances, in presence of overlapping cases. Hence, the concept of *ATL* pair is defined. The instances forming *ATL* pairs are promoting maximum noise as a slight deviation in feature values will lead to misclassify them. Hence, both minority and majority cases of *ATL* pairs are selected for elimination.

Input: $S_{\min}$, S_{maj}, ovr_reg_{maj}, $ovr_reg_{\min}$, reg_{ovr}, K1= K-NN of minority instance, K2= K-NN of majority patter, K3= K-NN of overlapped majority instance, set K1=1, K2=5, K3=1.

Step 1: For $\forall\, x_i \in S_{\min}$, determine its K1-NN from $S_{n\times l}$, for K1=1, by using Euclidean distance.

Step 2: for $\forall\, x_i \in S_{\min}$, determine NN_{maj}, i.e. nearest neighbor belonging to S_{maj}; and create the set *TL* as:

$$TL = \left\{ \left(x_i, x_m \right) \mid x_m = NN_{maj}\left(x_i \right); x_i \in S_{\min}, x_m \in S_{maj} \right\} \tag{6}$$

Step 3: Extract the Abnormal Tomek- link, *ATL* pairs as:

$$ATL = \left\{ \left(x_c, x_d \right) \mid x_c, x_d \in TL; x_c \in ovr_reg_{\min}, x_d \in ovr_reg_{maj} \right\} \tag{7}$$

Step 4: For $\forall\, (x_c, x_d) \in ATL$, eliminate x_c and x_d from $ovr_reg_{\min}$ and ovr_reg_{maj} respectively, and update ovr_reg_{maj}, $ovr_reg_{\min}$, reg_{ovr}.

$$ovr_reg_{maj}{}' = ovr_reg_{maj} - \left\{ x_d \right\}; x_d \in ATL \tag{8}$$

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$$ovr_reg_{min}{}' = ovr_reg_{min} - \{x_c\}; x_c \in ATL \tag{9}$$

$$reg_{ovr}' = ovr_{regmaj}{}' + ovr_{regmin}{}' \tag{10}$$

Step 5: Update $S_{\min}$ and S_{maj} as

$$S_{min}' = S_{min} - \{x_d\}; x_d \in ATL \tag{11}$$

$$S_{maj}' = S_{maj} - \{x_d\}; x_d \in ATL \tag{12}$$

Step 6: Update *TL* to TL' as

$$TL' = \left\{ \left(x_c', x_d'\right) \mid x_c', x_d' \notin ATL; x_c' \in S_{\min}', x_d' \in S_{maj}' \right\} \tag{13}$$

The Instances in TL'

The instances in TL' are considered as potential boundary cases and crucial in defining a distinctive decision boundary. Based on the existence of the associating instances either in overlapping zone or non-overlapping zone; three different scenarios are investigated:

Scenario 1: If the minority case associating instance resides in the overlapping zone while majority case associated instance lies in the non-overlapping zone; the minority instances are retained in the training case set. Elimination of such minority case instances can incline the decision boundary more towards the majority case which will lead to degrade the classification rate of minority cases.

Step 7: *Scenario 1:*

For $\forall\left(x_c', x_d'\right) \in TL'$; if $x_c' \in ovr_reg_{min}{}'$ and $x_d' \notin ovr_reg_{maj}{}'$; then retain x_c' in S_{min}'.

Scenario 2: If the majority associating instance resides in the overlapping region with minority being in the non-overlapping region; the concept of sparse neighborhood is employed to detect the hard-to-classify outlier majority case instances. Sparse neighborhood is defined as K-NN estimation of a case instance where most of its neighbors have different class labels. For an outlier with sparser neighborhood, it will carry maximum chances of misclassification and hence is selected for elimination.

Step 8: *Scenario 2:*

For $\forall\left(x_c', x_d'\right) \in TL'$; if $x_d' \in ovr_reg_{maj}{}'$ and $x_c' \notin ovr_reg_{min}{}'$; x_d' is extracted and stored in the set, ovr_{out_maj} as

$$ovr_{out_maj} = \left\{ x_d^{ovr} \mid x_d^{ovr} \leftarrow x_{d,}' x_d' \in TL', x_d' \in ovr_reg_{maj}{}' \right\} \tag{14}$$

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Step 9: For ovr_{out_maj}, detection of sparse-neighborhood is performed with the following sub-steps:

a. For $\forall x_d^{ovr} \in ovr_{out_maj}$, determine K2-NN from reg_{ovr} ' for K2=5.

b. Determine $NN_{hits}(x_d^{ovr})$.

c. Determine $NN_{miss}(x_d^{ovr})$.

d. For $\forall x_d^{ovr}$, compare $NN_{hits}(x_d^{ovr})$ and $NN_{miss}(x_d^{ovr})$.

e. If $NN_{miss}(x_d^{ovr}) > NN_{hits}(x_d^{ovr})$; extract x_d^{ovr} and store in a set sp_{NN} as

$$sp_{NN} = \left\{ x_d^{ovr} \mid NN_{miss}\left(x_d^{ovr}\right) > NN_{hits}\left(x_d^{ovr}\right) \right\} \tag{15}$$

f. Otherwise, retain x_d^{ovr} in ovr_{out_maj}.

g. Update ovr_{out_maj} as

$$ovr'_{out_{maj}} = ovr_{out_{maj}} - sp_{NN} \tag{16}$$

h. Update TL' as

$$TL'' = TL' - sp_{NN} \tag{17}$$

i. Update $ovr_reg_{maj}{}'$ as

$$ovr_{regmaj}{}'' = ovr_{regmaj}{}' - sp_{NN} \tag{18}$$

j. Update S'_{maj} *as*

$$S_{maj}{}'' = S'_{maj} - sp_{NN} \tag{19}$$

Scenario 3: If both the associating case instances reside outside the overlapping region; they are assumed to be the *Normal Tomek-link* (*NTL*) pairs. The majority instances forming *NTL* pairs are subjected to redundancy check. The most redundant instances with least significance are selected for elimination, out of each redundant pair. The significance of an instance is determined through intra-cluster significance.

Step 10: *Scenario 3:*

For $\forall \left(x_c{}', x_d{}'\right) \in TL'$; if $x'_c, x_d{}' \notin reg_{ovr}$; extract $x'_c, x_d{}'$ and store in a set, *NTL* as

$$NTL = \left\{ \left(x_c{}'', x_d{}''\right) \mid x_c'' \leftarrow x'_c, x_d'' \leftarrow x'_c, x_c{}'', x_d{}'' \notin reg_{ovr}{}'; x_c'' \in S'_{\min}, x_d{}'' \in S'_{maj} \right\} \tag{20}$$

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Step 11: *Redundancy check*:

For $\forall x_d" \in NTL$, determine its redundant pair, x_e from $S_{maj}"$, by using K3-NN rule and Euclidean distance, for K3=1 and create a set *REDN* as:

$$REDN = \left\{ \left(x_d", x_e \right) \mid x_d" \in NTL, S_{maj}; x_e \in S_{maj}; d\left(x_d", x_e \right) is\ minimum \right\} \tag{21}$$

Step 12: *Check intra-cluster significance:*

Determine the centroid of S_{maj}' as

$$cen_{maj}\left(x_1, x_2, \ldots\ldots\ldots, x_l \right) = \frac{1}{q'} \left\{ \sum_{d''=1}^{q'} \left(x_{d1}", x_{d2}", \ldots\ldots\ldots, x_{dl}" \right) \right\} \tag{22}$$

where q' is total number of instances in S_{maj}'.

Step 13: For $\forall x_d"$, determine $d_{intra_cen}\left(x_d" \right)$ as

$$d_{intra_cen}\left(x_d" \right) = \frac{1}{q'} \left[\sum_{d''=1}^{q'} \left\{ \left(x_{d1}" - cen_{maj}\left(x_1 \right) \right)^2 + \left(x_{d2}" - cen_{maj}\left(x_2 \right) \right)^2 + \ldots\ldots\ldots + \left(x_{dl}" - cen_{maj}\left(x_l \right) \right)^2 \right\} \right] \tag{23}$$

Step 14: *Detection of least significant redundant instance:*

For each $\left(x_d", x_e \right)$ pair, if $d_{intra_cen}\left(x_d" \right) > d_{intra_cen}\left(x_e \right)$; then $x_d"$ is supposed to be less significant and is selected for elimination. Update $S_{maj}"$ as:

$$S_{maj}^{new} = S_{maj}" - \left\{ x_d" \right\} \tag{24}$$

Step 15: Obtain the new training set S_{new}. as:

$$S_{new} = S_{maj}^{new} + S_{min}' \tag{25}$$

Output: S_{new}, reg_{ovr}'

All those inferences furnish to develop an effective data pre-processing technique to solve issues of both of data imbalance and overlapping cases. The refined case set S_{new} then fed to the learning stage for training. A summarized algorithm for the above stage is presented below in algorithm 2:

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Algorithm 2.

Input: S_{min}, S_{maj}, ovr_reg_{maj}, ovr_reg_{min}, reg_{ovr}, K1= K-NN of minority instance, K2= K-NN of majority patter, K3= K-NN of overlapping majority instance, set K1=1, K2=5, K3=1.	
1	For $\forall x_i \in S_{min}$, determine $TL = \left\{ \left(x_i, x_m \right) \mid x_m = NN_{maj}\left(x_i \right); x_i \in S_{\min}, x_m \in S_{maj} \right\}$
2	Extract *ATL*, $ATL = \left\{ \left(x_c, x_d \right) \mid x_c, x_d \in TL; x_c \in ovr_reg_{\min}, x_d \in ovr_reg_{maj} \right\}$
3	Update ovr_reg_{maj}, ovr_reg_{min}, S_{maj}, S_{min}, reg_{ovr}, *TL* by using steps 4-6. Retrieve updated $ovr_reg_{maj}', ovr_reg_{min}', reg_{ovr}', S_{maj}', S_{min}', TL'$
4	For $\forall \left(x_c', x_d' \right) \in TL'$, a) If case 1 has occurred, retain x_c' in S_{min}'. b) If case 2 has occurred, estimate sparse neighborhood, sp_{NN} of x_d' by using steps 8(a) - 8(f). c) Update $S_{maj}', reg_{ovr}', TL'$ by using steps 8(g)- 8(j). Retrieve $S_{maj}'', reg_{ovr}'', TL''$. d) If case 3 has occurred, determine *NTL*, $NTL = \left\{ \left(x_c'', x_d'' \right) \mid x_c'' \leftarrow x_c', x_d'' \leftarrow x_c', x_c'', x_d'' \notin reg_{ovr}'; x_c'' \in S_{min}', x_d'' \in S_{maj}' \right\}$ e) Determine *REDN*, $REDN = \left\{ \left(x_d'', x_e \right) \mid x_d'' \in NTL, S_{maj}; x_e \in S_{maj}; d\left(x_d'', x_e \right) is\, minimum \right\}$ f) Determine $d_{intra_cen}\left(x_d'' \right)$ by using steps 12-13. g) For each $\left(x_d'', x_e \right)$, if $d_{intra_cen}\left(x_d'' \right) > d_{intra_cen}\left(x_e \right)$ h) Eliminate x_d'' i) Else j) Eliminate x_e k) Retrieve S_{maj}^{new} as $S_{maj}^{new} = S_{maj}'' - \left\{ x_d'' \right\}$
5	Retrieve refined case set, $S_{new} = S_{maj}^{new} + S_{min}'$
Output: S_{new}, reg_{ovr}'	

Learning Stage

In the learning stage, the refined case set, S_{new} is trained with ELM classifier which is then validated against a set of test cases, to detect whether a person is affected or healthy. ELM is an advanced Feed Forward Neural Network (FFNN) model which can work without hidden layer parameter tuning (Huang, Zhu, Siew, 2006) (Huang, Zhu, Siew, 2004). ELM is considered to have more generalization capability, and requires less learning time, than the standard Back Propagation Neural Network (BPNN). That is why, ELM has been considered for detection of PD in the learning stage. A brief illustration on working of ELM learning model is presented below:

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For a training set, $S_{n\times l} = \{(x_i, t_i) | \, i=1,2,\ldots,n\}$, with x_i is the training data vector, t_i is the target of each sample, and L denoting the number of hidden nodes, the output function for L-hidden nodes is given by (Tang, Deng, 2016):

$$f_L\left(x\right) = \sum_{i=1}^{L} \beta_i h_i\left(x\right) \tag{26}$$

where β_i is the output weight of *i-th* hidden node, and $h_i(x) = G(a_i, b_i, x)$ is the output function of *i-th* hidden node.

The hidden-layer output matrix, H of ELM is given by:

$$H = \begin{bmatrix} h\left(x_1\right) \\ \vdots \\ h\left(x_N\right) \end{bmatrix} = \begin{bmatrix} G\left(a_1, b_1, x_1\right) & \cdots & G\left(a_L, b_L, x_1\right) \\ \vdots & \vdots & \vdots \\ G\left(a_1, b_1, x_n\right) & \cdots & G\left(a_L, b_l, x_N\right) \end{bmatrix} \tag{27}$$

where $h(x) = [G(h_i(x),\ldots,h_L(x))]$ defines the hidden-layer output mapping.

From the view of learning, ELM provides to achieve the smallest training error as well as the minimum output weight during training. The objective function of ELM theory can be given as:

$$\text{Minimize: } \beta_p^{\sigma_1} + CH\beta - T_q^{\sigma_2} \tag{28}$$

Where $\sigma_1 > 0, \sigma_2 > 0, p, q = 0, \frac{1}{2}, 1, 2, \ldots + \infty$, and T is training data target matrix, denoted as

$$T = \begin{bmatrix} t_1 \\ \vdots \\ t_N \end{bmatrix} \tag{29}$$

The ELM learning algorithm has the following steps:

1. For L-hidden nodes, randomly assign the input weights, a_i and the biases, b_i as the hidden-node parameters.
2. Calculate the matrix, H
3. Calculate the output-weight vector, β as:

$$\beta = H^{\dagger}T \tag{30}$$

With $T=[t_1,\ldots,t_N]^T$; $H^{\dagger}$ is the Moore-Penrose generalized inverse of the matrix, H.

$H^{\dagger}$ can be calculated as $H^{\dagger} = (H^TH)^{-1}H^T$; providing H^TH is non-singular; or $H^{\dagger} = H^T(H^TH)^{-1}$; providing HH^T is non-singular

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According to ridge regression theory, a positive value $\left(\frac{1}{\lambda}\right)$ is suggested to be add to the diagonal of HH^T or H^TH; which facilitates the resultant to be equivalent to ELM optimization solution with $\sigma_1 = \sigma_2 = p = q = 2$.

Hence, the optimal output weight and output function can be given as shown in Table 2.

Table 2. Output weight and output function formulation of ELM

Optimal Output Weight	Optimal Output Function
$\beta = H^T\left(1/\lambda + HH^T\right)^{-1} T$	$f(x) = h(x)\beta = h(x)H^T\left(1/\lambda + HH^T\right)^{-1} T$
$\beta = \left(1/\lambda + HH^T\right)^{-1} H^T T$	$f(x) = h(x)\beta = h(x)\left(1/\lambda + HH^T\right)^{-1} H^T T$

Experimentations, Results, and Discussions

A number of experimentations are performed to evaluate the proficiency of the proposed methodology in detection of PD, while in comparison with state-of-the-art techniques and standard learning systems. Publicly available dataset for Parkinson Disease are considered for the experimentation purpose. The performance of the proposed intelligent diagnostic system has been evaluated in terms of average accuracy, confusion matrix and ROC curve.

Dataset Description

Parkinson Dataset [source: UCI machine learning repository] (UCI Machine Learning Repository) (Mohamed, 2016)

The Parkinson dataset was created by Max Little of the University of Oxford, in collaboration with the National Centre for Voice and Speech, Denver, Colorado, who recorded the speech signals. The dataset is composed of a range of biomedical voice measurements from 31 people, 23 of which effected with PD. The motive of the dataset is to classify healthy people from the affected ones, with two classes, 0 (zero) denoting the healthy individuals while 1 (one) denotes the affected individual with PD. The attributes (columns) denotes a particular voice measure while each row denotes an individual, with a total of 195 individuals. The details of the attributes are given in Table 3.

It is obvious from the data description that the dataset comprises of two classes, namely healthy and affected individuals. Hence, from the perspective of data imbalance, measure of imbalanced cases is determined by Imbalance Ratio (IR), which is defined as follows:

$$IR = \frac{no.of\ majority\ patterns}{no.of\ minority\ patterns} \tag{31}$$

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Table 3. Attribute information of Parkinson dataset

Sl. No	Attributes	Information
1	name	ASCII subject name and recording number
2	MDVP:Fo(Hz)	Average vocal fundamental frequency
3	MDVP:Fhi(Hz)	Maximum vocal fundamental frequency
4	MDVP:Flo(Hz)	Minimum vocal fundamental frequency
5	MDVP:Jitter(%)	Several measures of variation in fundamental frequency
6	MDVP:Jitter(Abs)	
7	MDVP:RAP	
8	MDVP:PPQ	
9	Jitter:DDP	
10	MDVP:Shimmer	Several measures of variation in amplitude
11	MDVP:Shimmer(dB)	
12	Shimmer:APQ3	
13	Shimmer:APQ5	
14	MDVP:APQ	
15	Shimmer:DDA	
16	NHR	Two measures of ratio of noise to tonal components in the voice
17	HNR	
18	RPDE	Two nonlinear dynamical complexity measures
19	Spread1	
20	Spread2	
21	PPE	Pitch Period Entropy
22	D2	Recurrence Period Density Analysis
23	DFA	Signal fractal scaling exponent
	status	Health status of the subject (one) - Parkinson's, (zero) - healthy

The data imbalance (IR) in the dataset is obtained as **3.06** which can be considered as a case of moderately low data imbalance.

For clear depiction of various nomenclatures used in this paper, their respective notations are presented in Table 4.

Comparison With State-of-the-Art Data Pre-Processing Methods

As a part of the comparison analysis, the proposed methodology has been compared with six state-of-the-art techniques, proposed in (Yang & Gao, 2013). The performance of the proposed methodology has been evaluated in terms efficiency of the defined data pre-processing stage which offers treatment of overlapping cases, data imbalance, and data redundancy. The following data pre-processing methods are considered for comparison analysis:

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Table 4. Notations of nomenclatures

Model/Classifier	Technical Term/ Nomenclature	Notation
Classifier	Feed Forward Neural network	FFNN
	Support Vector Machine	SVM
	Naïve Bayes	NB
	Extreme Learning Machine	ELM
Model	Neighborhood Cleaning Rule	NCL
	Neighborhood Cleaning Rule+ Borderline Noise Factor	NCL+BNF
	One Sided Selection+ Tomek-link	OSS+TL
	One Sided Selection+ Borderline Noise Factor	OSS+BNF
	SMOTE+ Tomek-link	SMOTE+TL
	SMOTE+ Borderline Noise Factor	SMOTE+BNF
	Proposed model with FFNN classifier	Proposed+ FFNN
	Proposed model with SVM classifier	Proposed +SVM
	Proposed model with Naïve Bayes classifier	Proposed +NB
	Proposed model with ELM classifier	Proposed+ELM

- **Neighborhood Cleaning Rule (NCL):** The NCL methods works on the principle of Edited Nearest Neighbor (ENN) (More, 2016). ENN can be defined as an undersampling approach which eliminates majority instances on the context of K-Nearest Neighbors of different class.
- **NCL+BNF:** Borderline Noise Factor (BNF) defines the degree of remoteness of a borderline instance, based on its neighborhood. In (Yang & Gao, 2013), the concept of BNF is defined as an outlier detection approach to clean up the overlapping cases. In NCL+BNF method, undersampling of majority instances is performed by NCL technique, followed by BNF technique to detect and clean-up the outliers.
- **OSS+TL:** In OSS+TL, One-sided-selection (OSS) (Kubat & Matwin, 1997) technique is used to eliminate significant majority instances, followed by removal of noisy cases by Tomek-link pair detection. Cleaning up of outliers is achieved through noise (noisy instances) removal. The approach of OSS+TL is deployed in this chapter is same as in defined in (Yang & Gao, 2013).
- **OSS+BNF:** A hybrid of OSS and BNF is employed which provides to undersample the majority instances by using OSS method while outlier detection and elimination are achieved by using BNF. The mechanism of OSS+BNF is employed from (Yang & Gao, 2013).
- **SMOTE+TL:** Synthetic Minority Oversampling Technique (SMOTE) (Chawla *et al.,* 2002) facilitates to generate synthetic minority instances, and to rebalance the data space. SMOTE is integrated by Tomek-link (TL) method for treating the overlapping of classes. The SMOTE+TL approach discussed in (Yang & Gao, 2013) is deployed in this chapter.
- **SMOTE+BNF:** SMOTE is employed to reduce the imbalance ratio, while BNF is implemented to detect and clean-up the overlapping instances. The mechanism of SMOTE+BNF considered in this chapter is same as defined in (Yang & Gao, 2013).

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Parameter Settings

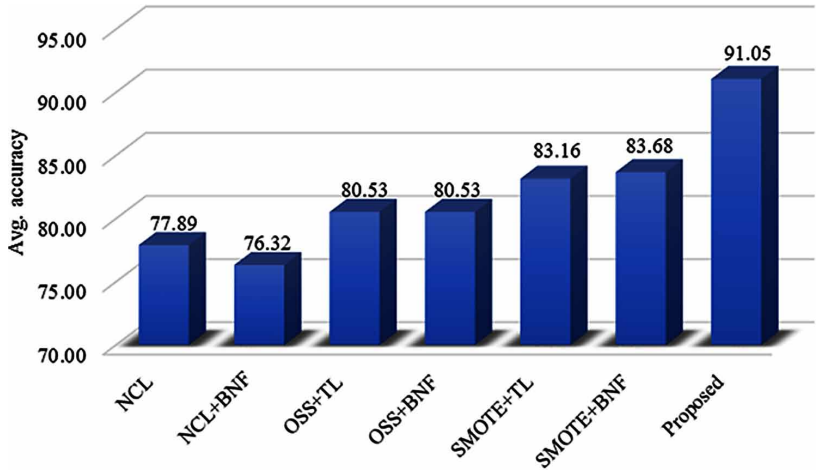
The various parameter settings for comparison analyses with the considered state-of-the art methods are discussed below*:*

1. *Threshold, t1*: The parameter, *t1* in BNF has defined a threshold for detecting overlapping instances, based on its estimated BNF-value. By experimenting, the best range of *t1*-values has been attained as [2.35-2.55], and the one yielding highest performance is considered for further experimentation. The K-NN estimation in BNF technique is performed for K=5.
2. For SMOTE algorithm, the K-NN estimation is performed for K=5.
3. For the proposed method, the K-NN estimation for detection of hard-to-classify outlier majority cases, is done for K=5. Typically, the value of K is considered to be an odd number, so as to detect maximum number of possible cases for hard-to-classify outlier majority instances, occurred in the overlapping zone.

Results and Discussions

The proposed method and the state-of-the-art techniques are validated with the Parkinson dataset, with ELM used as the learning model. Prior to testing, the data space is normalized by using Min-Max Normalization in the range [0, 1]. By performing 10-fold cross validation, the proposed model is validated with 10 independent training and testing sets of cases. The treatments of overlapping and imbalanced cases have been implemented with respect to each 10-fold. The average of 10-fold is considered as the concluding performance marker. Figures 5 presents the graphical representations of the average accuracies obtained for the proposed method and the considered state-of-the-art methods. By analyzing the experimental results, it is observed that the proposed method has outperformed the considered state-of-the-art methods in most of the cases.

Figure 5. Average accuracy graph of comparison analysis with state-of-the-art data pre-processing methods for ELM classifier



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It is observed from Figure 5 that the proposed data pre-processing method has outperformed the considered state-of-the-art data pre-processing techniques for effective detection of PD (accuracy: 91.05%). Analysis of the experimental scenario, the following conclusions can be drawn:

1. The proposed data pre-processing method performs well in case of datasets with low or moderately low IR. In such scenario, undersampling of majority instances is a good choice as it requires elimination of only less significant cases to achieve a balanced data distribution. The considered Parkinson dataset has a moderate IR of IR=3.06 which establishes this inference.
2. The proposed data pre-processing method is successful in minimizing the misdiagnosis rate in detection of PD, even in presence of similar/ overlapping cases of patients. The defined Abnormal Tomek Link (*ATL*) pair offers to eliminate the overlapping cases. *ATL* furnishes to eliminate the Tomek-link paired instances, with both the associating instance cases residing in overlapping zone, but not necessarily along the decision boundary; thus are completely insignificant from classification point of view.
3. The proposed method is effective in treating issues of data imbalance and data redundancy. In the proposed method, an adaptive undersampling strategy is employed which provides elimination of hard-to-classify majority cases followed by elimination of Normal Tomek-link (*NTL*) pairs with the aspects of redundancy and intra-cluster significance. It results the proposed model to perform well than the state-of-the art sampling techniques such as NCL, OSS and SMOTE. Detection of the hard-to-classify outlier majority cases provides to eliminate the instances with higher probabilities of misclassification from the overlapping zone. Moreover, it furnishes to reduce the size of the majority cases as well the size of the overlapping zone; thus treat the both the overlapping and imbalance cases and issues concurrently.

Comparison With State-of-the-Art Learning Models

As part of the comparison analysis, the proposed method of intelligent diagnostic system is evaluated with state-of-the-art learning models. The analytical results provide to yield the best paring of the proposed data pre-processing method, with considered four state-of-the-art learning models, which are as follows:

- Extreme Learning Machine (ELM) (Huang, Zhu, Siew, 2006) (Huang, Zhu, Siew, 2004)
- Feed Forward Neural Network (FFNN). (Siddiquee, Mazumder, Kamruzzaman, 2010)
- Support Vector Machine (SVM). (Fradkin & Muchnik, 2000)
- Naïve Bayes (NB). (Murphy,2006)

The classifiers considered are state-of-the-art in the domain of machine learning, used in many past and recent studies (Li *et al*., 2010) (Das *et al.,* 2013) (Krawczyk *et al*., 2016) (Nguyen *et al*., 2010). The proposed intelligent diagnostic system model provides a data pre-processing method which furnished to alter the prior probability of the classes during data pre-processing. Hence, for learning, a set of both of probabilistic (Naïve Bayes) and non-probabilistic (FFNN, SVM, ELM) classifiers is considered which can validate the proposed model in both the scenarios.

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Parameter Settings

1. Non-single hidden layered neural network has the fault of local minima. Hence, neural network model with single hidden layer is chosen, and the optimal network structure is determined by varying the number of neurons in the hidden layer. The number of neurons in the hidden layer for FFNN learner is varied in between (k+1) to 2k where k depicts number of inputs in the input layer. In the present study, "k" implies to number of attributes of the considered Parkinson dataset. With this consideration, the optimal architecture is obtained as 23-37-1, which is in the form of (input layer node- hidden layer node-output layer node). The parameter values which yield minimum training errors are selected.
2. Table 5 presents a statistics of different parameters used in SVM and Naive Bayes classification models. The optimal parameter settings are achieved through adjusting the learning models with varying parameter values and the parameter values which produce the highest average accuracy are taken for further experimentation.

Table 5. Parameter settings for SVM and naïve bayes classifiers

Classifier	Parameter Name	Value of the Parameter Considered
SVM	Kernel function	Gaussian Radial Basis function
	Method	Least squares (LS)
	Scaling factor(rbf_sigma)	1-10
Naïve Bayes	Distribution	Kernel, mvmn
	Prior	Empirical, Uniform

Results and Discussions

The objective of proposed intelligent diagnostic system is to effective early detection of PD. The proposed data pre-processing method offers to mend the case set against adversities of overlapping cases, data imbalance and data redundancy. The task of detecting PD involves some efficient learning mechanism with fast learning and more generalization capability. All these factors require defining a best learning platform. The proposed method is validated in terms of four learning models, to find out the best one, for a given experimental or clinical scenario. The result obtained is presented figure 6.

As shown in Figure 6, the experimental results obtained have manifest the efficiency of ELM learning model as compared to rest state-of-the-art learning models in early detection PD. As discussed earlier, the working principle of ELM offers to learn without hidden layer parameter tuning which is a prime step in FFNN learning model. Both ELM and FFNN learning models performed significantly well in PD detection (FFNN: 87.37%, ELM: 91.05%), while a low performance is achieved in case of Naïve Bayes classifier (accuracy: 77.89%). It is due to the fact of altering of the prior probabilities of the minority and majority cases due to the proposed data pre-processing technique. The performance of SVM classifier is found to be fairly good with the proposed data pre-processing method (accuracy: 84.74%). By analyzing the results, it can be concluded that the proposed method can efficiently detect PD, while employed in a non-probabilistic learning platform.

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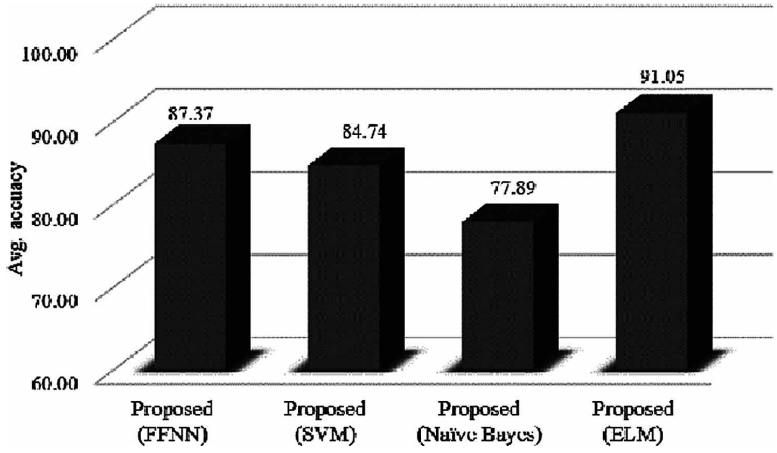
Figure 6. Average accuracy graph of the proposed method with respect to four learning models



Performance Analysis

A series of performance analyses tests is performed to evaluate the efficiency of the proposed method as well as the state-of-the art data pre-processing methods. Two well-known performance measures are considered, which are presented below:

Confusion Matrix

The confusion matrix contains information about actual and predicted classifications done by a classifier. Performance of such classifier is commonly evaluated using the data in the matrix. The confusion matrix for a binary class classifier is presented in table 6 (Sokolova, 2009).

Table 6. Confusion matrix for binary classifier

Data Class		Classified	
		Positive	**Negative**
Actual	**Positive**	TP	FN
	Negative	FP	TN

Based on the values of confusion matrix, a number of performance measures can be defined, some of which are considered in this chapter are presented in table 7 (Sokolova, 2009).

Receiver Operating Characteristics (ROC) Curve

ROC curve is a graphical plot that depicts the performance of a binary classifier with respect to its varying discrimination threshold. The ROC curve is formed by plotting False Positive Rate (FPR) along the x-axis and True Positive Rate (TPR) along the y-axis. The convergence of a ROC curve towards top-left corner of the ROC-space defines its proficiency. In table 4, the abbreviations of the legends, used in the ROC graphs are listed down.

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Table 7. Performance measures formulation from confusion matrix

Measure	Formulae
Precision	$\frac{TP}{TP+FP}$
Recall	$\frac{TP}{TP+FN}$
Specificity	$\frac{TN}{TN+FP}$
F-measure	$\frac{2 * precision * recall}{precision + recall}$
MCC	$\frac{TP \times TN - FP \times FN}{\sqrt{\left(TP+FP\right)\left(TP+FN\right)\left(TN+FP\right)\left(TN+FN\right)}}$
AUC	$\frac{1}{2} \times \left\{ \frac{TP}{TP+FN} + \frac{TN}{TN+FP} \right\}$

Performance Analysis With State-of-the-Art Data Pre-Processing Techniques

The performance analysis of the proposed method by using confusion matrix in comparison with the considered state-of-the-art data pre-processing techniques is presented table 8.

Table 8. Assessment of confusion matrix performance measures for data pre-processing techniques for ELM classifier

Methods	Precision	Recall	Specificity	F-Measure	MCC	AUC
Classifier: Feed Forward Neural Network						
NCL(ELM)	66.8333	82.9167	94.3736	70.5018	0.6424	0.8386
NCL+BNF(ELM)	48.1667	61.25	86.4962	51.6017	0.3837	0.719
OSS+TL(ELM)	61.8571	87.5	96.1635	67.1111	0.6255	0.8509
OSS+BNF(ELM)	60.4048	64.1667	89.5694	59.1313	0.5008	0.7545
SMOTE+TL (ELM)	72.3333	66.25	89.3957	65.9145	0.5913	0.787
SMOTE+BNF(ELM)	65.6667	68.75	89.9296	63.1612	0.5441	0.7896
Proposed(ELM)	98.75	97.5	99.375	97.9048	0.9734	0.9833

Through the analysis, it has been observed that the proposed method of data pre-processing has outperformed the considered state-of-the-art methods, for all performance measures considered. In case of the proposed method, higher precision and recall values are achieved for most of the cases than the considered state-of-the-art methods. Achievement of higher precision and recall values is a resultant of

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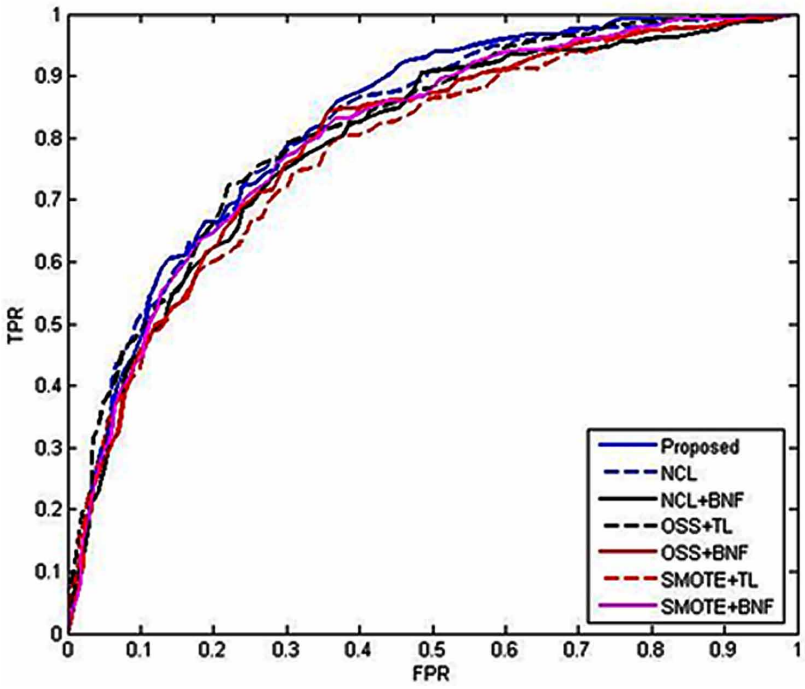
higher TP-values which infers increasing of minority case (detection of healthy individuals, in context of this chapter) classification rate. This in turn infers the reducing of misdiagnosis rate of healthy individuals as the affected ones, which is one of the objectives of this chapter. Moving over to F-measure, higher F-measure and specificity values are achieved for the proposed scheme as compared to the state-of–the-art techniques, which infers improving the minority case classification rate without hindering the classification rate of majority cases (i.e., detection of individuals with PD). The MCC values obtained lies in the range [0, +1] which infers accurate predictability of the proposed scheme. The AUC-value obtained for the proposed scheme is of higher range, i.e. (0.9833) than the state-of-the-art methods [0.70-0.85]. This establishes the efficiency of proposed scheme as compared to the considered methods, in terms of all test cases.

Figure 7 has presented the ROC curve based performance analysis assessment of the proposed method with the considered data pre-processing techniques. From the Figure 7, it can be seen that the ROC curve obtained for the proposed model is superior with an AUC of 0.9833, as compared to the rest of the techniques.

Figure 7. ROC graph plot of proposed method with data pre-processing techniques for ELM classifier



Performance Analysis With State-of-the-Art Data Learning Models

Table 9 has presented the performance analysis statistics of the proposed method in comparison with the state-of-the-art learning models.

The obtained performance analysis in table 9 has proven the pairing of proposed method with ELM to be most effective in early detection PD. The performance of the proposed method has been evaluated with four different learning platforms. As discussed earlier, the performance is elevated while working

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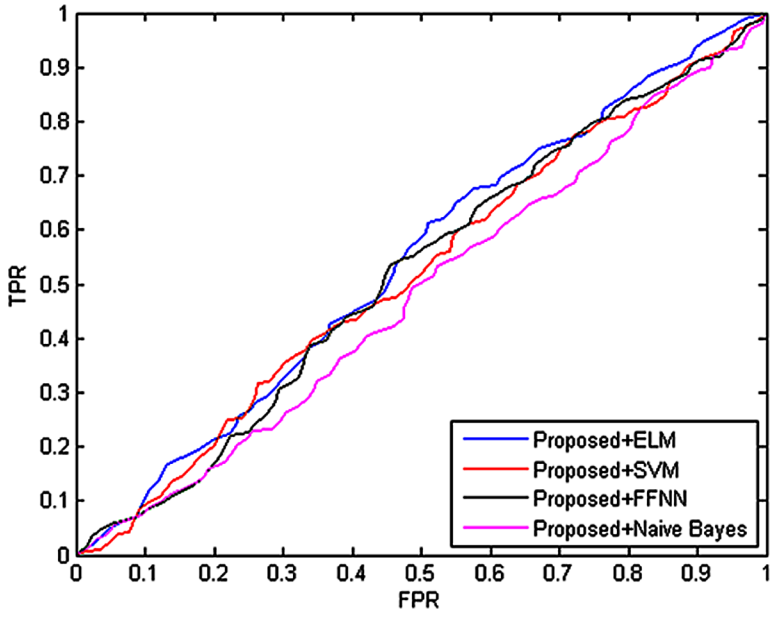
with a non-probabilistic classifier, with all the considered performance measures yielding higher values. In case of probabilistic classifier (Naïve Bayes), a relatively lower precision and recall values are achieved, which implies increasing of misdiagnosis rate of healthy individuals as the affected ones. Hence, it can be concluded that pairing of the proposed method with probabilistic classifier is not recommended for effective detection of PD.

Figure 8 has presented the ROC curve assessment of the proposed method with the considered learning models. It has been observed that from figure 8, that the combination of proposed method+ELM has outperformed the rest three pairings with learning models. The ROC plot for proposed method+ELM pairing has converged with an AUC-value of 0.9833, which infers its superiority over the rest. From the ROC-curve analysis, the pairing of the proposed method+ELM has the highest recommendation as the intelligent diagnostic system for detection PD.

Table 9. Assessment of confusion matrix performance measures for various learning models

Methods	Precision	Recall	Specificity	F-Measure	MCC	AUC
Proposed+FFNN	85.881	75.8333	91.3613	77.5326	0.7321	0.8724
Proposed+Naïve Bayes	50.0303	76.25	90.889	58.3857	0.4575	0.7743
Proposed+SVM	60.5635	80.4167	92.9391	67.6212	0.5858	0.8302
Proposed+ELM	98.75	97.5	99.375	97.9048	0.9734	0.9833

Figure 8. ROC graph plot of proposed method with standard learning models



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Recommendations

The intention of the proposed intelligent diagnostic system of PD is to offer adequate detection of PD, without compromising any life-value of the individuals. The detection of PD in an affected individual is as much crucial as to detect an individual without PD; as both the situations can be miserable on its opposite side. The proposed diagnostic system involves an advanced data pre-processing technique which offers to mine the case set, to solve the issues of similar/overlapping cases, data imbalance and data redundancy. The manual diagnosis system of PD is often subjective to the various underlying issues of clinical data. Based on the experimental results and performance analysis assessments, the proposed diagnostic system has been proven to be effective against the considered underlying issues of clinical data/ case sets. Hence, the proposed intelligent diagnostic system can be readily recommended for effective and early detection of PD.

FUTURE RESEARCH DIRECTIONS

As direction to future works, a few scopes are listed down below:

- The proposed intelligent diagnostic system can be extended in amalgamation with image processing techniques, to define visual-based diagnostic system.
- The proposed algorithm has not been validated against real-time clinical data, which requires advanced data mining tools, for data pre-processing. In extension of the proposed algorithm, it can be combined with feature extraction/ feature section techniques to extract the important clinical features for learning.
- The treatment of data imbalance and data redundancy can also be investigated through classifier-level solutions or ensemble learning techniques.

CONCLUSION

In this chapter, an intelligent diagnostic system for early detection of Parkinson's disease is proposed. Early detection of PD is much needed as most of the initial symptoms of PD often get unnoticed. By the time, it get diagnosed the loss of dopamine has progressed to a higher level, and PD become incurable. In modern medical science, biomarkers like DaTSCAN are available, which provides to assess the dopamine transporter in the brain through SPECT imaging. However, not many biomarkers are approved as they might hazardous to patient health and the surrounding environment. Clinical diagnosis of PD is effected by the underlying characteristics of patients' data, which come up with issues such similar/ overlapping cases of patients, data imbalance and data redundancy. Statistical techniques which can take up the raw clinical data to mine and then extract the hidden useful information for detection of PD are much of demand.

Through this chapter, the issues occurred during detection of PD in case of clinical diagnosis are discussed in details. An advanced data pre-processing method is proposed to which facilitates to detect the similar cases of patients so that misdiagnosis rate can be minimized. The concept of Tomek-link pair is redefined with respect to the proximity of its associating instance cases, in the overlapping or non-

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overlapping zone, to yield two sub-concepts, namely Abnormal Tomek-link (*ATL*) and Normal Tomek-link (*NTL*) pairs. Cleaning up of overlapping cases is achieved by *ATL* and sparse neighborhood estimation of majority outliers. *NTL* pairs are integrated with redundancy check and intra-cluster significance to obtain the most redundant and least significant noisy majority cases. The proposed method is validated with four standard learning models, so as to obtain the best paring of data pre-processing and learning method. ELM learning model is found to be most effective for learning during detection of PD. Based on the experimental results; the proposed method with ELM classifier is proven to be effective in early detection of PD. Through the proposed method, the authors have analyzed its effectiveness in various experimental scenarios, against all possible adversities. Both the experimental results and performance analysis assessments have manifested its proficiency in detection of PD, even in presence of similar/ overlapping cases, data imbalance and data redundancy.

With available past medical history records, the proposed diagnostic system can be readily used for detection of healthy/ affected individuals. There is no hardware cost associated while designing the proposed diagnostic system; hence it also feasible to be applied in low-budget maintained medical institutions or clinical diagnostic centers.

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KEY TERMS AND DEFINITIONS

Bradykinesia: Bradykinesia is a symptom of human motor-system that describes slow/difficulty moving of body parts (limbs/legs). It is one of the basic symptoms of Parkinsonism.

Central Nervous System: The central nervous system consists of the brain and spinal cord of the human body and is responsible for incorporating and coordinating activities among all the parts of human body.

Data Imbalance: Data imbalance defines a classification problem where the distribution of data is not even and leads to yield biased results with higher misclassification rate of the minority class data.

Dopamine: Dopamine is defined as a neurotransmitter, which is responsible for transmitting neural signals from the brain to the various body parts and organs.

Extreme Learning Machine: Extreme learning machine is a form of regularized feed-forward neural network without the need of hidden-layer parameter tuning. ELM is popular due to its high regularization ability and low execution time.

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One-Class SVM: One-class SVM is a classification model which provides to detect the novel instances, within a region of definite range. It is also known as ϑ-SVM, as its performance is influenced by the parameter, ϑ.

Overlapping Cases: The cases which have equal probability of belonging to the proximity of two regions are termed as overlapping cases. It is very difficult to distinguish the exact class of these cases.

Tomek-Link: Tomek-link defines the concept boundary pairs in a data distribution. When two instances, *a* and *b* are nearest of each-other, with *class (a)≠ class (b*); then the pair *(a,b)* is termed as Tomek-link pair. These pairs are noise-promoting in the data distribution.

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Chapter 17
Soft Computing-Based Early Detection of Parkinson's Disease Using Non-Invasive Method Based on Speech Analysis

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ABSTRACT

This chapter aims to use the speech signals that are a behavioral bio-marker for Parkinson's disease. The victim's vocabulary is mostly lost, or big gaps are observed when they are talking or the conversation is abruptly stopped. Therefore, speech analysis could help to identify the complications in conversation from the inception of the symptoms of Parkinson's disease in initial phases itself. Speech can be regularly logged in an unobstructed approach and machine learning techniques can be applied and analyzed. Fuzzy logic-based classifier is proposed for learning from the training speech signals and classifying the test speech signals. Brainstorm optimization algorithm is proposed for extracting the fuzzy rules from the speech data, which is used by fuzzy classifier for learning and classification. The performance of the proposed classifier is evaluated using metrics like accuracy, specificity, and sensitivity, and compared with benchmark classifiers like SVM, naïve Bayes, k-means, and decision tree. It is observed that the proposed classifier outperforms the benchmark classifiers.

INTRODUCTION

Parkinson's disease is caused by deteriorating condition of the central nervous system which primarily disturbs the motor function. The symptoms gradually start to appear as time progresses. Common symptoms in the beginning stage of Parkinson are reduced cognition, gait abnormality, decreased body movement, tightness of muscles or oscillating movement of some parts of the body. The brain starts

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getting affected as the disease starts progressing through advanced stage (Carroll et al., 2016). Mental disorder is yet another common behaviors exhibited by the Parkinson patients. The factor which influences the Parkinson disorder is quite mystery but it is assumed that both genes as well as the environment contributes to the development of the disorder (Lorraine and Anthony, 2015). There is high possibility for the family members to be affected by this disorder. People smoking tobacco and taking hot beverages might have reduced risk while those who suffer from injury in head or having exposure to pest control chemicals have high possibility of getting this disorder.

Periodic automated non-invasive early Parkinson's disease detection method could recover the life of the patients and avert higher treatment costs. This chapter aims to use the speech signals which is a behavioral bio-marker for Parkinson's disease. Although, Parkinson's disease detection could be performed based on psychological, cognitive and physiological bio-markers, speech and conversation will start getting affected from the initial stage onwards. The victim's vocabulary is mostly lost or big gaps are observed when they are talking or the conversation is abruptly stopped. Therefore, speech analysis could help to identify the complications in conversation from the inception of the symptoms of Parkinson's disease in initial phases itself. Speech can be regularly logged in an unobstructed approach and Machine Learning techniques can be applied and analyzed. The Parkinson's dataset from UCI repository is used for Parkinson's disease detection.

Fuzzy Logic based classifier is proposed for learning from the training speech signals and classifying the test speech signals. Brainstorm optimization algorithm is proposed for extracting the fuzzy rules from the speech dataset, which is used by fuzzy classifier for learning and classification. The performance of the proposed classifier is evaluated using metrics like accuracy, specificity and sensitivity and compared with benchmark classifiers like SVM, Naïve Bayes, k-Means and Decision Tree. It is observed that the proposed classifier outperforms the benchmark classifiers. Parkinson Disorder affects the communication of the patient (Smith & Caplan, 2018). This will lead to loss of control on speech and linguistic. The impairment of cognition and motor in open for more research opportunities. Even though several people are affected by this disorder, the symptoms exhibited are varying from one person to another. Diagnosing the disorder in the preliminary stage is vital for accurate remedy because it could extend the life span of the victim (Gupta et al., 2018). Even though several methods are existing for early diagnosis of the disorder, they are inefficient. It is highly necessary to diagnose the disease in early stage because, as the severity of the disorder progresses, it leads to other disabilities related to walking or even standing because the muscles get so rigid in the legs. Thus, analyzing the speech signals would be an effective means to diagnose the disorder in its preliminary stage. Recently, with the advent of sophistications in Artificial Intelligence techniques, automating the learning and analysis of speech signals would be on high expectations.

Amongst the learning mechanisms used by the Machine Learning algorithms, rule-based learning is gaining popularity amongst researchers. Especially in the recent years, biologically inspired optimization algorithms are frequently used for learning purpose. Swarm Intelligence based optimization algorithms like Particle Swarm Optimization, Ant Colony Optimization, Artificial Bee Colony, Bat optimization and so on are based on the swarm intelligence of simple agents like birds, ants, bees, bats and so on. But the brain storm optimization algorithm is based on the brain storming behavior of human beings. Since humans are superior to these small agents and that the cognitive behavior of humans are unique, Brain Storm Optimization algorithm is expected to perform better learning of rules for the Fuzzy System.

Fuzzy Logic classifiers have proven to be effective classifiers due to their ability to handle uncertainty and the much easier to understand Fuzzy rules. Thus, the biologically inspired learning algorithm

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coupled with Soft Computing technique like Fuzzy Logic classifier would be an ideal option to explore for analyzing the speech signals for detecting the Parkinson disorder.

LITERATURE REVIEW

Table 1 summarizes the related literature review of technique using Fuzzy classifier or Biological Inspired optimization algorithm for detecting Parkinson disorder. (Zhai et al., 2018) extended the Decision Tree to Rough Fuzzy Decision Tree from which Fuzzy rules for classification were derived and applied for Parkinson diagnosis based on voice biomarker. (Gupta et al., 2018) optimized the Cuttlefish algorithm and used it for feature selection from speech dataset from UCI repository. These features were then classified using knn and Decision Tree classifiers. Again, (Gupta et al., 2018) optimized the Crow Search Algorithm and applied to handwriting dataset and extracted the features which were then classified using Decision Tree, K-Nearest Neighbor and Random Forest models. (Ornelas-Vences et al., 2017) used the gait biomarker to measure the turning score using a Fuzzy Inference System. (Shrivastava et al., 2017) used the Modified Cuckoo Search Algorithm, Particle Swarm Optimization, Binary Bat algorithm and Genetic Algorithm to extract features from gait biomarkers. Neural Network was applied on the extracted features for Parkinson diagnosis. (Nilashi et al., 2016) used Principal Component Analysis on speech dataset for dimensionality reduction and applied Support Vector Regression and Adaptive Neuro-Fuzzy Inference System for Parkinson diagnosis. (Abiyev & Abizade, 2016) used Neural Network for feature extraction from voice dataset and clustered them using Fuzzy Inference System. (Chakraborty et al., 2016) used Fuzzy Inference System to diagnose Parkinson using voice dataset. (Liu et al., 2014) integrated Fuzzy Inference System to a tablet game for Parkinson diagnosis. (Chen et al., 2013) applied the Fuzzy based Neural Network on UCI voice data for Parkinson diagnosis. (Zuo et al., 2013) applied the Particle Swarm Optimization algorithm for feature selection on UCI voice data and used Fuzzy based Neural Network for Parkinson diagnosis.

From the literature review, it is evident that the utilization of Fuzzy Inference System or bio inspired optimization techniques have proven to improve the accuracy of classification. Hence a Fuzzy Logic based classifier in combination with a biologically inspired optimization algorithm is proposed in this chapter. Mamdani Fuzzy Inference System is used for classification. The rules and membership functions for the fuzzy inference system are designed using the Brain Storm Optimization, Shi (2011), algorithm which is a biological inspired optimization algorithm. Fuzzy Logic based classifier has the advantage of having interpretable rules and dealing with uncertainty. Brain Storm Optimization (BSO) algorithm is used because it has the advantage of searching based on human idea generation activity called as Brainstorming. Brainstorming is an activity where a group of people work together to propose the solution to a problem. Since the solution is a result of multiple ideas generated from human brain, it is believed to be more efficient. Moreover, when compared to other Swarm Intelligence algorithms like Ant Colony Optimization, Particle Swarm Optimization, Cuckoo Search and so on, Brain Storm Optimization algorithm is assumed to be superior. This is because, Ant Colony Optimization, Particle Swarm Optimization and Cuckoo Search algorithms are based on the group activity done by ants, birds and cuckoo respectively whereas Brain Storm Optimization is based on the brain storming activity of humans. Since, humans are considered to be superior in the hierarchy of the ecosystem, the Brain Storm Optimization is expected to perform superior to other optimization algorithm. On the other hand, the fuzzy inference system can perform well only if the rules and membership functions are robustly designed for it. Hence, the Brain

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Table 1. Literature review summary

Reference	Machine Learning Technique	Advantages
(Zhai et al., 2018)	Rough Set, Fuzzy Set, Decision Tree	Speed of learning is fast
(Gupta et al., 2018)	Crow Search Algorithm, Decision Tree, Random Forest, k-Nearest Neighbor	Reduced features, computational time, accuracy
(Gupta et al., 2018)	Cuttlefish Algorithm, Decision Tree, K-Nearest Neighbor	Optimal features, increased accuracy
(Ornelas-Vences et al., 2017)	Fuzzy Inference System	Scalable, interpretable knowledge
(Shrivastava et al., 2017)	Binary Bat Algorithm, Neural Network	Increased accuracy
(Nilashi et al., 2016)	Principal Component Analysis, Expectation Maximization, Adaptive Neuro-Fuzzy Inference System and Support Vector Regression	Improved accuracy
(Abiyev & Abizade, 2016)	Fuzzy clustering and Gradient Descent Learning algorithms	Improved accuracy
(Chakraborty et al., 2016)	Fuzzy C-Means Clustering, Fuzzy Inference System	Improved accuracy and efficiency
(Liu et al., 2014)	Fuzzy Logic	Better risk prediction
(Chen et al., 2013)	Fuzzy Logic, k-Nearest Neighbor	Improved accuracy, sensitivity, specificity
(Zuo et al., 2013)	Particle Swarm Optimization, Fuzzy k-Nearest Neighbor	Improved accuracy, sensitivity, specificity
(Polat, 2012)	Fuzzy c-Means Clustering, K-Nearest Neighbor	Improved accuracy

Storm optimization algorithm can be used to search for an optimal combination of membership function and rules that can increase the accuracy of classification of the Fuzzy Inference System.

The Brain Storm Optimization algorithm can help to design a robust rule base with rules having optimal length, size, precision and class variance and a robust membership function having optimal membership function type, count and parameters. Thus the combination of Fuzzy Inference System with biologically inspired algorithm, like Brain Storm Optimization algorithm, which has individually proven to be suitable for Parkinson detection in literature, can be expected to yield high accuracy and efficiency.

PROPOSED METHODOLOGY

The proposed methodology consists of two phases namely the training phase and test phase as shown in Figure 1. In the training phase, the training data is given to the Brain Storm Optimization algorithm. The Brain Storm Optimization algorithm searches for the optimal combination of rules and membership combination that suits the characteristics of the training data and that will yield the best accuracy of classification. Optimal rule base implies the rule base that has the optimal number of rules, with optimal number of attributes, with optimal matching of rules with the training dataset and optimally proportional number of rules for each target class. Optimal membership function implies the optimal

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membership function types that suits each attribute, optimal number of membership function for each attributes and the optimal parameter values for each membership function of the attributes. This is the output of the training phase. This learned model is applied to the test phase. In the test phase, the fuzzy inference system uses this optimal rule base and optimal membership functions to classify the test data. The fuzzy inference system consists of the fuzzyfier, defuzzyfier, rule base and the inference engine. The fuzzifier and the defuzzifier uses the membership functions derived in the training phase. The rule base derived in the training phase is used as the rule base for the fuzzy inference system.

The Brain Storm Optimization algorithm is tailored, as shown below, for the proposed methodology. The initial population in the Brain Storm Optimization algorithm is called as an idea. The initial ideas in the proposed format along with the configuration inputs and the fitness function tailored for the proposed methodology is given as input to the Brain Storm Optimization algorithm. The initial ideas are clustered and the idea having the highest fitness value in the cluster is made as the center of cluster. Then using some predefined probabilities, some weak ideas are chosen and they are replaced with new ideas. This process is repeated until the optimal idea is generated or until the termination criteria is satisfied.

```
Inputs : Parkinson Training dataset
Output : Optimal rule base and membership function for Fuzzy System
Procedure:
Begin
      Initialize the initial ideas in the proposed format
      Cluster the ideas
      Repeat
            Evaluate fitness of ideas using the proposed fitness function for
rule base and membership function design
            Generate new ideas
            Replace bad ideas with good ones
      Until termination criteria
      Return the optimal idea
End
```

The initial idea, shown in Figure 2, is formatted as per the requirement suitable for the proposed methodology. The idea is a vector consisting of two parts. The first part represents the rules and second part represents the membership function. The first part consists of 1+(n*r) elements, where 'r' indicates the number of rules and 'n' indicates the number of attributes in the dataset. The 'n' elements of each rule consists of the membership index of the corresponding variable. If a variable is not included in the rule, then the corresponding element in the vector is represented by -1. The first element indicates the number of rules. Second to [1+(n*r)] contains all 'n' attributes of all 'r' rules. The 'n' attributes or each rule consists of the (n-1) attributes and the class attribute. The value of the elements from second to [1+(n*r)] contains the membership index of the corresponding variable. The index of the membership function indicates the linguistic term associated with the corresponding variable. This index can range from 1 to #MF which determines the number of membership function for each variable. A sample rule is given in the below figure. It says 1,2,2 which means that there are three variables in the dataset, including the class variable. If the first variable is LOW and second variable is HIGH then the class variable is HIGH. This is the meaning if 1,2,2. If a particular variable need not be included in the rule then it can

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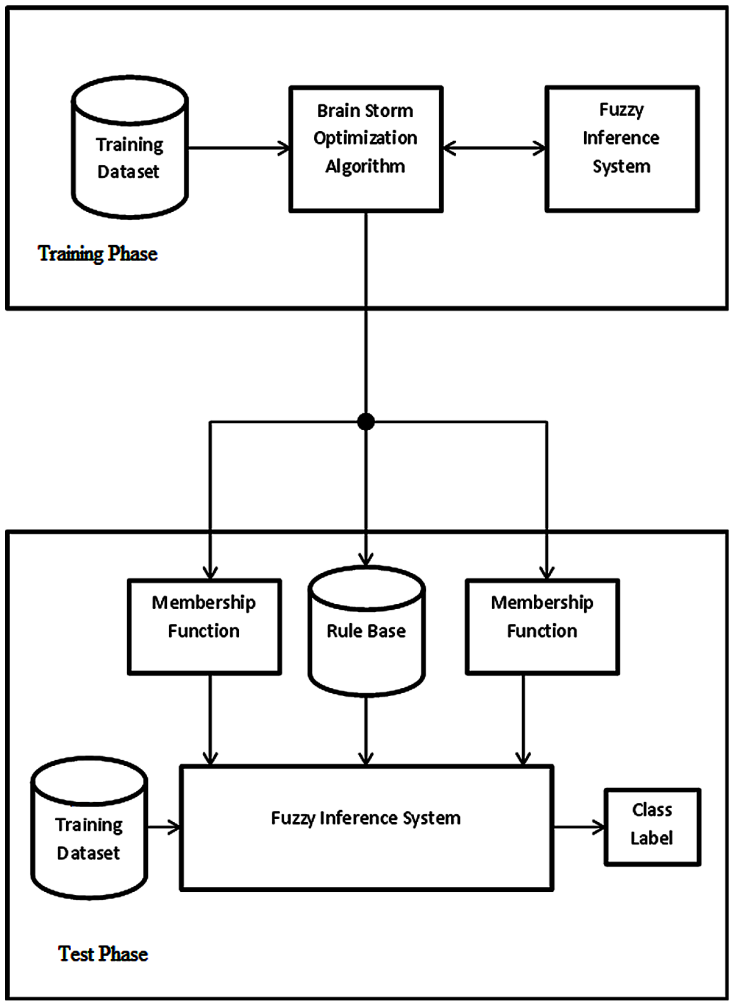
Figure 1. Proposed Methodology



be mentioned by -1. Say for example, 1,-1,1 indicates that, if first variable is LOW then class variable is LOW invariable of the second attribute. The second half of the idea vector represents the membership function design. It consists of 14*n elements. Out of the 14 elements, first element represents the type of membership function. There are several types of membership functions like triangular membership function, trapezoidal membership function, sigmoidal membership function, Gaussian membership function, Gaussian bell membership function, and so on. These membership functions take atmost four parameters. Upto there membership functions are allowed for each attribute. Hence, we need twelve elements to represent the four parameters of all three membership functions. In addition to these twelve elements, there are the first to elements which indicates the membership function type and the number of membership function. Hence there are totally fourteen elements for each attribute. Second element represents the number of membership function and the remaining 12 elements represents the parameters for a maximum of 3 membership functions. Hence for each of the 'n' attributes, there will be (14*n) elements. Thus, in the second part, [1+(n*r)]+1 to [1+(n*r)]+14 holds the membership function information of a single attribute. Thus for 'n' attributes the total number of elements will be [1+(n*r)]+(14*n).

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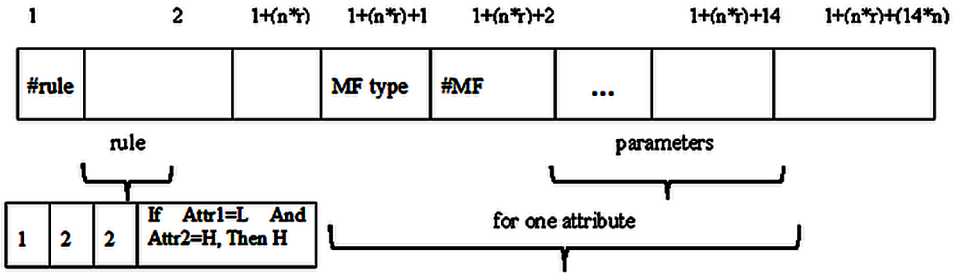
Figure 2. Idea format



Equation (1) shows the formulation of fitness function for the rule base generated using Brain Storm Optimization algorithm based on the proposed methodology. The fitness function is based on the length of the rule and the correlation of the rule with the dataset. Since rules with lesser length are preferred, the fitness value is inversely proportional to the length of the rule. Since the rules matching the characteristics of data is preferred, fitness of the rule is directly proportional to the preciseness of the rule. The average of two parts are taken to normalize the fitness value in the range of 0 to 1. In the below equation, 'n' indicates the number of attributes, 'r' indicates the number of rules, 'L' indicates the total length of the rules, 'm' indicates the number of instances in the dataset and 'M' indicates the total number of attributes in the rule that matches the dataset. 'L' the total length of the rules is the sum of number of significant attributes in each rule. The denominator in the first half indicates the total number of attributes in all the rule which are both significant as well as insignificant. Hence it is represented by the product of 'n' the number of attributes and 'r' the number of rules. Thus the ration of 'L' and (n*r) will give the significance of the number of attributes in each rule. But since this has to be minimized to have efficient rule base, it is subtracted from 1. 'M' indicates the sum of number of records that each rule matches the dataset. The denominator in the second half indicates the product of number of records and the number of rules in the dataset. Thus the ration of numerator and denominator gives the significance of degree of matching of each rule with the dataset. This ratio has to be maximum to achieve better rules. The average of both the ratios yields the optimal fitness function for the membership function.

$$\mathbf{F} = 0.5 * \left[\left(1 - \frac{\mathbf{L}}{\mathbf{n} * \mathbf{r}} \right) + \left(\frac{\mathbf{M}}{\mathbf{r} * \mathbf{m}} \right) \right] \tag{1}$$

DATASET

The Parkinson's dataset. Little et al. (2007), from UCI repository is used for Parkinson's disease detection. It consists of a collection of voice measurements of thirty-one people, out of which twenty-three were suffering with Parkinson's disease. There are around six recordings per patient totaling about 195 voice recording. The primary objective of this data is to differentiate healthy people from those with Parkinson's disease, according to status attribute which is set as 1 for Parkinson's disease and 0 otherwise. The proposed methodology is compared with benchmark Machine Learning algorithms like Support

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Vector Machine, Naïve Bayes, k-Means and Decision Tree. Accuracy, Specificity and Sensitivity are used as the comparison metrics.

Results

Equations (2), (3) and (4) shows the formulae for accuracy, specificity and sensitivity. Accuracy is the ratio of number of correctly diagnosed patients to the total number of patients who have undergone the diagnosis. In other words, it is the ratio of sum of true positive and true negative to the sum of true positives, true negatives, false positives and false negatives. Specificity, also called as the true negative rate, is defined as the ratio of true negative to the sum of true negatives and false positives. Sensitivity, also called as the true positive rate, is defined as the ratio of true positive to the sum of true positives and false negatives. Here, True positive is defined as the number of disorder patients diagnosed as disorder patients. False positive is defined as the number of normal patients wrongly diagnosed as disorder patients. True negative is defined as the number of normal patients diagnosed as normal patients. False negative is defined as the number of disorder patients wrongly diagnosed as normal patients.

$$\mathbf{Accuracy} = \frac{\mathbf{TP} + \mathbf{TN}}{\mathbf{TP} + \mathbf{TN} + \mathbf{FP} + \mathbf{FN}} \tag{2}$$

$$\mathbf{Specificity} = \frac{\mathbf{TN}}{\mathbf{TN} + \mathbf{FP}} \tag{3}$$

$$\mathbf{Sensitivity} = \frac{\mathbf{TP}}{\mathbf{TP} + \mathbf{FN}} \tag{4}$$

DISCUSSION

Table 2 compares the performance of the algorithms with the metrics and the same has been plotted in Figure 3, Figure 4 and Figure 5. It is evident from the graphs that the proposed Fuzzy Inference System with the Brain Storm Optimization algorithm outperforms Parkinson disorder detection implemented using benchmark algorithms like Support Vector Machine, Naïve Bayes, k-Means and Decision Tree.

Table 2. Performance Comparison

Machine Learning Technique	Accuracy (%)	Specificity (%)	Sensitivity (%)
NB	70	65	71
SVM	84	75	70
k-Means	78	75	80
Decision Tree	81	65	80
Proposed Methodology	86	81	85

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Figure 3. Accuracy Comparison

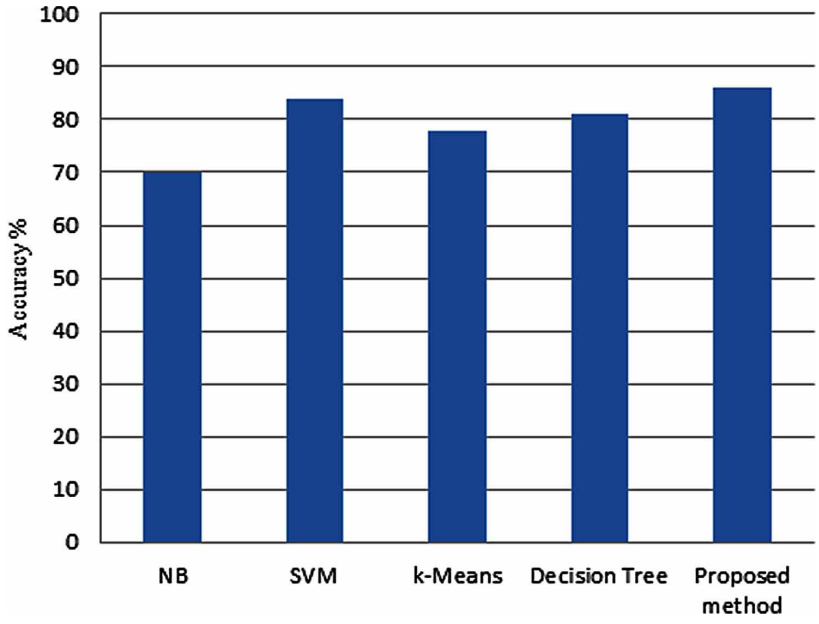

Figure 4. Specificity Comparison

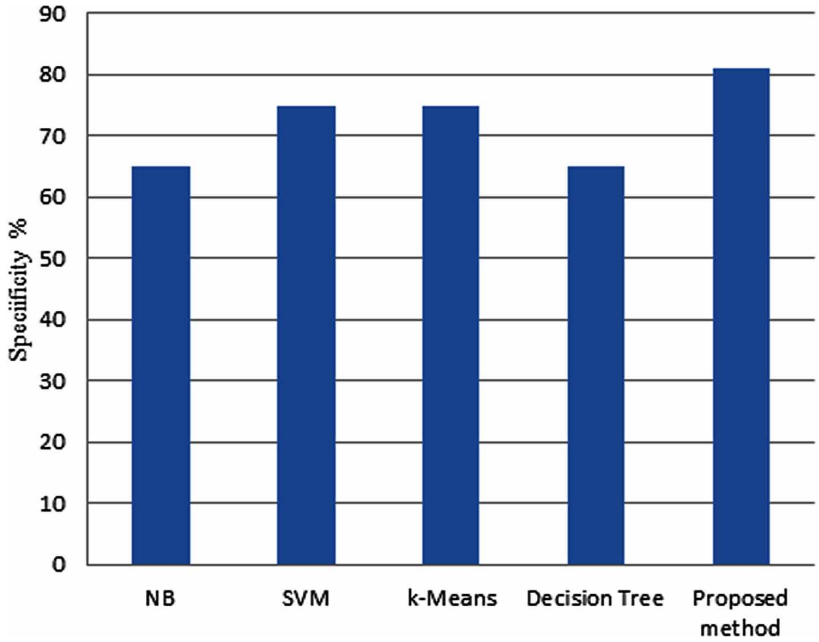

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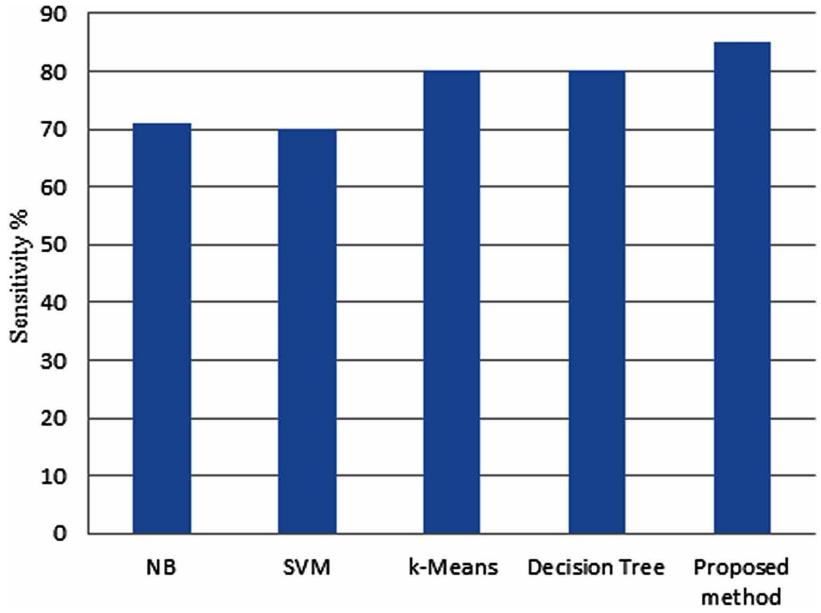
Figure 5. Sensitivity Comparison



From Table 2, it is observed that, the accuracy of Naïve Bayes classifier, Support Vector Machines classifier, k-Means classifier, Decision Tree classifier and the proposed Soft Computing based classifier are 70%, 84%, 78%, 81% and 86% respectively. Similarly, the specificity of Naïve Bayes classifier, Support Vector Machines classifier, k-Means classifier, Decision Tree classifier and the proposed Soft Computing based classifier are 65%, 75%, 75%, 65% and 81% respectively. Similarly, the sensitivity of Naïve Bayes classifier, Support Vector Machines classifier, k-Means classifier, Decision Tree classifier and the proposed Soft Computing based classifier are 71%, 70%, 80%, 80% and 85% respectively. Hence, it is evident that the proposed Fuzzy Inference System with the Brain Storm Optimization algorithm outperforms Parkinson disorder detection implemented using benchmark algorithms like Support Vector Machine, Naïve Bayes, k-Means and Decision Tree.

CONCLUSION AND FUTURE SCOPE

This chapter uses the speech signals which is a behavioral bio-marker for Parkinson's disease. Although, Parkinson's disease detection could be performed based on psychological, cognitive and physiological bio-markers, speech and conversation will start getting affected from the initial stage onwards. The victim's vocabulary is mostly lost or big gaps are observed when they are talking or the conversation is abruptly stopped. Therefore, speech analysis will help to identify the complications in conversation from the inception of the symptoms of Parkinson's disease in initial phases itself. Speech can be regularly logged in an unobstructed approach and Machine Learning techniques can be applied and analyzed. The Parkinson's dataset from UCI repository is used for Parkinson's disease detection. Fuzzy Logic based classifier is proposed for learning from the training speech signals and classifying the test speech signals. Brainstorm optimization algorithm is proposed for extracting the fuzzy rules and membership function from the

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speech dataset, which is used by fuzzy classifier for learning and classification. The performance of the proposed classifier is evaluated using metrics like accuracy, specificity and sensitivity and compared with benchmark classifiers like SVM, Naïve Bayes, k-Means and Decision Tree. It is observed that the proposed classifier outperforms the benchmark classifiers. The proposed methodology can be extended from voice intensity data to speech semantics data. The speech can be recorded and feature extraction algorithms can be applied to extract the semantic features from speech and the proposed method can be applied on it for Parkinson detection.

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Chapter 18
Tremor Identification Using Machine Learning in Parkinson's Disease

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ABSTRACT

Tremor is an involuntary quivering movement or shake. Characteristically occurring at rest, the classic slow, rhythmic tremor of Parkinson's disease (PD) typically starts in one hand, foot, or leg and can eventually affect both sides of the body. The resting tremor of PD can also occur in the jaw, chin, mouth, or tongue. Loss of dopamine leads to the symptoms of Parkinson's disease and may include a tremor. For some people, a tremor might be the first symptom of PD. Various studies have proposed measurable technologies and the analysis of the characteristics of Parkinsonian tremors using different techniques. Various machine-learning algorithms such as a support vector machine (SVM) with three kernels, a discriminant analysis, a random forest, and a kNN algorithm are also used to classify and identify various kinds of tremors. This chapter focuses on an in-depth review on identification and classification of various Parkinsonian tremors using machine learning algorithms.

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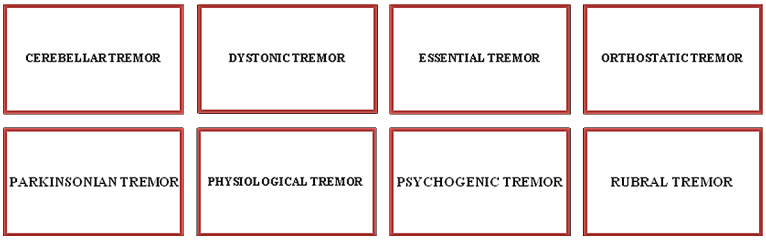
INTRODUCTION

Tremor and Its Classifications

An involuntary action which is rhythmic is known as tremor which is caused by either alternating or synchronous contractions of antagonistic muscles. It is movement of muscle contraction and relaxation involving twitching movements of one or more body parts. It affects the hands, arms, eyes, face, head, vocal folds, trunk, and legs. Tremor is the most common of all movement disorders, which occurs in most normal individuals in the form of physiologic tremor (Hallett, 1991).

Figure 1. Types of tremor



Tremor is most commonly classified by clinical features, cause or origin. Figure 1 shows the various types of tremors.

- **Cerebellar Tremor (Intention Tremor):** It is a slow, broad tremor of the extremities that occurs at the end of any kind of body movement, such as trying to press a button or touching a finger to the tip of one's nose. It is mostly caused by lesions in or damage to the cerebellum resulting from stroke, tumor, or disease such as multiple sclerosis or any degenerative disorder. It can also result from chronic alcoholism or overuse of some medicines. The tremor is often most prominent when the affected person is active or is maintaining a particular posture. Cerebellar tremor may be accompanied by other manifestations of ataxia, including speech problems, rapid, involuntary rolling of the eyes, gait problems (Elble, 2017).
- **Dystonic Tremor:** It occurs in individuals of all ages who are affected by dystonia. Dystonia is a movement disorder in which sustained involuntary muscle contractions cause twisting and repetitive motions followed by painful and abnormal postures. Dystonic tremor may affect any muscle in the body and is seen most often when the patient is in a certain position or moves a certain way. It occurs irregularly and often can be relieved by complete rest. Touching the affected body part or muscle may reduce tremor severity (Elble, 2017).
- **Essential Tremor**: It is of the most common type of tremor. Although the tremor may be mild and non-progressive in some people, but it is slowly progressive, starting on one side of the body and gradually affecting both sides. The hands are most often affected body part. Other parts like the head, voice, tongue, legs, and trunk may also be involved in some cases. Mild gait disturbance is also a symptom in essential tremor. Tremor frequency may decrease as the person ages, but the severity may increase, affecting the person's ability to perform certain tasks or activities of daily

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living. Heightened emotion, stress, fever, physical exhaustion, or low blood sugar increases their severity. Onset is most common after age 40, although symptoms can appear at any age (Elble, 2017).

- **Orthostatic Tremor:** It is characterized by fast rhythmic muscle contractions that occur in the legs and trunk immediately after standing. Cramps are felt in the thighs and legs and the patient may shake uncontrollably when asked to stand in one spot. The high frequency of the tremor often makes the tremor look like rippling of leg muscles while standing. Orthostatic tremor may also occur in patients who have essential tremor, and there might be an overlap between these categories of tremor(Elble, 2017).
- **Parkinsonian Tremor:** It is caused by damage within the brain that controls the body movement. This resting tremor is often a precursor to Parkinson's disease but can also be seen in other movement disorders. The tremor, which is classically seen as a "pill-rolling" action of the hands that may also affect the chin, lips, legs, and trunk. This kind of tremor increases by stress or emotion. Onset is generally after age 60. Movement starts in one limb or on one side of the body and usually progresses to include the other side of the body(Marjama-Lyons & Koller, 2000).
- **Physiological Tremor**: It occurs in every normal individual and has no clinical significance. It is rarely visible and may be increased by strong emotion, physical exhaustion, hypoglycemia, hyperthyroidism, heavy metal poisoning, stimulants, alcohol withdrawal or fever. It can be seen in all voluntary muscle groups and can be detected by extending the arms and placing a piece of paper on top of the hands (Elble, 2017).
- **Psychogenic Tremor**: It can occur at rest or during postural or kinetic movement. The characteristics of this kind of tremor may vary but generally include sudden onset and remission, increased incidence with stress. Many patients with psychogenic or another psychiatric disease(Elble, 2017).
- **Rubral Tremor:** It is characterized by slow tremor which is present at rest, at posture and with intention. This tremor is associated with conditions which affect the red nucleus in the midbrain (Elble, 2017).

Figure 2 shows a person having tremor on his hand and leg.

Biological Significance of Tremor

Tremor is associated with disorders in those parts of the brain that control muscles throughout the body or in particular areas, such as the hands or legs. Neurological disorders or conditions that can produce tremor include multiple sclerosis, stroke, traumatic brain injury, chronic kidney disease and a number of neurodegenerative diseases that damage or destroy parts of the brainstem or the cerebellum. Parkinson's disease being the one most often associated with tremor (Louis, 2014).

Other causes of tremor include the use of drugs or alcohol. Tremors can also be seen in infants with sphenylketonuria (PKU), overactive thyroid or liver failure. Tremors can be an indication of hypoglycemia, along with palpitations, sweating and anxiety. It can also be caused from lack of sleep, lack of vitamins, or increased stress. Deficiencies of magnesium and thiamine have also been known to cause tremor. Some forms of tremor are inherited in families, while others have no known cause. Characteristics may include a rhythmic shaking in the hands, arms, head, legs, or trunk; shaky voice; and problems holding things such as a fork or pen (Stein & Oğuztöreli, 1976).

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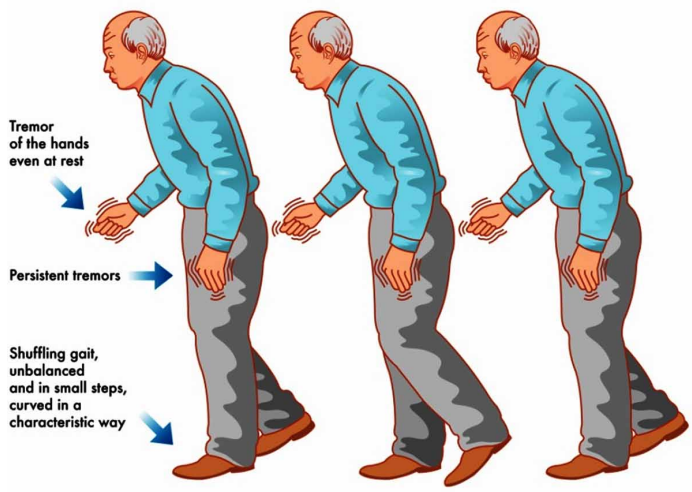
Figure 2. Tremor on hand and leg



Tremor may occur at any age but is most common in middle-age and older persons. It may be occasional, temporary, or occur intermittently which affects men and women equally.

Tremors Can Result From

- Alcoholism, excessive alcohol consumption, or alcohol withdrawal can kill certain nerve cells, resulting in a tremor known as asterixis. Conversely, small amounts of alcohol may help to decrease familial and essential tremor, but the mechanism behind it is unknown.
- Tremor in peripheral neuropathy may occur when the nerves that supply the body's muscles are traumatized by injury, disease, abnormality in the central nervous system, or as the result of systemic illnesses. Peripheral neuropathy can affect the whole body or certain areas, such as the hands, and may be progressive. Resulting sensory loss may be seen as a tremor or ataxia of the affected limbs and problems with gait and balance.
- Clinical characteristics may be similar to those seen in patients with essential tremor.
- Tobacco withdrawal symptoms also include tremor.

PARKINSON'S DISEASE (PD) AND ITS SYMPTOMS

PD and Its Causes

Parkinson's disease (PD) is a neurodegenerative disorder that affects people over 60 years of age in industrialized countries. It is a progressive disorder that causes motor dysfunctions: involuntary and oscillatory movements (tremor), slowness of movements (bradykinesia), increased muscle tone (rigidity) and postural instability. A common type of Parkinsonian tremors is rest tremor but also postural, kinetic and intention tremors have been reported. According to current diagnostic criteria, patients can be considered to have PD when they have two of the four symptoms of PD (tremor, bradykinesia, rigidity

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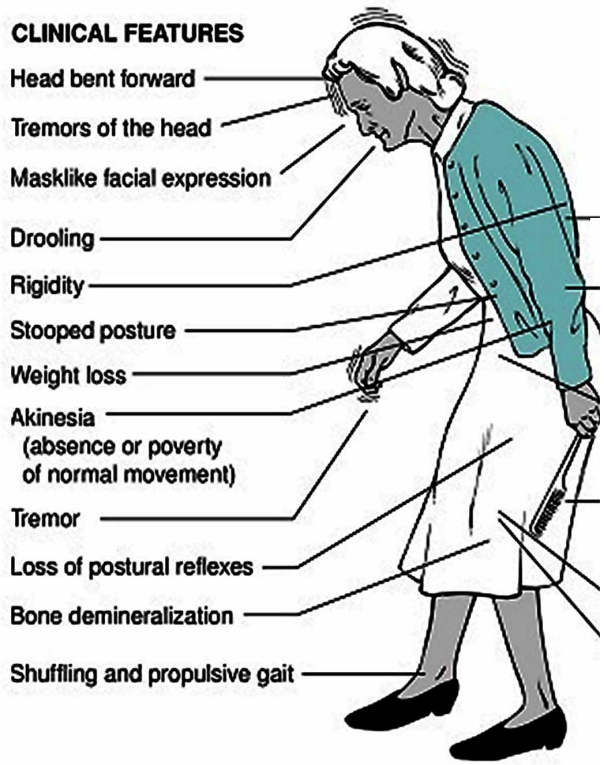
and postural instability). Although these dysfunctions can be assessed by electromyography, it is still used rarely in the clinical evaluation of PD (Checkoway & Nelson, 1999).

Parkinson's disease occurs when nerve cells, or neurons, in the brain die or become impaired. Although many brain areas are affected, the most common symptoms result from the loss of neurons in an area near the base of the brain called the substantia nigra. Normally, the neurons in this area produce an important brain chemical known as dopamine. Dopamine is a chemical messenger responsible for transmitting signals between the substantia nigra and the next "relay station" of the brain, the corpus striatum, to produce smooth, purposeful movement. Loss of dopamine results in abnormal nerve firing patterns within the brain that cause impaired movement (Bunting-Perry, 2006).

Figure 3. Person suffering from PD (Ejlerskov, 2015)



Genetic Factors

Scientists have identified several genetic mutations associated with PD, including the alpha synuclein gene, and many more genes have been tentatively linked to the disorder. Studying the genes responsible for inherited cases of PD can help researchers understand both inherited and sporadic cases. The same genes and proteins that are altered in inherited cases may also be altered in sporadic cases by environmental toxins or other factors. Researchers also hope that discovering genes will help identify new ways of treating PD (Surathi, Jhunjhunwala, Yadav, & Pal, 2016).

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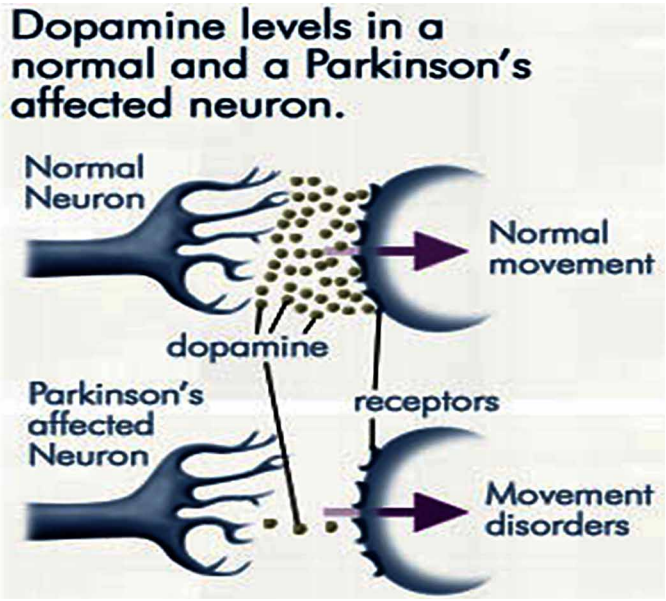
Figure 4. Dopamine levels (Medications, 2016)



Environmental Factors

Exposure to certain toxins has caused PD symptoms in rare circumstances (such as exposure to MPTP, an illicit drug, or in miners exposed to the metal manganese). Other still unidentified environmental factors may also cause PD in genetically susceptible individuals (Surathi et al., 2016).

Symptoms of PD

Motor Symptoms

- **Bradykinesia:** Bradykinesia means "slow movement." A defining feature of Parkinson's, bradykinesia also describes a general reduction of spontaneous movement, which can give the appearance of abnormal stillness and a decrease in facial expressivity. Bradykinesia causes difficulty with repetitive movements, such as finger tapping (Chapuis, Ouchchane, Metz, Gerbaud, & Durif, 2005).
- **Rigidity:** Rigidity causes stiffness and inflexibility of the limbs, neck and trunk. Muscles normally stretch when they move, and then relax when they are at rest (Chapuis et al., 2005).
- **Tremor:** Tremor, or shaking, often in a hand, arm, or leg, occurs when you're awake and sitting or standing still (resting tremor), and it gets better when you move that body part (Chapuis et al., 2005). Tremor is often the first symptom that people with Parkinson's disease or their family members notice.
- **Postural Instability:** One of the most important signs of Parkinson's is postural instability, a tendency to be unstable when standing upright (Chapuis et al., 2005).

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Non-Motor Svymptoms

- **Neuropsychiatric:** Neuropsychiatric symptoms are common in Parkinson's disease, even at the earliest stages, and have important consequences for quality of life and daily functioning, are associated with increased care burden and increased risk for nursing home admission (Factor et al., 2003).
- **ICDs**: Impulse control disorders (ICDs), specifically those related to excessive gambling, eating, sex and shopping, have been observed in a subset of people with Parkinson's disease (PD) (Factor et al., 2003).
- **Sleep Disorder**: Sleep disorders in Parkinson's disease (PD) are frequent and have numerous etiologies. Both nighttime sleep disturbances and daytime sleepiness can occur (Wilcox, 2010).
- **Autonomic Dysfunction**: Autonomic nervous system dysfunction symptoms in PD include sexual dysfunction, swallowing and gastrointestinal disorders, bowel and bladder abnormalities, and derangements of cardiovascular regulation, particularly, orthostatic hypotension (Wilcox, 2010).
- **Sensory**: Nineteen of 50 Parkinson patients had sensory complaints of numbness, coldness, burning, or pain. There was no objective sensory loss, and sensory symptoms did not correlate with specific motor or autonomic signs (Wilcox, 2010).

LITERATURE REVIEW

The literature review is shown in Table 1.

PROBLEM DEFINITION AND A WAY TOWARDS SOLUTION

Identification of tremor using an automated or computing system is a bit of difficult process. The following problems are the basic and common nature of identifying the tremor.

The Non-Linear Nature of Each Case

Each human body has the unique nature of itself by which we can differentiate the each and every person even classifying a small sector like retina or fingerprint of whole body. This unique nature also has been seen in the symptoms level for each person. Each tremor level associated with Parkinson's disease is unique in nature for each person. This is the non linear nature of the problem while identifying tremor and this type of problem leads us to find the solution in Non-deterministic algorithm.

Common Symptoms Hazards

In some particular survey it was found that tremor is a common symptom for near about 14 different neurological disorders both in acute and chronic types. Not only tremors but also there are 22 different symptoms including tremor are common in these 14 types of individual neuronal disorder like Parkinson's disease, Huntington disease, Alzheimer's disease, PANDAS etc. So classification of the tremor for identifying PD is also very difficult in this aspect (Chen, Garcia, Huang, & Constantini, 2014).

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Table 1.

AUTHOR	YEAR	CONTRIBUTION
Enas Abdulhay. et al	2018	They proposed a machine learning algorithm to diagnose PD using the gait analysis. Various gait features were extracted using the peak detection and pulse duration. An average accuracy of 92.7% was achieved for the diagnosis of PD from gait analysis (Abdulhay, Arunkumar, Narasimhan, Vellaiappan, & Venkatraman, 2018).
Taigo Italo Pedrosa. et al,	2018	Proposed two predictive models using a supervised machine learning approach. These model classify the Parkinson disease's rest tremor between high or low frequencies, showing the intensity of Parkinson's motor symptom. They applied leave-one-out cross-validation methods to classify the level of the PD tremor and reached a classification accuracy of 92.8% (Pedrosa, Vasconcelos, Medeiros, & Silva, 2018).
Hyoseon Jeon. et al	2017	They worked to maximize the scientific validity of automatic tremor-severity classification using machine learning algorithms to score Parkinsonian tremor severity in the same manner as the unified Parkinson's disease rating scale (UPDRS) used to rate scores in real clinical practice. The optimal feature configuration was decided using the wrapper feature selection algorithm or principal component analysis, and decision tree, support vector machine, discriminant analysis, and *k*-nearest neighbor algorithms are considered to develop an automatic scoring system for UPDRS prediction. The highest accuracies are 92.3%, 86.2%, 92.1%, and 89.2% for resting, resting with mental stress, postural, and intention tremors, respectively (Jeon et al., 2017).
Bjoern M. Eskofier. et al	2016	They focused on the detection of bradykinesia in PD. For this, they compared standard machine learning pipelines with deep learning based on convolutional neural networks. Results showed that deep learning outperformed other state-of-the-art machine learning algorithms by at least 4.6% in terms of classification rate(Eskofier et al., 2016).
Andrea Cherubini. et al	2014	Distinguished patients who had tremor-dominant Parkinson's disease (tPD) from those who had essential tremor with rest tremor (rET). They combined voxel-based morphometry-derived gray matter and white matter volumes and diffusion tensor imaging-derived mean diffusivity and fractional anisotropy in a support vector machine (SVM) to evaluate 15 patients with rET and 15 patients with tPD. SVM classification of individual patients showed that no single predictor was able to fully discriminate patients with tPD from those with rET. By contrast, when all predictors were combined in a multi-modal algorithm, SVM distinguished patients with rET from those with tPD with an accuracy of 100% (Cherubini et al., 2014).
S.Gokul. et al	2013	Proposed the application of a Fully Complex-Valued Radial Basis Function network (FC-RBF), Meta-Cognitive Fully Complex-Valued Radial Basis Function network (Mc-FCRBF) and Extreme Learning Machine (ELM) for the prediction of Parkinson's disease. With the help of Unified Parkinson's Disease Rating Scale (UPDRS), the severity of the Parkinson's disease is predicted and for untreated patients, the UPDRS scale spans the range (0-176). The result indicated that the Mc-FCRBF network has good prediction accuracy than ELM and FC-RBF network (Gokul, Sivachitra, & Vijayachitra, 2013).
N.D. Darnall. et al	2012	Compared the accuracy of various data analysis techniques to quantify tremor severity (TS) in a clinical context, with the aim of improving the reliability of tremor evaluation in patients with Parkinson∉s disease (PD) or essential tremor (ET). The machine learning method matched the clinical rating with 82% accuracy, the digital pen with 78% accuracy, and RMS with 42% accuracy. They also obtained the best accuracy of 82% using the decision tree machine learning approach with gyroscope data measured with the Shimmer (Darnall et al., 2012).
Lingmei Ai et al	2011	They worked on a novel approach using singular value decomposition (SVD) to extract the features of intrinsic mode functions (IMFs) and support vector machine (SVM) is proposed to distinguish between them. Due to the accuracy, sensitivity, and specificify could arrive at 98%, 97.5% and 98.33% respectively, thus, practical guiding significance for diagnosing tremor types in clinic is provided (Ai, Wang, & Yao, 2011) .

Identification of Tremor Type

As we discussed earlier that the there are different types of tremor can be present within a person that may not lead the patient to the Parkinson's disease. This type of problem is very difficult to analyze using deterministic algorithms. May be a person can has several types of tremor for different types of

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disease including Parkinsonian Tremor. So identify and classify tremor type is very much essential in this scenario.

Complexity of the Problems

Complexity analysis is very much crucial factor to find the solution of a particular problem. In computer technology each type of problem can be classified into two broad categories like Time and Space complexity. But in case of solving nondeterministic types of problems; which are very difficult to solve in polynomial time, we need special technique to come in the domain in Polynomial time range or we can say NP-Complete class. Above mention three points lead us to the problem that is nondeterministic type and cannot be solved in polynomial time using conventional algorithm.

Concerning about the above discussion this Nondeterministic polynomial time complexity problem (NP Problem) can be solved using the help of *Machine Learning*; an intelligent domain of computer science belongs to area of Artificial Intelligence. Using Machine learning we can solve the NP Problem within polynomial time and make the NP-Hard problem to NP-Complete Problems.

MACHINE LEARNING SYSTEM

Machine learning can be termed as a subset of artificial intelligence (AI). The aim of machine learning commonly is to figure out the structure of data and fit that into models which can be accepted and utilized by people (Koza, Bennett, Andre, & Keane, 1996; Robert, 2014).

Machine learning is a sector within computer science, but it differs from traditional computational methods. Commonly algorithms are sets of accurately programmed instructions used by computers to calculate or solve problem. Machine learning algorithms rather allow for computers to train on data inputs. Also statistical analysis is used in order to output values that fall within a specific range. As a result, machine learning accelerates computers in building models from sample data in order to automate decision-making processes based on data inputs (Robert, 2014).

Machine learning tasks are typically classified into different categories:

- **Supervised machine learning algorithms** can apply what has been trained in the past to new data using labelled examples to predict future events. Ranging from the analysis of a known training dataset, the learning algorithmic program produces an inferred operates to create predictions regarding the output values. The system is ready to supply targets for any new input after adequate training. The learning algorithm can even compare its output with the proper, supposed output and notice errors in order to change the model consequently(Kotsiantis, Zaharakis, & Pintelas, 2007; Lloyd, Mohseni, & Rebentrost, 2013). The majority of practical machine learning uses supervised learning. Supervised learning is where you have input variables (x) and an output variable (Y) and you use an algorithm to learn the mapping function from the input to the output.

$$Y = f(X) \tag{1}$$

The goal is to approximate the mapping function so well that when you have new input data (x) that you can predict the output variables (Y) for that data. It is called supervised learning because the

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process of an algorithm learning from the training dataset can be thought of as a teacher supervising the learning process. We know the correct answers; the algorithm iteratively makes predictions on the training data and is corrected by the teacher. Learning stops when the algorithm achieves an acceptable level of performance.

- Supervised learning problems can be further grouped into regression and classification problems.
- Classification: A classification problem is when the output variable is a category, such as "red" or "blue" or "disease" and "no disease".
- Regression: A regression problem is when the output variable is a real value, such as "dollars" or "weight".
- Some common types of problems built on top of classification and regression include recommendation and time series prediction respectively. Some popular examples of supervised machine learning algorithms are:
- Linear regression for regression problems.
- Random forest for classification and regression problems.
- Support vector machines for classification problems.
- Unsupervised machine learning algorithms are used when the information applied to train is neither classified nor categorised. Unsupervised learning studies how systems will infer a performance to explain a hidden structure from unlabeled data. The system doesn't work out the proper output, but it explores the data and may draw inferences from datasets to explain hidden structures from unlabeled data(Lloyd et al., 2013). Unsupervised learning is where you only have input data (X) and no corresponding output variables.

The goal for unsupervised learning is to model the underlying structure or distribution in the data in order to learn more about the data. These are called unsupervised learning because unlike supervised learning above there is no correct answers and there is no teacher. Algorithms are left to their own devises to discover and present the interesting structure in the data.

Unsupervised learning problems can be further grouped into clustering and association problems.

- **Clustering**: A clustering problem is where you want to discover the inherent groupings in the data, such as grouping customers by purchasing behavior.
- **Association**: An association rule learning problem is where you want to discover rules that describe large portions of your data, such as people that buy X also tend to buy Y.
- Some popular examples of unsupervised learning algorithms are:
- k-means for clustering problems.
- Apriori algorithm for association rule learning problems.
- **Semi-supervised machine learning algorithms** come somewhere in between supervised and unsupervised learning, as they use each labelled and unlabeled data for training – usually a small quantity of labelled data and huge quantity of unlabeled data. The systems that use this technique are able to noticeably improve learning accuracy. Usually, semi-supervised learning is chosen once the acquired labelled data needs competent and relevant resources so as to train it or learn from it. Otherwise, getting unlabeled data usually doesn't need additional resources(Chapelle, Scholkopf, & Zien, 2009). Problems where you have a large amount of input data (X) and only some of the data is labeled (Y) are called semi-supervised learning problems. These problems sit

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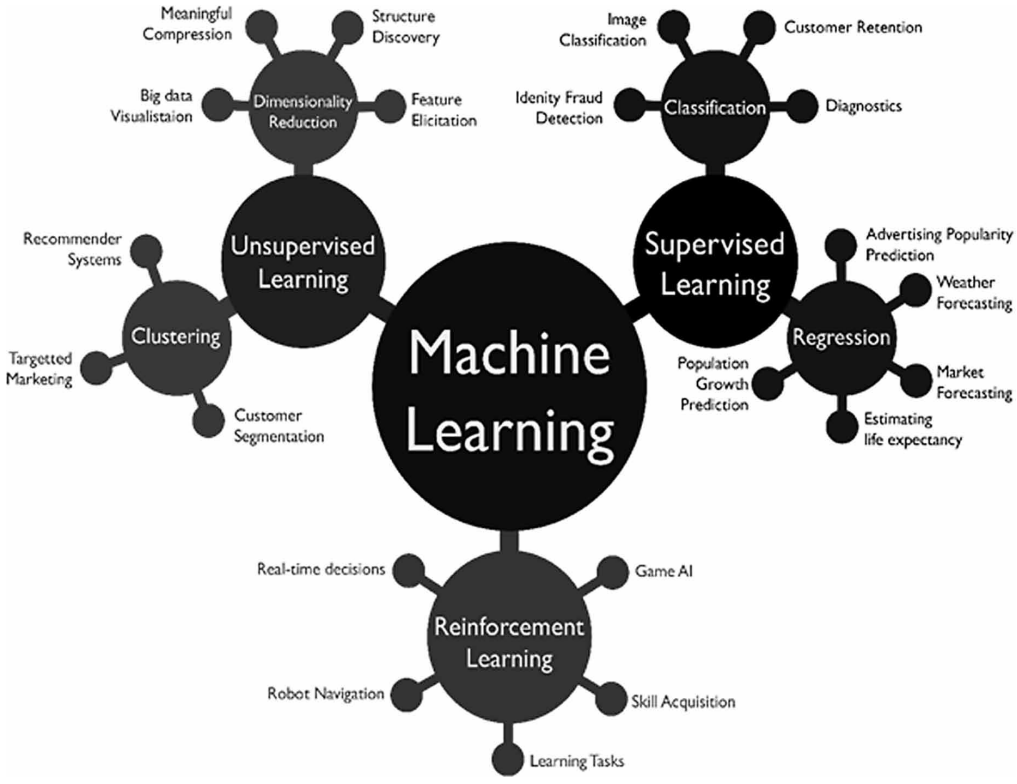
in between both supervised and unsupervised learning. A good example is a photo archive where only some of the images are labeled, (e.g. dog, cat, person) and the majority are unlabeled.

- Many real-world machine learning problems fall into this area. This is because it can be expensive or time-consuming to label data as it may require access to domain experts. Whereas unlabeled data is cheap and easy to collect and store. We can use unsupervised learning techniques to discover and learn the structure in the input variables. It is also use supervised learning techniques to make best guess predictions for the unlabeled data, feed that data back into the supervised learning algorithm as training data and use the model to make predictions on new unseen data.
- Reinforcement machine learning algorithms is a learning method that interacts with its environment through producing actions and discovers problems or rewards. Trial and error search and delayed reward are the most relevant features of reinforcement learning. This method permits machines and software agents to automatically determine the ideal behaviour within a specific context in order to maximize its performance. Simple reward feedback is required for the agent to learn which action is best; this is known as the reinforcement signal (Mnih et al., 2016).

Figure 5. Classification of Machine Learning ("Machine Learning Algorithm - Backbone of emerging technologies")



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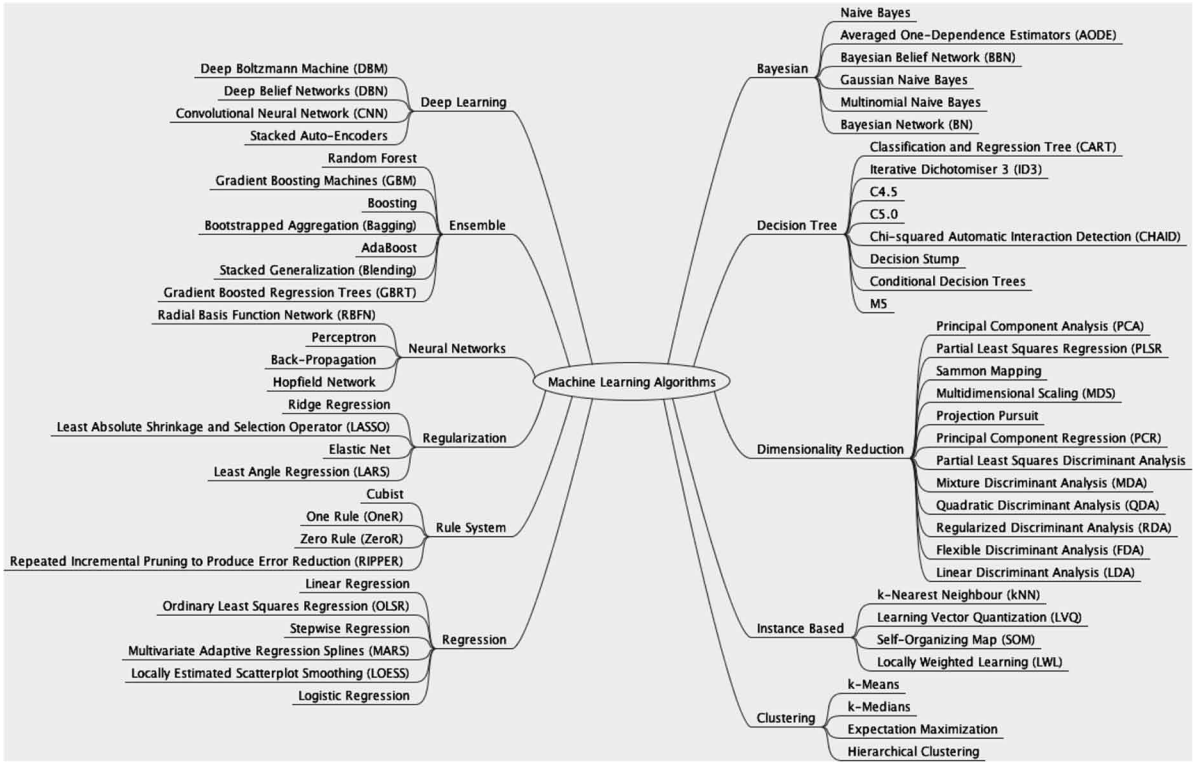
Machine learning allows analysis of huge quantities of data. Whereas it usually delivers quicker, a lot of accurate results in order to spot profitable opportunities or dangerous risks, it may also need extra time and resources to train it properly. Combining machine learning with AI and cognitive technologies will create it even more effective in processing large volumes of information (Robert, 2014).

Figure 6. Different types of Machine Learning Algorithms ("Machine Learning Algorithms Mindmap," 2015)



CLUSTERING

Clustering is a Machine Learning approach that associates the grouping of data points. Given a set of data points, we can use a clustering algorithm to classify each data point into a specific group. In theory, data points that are in the same group should have similar properties and/or features, while data points in different groups should have highly dissimilar properties and/or features. Clustering is a process of unsupervised learning and is a regular process for statistical data analysis used in many fields (Hartigan & Wong, 1979).

Clustering is the task of dividing the population or data points into a number of groups such that data points in the same groups are more similar to other data points in the same group than those in other groups. In simple words, the aim is to segregate groups with similar traits and assign them into clusters.

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Types of Clustering

Broadly speaking, clustering can be divided into two subgroups:

- **Hard Clustering:** In hard clustering, each data point either belongs to a cluster completely or not. For example, in the above example each customer is put into one group out of the 10 groups.
- **Soft Clustering**: In soft clustering, instead of putting each data point into a separate cluster, a probability or likelihood of that data point to be in those clusters is assigned. For example, from the above scenario each costumer is assigned a probability to be in either of 10 clusters of the retail store.

Types of Clustering Algorithms

There are more than 100 clustering algorithms known. But few of the algorithms are used popularly. They are:

- **Connectivity Models:** As the name suggests, these models are based on the notion that the data points closer in data space exhibit more similarity to each other than the data points lying farther away. These models can follow two approaches. In the first approach, they start with classifying all data points into separate clusters & then aggregating them as the distance decreases. In the second approach, all data points are classified as a single cluster and then partitioned as the distance increases. Also, the choice of distance function is subjective. These models are very easy to interpret but lacks scalability for handling big datasets. Examples of these models are hierarchical clustering algorithm and its variants.
- **Centroid Models:** These are iterative clustering algorithms in which the notion of similarity is derived by the closeness of a data point to the centroid of the clusters. K-Means clustering algorithm is a popular algorithm that falls into this category. In these models, the no. of clusters required at the end have to be mentioned beforehand, which makes it important to have prior knowledge of the dataset. These models run iteratively to find the local optima.
- **Distribution Models:** These clustering models are based on the notion of how probable is it that all data points in the cluster belong to the same distribution (For example: Normal, Gaussian). These models often suffer from overfitting. A popular example of these models is Expectation-maximization algorithm which uses multivariate normal distributions.
- **Density Models:** These models search the data space for areas of varied density of data points in the data space. It isolates various different density regions and assign the data points within these regions in the same cluster. Popular examples of density models are DBSCAN and OPTICS.

Applications of Clustering

Clustering has a large no. of applications spread across various domains. Some of the most popular applications of clustering are:

- Market segmentation
- Social network analysis

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- Search result grouping
- Medical imaging
- Image segmentation
- Anomaly detection
- Recommendation engines

K-Means Clustering

K-Means is probably the most well know clustering algorithm. It's taught in a lot of introductory data science and machine learning classes. It's easy to understand and implement in code! Check out the graphic below for an illustration (Kanungo et al., 2002).

1. To begin, we first select a number of groups to use and randomly start their respective centre points. To figure out the number of classes to use, it's good to take a quick look at the data and try to identify any distinct groupings. The centre points are vectors of the same length as each data point vector and are the "X's" in the graphic above.
2. Each data point is allocated by computing the distance between that point and each group centre, and then classifying the point to be in the group whose centre is closest to it.
3. Based on these classified points, we recomputed the group centre by taking the mean of all the vectors in the group.
4. Repeat these steps for a set number of iterations or until the group centres don't change much between iterations. It can also opt to randomly initialize the group centres a few times, and then select the run that looks like it provided the best results.

K-Means has the advantage that it's quite fast, as all we're really doing is computing the distances between points and group centres; clustering has a linear complexity $O(n)$.

On the other hand, K-Means has also disadvantages. It is need to be selected how many groups/classes there are. This isn't always trivial and ideally with a clustering algorithm. K-means also starts with a random choice of cluster centres and therefore it may provide different clustering results on different runs of the algorithm. Thus, the results may not be repeatable and lack consistency.

K-Medians is another clustering algorithm related to K-Means, except rather than re-computing the group centre points using the mean we use the median vector of the group. This technique is lesser sensitive to outliers (because of using the Median) however is much slower for larger datasets as sorting is needed on every iteration when computing the Median vector(Hartigan & Wong, 1979; Kanungo et al., 2002; Likas, Vlassis, & Verbeek, 2003).

Mean-Shift Clustering

Mean shift clustering is a sliding-window-based algorithm that attempts to find compressed areas of data points. It is a centroid-based algorithm meaning that the goal is to locate the centre points of each class, which works by updating candidates for centre points to be the mean of the points within the sliding-window. These candidate windows are then filtered in a post-processing stage to eliminate near-duplicates, forming the final set of centre points and their corresponding groups.

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1. To explain mean-shift we will consider a set of points in two-dimensional space like the above illustration. A circular sliding window cantered at a point C (randomly selected) and having radius r as the kernel. Mean shift is a hill climbing algorithm which involves shifting this kernel iteratively to a higher density region on each step until convergence.
2. At every iteration the sliding window is shifted towards regions of higher density by shifting the centre point to the mean of the points within the window. The density within the sliding window is proportional to the number of points inside it. Naturally, by shifting to the mean of the points in the window it will gradually move towards areas of higher point density.
3. We continue shifting the sliding window according to the mean until there is no direction at which a shift can accommodate more points inside the kernel. Check out the graphic above; we keep moving the circle until we no longer are increasing the density (i.e number of points in the window).
4. This process of steps 1 to 3 is done with many sliding windows until all points lie within a window. When multiple sliding windows overlap the window containing the most points is preserved. The data points are then clustered according to the sliding window in which they reside.

In contrast to K-means clustering there is no need to select the number of clusters as mean-shift automatically discovers this. That's a massive advantage. The fact that the cluster centers converge towards the points of maximum density is also quite desirable as it is quite intuitive to understand and fits well in a naturally data-driven sense. The drawback is that the selection of the window size/radius "r" can be non-trivial(Cheng, 1995; Comaniciu & Meer, 1999, 2002).

Density-Based Spatial Clustering of Applications With Noise (DBSCAN)

DBSCAN is a density based clustered algorithm similar to mean-shift, but with a couple of notable advantages.

1. DBSCAN begins with an arbitrary starting data point that has not been visited. The neighbourhood of this point is extracted using a distance epsilon ε (All points which are within the ε distance are neighbourhood points).
2. If there are a sufficient number of points (according to midpoints) within this neighbourhood then the clustering process starts and the current data point becomes the first point in the new cluster. Otherwise, the point will be labelled as noise (later this noisy point might become the part of the cluster). In both cases that point is marked as "visited".
3. For this first point in the new cluster, the points within its ε distance neighbourhood also become part of the same cluster. This procedure of making all points in the ε neighbourhood belong to the same cluster is then repeated for all of the new points that have been just added to the cluster group.
4. This process of steps 2 and 3 is repeated until all points in the cluster are determined i.e all points within the ε neighbourhood of the cluster have been visited and labelled.
5. Once we're done with the current cluster, a new unvisited point is retrieved and processed, leading to the discovery of a further cluster or noise. This process repeats until all points are marked as visited. Since at the end of this all points have been visited, each point well has been marked as either belonging to a cluster or being noise.

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DBSCAN poses large advantages over other clustering algorithms. Firstly, it does not require a preset number of clusters at all. It also identifies outliers as noises unlike mean-shift which simply throws them into a cluster even if the data point is very different. Additionally, it is able to find arbitrarily sized and arbitrarily shaped clusters quite well.

The main drawback of is that it doesn't perform as well as others when the clusters are of varying density. This is because the setting of the distance threshold ε and midpoints for identifying the neighbourhood points will vary from cluster to cluster when the density varies. This drawback also occurs with very high-dimensional data since again the distance threshold ε becomes challenging to estimate(Tran, Drab, & Daszykowski, 2013; Wang, Wu, Tang, & Hor, 2015).

Expectation–Maximization (EM) Clustering Using Gaussian Mixture Models (GMM)

One of the major drawbacks of K-Means is its naive use of the mean value for the cluster centre. We can see why this isn't the best way of doing things by looking at the image below. On the left hand side it looks quite obvious to the human eye that there are two circular clusters with different radius' centred at the same mean. K-Means can't handle this because the mean values of the clusters are a very close together. K-Means also fails in cases where the clusters are not circular, again as a result of using the mean as cluster centre. Gaussian Mixture Models (GMMs) give us more flexibility than K-Means. With GMMs we assume that the data points are Gaussian distributed; this is a less restrictive assumption than saying they are circular by using the mean. That way, we have two parameters to describe the shape of the clusters: the mean and the standard deviation! Taking an example in two dimensions, this means that the clusters can take any kind of elliptical shape (since we have standard deviation in both the x and y directions). Thus, each Gaussian distribution is assigned to a single cluster. In order to find the parameters of the Gaussian for each cluster (e.g the mean and standard deviation) we will use an optimization algorithm called Expectation–Maximization (EM). Take a look at the graphic below as an illustration of the Gaussians being fitted to the clusters. Then we can proceed on to the process of Expectation–Maximization clustering using GMMs.

1. We begin by selecting the number of clusters (like K-Means does) and randomly initializing the Gaussian distribution parameters for each cluster. One can try to provide a good guesstimate for the initial parameters by taking a quick look at the data too. Though note, as can be seen in the graphic above, this isn't 100% necessary as the Gaussians start our as very poor but are quickly optimized.
2. Given these Gaussian distributions for each cluster, compute the probability that each data point belongs to a particular cluster. The closer a point is to the Gaussian's centre, the more likely it belongs to that cluster. This should make intuitive sense since with a Gaussian distribution we are assuming that most of the data lies closer to the centre of the cluster.
3. Based on these probabilities, we compute a new set of parameters for the Gaussian distributions such that we maximize the probabilities of data points within the clusters. We compute these new parameters using a weighted sum of the data point positions, where the weights are the probabilities of the data point belonging in that particular cluster. To explain this in a visual manner we can take a look at the graphic above, in particular the yellow cluster as an example. The distribution starts off randomly on the first iteration, but we can see that most of the yellow points are to the right

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of that distribution. When we compute a sum weighted by the probabilities, even though there are some points near the centre, most of them are on the right. Thus naturally the distribution's mean is shifted closer to those set of points. We can also see that most of the points are "top-right to bottom-left". Therefore the standard deviation changes to create an ellipse that is more fitted to these points, in order to maximize the sum weighted by the probabilities.

4. Steps 2 and 3 are repeated iteratively until convergence, where the distributions don't change much from iteration to iteration.

There are really 2 key advantages to using GMMs. Firstly GMMs are a lot more flexible in terms of cluster covariance than K-Means; due to the standard deviation parameter, the clusters can take on any ellipse shape, rather than being restricted to circles. K-Means is actually a special case of GMM in which each cluster's covariance along all dimensions approaches 0. Secondly, since GMMs use probabilities, they can have multiple clusters per data point. So if a data point is in the middle of two overlapping clusters, we can simply define its class by saying it belongs X-percent to class 1 and Y-percent to class 2 i.e. GMMs support mixed membership (Reynolds & Rose, 1995; Singh, Pal, & Jabr, 2010).

Agglomerative Hierarchical Clustering

Hierarchical clustering algorithms actually fall into 2 categories: top-down or bottom-up. Bottom-up algorithms treat each data point as a single cluster at the outset and then successively merge (or agglomerate) pairs of clusters until all clusters have been merged into a single cluster that contains all data points. Bottom-up hierarchical clustering is therefore called hierarchical agglomerative clustering or HAC. This hierarchy of clusters is represented as a tree (or dendrogram). The root of the tree is the unique cluster that gathers all the samples, the leaves being the clusters with only one sample(Steinbach, Karypis, & Kumar, 2000).

1. We begin by treating each data point as a single cluster i.e if there are X data points in our dataset then we have X clusters. We then select a distance metric that measures the distance between two clusters. As an example we will use *average linkage* which defines the distance between two clusters to be the average distance between data points in the first cluster and data points in the second cluster.
2. On each iteration we combine two clusters into one. The two clusters to be combined are selected as those with the smallest average linkage i.e. according to our selected distance metric, these two clusters have the smallest distance between each other and therefore are the most similar and should be combined.
3. Step 2 is repeated until we reach the root of the tree i.e we only have one cluster which contains all data points. In this way we can select how many clusters we want in the end, simply by choosing when to stop combining the clusters i.e when we stop building the tree!

Hierarchical clustering does not require us to specify the number of clusters and we can even select which number of clusters looks best since we are building a tree. Additionally, the algorithm is not sensitive to the choice of distance metric; all of them tend to work equally well whereas with other clustering algorithms, the choice of distance metric is critical. A particularly good use case of hierarchical clustering methods is when the underlying data has a hierarchical structure and we want to recover the hierarchy;

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other clustering algorithms can't do this. These advantages of hierarchical clustering come at the cost of lower efficiency, as it has a time complexity of $O(n^3)$, unlike the linear complexity of K-Means and GMM (Davidson & Ravi, 2005; Steinbach et al., 2000).

APPLICATION OF MACHINE LEARNING IN TREMOR MEASUREMENT

Random Forest, Decision Tree, Nearest Neighbor (NN), Bayes, Multilayer Perceptron (MLP), and Support Vector Machine (SVM) are six classifiers which used in measuring tremor. In a decision tree classifier, entropy is measured as:

$$Entropy(S) = -p_{+}\log_2 p_{+} - p_{-}\log_2 p_{-} \tag{2}$$

where S is the set of data points, "p_{+}" is the number of data points that belong to the positive class and "p_{-}" is the number of data points that belong to the negative class. The information gain for each attribute is described by the equation:

$$Gain\left(S, A\right) = Entropy\left(S\right) - \sum_{v \in Values\left(A\right)} \frac{S_V}{S} Entropy\left(S_V\right) \tag{3}$$

where Values(A) is the set of all possible values for feature A. Gain(S,A) measures how well a given feature separates the training examples according to their target classification. A tree is grown from independent random vectors using a training set, resulting in a classifier. After a large number of trees is generated, random forest outputs the class that is the mode of the class's output by individual trees. NN calculates instances using Euclidean distance and correspond to points in an n-dimensional space. The algorithm assigns a class label to a data point that represents the most common value among the k training examples nearest to the data point. We used the IBK scheme from Weka with parameter n=1 in our experiment. SVM maximizes the margin between the training examples and the class boundary. SVM generates a hyperplane which provides a class label for each data point described by a set of feature values. Artificial Neural Networks (ANNs) are computational models mimicking a neuronal organizational structure. ANNs are built from an interconnected set of sample units, which takes a number of real-valued inputs and produces a single real-valued output. Using back propagation, ANN minimizes the squared error between the network output and target values. We applied this technique by using Weka's MLP algorithm to classify TS. Naive Bayes Classifier is a probabilistic classifier which assumes the presence of a particular feature of a class is independent of other features. It learns a classification label by mapping features with Bayes' theorem:

$$argmax_{t_i \in T} P(t_i \mid F) = \frac{P(F \mid t_i) P\left(t_i\right)}{P\left(F\right)} \tag{4}$$

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where T represents the tremor class label and F represents the features values. P(t_i) is estimated by counting the frequency with which each target value t_i occurs in the training data. P(F) is calculated from the frequency of feature values. Based on the simplifying assumption that feature values are independent given the target values, the probability of observing the features is the product of the probabilities for the individual features.

SIGNIFICANCE OF TREMOR THROUGH ELECTROMYOGRAPHY

Electromyography works usually with surface electrodes, but sometimes needles or fine electrodes can be used. EMG can give the accurate measurement of frequency rhythm city and also the magnitude. It is best to use at least 2 channels and to record EMG together from an antagonist pair so that there will be additional information's.(Milanov, 2001).

Surface electromyography provides essential info on the neurophysiological characteristics of tremor. The tremor frequency, amplitude, burst period and burst pattern are evaluated by surface electromyography examination. On the conception of those parameters, numerous forms of tremor can be recognized. All tremors can be subdivided into two major groups as per the pattern of muscle activation, either synchronous or alternating in the antagonistic muscles. The tremor amplitude is variable and isn't specific for various kinds of tremor and therefore its diagnostic value is restricted whereas tremor frequency more constant parameter. The tremors could be subdivided into low frequency (below 4Hz), middle frequency (4-9 Hz) and high frequency (above 9 Hz) tremors. Spectral analysis of EMG activity of a tremor that shows distinct peaks has sometimes been assumed to point the presence of motor units firing at totally different frequencies. Actually, the peaks could reflect fluctuations in the variety of motor units recruited and interference in the timing of their burst activity.

Figure 7 shows the diagram indicating central nervous system influences on a Limb. There may be a peripheral reflex loop, a central reflex loop and a central oscillator. The central oscillator is characterized by relative isolation from sensory input.

CASE STUDY

Some of the case studies undergone in different hospitals in Assam and Meghalaya for tremor in PD are shown in Table 2.

It has been seen from the case study that tremor is very must common in PD and it starts from the early stage. Mostly it is resting tremor with different symptoms. Various machine learning techniques can be used to classify the symptoms with the kind of tremor. The techniques mentioned in this chapter are used for this classification which is reliable, user friendly and fast technique.

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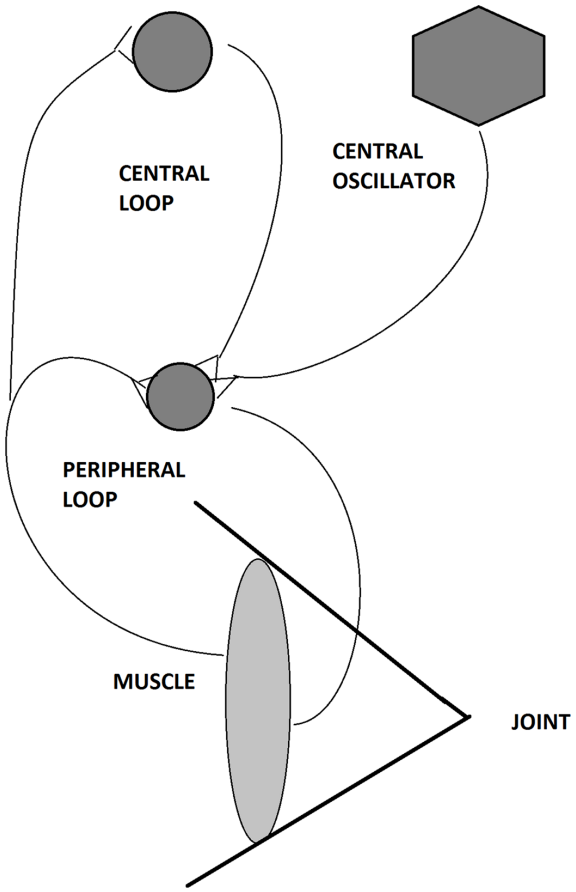
Figure 7. Diagram indicating central nervous system



CONCLUSION

Tremors are the results of variety of mechanisms like peripheral and central loops and central oscillators. Tremors may derive from mechanical oscillations, mechanical reflex oscillations, normal central oscillators and pathologic central oscillators. Methods of studying tremor include accelerometry and electromyography (EMG). Identification of exact location, type and cause of tremor is very much necessary for the detection of various diseases. The physiology of tremor is incompletely known and the definitive identification of a central oscillator for any tremor has not yet been established. Disease like Parkinson's diseases main symptoms starts with early tremor in the fingers and gradually increases in hands and legs followed by tremor in the mouth. Hence its identification is very much essential. Tremor can be identified using various techniques. Nowadays Machine learning is one of the major tools for the tremor identification. Classification of various kinds of tremor can be done by using various machine learning techniques. These techniques are very much accurate and also less time consuming. Hence, this chapter gives a brief review of various kinds of tremor and its classification with respect to Parkinson's disease. Further, this will help the clinicians and researchers to study various kinds of machine learning techniques associated with identification of tremor in various neurological disorders.

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Table 2. Case studies on PD tremor

Patient no	Age	Gender (M-male; F-female)	Initial Symptoms	Family History (Immediate Relatives)
1	55	M	Left foot resting tremor.	Mother with PD
2	60	M	Right thumb resting tremor.	Father with tremor
3	62	F	Left hand resting tremor.	None
4	65	F	Right hand resting tremor	Brother with tremor
5	59	M	Right foot resting tremor	Mother and sister with PD
6	70	M	Left hand resting tremor	Mother with tremor
7	73	F	Right thumb resting tremor	None
8	69	M	Left foot resting tremor	None
9	58	M	Right foot resting tremor	Mother with PD and brother with tremor
10	52	M	Left hand resting tremor.	None
11	56	F	Right hand resting tremor	None
12	51	F	Right thumb resting tremor	None
13	77	M	Left foot resting tremor	None
14	73	M	Right foot resting tremor	Father with tremor
15	66	M	Left hand resting tremor	Father with tremor

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Chapter 19
QSAR and QAAR Studies on Mixtures of 3-(Benzylidene) Indolin-2-One Isomers as Leads to Develop PET Radiotracers for Detection of Parkinson's Disease

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ABSTRACT

Deposition of α–synuclein, tau and β–amyloid protein plaques in brain leads to neurodegeneration. A series of indolin derivatives, which can bind to α–synuclein and detect Parkinson's disease (PD), were used for development of QSAR and QAAR models. It is the first attempt of QSAR for any radiotracer agents used for detection of PD. The binding affinity against α–synuclein was used as dependent variable while independent variables, such as structural, topological, E-state keys, electronic, molecular shape analysis and spatial molecular descriptors were used for QSAR modeling. For QAAR modeling, the binding affinities of molecules for tau and β–amyloid along with different molecular descriptors were used as independent variables. All models were successfully developed using multiple linear regression method, and validated internally and externally, based on different standard criteria. This article describes how the derived models postulate that conformation of molecules and presence of unsaturated hydrocarbon chains, nitro, methoxy and amine functionalities play an important role in determining binding affinity.

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INTRODUCTION

Parkinson's disease (PD) is second most common incurable and progressive neurodegenerative disorder after Alzheimer's disease (AD) which gradually takes control of motor function in body (Dexter & Jenner, 2013). The PD has been diagnosed in 1% of the population with age more than 65 years and considered as sporadic or idiopathic disease. The characteristic features of PD are degeneration and loss of dopaminergic neurons in substantia nigra of brain due to development of protein plaques from accumulation of insoluble misfolded protein (Skovronsky, Lee, & Trojanowski, 2006). The α-synuclein protein is responsible for forming insoluble aggregates like Lewy bodies (LB) and Lewy neurites (LN) (Lee & Trojanowski, 2006; Kim, Kågedal, & Halliday, 2014). Both protein aggregates are morphologically different. The α-synuclein protein regulates release of neurotransmitters, synaptic vesicle recycling and synthesis as well as vesicular storage in central nervous system (CNS) (Bendor, Logan, & Edwards, 2013). Apart from PD, these protein aggregates are also found in other synucleinopathies such as dementia with Lewy bodies (DLB), multiple system atrophy (MSA) and Pick's disease (Marques & Outeiro, 2012). Another protein aggregates, called neurofibrillary tangles which are common in AD are also found in PD patients along with β-amyloid (Ho, Troncoso, Knox, Stark, & Eberhart, 2014). Neurofibrillary tangles are aggregates of tau proteins.

As PD is a sporadic disease, there is an urgent need of detecting the disease in an early stage. Studies have shown that protein aggregates start forming way before development of motor symptoms in PD patients. Therefore, detecting LB and LN in PD is more sensible than relying on changes in dopaminergic neuronal cells (Dauer & Przedborski, 2003). In addition, dopaminergic biomarkers have failed to correlate with clinical status PD patients(Sharma et al., 2013; Brooks et al., 2003). These protein aggregates can be detected by radiotracer imaging agents using techniques such as positron emission tomography (PET). Good tracer imaging agents for α-synuclein should be selective towards α-synuclein, able to cross blood brain barrier (BBB), able to locate and distinguish LB for different synucleinopathies producing minimum radioactive metabolite and able to identify post translational modified α-synuclein (Eberling, Dave, & Frasier, 2013). Several α-synuclein radiotracer ligands, such as tricyclic phenothiazine derivatives SIL5, SIL23 and SIL 26, benzoxazole analogue BF-227 and a benzothiazole analogue PIB (Pittsburgh compound B), fluorescent dyes LDS 798 and LDS 730, and indolinone 5 have been successfully utilized for detecting LB in PD affected patients (Bagchi et al., 2013; Zhang et al., 2014; Neal et al., 2013; Yu et al., 2012). Although these compounds have shown reasonable ability to detect insoluble protein aggregates, *in vitro* instability and inadequate selectivity towards α-synuclein among tau and β-amyloid make them meager radiotracer imagining agents. In order to overcome these limitations, Chu *et al.* introduced indolinone-diene derivatives which serve as second generation radiotracer imaging agents for α-synuclein (Chu et al., 2015). In the present study, quantitative structure-activity relationship (QSAR) modeling on a set of indolinone-diene derivatives has been performed to identify structural features contributing to the binding affinity towards α-synuclein in comparison to that against tau and β-amyloid proteins (Chu et al., 2015). The QSAR models were developed using the binding affinity of molecules against α-synuclein as the dependent variable while quantitative structure activity-activity relationship (QAAR) models were developed using the binding affinity of molecules against α-synuclein as the dependent variable while additionally using binding affinities against tau and β-amyloid proteins among the independent variables.

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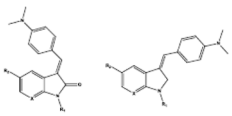
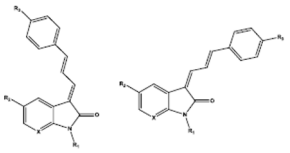
The QSAR study helps to establish relationship between the end point activity of compounds and their physical and chemical properties, while QAAR study assists to find relationship between different end point activities for the same target or different targets provided that the compounds used for the study remain same (Sangion & Gramatica, 2016; Roy & Roy, 2009).

Table 1. Structures of all the compounds in dataset along with their activity against α-synuclein, tau and β-amyloid



Compound	R_1	R_2	X	E:Z	Activity (pKi) α-synuclein	tau	β-amyloid
1	H	H	CH	75:25	7.07	6.58	7.03
2	H	OH	CH	67:33	6.39	6.72	7.02
3	CH_3	H	CH	84:16	6.29	6.20	6.80
4		H	CH	83:17	6.84	6.09	6.58
5		H	CH	52:48	6.94	6.36	6.59
6		H	CH	77:23	6.82	6.43	7.05
7		H	CH	62:38	6.46	5.95	6.85
8		H	H	94:6	6.53	6.10	6.74
9	H	H	N	26:74	6.90	6.71	7.39
10		H	N	66:34	6.45	6.06	6.72
11		H	N	69:31	7.09	6.06	6.94



Compound	R_1	R_2	R_3	X	EE:ZE	α-synuclein	tau	β-amyloid
12	H	H	H	CH	77:23	6.68	6.28	6.57
13	H	H	OCH_3	CH	78:22	7.21	6.77	6.90
14	H	H		CH	41:59	7.39	7.27	7.55
15	H	OH		H	38:62	7.26	7.31	7.43
16		H	H	CH	0:100	6.64	6.16	6.15
17		H	OCH_3	CH	84:16	7.13	6.14	6.13
18	CH_3	H		CH	63:37	7.19	6.63	7.25
19		H		CH	65:35	7.38	6.42	6.44
20		H		CH	52:48	7.26	6.62	6.88
21		H		CH	65:35	8.37	7.04	7.03
22		H		CH	50:50	7.03	6.27	7.33
23		H		CH	51:49	7.34	6.57	7.075
24		H		CH	55:45	7.36	6.88	7.00
25		H		CH	29:71	7.16	6.33	6.54
26	H	H	NH_2	CH	-	7.34	7.41	7.29
27	H	H		N	38:62	7.93	7.45	7.81
28		H		N	80:20	7.16	6.59	7.07

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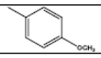
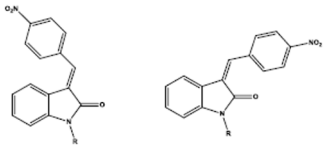
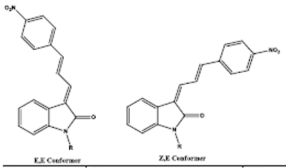
Table 1. Continued

29		H		N	87:13	7.52	6.68 6.97



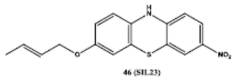
E Conformer Z Conformer

Compound	R	E or Z	α-synuclein	tau	β-amyloid
30	H	Z	6.45	6.44	6.48
31	H	E	6.20	6.27	6.35
32		Z	6.31	5.75	6.33
33		E	6.01	5.85	6.15

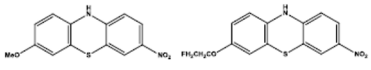


E,E Conformer Z,E Conformer

Compound	R	EE or ZE	α-synuclein	tau	β-amyloid
34	H	ZE	7.83	7.56	7.44
35	H	EE	6.67	6.68	7.22
36		ZE	7.60	6.91	6.66
37		EE	6.71	6.22	6.62
38		ZE	7.88	7.14	6.88
39		EE	7.08	6.49	6.85
40		ZE	8.42	6.64	6.95
41		EE	7.18	6.45	6.57
42		ZE	8.45	6.81	7.13
43		EE	7.27	6.20	6.88
44		ZE	8.67	7.09	6.84
45		EE	7.11	6.34	6.90



46 (SIL23)



47 (SIL5) 48 (SIL26)

Compound	α-synuclein	tau	β-amyloid
46	6.63	6.19	6.82
47	6.86	6.95	7.17
48	6.90	6.98	7.80

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MATERIALS AND METHODS

Dataset Preparation

A molecular dataset of 48 data points (Chu et al., 2015) with activity data provided as binding affinities (Ki) in nano molar (nM) range towards α-synuclein, tau and β-amyloid proteins as shown in Table 1 was selected for this study. Out of the 48 data points, Ki values of 28 cases are available as a mixture of either E and Z or EE and ZE isomers in various proportions, Ki values for 17 cases were for E, Z, EE or ZE isomers and remaining 3 data points correspond to tricyclic phenothiazine derivatives. As usual in QSAR analysis, the dependent variable values (Ki) were converted into negative logarithmic values (pKi = -log Ki).

Structural, topological, E-state keys, electronic (Dipole-mag, HOMO, LUMO and Superdelocalizability), spatial and molecular shape analysis descriptors for the molecules in the dataset were calculated using Cerius2 version 4.16 (Cerius2, 2005). Computation of 3D descritptors based on molecular shape analysis involves energy minimization and conformational analysis of dataset compounds, hypothezing an active conformer based on biological activity and selecting reference compound for pairwise shape alignment to measure shape similarity is important here (Leonard & Roy, 2008). In this case, compound 44 was selected as reference for shape alignment. A total 123 descriptors were obtained for QSAR analysis. The descriptors values were recalculated for mixture of isomers (28 data points) by multiplying descriptor values with respective fraction of the isomer and then adding resultant values to get new descriptors. This was done to account the (mixture) effect of two different isomers. For rest of the data points, original descriptors were used. The number of descriptors was then narrowed down by removing constant and inter-correlated descriptors with cut off of variance < 0.0001 and correlation coefficient ≥ 0.99, respectively using *in-house* developed software tool DataPreTreatment 1.2 (http://dtclab.webs.com/sotware-tools). After data pretreatment, only 93 descriptors were retained.

After the pretreatment of the independent variable matrix, the dataset was divided into training and test sets using different methods, such as Kennard-Stone, Euclidean Distance and Sorted response based methods to ensure uniform presentation of structural as well as activity diversity in both the training and test sets using the software tool Datasetset Division 1.2 (http://dtclab.webs.com/sotware-tools). In all divisions, the highest and least active compounds were kept in the training set.

Model Development and Validation

Initial models were generated with multiple linear regression (MLR) in a stepwise manner employing the tool S-MLR 1.2 (http://dtclab.webs.com/sotware-tools). Different settings of alpha (alpha-to-enter and alpha-to-remove) as well as F – test were used to decide when to enter and remove descriptors in/from MLR equations in different runs. A new set of descriptor pool was created based on descriptors selected in multiple models generated through stepwise MLR. This pool of descriptors was further subjected to genetic function algorithm (GFA) technique implemented in Cerius2 version 4.16 (Cerius2, 2005) to add spline terms and improve the quality of models. Regression with spline term helps to include descriptors in a model having a non-linear effect. The spline terms are usually expressed as truncated power splines and denoted with angular brackets. For example, $< f(x) – a >$ is equal to zero if the value of f(x) – a is negative, else it is equal to f(x) – a. The constant 'a' is called the knot of the spline. Finally, the best subset selection for the set of linear as well as spline terms was performed to obtain the best

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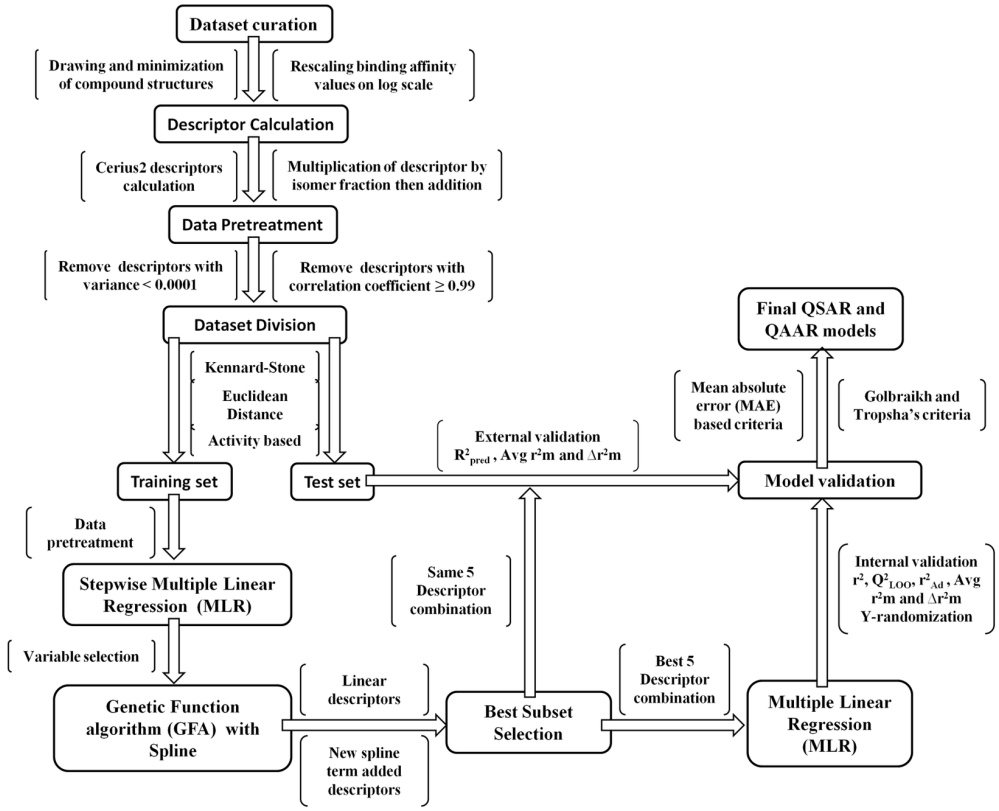
Figure 1. Flowchart of steps performed for development of QSAR and QAAR models



model with optimum number of descriptors using the software tool BestSubsetSelection 2.1 (http://dtclab.webs.com/sotware-tools). The final QSAR models were built and validated using the software tool MLRPlusValidation 1.3 (http://dtclab.webs.com/sotware-tools).

Various statistical metrics were employed for internal (training set) and external (test set) validation of the final models. Internal validation and quality assesment were done by calculating coefficient of determination (r^2), adjusted r^2 (r^2_{ad}), leave-one-out (LOO) cross-validated coefficient of determination (Q^2_{LOO}), and r_m^2 metrics, such as average r_m^2 and Δr_m^2 (Mitra, Roy, Kar, Ojha, & Roy, 2010; Ojha, Mitra, Das, & Roy, 2011; Roy et al., 2012). For external validation, $r^2_{prediction}$ (r^2_{pred}), average r_m^2 and Δr_m^2 metrics were used. The Y-randomization test was also performed on the training set to check whether model was generated by chance or not (Ru & Ru, 2007). In this work, 50 random models were generated by changing the values of the dependent variable randomly and keeping independent variables intact. Golbraikh and Tropsha's criteria (Golbraikh & Tropsha, 2002) for validation of QSAR models were also used to assess the quality of models. Further, mean absolute error (MAE) (Roy, Das, Ambure, & Aher, 2016) based criteria were used to assess the quality of training and test sets with the help of software tool XternalValidationPlus 1.2 (http://dtclab.webs.com/sotware-tools). A schematic presentation of the steps involved from dataset preparation to model development and validation is shown in Figure 1.

The Euclidean distance based approach was employed to study the applicability domain of the developed model using MLRPlusValidation 1.3 tool (http://dtclab.webs.com/sotware-tools). The normalized mean distance scores were calculated based on the set of descriptors of the developed model for

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Table 2. Statistically significant chemometric parameters used to validate QSAR and QAAR models

Model	Division (N_{Train}/N_{Test})	r^2	r^2_{Ad}	$Q^2_{(LOO)}$	r^2_{pred} (Q^2_{F1})	Q^2_{F2}	Q^2_{F3}	RMSEP (Test)	r^2m criteria				Golbraikh and Tropsha's criteria			Y-randomization test[a]	
									Train		Test						
									Avg r_m^2	Δr_m^2	Avg r_m^2	Δr_m^2	$\lvert r_0^2 - r'^2_0 \rvert$	k	k`	Avg r^2	Avg $Q^2_{(LOO)}$
1	DBD (38/10)	0.77	0.73	0.70	0.73	0.73	0.77	0.28	0.60	0.15	0.68	0.10	0.02	1.00	0.99	0.14	-0.32
2	DBD (36/12)	0.87	0.85	0.82	0.75	0.75	0.82	0.26	0.75	0.08	0.61	0.19	0.09	0.99	1.00	0.17	-0.22
3	DBD (36/12)	0.85	0.83	0.79	0.75	0.75	0.82	0.25	0.72	0.05	0.63	0.17	0.05	0.98	1.01	0.14	-0.27

[a]Average for 50 random models

N_{Train} = Number of compounds in training set, N_{Test} = Number of compounds in test set, DBD = Euclidean distance based division, r^2 = Coefficient of determination, r^2_{Ad} = adjusted coefficient of determination, LOO = Leave one out, r^2_{pred} = Coefficient of determination for test set, RMSEP = Root mean square error prediction, MAE = Mean absolute error, Avg. = Average

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each compound first in the training set and then in the test set. The scores range from 0 (least diverse) to 1 (most diverse); any compound with a score of more than 1 is considered outside the applicability domain of the model.

RESULTS AND DISCUSSION

Based on the binding affinity against three proteins and different dataset divisions, multiple QSAR models were developed; however based on internal and external validation criteria, only the final best QSAR and QAAR MLR models are reported here. Initial models were developed using stepwise MLR (using different settings) to obtain a pool of descriptors contributing to the response. A total of 17 descriptors was chosen from initial multiple S-MLR models. With the same dataset division, a pool of 17 descriptors was used to perform GFA-spline to obtain 13 new spline terms. A total set of 30 descriptors was used to perform best subset selection for QSAR models, and in case of QAAR models 31 descriptors were used after adding the response data against Tau or β-amyloid additional independent variables to the pool of 30 descriptors. The QAAR model development was chosen over conventional QSAR models against binding affinities for Tau or β-amyloid because the activity range of compounds for tau and β-amyloid protein was less than 2 in log units. Based on the best 5-descriptor combinations obtained from the best subset selection, the final QSAR and QAAR MLR models (Box 1) were obtained. The contribution of the selected descriptors to the α-synuclein binding affinity and their mechanistic interpretation are explained after statistical analysis of the models.

Table 3. Prediction qualities of training and test sets for respective models based on error-based metrics parameters

Model	Set	$MAE_{(100\%)}$	$SD_{(100\%)}$	$MAE_{(95\%)}$	$SD_{(95\%)}$	$MAE_{(95\%)} + 3 \times SD_{(95\%)}$	Prediction quality	Activity	
								range	mean
1	Train	0.219	0.192	0.197	0.172	0.713	Bad	2.659	7.100
	Test	0.220	0.190	0.180	0.153	0.640	Moderate	2.104	7.147
2	Train	0.188	0.116	0.172	0.097	0.463	Good	2.659	7.110
	Test	0.202	0.172	0.162	0.105	0.477	Good	2.104	7.108
3	Train	0.197	0.123	0.180	0.103	0.491	Good	2.659	7.110
	Test	0.207	0.157	0.182	0.137	0.594	Moderate	2.104	7.108

MAE = Mean absolute error, SD = Standard deviation

Chemometric Analysis

The quality parameters of the selected best models (Box 1) are listed in Table 2. All the reported models are obtained from Euclidean distance based division method and passed both internal as well as external validation criteria. The QSAR model 1 shows a r^2 value of 0.77 as compared to 0.87 and 0.85 for QAAR models 2 and 3, which have activities against Tau and β-amyloid, respectively as one independent variable. Conventional r^2 signifies goodness of fit for models. Adjusted r^2 (r^2_{Ad}) is conventional r^2 with penalty

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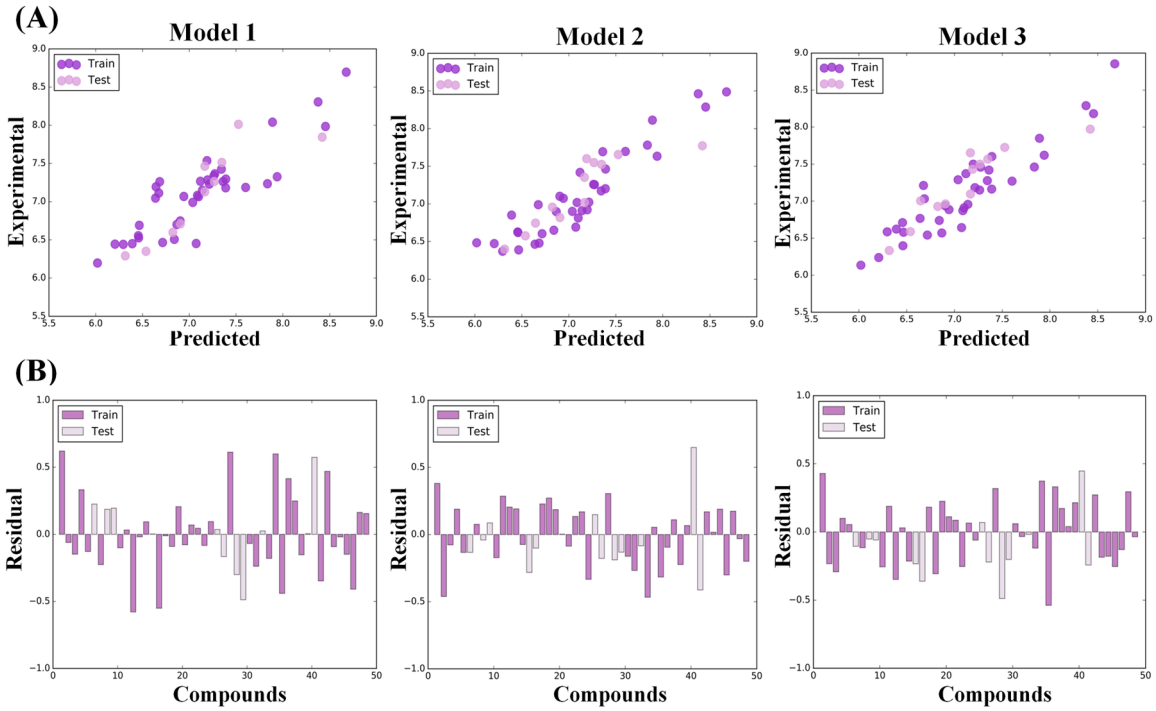
term added for the number of descriptors in the model. The values of leave-one-out cross-validated r^2 (Q^2_{LOO}) which represents internal prediction quality of models are found to be 0.70, 0.82 and 0.79 for models 1, 2 and 3, respectively. Important external validation parameters, such as r^2_{pred} (or Q^2_{F1}), Q^2_{F2} and Q^2_{F3} were calculated and all these metrics should have threshold value greater than 0.5 to pass a model. In all models, the values of both Q^2_{F1} and Q^2_{F2} parameters are found to be close. In model 2, all three parameters are found to be higher as compared to other two models. Lower RMSEP value for the test set for each model reveals good prediction ability of respective model. As prediction parameters, like Q^2_{LOO} and r^2_{pred} may or may not reflect true prediction ability of models (Ojha et al., 2011), r_m^2 metric-based analysis was performed on the training and test sets. The average r_m^2 (threshold = > 0.5) scores for both training and test sets for all models are found to be higher than prescribed limit. However, Δr_m^2 (Threshold = < 0.2) scores remain within the given limit for training and test sets of all models. In Y-randomization test, the mean of r^2 and Q^2_{LOO} for random models should be below 0.5. The average r^2 and Q^2_{LOO} values for all models are significantly low which suggests that the models are robust and not generated by chance. As per Golbraikh ($|r_0^2 - r'^2_0| < 0.3$) and Tropsha's criteria ($0.85 < k < 1.15$ or $0.85 < k' < 1.15$) for judging quality of models, all the parameters remain well within the limit. The plot of observed versus predicted activity of all models shows a good correlation (Figure 2A). The residuals between observed and predicted activity of different compounds are depicted in Figure 2B.

Figure 2. (A) Plot of observed Vs. predicted activity and (B) residual error between same for training and test set



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Mathematical expressions of QSAR and QAAR models with some validation metrics

QSAR model

Model 1

$$Activity = 6.08081\left(+/-0.21237\right) - 2.55628\left(+/-0.77408\right)\ "< ShapeRMS - 2.66 >"$$
$$+2.46805\left(+/-0.53732\right)"\left\langle CHI - 3_C - 1.67\right\rangle" + 0.25196\left(+/-0.03547\right)\ "\left\langle S_dsCH - 1.79\right\rangle" \quad (1)$$
$$-0.10419\left(+/-0.03883\right)"LogP" + 0.00552\left(+/-0.00143\right)"COSV"$$

Validation metrics

Training set: SEE = 0.315, PRESS = 3.194, F = 21.481

Test set: r^2_{ext} = 0.765, CCC = 0.873

QAAR models

Model 2

$$Activity = 0.62217\left(+/-0.73262\right) + 0.89747\left(+/-0.10108\right)"\text{pKi_Tau}" - 2.06481\left(+/-0.66902\right)$$
$$"<\text{ShapeRMS-2.66}>" - 0.29996\left(+/-0.35922\right)"\text{CHI-V-3_C}" + 0.00043\left(+/-0.00007\right)"Wiener". \quad (2)$$
$$+1.25437\left(+/-0.75065\right)\ "\left\langle S_dO - 34.7\right\rangle"$$

Validation metrics

Training set: SEE = 0.241, PRESS = 1.754, F = 40.809

Test set: r^2_{ext} = 0.761, CCC = 0.856

Model 3

$$Activity = 2.15972\left(+/-0.83897\right) + 0.51802\left(+/-0.1161\right)"\text{pKi_}^2\text{-Amyloid}"$$
$$-2.43284(+/-0.60662)"\left\langle ShapeRMS - 2.66\right\rangle" + 0.1952\left(+/-0.02617\right)\ "\left\langle S_dsCH - 1.79\right\rangle" \quad (3)$$
$$+3.01465\left(+/-0.66822\right)"\left\langle S_dO - 34.7\right\rangle" + 0.00614\left(+/-0.001\right)\ "COSV"$$

Validation metrics

Training set: SEE = 0.253, PRESS = 1.932, F = 36.499

Test set: r^2_{ext} = 0.812, CCC = 0.870

The MAE-based analysis was performed for 95% of compounds in training and test sets after removing top-5% compounds with high residuals between observed and predicted activity for each model (Ambure & Roy, 2016; Roy et al., 2016). The criteria determining the quality of predictions of the models are listed in supporting information (Table S1). As per the MAE criteria, for model 1 the quality of predictions for the training set was bad and that for the test test set was moderate (Table 3). For model 2, the prediction quality for both training and test sets was judged as good, while for model 3 the training set prediction quality was found to be good and the test set prediction quality was moderate. The applicability domain of models was determined by the Euclidean distance method (Supporting information, Table S2): a plot

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of normalized mean distance against observed activity of compounds in the dataset for all models shows none of the compound is outside applicability domain of models (Figure 3). Most active compound 44 was found to be most diverse (X-outlier) in all models. Compound 45 which is 'E,E' analogue of 44 is also found to be the most diverse in model 2. The applicability domain plots for model 1 and 3 are very much similar, which suggest that activity of compounds in the dataset against β-amyloid is least diverse as compared to α – synuclein and descriptor similarity in both models. On the other hand, in model 2, the plot is more scattered compared to other plots, due to large activity deviation of dataset compounds against tau protein with respect to α – synuclein and different set of descriptors in the model except "<ShapeRMS-2.66>".

Figure 3. Plot of normalized mean distance calculated by Euclidian distance method against observed activity for training and test set of each model

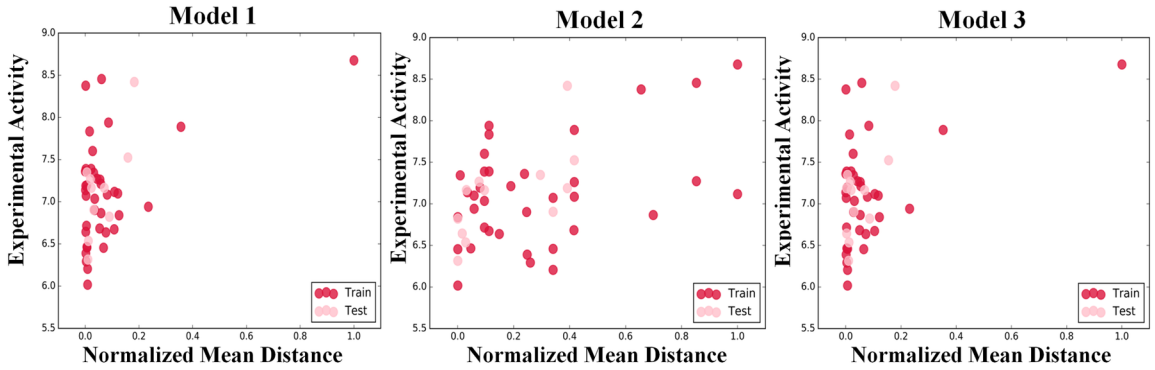
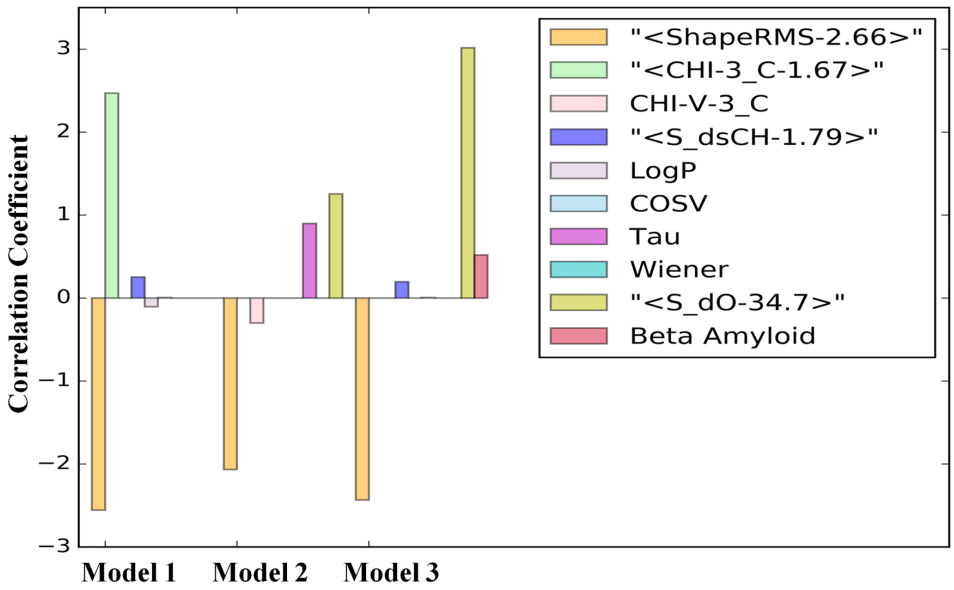


Figure 4. Contribution of each variable in QSAR and QAAR models



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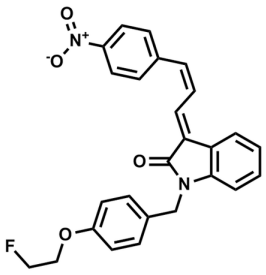
Descriptor Contributions

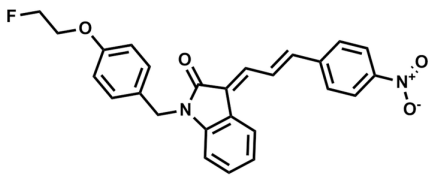
In this section, molecular descriptors contributing to α – synuclein activity are discussed. The contribution of each variable present in all models is depicted in Figure 4. This plot shows positive and negative contribution of individual descriptors in each model. The descriptor "<ShapeRMS-2.66>" contributes negatively in all models, whereas the descriptor "<S_dO-34.7>" is found to contribute positively in models 1 and 2. The descriptors "<S_dsCH-1.79>" and "COSV" contribute positively in models 1 and 2, but the contribution of "COSV" is negligible (< 0.1). The descriptor values of respective compounds used for development of the final models are given in supporting information (Table 3).

"<ShapeRMS-2.66>": ShapeRMS is a molecular shape analysis descriptor and found to be common in all models, contributing negatively, but significantly to α – synuclein activity of molecules (Figure 4). It is root mean square (RMS) difference to the shape of reference or most active compound in the dataset, the more the difference, the less is the contribution to the response. Compounds which have conformation resembling to compound 44 show higher activity. The activity of compound 45 in comparison to 44 decreased by 36 times due to 'E,E' conformation (Figure 5). Compounds 37, 39, 43, and 45 having 'E,E' conformation show ShapeRMS values greater than zero. Compounds 21 and 22 which are a mixture of 'E,E' and 'Z,E' conformation also show higher RMS than compound 44.

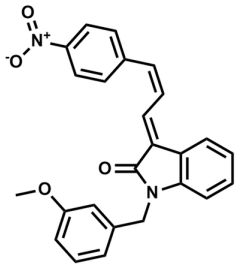
Figure 5. Most active compounds 40 and 44 having 'Z,E' confirmation with lower descriptor values for ShapeRMS and least active compounds 39 and 45 having 'E,E' confirmation with higher descriptor values



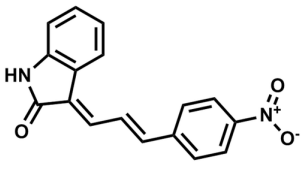
(44, "<ShapeRMS-2.66>":0, pKi = 8.67)



(45, "<ShapeRMS-2.66>":0.19, pKi = 7.11)



(40, "<ShapeRMS-2.66>":0, pKi = 8.42)



(39, "<ShapeRMS-2.66>":0.25, pKi = 7.08)

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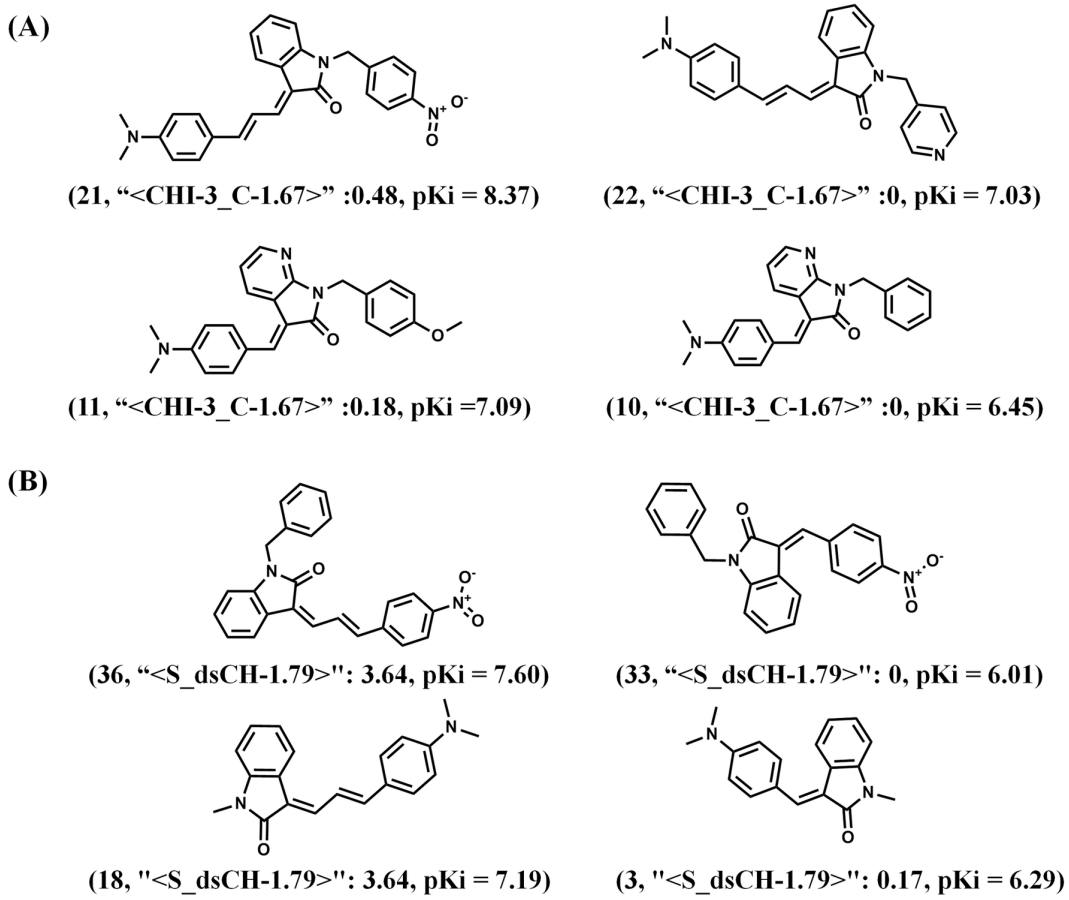
"<CHI-3_C-1.67>": CHI-3_C is Kier and Hall molecular connectivity index for third-order subgraph called cluster, contributing positively in model 1. The mentioned cluster consists of four skeletal atoms in a trigonal form. This descriptor suggests that in the present dataset nitro, dimethylamine and methoxy groups attached to aromatic ring and nitrogen atom of indoline ring forming trigonal geometry with neighboring atoms are important for the activity (Figure 6A). Highly active compounds such as 21, 40, 42 and 44 have at least two of the above-mentioned functional groups. Compounds containing one or none (Compound 12 and 16) of the functional group are either moderately active or least active.

"<S_dsCH-1.79>": S_dsCH is a type of electrotopological state key descriptor contributing positively to α – synuclein binding affinity of compounds. This descriptor is common in models 1 and 3, and it signifies sum of carbon atoms bonded to one hydrogen atom and connected to a single bond and a double bond. Compounds having aliphatic unsaturated hydrocarbon chain of three carbon linking indolin-2-one and benzene ring show higher activity compared to compounds having only one carbon connecting two rings (Figure 6B).

Figure 6. (A) Descriptor "CHI-3_1.67" represents nitro, methoxy and dimethylamine functional group, and heterocyclic ring nitrogen (B) Unsaturated aliphatic hydrocarbon chain linking indoline-2-one and benzene ring plays an important role in enhancing binding affinity of compounds towards α – synuclein



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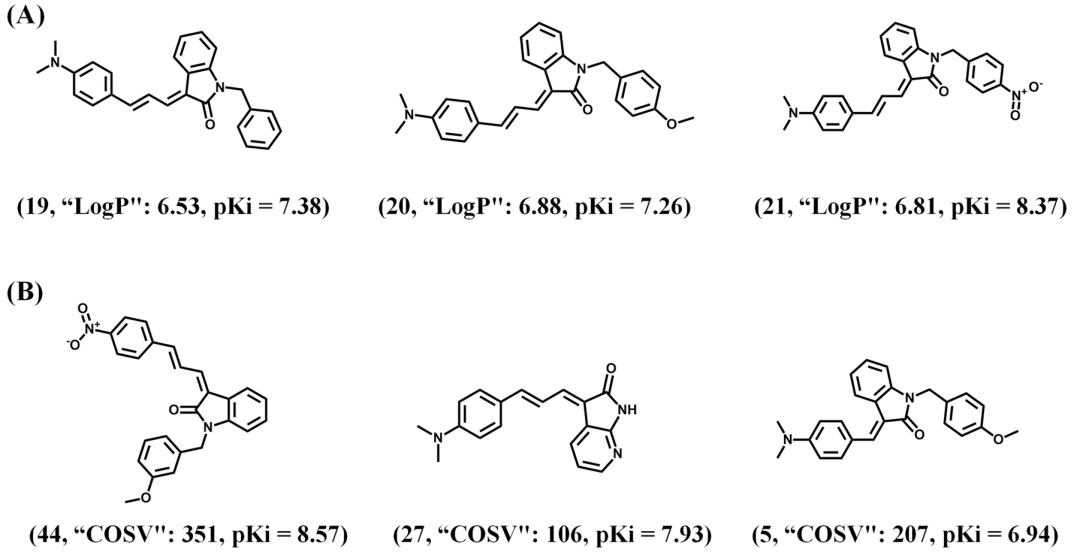
"LogP": It is partition coefficient, which determines solubility of solutes or compounds between two immiscible liquids. It is an important measure of lipophilicity of compound, which plays an important role in absorption, solubility, membrane and CNS penetration, plasma protein binding, etc. This descriptor contributes negatively and only present in model 1. Increase in lipophilicity of compounds decreases the binding affinity towards α – synuclein; however, its effect on overall activity is negligible (Figure 7A). Compounds 21 and 20 have a small difference in partition coefficient values, but the former is more active while the latter moderately active. However, compound 19 has partition coefficient lesser than 20 and 21, but its activity is in-between both compounds. This indicates that other descriptor of compounds plays major role in binding affinity to α – synuclein.

Figure 7. (A) Effect of partition coefficient (LogP) on binding affinity of compounds towards α – synuclein. (B) Compound 5 having common overlap steric volume (COSV) close to most active compound 44 shows 100 fold less activity than compound 27



"COSV": It is a molecular shape analysis descriptor, present in models 1 and 3. It stands for common overlap steric volume between most active compound 44 and individual compounds in the dataset. Increasing similarity between steric volume between most active and other compounds can increase binding affinity. Similar to LogP, the effect of this descriptor on the overall activity is only moderate (Figure 7B).

"CHI-V-3_C": It is modification of CHI-3_C descriptor, known as Kier & Hall valence-modified connectivity index. This descriptor reckons the electronic configuration of molecule having index of third order subgraph cluster (δ^v). of four atoms forming a trigonal geometry. It is calculated by following equation:

$$\delta^v = \frac{\left(Z^v - h\right)}{\left(Z - Z^v - 1\right)}$$

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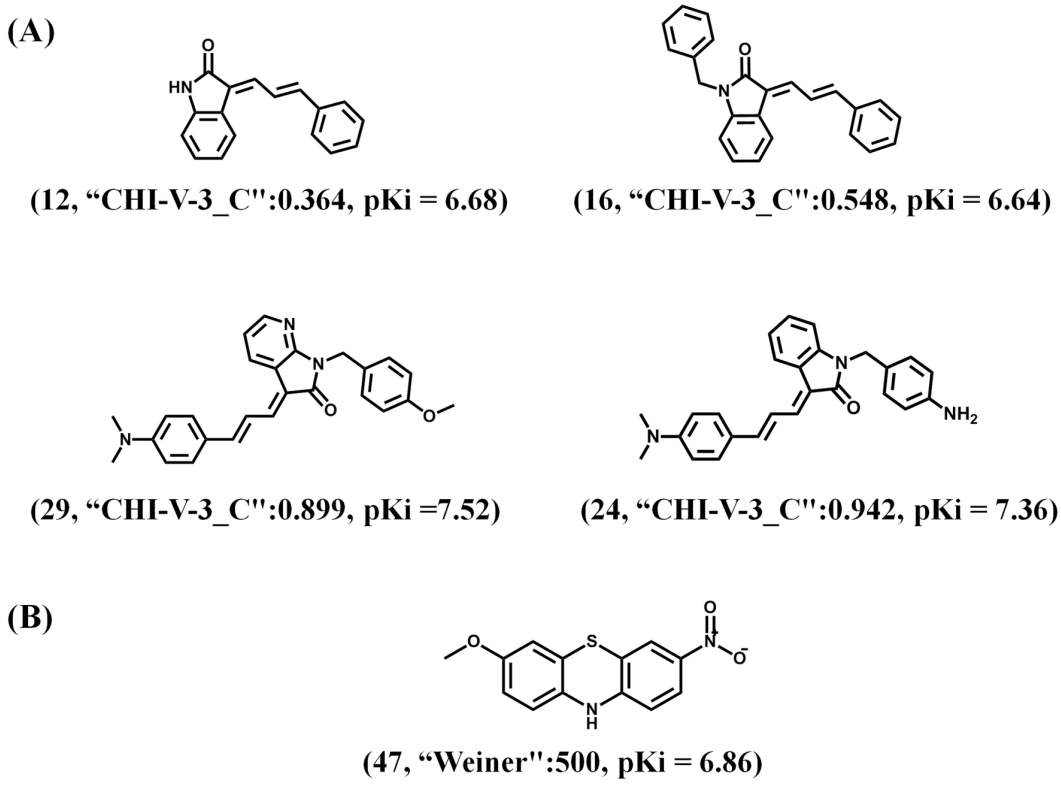
where Z^v is number of valence electrons of atom, h is number of hydrogens attached and Z is atomic number (Cerius2, 2005). As per model 2, it has a negative effect on binding affinity of compounds for α – synuclein. As mentioned earlier, functional group such as nitro, dimethylamine and methoxy group as well as nitrogen atom forming trigonal geometry with neighboring atoms contribute immensely to binding affinity. All these have heteroatoms with a lone pair of electrons and atoms which are attached to them influence electronic configuration of molecule, and hence the activity. Presence of two or more of these groups increases the descriptor values, e.g., compound 5, 20, 21, 24, etc. Introduction of a phenylmethyl moiety to the indoline ring nitrogen increases descriptor value in compound 16 and results in decreased activity (Figure 8A). The same way replacement of amine at the para position of the toluene ring of compound 24 by a methoxy group resulted in an increased activity in compound 29. Pair of compounds such as 5 and 20, 30 and 31, 32 and 33, 42 and 43, 46 and 48, etc. share same descriptor values, but the binding affinity varies for compounds in each pair which postulates that this descriptor has a secondary influence on the binding affinity.

Figure 8. (A) The binding affinity of some molecules decreased due increased influence of "CHI-V-3_C" descriptor. (B) Compound 47 with lowest Wiener index shown moderate binding affinity



"Weiner": It describes topology of molecules by calculating sum of number of chemical bonds present between pair of heavy atoms in them. Its contribution is very small and positive in model 2. The more the number of chemical bonds between heavy atoms in molecules, the more will be their binding affinity for α – synuclein. Compounds 44 and 45 have highest wiener index (WI) of 3750 followed by

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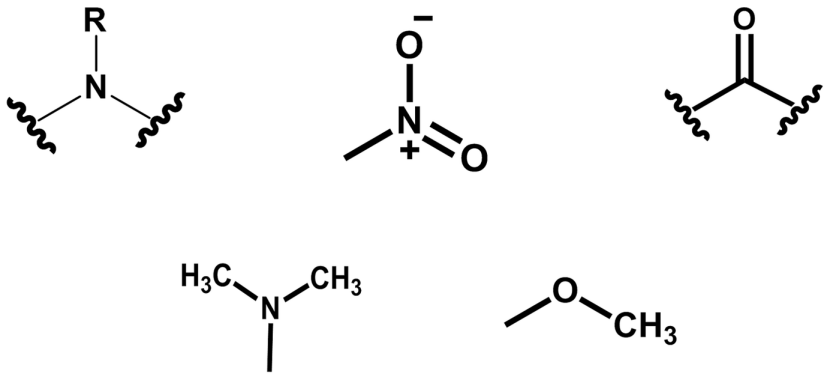
compounds 42 and 43, but the activity difference between these compounds in each pair is very high which imply that number of chemical bonds between heavy atoms play a secondary role in controlling the activity. Compounds such as 12 (WI: 772) and 47 having moderate activity showed lowest wiener index (Figure 8B).

"<S_dO-34.7>": S_dO is an electrotopological descriptor which stands for sum of the oxygen atoms with double bond in molecule. Its immense and positive contribution in models 2 and 3 shows its importance for binding affinity towards α – synuclein. In the present dataset, all the compounds with indoline ring have oxygen with double bond at 2nd position. However, it is the oxygens of nitro functional group that creates huge difference in binding affinity. Compounds such as 21, 40 to 45 which have high descriptor values are highly or moderately active. Compounds from 1 to 29 (except 21) without nitro group are moderately active.

Based on descriptor contribution and observations, importance of descriptors is in the following order "<ShapeRMS-2.66>" > "<S_dsCH-1.79>" > "<CHI-3_C-1.67>" > "<S_dO-34.7>" > "CHI-V-3_C" > "LogP" > "COSV" > "Weiner". Primary descriptors "<ShapeRMS-2.66>", "<S_dsCH-1.79>", "<CHI-3_C-1.67>" and "<S_dO-34.7>" play a decisive role regarding the binding affinity. Descriptors "CHI-V-3_C", "LogP", "COSV" and "Weiner" play a secondary role as their effect on overall activity of compound is not evident. Conformation of molecules plays a very important role in determining binding affinity. A "Z,E" conformation are found to immensely contribute towards binding affinity followed by presence of unsaturated hydrocarbon chain between heterocyclic and aromatic ring. Presence of nitro, methoxy, dimethylamine, etc is important for the binding affinity, but based on neighboring atoms, their electronic configuration can change which can cause a small decrease in the binding affinity. The presence of oxygens with double bond in molecules such as carbonyl and nitro group can enhance the activity. Important fragments required for binding affinity are depicted in Figure 9.

Figure 9. Important fragments contributing to binding affinity of molecules towards α –synuclein



CONCLUSION

The PD is a neurodegenerative disorder characterized by deposition of protein plaques of α – synuclein and tau. Considering the life threatening and incurable nature of disease, it is utmost important to detect disease at primary stages. Imaging agent which specifically binds and detect protein aggregates are more reliable for diagnosis of neurodegenerative disorders than clinical or metabolism based imaging agents.

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Multiple linear regression-based QSAR and QAAR models for indoline based second generation PET radiotracers have been successfully developed in this work with the aim for developing efficient molecules with binding affinity towards α – synuclein for detection of PD. All the models were validated using classical Q^2 metrics, Golbraikh–Tropsha's criteria, r_m^2 and MAE based metrics. Validated models have shown reasonable predictivity and robustness. The applicability domain study ensured that all the test molecules in the dataset are within the domain. Developed QAAR models are more robust and better predictive, compared to the QSAR model. Compounds in the dataset have more selectivity towards α – synuclein with respect to tau, which reflects the number of uncommon descriptors appearing in the QSAR and tau activity-based QAAR models. On the other hand, in QSAR and β – amyloid activity-based QAAR models, the number of common descriptors is more due to lower binding affinity difference and selectivity between α – synuclein and β – amyloid for compounds in the dataset.

The selected descriptors in the models show that "Z, E" conformation of the molecules plays an important role in the binding affinity. Some of the descriptors able to pinpoint the structural feature and fragments such as nitro, dimethylamine, carbonyl group, etc. contribute positively to the binding affinity of molecules for α – synuclein. A minor decrease in hydrophobicity can lead to increase in binding affinity. As the descriptors are quantitative, this study can further utilized to optimize binding affinity and selectivity radiotracer agents towards α – synuclein in a systemic manner by setting descriptor priority. Taking into consideration of the applicability domain of models, binding affinity of newly optimized molecules can be also predicted using developed models.

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APPENDIX

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Section 3

Immunotherapy, Pharmacotherapy, and Technological Treatments

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Chapter 20
Alpha-Synucleinopathies: Parkinson's Disease, Dementia With Lewy Bodies, and Multiple System Atrophy

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ABSTRACT

Alpha-synuclein is a protein that forms a major component of abnormal neuronal aggregates known as Lewy bodies. A particular group of neurodegenerative disorders (NDs) is characterized by the abnormal accumulation of α-synuclein; termed the α-synucleinopathies, this group includes Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Lysosomal storage diseases have also been linked to α-synuclein toxicity. Several therapeutic targets have been chosen among steps of metabolism of α-synuclein. Reducing α-synuclein synthesis or expression and increasing the clearance can be achieved in many ways. The development of immunotherapeutic approaches targeting α-synuclein has received considerable attention in recent years. The aim of this chapter is to present the α-synucleinopathies, as well as to present the most recent researches about treatment of synucleinopathies based on knowledge of the pathophysiology of α-synuclein pathways.

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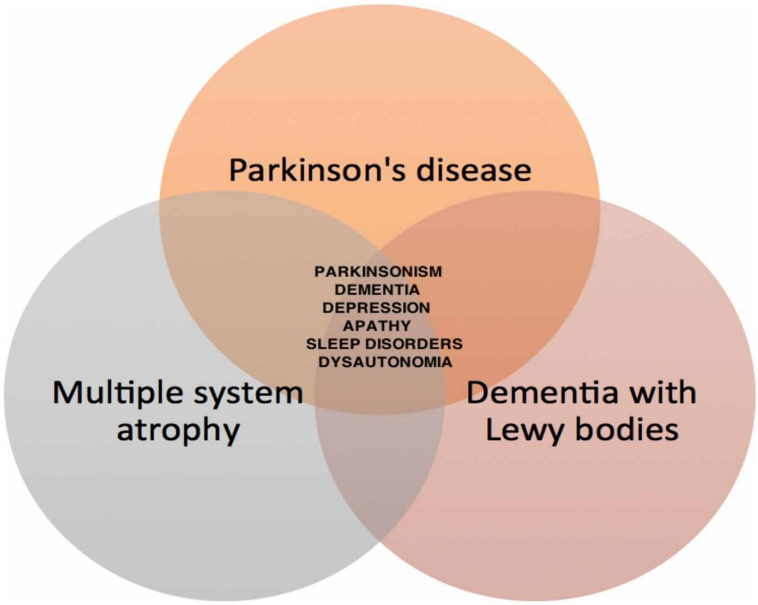
INTRODUCTION

A common feature among a number of neurological disorders is the abnormal aggregation of a protein as observed with amyloid beta in Alzheimer's disease (Selkoe et al., 1990) and huntingtin protein in Huntington's disease (Vonsattel et al., 2011). In 1912, Frederick Lewy first described the cytoplasmic inclusions now known as Lewy bodies in the substantia nigra in PD Cortical Lewy bodies were first reported in association with dementia in 1961 (Okazaki et al., 1961) but they were felt to be a relatively rare finding until the 1980s, when first ubiquitin and later α-synuclein immunostains made it easier to see them (Spillantini et al., 1997) and demonstrated that Lewy bodies were a common neuropathologic finding in dementia (Gomperts, 2016). α-Synucleinopathies is a particular group of NDs characterized by the abnormal accumulation of α-synuclein (Gomperts, 2016; Kahle, 2008) (Figure 1). Lysosomal storage diseases have also been linked to α-synuclein toxicity (Wong and Krainc, 2017). There are new treatments being researched based on the pathophysiology of alpha-synuclein, and immunology. The aim of this chapter is to present the α-synucleinopathies, as well as to present the most recent researches about treatment of synucleinopathies based on knowledge of the pathophysiology of α-synuclein pathways.

Figure 1. Main common features among α-synucleinopathies



BACKGROUND

Despite the early knowledge of the involvement of α-synuclein in several neurodegenerative disorders, only recently has there been, as a Holy Grail, a search for the cause and cure of these diseases through α-synuclein cellular and extracellular mechanisms and pathways. A heated discussion on this topic was triggered after studies suggesting a prion-like role of α-synuclein in parkinsonisms (Brundin et al., 2016). After that, studies suggested the shaping of prions from gut sharing to central nervous system. Finaly,

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gut microbiota changes in PD patients increased discussions and interest in this subject (Scheperjans et al., 2015).

These are not the only controversies related to synucleinopathies. Neurologists have not always contented the term synucleinopathies, a clustering of various diseases that have the Lewy bodies and alpha synuclein as the center of pathophysiology. However, this chapter will try to demonstrate after describing the differences and similarities between these diseases, new findings on the pathophysiology of α-synuclein have helped to understand the clinical differences and, therefore, generating new researches for general treatments of synucleinopathies and also specific for them.

ALPHA SYNUCLEIN

There are different strains of α-synuclein, defined as conformational variants of α-synuclein — that exhibit distinct properties such as differences in structure and toxicity and ability to seed, propagate and cross-seed tau fibrillization. α-synuclein is able to transition between multiple different conformations, including monomers, tetramers, higher-level oligomers (soluble conformations), fibrils (highly ordered insoluble conformations characterized by β-sheet conformation) and aggregates. In addition, differences in α-synuclein strains also exist between synucleinopathies, such as PD and MSA (Bendor et al., 2013; Wong and Krainc, 2017).

The presynaptic location of α-synuclein has been recognized since its original identification as a protein associated with synaptic vesicles (Maroteaux et al., 1988). The protein is relatively specific to the nervous system (Iwai et al., 1995). In addition, α-synuclein is widely expressed by many neuronal populations within both central and peripheral nervous systems, suggesting a general role in neuronal function. However, α-synuclein appears to be one of the last proteins that localizes to developing synapses, arriving after integral membrane proteins of the synaptic vesicle and the peripheral membrane synapsin proteins (Withers et al., 1997).

ALPHA SYNUCLEINOPATHIES

Parkinson's Disease

PD is a neurodegenerative disorder, characterized by movement disorders and non-motors symptoms (Salat et al., 2016), associated mainly with dopaminergic neurons death in the substantia nigra, the progressive depletion of dopaminergic nigrostriatal and mesocorticolimbic neurons (Callesen et al., 2013), abnormal deposition of α-synuclein in remaining cells and gliosis in specific areas of the nervous system (Lees et al., 2009; Salat et al., 2016). However, the changes are not restricted to these brain regions and can be found in other nuclei of the brainstem, in the cerebral cortex and even in peripheral neurons, such as those in the myenteric plexus. The presence of degenerative processes in the dopaminergic system and in different brain areas, for example the frontal lobe, can explain a series of non-motor signs and symptoms such as cognitive impairment and dementia (Lees et al., 2009). Non-dopaminergic pathways are also involved, including the serotoninergic and cholinergic neurons at, in addition to the spinal cord and peripheral nervous system, correlating with the main non-motor symptoms of the disease (Poewe, 2008).

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PD was for a long time characterized by its motor symptoms and signs (Parkinson, 1817). In the International Parkinson's Disease and Movement Disorders Society 2015 Criteria for PD (MDS-PD criteria), the centrality of the motor syndrome remains the core feature by which clinical PD is defined. The prerequisite to apply the MDS-PD criteria is the diagnosis of parkinsonism, which is based on three cardinal motor manifestations. Parkinsonism is defined as bradykinesia, in combination with either rest tremor, rigidity, or both. These features must be clearly demonstrable and not attributable to confounding factors. Having established that the patient has parkinsonism, the MDS-PD criteria will be applied to determine whether the patient meets criteria for PD as the cause of this parkinsonism. The diagnosis of clinically established PD requires: absence of absolute exclusion criteria (e.g. cerebellar abnormalities), at least two supportive criteria (e.g., marked improvement with dopaminergic therapy), no red flags (e.g. rapid progression of gait impairment) (Table 1) (Postuma et al., 2015).

Table 1. Summary of Parkinson's disease Movement Disorders Society criteria 2015 (Postuma et al., 2015).

Supportive Criteria	1. Response to dopaminergic therapy 2. Presence of levodopa-induced dyskinesia 3. Rest tremor of a limb 4. Positive results from at least one ancillary diagnostic test a. Olfactory loss b. Scintigraphy clearly documenting cardiac sympathetic denervation
Absolute Exclusion Criteria The presence of any of these features rules out PD	1. Unequivocal cerebellar abnormalities on examination 2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades 3. Diagnosis of probable behavioral variant frontotemporal dementia within the first 5 y of disease 4. Parkinsonian features restricted to the lower limbs for more than 3 y 5. Drug-induced parkinsonism 6. Absence of observable response to high-dose levodopa 7. Unequivocal cortical sensory loss, clear limb ideomotor apraxia, or progressive aphasia 8. Normal functional neuroimaging of the presynaptic dopaminergic system 9. Documentation of an alternative condition known to produce parkinsonism
Red Flags	1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset 2. A complete absence of progression of motor symptoms or signs over 5 or more years 3. Early bulbar dysfunction 4. Inspiratory respiratory dysfunction 5. Severe autonomic failure in the first 5 y of disease. 6. Recurrent (>1/y) falls because of impaired balance within 3 y of onset. 7. The presence of disproportionate anterocollis (dystonic in nature) or contractures of hand or feet within the first 10 y. 8. Absence of any of the common nonmotor features of disease despite 5 y disease duration. 9. Otherwise unexplained pyramidal tract signs 10. Bilateral symmetric parkinsonism throughout the disease course

However, over the years the non-motor manifestations became better characterized and can now be identified in most, if not all, patients (Seppi et al., 2011: Simuni et al., 2013). The non-motor manifestations of PD involve autonomic, neuropsychiatric dysfunctions, changes in sleep-wakefulness and in pain perception (Goldman and Weintraub, 2015; Poewe, 2008). The most common neuropsychiatric phenomena include dementia, visual hallucinations, apathy and depression (Aarsland et al., 2009; Lieberman, 2006).

In recent decades various sensory abnormalities have been identified as a result of more effective diagnosis and improved treatment strategies (Hughes et al., 1992). Pain is present in around 60% of PD patients and occurs two to three times more frequently in this population than in age-matched individuals

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without PD (Beiske et al., 2009; Defazio et al., 2008; Nègre-Pagès et al., 2008). It is an early symptom and can precede motor symptoms by several years (Kim et al., 2013; Lin et al., 2013; Pont-Sunyer et al., 2015). In the case of smell, which appears to be the sense that is involved the earliest, the prevalence of dysfunction can reach 90% (Doty et al., 1988).

The initial pathological description of PD changed drastically after functional and neuropathological studies showed the extensive involvement of extranigral pathways (Rajput et al., 1991). In addition, following studies like that by Braak et al. (2003), who showed that Lewy bodies are found throughout the nervous system and affect even the peripheral nervous system, a search began for nonmotor clinical findings and pathophysiological responses in PD, particularly dysautonomias, olfactory dysfunctions and sleep disorders (Jellinger, 2009).

Hereditary Parkinson's Disease

In 1997, mutations responsible for the disease were identified in the α-synuclein gene (*SNCA*) (Polimeroloulos et al., 1997). Understanding the monogenic forms of PD provides insight more broadly into the genetic architecture of this disease, and as described later, there appears to be overlap in the genes that contain disease causing mutations and those that contain risk variants (Table 2). Mutations in three genes, *SNCA* (*PARK1*; encoding α-synuclein), *LRRK2* (*PARK8*; encoding dardarin) and *VPS35* (encoding vacuolar protein sorting 35) have been shown to cause autosomal dominant forms of PD. Mutations in six other genes, *PINK1* (*PARK6*; PTEN induced kinase-1), *DJ-1* (*PARK7*), *Parkin* (*PARK2*), *ATP13A2* (*PARK9*), *FBXO7* and *PLA2GB* have been shown to cause autosomal recessive parkinsonism. All known monogenic forms of PD combined explain only about 30% of familial and 3–5% of sporadic cases (Hernandez et al., 2016; Kumar et al., 2011).

Following the discovery of *SNCA* mutations causing a rare familial form of PD, Spillantini et al. (1997) determined that α-synuclein was a major constituent of Lewy bodies, the pathological hallmark of PD. In addition to *SNCA*, autosomal-dominant PD-causing mutations have been found in the gene encoding Leucine-rich repeat kinase 2 *(LRRK2).* Mutations in *LRRK2* are the most common known genetic cause of late-onset PD and are found in both autosomal dominant and sporadic cases (Hernandez et al., 2016). *LRRK2* encodes a large the ROCO protein family, dardarin (Beilina et al., 2014; Greggio et al., 2009; Li et al., 2009), widely expressed in brain tissue.

During recent years several susceptibility genes and numerous risk loci associated with PD have been identified. While success in this regard has been driven by largely unbiased genome wide studies, some limited success was achieved through candidate gene-based assessments in three genes: *SNCA*, *LRRK2* and *GBA (*Hernandez et al., 2016).

Lewy Bodies Dementias

DLB and dementia that arises in PD (ie, Parkinson disease dementia [PDD]) together comprise the Lewy body dementias. Despite the different temporal sequences of motor and cognitive deficits, PDD and DLB show remarkably convergent neuropathologic changes at autopsy. These changes include widespread limbic and cortical Lewy bodies and Lewy neurites composed of aggregates of α-synuclein that involve the brainstem as well as limbic and neocortical regions (referred to as Lewy body disease), loss of midbrain dopamine cells, and loss of cholinergic neurons in ventral forebrain nuclei. Neuritic

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Table 2. Monogenic forms of hereditary Parkinson's disease (Funayama et al., 2015; Hernandez et al., 2016; Kalinderi et al., 2016; Lesage et al., 2016).

Locus	Gene	Protein	Model
Park1	*SNCA*	α-Synuclein	Autosomal Dominant
Park2	*PARK2*	Parkin	Autosomal Recessive
Park3	*unknown*	unknown	Autosomal Dominant
Park4	*SNCA*	α-Synuclein	Autosomal Dominant
Park5	*UCHL1*	Ubiquitin c terminal hydrolase	Autosomal Dominant
Park6	*PINK1*	Pten-induced putative kinase 1	Autosomal Recessive
Park7	*PARK7*	DJ-1	Autosomal Recessive
Park8	*LRRK2*	Leucine rich repeat kinase 2 (dardarin)	Autosomal Dominant
Park9	*ATP13A2*	lysosomal type 5 ATPase	Autosomal Recessive
Park10	*unknown*	unknown	Risk Locus
Park11	*GIGYF2*	GRB interacting GYF protein 2	Autosomal Dominant
Park12	*unknown*	unknown	X-Linked
Park13	*HTRA2*	HTRA serine peptidase 2	Autosomal Dominant
Park14	*PLA2G6*	Phospholipase A2	Autosomal Recessive
Park15	*FBXO7*	F-box only protein 7	Autosomal Recessive
Park17	*VPS35*	Vacuolar protein sorting 35	Autosomal Dominant
Park18	*EIF4G1*	Eukaryotic translation initiation factor 4 gamma 1	Autosomal Dominant
Park19	*DNAJC6*	DNAJ/HSP40 homolog subfamily C member 6	Autosomal Recessive
Park20	*SYNJ1*	SYNJ1	Autosomal Recessive
Park21	*DNAJC13*	DNAJ/HSP40 homolog subfamily C member 13	Autosomal Dominant
Park22	*CHCHD2*	CHCHD2	Autosomal Dominant
Park23	*VPS13C*	Vacuolar protein sorting 13C	Autosomal Recessive
-	*SNCA*	α-Synuclein	Risk Locus
-	*LRRK2*	Leucine rich repeat kinase 2	Risk Locus
-	*GBA1*	Glucocerebrocidase	Risk Locus

plaques that contain amyloid and neurofibrillary tangles are found in the majority of cases of DLB and are common in PD (Gomperts, 2016).

A related Lewy body disease is PD, in which dementia may ensue and thereby, shares many clinical and cognitive features with DLB (Emre et al, 2007; Goldman et al., 2014). At early stages, DLB and PDD are easy to differentiate by the predominance of dementia in DLB and of parkinsonian motor features in PD. Nevertheless, in some patients, dementia and motor signs occur in close succession, provoking debate about their nosology. For research purposes, the "one-year" rule regarding timing of dementia and parkinsonian features is used (Emre et al, 2007; Goldman et al., 2014; McKeith et al., 2005). In clinical practice, however, a diagnosis is made based on the relative prominence of the clinical features. The separation between DLB and PDD is considered by some to be artificial, since it implies that the two clinical syndromes have different pathophysiologies (Aarsland et al., 2004; Goldman et al., 2014).

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DLB is the second most common form of degenerative dementia after Alzheimer's disease, with prevalence rates of up to 5% in the elderly and up to 30% of all dementia cases (McKeith et al., 2005; Zaccai et al., 2005). PDD affects about 40% to 80% (Poewe, 2008; Pigott et al., 2015) of individuals with PD during the course of the disease. It is believed that 3% to 4% of cases of dementia in the general population are related to PD, and the estimated prevalence of PDD in the general population aged over 65 years is 0.2 to 0.5% (Aarsland et al., 2007). Mild cognitive impairment in PD (MCI-PD) has been shown to be a symptom that can progress to PDD. PDD has an insidious onset and progressive evolution (Goetz et al., 2008), being a major cause of the increase in the need of care at the old people's home, higher costs in healthcare and increased mortality (de Lau et al, 2005; Poewe e Mahlknecht, 2009). When dementia becomes clinically significant, the average survival of patients drops to 5 years (Poewe e Mahlknecht, 2009). However, cognitive decline is not limited to PD advanced stages and has been identified in 20 to 35% of patients recently diagnosed with PD or in the initial stages of the disease. This high prevalence and the major impact the condition has on the patient and family members make it essential to detect and diagnose cognitive changes in PD patients as early as possible (de Lau et al, 2005; Poewe e Mahlknecht, 2009).

The characteristic features of DLB are spontaneous parkinsonism, recurrent visual hallucinations, fluctuating cognition, rapid eye movement sleep behaviour disorder (RBD), severe sensitivity to antipsychotic medications and reduction in striatal dopamine transporters on single photon emission computed tomography (SPECT) or positron emission tomography (PET) (Donaghy e McKeith, 2014). The cognitive domains affected in patients with Lewy body dementia are: attention, memory, executive function, construction and apraxia, visuospatial function and language (Goetz et al., 2008). However, Lewy body dementia is mainly a dysexecutive syndrome characterized by impaired planning, a deficit in executive function (including organization of goal-directed activities), dyspraxia, bradyphrenia, reduced problem-solving ability, learning difficulty and short-term memory loss. Most patients also present concomitantly fluctuations in attention, mood and personality, as well as hallucinations and psychoses (Emre et al., 2007; Aarsland et al., 2010). This cognitive impairment is sufficient to compromise the ability to perform activities of daily living and planning, organizational, executive, visuospatial and language abilities (Aarsland et al., 2007).

PDD and DLB are associated with dopamine loss in dopaminergic pathways to the prefrontal cortex, and, to a lesser extent, the ventral tegmental area. In PDD, the appearance of Lewy bodies, which normally occurs in the advanced stages of PD, contributes to the development of severe dementia (Aarsland et al., 2009; de la Fuente-Fernández, 2012). As PD and PDD, the main pathological lesions seen in DLB are Lewy bodies and Lewy neurites, both containing α-synuclein. The pattern of distribution of Lewy bodies pathology in DLB, PD and PDD as seen at end stage is very similar, although cortical involvement may occur earlier in DLB and brainstem involvement may be minimal (Donaghy e McKeith, 2014).

There has been shown to be an association between hypofunction in the pathways involving the dorsal caudate nucleus and the orbitofrontal cortex (including connections with the amygdala), the same circuits that have been associated with the onset of PD, when PDD is less prevalent. This may explain the finding that depression is more correlated to less severe cognitive changes (den Brok et al., 2015; Remy et al., 2005). As the disease progresses, hypofunction of the circuit involving the anterior cingulate cortex and nucleus accumbens (including connections with the amygdala) occurs in patients with apathy, followed by changes in the pathways involving the ventral caudate nucleus and orbitofrontal cortex (Monchi et al., 2007; Remy et al., 2005; Reijnders et al., 2010). In the advanced stages of PD, patients have dopamine depletion in the corpus striatum (putamen, globus pallidus and caudate nucleus) as well as the frontal

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cortex, increasing the prevalence and severity of apathy as dementia and Lewy bodies' progresses (Emre et al., 2007; Reijnders et al., 2010), in agreement with the findings of the present study. Apathy, rather than depression, therefore has the strongest association with more severe cognitive dysfunction in PD (Emre et al., 2007; Reijnders et al., 2010; Seppi et al., 2011). The good effect caused by levodopa in motor PD treatment was not observed in the assessment of neuropsychiatric dysfunctions. The explanation for this paradox is that levodopa does not cause significant changes in the activity of dopaminergic projections to the frontal cortex, as they are mediated largely by D1 dopamine receptors, but stimulates mainly D2 receptors, which predominate in the corpus striatum. Levodopa therapy is therefore not expected to lead to fluctuations in non-motor disturbances in PD (de la Fuente-Fernández, 2012; Remy et al., 2005).

Multiple System Atrophy

The term multiple system atrophy (MSA) was coined in 1969 to encompass three previously distinct neurodegenerative disorders, striatonigral degeneration, olivopontocerebellar ataxia, and "Shy-Drager syndrome" (Graham and Oppenheimer, 1969).

While in recent years considerable effort has been devoted at understanding the pathogenesis of PD, less is known about MSA, which is a rapidly progressive and fatal ND characterized by parkinsonism, dysautonomia (Dickson et al., 1999; Wenning et al., 2001) and α-synuclein accumulation within oligodendroglial and neurons. This accumulation is accompanied by neuroinflammation, demyelination and neurodegeneration (Valera et al., 2016). Additionally, MSA patients can develop pyramidal and behavioral alterations such as depression and executive dysfunction that suggest frontal lobe impairment (Dujardin et al., 2003; Ubhi et al., 2011). The autonomic dysfunctions most commonly are urogenital, gastrointestinal and cardiovascular dysfunction in the form of orthostatic hypotension (Pfeiffer, 2007).

Parkinsonian features reflecting striato-nigral neurodegeneration predominate in 80% of MSA patients (MSA-P subtype), while the major motor feature in 20% of patients is cerebellar ataxia due to olivopontocerebellar atrophy (MSA-C subtype) (Gilman et al., 2008). However, epidemiological studies in North America (Gilman et al., 2008) and Japan (Yabe et al., 2006) have suggested an ethnic variation with regards to the incidence rates of MSA-P or MSA-C. The North American Study reported 60% of their patients as having MSA-P and 13% exhibiting MSA-C (Gilman et al., 2008). In contrast, the Japanese study reported a much higher percentage of patients (83.8%) exhibiting MSA-C features with only 16.2% of patients being categorized as MSA-P (Yabe et al., 2006). The underlying cause of this variability remains undetermined but may involve genetic or environmental factors, or a combination thereof (Ubhi et al., 2011).

Clinically, the rapid progression, the lack of response to levodopa (Wenning et al., 1994), and pathologically the extensive accumulation of α-synuclein within oligodendrocytes differentiates MSA from other synucleinopathies (Dickson et al., 1999b; Valera et al., 2016). However, the mechanisms through which α-synuclein accumulates within oligodendroglial cells in MSA are not completely understood. One possibility is that α-synuclein is produced by oligodendroglial cells, which in turn over-express or fail to intrinsically clear α-synuclein; the other is that α-synuclein propagates from neurons to oligodendrocytes due to neurons over-expressing and/or displaying defects in the physiological mechanisms of α-synuclein clearance (Valera et al., 2016).

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STORAGE DISEASES ASSOCIATED WITH ALPHA SYNUCLEIN TOXICITY

α-Synuclein has been implicated in several diseases, and lysosomal storage diseases have also been linked to α-synuclein toxicity.

Gaucher's Disease

Gaucher's disease (GD) is a rare, autosomal recessive lysosomal storage disorder that results from loss-of-function mutations in glucocerebrosidase (GCase) (Brady et al., 1965).

Three types of GD have been described, based on the rate of clinical progression and involvement of the nervous system (Grabowski, 2008). Type I GD is classically defined as non-neuronopathic and is typically characterized by visceral and hematopoietic abnormalities. Types II and III are differentiated from type I by neurodegeneration with either rapid (type II) or chronic progression (type III). A common feature is accumulation of GlcCer in the affected tissues, but the reasons for variability of GD are not known (Bultron et al, 2010).

A subgroup of type I GD with parkinsonism suggest a possible link between the two disorders (Neudorfer et al., 1996). Neuropathology revealed α-synuclein-positive Lewy bodies (Wong et al., 2004), suggesting the involvement of α-synuclein aggregation. Several genetic studies in large patient cohorts demonstrated that patients with parkinsonism have an increased incidence of *GBA1* mutations (Sidransky et al., 2009), making *GBA1* the most common known genetic risk factor for PD to date.

GBA1 mutations have also been identified in patients with the diagnosis of DLB (Goker-Alpan et al., 2006). The complete mechanism of the linkage between GlcCer and α-synuclein has not been explained.

Metabolism of GlcCer and α-synuclein show a reverse control, with the elevation of α-synuclein contributing to a pathogenic cycle by inhibiting the maturation of normal GCase and the GlcCer accumulation providing α-synuclein oligomer formation (Mazzulli et al., 2011).

It's not completely clear why patients carrying one *GBA1* mutation have increased risk of PD, although many of these patients have well above 50% of control GCase activity.

Thus, it is quite likely that multiple factors, many of which are impacted by the aging process, play a role with deficient GCase to cause parkinsonism (Aflaki et al., 2017).

Additional Lysosomal Storage Disorders

Mucopolysaccharidoses

In the mucopolysaccharidoses (MPS), glycosaminoglycans (mucopolysaccharides) accumulate as a result of impaired function of any of 11 lysosomal enzymes that degrade the glycosaminoglycans (Vitner et al., 2010).

In human MPS IIIB brain tissue, neuronal loss was observed only in the SN, but no Lewy Body-like inclusions were detected. In both MPS IIIB and MPS II brains, α-synuclein was phosphorylated mainly in neurons containing high levels of storage materials (Hamano et al., 2008). In an MPS IIIA mouse model the block in autophagy can lead to accumulation of polyubiquitinated proteins and mutant α-synuclein (Settembre et al., 2008).

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Tay-Sachs and Sandhoff Diseases

The GM2 gangliosidosis (including Tay–Sachs and Sandhoff diseases) are caused by defective b-hexosaminidase activity (Vitner et al., 2010) with numerous case reports linking with PD. Adults patients with GM2 gangliosidosis can present various parkinsonian symptoms including bradykinesia, rigidity, bilateral tremor and resting tremor (Argov and Navon, 1984).

Immunohistochemical analyses in neurons of a Sandhoff disease mouse model demonstrated accumulation of α-synuclein and b-synuclein in striatal terminals and in the SN. Neurons that accumulated α-synuclein were negative for ubiquitin, suggesting a different form from that in classical Lewy bodies' disease (Suzuki et al., 2003). α-Synuclein is also observed in the cerebrum, cerebellum, and brain stem of both Sandhoff and Tay–Sachs disease human patients (as young as 2–3 years old) (Suzuki et al., 2007).

A biochemical association between GM2 gangliosidosis and PD has been demonstrated through the reduced levels of UCH-L1 in cultured fibroblasts from brain extracts from a Sandhoff disease mouse model, as seen in PD (Leroy et al., 1998; Liu et al., 2002).

Niemann-Pick Type C

Niemann–Pick C (NPC) disease is caused by the defective activity of either NPC1 or NPC2, resulting in cholesterol and sphingolipid accumulation (Vitner et al., 2010).

α-Synuclein was observed in the midbrain and amygdala, and classical Lewy bodies were found in the SN of NPC patients (Shachar et al., 2011).

Anecdotal reports linked NPC to sporadic parkinsonian syndrome in younger patients (Coleman et al., 1998).

Neurodegeneration With Brain Iron Accumulation

Neurodegeneration with brain iron accumulation (NBIA) is a group of ND characterized by iron accumulation in the basal ganglia, specifically in the globus pallidus (GP) and the substantia nigra (SN) and can be visualized with MRI. The cortex and the cerebellum can be affected, and cerebellar involvement correlates with the most severe NBIA subtypes (Wray et al, 2016).

α-Synuclein pathology is not usual in this class. Authors presented the NBIA forms with α-synuclein presentation, described at Table 3.

PLA2G6-Associated Neurodegeneration

PLA2G6-associated neurodegeneration (PLAN) is the second core NBIA syndrome (NBIA type II, OMIM 256600 and 610217) and is associated to mutations in the PLA2G6 gene (Morgan et al., 2006). It can present as infantile neuroaxonal dystrophy (classic INAD) and as atypical neuroaxonal dystrophy (atypical lNAD). INAD has an early onset presentation, usually with psychomotor regression and has a rapid progression with severe neurological deterioration.

The atypical INAD has a later onset and a less homogeneous presentation with gait problems, ataxia or speech difficulties being the most common symptoms (Gregory et al., 2008). The progression of the disease usually allows a longer life span than classic INAD.

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Table 3. Human forms of neurodegeneration with brain iron accumulation, genes and presence of α-synuclein pathology (Adapted from Wray et al., 2016).

Human Disorder	MRI	Symptomatology	Gene	α-Syn Pathology
Pantothenate kinase-associated neurodegeneration (PKAN) (NBIA1)	Hypointensity with central hyperintensity of the GP, referred to as 'eye of the tiger'	Dystonia, spasticity and parkinsonism cognition often spared	*PANK2*	No
COASY protein associated neurodegeneration (CoPAN)	Hypointensity with central hyperintensity of the GP	Spasticity, dystonia, dysarthria, parkinsonism and cognitive decline	*COASY*	Unknown
Mitochondrial membrane-associated neurodegeneration (MPAN) (NBIA4)	Hypointensity of the GP and SN plus hyperintensity in the GP	Spasticity, dystonia, dysarthria, parkinsonism and cognitive decline	*C19orf12*	Severe Lewy bodies and Lewy neuritis GP, SN, cortex, striatum
PLA2G6-associated neurodegeneration (PLAN) (NBIA2)	Hypointensity of the GP in a subset of patients Cerebellar atrophy. Some cortical atrophy	Hypotonia, spasticity, dystonia, parkinsonism and cerebellar ataxia Motor and mental retardation	*PLA2G6*	Severe, Lewy bodies and Lewy neurites Ubq, α-syn SNc, cortex
FA2H-associated neurodegeneration (FAHN)	Hypointensity of the GP Cerebellar and cortical atrophy	Spasticity, ataxia and dystonia	*FA2H*	Unknown
β-propeller-associated neurodegeneration (BPAN)	Hypointensity of the GP/SN with central hyperintense line Cerebral and cerebellar atrophy	Parkinsonism, dystonia and dementia, developmental delay, cognitive disturbances	*WDR45*	No
Kufor-Rakeb syndrome	General atrophy and hypointensity in the basal ganglia/caudo-putamen	Parkinsonism, dementia and some pyramidal signs	*ATP13A2*	Unknown
Woodhouse Sakati syndrome	Hypointensity of the GP and SN	Diabetes, alopecia, hypogonadism, deafness	*DCAF17*	Unknown
Aceruloplasminemia	Hypointense striatum, thalamus and dentate	Dystonia, dyskinesia and cerebellar ataxia, cognitive impairment	*CP*	Unknown
Neuroferritinopathy (NBIA3)	Hypointensity in basal ganglia, especially GP and SN. Also motor cortex	Dystonia, spasticity, rigidity and parkinsonism. Some cognitive impairment	*FTL*	Unknown

The PLA2G6 gene encodes an 806 amino acid protein with predicted size of 88 kDa. (Mak et al., 2011). PLA2G6 has been shown to be expressed with protective function in the mitochondria (Saito et al, 2000).

Autosomal recessive mutations are found throughout PLA2G6 and lead to reduced enzyme activity, with the magnitude of enzymatic effect correlating with the disease severity (Morris et al., 1992).

PLA2G6 is classified as a PD gene (PARK14), and also, a reduction in PLA2G6 protein levels has been shown in the brains of Alzheimer's patients (Kupsch et al., 2003).

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Pathology

The major pathological hallmark of PLAN is the presence of axonal swellings throughout the cortex, GP, striatum, cerebellum, brain stem and spinal cord. These are also present throughout the peripheral nervous system and can be diagnostic via peripheral nerve biopsies. There is evidence for PLA2G6 mutation-associated PLAN without spheroids (Morris et al., 1992). Peripheral spheroids are not observed in dystonia-parkinsonism subset of PLAN patients (Eidelberg et al., 1987).

α-Synuclein positive Lewy bodies are found throughout the degenerating brain areas to a very high degree, and a proportion of the axonal swellings also stained positive for α-synuclein (Williams et al., 2012; Lee et al., 2006).

Atrophy is evident in the cortex, GP, white matter and cerebellar cells and was shown to be associated with gliosis in the cortex and the striatum (Lee and Andersen, 2006). Excess iron deposition was specifically observed in the GP and the SN pars reticulata and there is extensive cortical involvement in disease with Lewy bodies seen in all cases whereas tau deposition is rarer.

Mitochondrial Membrane-Associated Neurodegeneration

Mutations in the *C19orf12* gene are associated with mitochondrial membrane-associated neurodegeneration (MPAN), an autosomal recessive disorder that represents between 5 and 30% of NBIA cases (Hartig et al., 2011; Hogarth et al., 2013; Panteghini et al., 2012). These patients are characterized by pyramidal and extrapyramidal signs, cognitive decline, neuropsychiatric changes, optic atrophy, and upper and lower motor neuron signs (Hartig et al., 2011; Hogarth et al., 2013).

Great variability is present in disease onset (between 3 and 30 years) and progression. Gait instability or visual impairment are often the initial symptoms, then followed by muscular weakness and atrophy, dystonia and dysarthria. Almost constant is the cognitive decline leading to dementia as well as the appearance of neuropsychiatric symptoms (Arber et al, 2016).

Brain iron accumulation is the most significant sign at MRI. It involves both the GP and the substantia nigra; it can be accompanied by cortical and cerebellar atrophy. Neuropathologic assessment performed in two cases showed very similar results with iron accumulation, axonal spheroids, tau and Lewy pathology in basal ganglia, the archicortex, the neocortex, and the spinal cord. Iron was evident in the GP and the substantia nigra and associated with neuronal loss and gliosis. Eosinophilic axonal spheroids were evident and were strongly immunoreactive for ubiquitin, and less positive for tau or APP staining (Hogarth et al, 2013).

Lewy pathology was present in many brain regions. In one case the overall burden was greater than that observed in cases of sporadic Lewy body disease (Hogarth et al., 2013).

The *C19orf12* gene consists of three exons and codes for two alternative mRNA isoforms (NM_001031726.3 and NM_031448.4) and proteins that differ for the presence of a stretch of 11aminoacids at the N-terminus of the longer form (Arber et al, 2016). Different types of mutation have been identified and many of them lead to truncated, non-functional proteins. The missense mutation c.32C>T is the most common and affects tyrosine 11, exclusively present in the longer form. The protein has a hydrophobic domain that could represent a transmembrane region. Its expression appears to be involved with CoA and lipid metabolism and mitochondria. No other information is available to explain the connection between the protein function, the neurodegenerative process, and iron accumulation in the brain. Recently, a *Drosophila* model with impaired expression of the two orthologs of human *C19orf12*, was

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obtained (Iuso et al., 2014); those flies showed reduced life span, signs of neurodegeneration (vacuoles) but not of iron accumulation (negative Prussian blue staining) (Arber et al, 2016).

THERAPEUTIC POSSIBILITIES

Reducing α-Synuclein Synthesis

Given that increased α-synuclein uclein expression causes familial PD, several studies have aimed to decrease its synthesis by using siRNA that targets α-synuclein mRNA. In mice, direct siRNA infusion decreases hippocampal and cortical α-synuclein levels for a week after infusion (Lewis et al, 2008), whereas in mice expressing a human form of α-synuclein, injecting siRNA-containing exosomes decreases protein aggregation in the SNc (Cooper et al, 2014).

Given that antisense oligonucleotide (ASO)-mediated therapies are being tested in clinical trials currently as potential therapeutics for other ND, ASO targeting of α-synuclein may also be effective.

Increasing α-Synuclein Degradation

Increasing the clearance could be achieved in many ways but basically consists of restoring the autophagy-lysosomal pathways that are impaired in PD. Overexpression of the lysosomal transcription factor EB (TFEB), which was reported to coordinate cellular clearance via macroautophagy and exocytosis, in rats expressing α-synuclein decreases α-synuclein oligomer levels and prevents lysosomal dysfunction decline and neurodegeneration. In addition, alteration in TFEB activity was reported in induced pluripotent stem cell-derived neurons from GD patients who present α-synuclein pathology. In parallel, academic and industrial laboratories are screening for clinically approved drugs that can enhance TFEB function (Dehay et al., 2016; Wong and Krainc, 2017).

In addition to attempting to boost lysosomal biogenesis, acidic NPs (aNPs) of poly DL-lactide-*co*-glycolide (PLGA), which are FDA approved, have been reported to traffic to lysosomes and to act on lysosomal pH. However, whether PLGA-aNPs can acidify sick lysosomes and restore lysosomal/autophagic function in pathological conditions remains to be determined. Reacidification of defective lysosomes following PLGA-aNP treatment restores lysosomal function in different pathological contexts (Dehay et al., 2016). An alternate protective strategy could be to prevent endosomal uptake of pathological α-synuclein into cells increased expression of other lysosomal proteins, including LIMP2 and ATP13A2, also promote α-synuclein degradation in various models, presenting additional targets for the acceleration of α-synuclein degradation (Wong and Krainc, 2017).

Reducing α-Synuclein Agregation

Given that α-synuclein oligomers and fibrils are implicated in α-synuclein toxicity, several strategies have been attempted to reduce their formation. The porphyrin phthalocyanine tetrasulfonate binds and stabilizes vesicle-associated α-synuclein, which thus delays its misfolding and aggregation (Fonseca-Ornelas et al., 2014).

Passive immunization using a protofibril-selective antibody decreases soluble and membrane-bound α-synuclein protofibrils in the spinal cord and decreases motor dysfunction in mice expressing PD-

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associated mutant A30P α-synuclein (Lindstrom et al., 2014). In addition, if native α-synuclein exists predominantly as a tetramer, compounds that stabilize α-synuclein in this conformation—as has been applied for transthyretin, which misfolds in the multisystem disorder transthyretin-related amyloidosis—might be effective at combating α-synuclein toxicity (Dettmer et al., 2015).

Several clinical trials are currently using small molecules (Schneeberber et al., 2016) to inhibit either α-synuclein aggregation (glycerol phenylbutyrate (University of Colorado, Denver); nilotinib (Georgetown University) or α-synuclein oligomer formation (EGCG (University of Munich).

Blocking α-Synuclein Propagation

Because α-synuclein propagation may contribute to the spreading of α-synuclein toxicity, passive immunization studies to block spreading have also been performed. Antibodies against C-terminal truncated α-synuclein decrease its propagation in vitro and rescue motor and memory impairments in an α-synuclein mouse model (Games et al., 2014), and monoclonal α-synuclein antibodies prevent propagation and uptake of α-synuclein and rescue dopaminergic neuron loss and motor deficits in mice injected with α-synuclein pffs (Tran et al., 2014).

Importantly, understanding the role of propagation in disease will help to clarify whether these therapies will be successful for patients.

Passive and Active Immunization

The development of immunotherapeutic approaches targeting α-synuclein has received considerable attention in recent years. In this sense, both humoral (active and passive) and T-cell-based approaches have been explored. While active immunization stimulates the immune system to produce antibodies against target proteins (the response takes days/weeks to develop but may be long lasting—even lifelong), passive immunization consists in directly administering IgG antibodies that confer temporary protection against the disease (several weeks to few months) (Valera et al., 2016-b). Monoclonal antibodies against α-synuclein can regulate inflammation and facilitate the clearance of target protein via autophagy or microglia (Valera et al., 2016-b).

Immunotherapy has been shown to induce a physiological microglial response (M2 type) and reduce the production of proinflammatory cytokines, thus exerting an anti-inflammatory effect in neurodegenerative disorders (Valera et al., 2016-b). Among the cell types that can internalize α-synuclein aggregates, microglia exhibit the most rapid clearance of these proteins. Microglia became better scavengers for extracellular α-synuclein aggregates in the presence of specific antibodies against α-synuclein. Antibody-α-synuclein immune complexes entered microglia through the Fcγ receptors, which led to efficient delivery of these immune complexes to lysosomes, hence resulting in fast degradation. By clearing extracellular α-synuclein, antibody treatment significantly reduced the extent of cell-to-cell transmission of the protein in mouse models. Furthermore, clinical advantages might be expected if extracellular α-synuclein is selectively targeted by immunotherapy with the intraneuronal α-synuclein being left intact (Lee and Lee, 2016).

The first study vaccinated transgenic LBD-mice using full human α-synuclein, which cleared α-synuclein aggregates, potentially via lysosomal pathways (Maliash et al., 2005). These results suggested that α-synuclein vaccination is effective in reducing neuronal accumulation of α-synuclein aggregates and that further development of this approach might have a potential role in the treatment of synucle-

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inopathies (Valera et al., 2016-b). Other active immunization approaches using a next-generation active vaccination technology with small peptides, or AFFITOPEs® (AFFiRiS AG) (Mandler et al., 2014). AFFITOPEs® that mimic the C-terminal region of α-synuclein are able to elicit an immune response specific to α-synuclein oligomers. Vaccination with one of these AFFITOPEs® (AFF 1) resulted in high antibody titers against α-synuclein aggregates, decreased accumulation of α-synuclein oligomers. When administered to a transgenic model of MSA, AFF 1 also induced a reduction in neurodegeneration and demyelination in neocortex, striatum, and corpus callosum. The clearance of α-synuclein induced by AFF 1 involved activation of microglia, increased anti-inflammatory cytokine production, and reduced spreading of α-synuclein to astroglial cells (Mandler et al., 2014).

Passive immunization approaches using antibodies against α-synuclein are also being actively pursued. Studies observed that antibodies that recognize an epitope in the C-terminal of α-synuclein are more effective at ameliorating the pathology in transgenic mouse models of PD, as they clear intracellular aggregates, inhibit α-synuclein propagation, and prevent C-terminal cleavage of the protein, which may lead to increased aggregation. The reports support the value of immunotherapy with monoclonal antibodies directed against α-synuclein for PD, and in this sense the C-terminal antibody PRX002 (Prothena, South San Francisco, CA, USA) and the antibody BIIB054 (Biogen, Cambridge, MA, USA) are currently being tested in phase I clinical trials (Valera et al., 2016; Schenk et al., 2017).

FUTURE RESEARCH DIRECTIONS

The main future expectations are related to the progress of treatments based on pathophysiology, mainly in the α-synuclein:

- Researchers and pharmaceutical companies are starting studies with immunotherapy for PD and MSA (Valera et al., 2016-b; Schenk et al., 2017). There is great expectation regarding immunological treatments for α-synucleinopathies.
- The knowledge of aggregation and clearance of α-synuclein will be the source of much research for many years towards better treatments for α-synucleinopathies (Schneeberber et al, 2016).
- The action of the gut and gut's flora on the pathophysiology of PD, as well as the involvement of the vagus nerve in the propagation of α-synuclein like the prions, will remain in the target of the scientists in the next years (Lee et al., 2011). It is hoped that new treatments may emerge from research in this area.

CONCLUSION

The studies to date have demonstrated the important participation of α-synuclein and Lewy bodies in the pathophysiology of several ND. However, a long road of discovery and understanding still awaits us. Research into the production of new drugs for the treatment of α-synucleinopathies has developed a lot, demonstrating new ways and unexpected and very interesting solutions. Regarding new treatments, the knowledge of recent years has brought many doors that need to be opened.

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Chapter 21
Alzheimer's and Parkinson's Disease Novel Therapeutic Target:
The Mitochondrial Pyruvate Carrier – Ligand Docking to Screen Natural Compounds Related to Classic Inhibitors

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ABSTRACT

Thiazolidinedione (TZD) drugs (Takeda Pharmaceuticals and Metabolic Solutions Development Company) targeting inhibition of the mitochondrial pyruvate carrier (MPC) are currently being tested in clinical trials to prevent progression into mild cognitive impairment of Alzheimer's disease (AD) or in the pipeline to prevent neurodegeneration in Parkinson's disease (PD). These have Ki values in the μM range. This study was focused on identifying candidate drug precursors of the natural cinnamic acid products that might have good bioavailability in the nM ranges forming covalent thiol bonds with targets. In silico protein homology modeling and ligand docking has demonstrated that binding cysteine residues within the transport channel is a key part of the inhibitory mechanism. These are covalent thiohemiacetal bonds with the alpha-carbon, carboxylate group, off a phenol ring. Like the classic MPC inhibitors, these natural derivatives of hydroxycinnamic acid have a conjugated pi-system used to form thiol bonds with the cysteine residue via Michael addition.

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INTRODUCTION

The 3-carbon metabolite, pyruvate, is a major substrate for energy production in the mitochondrion where it is converted into acetyl-coenzyme A by the pyruvate dehydrogenase complex. In 2012, a family of mitochondrial pyruvate carrier (MPC) membrane proteins were characterized (Herzig et al., 2012). These transporters were shown to carry pyruvate across the inner mitochondrial membrane. As a novel drug target, inhibition of the MPCs by thiazolidinedione (TZD) (Divakaruni et al., 2013) drugs is being tested for the prevention of mild cognitive impairment from Alzheimer's disease and the prevention of neurodegeneration from Parkinson's disease (Divakarini et al., 2017; Ghosh et al., 2016; Shah et al., 2014); see also a companion paper in this issue (Phelix, Bourdon, Dugan, Villareal, & Perry, 2017). Since the standard control MPC inhibitors, used in validation studies of the novel MPC inhibitors, are cyano-derivatives of a synthetic form of cinnamic acid, we were curious why no one has ever tested any of the natural cinnamic acid compounds for MPC inhibition. Relative to Alzheimer's disease we are also interested in the numerous natural derivatives that have potent anti-oxidant properties, since a key research focus has been on oxidative stress as the earliest measurable events in progression of this disease (Hammack, Perry, LeBaron, Villareal, & Phelix, 2015; Nunomura et al., 2001; Sayre, Smith, & Perry, 2001). Interestingly, caffeic acid phenethyl ester (2-phenylethyl (2E)-3-(3, 4-dihydroxyphenyl) acrylate, CAPE; also, a natural product from cinnamic acid) has been shown to prevent dementia in rats that had received intracerebroventricular streptozotocin (Kumar, Kaur, & Bansal, 2017).

The original inhibitors of mitochondrial pyruvate transport arose from analogues of the enol form of pyruvate actually intended to inhibit enzymes for pyruvate metabolism. The most potent transport inhibitors turned out to be derivatives of cinnamic acid with electron withdrawing groups promoting Michael addition reactions with cysteine residues in the MPC channel, i.e., α-cyanocinnamic acid and α-cyano-4-hydroxycinnamate (Halestrap, 1978; Halestrap & Denton, 1974; Nałęcz, Müller, Zambrowicz, Wojtczak, & Azzi, 1990). Later more potent inhibitors were developed with emphasis on the α-cyanopropenoate group and a hydrophobic aromatic side chain, e.g., α-cyano-β-(2-phenylindol-3-yl) acrylate (UK-5099) the most potent cinnamic acid derivative in micromolar (μM) ranges (Halestrap, 1975, 1978); or discovered as even more potent nanomolar range inhibitors as thiazolidine compounds, i.e., GW604714X and GW450863 (Hildyard, Ämmälä, Dukes, Thomson, & Halestrap, 2005). These drugs were rarely used for tissue or *in vivo* studies due to poor bioavailability attributed to both inhibition of the monocarboxylate transporter (MCT) and binding to albumin (Halestrap & Denton, 1975). Intestinal MCT is critical for absorption of many types of drugs and compounds for adequate oral bioavailability (El-Kattan, 2017). When they have been used for *in vivo* testing, large doses had to be administered via the intraperitoneal route due to binding to plasm proteins and lower potency for inhibiting MCT versus MPC (Granja et al., 2013; Patterson et al., 2014; Zhang et al., 2016). However, modifications of α-cyanocinnamic acid that greatly increased potency as MCT inhibitors, did not diminish oral bioavailability once sodium salt compounds were developed (Gurrapu et al., 2015) and it is not known if such modifications equally increase potency for MPC inhibition. Actually, all these *in vivo* studies neglect potential involvement of MPC inhibition in the focus of the experimental designs. Oddly, natural derivatives of cinnamic acid have not been tested directly for MPC inhibition (Adisakwattana, 2017; Alam et al., 2016; Ruan et al., 2014). Ferulic acid was shown to bind human MPC2 subunit using homology modeling and *in silico* molecular docking analyses (Otero, Papadakis, Gupta Udatha, Nielsen, & Panagiotou, 2010) and chlorogenic acid was shown to inhibit pyruvate oxidation in cardiac mitochondria (Bernatoniene et al., 2014). Chlorogenic acid has recently been reported, in a retrospective meta-analysis, to have positive

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cognitive and neuroprotective effects (Heitman & Ingram, 2017). This *in silico* study is a first step in a more thorough investigation of these natural compounds as MPC inhibitors.

Oddly as well, there are no comprehensive reports on the pharmacokinetics of the cyano-derivatives of cinnamic acid (Gurrapu et al., 2015), but numerous reports are available on pharmacokinetics and bioavailability of the natural compounds in animals and humans (Farah, Monteiro, Donangelo, & Lafay, 2008a, 2008b; Mckay, Chen, & Blumberg, 2010; Stalmach et al., 2009; Wang et al., 2009). Additionally, some of these natural compounds have been examined as candidate substrates of the p-glycoprotein (P-gp; aka. multidrug resistance protein 1, MDR1, or ATP Binding Cassette Subfamily B Member 1, ABCB1 gene product) (Gou et al., 2016; Mckay et al., 2010; Muthusamy et al., 2016; Najar et al., 2010; Tatsuzaki et al., 2006). There are standard tests required by the (FDA, 2015) focused on whether a drug is a substrate or inhibitor of P-gp, in part related to bioavailability via oral route of administration. As well for research purposes, protein homology modeling of the human P-gp and *in silico* protein docking analyses have become more common (Ali et al., 2015; Bikadi et al., 2011; Desai, Raub, & Blanco, 2012; Palestro, Gavernet, Estiu, & Blanch, 2014). A novel MPC inhibitor, lonidamine, and its derivative, adjudin, have limited bioavailability due to being a substrate for P-gp at the target cell level (Cervantes-Madrid, Romero, & Dueñas-González, 2015; Mansi et al., 1991; Nancolas et al., 2016; Su et al., 2013; Xie et al., 2013). The natural compounds have a high safety margin and can reach pharmacologically relevant concentrations in plasma with consumption of either whole food products, e.g., cooked potatoes, or processed food products and ethanol extracts in pill form, e.g., cranberry juice, not to mention caffeinated and de-caffeinated drinks (Farah et al., 2008a, 2008b; Mckay et al., 2010; Noguchi-Shinohara et al., 2015; Piñeros-Niño, Narváez-Cuenca, Kushalappa, & Mosquera, 2017; Stalmach et al., 2009). They may even be safe when co-administered with TZD drugs (Prabhakar, Prasad, Ali, & Doble, 2013). The safety profile for maximal inhibition of MPC for significant periods of time comes from the clinical trials on lonidamine, a substituted indazole-3-carboxylic acid that has a K_i of 2.5 μM for inhibiting MPC activity (Nancolas et al., 2016). Doses generating sustained plasma concentrations of 30 μM have been tolerated in Phase II cancer trials for up to two months (Mansi et al., 1991). Muscle pain due to buildup of lactic acid begins within 6 hours of oral administration of a 150 mg dose, an effect that is temporary with each dose, but over a period of days resolves spontaneously. Large doses in the animal studies have demonstrated high safety margins as well. All of this is important because if the current genetic marker, TOMM40 (Hayden et al., 2012), for pre-Alzheimer's disease – currently in year 3 of a 5 year Phase III clinical trial (Crenshaw et al., 2015) – becomes a standard companion diagnostic test (AmplideX® PCR/CE *TOMM40* Kit; Asuragen, Inc.), the patients will have to take the drug for the remainder of their lives.

The present study was focused on identifying candidate drug precursors with good bioavailability (in the nanomolar ranges) while forming covalent thiol bonds with targets. Thioether bond formation occurs through a Michael addition reaction with the conjugated pi-system of the drug candidate and the thiol functional group of a cysteine residue on the MPC. A Michael addition reaction relies on conjugate addition typically with an α, β-unsaturated carbonyl (e.g. hydroxycinnamic acid) in the presence of a nucleophilic carbanion (e.g. thiolate). This line of thinking is consistent with current strategies of generating reversible and irreversible protein-target inhibitors via Michael addition reactions with cysteine residues (Krenske, Petter, & Houk, 2016; Krishnan et al., 2014).

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METHODS

The methods used in this study have been described in great detail in two companion papers in this issue (Dugan, Bourdon, & Phelix, 2017; Phelix et al., 2017). Homology modeling was performed because the 3D crystal structure of MPC is not available. Uniprot (www.uniprot.org) was used to identify the primary sequence of MPC1 (UniProtKB - Q9Y5U8 (MPC1_HUMAN)) and MPC2 (UniProtKB - O95563 (MPC2_HUMAN)) and human P-gp (UniProtKB P08183 (MDR1_HUMAN)) that were then loaded into RaptorX (www.raptorx.uchicago.edu) to generate monomeric 3D protein models as protein database (pdb) files. MPC1 and MPC2 pdb monomeric files were submitted to PyDockWeb (https://life.bsc.es/servlet/pydock/home/) to form MPC1-2 heterodimers, where MPC2 was the receptor protein and MPC1 was the ligand protein. Single pdb files of heterodimeric MPC1/2 from PyDock were then loaded into LigPlot+ (www.ebi.ac.uk/thornton-srv/software/LIGPLOT/) for identifying hydrogen (H)-bonds at ligand-protein docking sites. All ligands were accessed either via PubChem or ChemSpider. Using AutoDock/Vina, protein ligand docking was performed to determine deltaG values (kcal/mol). The grid box 25 X 25 X 25 of 1 Å was centered on Cys61 of open-outward/closed-inward MPC1/2 heterodimer (Figure 1) and intramembrane substrate binding domain of P-gp. The exhaustiveness option was set at 20 for MPC1/2 and 8 (average accuracy) for P-gp as used by (Bikadi et al., 2011). A total of 20 conformers were generated for each substance. Results are reported as highest affinity and averaged of these 20 values. AutoDock uses a rigid protein and flexible ligand to generate pdb result files containing multiple conformers coordinates for the ligand. PDB Editor was used to combine each conformer, singularly, within the protein file, generating new pdb file for viewing and structural analysis with Swiss PDB Viewer (www.spdbv.vital-it.ch/), or Visual Molecular Dynamics (VMD; http://www.ks.uiuc.edu/Research/vmd/). Additionally, Swiss PDB Viewer was used for the computation of hydrogen bonds and various data collections (e.g. distance measurements). AutoDock/Vina PyMol Viewer was also used for 3D viewing and distance/angle measurements.

RESULTS AND DISCUSSION

Using AutoDock Vina, natural hydroxycinnamic acid compounds were screened for their affinity for MPC as a comparison against those standard controls mentioned (Table 1). CAPE had the highest affinity for MPC1/2 with a dissociation constant (K_d) nearly 10-fold different from the next natural compound, UK-5099, and any novel inhibitor. The other relevant natural compounds are, in order of highest to lowest affinity, chlorogenic acid, ferulic acid, rosmarinic acid, isoeugenol, trans-cinnamic acid, cinnamaldehyde, and sinapic acid (deltaG values from -7.2 to -5.6 kcal/mol). The potent, classic and novel MPC inhibitors had similar affinities: alpha-cyano-4-hydroxycinnamate (-6.0) and UK-5099 (-6.1), GW-compounds (-5.4 & -6.4), that were oddly lower than the less potent TZDs (-7.5 to -6.7). Lonidamine had a high affinity (-7.3), but it did not penetrate the channel to access the cysteine residue. The alpha-carbon carbonyl groups or double bonds (Figure 2) were positioned within 4 Å of the cysteine residue, proximities allowing thiohemiacetal and Michael addition reactions (Figure 3) (Chinchio, Czaplewski, Liwo, Ołdziej, & Scheraga, 2007; Muscatello, Muller, Mostofi, & Sutton, 2017).

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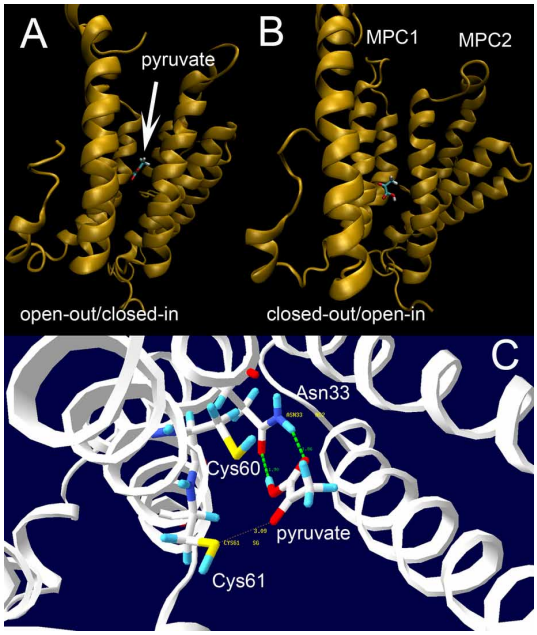
Figure 1. Ribbon views of the wt-MPC1/2 heterodimer with the alternating access conformations shown (A & B) and with pyruvate (arrow) bound in the mid-channel region where hydrogen bonds are formed with Asn33 of MPC1 (C) and the two cysteine residues are nearby for covalent bonding



Binding to P-gp was performed for known inhibitors that are not transported (elacridar and pivampicillin) (Chanteux et al., 2003; Chanteux, Van Bambeke, Mingeot-Leclercq, & Tulkens, 2005; Palmer, Chan, Dieckmann, & Honek, 2012) and substrates that are transported freely (propranolol) (Bachmakov, Werner, Endress, Auge, & Fromm, 2006) or highly lipophilic and transported from the cytoplasm (latanoprost), as well as a classic standard inhibitor (verapamil; (FDA, 2015)). An accepted negative control (metoprolol) was also tested (Bachmakov et al., 2006). The results are shown in Table 2 and for CAPE in Figure 4. I would seem that a deltaG value at or below -5.8 kcal/mol could be used as a gauge to predict whether a compound was a candidate substrate, and around >-7.0 kcal/mol as a candidate inhibitor. An *in silico* study on plant/seed fatty acids using the mouse P-gp as a template to generate a rat homology model and AutoDock Vina found deltaG values from -9.95 to -11.92 kcal/mol (Ali et al., 2015). It would seem these fatty acids would be candidates as inhibitors and not be expected to be transported. Equally important are the strength and number of hydrogen bonds (See Figure 4D, F, G) between the substrate and human P-gp (Desai et al., 2012). Another report using I-TASSER rather than RaptorX to generate the homology model of human P-gp protein, and AutoDock Vina for the ligand docking analyses, combined with FDA-expected *in vitro* testing, found highly reliable ranges of about -8 to -11 for binders and about -7 to -5 for non-binders concluding that a docking score of -9.7 or lower classified a binder and -6.5 or higher would predict non-affinity for the human P-gp active site (Palestro et al., 2014). Of the molecules we tested, only verapamil was included in their analysis, and since they did not provide the deltaG value from their analyses for verapamil in their study, we cannot resolve the discrepancy with our results. As well, our results with adjudin and lonidamine would disagree with their cutoff value of -9.7 and the evidence is strong that they are substrates of P-gp (Su et al., 2013). There are

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Table 1. MPC1/2 heterodimer binding affinities for test compound

Affinity (kcal/mol)	Hydroxycinnamic Acid Derived
-8.4	caffeic acid phenethyl ester
-7.2	3-chlorogenic acid
-6.9	5-chlorogenic acid
-6.9	ferulic acid
-6.9	rosmarinic acid
-6.8	isoeugenol
-6.6	3,5-O-dicaffeoylquinic acid
-6.6	caffeic acid
-6.5	4,5-O-dicaffeoylquinic acid
-6.2	trans-cinnamic acid
-6.1	1,3-O-dicaffeoylquinic acid
-6.1	5-cis-caffeoylquinic acid
-6.0	cinnamaldehyde
-5.8	3-O-trans-caffeoylquinic acid
-5.7	chlorogenic acid
-5.6	sinapinic acid
-5.6	sinapic acid
-5.5	vanillin
-5.3	β-ketoisocaproic acid
-5.3	ketoleucine
-5.2	α-ketoisocaproic acid
	Classic Inhibitors
-6.1	UK-5099
-5.9	phenylpyruvate
-5.7	α-cyanocinnamate
-5.6	α-cyano-4-hydroxycinnamic acid
-5.5	ethyl-α-cyanocinnamate
	Novel Inhibitors
-7.5	MSDC-0602
-7.5	adjudin
-7.3	lonidamine
	Endogenous Substrate
-5.0	pyruvate
-4.5	pyruvic acid

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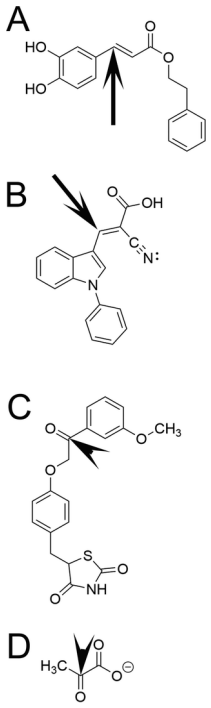
Figure 2. Molecular structures of (A) caffeic acid phenethyl ether, (B) UK-5099, (C) MSDC-0602, and (D) pyruvic acid. In the presence of a cysteine residue (i.e. in the mitochondrial inner membrane transporter) the thiol group, being a good nucleophile, can undergo reaction through two mechanisms; either a 1,4-addition (Michael reaction) or the formation of a thiohemiacetal bond through enolate chemistry. Conjugated pi-systems of A & B facilitate covalent bond formation thorough a Michael addition reaction at the β-carbon, labelled with an extended arrow. Compounds C & D lack accessible conjugated carbon atoms, and therefore must rely on the formation of a covalent thiohemiacetal bond at the carbonyl carbon; labeled by the arrow heads.



reports that CAPE (Gou et al., 2016), chlorogenic acid (Farrell, Dew, Poquet, Hanson, & Williamson, 2011; Najar et al., 2010), and ferulic acid (Muthusamy et al., 2016) are substrates. Sinapic acid and chlorogenic acid also are likely to induce expression of MDR1 (Li, Wang, Yao, & Li, 2010; Schelz et al., 2006); isoeugenol is reportedly not a substrate (Tatsuzaki et al., 2006). In the case of ferulic acid, our deltaG is higher than the -6.31 kcal/mol reported, but they also had binding interaction data with purified P-gp to substantiate their claim for substrate candidacy.

CONCLUSION

Exploiting Michael addition reactions, reversible or not, is becoming more common in covalent drug design and development. (Krenske et al., 2016; Krishnan et al., 2014) These are interesting natural compounds that reach relevant blood concentrations with food, spices, and drink intake, such as potatoes, wheat, broccoli, cinnamon, cranberries, tea, and coffee. Docking software that accounts for thiol bonding to determine affinities will be needed to advance these *in silico* screening technologies (Kumalo, Bhakat,

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Figure 3. Ribbon views of the MPC1/2 heterodimer with the pyruvate (A) in a thiohemiacetal bond (arrow) with Cys61. In (B) CAPE covalent bonding (double arrowheads) is superimposed and pyruvate (arrow) is bound in the mid-channel region where hydrogen bonds are formed with Asn33 of MPC1 and other residues nearby.

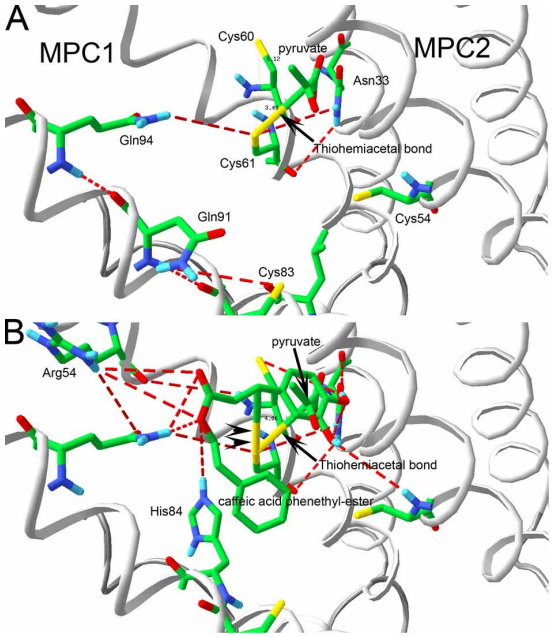

Table 2. Bioavailability index based upon binding affinity to MDR1 / p-glycoprotein / MDR1 / ABCB1

Affinity (kcal/mol)	Controls
-11.9	elacridar
-8.0	pivampicillin
-7.0	propranalol
-6.9	latanoprost
-6.6	verapamil
-5.8	metoprolol
-8.0	adjudin
-8.0	lonidamine
	Hydroxycinnamic acid derived
-7.3	caffeic acid phenethyl ester
-7.2	5-caffeoylquinic acid
-7.0	chlorogenic acid
-6.0	isoeugenol
-5.8	trans-cinnamic acid
-5.6	cinnamaldehyde
-5.6	ferulic acid
-5.6	sinapinic acid
-5.5	caffeic acid

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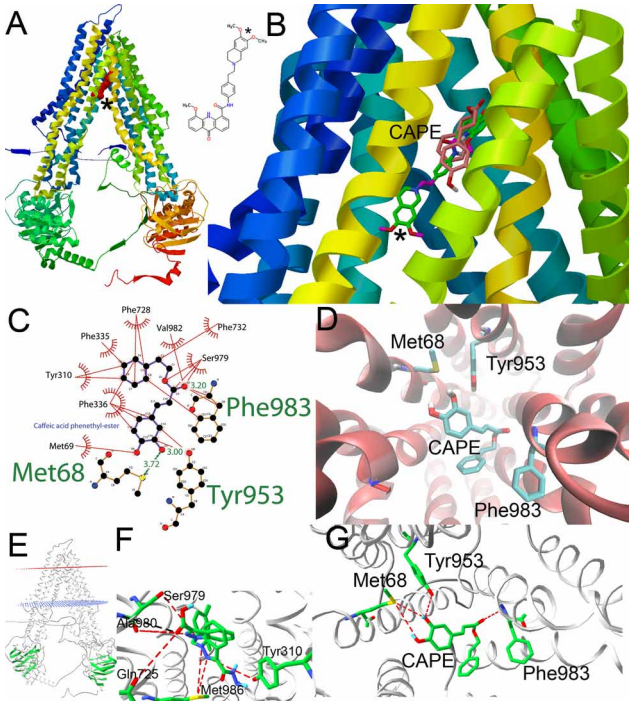
Figure 4. MDR1 (p-glycoprotein) binding assesses bioavailability of compounds. See Table 2. A&B) elacridar (asterisk) is not transported and is a potent inhibitor. Others are pivampicillin (not transported – inhibitor); propranalol (freely transported); latanoprost (highly lipophilic – transported from cytoplasm); verapamil (classic standard inhibitor); metoprolol (negative control); adjudin & lonidamine (f) are non-steroid male contraceptive and cancer therapeutics that inhibit MPC at nM range. B, C, D, & G) caffeic acid phenethyl ester (CAPE) had the highest affinity for both MPC1/2 and MDR1 of the test compounds and forms bonds in the transport zone of the MDR1 within the membrane (E) C) ligplot generates a 2D image of the ligand (CAPE) and H-bonds (dashed lines with distance in Å and residues identified with large font) and hydrophobic interactions (residues in small font, 'eyelashes', and red dotted lines). D&G) CAPE shown in 3D images with VMD and Swiss PDB viewer, respectively. F) Superimposition of adjudin and lonidamine showing H-bonds that are either strong (red dashed lines) or weak (black dashed line).



& Soliman, 2015). It will be intriguing to assess the role of Michael addition reactions in the pathology of neurodegenerative diseases and whether compounds with these properties can lower the 'bad' reactions and preserve normal function of the cysteine proteome (Butterfield & Abdul, 2010; Go, Chandler, & Jones, 2015; Haynes, Szweda, Pickin, Welker, & Townsend, 2000; Sayre et al., 2001).

It is unassailable that a well-balanced diet and regular physical exertion contributes to a healthier life. However, in this age of increasing technology reliance for work and entertainment there has been a sharp spike of sedentary habits in our global society. Combined with a high caloric (fatty/carbohydrate) diet prolong exposure to these quotidian factors can lead to chronic diseases such as hyperglycemia, arthritis, liver cirrhosis, inflammation, pancreatitis, asthma and heart disease. (Alam et al., 2016) Evidence has suggested that foods such as cereals, fruits and vegetables containing phenolic and polyphenol compounds lead to beneficial health outcomes. (El-Seedi et al., 2012) But, reabsorption and individual

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metabolism remain critical challenges in designing pharma and nutraceutical compounds. (Farah et al., 2008a, 2008b) Mitochondrial deficits have been observed in obesity, which is also associated with hyperglycemia and insulin resistance and are highly suspect in neurodegenerative diseases (Hirai et al., 2001; Sayre et al., 2001). Finally, these substance on their own might not become first line therapy for neurodegenerative disease, but they might serve well as prodrugs for improvements on other top candidates or serve as a modified combined therapy (Fu, Zhuang, Zhou, & Wang, 2015; Prabhakar et al., 2013; Urbaniak, Kacprzak, Senol, Orhan, & Radominska-pandya, 2017).

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Chapter 22
MSDC-0160 and MSDC-0602 Binding with Human Mitochondrial Pyruvate Carrier (MPC) 1 and 2 Heterodimer:
PPARγ Activating and Sparing TZDs as Therapeutics

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ABSTRACT

The mitochondrial pyruvate carrier (MPC) is a novel target for therapeutic drugs to treat Alzheimer's and Parkinson's disease, diabetes mellitus, and non-alcoholic steatohepatitis (NASH). Metabolic Solutions Development Company (MSDC) has two thiazolidinediones, MSDC-0160 and MSDC-0602, in the pipeline. This report describes results for a MPC1/2 heterodimer homology model. The FASTA sequences for MPC1 and MPC2 were accessed from UniProt and submitted to RaptorX, resulting in best candidate monomeric "protein data base" files for each. One mutant form of MPC1, L36I, was also processed. These were submitted to PyDock to generate best candidate MPC1/2 heterodimer models that were used for ligand docking analyses with AutoDock Vina and "Rosetta Online Server that Includes Everyone" (ROSIE). Multiple binding sites for pyruvate and both drugs were found on both MPC1 and MPC2 subunits with drugs having nearly double the affinity in each case except the intermediate and open-in states for the L36I mutant transporter.

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INTRODUCTION

The mitochondrial pyruvate carrier (MPC) had been studied extensively in the 1970s through 1990s by two lab groups primarily, Andrew Halestrap and Katarzyna Nalęcz, providing many predictions on the functional protein structure and the mechanism of substrate binding. (Halestrap, A P, Denton, 1974; Halestrap, 1975, 1976, 1978a, 1978b; Hildyard, Ämmälä, Dukes, Thomson, & Halestrap, 2005; K. Nałęcz, 1994; Nałecz, Kamińska, Nałecz, & Azzi, 1992; K. A. Nałęcz, Müller, Zambrowicz, Wojtczak, & Azzi, 1990; M. J. Nałęcz et al., 1986) The two genes for MPC had been identified in 2012, along with evidence for pyruvate transport, but there was still doubt as to whether an MPC1 – MPC2 complex within the inner mitochondrial membrane (IMM) had pyruvate transport abilities (Bricker et al., 2012; Halestrap, 2012; Herzig et al., 2012). Recently, Halestrap and coworkers have utilized homology modeling and molecular dynamic simulations to generate 3 dimensional models of proton-linked monocarboxylate transporters (MCTs) and to identify key amino acid residues in the transport cargo and blocker binding sites (Manoharan, Wilson, Sessions, & Halestrap, 2006; Nancolas, Sessions, & Halestrap, 2015; Wilson, Meredith, Bunnun, Sessions, & Halestrap, 2009). Likewise, for MPC, still since 2012, no crystal structure has yet been registered or deposited in a protein data bank (PDB); and thus, a similar approach is reasonable. One homology model of the MPC1/2 heterodimer has been proposed using the bacterial semiSWEET (4QND.PDB) transporter as a template with indications of residues involved in the ligand binding site (Vanderperre, Bender, Kunji, & Martinou, 2015). This present report describes results for another MPC1/2 heterodimer homology model, based on a template using the *E. coli* respiratory complex I membrane domain B (3RKO.PDB), residues 242-366 and rmsd ranging from 2 to 9 Å. Along with the ligand docking results, this model is entirely consistent with and supports the hypothetical models proposed by both Halestrap and Nalęcz (Halestrap, 1978a, 1978b; K. Nałęcz, 1994). The predicted amino acid sequences for human MPC1 and MPC2 from UniProt (Bateman et al., 2015) were used.

Inhibition of the MPC as a novel therapeutic target is being tested currently at Phase 2 (MSDC-0160; NCT01374438) (Shah et al., 2014) clinical trial focused on progression from mild cognitive impairment to dementia of Alzheimer's disease, (MSDC-0602; NCT02784444) for non-alcoholic steato-hepatitis (NASH) (Chen et al., 2012; McCommis, Hodges, Brunt, et al., 2016), and diabetes mellitus (MSDC-0160; NCT00760578) (Colca, VanderLugt et al., 2013); and soon for Parkinson's disease (MSDC-0160) (Ghosh et al., 2016). Another study on treatment to delay onset of Alzheimer's disease is in Phase 3 (pioglitazone, aka AD-4833; NCT01931566) (Crenshaw et al., 2015) and there is some evidence that it can bind MPC but that is not the stated target for this treatment. Thiazolidinediones (TZDs), pioglitazone (a peroxisome proliferator-activated receptor-gamma, PPARγ, agonist) and MSDC-0160 and MSDC-0602 (PPARγ-sparing TZDs) (Chen et al., 2012), are the drugs being tested. Thus, any new information and insight on the mechanisms of actions of these drugs are valuable and the 3D standard data file (SDF) formats, required for ligand docking *in silico*, are available for each of these drugs, as well as most of the classical inhibitors used in the very early biochemical studies. This study focuses only on the two MSDC drugs.

Thirty four non-synonymous single nucleotide polymorphisms (nsSNPs, or missense mutations) https://www.ncbi.nlm.nih.gov/SNP/SNP_ref.cgi?locusId=51660 are posted for human MPC1 while human MPC2 has 37 nsSNPs listed on the NCBI dbSNP https://www.ncbi.nlm.nih.gov/SNP/SNP_ref.cgi?locusId=25874 Short Genetic Variations page. Recently, in 2016, an online large-scale reference data set of human genetic variation, generated as part of the Exome Aggregation Consortium (ExAC), has become available and contains an aggregation and analysis of high-quality exome (protein-coding

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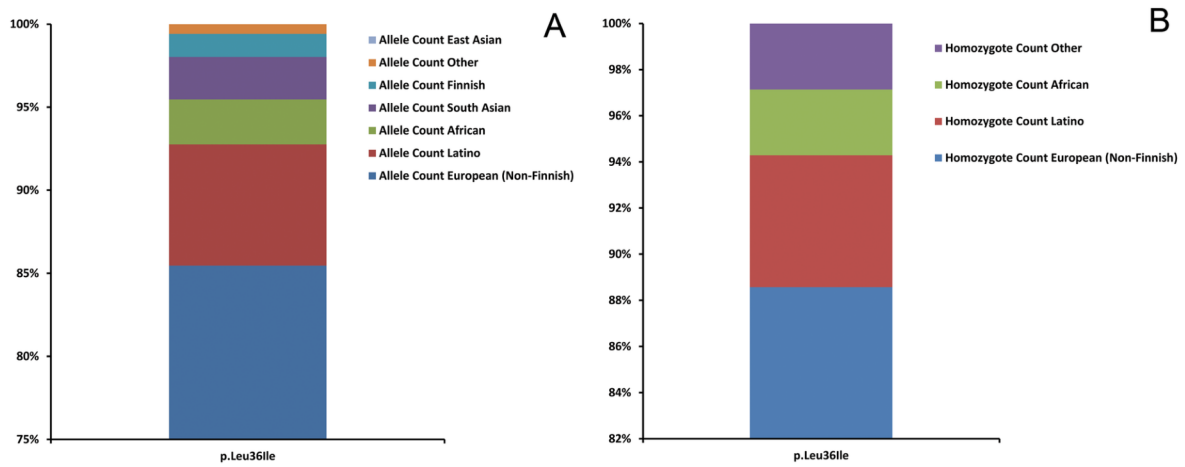
Figure 1. Percent stacked column graphs displaying results from the EXAC web site on L36I nsSNP allele count (A) and homozygote count (B)



region) DNA sequence data on SNPs for 60,706 individuals of diverse ancestries. (Lek et al., 2016) The nsSNP for MPC1 gene of highest allele frequency in this population of humans was leucine substituted by isoleucine in the 36th amino acid residue (L36I) at 0.01675 (Figure 1). Therefore, this nsSNP was also modeled and tested for binding properties.

Other than that hypothetical data from biochemical analyses during the 1970s-1990s showing a critical role for an even number of cysteine residues, likely forming thiohemiacetal bonds with transporter substrate (Egger et al., 2012; Halestrap, 1978a, 1978b; K. Nałęcz, 1994; Zarate-Romero, Murillo-Melo, Mujica-Jimenez, Montiel, & Munoz-Clares, 2016), along with arginine and possibly histidine and lysine residues (Denton & Halestrap, 1979), no conclusive structural evidence has yet appeared in the literature for studies of the pyruvate and inhibitor interactions with MPC1&2. Colca and coworkers have demonstrated that their specialized TZD photoprobe, MSDC-1101, binds to fruit fly and rat MPC2 and can be competitively blocked by MSDC-0602 and MSDC-0160 (Colca, McDonald, et al., 2013). Regardless, this complicated molecular approach provides no definitive evidence about the binding sites for these drugs in the MPC complex, i.e., human MPC, in particular relative to the binding site for pyruvate. There are some existing 3D crystal structures of pyruvate bound within enzyme active sites, i.e., human pyruvate carboxylase and a protozoan parasite lactate dehydrogenase (Cook, Senkovich, Hernandez, Speed, & Chattopadhyay, 2015; Xiang & Tong, 2008) for download and close examination (See Figure 2), but not with any transporters.

A) Pyruvate forms hydrogen bonds with two arginine residues of human pyruvate carboxylase and biotin. 3bg3.PDB. arrow – pyruvate. (Xiang & Tong, 2008); B) residues Arg571 and Arg644 of human pyruvate carboxylase form hydrogen bonds with pyruvate; C) pyruvate binds to the enzyme between the nicotinamide ring and several lactate dehydrogenase (LDH) residues. Model 4nd4.PDB. arrow – pyruvate. (Cook et al., 2015); D) Four LDH residues form hydrogen bonds with pyruvate and two form hydrogen bonds with one of those, His195. NAD is shown at the left; E) betaine aldehyde (BAL) forms a thiohemiacetal bond with Cys450 of betaine aldehyde dehydrogenase. The BAL forms hydrogen bonds with Tyr160 (above), Cys291, Gln448 (left), Pro449 (foreground), and Trp456 (right). Model 5a2d.PDB. arrow – thiohemiacetal bond (inset also); arrowhead – Cys291. (Zarate-Romero et al., 2016); F) LigPlot

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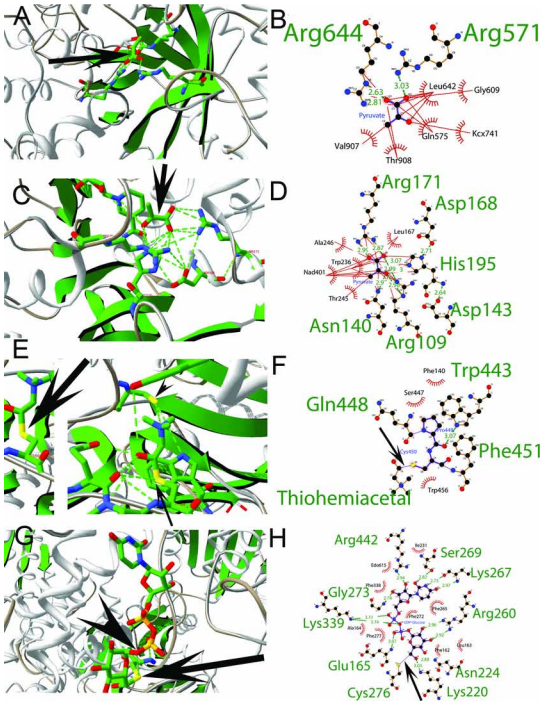
Figure 2. Examples of pyruvate binding sites on pyruvate carboxylase (A&B) and lactate dehydrogenase (C&D) and thiohemiacetals of betaine (E&F) and UDP-glucose (G&H). 3D-ribbon views with Swiss PDB viewer (A, C, E, G) and 2D-ligplot (B, D, F, H).



shows the thiohemiacetal bond between Cys450 and betaine aldehyde but does not detect the residues of the dehydrogenase enzyme that also form hydrogen bonds with the BAL (bottom left); G) UDP-glucose forms a thiohemiacetal with Cys276 of human UDP-glucose dehydrogenase; sulfur with C6 of glucose. Two hydrogen bonds are seen below from the UDP-glucose onto the backbone of Cys276. 3khu.PDB. arrow – thiohemiacetal bond; arrowhead – C1 of glucose bonded with phosphate group of UDP. (Egger et al., 2012); H) Three UGDH residues, Lys220, Asn224, & Arg260 form four hydrogen bonds with the glucose molecule involved in the thiohemiacetal bond. Six others form bonds with UDP.

Bricker et al. had earlier demonstrated that MPC1 is a site of interaction of UK-5099, a potent pyruvate transport inhibitor (Bricker et al., 2012). However, that study was on a yeast mutant of MPC1, at amino acid residue Asp118Gly, that is no longer responsive to inhibition by UK-5099. Binding and inhibition for human MPC cannot be considered analogous since the human MPC1 has only 109 amino acids and shares minimal homology with the C-terminal sequence of yeast. Additionally, this is inconsistent with the proposed Michael addition of UK-5099 to a cysteine residue, which forms a covalent alkyl sulfide bond to the MPC (Divakaruni et al., 2013; Halestrap, 1976, 1978a; Hildyard et al., 2005). The first 16-22 residues of mouse and human MPC2 are not required for the blocking effects of UK-5099, MSDC-0160, and MSDC-0602 (Vigueira et al., 2017). There are still many challenges to crystalizing proteins of the IMM, due to processing by transporter protein complexes of the outer (TOMM) and inner (TIMM) mitochondrial membranes (Kühlbrandt, 2015; Neupert & Herrmann, 2007) not to mention the critical role of cardiolipins in the assembly of mitochondrial carrier proteins (Claypool, 2009). Anne N. Murphy and Geoffrey A. Chang have a specific aim to determine a high-resolution structure of the human MPC

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protein complex in a NIH grant funded since 2014 with no crystal structure yet posted (http://grantome.com/grant/NIH/R01-NS087611-02) (Divakarini et al., 2017). Thus, homology modeling is the likely starting point to gain insights into the pyruvate and drug binding sites on the human MPC complex.

Our major objectives in this project emerged from a discourse by Colca and coworkers via letters to the editor about their recent publication on MSDC-0602 effects on a mouse model of NASH (McCommis, Hodges, Brunt, et al., 2016; McCommis, Colca, & Finck, 2017; Musso & Gambino, 2017): The "next generation" TZDs, i.e., MSDC-0160 and MSDC-0602, do have limited affinity for binding and direct activation of the PPARγ. Do both pioglitazone and rosiglitazone bind the MPC complex as an alternative target? If, yes, then is there a difference in the binding affinity? The "next generation" TZDs do bind the MPC complex and are more potent than 'prior generation'. These were in addition to some basic questions: What is the structure of MPC complex and how is it affected by the L36I mutation as a nsSNP? Is the MPC a viable therapeutic drug target for novel treatments of these disorders? Finally, can pyruvate or either of these new drugs form covalent, i.e., thiohemiacetal or Michael addition, bonds with the cysteine residues in the MPC subunits?

MATERIALS AND METHODS

Homology Modeling and Protein-Protein Docking (SNP Predicting Structure)

Since the 3D crystal structure for MPC is not yet available, homology modeling was performed. The primary sequence of wild type (wt) MPC1_Human (Q9Y5U8) and MPC2_Human (O95563) were acquired from UniProt http://www.uniprot.org/ and loaded to RaptorX (Källberg et al., 2012) online http://raptorx.uchicago.edu/ to use templates and generate monomeric 3D protein models in protein database (PDB) files. Mutant forms were generated simply by editing the text in the FASTA files. Uniprot FASTA sequences for wt-MPC1 and MPC2 were submitted to RaptorX that uses templates. FASTA sequence was altered for one mutant and also submitted to RaptorX:

L36I – nsSNP rs11557064; no clinical evidence, highest MPC1 allelic frequency, and considered benign.

A template (3RKOB.PDB) that worked best for MPC2 was used in common to both MPC1 model predictions. MPC1 and MPC2 PDB monomeric files were then submitted to pyDockWeb to form MPC1-2 heterodimers. MPC2 was used as the receptor protein and MPC1 as the ligand protein; http://life.bsc.es/servlet/pydock/home/ (Jiménez-García, Pons, & Fernández-Recio, 2013).

One of the nsSNPs listed on UniProt for MPC1, L36I (leucine substituted by isoleucine in the 36th amino acid residue) was also modeled this way. These single PyDock PDB files, of heterodimeric MPC1/2, were then loaded into the LigPlot^{+} for using the DimPlot function to analyze the protein-protein docking studies; http://www.ebi.ac.uk/thornton-srv/software/LIGPLOT/ (Laskowski & Swindells, 2011).

Protein and Ligand Docking (SNP Affecting Drug Binding)

Protein ligand docking was performed with AutoDock/Vina (Trott & Olson, 2010) to determine affinity as deltaG values in kcal/mole. Based upon early studies of MPC properties (Phelix & Dugan, 2016; Phelix, Villareal, LeBaron, Perry, & Roberson, 2014), the grid was centered on the cysteine residues

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within the heterodimeric channel using 32 X 20 X 20 grid points and a 1 Å spacing. Other sites along the length of the transporter channel were identified and used as grid centers also. AutoDock uses a rigid protein and flexible ligand, generating a results PDB file containing multiple conformers coordinates for the ligand. This conformer PDB file is needed for the rigid ligand – flexible protein method of ROSIE Ligand Docking on line (Combs et al., 2013) http://rosie.rosettacommons.org/ligand_docking, which generates a single PDB file containing coordinates for both the heterodimeric protein and ligand for viewing and structural analyses, e.g., with Swiss PDB Viewer http://sPDBv.vital-it.ch/ (Kaplan & Littlejohn, 2017) Swiss PDB Viewer was also used for computation of hydrogen bonds and other data collections, such as distance measurements; along with LigPlot+. AutoDock/Vina PyMol Viewer was also used for 3D viewing and distance and angle measurements (Sanner, 1999).

The 3D ligand SDF files for the following molecules were downloaded from PubChem https://pubchem.ncbi.nlm.nih.gov/, and converted to PDB files using Babel https://openbabel.org. Babel was also used to convert AutoDock/Vina ligand conformer PDBQT files to SDF files for use on ROSIE Ligand Docking:

1. Pyruvate (CID 107735)
2. Pyruvic acid (CID 1060)
3. MSDC-0160 (CID 146062-49-9)
4. MSDC-0602 (CID 1133819-87-0)
5. Avandia or rosiglitazone (CID 25058199)
6. Pioglitazone (CID 4829)
7. UK-5099 (CID 6438504)

The TZDs, MSDC-0602 and MSDC-0160 were tested as novel MPC inhibitors and compared with pyruvate, UK-5099, as well as 'classic' TZDs rosiglitazone and pioglitazone binding. The inactive compound, MSDC-1473 (3D file provided by Kalexsyn, Inc.), was also tested for MPC binding (Colca, McDonald, et al., 2013).

Two sets of PPARγ crystal structures were used to test binding of ligands: 1rpg.PDB (apo) and 2rpg.PDB (holo with rosiglitazone) (Nolte et al., 1998), and 4ema.PDB (holo with rosiglitazone) and 2xkw.PDB (holo with pioglitazone) (Liberato et al., 2012). PPARγ models 2xkw.PDB and 4ema.PDB are aligned but offset from each other and key ligand binding domain (LBD) residues were Cys285, Gln286, Ser289, His323, His449, and Tyr473, as determined by LigPlot+ analyses of original holo crystal files. For all binding studies His323 was set as the target, deep within the LBD. The original 2xkw.PDB model shows pioglitazone bound to Tyr473 and His323 through hydrogen (H)-bonds with the thiazolidinedione (TZD) ring of the acidic head of the drug. The Cys285 forms a H-bond with the sulfur within the TZD ring of pioglitazone. The rosiglitazone was deleted from the 4ema.PDB model, and pioglitazone from the 2xkw.PDB model, and the remaining PPARγ 4ema*.PDB and 2xkw*.PDB models were used for testing binding of pioglitazone and rosiglitazone into the LBD as a control for accuracy of binding with the AutoDock/Vina and to determine affinity values.

RESULTS AND DISCUSSION

Figure 3 shows the results of the ligand binding of rosiglitazone and pioglitazone, as well as MSDC-0160 and MSDC-0602 to PPARγ (panels A-D), and of rosiglitazone and pioglitazone to the MPC1/2

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heterodimer model (panels E&F). Neither MSDC-0602 (Figure 3A) nor MSDC-0160 (Figure 3C) fully entered the T-shaped cavity deep within the full LBD of PPARγ that is made up of 13 α-helixes and a small four-stranded β-sheet (three of which can be seen as green arrows in Figure 3). They only bound in the outer domain between helix-3 (H3) and the β-sheet and never successfully penetrated through the ligand-entry site such that the TZD head never made several specific bonds with the amino acid residues (His323, His449, and Tyr473) in H3, H4, H10 and the AF-helix. When rosiglitazone and pioglitazone (Figure 3B & D) bind within the T-shaped cavity (location 1 Figure 3), the sulfur of the TZD head group is positioned in a hydrophobic pocket near Gln286, the central benzene ring extends outward through a narrow pocket between Cys285 and Met364, resulting in the ring at the opposite end of the molecule resting in the pocket (location 2 Figure 3) between H3 and the β-sheet. This deep positioning of the TZD head group and high affinity binding to the residues listed is required for receptor activation (Nolte et al., 1998). These *in silico* binding results are entirely consistent with *in vitro* binding and activation results (Chen et al., 2012).

The affinity (deltaG) of rosiglitazone for PPARγ was -8.1 and pioglitazone was -7.5 kcal/mole. These deltaG values would give rosiglitazone a dissociation constant (Kd) value 3-fold that of pioglitazone, which agrees with general values reported of ~50 nM and ~200 nM, respectively. It is important to note that when the delta_deltaG (difference between the deltaG values) for the two binding states is equal to 1 kcal/mole, the K_d for condition 2 is about 5-fold different (lower affinity constant, K_a, concentration value; thought of as high affinity binding) than that for condition 1; and 1.4 kcal/mole is a 10-fold difference. (Borea, Dalpiaz, Varani, Gilli, & Gilli, 2000; Borea, Varani, Gessi, Gilli, & Dalpiaz, 1998; Encinar & Fernández-, 2015) These deltaG values of these TZDs all are much lower than the range of -10.0±0.9 to -11.4±0.9 kcal/mole for plant-derived polyphenols using these same PPARγ PDB models and AutoDock/Vina (Encinar & Fernández-, 2015). From these present *in silico* results, rosiglitazone has a higher affinity than pioglitazone for binding this crystal structure of PPARγ, consistent with accepted knowledge in the field. It is important to note here that three of these crystal structures (2xkw. PDB, 4ema.PDB, and 2rpg.PDB) are in the ligated state and have already undergone the conformational change to activate the receptor. Also, the conclusion can be made that the MSDC-0160 binding location, because its TZD head group does form H-bonds in the T-shaped LBD of PPARγ is consistent with its 9.58-fold lower activation than pioglitazone versus the 12.96-fold lower activation for MSDC-0602 than pioglitazone (Chen et al., 2012). However, because only the TZD ring is involved in the actual binding among these very similar molecules, the hydrophobic tail might also be associated with the conformational changes required for activation (Dixit & Bharatam, 2013; Liberato et al., 2012). These studies cannot effectively determine whether these bindings of the MSDC drugs could induce such changes in the PPARγ, but they do show that the binding locations are far too inconsistent with those required for full transcriptional activation (De Groot et al., 2013).

For the MPC1/2 heterodimer, open-outward / closed-inward conformation, tested in this case, the deltaG for pioglitazone was -4.9 and rosiglitazone was -4.8; whereas MSDC-0160 was -6.7 and MSDC-0602 was -7.5. With this same MPC1/2 heterodimer model, pyruvate bound with an affinity of -4.0, approximately 4-fold less than pioglitazone and rosiglitazone. In another model of a MPC1/2 heterodimer, pioglitazone had an affinity of -6.8. (Phelix & Dugan, 2016) These *in silico* binding results are consistent, for the most part, with *in vitro* results for these TZDs affecting MPC functionally (Divakaruni et al., 2013).

A) MSDC-0602 is bound in the outer LBD of PPARγ near the β-sheet (green arrows within protein structure). The thiazolidinedione (TZD) head group is oriented opposite to that required to enter the inner T-shaped cavity (1). When rosiglitazone (Ros) and pioglitazone (Pio, Figure 3B & D) bind within

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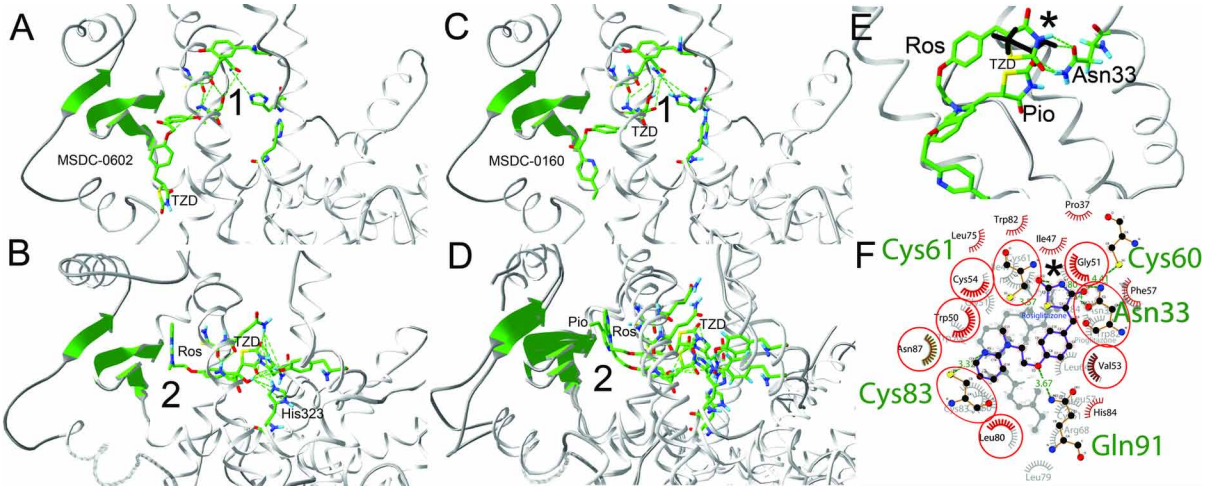
Figure 3. Swiss PDB viewer (3D view; A-E) and LigPlot (2D view; F) were used to visualize binding sites of PPARγ (A-D) and MPC1/2 (E, F) for rosiglitazone and pioglitazone (B, D, E, & F) as well as MSDC-0160 and MSDC-0602 for PPARγ (A&C).



the T-shaped cavity (location 1), the sulfur of the TZD head group is positioned in a hydrophobic pocket near His323, the central benzene ring extends outward through a narrow pocket between Cys285, resulting in the ring at the opposite end of the molecule resting in the pocket (location 2) between H3 and the β-sheet. C) MSDC-0160 is bound in the outer LBD near and its TZD head group partially enters the narrow pocket but not fully into the T-shaped cavity. It forms a hydrogen bond with only Gln286. D) Dual display of crystals 4ema.PDB and 2kxw.PDB showing that their 3D coordinates are offset conveniently to compare position of rosiglitazone (Ros) and pioglitazone (Pio) in the activating binding orientation. E) The TZD rings (asterisk) of both pioglitazone (Pio) and rosiglitazone (Ros) form H-bonds with Asn33 of MPC1/2 heterodimer; where pyruvate (black) is also bound. F) LigPlot+ shows amino acid structures and labels in large font when illustrating the H-bonds (dashed line with distance in Å); the eyelash shape with small font labels for amino acid residues and solid red lines show hydrophobic interactions with the ligand. The red circles and oval show items common to both models analyzed by the LigPlot+ algorithm. A triple overlay of all three ligands in (E) with the asterisk again showing the location of the TZD rings and pyruvate (in the far background, grey shade). Rosiglitazone is shown in the foreground (colored) to demonstrate 4 unique H-bonds with Cys60, Cys61, Cys83, and Gln91 in addition to ones with Asn33 in common with both pioglitazone and pyruvate.

RaptorX (Källberg et al., 2012) generated 5 top ranked monomeric 3D models for both human MPC1 and human MPC2. For MPC1 the best template was 3rkoB, p-value 1.20e-03, overall uGDT (GDT) [u = un-normalized; GDT = global distance test score]: 30 (27); 109(100%) residues were modeled, 6(5%) positions predicted as disordered, with secondary structures of: 67% helixes, 4% extended strand in β ladder, 27% coil and solvent access of: 22% exposed, 21% medium, 55% buried residues. The MPC1 sequence was aligned to residues 259 through 356 of 3rkoB, i.e., the B subunit of the membrane domain of respiratory complex I from E. coli. (Efremov & Sazanov, 2011) For MPC2 the best template was 3rkoB, p-value 2.31e-03, overall uGDT (GDT): 35 (28); 127(100%) residues were modeled, 15(11%) positions predicted as disordered, with secondary structures of: 76% helixes, 6% extended strand in β ladder, 17%

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coil and solvent access of: 20% exposed, 27% medium, 51% buried residues. The MPC2 sequence was aligned to residues 242 through 366 of 3rkoB. The estimated model error rounded to the nearest integer was 3 to 9 Å for MPC1 and 2 to 9 Å for MPC2. The number of identical residues in the alignment for each MPC was less than 15%. With overall scores of 53 and 56, respectively, these are average models for MPC1 and MPC2 but more detailed than the top randomly-generated models, e.g., as used in a prior preliminary report (Phelix, Perry, & McHardy, 2015). Still these were preferable because they each had 3 alpha helixes that could include transmembrane spanning segments (TMHs) and they appeared compatible for dimerization (Figure 4). The first two TMHs of MPC1 and all three of MPC2 matched those predicted on UniProt. This third TMH at the carboxy-end of MPC1 is still controversial. And if we are to draw any analogies from the semiSWEET model of heterodimeric MPC1/2 (Vanderperre et al., 2015), then two monomers with 3 TMHs each are expected. The Cys83 residue in this TMH3 would be the one to form the interchain/interdomain disulfide bond with the Cys54 of MPC2 (Figure 5B) as predicted (K. Nałęcz, 1994). Additionally, this third TMH in MPC1 is key for associating it with the PQ-loop family of membrane transporters (Bender, Pena, & Martinou, 2015; Jezegou et al., 2012; McCommis & Finck, 2015). This might be a faulty association in that only MPC1 has a single PQ (actually a QP) within this inter-TMH loop and MPC2 has none, thus failing the 'pairs of repeats' criterion for this family (Pfam Family: *PQ-loop,* PF04193; http://pfam.xfam.org/family/PQ-loop) – again assuming a heterodimeric MPC1/2 complex.

PyDock generated different models of the MPC1/2 heterodimer, which could be sorted into the conformations matching an alternating access model similar to other proton substrate symporters (Dang et al., 2010; Wisedchaisri, Park, Iadanza, Zheng, & Gonen, 2014; Yan, 2013). Figures 4 and 5 show the conformations of open-outward / closed-inward, intermediate, and closed-outward / open-inward for these wild type MPC1/2 homology models. Table 1 shows the binding affinity values for pyruvate in each of these conformations where the binding grid was centered on different residues. Four different locations of pyruvate binding were identified along the length of the transporter channel (Figure 4). At least 10 key locations on the MPC1/2 heterodimer complex were identified in association with pyruvate binding, transport and conformation changes associate with alternating access (Figure 5). A video is posted on YouTube to demonstrate the events for pyruvate transport across the mitochondrial inner membrane into the matrix https://www.youtube.com/watch?v=KdlIBhAT6Mo.

A) Ribbon view of MPC1/2 heterodimer as a 'frontview' using Swiss PDB viewer for 15 results of ROSIE ligand docking. Select residues are shown with licorice view, as are all the pyruvate conformers at positions 1 through 4 within the transporter channel. The asterisks at top on left mark positions of Ile41 and Glu49 on MPC1; and the single asterisk at top right indicates location of both Arg39 and Thr40 of MPC2. This is the open-outward position and the Lys residues at the bottom (collectively Lys72 on MPC1 at left and Lys122 and Lys124 on MPC2 on right) show closed-inward position on the matrix side. Pyruvate (licorice green with red) is bound at 4 locations from MIMs to matrix side of the transporter channel. Location 1 has hydrogen bonds with Arg54 of MPC1; location 2 with Glu21 of MPC2; location 3 with Asn33 of MPC1 (representing Asn33, Gly29, & Cys60 complex); and location 4 with Arg68 of MPC1. Interchain hydrogen bonds would be between Trp34 of MPC1 and Gln71 of MPC2, and His26 of MPC1 and Ser68 of MPC2. Only one interchain bond was detected between Asn33 of MPC1 and Glu21 of MPC2 with PyMol after autodock/vina ligand protein docking in panel B. ROSIE ligand docking uses rigid ligand conformers and flexible protein; whereas vina uses flexible ligand and rigid protein. Inset bottom left is smaller scale showing pioglitazone and MSDC-0602 binding at location 1 in (A). MPC1-Arg54, Gln91, and Gln94 are forming H-bonds with the TZD ring

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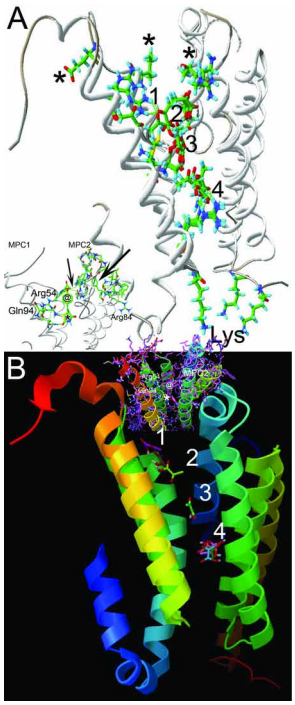
Figure 4. Hypothetical transport path of pyruvate (1, 2,3,4) through the transport channel between MPC1 (left) and MPC2 (right). Heterodimer in the open-outward/closed-inward, holo, conformation. The mitochondrial intermembrane space (MIMs) is at the top and matrix at the bottom.



(asterisk) and MPC2-Arg39 is forming H-bonds (just beyond tip of small arrow) with the oxygen (red) off the benzene ring (@) of the linker. MPC2-Tyr32 does not bind pioglitazone but does form a H-bond (at tip of small arrow) with oxygen off the terminal ring of MSDC-0602; otherwise when pioglitazone is bound it forms three intrachain H-bonds across the first MIMS interhelix loop of MPC2. MPC2-Tyr85 (large arrow) extends from the beginning of the second MIMS side interhelix loop into the first interhelix loop forming H-bonds with the backbones of Glu26, Lys27, and Tyr32. These are all Included in the residues pulled down with the crosslinked photoprobe and they all are shown only as the backbone except the sidechains of Tyr32, Arg39, Arg84, and Tyr85 are Shown. B) Ribbon view of MPC1/2 heterodimer as in panel A 'frontview' using PyMol viewer for 8 pyruvate conformers at binding sites identified by vina. Sites 1 and 2 were bound to Arg54, 3 to Asn33, and 4 to Trp34, all residues of MPC1. Glu21 of MPC2 was occupied as an interchain hydrogen bond with the backbone of Asn33 on MPC1. The chains are rainbow colored in this image with dark blue being the N-terminus and red being the C-terminus. Transmembrane helix 3 (TMH3) of MPC1 is yellow on the left. TMH1 of MPC2 is at the Foreground and green on the right. Inset in (B) shows the MIMS side at a smaller scale with all residues shown in licorice view and ribbons in rainbow color. MPC2 Residues that crosslinked with the MSDC-1101 photoprobe are at right. MPC1 residues, Arg54 and Gln94, form H-bonds with pioglitazone (on which MSDC-1101 was modeled) and MSDC-0602, to which also binds Gln91 – both shown in licorice with near exact superimposition in 3D-space within location 1 shown in B. The asterisk is in the TZD ring and the @ is in the benzene ring of the linker region.

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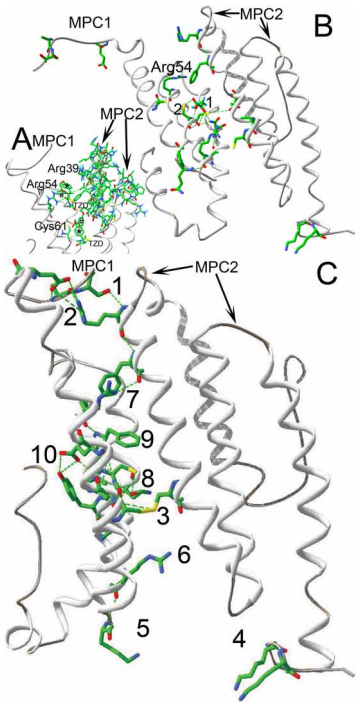
Figure 5. The open-outward / closed-inward (A), intermediate (B) and closed-outward/open-inward (B) conformations of the MPC1/2 heterodimer are shown in ribbon views using Swiss PDB viewer; amino acid residues, MSDC-1473(A) and pyruvate (B) are shown in licorice view using the CPK coloring scheme for atoms. A 'frontview' with MPC2 on the rght.



A) Low affinity binding sites for MSDC-1473 in the transporter channel entry at Arg54 (-3.1 kcal/mole) and middle channel at Cys61 (+22 kcal/mole). Sulfur is yellow in the methylated TZD ring; *-Benzene ring; #-distal ring. At the outer site H-bonds are formed with MPC1-Arg54 and MPC2-Tyr32 but at negligible affinity. On MPC2 the arrows point to the MIMS side interhelix loops with key residues for binding the photoprobe shown in licorice (MPC2- 20-27, 29-49, and 84-92-arrow on right). B) The C-terminus on TMH3 of MPC1 is rotated to the left on the MIMs side (top) and the residues identified in panel A of Figure 4 are shown on it as well as on the interhelix loop of MPC2 (arrows). Moving into the transporter channel, Arg54-MPC1 and Phe43-MPC2 are encountered. Then pyruvate can be seen to the left of number 1 and Cys61 to the right of number 2. Cys60 (just below the 1) has an interchain H-bond with Glu21-MPC2 on the right. Pyruvate has H-bonds with Asn33 (farther below 1) and Cys61 (both sulfur in the side chain and its backbone). This positions the α-carbon of pyruvate for the formation of a thiohemiacetal with Cys61. B) ten critical structural components of the closed-outward/open-inward conformation of the MPC1/2 heterodimer. 1 - Ala107 and Ser108 on the MPC1 C-terminus forming interchain H-bonds with Arg39 of MPC2 atop TMH1 on the MIMs-side; 2 – Glu102 also on the MPC1 C-terminus and bonding with Arg39; 3 – disulfide interchain bond between MPC1-TMH3-Cys83 (on left; sulfur is yellow) and MPC2-TMH1-Cys54 (on right); 4 – Lys122 and Lys124 on MPC-2 C-terminus on matrix side; 5 – Lys72 on matrix side of TMH3 of MPC1; 6 – Arg68 of MPC1, the final pyruvate binding site before release into the matrix; 7 – MPC1-Arg54, the first binding site as pyruvate enters the transport channel from the MIMs, forming an interchain hydrogen bond with backbone of Phe43 of

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Table 1. Binding affinities as deltaG values (kcal/mole) for pyruvate and drugs in wild type and mutant MPC1/2 complex. The conformation of the transporter is shown in the top column for different PyDock model predictions. The residues associated with the corresponding binding sites are shown in bold for both wild type and mutant.

Conformation	Open-Out	Early Intermediate	Intermediate	Open-In	Open-In
wild type	**Arg54**	**Asn33**	**Cys60**	**Arg68**	**Arg68**
pyruvate	-4.0	-4.1	-3.7	-3.4	-3.5
MSDC-0602	-7.5	-7.5	-7.0	-6.3	-7.3
MSDC-0160	-6.7	-7.4	-7.7	-6.0	-7.8
L36I mutant	**His84**	**Cys61**	**Tyr32**	**Arg68**	**Trp44**
pyruvate	-3.2	-3.9	-4.1	-3.8	-4.0
MSDC-0602	-8.2	-8.1	2.6	-8.1	-2.9
MSDC-0160	-8.0	-8.0	-1.4	-8.4	-3.4

MPC2; 8 – Asn33 of MPC1 TMH2, second binding site of pyruvate, is forming interhelical hydrogen bonds with Cys60 of MPC1-TMH2, the fourth binding site, and intrahelical bond with Gly29 of MPC1 (the third pyruvate binding site); 9 – Phe57 of MPC1-TMH2 is forming intrahelical hydrogen bonds with Cys60 and Cys61 of MPC1; 10 – Glu88 of MPC1-TMH3 is forming interhelical hydrogen bonds with Tyr62 of MPC1-TMH2 and intrahelical with His84 of MPC1-TMH3 that is also bonding with Cys61 of MPC1-TMH2.

Previously reported initial studies using a 2D prediction showed both MPC1 and MPC2 each having two transmembrane spanning alpha helical segments containing cysteine residues (C60&61 in MPC1 and C54 in MPC2). Both N- and C-terminals for each monomer subunit projected to the same side of the membrane, intermembrane space (MIMS) for MPC2 and matrix for MPC1 (Phelix et al., 2015), the latter of which agreed with (Bender et al., 2015). The current model (Figure 4B) has 3 TMHs per monomer and C-terminals in opposing sides of the IMM, i.e., MIMs for MPC1 and matrix for MPC2; the N-terminus for MPC1 is within the membrane on the matrix side and for MPC2 is on the MIMS side. A companion paper compares this human MPC1/2 heterodimer with homology models of several plant MPC1/2 heterodimers, replicating this prediction over and over, emphasizing these terminal localizations as relevant for regulation of MPC function (Dugan, Bourdon, & Phelix, 2017). This topology agrees with recent published illustrations for MPC2, but not for MPC1 which is illustrated with 2 TMHs and both the N-&C-termini on the matrix side (Bender et al., 2015; Compan et al., 2015). More informative and instructive to the present study, pyruvate had 8 binding sites on the entire MPC1/2 complex and both TZDs and known inhibitors bound only to 7 or less, including the critical ones at the cysteine residues of MPC1/2 within the IMM. The multiple binding sites for the transport cargo or inhibitors is consistent with both the Halestrap and Nalęcz models (Halestrap, 1978a, 1978b; Nałęcz, 1994; Soares-Silva et al., 2011) and with the idea of a 'trajectory-like' substrate displacement through the transporter channel (Soares-Silva et al., 2011). The TZDs had higher affinities comparable to the known inhibitors in each of the reported studies to date (Dugan et al., 2017; Phelix & Dugan, 2016; Phelix et al., 2015, 2014).

MSDC-0160 and MSDC-0602 did bind to the wild type MPC1/2 heterodimer complex and overlapped the location where pyruvate binds (Figure 6) and where pioglitazone binds (Figure 4, insets in A&B). The inactive compound, MSDC-1473 (Figure 5A), showed low affinity binding at the transporter channel

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entry and mid-channel locations but at such low affinities (plus 22 kcal/mole for the latter) that effective binding is highly unlikely or impossible. Also shown in Figure 4-insets and Figure 5A are the MPC2 residues identified by the crosslinking studies using the photoprobe MSDC-1101(Colca, McDonald, et al., 2013) and that MSDC-1473 would not interfere with the MSDC-1101 binding to the MIMS side of MPC2. Since MSD-1101 is modeled after pioglitazone (with an iodinated fourth ring for extension and photoaffinity activation) the binding affinity might be similar, -6.9 kcal/mole, at the channel entry site. At this same site, MSDC-0602 had a binding affinity of -7.2 and MSDC-0160 had an affinity of -7.9. This would be a 1.5 to 5-fold difference in K_d values versus the photoprobe that could explain how they effectively competed off the radiolabeled photoprobe. At this site, MPC1-Arg54, along with Gln91 and Gln94 formed H-bonds with all three ligands, but in addition the Swiss PDB viewer detected H-bonds with MPC2-Tyr32 and Arg39 (Figure 4A-inset). Most notably, Tyr32 formed intrachain H-bonds across the first MIMS side interhelix loop with backbones of Thr40 and Val41; and Tyr32 along with the backbones of Glu26 and Lys27 formed interhelix-intrachain H-bonds with Tyr85 at the beginning of the second MIMS side interhelix loop. It seems reasonable to conclude that MSDC-1101 binds similarly to pioglitazone with MPC2-Tyr32 and Arg39 and the photoaffinity activation favored crosslinking with the MPC2 monomer at these nearby residues 20-27 & 29-49 and via Tyr85 included the MPC2 residues nearby in that stretch of residues from 84-92. The current model supports their proximity on the MIMS side of the MPC1/2 heterodimer for ready access to MSDC-1101 upon entry into this intermembrane space.

The affinity of the MSDC-0160 and MSDC-0602 binding in all conformations of the complex was nearly double that of pyruvate in each case (Table 1). The conformation of the complex was affected by drug binding as indicated by the position of amino acid residues within the binding site (Figure 6C) and by the interactions between the two subunits, i.e., interdomain interactions (Figure 7).

Figure 6. MSDC-0160 (A&B) and MSDC-0602 (C&D) form H-bonds with wild type MPC1/2 heterodimer and overlap in space with pyruvate at the Asn33 binding site.

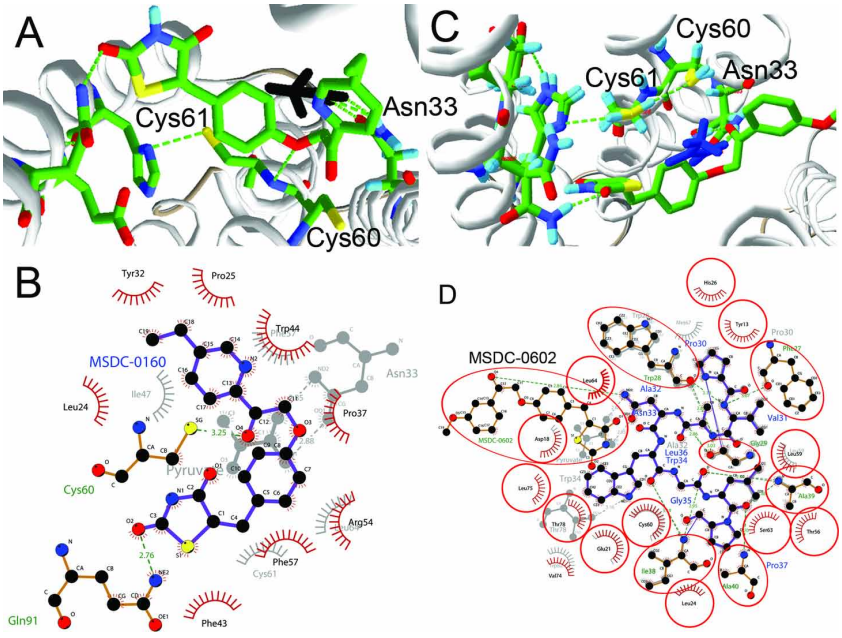

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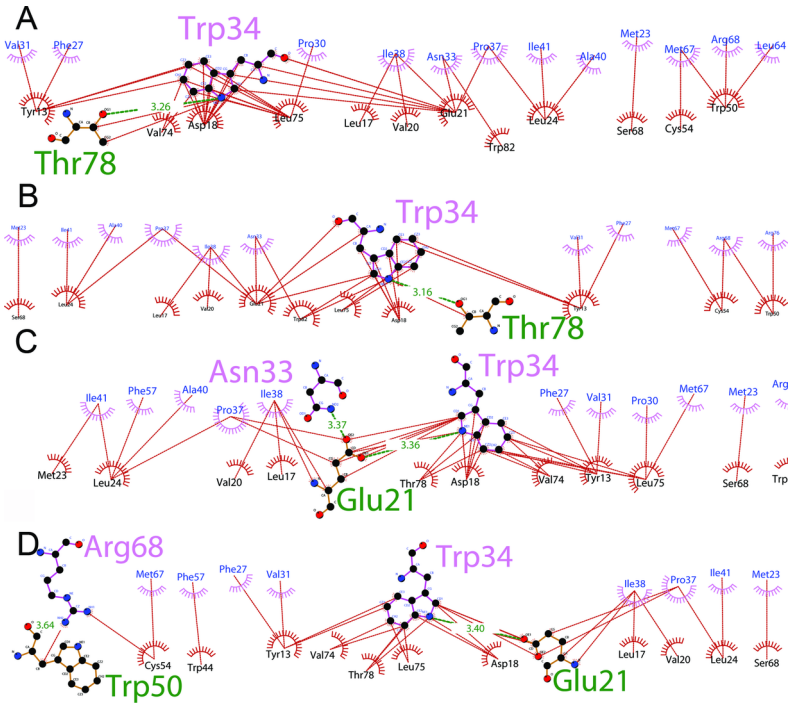
Figure 7. Plot analysis of wild type MPC1/2 heterodimer. Interactions between domains of the heterodimer change with ligation by substrate or antagonist. MPC1 is shown in pink on top and MPC2 in green on bottom. A) Non-ligated. W34 is on TMH1 of MPC1 and T78 is on TMH2 of MPC2; B) Pyruvate ligated with H-bonds only to Asn33 MPC1; C) MSDC-0160 ligated with H-bonds to Cys60 and Gln91 (see panels A&B Figure 6); D) MSDC-0602 ligated with H-bonds to Asn33 & Asn87 MPC1 (see panels C&D Figure 6).



The TZD ring of MSDC-0160 (top in A and bottom in B) forms a H-bond with Gln91 of MPC1 and the oxygen (red) on the linker with the backbone of Cys61 (A) and of the carbonyl group with Cys60 side chain sulfur (B). Pyruvate (black in A) is bound to Asn33 of MPC1. In panel (C) MSDC-0602 has caused a conformational change and residues no longer overlap perfectly; follow Cys60 at top right to the left, Cys61, then His84 directly left, then Glu88 just above, and Asn87 in the far-left center/bottom in the foreground. Note the H-bond between Cys60 and Cys61 is present when MSDC-0602 is bound; and the H-bond 'strand' from Cys61 to His84 to Glu88 occurs with pyruvate binding. Note also that Asn87 has rotated forward and down to form the H-bond with the TZD ring of MSDC-0602 (bottom in C positioned horizontally, and left center in D). This conformation positions the carbonyl group between the linker and hydrophobic tail of MSDC-0602 to form a H-bond with Asn33 overlapping in space with pyruvate (purple) also bound here. Other intramolecular bonds and hydrophobic interactions that might be affected by ligand binding or involved in conformational changes are shown to the right in panel (D).

The effect of the L36I mutation on pyruvate and drug binding affinities is shown on Table 1. The affinity for pyruvate is slightly reduced in some cases and for the MSDC drugs is increased, except for the intermediate and open-inward conformations. The more dramatic differences were the amino acid residues involved in binding substrate and drugs (Figure 8). Also, the interdomain interactions were more numerous and distinctively changed with either substrate or drug binding (Figure 9).

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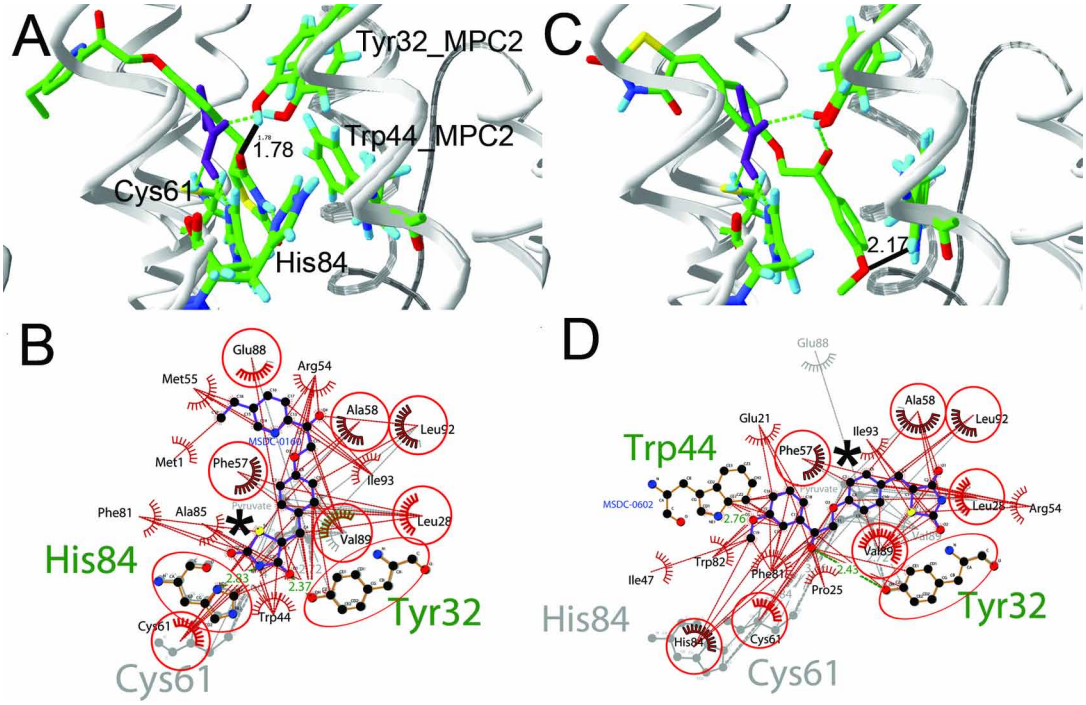
Figure 8. MSDC-0160 (A&B) and MSDC-0602 (C&D) form H-bonds with L36I mutant MPC1/2 heterodimer and overlap in space with pyruvate at an alternate binding site involving H-bonds with His84 and Cys61 of MPC1 and Tyr32 of MPC2.



The TZD ring of MSDC-0160 (bottom in both A & B) forms H-bonds with His84-MPC1 and Tyr32-MPC2 (1.78 Å distance when protonated is shown by black line; when deprotonated in B it is 2.37 Å); neither the oxygen (red) on the linker with the backbone or of the carbonyl group form H-bonds in this case. Trp44-MPC2 is shown on the right (A) to reveal ring-stacking with the TZD ring, for hydrophobic interactions (B bottom center) versus forming a H-bond with the oxygen of the carbonyl extension of the phenol ring in the hydrophobic tail of MSDC-0602 (2.17 Å distance when protonated is shown by black line in C; and when deprotonated in D it is 2.76 Å). Pyruvate (purple in A and to right of asterisk in B) is also bound to His84-MPC1 and Tyr32-MPC2, as well as Cys61-MPC1. The phenyl ring of the linker overlaps in space with pyruvate. Note in panel (A) the conformational change to reposition Tyr32, Cys61, and His84 due to MSDC-0160 binding. In panel (C) MSDC-0602 has caused far less of a conformational change than MSDC-0160 in this mutant, and even more dramatically less than versus itself in the wild type heterodimer (Figure 6); and residues overlap more perfectly. This reverse orientation of the TZD ring and hydrophobic tail of MSDC-0602 versus MSDC-0160 Still positions the linker phenol ring to overlap in space with pyruvate (purple in C and below asterisk in D in grey shaded background) also bound here.

The MSDC drugs both bound to key locations and amino acid residues along the length of the transporter channel (Figures 10&11). From the MIMs side of the channel, Arg54 was a common binding site for pyruvate and drugs (Figure 10B); Asn33 in the mid-region of the channel (Figure 10C), and Arg68 on the matrix side (Figure 11).

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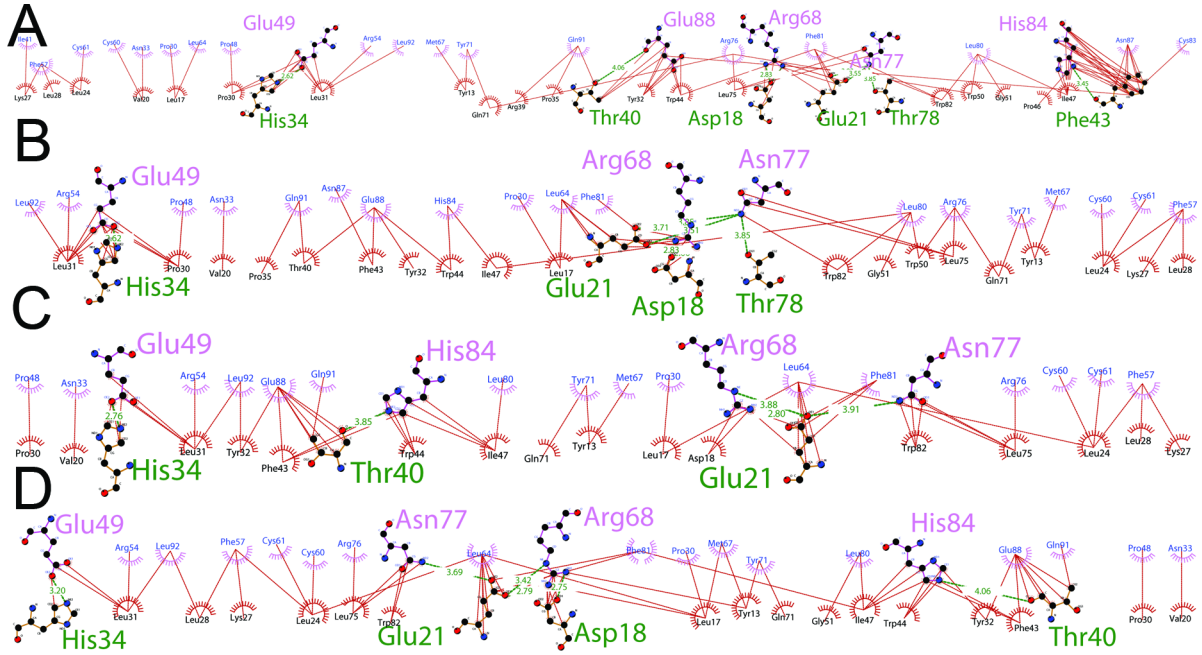
Figure 9. DimPlot analysis of L36I mutant MPC1/2 heterodimer. Interactions between domains of the mutant heterodimer differ vastly from wild type (Figure 6) and still change with ligation by substrate or antagonist. MPC1 is shown in pink on top and MPC2 in green on bottom. A) Non-ligated. Five residues of MPC2 and six of MPC1 are involved in 6 interdomain H-bonds and 48 residues total are engaged in these bonds and numerous hydrophobic interactions; B) Pyruvate ligated with H-bonds to both Cys61 and His84 of MPC1 as well as Tyr32 of MPC2; C) MSDC-0160 ligated with H-bonds to His84-MPC1 and Tyr32-MPC2 (see panels A&B Figure 8); D) MSDC-0602 ligated with H-bonds to Tyr32 and Trp44 of MPC2 (see panels C&D Figure 8).



In the open-out/closed-in conformation of the wild type MPC1/2 heterodimer (as in Figure 4), MSDC-0160 and MSDC-0602 bind at locations 1 and 3. Without showing H-bonds, the positions of key residues and ligands are easily seen when shown in licorice view with CPK coloring (A) and in greater detail with H-bonds (B&C). A) Pyruvate is at the tip of the small arrow and the space between its α-carbon of the ketone carbonyl group and the sulfur on the side chain of Cys61 is indicated with the black line (3.89 Å shown at large arrow in panel C). The asterisk is positioned in the space (4.95 Å shown again in panel C) between the same sulfur of Cys61 and the carbonyl group between the linker and hydrophobic tail of MSDC-0602. If they each could form thiohemiacetal bonds with the Cys61, they might appear as shown in panel (C; large arrow for the former and asterisk for the latter case); however, not simultaneously. B) The TZD ring of MSDC-0160 forms a H-bond with 3 residues, Arg54 and Gln94 of MPC1 and Arg39 of MPC2. The linker phenyl ring overlaps with pyruvate (small arrow) binding to Arg54. C) In this instance of MSDC-0602 binding, contrasted with that shown in panel (C) of Figure 6, the TZD ring overlaps pyruvate (small arrow) in space and like pyruvate binds also to Asn33. The oxygen at the phenol ring linker of MSDC-0602 in this case is forming a H-bond with Gln91-MPC1. D) UK-5099 when suspended by hydrophobic interactions with several residues has its activated double bond (long tiny arrow within inset LigPlot illustration at bottom left) positioned appropriately with the Cys61 thiol

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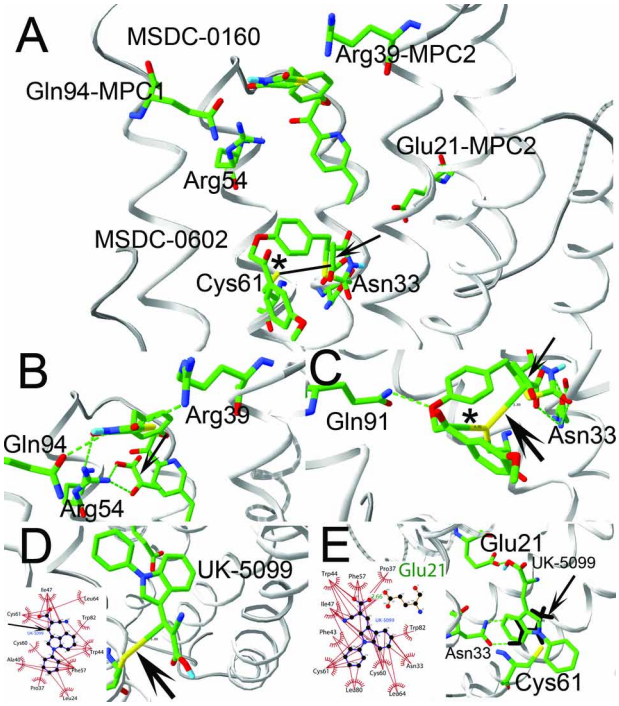
Figure 10. Hypothetical thiohemiacetal (asterisk and large arrow) formation of Cys61 with pyruvate as well as MSDC-0602 (C) and Michael addition with UK-5099 (D).



for the Michael addition site (large arrow). E) Another positioning of UK-5099 allows a H-bond to form with Glu21-MPC2 and hydrophobic interactions with Asn33 and Cys61 (LigPlot illustration inset at bottom left) causing direct spatial overlap with pyruvate (black and small arrow) when bound to Asn33.

Similarly, interchain H-bonds are seen at locations 1, 2, and 3 on this image, securing the transporter channel as closed-outward to the MIMS. Likewise, the three Lys residues at location 4 in this image (corresponding to 4&5 of Figure 5) have been repositioned to each side of the matrix end of the channel creating the open-inward access point for blockers and for pyruvate exit. At this point of pyruvate transport, Arg68 has a H-bond with it, then Arg78 will form one also such that they cooperate to expel it into the matrix. At this point, Arg76 has two interhelical (intrachain) H-bonds with the backbone of Arg68-MPC1 that has three interchain (or interdomain) H-bonds with Ser68-MPC2; there is an additional intrachain H-bond between the backbone of Lys72 and Arg76. At this point also, there is an interdomain diulsfide bond (see Figure 5B) not shown on this image. When MSDC-0160 is bound the interchain bonds remain; the TZD ring has a H-Bond with Ser68 and the oxygen of the carbonyl group toward the hydrophobic tail has a H-bond with Arg76. When MSDC-0602 is bound the differences from MSDC-0160 binding are an additional H-bond of the TZD ring with Arg68 and along the linker and at the hydrophobic tail, where the oxygen on the phenyl ring linker and extending off the tail form the H-bonds with Arg76, not that of the carbonyl group. Note that the phenyl ring of the linker overlaps in space with pyruvate in both cases. The inset in the top right is a LigPlot 2D illustration of the overlap of all three ligands here.

Finally, an analysis of the localization of pyruvate and drugs, including UK-5099, allowed generation of hypothetical bonds with Cys61 in the mid-region of the channel using Swiss PDB Viewer. In each case

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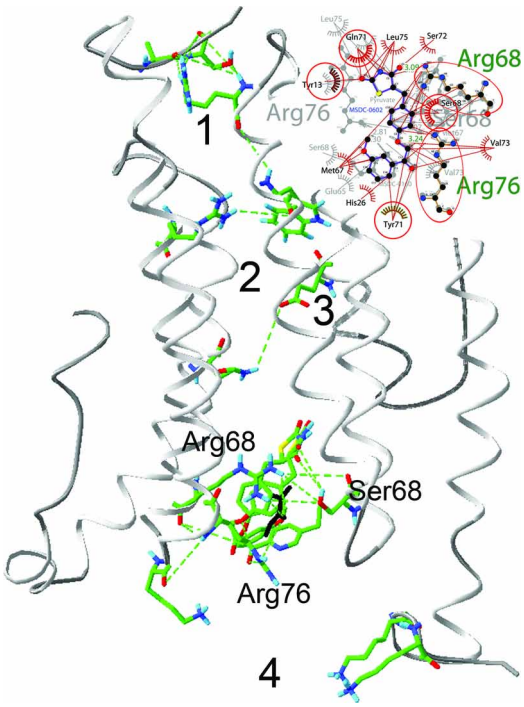
Figure 11. In the closed-outward/open-inward conformation of wild type MPC1/2 heterodimer (as in panel B, Figure 5), substrate and both antagonists bind and overlap in space at location 4 (Figure 4) and 6 (Figure 5).



the appropriate carbon atom was located within distances reported for reactions with sulfhydryl groups to occur, e.g. Michael addition (Chinchio, Czaplewski, Liwo, Ołdziej, & Scheraga, 2007; Muscatello, Muller, Mostofi, & Sutton, 2017; Wu et al., 2007). The carbonyl groups of pyruvate and along the linker of MSDC drugs can allow thiohemiacetal formation consistent with predictions (Halestrap, 1978a; K. Nałęcz, 1994) (Figure 10C and YouTube video https://www.youtube.com/watch?v=KdlIBhAT6Mo) and the conjugated double bond in UK-5099 (Figure 10D&E) being a target of Michael addition (Halestrap, 1976, 1978a; Hildyard et al., 2005). Both of these types of covalent bonds are reversible. (Krenske, Petter, & Houk, 2016; Krishnan et al., 2014; Zarate-Romero et al., 2016) Perhaps differences in kinetics can help explain observed time effects of UK-5099 on blocking pyruvate transport versus TZDs reported by Colca and coworkers (Divakaruni et al., 2013); in that a reported equilibrium constant for thiohemiacetals is 17.4 (Lienhard & Jencks, 1966) and for reversible thiol-ene reaction via Michael additions is 106. (Krenske et al., 2016) The pyruvate and MSDC binding to Cys61 via thiohemiacetal formation should reverse faster than UK-5099 and other TZD-ring-bearing, thiazolidine compounds that form alkyl thiol bonds through Michael additions (Hildyard et al., 2005).

As a proton-ketoacid symporter, our new MPC1/2 heterodimer 3D model has features common to LacY (Kumar et al., 2014): Lactose(pyruvate)-proton symporter [major facilitator superfamily (MFS) member (Yan, 2013)]; Gly-Gly pairs at 'inlet'; Cys at substrate binding site (Figures 4&5); likely to be alternating-access model; and analogous residue organization for proton translocation (Sahin-Toth & Kaback, 2001; Sahin-Tóth, Karlin, & Kaback, 2000). A hypothetical mechanism of pyruvate translocation had been proposed in the 1990s: 1) Binding of the substrate at the outer side of the inner mitochondrial

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membrane, facilitated by a positively charged guanidyl group of arginine (Arg54, Figure 4&5a) and lower pH, promoting an interaction of pyruvate with cysteine; 2) Movement of the substrate around a guanidyl residue due to the rotation of the pyruvate molecule, followed by interaction with another thiol (SH) group within the carrier molecule (Figures 4,5,&10C); 3) Breakage of semimercaptal bond at high pH inside the mitochondria; 5) Binding of the substrate moves at least one SH group per monomer of the carrier molecule in such a way, that it can interact with an additional SH group of another monomer forming a disulfide bridge, giving a dimer (Figure 5B and YouTube video); 6) This conformational change allows exposure of another internal SH group towards a more hydrophilic environment, the group become more accessible for the internal substrate (Figures 5B&11) and less accessible for N-ethylmaliamide (NEM), which is then unable to inhibit the process of exchange; 7) When SH groups are blocked, binding of the substrate or SH group modifying reagent opens a channel in the carrier protein (Figure 5A); an unspecific leak occurs. (K. Nałęcz, 1994) And there is agreement not only with the Halestrap model for pyruvate transport, but also for inhibitor binding and actions: "It is proposed that pyruvate is bound along with a proton which is attached to a weak base B (pKa, 8.35). An SH group (cysteine) then attacks the α-carbon to form a tetrahedral addition product whose O^-group is stabilized by a protonated weak base AH^+. This intermediate is transported, whereupon the process is reversed to release pyruvate and a proton. The free carrier must then return to the original conformation…" (Halestrap, 1978b); "It is proposed that inhibition occurs by binding to the substrate site and subsequent reaction with an –SH group on the inside of the membrane." (Halestrap, 1978a) "We have suggested previously that … the presence of a hydrophobic binding pocket on the matrix surface of the carrier … inhibitors may reach this site by binding to the outer face of the carrier, which then undergoes a conformational change translocating the inhibitor into a hydrophobic matrix facing binding pocket." (Hildyard et al., 2005).

Accepting that the MPC complex is a heterodimer (Bender et al., 2015; Compan et al., 2015; McCommis, Hodges, Bricker, et al., 2016) of 26.6 kDa and has a concentration of 100 pmol/mg mitochondrial protein (Shearman & Halestrap, 1984) with a pyruvate transport rate of 42 nmol/min per mg mitochondrial protein at 37 °C (Halestrap, 1975), and once converting this to ~421 trillion molecules of pyruvate being transported per second per mg mitochondrial protein by ~61trillion molecules of MPC1/2 heterodimer per mg mitochondrial protein, about 7 pyruvate molecules are transported by a single MPC complex per second. This estimate is consistent with a value of 200 min^{-1} at 0° C reported by (Thomas & Halestrap, 1981). A well-recognized range of turnover numbers for typical carriers is 1-50/sec substrate at the 'slow-end' and 500-2000/sec at the 'fast-end'. (Schultz, 1987; Wohlrab, Bukusoglu, & H, 1989) This would be about 145 milliseconds to transport one pyruvate across the inner mitochondrial membrane, a distance of approximately 30 Å or about 4.8 Å/msec. This is much slower than the 0.7 Å/nsec used in a steered molecular dynamics simulation of the glucose transporter (Park, 2015); at that faster rate, it should take only about 43 nsec to transport one pyruvate, a difference by about 3.4 million times. Perhaps this discrepancy will be settled with more widespread use of contemporary assays (Compan et al., 2015; Gray, Rauckhorst, & Taylor, 2016).

There is one obscure but intriguing study of the human BRP44 gene (Otero, Papadakis, Gupta Udatha, Nielsen, & Panagiotou, 2010) before being reported as the MPC2 gene in 2012. In an integrated omics study with metabolic challenges to yeast testing antioxidant effects of ferulic acid, the yeast gene FMP43 was identified as one of the primary contributors of the environmental and internal sensing mechanisms to achieve network dynamics. They demonstrated that the human orthologue gene, BRP44, could rescue a yeast FMP43 mutant. Now we know that FMP43 is an alias for yeast MPC3 and BRP44 is an alias for human MPC2. Homology modeling was performed using two proteins as templates, methyltrans-

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ferase-like protein (3CVO.PDB) and human semicarbazide-sensitive amine oxidase/vascular adhesion protein-1 (2C10.PDB), followed by protein-ligand docking using ferulic acid as the ligand. That study was in fact an initial inspiration for the ongoing studies of our group and support for looking beyond the semiSWEET as a template to model the MPC gene products (additionally, semiSWEET is not a proton-symporter). As a functional confirmation, in 2013, both MPC1 and MPC2 gene expressions were shown to be involved in yeast oxidative stress (Timoń-Gómez, Proft, & Pascual-Ahuir, 2013). Up to this point few functional studies were reported, e.g., BRP44 (MPC2) gene expression was shown to change dramatically in hematopoietic cells (Vladan, Č, Jov, Puri, & Schechter, 2012). In another interesting study in 2009 on a role in spinal cord tissue regeneration for a species of *Gekko*, the BRP44l gene (now known as MPC1) that had been identified as being differentially expressed in the spinal cord during tail regeneration was chosen randomly for more detailed study. They demonstrated species homologies conserved among vertebrates and invertebrates and implicated a role in either apoptosis or rapid cell growth (Jiang et al., 2009). This evidence becomes even more relevant for human pathologies, since the MPC complex has been reported to regulate autophagy and neurodegeneration in Parkinson's disease (Ghosh et al., 2016), and to play a role in glutamate-mediated, excitotoxic, neuronal death (Divakarini et al., 2017). Thus, very little was known about the MPC1 and MPC2 genes up to 2012, but it becomes relevant for justifying our studies. Generating knock-out animal models has been challenging but was accomplished eventually (Gray et al., 2015; Li et al., 2016; Vanderperre et al., 2016; Vigueira et al., 2014); we have yet to see how informative they might be on the level of MPC complex structure and function. Colca and coworkers warn that caution must be used when comparing MPC knockout data to pharmacological inhibition of the MPC complex *in situ* (McCommis et al., 2017).

The L36I nsSNP showed up in one individual out of 17 Alzheimer's patients and 21 total including control samples (Parcerisas et al., 2014). This L36I nsSNP did not appear in a study of 464 Alzheimer's subjects, of European ancestry, but may simply not have been included in the 434,271 SNPs investigated in the study (Silver, Janousova, Hua, Thompson, & Montana, 2012). The L36I nsSNP also showed up in one of 42 patients with infantile mitochondrial disease but was not determined to be a pathogenic variant. In that same study, the L36I allele frequency of 371 controls was 0.0316 (Calvo et al., 2012). One might confidently but cautiously conclude that the L36I nsSNP has a fair representation in the human population and we need to know if this allele can affect MPC complex function and responses to drugs.

Caution is taken as with bioinformatics and in *silico studies* in many cases; this work is hypothetical with "…conjecture and speculation that is meant to provoke new thoughts and to stimulate further work to elucidate…" (Islam & Lam, 2013) the structure of human MPC and mechanisms of mitochondrial pyruvate transport, regulation, and actions of blockers. Additionally, follow up with human clinical studies and trials on the relevance of mutated and missense MPC conformations would also be necessary (Eckert et al., 2013). These single amino acid substitutions originating as nsSNPs in the genetic code can affect protein function (as either a gain or loss), or protein-protein interactions, and consequently human health; there are approximately 67,000 – 200,000 common nsSNPs in the human population, with each person likely to be heterozygous for 24,000 – 40,000 nsSNPs (Ng & Henikoff, 2006; Zhao, Han, Shyu, & Korkin, 2014).

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CONCLUSION

A convergence of pyruvate, characterized inhibitors, and TZD binding sites were localized at cysteine residues of the MPC1/2 transmembrane regions, consistent with biochemical predictions made in the 1970s and 90s by A.P. Halestrap and K.A. Nalecz laboratories, respectively:

- MPC1/2 heterodimer fits a model for 'a' pyruvate-proton transporter fitting into the inner mitochondrial membrane;
- Known mutations of MPC1 provide excellent study tools;
- Several known blockers are also useful study tools;
- More extensive modeling of ligands forming covalent bonds and dynamic simulation studies are needed, e.g. (Hempel, Kraut, & Wymore, 2009; Kumalo, Bhakat, & Soliman, 2015).

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Chapter 23
User-Independent Detection for Freezing of Gait in Parkinson's Disease Using Random Forest Classification

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ABSTRACT

Freezing of gait (FOG) is a gait impairment which occurs in Parkinson's disease (PD) patients. As PD progresses, the patient is unable to perform locomotion normally. This increases the risk of falls and adversely affects the patient's quality of life. In this article, a user-independent method has been proposed to detect FOG events in PD patients. The proposed method is divided into three phases. Phase-1 extracts the statistical features from a FOG dataset. Phase-2 divides the data into two clusters based on FOG events. Phase-3 selects significant factors, using a randomized block design with replication. A Random Forest model is built using a combination of significant factors obtained from the design of experiments. The proposed method classifies FOG events with an average sensitivity up to 94.33% and specificity up to 92.77%. This model can be integrated along with non-pharmaceutical treatments to generate sensory-motor feedback at the onset of a FOG event.

INTRODUCTION

Parkinson's disease (PD) is a chronic neurological condition that affects a patient's ability to perform complex neuro-motor tasks such as walking, body balance, and writing (Morris, Iansek, & Churchyard, 1998). This arises due to the loss of neuromelanin containing dopamine neurons (Fahn, 2003). A PD

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patient shows four primary motor-based symptoms often grouped under the abbreviation TRAP, which stands for Tremor at rest, Rigidity, Akinesia, and Postural instability (Jankovic, 2008).

Freezing of gait (FOG) is a brief, and unpredictable period where a patient suffers from a sharp reduction that affects movement, despite the inclination to walk (Heremans, Nieuwboer, & Vercruysse, 2013; Nutt et al., 2011). Some features of FOG include a decrease in step length despite the willingness to move, not being able to clear the ground with one's feet or toes, the sensation of not being able to move one's feet along with freezing episodes, trembling in one or both legs (Nutt et al., 2011). FOG events can lead to frequent falling and injuries, which discourages a patient to walk and negatively impacts their quality of life.

Levodopa is the most effective drug to treat PD (Joseph Jankovic & Aguilar, 2008). Other available drugs are dopamine agonists (DA), catechol-o-methyl-transferase (COMT) inhibitors, and non-dopaminergic agents (Joseph Jankovic & Aguilar, 2008). Once the drug has been consumed, the period until another consumption can be divided into two stages: 'ON' stage, when the drug is active, and 'OFF' stage, when the effect of the drug has faded (Bächlin et al., 2010). About 70% of FOG events are observed in advanced stages of PD; however, 26% of FOG events are reported in the early stages where patients have not undergone levodopa therapy (Heremans et al., 2013).

As the disease progresses, FOG becomes more resistant to pharmacologic treatments (Bloem, Hausdorff, Visser, & Giladi, 2004). In such cases, non-pharmaceutical treatments such as visual, auditory, tactile cueing (Boelen, 2007), physiotherapy (Nieuwboer, 2008), and deep brain stimulation (Ferraye, Debû, & Pollak, 2008) can act as alternative treatments.

Wearable sensors are placed on different parts of the body to understand the pattern of FOG events and continuously monitor the PD patient. Some commonly used sensors to collect FOG data are tri-axial accelerometers, gyroscopes, and magnetometers. The data collected can be further used to develop methods to detect and classify FOG events. Such methods can be incorporated along with non-pharmaceutical treatments to generate sensory-motor feedback such as the previously mentioned forms: visual, auditory, and tactile cueing. This feedback can be provided to PD patients at the onset of a FOG event. Thus, creating a closed loop sensory-motor feedback to the PD patients in order to overcome the FOG, which can prevent fall and injuries.

This paper aims to improve FOG detection and classification by developing a user-independent model to provide sensory-motor feedback. Misclassification during the prediction of FOG events as "no FOG" can be dangerous for the life of the patient. Conversely, the vice-versa scenario can generate false feedback, which gives misclassified no FOG but is harmless for the patients. Thus, the prediction of FOG events is more important than no FOG events. Hence, this paper focuses on enhancing the prediction of FOG events. As the patient may have a varying range of FOG events, a single classification model may not perform well over an entire group of patients, and training an individual classifier for each patient is time-consuming, costly, and infeasible. Therefore, this study presents a new approach based on clustering and classification of FOG events. To achieve this, patients are grouped into different clusters based on up to 99 features and a Random forest classifier is developed for each cluster.

This paper has organized an order: background is present in section 2, database and approach present in section 3, description of the methodology and results is in section 4, discussion is in section 5 and finally the conclusion in section 6.

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BACKGROUND

A significant amount of research has been done to develop a model to detect and classify FOG events. When training and testing data is carried out from single patient data, the experiment is referred to as a user-dependent experiment. Whereas, when training and testing is performed using the data average over a group of patients, such an experiment is referred to as a user-independent experiment. Han et al. (Han, Lee, Tae Beom, Beom Suk, & Kwang Suk, 2003) used frequency domain analysis to distinguish between freezing and normal gait movement. Moore et al. (Moore, MacDougall, & Ondo, 2008) studied gait on eleven PD patients and collected vertical linear acceleration data using an ankle mounted sensor. They used Freeze index (FI) to detect FOG events. The algorithm had a user-dependent sensitivity of 89% with 10% of false positives and a user-independent sensitivity of 78% with 20% of false positives. Delval et al. (Delval et al., 2010) studied equal groups of FOG and no FOG patients using control variables. Data was collected by making the patients walk on a treadmill and analyzed in the frequency domain. The algorithm was able to identify FOG events with a sensitivity of 75-83% and specificity >95%. Mahabier et al. (Nanhoe-Mahabier et al., 2013) conducted an experiment on fourteen PD patients using ten health control variables, while making them walk on the treadmill with split belts at different speeds and analyzed them by modulating the stride length and stride time. Niazmand et al. (Niazmand et al., 2011) used a garment with integrated accelerometers to collect data from PD patients and developed a system to detect FOG events with a sensitivity of 88.3% and specificity of 85.3%. Tripoliti et al. (Tripoliti et al., 2013) developed a four-stage automated methodology by analyzing the various positions of sensors, and different classifiers such as Naïve Bayer, Decision Tree, Random Forest, and Random Tree to detect FOG events. Random Forest classifier with all sensors had the highest performance where sensitivity was 81.94% and specificity was 98.74%. Zach et al. (Zach et al., 2015) studied twenty-three patients, while performing various walking tasks, and collected data using tri-axial linear waist mounted accelerometer. The algorithms were able to detect the FOG events with a sensitivity of 75% and specificity of 76%. Djuric-Jovicic et al. (Djuric-Jovicic et al., 2010) designed an algorithm for automatic recognition and classification of a walking pattern using perceptron neural network and rule-based classification. Cole et al. (Cole, Roy, & Nawab, 2011) used a dynamic neural network to detect FOG from PD patients, while performing an unconstrained and unscripted activity and achieved a sensitivity of 82.9% and specificity of 97.3%. Kim et al. (Kim et al., 2015) implemented an adaboost.M1 classifier in a smartphone to classify FOG events from a regular walk using two inbuilt phone sensors. The method achieved a sensitivity of 86% at the waist, 84% in the trouser pocket, and 81% at the ankle. Tzallas et al. (Tzallas et al., 2014) collected data from twenty-four patients in a laboratory and twelve PD patients in a home using accelerometer and gyroscope and devised a system to monitor, assess, and manage the patients, continuously. Palmerini et al. (Palmerini et al., 2017) designed a classification algorithm to understand the characteristics of gait and compared them with pre-FOG and non-precede FOG. All the above studies performed offline detection and classification.

Some studies performed online detection and classification. Jovanov et al. (Jovanov, Wang, Verhagen, Fredrickson, & Fratangelo, 2009) created a real-time system for detection of FOG and unfreezing of gait with an average latency of 332 ms and a maximum latency of 580 ms. Bachlin et al. (Bächlin et al., 2010) performed experiments on ten patients by attaching three acceleration sensors on the patients' bodies. This wearable assistant provided online feedback to the patient when FOG was experienced. It identified FOG events with a sensitivity of 73.1% and specificity of 81.6%. Mazilu et al. (Mazilu et al., 2012) detected FOG events online with smartphones and wearable accelerometers, using machine learn-

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ing algorithm. The system was able to identify FOG events with an average sensitivity and specificity of more than 95% and mean latency of 0.34s. Mazilu et al. (Mazilu et al., 2015) conducted a study on eleven patients to analyze electrocardiography and skin conductance data and identified statistically significant changes in the ECG and SC data just before the FOG events. They predicted 71.3% of the events correctly with an average of 4.2s before a FOG event happened. Mazilu et al. (Mazilu, Blanke, Hardegger, & Tr, 2014) developed an assistant system using a C4.5 pruned tree with FFT based features and provided feedback producing different types of rhythmic auditory cueing. Ahlrichs et al. (Ahlrichs et al., 2016) collected data from six PD patients using accelerometer sensors and analyzed the data using support vector machine (SVM) classifier. The algorithm achieved an accuracy of 98.7% and the geometric mean of 96%. Rezvanian et al. (Rezvanian & Lockhart, 2016) used a continuous wavelet transform to extract features from ten PD patients and achieved a sensitivity of 83.5%, and specificity of 67.2% when sensors were attached to lower back. Chen et al. (Bor-Rong Chen et al., 2011) developed a web-based home monitoring platform, MercuryLive, to store patient data and provide two-way video conferencing between the patient and clinician. A systematic review of all the other related studies is done in (Silva de Lima et al., 2017).

From the state-of-art mentioned above, the performance of user-independent classification models is likely to have reduced performance compared to user-dependent classification models, as the patient may have a varying range of FOG events. This leaves scope for improvement on this topic and a need for a more accurate model. Another disadvantage of the aforesaid methods is the dependency on the threshold to detect and classify FOG events, which varies from the sensor, patient, and selected feature(s).

DATASET AND APPROACH

Dataset

In this article, the Daphnet Freezing of Gait Dataset is used; it is publicly available (Bächlin et al., 2010). The experiment was performed at the Laboratory for Gait and Neurodynamics at the Department of Neurology of the Tel Aviv Sourasky Medical Centers (TASMC).

Three sensors are used to measure tri-axial acceleration—one attached to the shank just above the ankle, another attached to the thigh just above the knee, and one attached to the belt at the lower back of the patient. Each sensor read the data in three axes, X, Y, and Z axes, respectively. The X-axis represents the horizontal forward direction, Y-axis represents the vertical direction, and Z-axis denotes horizontal lateral direction. Overall, the dataset has nine independent variables and one dependent variable representing FOG and no FOG. In total, 8 hours and 20 minutes of data were collected for each patient.

The dataset consisted of seven male and three female patients within the age group of 59 to 75 years with disease duration of 2 to 30 years. Two of the patients were tested in 'ON' state, as they were recommended not to avoid medication. Each patient had to carry out three different walking activities, which included walking in a straight line with a 180-degree turn, a random walk with a 360-degree turn, and walking simulation activity.

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Approach

The proposed method for developing FOG classification model is shown in Figure 1.

Figure 1. Three phases of FOG classification model development

The method has been divided into three phases. In Phase-1 (feature extraction), statistical features were extracted from each of the three tri-axial acceleration sensors described in the previous sub-section. In Phase-2 (clustering), cluster analysis was carried out on a subset of data involving FOG events. In Phase-3 (model development and evaluation), Random forest classifier was used for FOG detection and classification model. Besides, the design of experiments was used to optimize the parameters of Random forest to achieve minimum FOG misclassification errors. Final Random forest classifier was obtained and evaluated.

DESCRIPTION OF THE METHODOLOGY AND RESULTS

In this section, details of each of the three phases are provided.

Phase -1: Feature Extraction

Data collected from the sensor at every 15-20 milliseconds was divided into the 3-second window. Thus, each window had about 150 to 198 rows of data for each of the nine variables. In this analysis, 50% overlapping window to extract statistical features was used. Eleven statistical methods viz., average, median, mode, standard deviation, variance, maximum, minimum, skewness, kurtosis, mean-1 (10% low valued trimmed) and mean-2 (20% low valued trimmed) were extracted from each of the nine variables. This process resulted in a total of 99 (9 variables × 11 statistical features) features were generated. In the future, the data collected from the three tri-axial accelerometer sensors will be referred to as the variable and data extracted using statistical methods will be referred to as features.

Phase-2: Clustering

In this phase, patients were divided into different groups based on FOG events using MacQueen (1967) k-means cluster analysis. Patient number four and ten were removed from cluster analysis, as they did not exhibit any FOG events. The analysis was performed in two different cases. In Case-I, k-means cluster analysis was carried out using all 99 features. In Case-II, highly correlated variables were identified and removed and k-means clustering was performed on the 50 remaining features.

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CASE-I: Cluster analysis of all 99 features resulted in the formation of two clusters (where k=2). The number of FOG data points in the two clusters for each of the eight patients was given in Table 1.

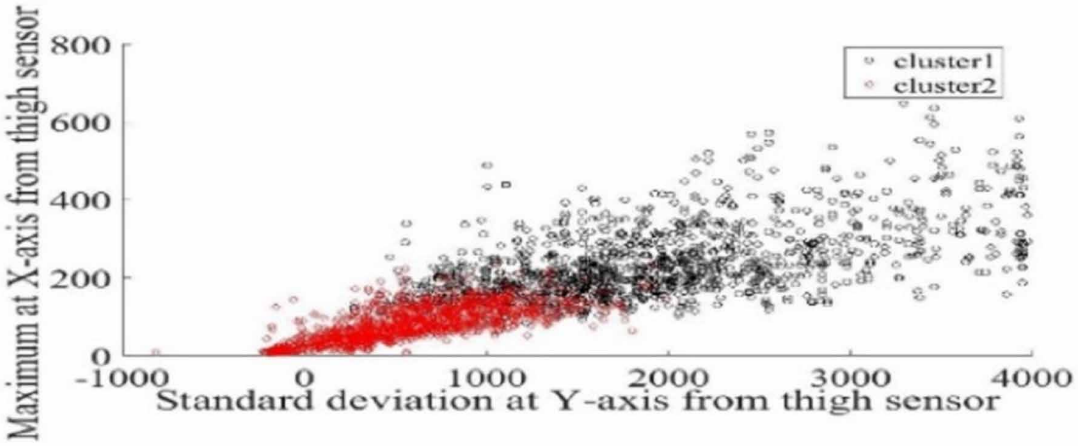
Table 1. Patient vs number of clusters with 99 features in fog events

	Patient Number							
Cluster	**1**	**2**	**3**	**5**	**6**	**7**	**8**	**9**
1	149	282	306	503	0	21	0	54
2	57	78	268	440	262	142	403	485

Table 1 depicts the majority of data points from FOG events for patients one, two, three, and five belong to cluster-1. Similarly, for patient six, seven, eight, and nine the majority of data points from FOG events belong to cluster-2.

To have an explicit representation of the cluster formation, two features (maximum at X-axis from thigh sensor and standard deviation at Y-axis from thigh sensor) were selected, as they have more considerable center value. A scatterplot of these two features shows the two clusters with some overlap in Figure 2.

Figure 2. CASE-I - Scatterplot maximum at X-axis from thigh sensor and standard deviation at Y-axis from thigh sensor



CASE-II: Since the number of features were large, there may be a chance that some features were highly correlated. Therefore, we also explored the impact of removing one out of every two highly correlated features on the model performance. To achieve this, the function findCorrelation was used with an absolute cutoff value of 0.7 in R. Removal of these features resulted in a drop from 99 features to 50 features. Cluster analysis was performed on these 50 features, where it also resulted in the formation of two clusters (where k = 2). Table 2 displays the division of FOG related data points in the two clusters for each of the eight patients with 50 features.

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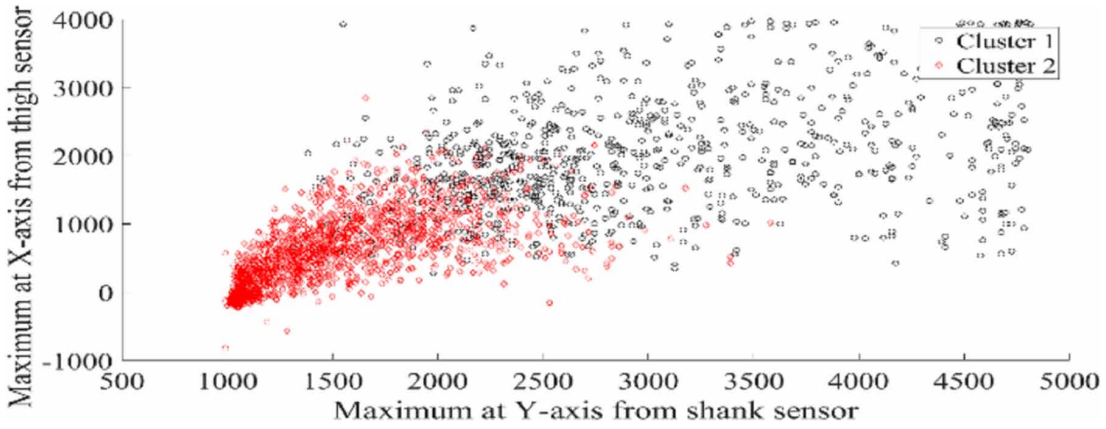
Table 2. Patient vs number of clusters with 50 features in fog events (removed correlated features)

	Patient Number							
Cluster	**1**	**2**	**3**	**5**	**6**	**7**	**8**	**9**
1	128	208	228	395	2	28	3	68
2	78	152	346	548	260	135	400	471

From Table 2, the majority of data points of FOG events contribution towards cluster-1 were from patients one two. Similarly, the majority of data points related to FOG events contributed towards cluster-2 were from patients three, five, six, seven, eight, and nine. To have a clear representation of the cluster formation, two features (maximum at X-axis from thigh sensor and maximum at Y-axis from shank sensor) were selected, as they have larger center values. Figure 3 represents a scatterplot for these two features showing the two cluster with some overlap.

Figure 3. CASE-II - Represent a scatterplot for maximum at X-axis from thigh sensor and maximum at Y-axis from shank sensor



The clusters formed using Case-I and II had higher center values on the thigh and shank sensors, as these locations experienced higher variation during movement as compared to the sensor attached by a belt at the lower back.

Phase-3: Model Development and Evaluation

Phase-3 developed a Random forest classifier on the whole dataset to detect and classify FOG events. The model's accuracy was impacted by factors such as, tuning parameters to optimize Random forest performance, the number of features, and the technique of splitting data into training and testing. To identify optimum levels of these factors, design of experiments (DOE) was utilized. Tuning parameters that optimize the performance of Random forest viz., the number of decision trees in the model and the optimum number of variables sampled at each split of a tree.

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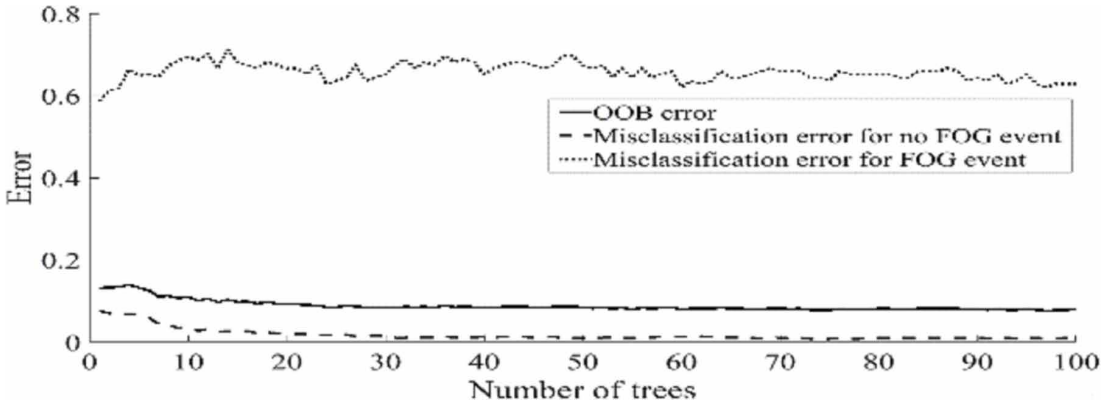
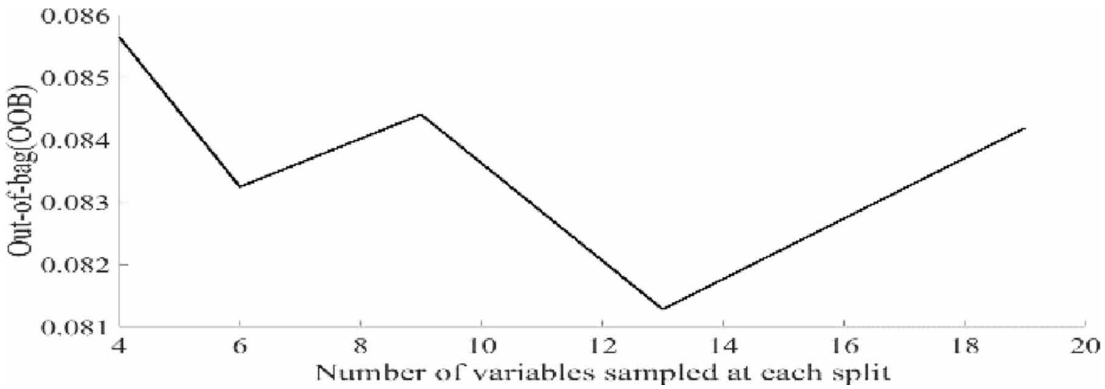
The first factor considered for DOE was the number of decision trees in the model. To select the optimal range of the number of decision trees, out-of-bag (OOB) error, and the misclassification error was utilized. OOB was used to measure prediction error using bootstrap sampling to subsample data that did not appear for training (James, Witten, Hastie et al., 2013). Misclassification error is the proportion of FOG and no FOG that is incorrectly detected by the system. Figure 4 shows the impact of increasing the number of trees on mentioned errors. The error curves stabilized after 20 trees, as the model converged to an optimal solution. Therefore, ±10 of 20, the optimal number of decision trees, was selected for further experimentation.

Figure 4. Error vs. number of trees



The second factor considered for DOE was the optimum number of variables sampled at each split of a tree. It represents random samples of possible variables selected at each node before splitting the tree. OOB error selected the optimum number of variables sampled at each split. Figure 5 shows the relationship between the optimum numbers of variables sampled at each split with respect to OOB error. The OOB error is reduced when the optimum number of variables sampled at each split was 13. Based on Figure 5, ±6 of 13, the optimum number of variables sampled at each split, was selected.

Figure 5. Out-of-bag (OOB) error vs. the optimum number of variables sampled at each split



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The third factor was the number of features identified from Phase-2. Both Case-I and II were considered for DOE. The model performance also depended on the fourth factor: the technique of splitting data into training and testing. Two techniques used to split the data were to divide the whole dataset or to split the individual patient data. A 70-30 split was considered while performing the DOE. These four factors and their levels for DOE are summarized in Table 3.

Table 3. Factors and their levels

Factor	Level		
Number of trees (A)	10	20	30
Number of variables sampled at each split (B)	7	13	19
Number of features (C)	99	50	-
Type of split (D)	70-30 split for each patient	70-30 split on the whole dataset	-

The dataset considered (Bächlin et al., 2010), consisted of overall 9.7% FOG events. Since the number of no FOG events (90.28%) was relatively much higher, even when all the data points were classified as no FOG, the accuracy rate will remain 90.28%. The classification of FOG events was more meaningful, overall accuracy was not a good indicator of model performance. Therefore, the response variables used for this experiment were sensitivity and specificity. Sensitivity measures the proportion of FOG events that are correctly detected by the classifier. Specificity measures the proportion of no FOG events that are correctly identified by the classifier.

In each experiment, a Random forest was trained using the combination of factors and their levels. The trained model was used to calculate sensitivity and specificity of the testing data. A full factorial design proposed 36 (3*3*2*2) combinations. In Phase-2, patients were grouped into two blocks where each block represented a cluster. This led to 72 (36*2) experiments. To check repeatability in the experiment, a replication factor of three was chosen, which led to an overall total of 216 (72*3) experiments. This full factorial design with a replication factor of three was used for screening the factors that contributed most to the response variables (sensitivity and specificity). The data obtained from these experiments were analyzed using Analysis of Variance (ANOVA).

ANOVA is a statistical test to identify the difference in the means among different groups, to identify statistically significant factors.

The degree of freedom (DF) is given by (1) where N is the total number of factors:

$$DF=N-1 \tag{1}$$

The sum of square of all the treatments (SSA) and the sum of square of error (SSE) is given by (2) and (3), respectively:

$$\text{SSA} = \sum_{i=1}^{k} n_i \left(x_i - \overline{x_{..}} \right)^2 \tag{2}$$

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where $\bar{x}$ is sample mean, k is total number of the population

$$SSE = \sum_{i=1}^{k}\sum_{j=1}^{n_i}\left(x_{ij} - \overline{x_i}\right)^2 \tag{3}$$

where n is total numbers of samples in a population

The total sum of square (SST) is calculated using (4):

$$SST = SSA + SSE \tag{4}$$

The mean square of all treatment and the mean square error are calculated using (5) and (6), respectively:

$$\text{MSA} = \frac{SSA}{k-1} \tag{5}$$

$$MSE = \frac{SSE}{N-k} \tag{6}$$

F-ratio is calculated as:

$$F = \frac{MSA}{MSE} \tag{7}$$

There are two hypotheses in the application of ANOVA.

H0 (Null Hypothesis) - differences in the mean among levels of a factor are not significant.
H1 (Alternate Hypothesis) - differences in the mean among levels of a factor plays a significant role.

The statistical decision is based on the following conditions:

1. Reject H0 if F-ratio > F-critical otherwise accept H0.
2. Reject H0 if p-value < alpha otherwise accept H0, where alpha is a level of significance (0.05).

The p-values for response variable sensitivity for factors A, B, C, and D were {0.00, 0.67, 0.02, 0.95}, respectively. Since B and D had p-value ≥ 0.05, they were non-significant. The p-values for response variable specificity for factors A, B, C, and D were {0.01, 0.00, 0.00, 0.01}, respectively. Figure 6 provides response curves for statistically significant factors (at 5% level of significance) for response variable sensitivity, with the main effects of factors A and C as well as all other significant interactions.

In Figure 6, the blue line represents the main effect for significant factors A and C. The orange line represents cluster-1, and the gray line represents cluster-2. From the interaction between A*cluster, it is inferred that cluster-1 with 30 trees (A3) and cluster-2 with 20 trees (A2) have higher sensitivity than all

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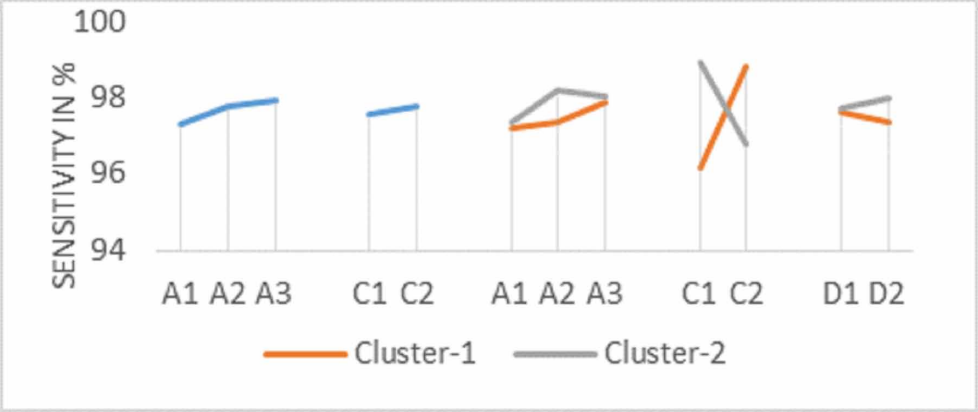
Figure 6. Response graph for significant factors and interactions – response variable sensitivity



other levels. In the interaction plot between C*cluster, sensitivity is best for cluster-1 with 50 features (C2) and cluster-2 with 99 features (C1). In the interaction plot between D*cluster, sensitivity is higher for cluster-1 with 70-30 split for each patient (D1) and cluster-2 with 70-30 split on the whole dataset (D2).

Figure 7 provides response curves for statistically significant (at 5% level of significance) factors for response variable specificity with the main effects of factors A, B, C and D as well as all other significant interactions.

In Figure 7, the blue line signifies the main effect for significant factors A, B, C and D. The interaction plot between A*C, the two lines characterize the levels of a number of features (C). The orange line represents 99 features (C1), and the gray line indicates 50 features (C2). From Figure 7, the highest specificity, as compared to that of other factors, is observed for 30 trees (A3) and 50 features (C2). For the interaction plot between C*D, the two lines represent the levels of a type of split (D). The yellow line indicates 70-30 split for each patient (D1), and the dark blue line represents 70-30 split on the whole dataset (D2). The interaction plot shows that 50 features (C2) with 70-30 split for each patient (D1)

Figure 7. Response graph for significant factors and interactions – response variable specificity

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has a higher specificity as compared to other levels. In the interaction plot with clusters, the green line represents cluster-1 and the purple line represents cluster-2. From the interaction between C*cluster, it is inferred that cluster-1 and cluster-2 with 50 feature (C2) have higher specificity than all other levels. In the interaction plot between D*cluster, specificity is highest for cluster-1 with 70-30 split for each patient (D1) and cluster-2 with 70-30 split on the whole dataset (D2).

Detailed by Figure 6 and Figure 7 the optimum level for the significant factors was selected to develop a Random forest classifier. The classifier was able to classify FOG events with an average sensitivity of 57.57% and an average specificity of 99.45% for cluster-1 and an average sensitivity of 60.87% and an average specificity of 97.02% for cluster-2.

Furthermore, classifier performance was analyzed based on different types of splits ranging from 50-50 to 90-10 and a cutoff value ranging between 0 and 1 for the two clusters. Table 4 and Table 5 summarizes the sensitivity and specificity for different types of split for each of the two clusters.

Table 4. Different split on cluster-1

Split	Sensitivity	Specificity
50-50	55.73	98.98
60-40	50.69	98.99
70-30	57.50	99.45
80-20	57.02	98.79
90-10	50.91	98.32

From Table 4 and Table 5, the optimum sensitivity for cluster-1 was obtained from 70-30 split and for cluster-2 was gained from 90-10 split. The specificity remained relatively unchanged in both the clusters. This suggests the size of split also played a crucial role in the classification of FOG events. As mentioned earlier, the overall percentage of FOG events was 9.7%, and that of no FOG events was 90.28% in the dataset. As the percentage of no FOG events was significantly higher, the classification model was dominated by data points from no FOG events. This was one of the reasons why specificity remained unchanged, even when the training data size increased

Receiver operating characteristics (ROC) curve signifies the true positive rate (sensitivity) against the false positive rate (1-specificity) at different cutoff values. Figure 8 represents ROC curve of Random forest at 70-30 split for cluster-1.

Table 5. Different split on cluster-2

Split	Sensitivity	Specificity
50-50	60.77	99.23
60-40	60.39	99.18
70-30	60.82	99.02
80-20	62.68	99.85
90-10	69.29	99.23

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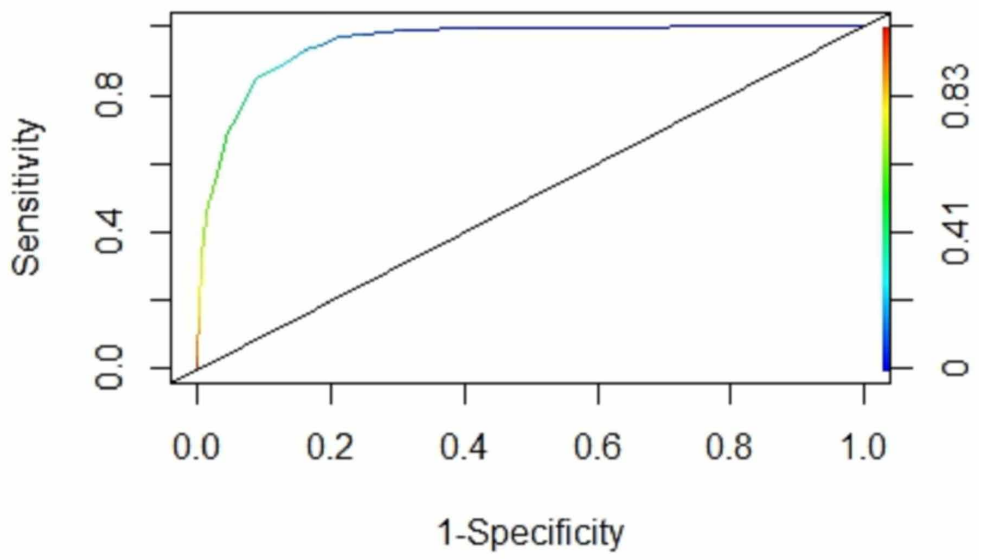
Figure 8. ROC curve of random forest at 70-30 split for cluster-1



The right y-axis in Figure 8 represents cutoff values between 0 (dark blue color) and 1 (dark red color). Note that the cutoff value of 0.5 corresponds to the sensitivity level of about 57.50%, which corresponds to Table 4. In Figure 8, as the cutoff value is reduced from 0.5 to about 0.2, sensitivity increase significantly from about 57.50% to 94.33%. Any further decrease in the cutoff value did not seem to improve sensitivity significantly, as observed from the flattening of the ROC curve. When the cutoff is reduced from 0.5 to 0.2, specificity decreased significantly from 99.45% to 89.84%. Similarly, the results at 90-10 splits were also obtained for cluster-2. The sensitivity and specificity were 88.89% and 92.77%, respectively.

Sensitivity for both clusters had increased significantly from about 57% to over 90%, but specificity had decreased. This indicated that cutoff value played an essential role in improving the classification of FOG events.

DISCUSSION

In this study, patient five experienced the maximum number of FOG events and patient six experienced the least events. Though the number of FOG events for patient six was less, the events' duration was longer. One possible reason can be that the patient was diagnosed twenty-two years ago. The shortest duration of FOG events was experienced by patient seven [mean 3.38 sec], albeit 24 FOG events were detected. A possible reason for this pattern can be that the patient was diagnosed just two years ago. The longest duration of FOG events was experienced by patient eight [mean 14.34 sec]. One possible reason for this experience can be that patient eight was at "ON" stage. The maximum variation in duration of FOG events was experienced by patient six [SD 14.32] and the least variation was experienced by patient seven [SD 2.73].

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A user-dependent experiment was performed, which obtained the best results for the patient six, i.e., 100% sensitivity and 99.9% specificity. The classifier for patient seven did not perform well and obtained sensitivity 68% and specificity 99%. A user-independent analysis was performed without clustering. The classifier performed well concerning specificity (>98%), but had poor sensitivity performance (<58%). This indicates a single classifier did not perform well on all the patients; therefore, clustering the patients into two clusters boosted the performance of the classifier.

The current model extracted data from a specific window length of 3 seconds. Thus, the proposed analyses could be extended to examine different sensor locations and different window lengths that may help further improve the performance of a user-independent model.

In the cases where the classifier was unable to classify FOG events correctly, the outcome was more harmful to the patients because they did not receive sensory-motor feedback. Whereas, in those cases where the classifier was unable to predict no FOG events correctly, the outcome was harmless to the patients, as it only resulted in false feedback. Since our primary aim was to classify FOG events more accurately, which was captured by sensitivity, any decrease in specificity was harmless to the patient.

One limitation of this study was that the database had a small number of patients. In the future, we plan to test the techniques presented on another dataset with a large number of patients to develop a more accurate classification model for FOG events, which might group patients into more clusters. Furthermore, the proposed technique will be designed into a real-time system such as smart-phone applications, embedded systems, etc.

CONCLUSION

In this paper, a robust classifier that can go along with non-pharmaceutical treatments by providing a warning to prevent injuries and falling was built. Eleven statistical features were extracted from the data collected using three sensors. To compute these features, a window with 50% overlap was selected to minimize loss at the edges. In all, 99 features were extracted from the dataset. Using clustering analysis, data were grouped into two clusters based on FOG events. Classifiers for each of the two clusters were developed using Random forest. Four-way randomized block design with replication was utilized to obtain the most significant variables for sensitivity and specificity.

With a different split of the dataset and a cutoff value of 0.5, sensitivity and specificity values of about 57% and up to 99%, respectively, were achieved. Since predicting FOG events accurately was more critical than predicting no FOG events, we further explored the use of the cutoff value to improve sensitivity. Using ROC curve, a cutoff value of 0.2 helped to improve sensitivity to over 88%.

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Chapter 24
Stroke Rehabilitation and Parkinson's Disease Tremor Reduction Using BCIs Combined With FES

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ABSTRACT

This article describes how Stroke and Parkinson's disease are two illnesses that particularly affect motor functions. With the advancements in technology, there is a lot of research focusing on finding solutions: to contribute to neuroplasticity in the first case, and to reduce symptoms in the second case. This manuscript describes the design of a brain-computer interface system (BCI) system paired with an electrical muscle stimulation suit for stroke rehabilitation and the reduction of tremors caused by Parkinson's disease. The idea is to strengthen the sensory-motor feedback loop, which will allow a more stabilized control of the affected extremities by taking into account the patient's motivation. To do so, his brain signals are measured to detect his intention to attempt to execute a movement, in contrast to the classical approach where the movement executions are imposed. A first feasibility study was completed. The author's next step is planning to test the system first with healthy subjects and finally with patients.

INTRODUCTION

This manuscript describes the design of a non-invasive EEG-based Brain-Computer Interface (BCI) system for motor recovery of stroke patients and for tremor reduction in patients with Parkinson's disease. Patients suffering from these diseases present motor impairments that prevent them to fully live their daily lives. In the case of stroke, some motor functions can be recovered some time after the stroke

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given a suitable rehabilitation therapy. Parkinson's disease symptoms on the other hand tend to worsen as time passes.

Several rehabilitation methods, such as Robot-assisted arms, Functional Electrical Stimulation (FES) and BCI combined with exoskeleton are examples of technology-based rehabilitation therapies (Ramos-Murguialday et al., 2012) being used, some with more success than others are. Nevertheless, in the end, the most important factor in the success of a rehabilitation therapy is the patient himself. Indeed, most of these therapies require the patient to perform the same movement multiple times. In the long term, the patient will lose interest since he gets bored by repeating the same exercise several times. This increasing boredom will consequently affect his motivation. Bhagat et al. (2014) demonstrated that a lack of the latter would limit the effectiveness of the rehabilitation process.

Lew et al. (2012) successfully extracted brain signals signatures indicating volitional upper limb movement intention from healthy persons, and detected the intention as early as 1500 ms before the movement onset. Bhagat et al. (2014), Ramos-Murguialday et al. (2015) and Yilmaz, (2015) performed similar experiments with stroke patients. Those studies suggest that it is possible to develop closed-loop brain-machines interfaces driven by the user's voluntary movement intention (Spüler et al., 2014). Plus, FES-based therapy has proven to be very promising for motor recovery during stroke rehabilitation (Noma et al., 2014).

Here, a system that combines BCI with a VisionBody suit that provides Electrical Muscle Stimulation (EMS) is proposed. The VisionBody suit is chosen to facilitate real-world applications. This suit, originally used in fitness and sports, provides Electrical Muscle Stimulation through electrode pads - located in the arms, legs, breast, etc. - directly to the skin in direct proximity to the muscles to be stimulated. The impulses delivered by these electrodes mimic the action potential coming from the Central Nervous System, causing the muscles to contract.

Our aim is to overcome patients' boredom and lack of engagement to the rehabilitation tasks by allowing them to execute voluntarily the required movements and detecting those intentions using their brain signals. As soon as an intent to move is being detected, the VisionBody suit will be used to deliver the electrical stimulation to the patient's muscles to assist him in the movement production in the case of stroke, and to suppress tremors that may occur while executing a movement in the case of Parkinson's disease. Otherwise, if no intention to move is detected, no support for the movement via Functional Electrical Stimulation (FES) will be provided. By doing so, it is intended to strengthen the sensorimotor feedback loop in order to stabilize the control of the affected extremities. A more positive engagement is then expected from the patients. This has the potential to increase the functionality of the affected limbs, and reduce fatigue by minimizing the energy consumption, the ultimate goal being the improvement of the daily lives of the patients.

The manuscript is organized as follows: first, an overview of stroke and Parkinson's disease is presented, followed by some rehabilitation techniques and treatments used for the two illnesses; then, the tools and methods used for the experiment were presented along with some results.

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BACKGROUND

Stroke

One of our target groups is stroke survivors. Stroke is among the leading causes of adult disability in the so-called developed countries.

Causes

It is caused by blocked or burst blood vessels in an area of the brain, which cause the blood flow in this area to be cut-off. The lack of oxygen will cause the brain cells to die and the abilities controlled by these areas, such as motor function or memory, will be lost (Bornstein, 2009).

Treatments and Rehabilitation Techniques

9 out of 10 stroke survivors have some degree of paralysis immediately after the stroke. They will then need to relearn those lost skills by the means of rehabilitation therapies, which may involve regular physical therapies or therapies that involve the use of technology, in order for them regain some independence and improve their daily lives (Kwakkel et al., 1999). Continuous rehabilitation and therapy can help stroke survivors regain voluntary movement even years following their stroke. For the moment, several methods are used to help movement recovery in stroke patients.

Functional Electrical Stimulation

Functional Electrical Stimulation uses electricity to stimulate weakened muscles and to cause them to contract. It has been successfully used to improve motor control in chronic stroke patients (Noma et al., 2014). Qu et al. (2016) built a network-based multichannel neuromuscular electrical stimulation system for people with paretic stroke to assist them with multi-joint movements. The system was tested both with nondisabled subjects and with subjects with stroke. Moreover, results showed that the patients improved their performance in executing these multi-joint movements.

The methods mentioned above require the patient to perform the same cue-based movement multiple times during a session. Over time, he may lose interest and this will affect his motivation. Which in turn, will reduce the effectiveness of the rehabilitation therapy. Engaging the patient in the therapy, by encouraging him to attempt to move on his own and at his pace, may overcome that. For stroke patients with some residual muscle activity, for example, EMG can be used to trigger FES. This allows the detection of voluntary movement even from the smallest electrical EMG signal. Which, in turn will be used to initiate the stimulation of these muscles and help produce an actual movement (Gabr, 2005).

EEG-Based Brain-Computer Interfaces

The first tool used in this study is the brain-computer interface (BCI). A BCI allows interfacing the brain and a computer by translating the electrical signal of the brain into control signals for external devices such as a robotic arm, a virtual keyboard or a virtual mouse. To do so, special electronic sensors are attached to the head and hooked to a computer where the electroencephalogram (EEG) is recorded. These

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sensors can be invasive or non-invasive. A typical BCI system consists of a signal acquisition module, a signal processing module, a module for features extraction and classification that translates the results of the features classification into a feedback or a device command.

Brain signals recorded from invasive electrodes have very good signal to noise ratio, as opposed to non-invasive electrodes. But invasiveness requires the electrodes to be implanted surgically. Anyhow, invasive-BCI has been widely used to restore mobility on paralyzed patients, especially those with spinal cord injury (Bouton, 2016; Leuthardt, 2004). The brain delivers information about a movement. It controls the corresponding muscles and triggers the movement. In case of spinal cord injury, the pathway from the brain to the extremities is compromised, resulting in the incapacity to perform voluntary movements. BCI can then be used as an alternative pathway to control the limbs. In other words, it is used as an artificial connection between the brain and the limbs, to bypass to some extent the lost connection. Brain-Computer Interfaces come into play by detecting the intention to move from the acquired brain signals, and by translating them into command to an external device, such as a robotic arm or to trigger an electrical stimulation to the muscles to produce the desired movement (Ethier, 2012).

A similar experiment has been conducted with non-invasive BCI, for the first time in 2003 in a patient suffering from tetraplegia (Pfurtschellera, 2003). The author wanted to prove the feasibility of controlling a FES using three pairs of surface electrodes by a patient with spinal cord injury with complete motor and sensory lesion. After 10 months of training, the patient was able to grasp a cylinder with the paralyzed hand.

As opposed to spinal cord injury where there is no brain damage, the messaging between the brain and muscles may not work properly when parts of the brain are damaged after a stroke. It usually concerns the side of the body opposite the side of the damaged brain, the arms or the legs most of the time. And this raises the question whether it is possible to use EEG signals from the damaged contralateral hemisphere to detect the patient's intention to move. Recent research on BCI for stroke rehabilitation shows that it can work as assistive BCI to support the patient in his daily life, but also as rehabilitation BCI to facilitate neuroplasticity (Soekadar et al., 2015). Earlier researches show that following a stroke, the hemisphere responsible for organizing a movement of the impaired limb depends on the patient's progress. For those who did not make a good functional recovery, the ipsilateral hemisphere plays the role. For those who made a nearly complete recovery, it is the contralateral hemisphere (Serrien, 2004). Antelis et al. (2015) were able to decode movement intentions from six severely affected stroke patients attempting to move their paretic arm by means of brain activity of the healthy contralesional motor cortex. Yilmaz et al. (2015) discovered that Movement-related slow cortical potentials (SCPs) amplitudes can be observed and are larger over the midline areas for paretic hand movement in severely paralyzed stroke patients. They are larger than in the contralateral and midline area compared to the ipsilateral area for healthy hand movement.

Thus, it is possible to detect movement intention from the brain activity of stroke patients. However, most research only focuses on the control of robotic devices and rehabilitation therapies consisting of repetitive cue-based movements. Furthermore, the devices used for rehabilitation, whether they are EEG-based or not, not only help the patient performing the movement but also completed it. The patient does not need then to make the effort to finish the movement; he just needs to start it. This lack of engagement from the patient will then result in an unsatisfying outcome of the training (Bhagat, et al. 2014). On the other hand, Soekadar et al. (2015) noticed remarkable improvements of motor and cognitive capacities in patients training with a goal-oriented behavioural therapy. This suggests that the patient's motivation and engagement play an important role in the rehabilitation process.

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Parkinson's Disease

The other target group of this research is Parkinson's disease patients. It affects the motor system and typically appears between the ages of 50 and 69, with symptoms worsening with time. At the beginning of the disease, the most obvious symptoms are shaking, rigidity, slowness of movement, and difficulty with walking. These symptoms are the result of the death of cells in the *subtantia nigra* that produce dopamine (Janvkovic & Tolosa, 2007).

Causes

It is known that secondary Parkinson's disease is caused by toxins, but there is no known cause for primary Parkinson's disease. There is no cure for the condition at the moment. However, the symptoms can be reduced or inhibited with medication and surgical procedures.

Treatments for Tremors

There are several types of tremor. Rest tremor is a well-known symptom of the condition. It appears mostly during rest and affects the patient in his everyday tasks. It affects mostly the hands and the head, and is an approximately rhythmic and roughly sinusoidal involuntary shaking at a frequency of 3 to 6 Hz (Grimaldi et al., 2010; Janvkovic et al., 2007; Manto et al., 2003). In contrast, action tremor appears when the patient is performing every day's task such as holding a magazine or drinking from a cup.

Tremors have been treated with medication, but with not much success and a lot of side effects. However, they have been well controlled by Deep Brain Stimulation (DBS) (Benabid, 2003; Limousin et al., 2008).

Deep Brain Stimulation

Deep Brain Stimulation (DBS) is a surgical procedure that place electrodes into parts of the brain such as the subthalamic nucleus, the globus pallidus interna or the thalamus. These electrodes produce electrical impulses to stimulate the target area. This will affect movement by altering the activity in that area of the brain. In case of tremor caused by Parkinson's disease, the electrodes are usually placed on the thalamus (Munhoz, 2016). Benabid et al. (1987) were able to relieve tremors from patients who were resistant to drug therapy by combining thalamotomy and stimulation to their brain. Like every other surgery, DBS surgery is a very risky procedure. Moreover, the patient selection process is also very competitive; not every subject who wants to undergo the procedure will be granted his wishes (Munhoz et al., 2016).

Other Methods

In their research, Manto et al. (2003) were able to successfully reduce tremors from patients. To do so, they extracted characteristics such as force, position, velocity and acceleration of the pathological tremor, and used them to define the loads or forces' parameters required to be able to counteract its action.

Zhang (2016) from Microsoft Research Cambridge built a tremor-reducing wearable device to counter the effects of tremors in a 33 years old woman diagnosed with Parkinson's disease, allowing her to write and draw more precisely than before.

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MOTIVATIONS

Previous researches have shown that despite the brain injury after stroke, it is possible to detect patients' movement intention. In addition, the importance of patients' motivation and engagement during rehabilitation has been demonstrated. Rehabilitation methods using robot-assisted arms or neuromuscular electrical stimulation require the patient to repeatedly perform a given movement. Over time, the monotony of these methods affects the patient's interest and decreases his motivation. This lack of motivation limits the effectiveness of the rehabilitation process. The proposed system aims at taking into account the patient's motivation and increasing his engagement in order to improve the outcomes of the therapies and the treatments. The hypothesis used in this approach is that due to the connection of the patient's intent with the supporting stimulation, the sensory-motor feedback loop will be to strengthen resp. re-established and this will allow future movements to be performed without engaging the system.

On the other hand, tremor has been quite unsuccessfully treated with medication, but has been well controlled by Deep Brain Stimulation (DBS). DBS is very invasive and the process to choose patients for the surgery is very selective. Electrical stimulation has the potential to counter the effect of tremors, with the advantage of being non-invasive. In this case, BCI will be used to detect the patient's intention to move and in addition, Electromyography will be recorded. The latter will then be used to define the electrical stimulation parameters necessary to counter the effect of the tremors. This has the potential to improve the daily lives of Parkinson's Disease patients by reducing fatigue for instance.

In both case, a VisionBody suit will be used to facilitate the application of the system in real life environment.

PROPOSED TOOLS AND METHODS

System Design

The overall system design is shown in Figure 1. The system consists of:

- **A computer screen:** This screen is mainly used to display the cues to the subjects during the experiment. The stimulus presentation was programmed using BCI2000;
- **A 16-channel g.USBamp acquisition device from g.tec (Austria) connected to a laptop on which BCI2000 is installed:** Brain signals are acquired using the g.tec amplifier. BCI2000 and self-written signal processing (see Figure 1) are used to process and classify the obtained raw signal. The laptop is also used to store the raw data;
- **A VisionBody exosuit:** Once the system detects patterns that indicate an intention to move, the computer sends a control signal to the VisionBody suit. That will then activate the electrical stimulation to the muscles. The communication between the computer and the suit is established via Bluetooth.

An experiment comprises two sessions, a calibration session and a training session. The calibration session is used to train the classifier for each and every subject. Figure 2 shows the course of a calibration session. Each session is composed of a number of trials and each trial starts with a preparation period of 1s. The EEG signals obtained during this period are used to establish a baseline. A second cue

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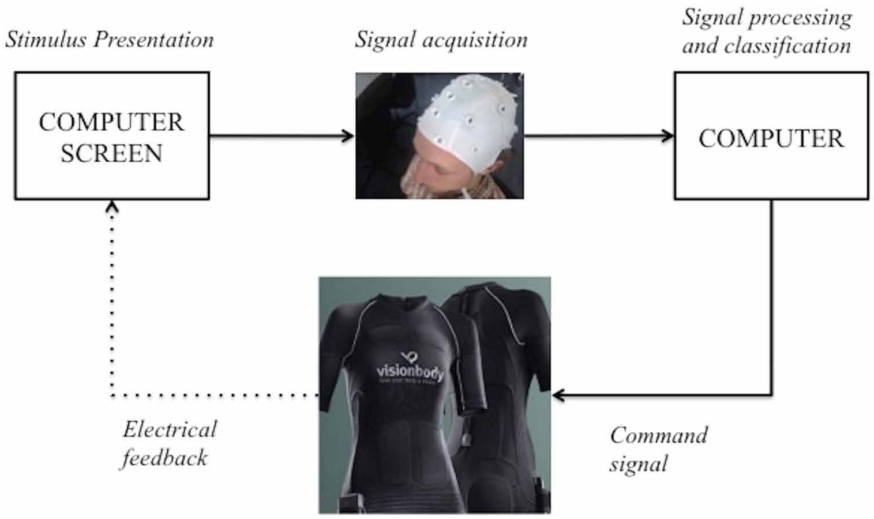
Figure 1. System design: The BCI system is composed of a computer for stimulus presentation and data analysis, a signal acquisition tool using a 16-channel g.USBamp from g.tec. The feedback loop is executed using a VisionBody suit that is triggered when the system detects the subject's voluntary movement intention.

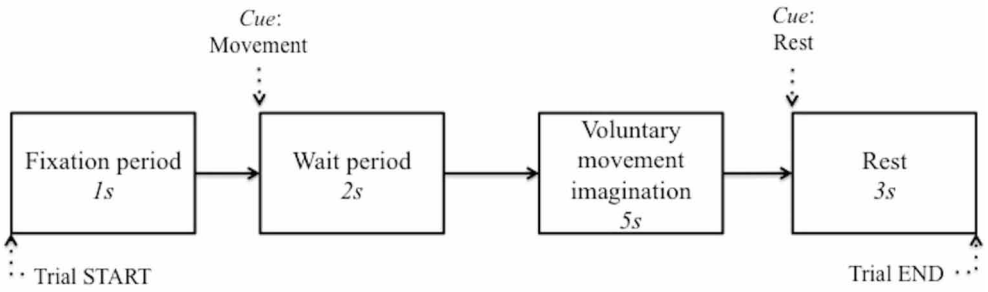


informs the participant of the type of movement to be performed. Prior to the start of the experiment, the participant is instructed to let at least 2s pass before executing or imagining the requested movement. The time frame available to execute the task is 5s. The patient's brain signals are continuously recorded, and movement related features are extracted. These features will be used as input to train the classifier.

This trained classifier is then used to detect voluntary movement intention during the 5s time window throughout the training session. The training session follows the same course as the calibration session, they differ only due to the fact that electrical stimulation is also activated in the meantime.

The detection of a movement intention triggers electrical stimulation to the muscles, and the stimulation is delivered until the target is reached. A trial will be considered successful when the movement is successfully executed during the allocated time. Each trial ends with a 3s rest period.

Figure 2. Experimental setup for the calibration session



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Participants in Prior Study

Two healthy, right-handed subjects participated in this preliminary study. All participants were informed of the purpose of the study.

Experimental Setup

Data Acquisition

Brain signal activity was measured with the g.USBamp amplifier at a sampling rate of 256 Hz. The electrodes were located at the International 10-20 system locations Fp1, Fp2, F3, F4, C3, C4, P3, P4, Fz, Cz, and Pz. The electrode FCz and AFz were used as reference and ground, respectively (Yilmaz, et al. 2015). These locations were chosen so that they are adequate for all subjects. The amplifier was set to filter the signal between 0.1 and 60 Hz, and an additional 50 Hz notch filter was used to remove noise introduced by the electric power. The EEG signals were then transferred to BCI2000 software (Schalk et al., 2004) for analysis and offline storage.

Electromyographic (EMG) data were also recorded at a 250 Hz sampling rate from one subject using medical grade stainless EMG sensors from a Myo armband (Myo TM) placed on the forearm for the tremor reduction task. This EMG will be used to predict the parameters needed during the tremor reduction process.

Task

The participants are seated in a chair, with hands resting on a desk in front of them. They were asked to imagine or execute hand opening or closing of the left or the right hand, depending on the cues presented on the screen using BCI2000. They were also instructed to avoid head or shoulder movements to reduce muscle artefacts.

Each experiment consisted of 40 runs; each run consisted of 8 trials. Trials started with a preparation phase of 1s, followed by a 7s movement imagination phase and a 3s rest phase (Figure 2). Preparation and imagination phases were initiated by visual clues presented on the screen.

Participants were also instructed to wait at least 2s after the cue before executing or imagining a movement. This is done to avoid the presence of an Event-Related Potential (ERP) called Contingent Negative Variation (CNV) that peaks 260 to 470 ms after a warning stimulus that requires a physical or mental response (Lew et al. 2012). It can be measured over the vertex with maximal amplitude of 20 μV (Nagai et al., 2004; Walter et al., 1964).

In addition, one subject was asked to simulate Parkinson's disease tremor. The simulated tremor will later be added to the recorded EMG to simulate tremor-contaminated EMG signal corresponding to a movement.

Data Analysis

The EEG signals were re-referenced using a common average reference (Ibanez et al., 2013; Schalk & Mellinger, 2010; Song, 2013). EEG signals are very susceptible to external artefacts such as eyes and muscles movements or other external sources. So, before this experiment, the authors performed another

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preliminary experiment in order to study how the electrical stimulation produced by the VisionBody suit was affecting the recorded EEG signals. One participant took part in this preliminary study, wearing the VisionBody suit while his brain signals were continuously recorded. The electrical stimulation is adjustable from 0 to 100% of the maximal intensity defined by the VisionBody suit. In this study, stimulation ranging from 0 to 35%, with an increment of 5% in each trial, was used since higher values of intensity were painful for the participant. Visual inspection of the recorded brain signals showed that, starting at 20% of electrical stimulation, rectangular signal bursts are visible, and their amplitudes increase with an increase of the level of stimulation (Adama et al., 2016). These artefacts were rejected after filtering and applying Independent Component Analysis (ICA) from the EEGLAB toolbox (Delorme et al., 2004). After filtering and artefacts removal, movement related features would be extracted from the collected brain signals.

Features Extraction and Classification

Movement related potentials and Event-Related Synchronization of beta and Event-Desynchronization of alpha waves to assess pre-movement cortical activity were used. Here a feature extraction procedure similar to the ones described by Antelis (2017) and Bhagat (2014) was followed.

First, the signals were segmented into trial epochs of duration -2 to +2s, according to the movement execution. To extract the movement related potentials, EEG data were band-pass filtered with a zero-phase shift second order Butterworth filter at 0.1 - 1Hz and down sampled to 20 Hz. The amplitudes of the signal in that frequency band constitute the MRCP features. In addition, the power values are estimated using Welch method, with a Hamming window of 1s and a 50% overlapping. The features extracted are the logarithmic power of the signals in the alpha (8-13 Hz) and beta bands (13-30 Hz).

For both processes, the features were extracted with a one second sliding window in steps of 125 ms. Features obtained previous to -1.5s were labeled 'rest' and those following -1.5s were labeled 'pre-movement'. These features are used to train a classifier. The movement intentions are detected using a trained classifier.

Movement Intention Detection

Movement production is an elaborate process. In order to produce a movement, the brain sends messages to the limbs. For self-paced hand and foot movements for instance, a slowly increasing surface-negative cortical potential called Readiness Potential (RP) can be measured 1.5 to 1s before the movement onset. This component, also known as Bereitschaftspotential (BP), presents a steeper decay 400 ms before the movement starts and can be measured over the primary motor cortex M1 (Jahanshah & Hallett, 2003). Its amplitude is maximal over the frontal rather than the occipital area, ranging from 10 to 15 μV. BP amplitude increases with intentional engagement and reduced by mental indifference of the subject. Yilmaz et al. (2015) were able to extract these slow cortical potentials from severe chronic stroke patients with no residual paretic hand movement. Their results showed that the SCPs appeared and peaked earlier during paretic hand movement compared to healthy hand movement. Paretic hand movement also elicited larger amplitude over the midline brain while for healthy hand movement, contralateral and midline amplitudes are much larger than ipsilateral activity. Which make them an interesting feature to use for our system.

Event-Related Synchronization/Event-Related Desynchronization is another useful feature. Largely used in motor imagery, it has also been used to detect the intention to move a limb, which is characterized

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by a decrease of power in the alpha bands (8 - 15 Hz) and an increase of power in the beta bands (16 - 31 Hz) (Bhagat et al., 2014; Kornhuber & Deecke, 1965; Shakeel et al., 2015; Shibasaki & Hallett, 2006).

One important part of a BCI system is the EEG classifier. Several have been used in Brain-Computer Interfaces, and in particular to predict movement onset. Several classification methods have been used to classify and detect movement intention, such as Support Vector Machines, Linear Discriminant Analysis, k-nearest Neighbours or naïve Bayes (Planelles, 2013).

In this study, Radial Basis Function (RBF) kernel Support Vector Machine (SVM) was used for classification. The features used were the movement-related cortical potentials and the power spectra of the EEG signals. The classification accuracy is computed as the ratio of the number of the correctly predicted trials to the total number of trials.

Parkinson's Disease Tremor Onset Detection and Suppression Algorithm

Tremors affected the way patients execute simple tasks in their every day's life. In the case of Parkinson's disease, they can be predicted from EMG signal as demonstrated by Wu et al. (2010), using Radial Basis Function Neural Networks who found that the tremor onset signal is between 1 and 10 Hz and that the pre-tremor signal contains a large amount of activity between 10 and 30 Hz. Apart from muscle activity, tremors can also be predicted using parameters like Event-Related Synchronization / Event-Related Desynchronization (ERS/ERD) and Movement Related Cortical Potentials (Grimaldi et al., 2010).

Pathological tremors generally appear at frequencies between 3 to 12 Hz while voluntary movements are combination of lower frequencies from 1 to 4 Hz. In particular, tremors caused by Parkinson's disease lay between 3.5 to 6 Hz (Manto et al., 2003; Rocon et al., 2010). The most popular method to counter the effect of pathological tremors on patients has been to estimate parameters such as amplitude and frequency of the tremor, and used these to calibrate a loading force to suppress it. Even though there are several sensors that can be used to measure the electromyographic signals, most of these researchers used gyroscope (Grimaldi et al., 2010; Manto et al., 2003; Rocon et al., 2010). The frequency and amplitude of the tremor are then estimated using methods based on Fast Fourier transform (Adhikri et al., 2015; Wang et al., 2016).

In this study, these parameters are estimated using the recorded EMG data and used afterwards to determine the characteristics of the electrical stimulation needed to counteract the tremor from VisionBody suit. Before applying the tremor estimation algorithm, the EMG data is filtered using a 5th order Butterworth pass band filter between the frequencies 5 to 20 Hz to remove unwanted low frequency drifts.

Note that this procedure was not applied on patients yet but performed to test the capability of the proposed signal processing for future use with patients. To the recorded EMG signal was added simulated tremor signal. This signal was created as a combination of 5 and 7 Hz sinusoidal waves with amplitudes of 1 and 0.5 respectively. The predicted tremor signal was estimated from the added signals using a Weighted Fourier Linear Combiner (WFLC) algorithm, as described by Adhikari and al. (2015). The WFLC algorithm is based on the Least Mean Square (LMS) algorithm and is widely used to reduce tremors and stabilize surgeons' hand during surgery.

Electrical Stimulation Delivery

The feedback loop is executed using a VisionBody exosuit that is triggered when the system detects the subject's voluntary movement intention. The suit then delivers an electrical stimulation through the pad

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electrodes with an amplitude chosen between 0 and 50 mA, and a frequency of 20 to 50 Hz. Stimulation is sent by pulses of 0 to 0.5 ms and inter-pulses delays between 10 and 100 μs (Lee et al., 2015; Ono et al., 2013; Qu et al., 2016). For stroke patients, the exact values of the amplitude and the frequency of the electrical stimulation signals depend on the level of impairment of each patient individually. In the case of Parkinson's disease, these parameters are obtained after applying the WFLC algorithm to the contaminated EMG signal. Once the patient reaches the end of the movement, the electrical stimulation is turned off.

RESULTS

This study aims at designing an EEG-based brain-computer interface system combined with a Vision-Body suit that provides electrical stimulation, for stroke rehabilitation and Parkinson's disease tremor reduction. Movement-related cortical potentials and power spectra of the alpha and beta waves were extracted from brain signals recorded from 11 electrodes as described above. In addition, EMG data were also recorded and used to determine the electrical stimulation parameters for the tremor reduction task.

Figure 3 shows an example of EEG signal recorded at electrode C4 when the participant is imagining opening his left hand (a), and during rest (b). The movement onset occurred at t=0s. Movement intentions were detected 1.25 to 0.9s prior to the movement onset. Literature shows that the typical values are between 1.5 and 1s prior to the movement onset (Jahanshani & Hallett, 2003).

Figure 3. Example of training data recorded at electrode C4: (a) When imagining a movement; and (b) During rest. The onset of the movement is at t = 0s.

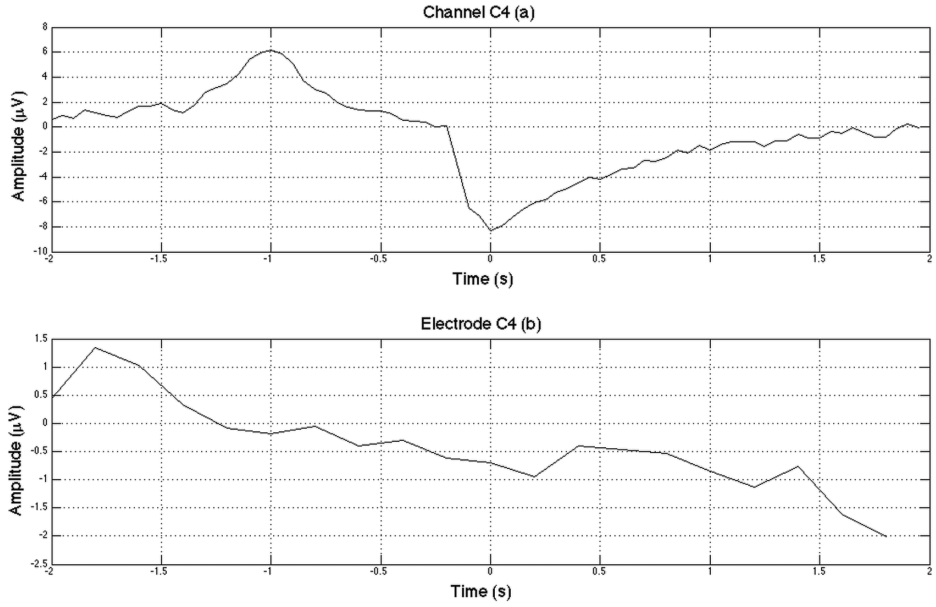

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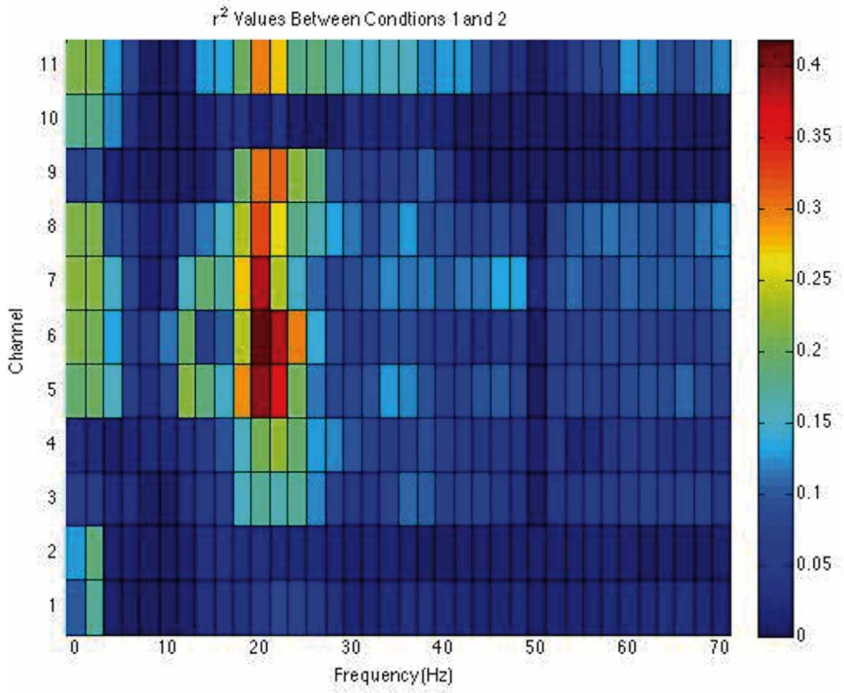
Figure 4. Selected features for the first participant where Condition 1: Rest and Condition 2: Left movement execution. The figure is a feature map in which the horizontal axis corresponds to frequencies and the vertical axis corresponds to the channels. The measured r-squared between 'rest' and 'left hand movement execution' are represented in colour codes. In this particular case, r-squared values are the largest for channels 5 (C3), 6 (C4), and 7 (P3) with 0.3964, 0.3799, and 0.3416 respectively, at 19 Hz.



For each participant, only channels with the higher r-squared values between 'rest' phase and 'movement' phase will be selected to implement the online system (training session) in order to reduce computation time. The channels with the higher r-squared values were located in the central and parietal areas (C3, C4 and P3) for Subject 1, and in the central and frontal areas (C3, C4, and Fz) for Subject 2 during both motor execution and motor imagination. Figure 4 is a feature map that represents the average channel/frequency matrices for a left hand movement execution of the first participant. The horizontal axis corresponds to the frequencies and the vertical axis corresponds to the channels. Condition 1 represents Rest while Condition 2 represents a left movement execution. The measured r-squared between the two conditions are represented in colour codes, and in this particular case, its values are the largest for channel 5 (C3), 6 (C4) and 7 (P3) with 0.3964, 0.3799 and 0.3416 respectively at 19 Hz.

The mean classification of the classifier is represented in Figure 5 for both subjects. It is calculated as the ratio of the number of true detections to the total number of attempts. The results show that the classification accuracy is higher during movement execution compared to movement imagination. Furthermore, it is higher while performing the task with the dominant hand. Left hand movement imagination classifications were the less reliable with less than 75% accuracy for both subjects. Overall, these results align to other similar research on movement imagination and execution researches with accuracies ranging from 64.5 to 87% for movement imagination, and from 69 to 99% for movement execution (Shakeel et al., 2015).

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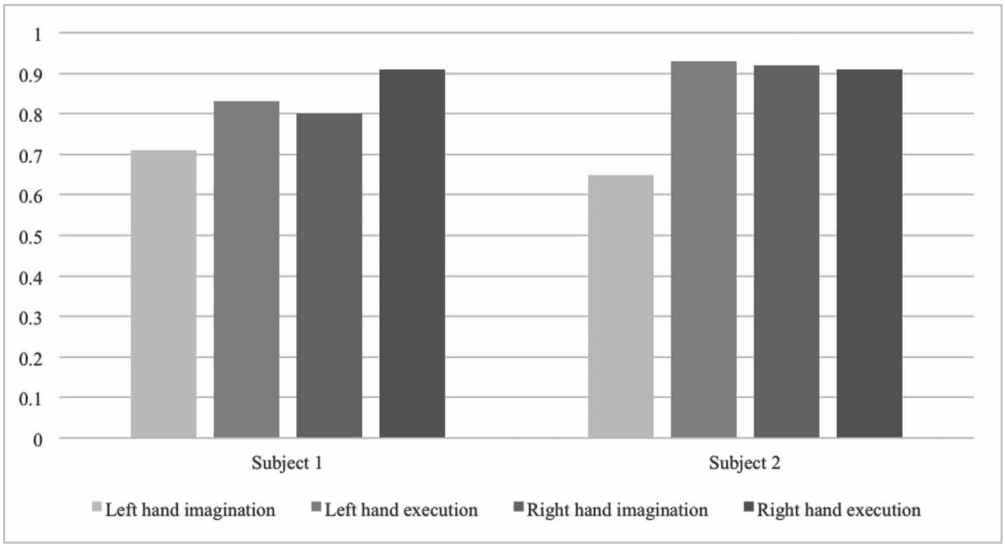
Figure 5. Average detection accuracy of the classifier, corresponding with the four tasks. The vertical axis represents the percentage of true positives, 1 equals 100%.



The tremor reduction task was tested with real EMG data to which simulated tremor data was added. A natural upper limb movement is composed of movements, which frequencies lay between 1 and 4 Hz. The signal was acquired at a 250 Hz sampling rate. Figure 6 shows a portion of the EMG signal used for this experiment and its periodogram. The latter shows that the dominant frequencies are effectively between 0.5 and 4 Hz, which correspond to the frequencies of a voluntary movement. Amplitudes are expressed in mV. A tremor signal was then generated as a combination of 5 and 7 Hz sinusoidal waves, with amplitudes of 1 and 0.5 respectively, to simulate Parkinson's disease tremor (cf. Figure 7). The predicted tremor signal and the residual tremor are presented in Figure 8. After applying the tremor reduction algorithm, the amplitude of the tremor is significantly reduced from 1.5 to less than 0.1 mV. The same conclusion can be deduced in Figure 9, which represents the periodogram of both signals. It shows a significant decrease in the signal power. A spectral coherence between the simulated tremor signal and the predicted tremor confirms that both signals have two correlated components around 5 and 7 Hz.

DISCUSSION AND CONCLUSION

This manuscript describes and proposes the design of an EEG-based Brain-Computer Interface combined with electrical stimulation intended for the rehabilitation of stroke and for tremor reduction in patients diagnosed with Parkinson's disease. The idea is to improve the outcomes of the rehabilitation therapy for stroke patients, in one hand, by engaging and motivating them in order to speed motor recovery. On the other hand, the system is expected to minimize the energy consumption of the arm with the patients experiencing tremors, thus reducing fatigue and possibly increasing its functionality. The VisionBody suit was chosen to deliver the electrical stimulation so that it can facilitate real-life application of the system.

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Figure 6. Recorded EMG signal. The image at the top shows the recorded EMG signal from one participant. The sampling rate is 250 Hz. The amplitude of the signal is expressed in mV. The image at the bottom shows the periodogram of the same EMG signal. Signal frequencies lie between 0.5 to 4 Hz, which correspond to the frequency of voluntary movements.

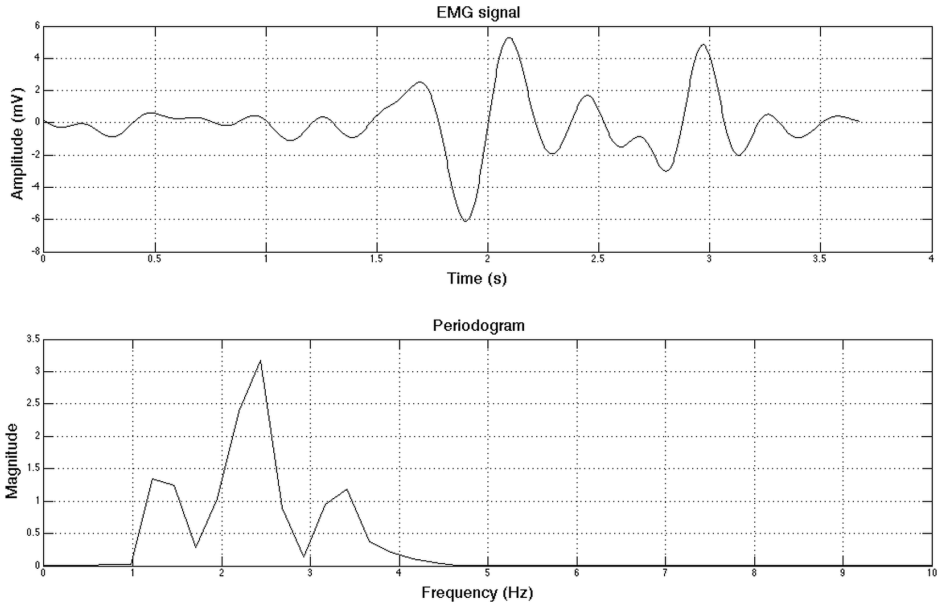

Figure 7. Simulated tremor signal. The tremor signal was created as a combination of 5 and 7Hz sinusoidal waves with amplitudes of 1 and 0.5 respectively, to simulate the Parkinson's disease tremor.

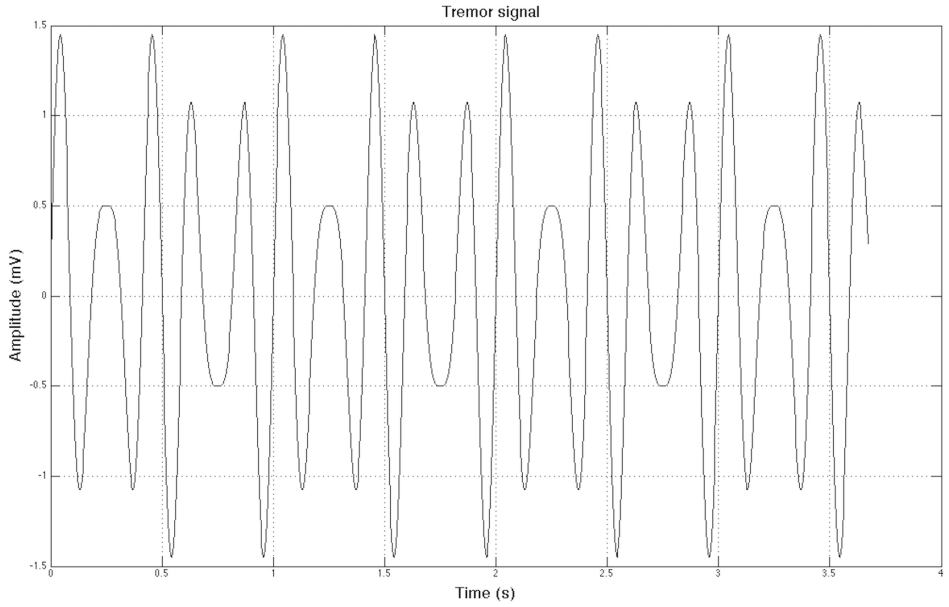

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Figure 8. Predicted tremor signal and residual tremor after tremor suppression. The predicted tremor signal is obtained from the tremor suppression algorithm and will be used to calibrate the electrical stimulation. The remaining tremor is shown in the figure on the bottom. The amplitude of the original tremor signal was 1.5 mV and the remaining amplitude after the suppression algorithm is less than 0.1 mV.

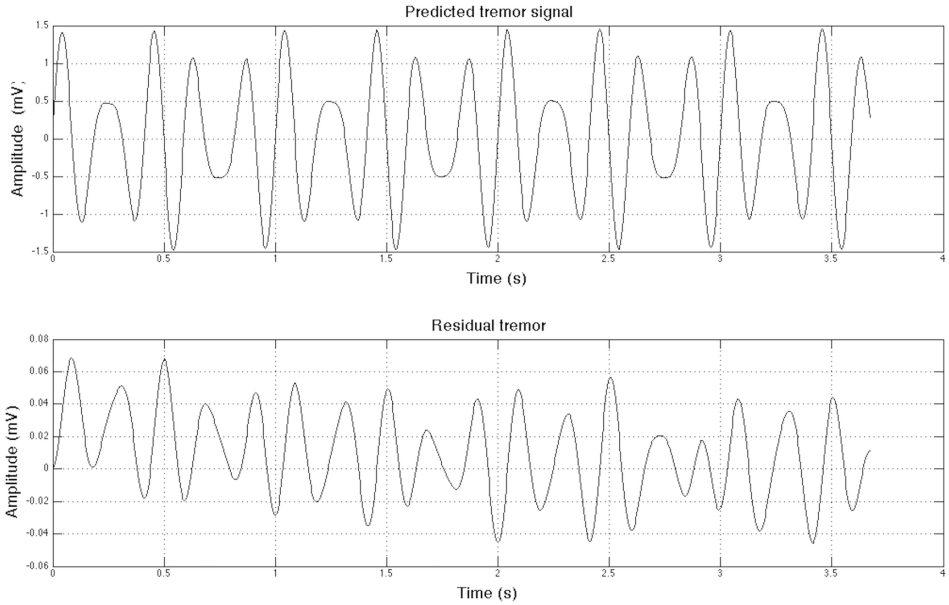
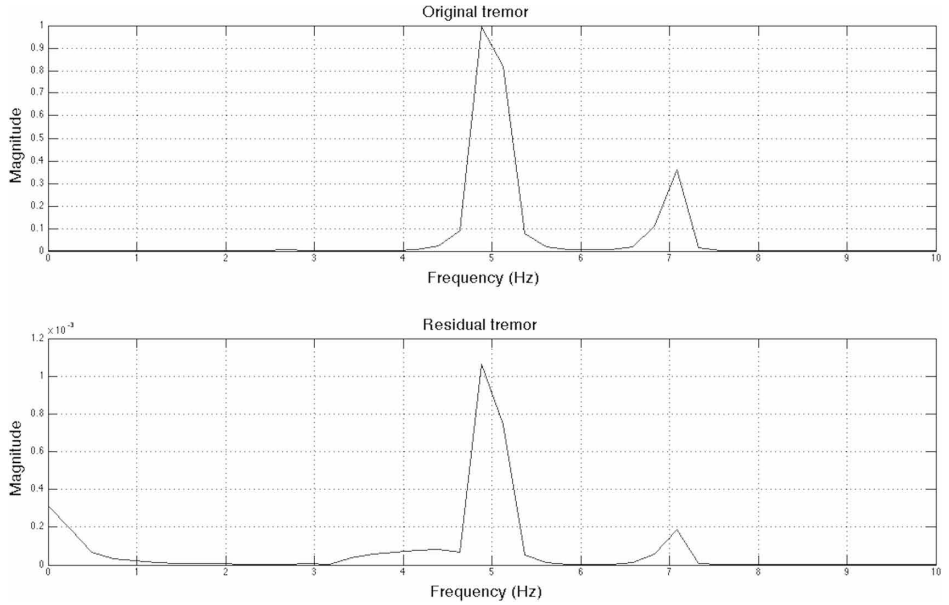


Figure 9. Periodogram of the original tremor (top) and the residual tremor (bottom). The power of the residual tremor is 1,2.10^6 times smaller than that of the original tremor, showing that the tremor is effectively reduced after applying the tremor suppression algorithm.



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Bereitschaftspotential and the power values of alpha and beta waves were extracted from the EEG signal to detect movement intention. These features were then used as input to a Radial Basis Function kernel Support Vector Machine classifier in order to implement the online rehabilitation session. Overall, the detection accuracy is satisfactory and aligns with the results of previous researches. However, it appears that this accuracy was lower for movement imagination and execution of the non-dominant hand. Moreover, the algorithm used to counter the effect of the tremor was able to reduce the original tremor signal by 150% in our simulation, which is very promising. However, the study needs to be extended to more healthy participants to obtain deeper and more reliable results.

Thus, the authors have shown that the approach is promising and feasible from a technical point of view and might be followed up with patients. With the rise of mobile non-invasive BCI, the feasibility of this project would mean a facilitated real-life application, for instance in home care to improve patients' life. Future steps would be to incorporate the closed loop BCI/FES/EMG approach and to perform experiments in real-time still with healthy subjects. Once those have been done successfully, the approach will finally be extended to patients, preferably with some residual limb movement. Some of the challenges will be to obtain good classification results with less training data, to avoid patient fatigue and to correctly calibrate the parameters of the electrical stimulation depending on the level of impairment of each patient.

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Chapter 25
Virtual Reality Therapeutic Environments in Autism Spectrum Disorder (ASD) and Alzheimer's:
Treatment, Diagnosis, and Refinement

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ABSTRACT

This chapter is devoted to observing and analyzing the role of virtual reality environments in the therapeutic treatment, analysis, and ongoing treatment planning of autistic spectrum disorders (ASD), Alzheimer's, and dementia. Using live real-world examples of the above activities in action and a literature review, the chapter will examine the level of empirical data and pre-existing qualitative and quantitative research to support these ongoing approaches. Critical analysis will also be made of the current level of empirical research available highlighting areas that should be focused on for future research.

INTRODUCTION

This researcher has been working in the field of virtual reality and digital interaction with both Google, the Chartered Institute of Marketing (LinkedIn, 2018) and the immersive VR agency Oncor Digital (Fair, 2015). Primarily with an approach focused on applied user psychology and marketing communications, the foci of the last decades' immersion in this field has nevertheless created links with many producers of Virtual Reality (VR) and Augmented Reality (AR) content across a wide range of other applications. These span entertainment, educational and promotional applications, all of which have significant realised and unrealised potential as fledgling VR/AR technology establishes itself as a mainstream technology. However, perhaps, the most affecting application of VR is in the field of healthcare – specifically

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mental healthcare. A great many aspects of mental health have been approached with VR treatments and diagnostics. However, although much anecdotal evidence of benefits has been shared in online and offline media, perhaps because of the widely (and therefore thinly) dispersed activities, there has been a distinct lack of collected empirical research data in these fields. (Mikropuolos & Natsis, 2011). Although not an academic researcher, this author's two decades in the field of marketing (where arguably 70% of activities are research, testing, measuring, recording and adapting to qualitative and quantitative analysis of research – Jain, 1989) has generated a strong interest in capturing reliable and comparable data which can be usefully applied across the ongoing and collective progression of VR in all of its applications – particularly healthcare where the sharing of information has always been a lynchpin of the disciplines' development. (Walker et al., 2005). Similarly, the rapid progressions of the field of offline and online marketing media consumption, from primarily text and image based media through to audio, video and most recently immersive/interactive communications, has seen technological, behavioural and even sociological parallels that span all areas of human behaviour (Napoli, 2011) – not least healthcare. Finally, coming from an ongoing perspective based around psychology and sociology (stemming from regular study and application of consumer psychology) have highlighted the strong bidirectional link between media consumption/interaction and the psychological (even psychophysiological) condition of the participant (Shrum, 2009). It is the bidirectional and interactive nature of VR communication that provides the three specific foci for this chapter on its application to mental healthcare – namely not only treatment, but observation and recording of progress, and the resultant diagnostic potential of live and ongoing observation to continuously assess progress and accordingly adapt treatment plans. This chapter will examine precedents for these abilities across Autistic Spectrum Disorders (ASDs) and Alzheimer's/Dementia.

ASD Virtual Environment Therapy

A recurrent issue in both lower and higher functioning Autistic Spectrum Disorders (ASD), most notably in younger sufferers, are the difficulties created by the breaking of routines (Schaaf et al., 2011). This is frequently an issue when coming into new and unfamiliar environments where ASD sufferers can be particularly prone to incidences of sensory overload and extreme resultant discomfort – but perhaps the most life restricting aspect of this is the avoidance behaviours which can result, restricting mobility, social interaction and even employment prospects in later life (Gustafsson & Papliński, 2004). Craig French Hendry (2018), a colleague working in the field of commercial and industrial immersive 360 walkthrough technology, was aware of this issue through a family connection with ASD. As a means of helping to prepare, and therefore alleviate, sufferers' symptoms, Hendry volunteered his services to a number of entertainment, historic and educational venues near his home base in Perth, Australia (Hendry, 2018). These services included capturing these areas using a combined infrared ranging and photogrammetry scanner. The output from this device is freely accessible via a cloud based online distribution network, viewable on devices from basic smartphones, tablets and computers through to VR Head Mounted Display (VR-HMD). To varying degrees, Hendry (2018) felt that, within a familiar home environment, and with the ability to pull out whenever the participant required, this approach would allow ASD sufferers and their carers to virtually 'pre-visit' the planned destination, familiarising themselves with the features and layouts of this new environment and beginning to form a more familiar pattern of awareness of the space. Although even a full VR walkthrough can only prepare the proposed visitor for a small section of the sensory stimulus likely to be encountered during a live visit - for instance, failing to replicate

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the noise and movement created by other visitors In-text: (Smith et al., 2014) – it was hoped that this would still go some way to alleviating symptoms caused by the unfamiliarity of environmental cues. Although responses to this and similar provisions elsewhere in the world have generated consistently positive anecdotal feedback from both sufferers, carers and hosts, as ad-hoc and not formally assessed activities, the empirical and quantifiable results of these have been extremely limited. Fortunately, a more structured application and assessment of this approach has been conducted by Cobb and Parsons (2011) conducting a comprehensive literature review of all similar applications of VR technology to ASD over a ten-year period. Their choice of VR in particular as a therapeutic medium was inspired by Parsons and Mitchel's (2002) assertion that virtual environments 'could be particularly helpful for people on the autism spectrum because: 1. The user has active control over their participation; 2. Interaction can take many forms and does not necessitate face-to-face communication (users may communicate via their avatars) which many people with autism might find particularly threatening; 3. The level and number of non-verbal and verbal features of communication can be directly controlled and manipulated; 4. Behaviours and responses can be practiced and built-upon in a context that shares some similarities with the real world, thereby offering greater potential for generalization; and 5. A more realistic representation of a situation on a computer-screen could, in theory at least, assist with the mental simulation of events, thereby improving social problem-solving'. Although Cobb and Parsons (2011) commented that there was (and still is) a surprising lack of large scale empirical studies on the topic, those studies included in their literature review still highlighted some very interesting findings. One set of studies in particular (Moore et al., 2005; Fabri & Moore, 2005; Fabri et al., 2007) were able to not only demonstrate far better real world participation in environments previously 'visited' in VR (in this case a café where they were asked to navigate to the counter, order a drink and take a seat), they were also able to demonstrate 'off target' behaviour in some of the participants, where they explored other areas of the café and even went behind the counter. What was particularly useful about this was that it allowed assessors to diagnose participants who might require extra support and preparation to be able to navigate the real world equivalent environment and task. Although the sample sizes on each of these studies were small (three sets of 12 ASD children, each grouped into a different age range from 4-5 up to 14-15), the results were consistent and borne out by subsequent qualitative monitoring. Familiarisation with environment was not the only application of VR examined in the context of young ASD sufferers – virtual environments were used to demonstrate safety procedures such as fire and tornado drills and even crossing a busy street. Not only were the vast majority (11 out of 12 and 5 out of 6 respectively) able to successfully complete these procedures in virtual reality, a lower but still significant proportion were also able to transfer this procedural learning to real world equivalent scenarios (Josman et al., 2008). To reiterate however, none of these studies were of a size which could be considered statistically significant enough for the results to be reliably repeatable, merely pointing towards the need for repetition amongst a larger sample size. As Cobb and Parsons (2011) themselves stated; 'Most of the studies tend to be fairly small-scale in nature, with limited extension beyond one or two preliminary investigations, which can present equivocal results. Although these do offer some positive support for the earlier arguments regarding potential of VR, there is still a considerable challenge in translating this into workable, useful tools that offer realistic applications'.

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Dementia Virtual Environmental Therapy

There has been a great deal of promising research into the beneficial effects of environmental therapies on sufferers of dementia; with changes to surroundings, furniture and even music to reflect that of the sufferer's pre-onset life experiences being shown to dramatically and consistently alleviate some of the most severe symptoms (Day et al., 2000). However the appropriate era of surroundings is very much dependent upon the age of each patient and the time of life when their symptoms came on, thus making an already complex and expensive process of recreation still more difficult to achieve across the range of sufferers, with the result that very few dementia patients are lucky enough to benefit from this type of immersion – referred to as 'Reminiscence Therapy' (Siriaraya & Ang, 2014). Suzanne Lee (2018) - at the time digital content communications specialist for Lloyds Banking Group - was very interested in VR technology and, having encountered dementia symptoms in two late members of her own family, began to explore if VR had ever been used for the condition. Initially encountering very promising video evidence of the application of immersive video for calming dementia patients by UK VR company TribeMix (2017). Lee (2018) was inspired to further this research directly. Undertaking bi-monthly visits to various care homes in collaboration with the Forget Me Not dementia training group (Elsley, 2018) Lee (2018) tested a variety of 360-degree videos on dementia patients depicting tranquil, calming environments. Not only did she notice consistent benefits in participants in terms of reduced agitation and increased post therapeutic engagement levels, she also noted that social interaction *between* these participants (limited or even absent beforehand) was dramatically increased – seemingly by their shared experience of the therapy. (Finkelstein et al., 2011). Based on this, Lee (2018) started to plan content which might be more meaningful to the specific patients, filming familiar local environments in 360 degrees which she was able to utilise with success in subsequent visits. Also, by observing online Alzheimers forums such as Twitter's "Alzchat" (Twitter.com, 2018), Lee (2008) observed and created content to address recurrent themes and threads based on their commonness, their impact etc. For example, in planning a virtual garden scene for the environment, Lee (2008) had learned that because of limitations to spatial navigation and decision making, and the confusion issues these could create, her interactive environments would need to avoid the incorporation of halting or forking paths, replacing these with continuous, looping pathways to facilitate smoother navigation. (Cushman, Stein & Duffy, 2008). Similarly, upon learning of the vision loss and depth perception issues common to many dementia sufferers, Lee (2008) was taught to avoid dark coloured areas, as these could be perceived as holes and therefore threatening obstacles. (Lewis & Griffin, 1997). For the same reasons, contrasts between different types of flooring could potentially be misinterpreted as changes in floor level or steps, so these were eliminated to avoid patients overcompensating in their step height. Conversely similarly coloured objects in relation to the floor, such as a blue bedspread over a blue carpet, cannot be easily differentiated as being at different heights, making identifying the object as a bed (if at all) very difficult. (Wallace et al., 2012). To illustrate these visual and spatial limitations and create greater understanding amongst to non-sufferers, a 3D modelling company - Wireframe Immersive in Glasgow – created a dementia simulation visor which showed first-hand how hard it is to differentiate colour and level changes in floors and walls, creating a need for extra definition of lines and outlines within VR environments to delineate, in particular, flat objects such as doors against the walls they were placed in (Mairs, 2018). Similarly, Alzheimer's research UK have created a 360 video of a dementia sufferer someone being lost, once again demonstrating the darkness/floor level colour misperception problems whilst seeking to generate empathy and understanding amongst non-sufferers. All these considerations had to be applied

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to Lee's next step – a connected series of virtual environments suitable for dementia sufferers to create benefits including memory recall, calming of agitation and building of real world community and communication in care homes and residential environments. A step beyond Reminiscence Therapy, Lee has titled this approach 'immersive reminiscence' (Lee, 2018). With a several year precedent of many of these sought after benefits having been achieved (albeit on a patient by patient basis) by a related system - Aloha VR based in San Francisco (Tsukayama, 2018), the observing physician concerned – Sonja Kim MD – stated that it over the two-year period of delivery it had proved more effective than any drug she might have been able to prescribe. It became apparent to Lee (2018) that, although there was real potential in this approach, there was also a wider audience for the content than she, or the likes of Dr Kim, could reach in person. Therefore, in order to reach a broader cross section of sufferers, carers and therapists, some form of hosting and platform would have to be created. Another precedent for this type of technology however – Rendever VR in Boston – applied a simultaneous multi user VR approach to focus on the social and communications benefits of VR. Allowing up to 4 people to participate in the same VR environment (which might include an Antarctic expedition or a canoeing excursion). These shared experiences appeared to generate some profound effects, with anecdotal results including one very withdrawn and incoherent patient being able to communicate clearly and continuing to do so for three months after a single exposure to the technology. More significantly however, sustained empirical research into the approach over the many sites using it reported quantitative feedback from participants of a 40% increase in stated happiness levels over the 12 month delivery period. (Zinck & Zinck, 2018). Like the ASD VR solutions mentioned earlier in this chapter – precedents for this type of technology have applications not only in treatment, but in research and diagnosis of Alzheimer's, in order to create more effective and bespoke treatment plans (Flynn et al., 2003). A freely available VR app – Sea Hero Quest – utilises a gaming format to monitoring spatial navigation abilities of people of any age, generating a huge dataset of comparative results across age ranges from its 2.5 million strong user-base. It's developers Alzheimers Research UK and University College London report that just 2 minutes of gameplay provides them with the equivalent of 5 hours of conventional research data, allowing them to leverage 'the collection, aggregation, and predictive analysis of large data volumes enabling timelier diagnosis and prevention strategies, and possibly overcoming current therapeutic limitations' (Ienca et al., 2018). There are a number of other virtual reality-based Alzheimer's diagnosis and data aggregation tools extant within the UK alone, including VITAE VR and Dorset NHS's 'VStore' gamified dementia diagnostic tool. This uses a realistic supermarket environment to assess the cognitive, spatial and decision making abilities of its users, allowing for remote diagnosis without the lack of real world application or observational bias inherent in most diagnostic procedures (McWilliam, 2018). These are just two of a growing number of VR diagnostic tools which include CogniSense and ACEmobile.

CONCLUSION

Ienca et al. (2018) state that although these tools provide an unprecedented level and range of big data, which can be used for everything from broader trend analysis and prediction to the creation of personalised treatment regimes, these distinct datasets could become far more than the sum of their respective parts if they can be shared and used together – something which intellectual property and attempts by the developers to leverage value out of their own ring-fenced aggregated data sets seems unlikely to allow. Conversely the risk of too open a disclosure of personal data could include discrimination from

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health insurance companies. It is difficult to predict the long term outcome of this combination of VR therapy, diagnosis and treatment planning – or to what extent data might be shared between applications. In the meantime, Lee is leveraging her knowledge of the developing field to develop a multi therapeutic environment including a Garden area, a period living room with a turntable selection of period appropriate music potentially involving the Playlist for Life Initiative (2018), a cinema screening area and 360 videos for both sufferers and carers of people with dementia. The VR environment is multi user, with no upper limit to user numbers, but for the purposes of social familiarity is likely to be kept to smaller groups and even families. Recording and sharing of both data and development plans aim to get medical professionals, carers, family and academia involved with the development of the virtual environment, with the hope that this cross discipline approach will leverage the best possible outcomes for all stakeholders (García-Betances et al., 2015).

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KEY TERMS AND DEFINITIONS

Augmented Reality (AR): It is a technology that uses real world environment and enhances it by overlaying digital information on top of it.

Head-Mounted Display: A device worn over a user's head, providing a visual display in front of one or both of the user's eyes.

Immersive Interactive Simulation System: It is a system that provides state-of-the-art interactive environment that blurs the line between the real and virtual world.

Immersive Reminiscence: A connected series of virtual environments suitable for dementia sufferers to create benefits including memory recall, calming of agitation and building of real world community and communication in care homes and residential environments.

Mixed Reality (MR): It merges the real and digital environments that co-exist and interact with each other to produce new environment for the user to explore and manipulate.

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Virtual Reality Exposure Therapy (VRET): The goal of VRET is to expose the patient to stimuli by combining advanced computer graphics, 3D visual displays, and body-tracking technologies to create realistic virtual non-threatening environment so that their mind and body can learn not to become alerted when they are exposed to similar stimuli in real life.

Virtual Reality (VR): It provides the user with computer-generated simulation of a real-life environment or situation. The headset gives the user a fully immersive experience, where what a user sees is a generated or an artificial environment and nothing of it is in the real world. Example of VR is gaming consoles.

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Section 4

Management, Monitoring, and Improving Quality of Life

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Chapter 26
Role of Diet, Functional Foods, and Nutraceuticals in Brain Disorders

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ABSTRACT

This chapter presents an overview of various complementary nutritional approaches for the management of brain disorders. Numerous epidemiological studies emphasize the growing burden of brain disorders worldwide. Due to the complex pathophysiology, lack of precise diagnostic and therapeutic options, there is growing need to have alternative approaches. One important strategy for the prevention and treatment of brain impairment is based on dietary supplements, functional foods, and nutraceuticals. The current chapter illustrates various aspects of available nutritional products for the brain disorder. Considering the recent surge in the nutritional products and as it destined to play an important role in future, existing regulatory framework is explained here which ensures purity, safety, and efficacy of the marketed products.

OVERVIEW OF BRAIN DISORDERS

Brain disorders are part of neurological disorders, which are described by WHO as diseases of the central and peripheral nervous system. These disorders include Alzheimer disease and other dementias, Parkinson's disease, traumatic disorders of the nervous system due to head trauma, brain tumors, epilepsy, cerebrovascular diseases including stroke, migraine and other headache disorders, multiple

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sclerosis, neuroinfections, and neurological disorders due to malnutrition. Symptoms and severity of brain disorders vary greatly.

Many bacterial, viral, fungal and parasitic infections can affect the nervous system. Brain disorders may be caused by aging, illness, genetics, or traumatic injury. Furthermore, the extension of life expectancy and the aging of the general populations in both developed and developing countries are likely to increase the occurrence of many chronic and progressive physical and mental conditions including neurological disorders. Harvard School of Public Health, World Health Organization (WHO) and the World Bank conducted a collaborative study called 'The Global Burden of Disease (GBD) study' which states that the neurological disorders were seriously underestimated by traditional epidemiological and health statistical methods that take into account only mortality rates but not disability rates (Murray, Lopez, WHO, World Bank, & Harvard School of Public Health, 1996). Based on these results, World Federation of Neurology (WFN) and WHO conducted an international Survey of Country Resources for Neurological Disorders including 109 countries and covering over 90% of the world's population. The findings show that there is a lack of resources for patients with neurological disorders in most of the parts of the world; they highlight inequalities in the access to neurological care across different populations, especially in those living in low-income countries and in the developing regions of the world (Janca, Aarli, Prilipko, Dua, Saxena, & Saraceno, 2006). Gooch et al. (2017) reported the United States alone carries a substantial fiscal burden resulting from the nearly 100 million Americans with a neurological disease which is nearly 800 billion dollars and is rapidly rising due to the aging of the U.S. (Gooch, Pracht, & Borenstein, 2017). There are various risk factors associated with the brain disorders. Older age and family history are the most significant factors for the neurodegenerative diseases. Brain tumors can affect people at any age. The personal risk of the brain disorders depends on the genetics and exposure to environmental risk factors like radiation. The risk of brain disorders is higher if the patient has stressful life experiences or a traumatic brain injury.

Diagnosis of Brain Disorders

Diagnostic tests and procedures are important tools that facilitate physicians to ensure or rule out the presence of a brain disorder or different medical condition. In the previous century, an autopsy of the dead patient was the only way to make a diagnosis of the neurological disorder. Due to the extensive research made regarding the characteristics of the illness, and advancement in the diagnostic techniques permit scientists and physicians to envision within the living brain and monitor neurological activity. This has given physicians a powerful tool for the diagnosis of the brain disorders at early stages. Evaluation and diagnosis of brain disorders are very complicated and complex process as similar symptoms appear in different disorders and also some brain disorders do not have definite causes, biomarkers or tests. Various diagnostic imaging techniques and biochemical tests are used for the detection and treatment of neurological disorders. The results of these tests help in planning an appropriate treatment.

Limitations of Current Treatment Approaches

The pharmaceutical industry has shown promising progress in the diagnosis and treatment of a number of diseases; however, it is lagging behind in the area of brain disorders. There is definite medical therapy for some brain disorders; for example, millions of people with mental disorders live normal lives whereas other disorders, like neurodegenerative diseases and some traumatic brain injuries, have no promising

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cure. Patients with these conditions significantly face permanent changes in their behavior and mental abilities. In such cases, treatment focuses on supporting people in learning to live with the disorder and retain as much independence as possible. Drug approvals for the treatment of various brain disorders are significantly fewer compared to other diseases. The factors affecting for this failure includes incomplete understanding of both disease pathophysiology and drug delivery systems to the brain, the complicated chemical reactions driving human consciousness, higher risk of clinical failure, extended drug development time and cost (Pardridge, 2002b). The outlook depends on the type and severity of the brain disorder. For example, receptor modifying drugs are used successfully in the treatment of Schizophrenia and depression; however, an incomplete understanding of the functionality of these receptors, in combination with the basic genetic differences between patients, has resulted in the variable therapeutic efficacy and substantial side effects. Additionally, lack of truly representative animal models to study brain disorders complicates the treatment process. Though several symptoms have been reproduced in animals, there will always be differences between the species which limits the prediction of treatment efficacy (Rockenstein, Crews, & Masliah, 2007). Central nervous system is protected by the blood–brain barrier (BBB) which is a homeostatic defense mechanism designed for the protection against pathogens and toxins by regulating solute entry via the transcellular route; however, this also limits the ability to deliver therapeutically beneficial compounds as well. Still small lipophilic molecules of size less than 400 Da can pass BBB and proves to be the effective treatment modality in various brain disorders but many biotechnologically derived products such as monoclonal antibodies, enzymes and engineered proteins having larger molecular size fails to pass through BBB and thus making them unsuitable candidates for the effective treatment (Fischer, Gottschlich, & Seelig, 1998; Pardridge, 2007). Currently, there is increasing interest of the researchers in the development of successful delivery systems using the principles of both biotechnology and nanotechnology. BBB permeability of many novel compounds has been improved significantly by using molecular engineering approach of biotechnology to develop complex therapeutic moieties with various functional ligands, such as monoclonal antibodies or receptor binding functionalities. Nanotechnology has been utilized to develop drug delivery systems capable of delivering high doses of the drug *in vitro* and *in vivo*. Efficacy of treatment of brain disorders has been enhanced successfully by combining these two technologies(Pardridge, 2002a).

Nano Systems Targeting the Blood Brain Barrier

Silva defined nanotechnology as the development of a system or device having a functional organization in at least one dimension on the nanometer scale (Silva, 2007). Nanoparticles have been used extensively in drug delivery systems as they offer various advantages over conventional delivery systems such as bioavailability enhancement, site-targeted drug delivery specifically to the CNS and for medical imaging (Kabanov & Gendelman, 2007; Kreuter, 2007). Nanoparticles have a solid core-shell structure of less than 1000 nm in diameter and preferably less than 100 nm for delivery to the CNS. Formulation of nanoparticles generally utilizes biocompatible materials to provide a small size, high surface materials capable of penetrating a number of biological tissues. The performance of nanoparticles *in vivo* is affected by various factors such as particle size, surface charge, and composition. Nanoparticles are rapidly cleared by the reticuloendothelial system (RES) which limits the *in vivo* residence time. Nanoparticles have been explored to enhance BBB penetration. To demonstrate the effect of nanoparticle properties on *in vivo* performance, Jallouli et al. (2007) studied the binding, uptake, and transcytosis of 60-nm highly porous maltodextrin nanoparticles based on surface charge and inner composition. They proved that

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differences in surface charge affect the mechanism of transport of nanoparticles across CNS (Jallouli, Paillard, Chang, Sevin, & Betbeder, 2007). Kuo et al. (2007) showed that nanoparticle composition and the carrier selection affects on the BBB penetration. In this study, they evaluated the *in vitro* performance of nanoparticles prepared separately by using solid lipids, methylmethacrylate-sulfopropylmethylacrylate, and poly butyl cyanoacrylate. They found that there was a synergistic effect of the carrier material with drug loading to affect BBB permeation (Kuo & Su, 2007). Trojan horse technologies can be used to enhance the delivery and targeting of nanoparticles. Liposomes have been explored extensively for CNS targeting. In contrast with the nanoparticles, liposomes have a lipid bilayer encapsulating the contents which are typically in liquid form. Schmidt et al. (2003) have successfully explored the use of PEGylated liposomes for the delivery of glucocorticosteroids in the treatment of multiple sclerosis. They used prednisolone as a model drug and proved that the PEGylated liposome formulation showed 5 fold higher therapeutic efficacy (Schmidt, Metselaar, Wauben, Toyka, Storm, & Gold, 2003). From the above examples, it is evident that various nanotechnology approaches have proven to be excellent drug delivery strategies for targeting CNS with higher drug loading.

NUTRITIONAL INTERVENTION IN BRAIN DISORDERS

The concept of having food which is enriched in therapeutically beneficial actives is largely based on the principle, *Let food be thy medicine, and medicine be thy food* advocated by Hippocrates (460–377 BC), the well-recognized father of modern medicine, emphasize the association between nutrition and human health, and conceptualized the relationship between the use of appropriate foods for health and their therapeutic benefits (da Costa, 2017; Katan, 2002). 'Nutraceuticals', 'dietary supplements' and 'functional foods', as well as other terms, are all used interchangeably, though these have significant differences – albeit not always evident (Hardy, 2000). Dietary supplements contain nutrients derived from food products and are commonly concentrated in capsule, powder, liquid or pill form. Kalra described 'functional food' as a product containing the necessary nutrients – including vitamins – for survival, while 'nutraceuticals', as per definitions, not only are complementary to the diet, but also aid in the prevention and/or treatment of disease and/or health disorder(s) (Kalra, 2003; da Costa, 2017).

DIETARY SUPPLEMENTS

Dietary supplements include a wide range of products, including vitamins and minerals, herbal products and botanical agents, and extracts from organs or glands (DeAngelis & Fontanarosa, 2003). The Dietary Supplement Health and Education Act (DSHEA) defines the term, 'dietary supplement', as 'a product (other than tobacco) that is intended to supplement the diet which contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total daily intake or a concentrate, metabolite, constituent, extract, or combination of any ingredient described above'. The law further states that dietary supplements in part as products taken orally that contain a 'dietary ingredient' mentioned above. Dietary supplements are provided in various forms such as tablets, capsules, powders, and liquids. Also according to DSHEA, the product should be labeled as a 'dietary supplement' and it is not represented for use as a conventional food or as a sole item of a meal or the diet (Kalra, 2003). Currently marketed

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dietary supplement products includes vitamin and mineral products, botanical or herbal products, amino acid products, enzyme supplements etc.

People use dietary supplements for a wide variety of reasons such as to compensate the conditions that limit the intake of essential vitamins and nutrients like improper diets, medical conditions, or eating habits. Postmenopausal women take dietary supplements to counter a rapid drop in estrogen levels (USFDA, 2016).

Understanding Dietary Supplements

FDA suggests that consumer must refer to the health care professionals prior the use of dietary supplements, though they are often claimed as safe and natural. Dietary supplements contain the components with strong biological effects. Hence, they cannot be taken blindly as there may be a risk for those who are suffering from any health-related problem. There is certain advice to be considered while taking the dietary supplements as discussed below:

1. Dietary supplements are the complementary health approaches and not proposed to treat, diagnose, or improve the disease condition and they should not be seen as a replacement for the drugs. However, FDA has approved various supplements that are useful in reducing the risk of certain diseases and are authorized to make label claims accordingly. For example, folic acid supplements may make a claim about reducing the risk of birth defects related to brain and spinal cord.
2. Many dietary supplements from the herbal origin contain a number of potent compounds with diverse biological activities. Taking a combination of supplements or using these products together with medicine can lead to untoward results.
3. Many dietary supplements are not advisable in certain conditions such as pregnancy, nursing mothers, or children. Similarly, these supplements are not tested for the possible unwanted effects before, during, or after surgery. For example, supplements containing garlic, ginkgo biloba, ginseng, and Vitamin E has bleeding as a potential side effect. Also, the supplements having kava and valerian act as sedatives which can synergies anesthetics activity during surgery (USFDA, 2015).

Dietary Supplements in Brain Disorders

It is well-established fact that relative abundance or deficiency of any specific nutrients can affect the normal cognitive functions. Dietary factors were shown to have effects on neuronal function and synaptic plasticity and its influences vital mechanisms that are responsible for the effects of diet on brain health and mental function. Several gut hormones that are produced in the brain itself are known to influence the cognitive ability. In addition, well-established regulators of synaptic plasticity, such as brain-derived neurotrophic factor, can function as metabolic modulators, responding to peripheral signals such as food intake. To understand how diet can affect or promote mental fitness, it is necessary to know molecular basis of the effects of food on cognition.

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Table 1. Dietary supplements for brain disorders

Dietary Supplements	Mechanism	References
Polyunsaturated Fatty Acids	Neuroprotective under conditions of reduced GST activity, diminished SAM, increased accumulation of SAH, and deprived folate	Panza et al., (2009)
Multivitamin and Mineral Supplements	During periconception promote lower incidence of ASD children Improve sleep, reduce autistic symptoms and ameliorate biomarkers of energy production and oxidative stress, improving mitochondrial function	Adams et al., (2011)
Vitamin B	Inhibit tau hyper-phosphorylation and accumulation in hippocampus and cortex	Wei et al., (2011)
Grape Seed Extract	Reduces Aβ levels and microgliosis in the brain and serum of the mice.	Y.-J. Wang et al., (2009)
Ginkgo Biloba Extract	Antioxidant elicits neuro recovery of damaged midbrain DA neurones, improves locomotion	(Rojas, Montes, Rojas, Serrano-García, & Rojas-Castañeda, 2012)
Rhinacanthus Nasutus	Glutamate and Amyloid-β Neurotoxicity	(Brimson, Brimson, Brimson, Rakkhitawatthana, & Tencomnao, 2012)

CURRENTLY USED DIETARY SUPPLEMENTS

Here, we will discuss various dietary supplements which are proven to be beneficial for improving various brain conditions. Various dietary supplements for brain disorders are summarized in Table 1.

Polyunsaturated Fatty Acids (PUFA's)

Saturated and monounsaturated fatty acids can be synthesized de novo within the brain, but PUFAs are mainly supplied by the food. The PUFAs linoleic acid (LNA) and α-linolenic acid (ALA) are obtained through the diet and act as precursors of arachidonic acid (ARA) and docosahexaenoic acid (DHA), which are also PUFA (Bazinet & Layé, 2014). Omega-3 fatty acids (e.g. alpha-linolenic acid) and omega-6 fatty acids (e.g. linoleic acid) are the key players among various families of polyunsaturated fatty acids. The human body is unable to synthesize linoleic acid hence it must be supplied as a dietary supplement. All other members of the omega–6 group are derivatives of linoleic acid while the parent compound of the omega–3 group is alpha-linolenic acid (ALA) (Yehuda, 2003). The human brain is highly augmented with fatty acids. In the brain, PUFA's are present in the form of esterified to the phospholipid cell membrane. PUFA's performs many vital biological functions such as signal transduction, regulate several processes within the brain, such as neurotransmission, cell survival, and neuroinflammation, and thereby mood and cognition. PUFA levels and the signaling pathways are altered in various neurological disorders, including Alzheimer's disease and major depression. PUFAs as dietary supplements open as a new array of complementary health approach for the prevention and treatment of brain disorders (Bazinet & Layé, 2014).

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Trace Elements

Adequate levels of various trace elements in the human body are essential for the brain to carry out its normal functions. Trace elements work as cofactors for the stabilization of proteins and transcription materials, catalysis of enzymes, and cellular transport (Parker, Koistinaho, White, & Kanninen, 2013). Enzymatic antioxidants such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (Gpx) act as a defense system against reactive oxygen species. Trace elements form the basic components of the enzymatic defense system. Their role in many diseases including neurological and psychiatric disorders have been examined by many researchers (Vural, Demirin, Kara, Eren, & Delibas, 2010) whereas their imbalance is associated with number of neurological conditions such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS) (Parker, Koistinaho, White, & Kanninen, 2013).

1. **Zinc:** Brain has the highest concentration of Zinc (Zn) as compared with the other organ systems and it is almost 10 times more than blood plasma level (Mocchegiani, Bertoni-Freddari, Marcellini, & Malavolta, 2005). Zn metabolism plays a central role in the synthesis and degradation of carbohydrates, lipids, proteins, nucleic acids and other micronutrients (Chasapis, Loutsidou, Spiliopoulou, & Stefanidou, 2012). The role of zinc in various brain disorders including behavior and cognitive functioning has been studied in relation to dietary zinc deficiency and catalysis of enzymes for a large number of cellular processes (Bitanihirwe & Cunningham, 2009). Zinc is essential in many important events such as neurogenesis, neuronal migration and synaptogenesis and its deficiency could interfere with neurotransmission and subsequent neuropsychological behavior (Bhatnagar & Taneja, 2001). Thus, an appropriate amount of zinc must be provided as dietary supplements for healthy brain functioning.
2. **Magnesium:** Magnesium (Mg) is one of the most important cofactors playing a crucial role in a number of metabolic events in the body including protein synthesis, production and storage of cellular energy, DNA and RNA synthesis, nerve transmission, muscular contraction, blood pressure, glucose, and insulin metabolism. In the case of brain disorders, Mg levels in plasma were found to be low in a study of patients with Alzheimer's disease (Vural, Demirin, Kara, Eren, & Delibas, 2010). In a study, it is demonstrated that patients suffering from Alzheimer's disease showed better improvement in the symptoms after receiving Mg with Memantine. Mg as dietary supplements has shown to improve the conditions of mental depressions with fewer side effects (Ozturk & Cillier, 2006).
3. **Selenium:** It is a well-known fact that the oxidative stress is responsible for the generation of reactive oxygen species (ROS) which is the major cause of many brain disorders (Wang & Michaelis, 2010). Selenium (Se) shows a promising neuroprotective effect against ROS-induced cell injury. Se has a crucial role in the brain disorders; not only due to its antioxidant property, but also through its involvement in the modulation of neurogenesis, regulating mitochondrial dynamics, redox balance, and maintenance of calcium channels (Cardoso, Roberts, Bush, & Hare, 2015). Thus, various neurological disorders caused by the deficiency of Se can be prevented and treated by supplementing it via diet.

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4. **Iron:** In the brain, iron is important for the oxygen transport, neurotransmitter synthesis, electron transfer, and myelin production (Stankiewicz, Panter, Neema, Arora, Batt, & Bakshi, 2007). Both the iron deficiency and iron excess is responsible for certain brain disorders. Various studies have shown that neurotransmitters and the associated receptors are altered due to reduced oxygen supply in case of iron deficiency leading to a number of brain disorders (Agarwal, 2001). On the other hand, high concentrations of reactive iron can enhance oxidative-stress-induced neuronal susceptibility (Zecca, Youdim, Riederer, Connor, & Crichton, 2004). Diet rich in iron can easily treat such complications of brain disorders.
5. **Copper:** Copper (Cu) is a vital trace element essential for a variety of enzymatic activities, proper neurodevelopment and neurological function (Desai & Kaler, 2008). It is involved in the generation of toxic ROS due to its redox activity which is responsible for mitochondrial damage, DNA breakage, and neuronal injury (Scheiber, Mercer, & Dringen, 2014). Impaired copper metabolism is additionally inferred in an increasing variety of different neurologic conditions (Bandmann, Weiss, & Kaler, 2015).

In conclusion, deficiency in some of these trace elements in the body can lead to various brain disorders characterized by progressive and permanent damage to the brain. Trace element deficiencies are caused majorly due to improper eating habits and diseases related with them can sometimes cause serious public health issues. It is possible to treat or stop the progression of these diseases through the early detection of deficiency and replacement of deficient trace elements with dietary interventions.

Botanical or Herbal Products

1. Ginkgo Biloba
   Ginkgo tree extracts are widely used as complementary products which have its origin in traditional Chinese and Japanese medicine. Biologically active components are Ginkgo flavonoids, obtained from leaf extracts; however, these constituents differ as per its botanical source. Ginkgo biloba has shown promise in various brain disorders by modulating excitotoxic glutamatergic neurotransmission, reduction of amyloid-β aggregation and free radical scavenging activity which reduces the damage to cell membranes causing malfunction and cell death in the brain. EGb 761®, is the widely studied Ginkgo biloba extract which is available on the market containing ginkgolides, bilobalide, and flavonoids (Nash & Shah, 2015). Ginkgold® and Ginkoba® are manufactured by Dr. Willmar Schwabe GmbH & Co. in Germany and are marketed in the United States by Nature's Way Products, Inc. and Pharmaton Natural Health Products, respectively (Tatli, 2015).

2. Bacopa Monnieri
   Bacopa monnieri (L.) Wettst. (family, Plantaginaceae) known commonly as Brahmi, is a perennial, creeping herb native to India which has been explored medicinally for thousands of years by Ayurvedic physicians in India. Numerous ancient Indian Ayurvedic texts including the Charaka Samhita (2500 B.C.) and the Sushruta Samhita (2300 B.C.) exhibits clear reference to its action on the central nervous system (Nemetchek, Stierle, Stierle, & Lurie, 2017). The active components of Brahmi are a mixture of saponins including bacoside A, bacopasides I and II, and bacopasaponin C. Number of studies shows Brahmi's neuroprotective effect both in *vitro* and *in vivo* Alzheimer's disease models. Similarly, Brahmi also has the ability to regulate neuroinflammation (Chauhan & Mehla, 2014).

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Vitamins

Various vitamins have reported being effective in the clinical management of neurological disorders, out of which vitamin D and vitamin B plays a crucial role.

1. Vitamin D
   Vitamin D is involved in neuroprotection, modulation of pro-inflammatory cytokine-induced cognitive dysfunction, and synthesis of calcium-binding proteins as well as acetylcholine which is a well-known neurotransmitter. Alzheimer's disease is associated with low serum vitamin D concentrations which can be treated effectively by providing dietary supplementation of vitamin D (Annweiler, Llewellyn, & Beauchet, 2013). Vitamin D also regulates signal transduction and gene expression. It shows promise in the prevention and treatment of brain disorders through the regulation of calcium-sensing receptor expression, increasing the clearance of amyloid β peptides, and modulating inflammatory cytokine expression (Annweiler, Rolland, Schott, Blain, Vellas, Herrmann, & Beauchet, 2012). Calciterol (1,25-dihydroxyvitamin D3) is the most effective supplementation form of vitamin D in treating the progression of Alzheimer's disease and Parkinson's disease (Suzuki, Yoshioka, Hashimoto, Murakami, Noya, Takahashi, & Urashima, 2013; Peterson, Murchison, Zabetian, Leverenz, Watson, Montine, & Quinn, 2013).

2. Vitamin B
   Parkinson's disease is characterized with the higher plasma homocysteine levels damaging dopaminergic nerves. Some studies have demonstrated increased risk of Parkinson's disease with decreased intake of vitamin B, as vitamin B9 (folate) and B12 plays a fundamental role in the metabolism of homocysteine thus halting the disease progression (Shen, 2015).

FUNCTIONAL FOODS

The term 'functional food' was originated in Japan. Apart from normal nutrition, functional foods offer various health benefits. These are different from medical foods and dietary supplements, but they may overlap with those foods which are developed for special dietary uses and fortified foods. Japan is the first country which has made certain regulatory legislation i.e. FOSHU (Foods of Specified Health Use) legislation and market the functional foods. There is no agreement between Europe and the USA regarding a concrete definition of functional foods, leading to a series of different terms: nutraceutical, designer food, pharma-food, etc., which has contributed to increasing the confusion among professionals and consumers.

It is important to highlight that functional food must be a food, not a drug. Functional foods must exhibit beneficial effects after consuming normal amounts within the normal diet. The ultimate goal of the food industry should be to develop functional foods for improving life quality of the general population. The 'American dietetic association' has given a glossary containing major basic definitions for functional foods. They are:

- **Functional Food:** Any food or modified ingredient that can make a beneficial effect beyond that provided by common nutrients;

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- **Chemopreventive Agent:** Food compound nutrient or otherwise that has been scientifically investigated as a potential inhibitor of carcinogenesis;
- **Designer Food:** Processed foods that are supplemented with food ingredients, naturally rich in substances that prevent diseases involving genetic engineering of foods;
- **Pharma-Food:** Food or nutrient with potential health or medical use, including prevention and treatment of diseases;
- **Phytochemical:** Substances found in fruits and vegetables that can be ingested daily (in grams) and those that exhibit a potential to modulate human metabolism by favoring prevention of cancer and other diseases;
- **Nutraceutical:** Substance considered as food or a part of it that offers health or medical benefits, including prevention and treatment of diseases.

Due to the increasing demand from the population for foods that promote health, functional foods are one of the fastest growing sectors of the food industry (Mollet & Lacroix, 2007). In 2015 the global functional foods market size was USD 129.39 billion which is expected to reach USD 255.10 billion by 2024 (Grand View Research, 2016). Functional foods must generally be provided to people with good organoleptic properties and in the usual daily dietary pattern (Augustin, 2001; Kwak & Jukes, 2001). Extensive research has been done in the development of functional foods for improving the health of the general public. New functional food products launched in the global food market have followed the route of fortification or addition of desirable nutrients and bioactive including vitamins, minerals, antioxidants, plant extracts, prebiotics, probiotics, and fiber augmentations. Many of these ingredients to be added are susceptible to degradation and can interact with other components of the food matrix which may lead towards a loss in quality of the functional food products.

To overcome issues related to fortification, the additional bioactive ingredient ought to be isolated from environments that promote degradation or undesirable interactions (Smith & Charter, 2010). Though certain natural foods such as strawberries or onions are claimed as functional foods, but only those foods which are submitted to certain methodologies such as addition or removal of a component, modification of the food processing, genetic engineering, etc., to develop new products with additional value are considered as functional foods. The most important components that can be added to food are:

- **Probiotics**: Certain living microorganisms (for example bacteria like Lactobacilli and Bifidobacteria) which when ingested in certain amounts, have a positive impact on host health, which offers additional nutritional effects (Isolauri, 2001). They can be given with fermented foods such as yogurt, fermented vegetables or meats.
- **Prebiotics**: These are the short-chain carbohydrates that may be fermented in a large bowl which provides beneficial health effects on the microflora on the host, such as fiber, inulin, lactulose, sugar alcohols.
- **Synbiotics:** A mixture of prebiotics and probiotics.
- **Nutrients**: Minerals, vitamins, fatty acids or dietary fiber, for example, that are specific and have a targeted action (Lopez-Varela, Gonzalez-Gross, & Marcos, 2002).

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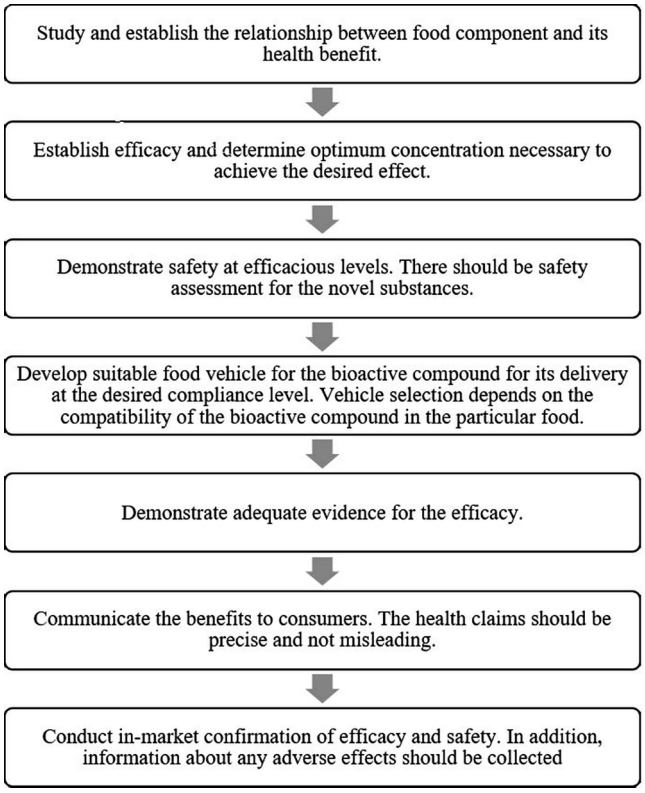
Health Effects of Functional Foods

Regular consumption of functional foods reduces the risk for several chronic diseases, such as neurological disorders, cardiovascular disease, cancer, diabetes, hypertension, and osteoporosis (Lopez-Varela, Gonzalez-Gross, & Marcos, 2002). Generally, all foods may be claimed as functional, as they provide some nutritive health effects, taste, or flavor. The term functional serves different meaning when applied to foods as providing an additional health benefit beyond that of basic nutritional needs. Functional food science has been originated from the joint collaborative venture of food sciences and the public need. It is the combination of food science, nutrition, and medicine as it produces nourishment that crosses between food and pharmaceuticals. Specifically, researchers study food components and their beneficial health effects. Functional food scientists determine the health effects and safe dosages of functional foods. Despite the extensive research, universal definition of functional foods is not available leading to numerous global consequences. Due to the ambiguity about the concept of 'functional food' between various regulatory bodies, the sense of overall mistrust about the health benefits claims prevail. While 'functional food' has generated billions of dollars in sales worldwide, the lack of a standard definition has prevented functional food scientists from delivering functional food to chronically ill populations (Martirosyan & Singh, 2015). There are various steps involved in the designing and development of functional foods as shown in Figure 1 (GEN, 2005).

Figure 1. Steps for the designing and development of functional foods



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Functional Foods in Brain Disorder

There is marked increase in the development of the functional foods due to the growing burden of chronic diseases such as neurological disorders and population aging. Alzheimer's disease is another important health problem that remains without cure so far. Functional foods have shown promise where drugs have failed to be efficacious. Functional foods containing antioxidants plays a crucial role in the treatment of neurodegenerative diseases by maintaining the integrity of neurons through suppression of apoptosis and necrosis. Alzheimer's disease is the most common form of dementia and which may be fatal at later stages. Accumulation of amyloid β proteins, mitochondrial dysfunction, and release of iron and copper are the most frequent causes of the disease progression. Quercetin proves to be helpful in the disease management by chelating these metals which could reduce the pathological severity. Tocopherol and ascorbic acid are used as promising nutritional therapy. Carotenoids have been explored successfully in the treatment of dementia. Caffeic acid and catechins inhibit peroxynitrite-induced dopamine oxidation thus exhibiting prominent anti-Alzheimer's activity (Ferrari & Torres, 2003). These all are the natural foods which are efficacious in the management of various brain disorders. There are three functional foods which are developed and marketed having regulatory approval that claims to offer symptomatic benefits in the treatment of Alzheimer's disease *viz.* Axona®, Souvenaid®, and CerefolinNAC®. Axona® provides ketone bodies as alternative energy source to the neurons, Souvenaid® provides precursors thought to enhance synaptic function and CerefolinNAC® minimizes the role of oxidative stress related to memory loss (Thaipisuttikul & Galvin, 2012).

Axona

It is a functional food developed by Accera, Inc., indicated for the clinical management of the impairment of metabolic processes associated with mild to moderate Alzheimer's disease. It contains caprylic triglyceride, a medium-chain triglyceride and it is Generally Recognised As Safe (GRAS) by the FDA which is obtained from fractionation of coconut oil. In Alzheimer's disease brain's ability to use glucose as a normal energy source gets impaired. During the digestion of Axona, the triglycerides get broken down into medium-chain fatty acids which rapidly pass to the liver where they undergo oxidation to form the ketone bodies which serves as alternative energy source to the brain. Axona was formulated for oral administration and was first sold in March 2009. Axona was being administered to about 30,000 patients in the US by 2012. Nestlé has been investing heavily in the area of medical nutrition and nutrition-based solutions designed to tackle neurodegenerative diseases. In July 2012, Nestlé acquired a stake in U.S.-based Accera, maker of Axona (Axona, 2017).

NUTRACEUTICALS

The industrialized world of this century forced to deal with new challenges such as excess healthcare costs, longer life expectancy and changes in a living manner. Nutritionists have enthusiastically accepted the idea of 'optimal nutrition', which focuses on optimizing daily diet quality in terms of its nutraceutical value for the proper health. As a result, development of nutraceuticals comes into play. The term 'Nutraceuticals' was coined by Stephen DeFelice, who defined it as a "foods (or part of a food) that provide medical or health benefits, including the prevention and/or treatment of a disease" (DeFelice, 1995). Due

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to the close resemblance of the term, 'Nutraceuticals' with 'dietary supplements' and 'functional foods', it is often used as interchangeably for later and vice versa. Similarly due to the lack of clear definition from regulatory bodies added to the confusion. So it is necessary to have a clear sharply defined and quantifiable concept, which will eventually help for effective regulatory implementation and will avoid conflicts. After studying the number of available definition in public domain, Palthur et al. comes up with the working definition which says 'A nutraceutical is a food or a part of a food for oral administration with demonstrated safety and health benefits beyond the basic nutritional functions to supplement diet, presented in a nonfood matrix or nonconventional food formats, in such a quantity that exceeds those that could be obtained from normal foods and with such frequency as required to realize such properties', and is labeled as a 'nutraceutical' (Palthur, Palthur, & Chitta, 2010).

Insights Into the Actions of Nutraceuticals

Here, we will discuss various nutraceuticals reported for assisting in the prevention and treatment of brain diseases by reducing doses of drugs or alleviating side effects. Traditional medicinal knowledge or tribal practices offer nutritious agents that serve as a basis for understanding their molecular actions that cure diseases. In recent years, there has been increasing evidence that shows that these nutraceuticals can act as effective neuroprotective agents. The goal then is to elucidate how these bioactive molecules make the brain healthier. Underlined mechanisms of neuroprotection at the cellular, biochemical, and molecular levels are often been due to a direct antioxidant effect and/or to an anti-inflammatory action (Kelsey, Wilkins, & Linseman, 2010; Costa, Garrick, Roque, & Pellacani, 2016).

Nutraceuticals in Brain Disorders

In past numerous attempts have been made to categories the nutraceuticals based on origin, form, in terms of their effects on the body etc., however classification based on their chemical nature and/or active ingredients remains the most accepted one (Espín, García-Conesa, & Tomás-Barberán, 2007; da Costa, 2017). Numerous studies have demonstrated the role of nutraceuticals in the prevention and treatment of neurological disorders. Various nutraceuticals explored for brain disorders are summarized in Table 2.

Polyphenols

Polyphenols are the rich source of antioxidants of our diet and are widely spread components of various fruits, vegetables, cereals, dry legumes, chocolates, and beverages. Many nutritionists attracted towards dietary polyphenols because of their promising health effects.

Antioxidant Activity of Polyphenols as Neuro Nutraceuticals

Antioxidant activity is the most explored effect of polyphenols (Shefa, Yeo, Kim, Song, Jung, Jeong, & Huh, 2017; Cilla, Alegría, Attanzio, Garcia-Llatas, Tesoriere, & Livrea, 2017). Among the major pathological reasons for neurodegenerative disorders are oxidative damage to neuronal molecules, accumulation of iron ion species in the brain, and decreased cellular reserve antioxidant pool. Polyphenols exert their antioxidant effects through different mechanisms like the interaction with the HIF-1 alpha pathway,

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Table 2. Nutraceuticals for brain disorders

Nutraceuticals	Mechanism	References
Blueberry Polyphenols	Augment the increased IGF-1 expression and antagonizes LPS, DA- Aβ (42)-induced deficits in CAR in primary hippocampus neuronal cells	(Shukitt-Hale, Lau, Carey, Galli, Spangler, Ingram, & Joseph, 2013; Joseph, Shukitt-Hale, Brewer, Weikel, Kalt, & Fisher, 2010)
Curcumin	Reduces Aβ levels in the brain and serum of mice	Y.-J. Wang et al., (2009)
Dihydroguaiaretic Acid	Inhibits Aβ fibril (f Aβ) formation and extension from Aβ (1–40) and Aβ (1–42)	(Ono, Hasegawa, Naiki, & Yamada, 2004)
(-) Epigallocatechin -3-Gallate (EGCG)	Inhibits in vitro fibril formation by RCM kappa-CN	(Hudson, Ecroyd, Dehle, Musgrave, & Carver, 2009)
Ellagic Acid	Inhibits beta-secretase (BACE1) activity	H.-M. Kwak et al., (2005)
Green Tea Polyphenol (*Camelia Sinensis*)	Ameliorates deleterious effects of d-galactose and Aβ (25–35) And improves animal's learning and memory	(Lü, Guo, & Yang, 2006)
Resveratrol	Inhibits Aβ polymerization	(Rivière, Richard, Quentin, Krisa, Mérillon, & Monti, 2007)
Genistein	Elicit neuroprotection from Aβ protein exposure, inhibits AChE, modulates estrogenic activity, Antioxidative activity, inhibit Aβ aggregation and exhibit metal chelating properties	(Lee, Lee, & Sohn, 2005; Qiang, Sang, Yuan, Li, Liu, Bai, Deng, 2014)
Luteolin	improve ASD symptoms by targeting JAK2/STAT3 signaling	Parker-Athill et al., (2009)
Sulforaphane	Activate Nrf2/ARE pathway, promoting the upregulation of GSH Antioxidant potential upon exposure to Aβ25–35, upregulate antioxidant enzymes via activation of Nrf2, prevent Aβ-mediated apoptosis	Tarozzi et al., (2013)
Myricetin	Reduces apoptotic changes and caspase-3 activation Decreases Aβ 1–40 and Aβ 1–42 levels in culture media Activates and up-regulates alpha-secretase (ADAM10) protein levels	(Shimmyo, Kihara, Akaike, Niidome, & Sugimoto, 2008)
Morin, Mangiferin	Inhibit glutamate-induced activation of calpains, normalize the levels of phosphorylated Akt kinase and Erk1/2, as well as of cytosolic Bax, inhibit AIF release from mitochondria, and regulate the nuclear translocation of NF-kappaB	(Campos-Esparza, Sánchez-Gómez, & Matute, 2009)

regulation of reactive oxygen species by interacting with oxidative pathways and scavenging metal ions as pathogenic free radicals (Ebrahimi & Schluesener, 2012; Kelsey, Wilkins, & Linseman, 2010).

Anti-Acetylcholinesterase Activity of Polyphenols

Neurodegenerative diseases are characterized by the impairment of cholinergic system which ultimately leads to the cognitive decline due to reduction in Acetylcholine (Ach) synthesis, choline uptake, cholinergic neuronal and axonal abnormalities, and degeneration of cholinergic (Bohnen, Kaufer, Hendrickson, Ivanco, Lopresti, Davis, & DeKosky, 2005; Fisher, 2008). One of the promising approach in the treatment of neurodegenerative diseases lies in the use of Acetylcholinesterase inhibitors, which exert their

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efficacy through stimulation of both muscarinic and nicotinic acetylcholine receptors. Several natural polyphenols have shown to exert anti-cholinesterase activity which was accompanied by improvement of cognitive functions, like learning and memory (Zhang, Cao, Wen, & Xu, 2009). Several polyphenols such as Epigallocatechin gallate (EGCG) have been shown their effectiveness in affecting cholinergic system by regulating nAChR signaling pathway through down-regulation of α9-nAChR expression as well as inhibition of (3H)-Nic/ α 9- nAChR binding activity (Tu, Ku, Ho, Chen, Huang, Lee, & Ho, 2011), whereas resveratrol blocks acetylcholine release from adrenal chromaffin cells (Chang-Mu, Jen-Kun, Shing-Hwa, & Shoei-Yn, 2010).

Polyphenol Activity Against NMDA Neurotoxicity

NMDA neurotoxicity and glutamate excitotoxicity play a significant role in progressions of neurodegenerative diseases and cognitive impairment associated with aging (Choi, Monyer, Giffard, Goldberg, & Christine, 1990). Excessive activation of NMDA receptors is associated with the formation of free radicals (e.g., NO and ROS) and other enzymatic processes that result in neuronal damage and cell death. Therefore, NMDA receptor inhibitors have been explored for cognitive impairment not only in neurodegenerative diseases but also in psychiatric disorders with cognitive dysfunction (Lipton, 2007; Shim, Hammonds, & Kee, 2008). There is strong evidence of protective effects of several natural polyphenols against NMDA neurotoxicity (Ebrahimi & Schluesener, 2012).

Quercetin

Quercetin is a potent polyphenolic antioxidant, exerts its activity through redox regulation of proteins, transcription factors and a broad range of kinase-dependent signaling cascades, some of which are linked to cellular survival mechanisms. Oral intake of quercetin associated with erratic absorption followed by metabolic steps. The nutraceutical additive actions of quercetin will be best served by its pharmaceutical formulation to expedite optimal delivery and such a preparation effectively produced recovery of brain activity with improved breathing, motor and feeding behavior in perinatal hypoxia (Blasina, Vaamonde, Silvera, Tedesco, & Dajas, 2015).

Alkaloids

Huperzine A

Huperzine A, is an alkaloid, obtained from the moss, *Huperzia Serrata*, and was a part of traditional Chinese medicines for centuries to treat various ailments such as fever and inflammation. Various research studies indicated that huperzine A could be a potent neuroprotective agent against the impairment of cholinergic neurons. Huperzine A has been proven to be efficacious in the treatment of multi-infarct dementia and for patients with short-term and long-term memory loss caused by cerebral arteriosclerosis. In addition, the latest research on the efficacy of huperzine, including its effects on Alzheimer's disease, proves the effectiveness and safety of this substance in human participants (McDougall, Austin-Wells, & Zimmerman, 2005).

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REGULATORY ASPECTS

1. **Dietary Supplements:** Dietary supplements are defined by the Dietary Supplement Health and Education Act (DSHEA) in 1994, as a food category which cannot contain anything that may have *a significant or unreasonable risk of illness or injury* when it is used as directed on the label, or with normal use if there are no directions on the label. DSHEA gives the roadmap for the registration of the dietary supplement for the marketing purpose. A dietary supplement is considered as "new" if it contains an ingredient which is not documented as a food substance unless it was sold as a supplement before October, 1994. As per the guidelines provided by DSHEA, FDA can stop a company from making a dietary supplement only when they can prove that the product shows a significant risk that means they are found unsafe only after they cause harm. This is in contrast to the practice of how prescription and non-prescription drugs are handled. Dietary supplements are usually self-prescribed, so there's no controlled system for reporting bad reactions and side effects. Doctors and patients can report problems but are not required to do so.
2. **Functional Foods:** Development and regulatory oversight of functional foods began in Japan in the early eighties with advances in the chemical identification of bioactive compounds, processing, and formulation of functional foods. In Japan, Functional foods had been registered under 'foods for specified health use' (FOSHU) policy. Since 1991 over 600 FOSHU products has been registered. According to International Food Information Council (IFIC), the functional foods are dietary components with a health benefit beyond basic nutrition. On the other hand, International Life Sciences Institute of North America (ILSI) also defines functional foods as physiologically active food components which provide health benefits. Another definition by Health Canada described the functional food which is capable of reducing the risk of chronic diseases. USA, European Union, and Canada, all of which now have various regulatory bodies to govern the manufacture and marketing of health-promoting food products.
3. **Nutraceuticals:** Despite the growth and need of nutraceuticals by global market there are no apparent regulatory definitions and approval process pathways available. There is a need for the development of regulatory guidelines for **t**he rapidly expanding global nutraceutical industry. Although regulations in the United States, the United Kingdom, and Europe are efficient and have become favorable in the development of various nutraceutical products (Ray, Joshi, & Gulati, 2016).

CONCLUSION

Brain disorders encompass a broad category which varies significantly in symptoms and severity including brain injuries, brain tumors, neurodegenerative diseases and mental disorders. Currently, most of the pharmaceutical industries engaged in the development of new drugs have come up with very few novel drug discoveries. Additionally, there is scarcity in the new drug development for the neurological disorders due to the complexity of the disease pathophysiology and lack of precise diagnostic tools. The hunt for new remedies is now focusing in various similar areas which include nutraceuticals, dietary supplements, and various herbal products. Many of the dietary supplements, functional foods and nutraceuticals have shown promising results in the prevention and treatment of various brain disorders. Currently, diet, in particular, has become the object of research in relation to cognitive function and neurodegenerative disease. One important strategy to prevent brain impairment is based on dietary

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supplements, functional foods, and nutraceuticals. Since brain disorders are often associated with tissue damage or neurodegeneration, regular consumption of these nutrients may help repair these damages and limit the risk of brain disorders. Specific nutrients are essential for promoting healthy brain development of infants and children and preserving the cognitive function of elders. Despite the usefulness of these diet, nutraceuticals and functional food and the ever-growing research, these products are not approved officially by the concerned regulatory authorities throughout the world. To date, Japan is the only country that has established a specific regulatory approval process for functional foods known as Foods for Specified Health Use (FOSHU). Along with nutrient deficiencies, the aspects of nutrient toxicities have to be considered. Thus, dietary supplements, functional foods, and nutraceuticals play an important role in the prevention and treatment of various brain disorders.

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Chapter 27
Dementia:
A Capability Deprivation for Elderly Women in India

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ABSTRACT

The high global prevalence, economic impact of dementia on families, caregivers, and communities, and the associated stigma and social exclusion present dementia as a significant public health challenge. Global as well as Indian data confirms a greater vulnerability of the women patients than their male counterparts. The global health community has recognized the need for action and to place dementia and its care and support services on the public health agenda. Dementia imposes significant physical, mental, and financial stress on caregivers who, again, often are women. In this context, the chapter aims to use capability approach and the concept of "disability paradox" to project dementia as a capability deprivation situation and through comparative analysis of various care models proposes a comprehensive economic care model and plan of action for a developing country like India to ensure dignified quality living for dementia patients and their caregivers.

1. INTRODUCTION

Aging is a universal phenomenon, but it has become a formidable challenge before developing countries. India stands second in its population next to China. As of March 1, 2012, the projected number stands at 98.5 million (The World Bank, n.d.). India's population is undergoing a rapid demographic transition. The number of "elderly" people in India[1] has increased by 54.77% in the last 15 years. It is important to note that this rapid demographic change is happening along with fast paced social restructuring accompanied by market driven economic development. Shrinking family network, almost non-existent welfare state and virtual absence of community initiatives are making geriatric care even more cumbersome. In general, old age induces certain amount of disability and demand care and attention but certain health conditions like 'dementia' throws immense challenges before elderly and their care givers on

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dignified living. Situations turn even more difficult with women elderly due to their socio-economic vulnerability. Situations turn even more difficult with women elderly due to their dependent position and socio-economic vulnerability. The high global prevalence, economic impact of dementia on families, caregivers and communities, and the associated stigma and social exclusion present a significant public health challenge. The global health community has recognized the need for action and to place dementia on the public health agenda (WHO, 2012).

2. UNDERSTANDING DEMENTIA

Although a vignette of dementia was widely recognized, the condition was not thought to constitute a health problem. Dementia was construed as a normal part of ageing and was not perceived as requiring medical care. Thus, primary health physicians rarely saw this condition in their clinical work, but community health workers frequently recognized individuals with dementia.

Dementia is caused when the brain is damaged by diseases, such as Alzheimer's or a series of strokes. Alzheimer's disease is the most common cause of dementia. The specific symptoms that someone with dementia experiences will depend on the parts of the brain that are damaged and the disease that is causing the dementia (Alzheimer's Society, 2015). It is estimated that worldwide 46.8 million people are living with dementia in 2015. These numbers will almost double in every 20 years, reaching 74.7 million in 2030 and 131.5 million in 2050. Much of the increase will be in developing countries. Already 58% of people with dementia live in developing countries, but by 2050 this will raise up to 68%. It is estimated that worldwide there will be 9.9 million new cases of dementia each year, implying one new case for every 3.2 seconds (Alzheimer's Disease International, n.d.). In India, among the dementia patients' women constitute 2.1 million and 1.5 million are men (The dementia India report, 2010,). This shows that an instance of dementia is far higher among older women than men. Women's systematic nutritional deprivation, stressful life throughout and skewed access to medical care could be the probable reason behind

The symptoms include memory loss, difficulties with thinking, problem-solving or language. Each person is unique and will experience dementia in their own way. A person with dementia will have cognitive symptoms (problems with thinking or memory). They will often have problems with some of the following (Alzheimer's Society, 2015):

- **Day-to-Day Memory Loss:** Difficulty in recalling events that happened recently;
- Difficulty in concentrating, planning or organising, i.e. making decisions, solving problems;
- **Language:** Difficulties in following a conversation or finding the right word for something;
- **Orientation:** Losing track of the day or date, or becoming confused about where they are;
- **Often Changes in Their Mood:** Feeling frustrated, irritable, anxious, easily upset or unusually sad;
- **Visual Hallucinations:** The person may see things that are not really there;
- **Delusions:** The person believe things that are not true.

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Table 1. Common symptoms experienced by people with dementia syndrome

EARY STAGE	MIDDLE STAGE	LATER STAGE
The early stage is often overlooked. Relatives and friends (and sometimes professionals as Well) see it as "old age", just a normal part of ageing process. Because the onset of the disease is gradual, it is difficult to be sure	As the disease progresses, limitations become clearer and more restricting. • Become very forgetful, especially of recent events and people's names. •Have difficulty comprehending	The last stage is one of nearly total dependence and inactivity. Memory disturbances are very serious and the physical side of the disease becomes more obvious. • Usually unaware of time and place • Have difficulty understanding what is
exactly when it begins. • Become forgetful, especially regarding things that just happened • May have some difficulty with communication, such as difficulty in finding words • Become lost in familiar places • Lose track of the time, including time of day, month, year, season • Have difficulty making decisions and handling personal finances • Have difficulty carrying out complex household tasks • Mood and behaviour: – may become less active and motivated and lose interest in activities and hobbies – may show mood changes, including depression or anxiety – may react unusually angrily or aggressively on occasion	time, date, place and events; may become lost at home as well as in the community • Have increasing difficulty with communication (speech and comprehension) • Need help with personal care (toileting, washing, dressing) • Unable to successfully prepare food, cook, clean or shop • Unable to live alone safely without considerable support • Behaviour changes may include wandering, repeated questioning, calling out, clinging, disturbed sleeping, hallucinations (seeing or hearing things which are not there) • May display inappropriate behaviour in the home or in the community (e.g. disinhibition, aggression)	happening around them • Unable to recognize relatives, friends and familiar objects • Unable to eat without assistance, may have difficulty in swallowing • Increasing need for assisted self-care (bathing and toileting) • May have bladder and bowel incontinence • Change in mobility, may be unable to walk or be confined to a wheelchair or bed • Behaviour changes, may escalate and include aggression towards carer, nonverbal agitation (kicking, hitting, screaming or moaning) • Unable to find his or her way around in the home

Source: WHO, 2012, pp: 7, World Alzheimer's Report 2009, World Health Organization, 2006.

2.1. Types of Dementia

Alzheimer's disease is the most common cause, accounting for 50 to 60 per cent of all dementia cases. It is a physical disease affecting the structure of the brain. Protein, known as 'clumps' and 'tangles', start to form which damage the brain cells (Stroke Association, 2012).

Vascular dementia is the second most common form, accounting for approximately 20 per cent of all cases. It is caused when stroke or small vessel disease affects the blood supply to the brain (Stroke Association, 2012).

Front temporal dementia (FTD) is a relatively rare form of dementia. Although it is thought to account for less than 5% of all dementia cases, FTD is caused by damage to cells in areas of the brain called the frontal and temporal lobes. The frontal lobes regulate our personality, emotions and behaviour, as well as reasoning, planning and decision making. The temporal lobes are involved in the understanding and production of language (Alzheimer's Research UK).

Dementia with Lewy bodies (DLB) is the third most common cause of dementia. It affects about 15% of people with dementia, Dementia with Lewy bodies is caused by small round clumps of a protein that build up inside nerve cells in the brain (Alzheimer's Research UK, n.d.).

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Mixed dementia, another type of vascular dementia has recently been identified. Alzheimer's disease and vascular dementia can occur at the same time, known as mixed dementia (MD) (Stroke Association, April 2012).

2.2. Dementia: The Global Scenario

The World Alzheimer Report 2015 led by King's College London found that there are currently around 46.8 million, nearly 47 million people living with dementia around the world, with numbers projected to nearly double every 20 years, increasing to 74.7 million by 2030 and 131.5 million by 2050. According to the report it is also found that nearly half of all people with dementia globally will live in Asia by 2050. The report showed that in 2015, East Asia is the world region with the most people living with dementia (9.8 million), followed by Western Europe (7.4 million). These regions are closely followed by South Asia with 5.1 million and North America with 4.8 million.

At the country level, ten countries are home to over a million people with dementia in 2015: China (9.5 million), US (4.2 million), India (4.1 million), Japan (3.1 million), Brazil (1.6 million), Germany (1.6 million), Russia (1.3 million), Italy (1.2 million), Indonesia (1.2 million) and France (1.2 million).

The new findings take into account both the growing numbers of older people (population ageing), and new and better evidence on the number of people living with dementia, and costs incurred. The current annual societal and economic cost of dementia is $818 billion, and it is expected to become a trillion dollar disease in just three years' time (LiveMint, n.d.).

2.3. Dementia: A Public Health Issue in India

Under the aegis of Indian constitution which guarantees free healthcare for all its citizens, Government of India in collaboration with state governments has built one or more Government hospitals; where everything from diagnosis to medicine is given for free; at each district headquarters in most of the Indian states. Due to increasing population burden and inadequate budgetary support, public health care system could not evolve as per expectations in terms of quality of services. The situation got further complicated in 1990's with embracement of structural adjustment policy and subsequent withdrawal of sate from all welfare activities including providing health-care facilities. This has led to all pervasive inroads of prohibitively costly, exclusionary private health care system. Rural public health delivery system is gasping for breath as only 2% of doctors are available in rural areas - where 68% of the population live (Britnell, 2015, p-59). According to National Family Health Survey-3 (2013) the private medical sector remains the primary source of health care for 70% of households in urban areas and 63% of households in rural areas. Geriatric care in general and treatment and care for dementia in particular is mostly unaddressed in public health care delivery system in terms of access and availability of trained doctors and paramedics.

At present, most of the geriatric outpatient department (OPD) services are available at tertiary care hospitals. Also, most of the government facilities such as day care centers, old age residential homes, and counselling and recreational facilities are urban based. A study conducted to assess the unmet needs of the geriatric population in rural Meerut observed that as many as 46.3% of the study participants were unaware of the availability of any geriatric services near their residence and 96% had never used any geriatric welfare service. About 59% of them stated that the nearest government facility was 3 kilometres from their homes. (Goei,1999, pp:165-66)

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Penetration of health insurance in India is low by international standards. Private health insurance schemes, which constitute the bulk of insurance schemes availed by the population, do not cover costs of consultation or medication. Only hospitalisation and associated expenses are covered. However, secondary/tertiary and outpatient care is very underdeveloped and is need of improvement According to the World Bank, about 25% of India's population had some form of health insurance in 2010. A 2014 Indian government study found this to be an over-estimate, and claimed that only about 17% of India's population was insured. Hardly any insurance plan is available to take care of cost burden of dementia treatment and care.

Care for those with dependency needs was almost entirely family-based with little or no formal services. Not surprisingly, fear for the future, and in particular 'dependency anxiety' was commonplace among older persons. There is stigma associated with the psychological and behavioural problems associated with dementia. People are often neglected in their homes and sometimes abused.

Dementia is one of the major causes of disability in later life. It accounts for 11.9% of the years lived with disability due to a no communicable disease *(WHO, 2008)*. People live for many years after the onset of symptoms of dementia. With appropriate support, many can and should be enabled to continue to engage and contribute within society and have a good quality of life. Dementia is overwhelming for the caregivers and adequate support is required for them from the health, social, financial and legal systems. Countries must include dementia on their public health agendas. Sustained action and coordination is required across multiple levels and with all stakeholders – at international, national, regional and local levels

It is the leading cause of dependency (i.e. need for care) and disability among older persons in both high-income countries and LMIC. The estimated worldwide cost of dementia is estimated to have been US$ 604 billion in 2010. Direct medical care costs contribute to just 16% of the global cost. In low-income countries, most costs are due to informal care (i.e. unpaid care provided by family members and others) (World Alzheimer's Report 2010). While the numbers and the costs are daunting, the impact on those with the illness and on their caregivers and families is extreme – medically, psychologically and emotionally.

There is a lack of awareness and understanding of dementia, at some level, in most countries. It is often considered to be a normal part of ageing or a condition for which nothing can be done. This affects people with dementia, their caregivers and families, and their support structure in a number of ways. Low awareness levels contribute to stigmatization and isolation. Poor understanding creates barriers to timely diagnosis and to accessing ongoing medical and social care, leading to a large gap in treatment. Lack of awareness also takes its toll of the resilience of the family unit and increases financial and legal vulnerability. In many countries, including those in economic transition, the members of the extended family[2], who may have been able to absorb the impact of caring across the family network in the past, now live far from their kin for economic reasons. This change is likely to result in an increase in the need for formal care in coming years. At national level, the lack of awareness and lack of infrastructure for providing timely and appropriate support early in the course of the disease increase the likelihood of high costs of supporting increased dependence and morbidity. No treatments are currently available to cure or even alter the progressive course of dementia, although numerous new therapies are being investigated in various stages of clinical trials. There is, however, much that can be offered to support and improve the lives of people with dementia and their caregivers and families. The principal goals for dementia care are:

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- Early diagnosis;
- Optimizing physical health, cognition, activity and well-being;
- Detecting and treating behavioral and psychological symptoms;
- Providing information and long-term support to caregivers
- Quality of life of people with dementia and their caregivers.

The following data will show that Dementia situation in India is like an unexploded bomb. Unless handled properly and with utmost urgency, it is going to cost our health system very dearly.

Table 2. Selected Indian state and projection of estimated number of patient by age group in India till 2026

States/Union Territory	Year	Projected Numbers (In 000) with Dementia by Age group					Percentage of change in Dementia's compared to 2006
		65-69	70-74	75-79	80+	Total	
Himachal Pradesh	2006	3	3.9	5.7	9.3	21.8	
	2011	3.3	4.3	5.5	13.7	26.8	23
	2016	3.9	4.9	6.2	16.1	31	42
	2021	4.7	5.8	7	18.6	36.1	65
	2026	5.5	7	8.4	21.4	42.3	94
Punjab	2006	11.5	16.8	23.3	35.3	86.9	
	2011	11.9	17.1	23.7	54.8	107.6	24
	2016	14.7	17.8	24.4	67.5	124.4	43
	2021	18.8	22.1	25.7	76.6	143.1	65
	2026	23	28.5	32	83.9	167.5	93
Rajasthan	2006	22.7	29.3	37.1	23.5	112.6	
	2011	24.5	33.1	40.8	66.6	164.9	46
	2016	29	36.2	46.7	98	209.9	86
	2021	36.2	43.1	51.6	126.2	257	128
	2026	44.6	54.3	62	150.7	311.6	176
Uttar Pradesh	2006	68.1	85.7	106.1	50.3	310.3	
	2011	72	96.5	115	172.7	456.3	47
	2016	83.1	104.4	133.2	259.7	580.4	87
	2021	102	122.4	147	340.4	711.7	129
	2026	123.7	152.1	174.6	411	861.4	177
Bihar	2006	33.3	40.9	40.2	19.6	134	
	2011	36.2	47.5	54.8	67.3	205.7	53
	2016	42.6	52.5	65.3	116.6	277	106
	2021	52.6	62.6	73.3	161.9	350.3	161
	2026	63.7	78.1	88.3	201.2	431.3	221

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Table 2. Continued

States/Union Territory	Year	Projected Numbers (In 000) with Dementia by Age group					Percentage of change in Dementia's compared to 2006
		65-69	70-74	75-79	80+	Total	
West Bengal	2006	33.5	41.9	53.6	53.7	182.7	
	2011	38.1	47.9	56.4	102.2	244.7	33
	2016	46.9	55.2	65.7	135.4	303.2	66
	2021	59.5	68.7	76.8	169.2	374.2	104
	2026	73.9	88	96.8	206	464.6	154
Gujarat	2006	21.6	26.8	32.5	42.6	123.5	
	2011	24.7	31.7	37	69	163.1	32
	2016	30.7	36.8	44.7	92.8	204.9	66
	2021	39.3	46.1	52.6	118.3	256.3	107
	2026	48.9	59.6	66.6	145.5	320.6	159
Maharashtra	2006	47.7	67.5	80	82.8	277.9	
	2011	47.7	68.2	89.2	155	360.1	29
	2016	56.4	69.1	92.2	211.8	429.5	54
	2021	71.2	82.7	95	252.1	501	80
	2026	88.8	105.4	115.3	282.3	591.7	112
Karnataka	2006	23.9	29.9	38.2	47.8	139.8	
	2011	26.8	34.7	41.1	80.5	183.1	31
	2016	33.3	39.4	48.4	104.6	225.8	61
	2021	41.3	49.4	55.8	130.3	276.8	98
	2026	49.4	61.8	70.5	156.7	338.4	142
Kerala	2006	18.4	24.7	33	58.1	134.3	
	2011	20.1	26.8	33.6	77.6	158.1	17
	2016	24.5	29.7	37.3	90.9	182.5	35
	2021	29.6	36.6	41.9	104.8	212.9	58
	2026	33.9	44.6	52.2	120.3	251	87
Tamil Nadu	2006	34	40.9	49.4	85.2	209.4	
	2011	38.2	48.3	54.3	114.6	255.4	22
	2016	45	55	65.4	140	305.5	45
	2021	53.4	65.8	75.9	171.9	366.9	75
	2026	61.8	78.8	92	207	439.5	110
North East States (Excluding Assam)	2006	4.1	5.1	7.1	8.5	24.8	
	2011	4.9	6	7.3	15.8	34	37
	2016	6.3	7.2	8.6	20.7	42.9	73
	2021	8.1	4.7	10.5	25.7	49	97
	2026	10.1	12.2	13.8	31.6	67.8	173

Source: Lok Sabha[3] Unstarred Question No. 5826,[4]

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2.4. Dementia: Challenges Before Care-Givers

The World Alzheimer Report (2010) focused on the economic impact of Dementia. A dementia is already significantly affecting every health system in the world, and large amount of money are being spent in caring people with dementia. Alzheimer's and other dementias are imposing huge societal and economic burdens, both through direct (medical and social care) and indirect (unpaid care giving by families and friends) costs. Evidence is just beginning to emerge of the extent of the economic burden in middle income countries (Wimo, 2010).

Caring for people with dementia is associated with a greater physical, mental, and financial burden on the care giver (Dias & Patel, 2004) Studies by the 10/66 Dementia Research Network in Goa[5] and Chennai [6]examined the impact of care giving for elders. Carers of people with dementia spent significantly longer time providing care than did carers and co-residents of depressed persons and controls. The highest proportion of time was spent in communicating, supervising, and helping with eating and toileting. Economic strain was indicated by the high proportion of caregivers of people with dementia who had given up work to provide care, coupled with the increased likelihood that the family had to meet relatively high health care costs. This was explained by the increased propensity for people with dementia to use expensive private medical care services rather than free or low-cost government services (Dias & Patel, 2004).

As per the Dementia Report 2010, it is estimated that the cost of taking care of a person with dementia is about 43,000 annually; much of which is met by the families as the state is virtually non-existent. At present the Institutional cost in private clinics ranges from Rs30, 000-40,000 which is prohibitively high for common citizen. The financial burden will only increase in the coming years making it impossible for the poor. In the present days, family support is shrinking and very few institutions have come forward to fill this vacuum. Few organizations such as Alzheimer's and Related Disorders Society of India (ARDSI) and the National Voluntary Organization are few dedicated to the care, support and research of dementia has been in the forefront to improve the situation since 1992 (The dementia India report, 2010).

Table 3. Nature of care required at different stages of dementia

Early Stage	Middle Stage	Later Stage
Family members become aware of changes and may prompt the person to seek assessment (in pre-diagnostic phase) *Caregivers become aware of their care giving role (often as a result of diagnosis)* • Provide emotional support following diagnosis and when the person is depressed or anxious • Prompt and remind the person about events, tasks and other things to help them maintain involvement and independence • Provide assistance with instrumental activities (e.g. personal finances, shopping).	*Caregivers become aware of their supervisory role* • Use communication strategies to aid understanding • Provide help with carrying out personal care • Provide help with other activities of daily living such as food preparation, dressing appropriately • Respond to and manage behavioural disturbance and inappropriate behaviour.	*Significant demands on caregivers as the care recipient becomes fully dependent and loses the ability to communicate needs and wishes* • Provide care, support and supervision around the clock • Provide full assistance with eating and drinking • Provide full physical care (bathing, toileting, dressing, mobilizing) • Manage behavioural problems

Source: WHO,2008

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Table 4. Nature of care services exclusively available for dementia patients in India

Types of Services		Approximate Number of Such Facilities in India
Residential Care Facilities	This facility is suited for those families who find it difficult to manage the basic day-to-day activities of the PwD. They could opt for long term care in a nursing home facility. This also includes respite services where the PwD is looked after for a short period to give the carer a break. There are six full time residential care facilities exclusively for PwD: 1.Harmony Home, Kottapadi, Kerala 2.Malabar Harmony Home, Calicut, Kerala 3.Snehasadanam, Trivandrum, Kerala 4.Nightingales Dementia Care, Bangalore, Karnataka 5.Cochin Harmony Home, Cochin, Kerala 6. Dignity Lifestyle Home, Neral. Maharashtra 7. Spandana, Bangalore	7
Day Care centres	Dementia Day Care facilities are designed for those PwD who have a need for medical attention and supervision, but who do not require institutionalization in a nursing home. In these facilities, the PwD are looked after during the day and after which they return home.	10
Domiciliary care services	The services are provided to the PwD at their services residence. Services could range from education, to providing tips on care giving to actual formal care. Could be provided by geriatric home nurses or other trained personnel. There is evidence that non specialist community workers can also be engaged in providing this service.	6
Support groups	Support groups are groups of people who have lived through the same difficult experiences and try to help themselves and others by sharing coping strategies. Recommended for carers of PwD.	Exact data not available
Memory clinics	Memory Clinics are specialized clinics that offer assessment, support, information and advice to those with memory problems and their careers.	>100
Dementia in Help Lines	These are special phone numbers dedicated to address queries on dementia. The calls are handled by trained personnel	10

Source: Dementia India, 2010pp 56, 57.

In India, under joint family[7] system elderly people, including the people suffering from dementia, (although often undiagnosed) were well taken care of by the family members especially women who were staying back at home. But in the present day the increasing Nuclearization of the family took place due to mass migration to cities for various pull factors of globalization. Women's education and emancipation and rising cost of living made both the couples working outside the home to meet both ends inevitable. This has its effect on care giving (Older Persons Maintenance, Care and Protection Bill, 2005). This gap is not filled up either by either the state or private players. Affordable quality care is still a distant dream.

As a result, elderly people are either forcefully under pressure from family, or sometimes willingly joining old age homes. There are number of old age homes to take care or to look after elderly people, who are normal in their behaviour and who can do their work by themselves. Even some government run affordable old age homes are also there. But hardly such facilities are there for elderly people suffering from dementia. Women due their lack of access to resources are in even more disadvantageous position to avail the benefits of Institutional care.

There are no accurate estimates for the treatment gap for dementia in India, but we estimate that this gap exceeds 90% in most parts of the country, with the exception of urban areas and the two southern states of Kerala and Tamil Nadu (Dias & Patel, 2004) Some research study based on Indian State Goa

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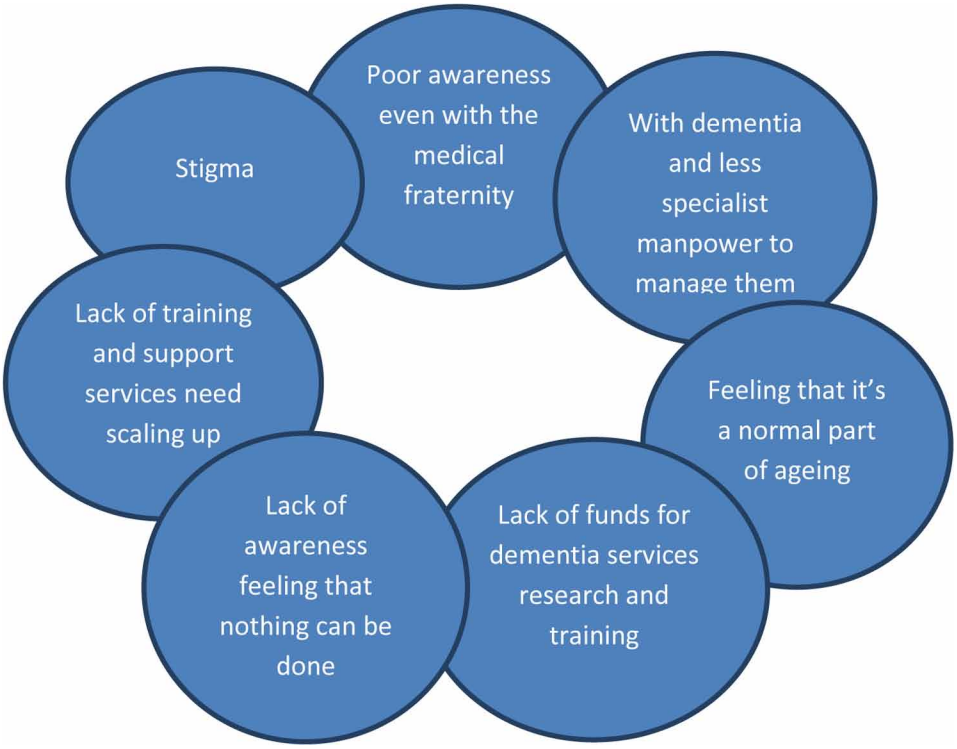
also reported that some families refused to take dementia specific medications mainly citing reasons including high cost, the family doctor advising not to take the medications, and fear of side effects. There are several major barriers to closing this treatment gap including the low levels of awareness about dementia as a medical disorder; however, the most significant barrier is the very low human resource capacity for the care of people with dementia (Dias & Patel, 2004) .

2.5. Poor Elderly Women Suffering From Dementia Are Trebly Discriminated

The elderly people who need special care are vulnerable and elderly women who are often financially dependent on others for their living made to feel as burden. Thus poor, elderly women suffering from Dementia are trebly vulnerable by virtue of their age, gender, and the disease. Since women are the primary care givers in any society when they themselves are in need of intense care, it becomes problematic. In developed countries, in the field of geriatric care the vacuum created by the absence of family is duly filled in by the social security measures provided by the state. In India a clear absence of required social security measures for the elderly turns the field of geriatric care extremely challenging (Mukherjee, 2014).

Figure 1. Barriers to dementia care in India
Source: Dementia India, 2010 pp: 61



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From above discussion it is very clear that in India:

- Absolute lack of awareness on Dementia among patients and family members
- Almost non-existent institutional dementia Care
- Whatever little facilities available are prohibitively costly and, therefore, not socially inclusive[8]
- Virtual absence of Government in policy frame-work of dementia and its care
- Due to lack of awareness and affordable-quality support services, elderly dementia patients especially women are forced to live undignified, traumatized life
- Care givers who are often women only are highly stressed both mentally physically and financially.

3. UNDERSTANDING DEMENTIA THROUGH THE PRISM OF CAPABILITY APPROACH

Poor, marginalized people, disabled [9]people and women are treated frequently as subordinate group in society. Individually and collectively, they have been denied rights and have faced discrimination, exclusion and isolation. When poor marginalized women suffer from dementia during old age, her dependence and subordination reaches its nadir. They have been deprived of their full participation in society as they continue to be marginalized socially, economically, physically and politically across the world (Oliver, 1996: 23-29, Coleridge 1993:4). Martha Nussbaum, a capability theorist has indicated that "unequal social and political circumstances give women unequal human capabilities (Nussbaum, 2000:1). The same perspective applies to the poor and disabled people. Disability is generally defined as limitation in actions or activities due to physical, mental and emotional conditions. Poverty and disability affect an individual's capabilities, especially women, impacting their participation in society. Poverty and disability reinforce each other, contributing to increased exclusion and vulnerability (Stewart et al, 2002, p. 64). It is evident dementia is increasing the vulnerability of the lives of already vulnerable like women.

Building on this perspective, the capabilities approach is appropriate for understanding disability of any kind and dementia in particular. Amartya Sen brought a range of ideas that are excluded from traditional approaches. Sen's approach arose from dissatisfaction with subjective states and command over resources as concepts or measures of well-being or advantage; and from the wish for a concept that presents persons as reasoning agents with the right to make choices. The core focus of the capability approaches is on what individuals are capable of doing. The five components in assessing capability are (Sen, 1985):

1. Real freedom for the person's advantage.
2. Individual differences in the ability to transform resources into valuable activities.
3. The multi-variant activities which will give rise to happiness.
4. A balance of materialistic and non-materialistic factors in evaluating human welfare.
5. Concern for the distribution of opportunities within society.

Sen is concerned with producing a general framework for evaluating the quality of lives people can lead that can incorporate the very diverse concerns and dimensions that may be applicable. Sen's capability approach in its normative developmental aspects is mainly concerned with practical incremental

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improvements and that is precisely what we are looking forward to for the care and support services for poor women dementia patients.

The root of the capability approach is an insistence on referring to a wide range of types of information, notably about how people actually live – what they do and are – and their freedom—what they are able to do and be. Sen further stresses on the inter-personal distribution of outcomes, persons' rights and other features of the decision situation. (Des Gasper, 2007). A person's capability is the alternative lives open to her, the extent of her positive freedom; the valuation of her positive freedom, her access to objective well-being based on the range and quality of attainable reassuringly valued outcomes. Sen stress on 'the capability to achieve valuable functioning's' (Sen, 1993, p. 31) and on judgement of opportunity freedom according to the opportunities to attain what 'one has reason to value' (Sen, 2002, p. 519).

A person who has a disability may have larger basket of primary goods and yet have less chances to lead a normal life (or to pursue her objectives) than an able bodied person with a smaller basket of primary goods. Similarly, an older person or a person suffering from dementia can be more disadvantaged in a generally accepted sense even with a larger bundle of primary goods (Sen 1999: p 74). Even if disabled people possess more income, they might require an even greater amount to accomplish the same functioning's as other non-disabled people.

Gary L. Albrecht and Patrick J. Devlieger in their article "The disability paradox: high quality of life against all odds" (1999) defined the concept 'disability paradox'. The disability paradox highlights the importance of personal experience with disability in defining the self, one's view of the world, social context and social relationships. This is in contrast to those who have not had such experiences. There is a decided negative bias in the attitudes and expectations of the public and health care workers toward persons with disabilities and dementia (Wright, 1988). Conversely, one can argue that if people have disabilities, they cannot be considered to be in good health nor possess a high level of life satisfaction. People with disabilities are assumed to be limited in function and role performance and quite possibly stigmatized and underprivileged (Brown et al, 1994). Kottke (1982, p:80), a distinguished expert in rehabilitation medicine, expresses this view when he states that ``the disabled patient has a greater problem in achieving a satisfactory quality of life. He has lost, or possibly never had the physical capacity for the necessary responses to establish and maintain the relationships, interactions, and participation that healthy persons have''. Research evidence, however, presents a more complex picture. In practice, the anomaly is that patients' perceptions of personal health, well-being and life satisfaction are often discordant with their objective health status and disability (Albrecht & Devliegerin, 1994).

Quality of life is broader than the notion of health-related quality of life. The latter notion developed as a result of major concerns in health care because of chronic illness, new technology, cost containment, interest in medical outcomes, and a concern to humanize health care (Albrecht, 1996). While the distinction between these two types of quality of life is important in many contexts, such as physical, role and social functioning, vitality, and mental health (Lerner and Levine, 1994), it is critical in studying disability not to restrict the notion of quality of life to health-related issues. The domain of disability extends far beyond health-related concerns to encompass the person's well-being, definition of self and social position. As a holistic concept, quality of life goes beyond activities of daily living and disease categories because it directs attention to the more complete social, psychological and spiritual being (Albrecht et al,1999).

My interpretation of quality of life in terms of balance shares many of the assumptions and findings of Antonovsky's theory of the sense of coherence (Antonovsky, 1987). Based on Antonovsky's work, we can understand how some people with disabilities establish and maintain a deep sense of well-being

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and manage stress well. Disability presents an enormous problem for the individual and community. For, as Stiker (1997) suggests, disability introduces chaos and ambiguity into the social world of the individual and the community. Individuals, families and communities are unprepared to recognize and seldom ready to accept disability (especially when it is not inborn, and one become disable in the course of life). Disability shatters preconceived expectations and norms and calls accepted values and notions of well-being into question (Albrecht et al, 1999). Antonovsky addresses the questions of chaos and ambiguity. He argues that individuals with a strong sense of coherence will make sense of their social worlds as rational, understandable, structured, and predictable places (comprehensible). They will also perceive that they have access to sufficient resources to help them cope adequately with the problems they confront (manageability). Finally, they will have the capacity to find meaning, values and the motivation to persist in the face of adversity with a disruptive condition such as disability (meaningfulness) (Antonovsky,1987).

The central concept in the framework has to do with establishing and maintaining a sense of balance between the body, mind and spirit and with the individual's social context and environment. We understand that some persons with disabilities may be able produce and maintain their balance and consequently experience a high quality of life while others may not be able to do so due to their health conditions, limited resources and lack of knowledge or environmental constraints (Albrecht et al, 1999).

Individuals who experience disability can find an enriched meaning in their lives secondary to the disability condition. On the one hand, individuals with impairments may internally experience organically based activity limitations which are expressed in disabilities. On the other hand, impairments are often defined by the social responses of others to the individual's impairment. Here, the disability may well be the result of a disabling physical or social environment and most often the interaction of the two (Albrecht et al, 1999).

Usually women suffering from dementia do not experience a high quality of life because:

- They do not have ordered and predictable worlds.
- They do not possess the knowledge, resources and social contacts that provide the social adhesiveness necessary to re-construct a balance and well-being in their lives.
- Often their low quality of life is related to impairments that produce fatigue, constant or unpredictable pain and to physical and social environments that discourage them from becoming empowered and acting as agents in their own lives.
- The sociological evidence suggests, then, that low quality of life for persons with dementia is based on difficult to manage impairments, lack of knowledge and resources and disabling environments.

Thus theoretical efforts to understand quality of life among women with dementia and intervention efforts designed to enable and empower these individuals will build on both the organic base of impairments and the social model of disability. Dearth of policies currently exists to assist individuals with dementia that face poverty. This situation is even more relevant to women since they are at an increased risk of becoming affected by dementia and they are at an increased risk of sicker, poorer, and more socially isolated than either men with disabilities or women without disabilities (International Labour Organization, 1989; McPherson, 1989).

Thus capability approach and 'disability paradox' helps us to identify 'dementia' as capability deprivation situation and with augmentation of capabilities, dementia patients can improve their quality of life from their perspective. Following section through discussion of various care models will throw

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light on how keeping individual differences in mind, capabilities of dementia patients can be improved with available resources.

4. VARIOUS CARE MODELS FOR DEMENTIA CARE

A model is an abstract map of ideas or concepts. Models tend to include theories - explanations for how the world works - and the building blocks of theories are concepts. These are abstract in that you cannot touch, see or easily measure them but they are nevertheless important in helping us understand an issue that is complex and/or has many parts.

4.1. The Medical Model

The medical model has its focus on the diagnosis and treatment of illnesses, which, of course is an important aspect of dementia care. However, in its most narrow form it can sometimes fail to address some other important influences on health and well-being. It is concerned with making a clear distinction between what is 'normal' and what is 'pathological'. It focuses on the diagnosis of disease based on signs and symptoms. It is a rational activity based on scientific knowledge gained from long, formal training and concerned with the pursuit of cures for disease (Mukherjee, 2015).

4.2. The Social Model

The social model emphasizes a broader range of factors than simply physical ones. Some believe that this has encouraged people to underestimate the importance of finding effective treatments for dementia. This model emphasizes the interaction of biological and social factors in the development of dementia. It is based on an understanding of the complexity of human health and well-being and emphasizes the importance of communities and social networks in supporting people who are vulnerable. It values the knowledge and understanding of those who experience dementia and their care givers. This model takes into consideration of the role of socioeconomic and political factors in the development and spread of disease (SCIE, n.d.).It is important to realize that the social model does not totally exclude or ignore the elements associated with the medical model, such as the importance of finding cures for disease. Instead, the social model incorporates elements of the medical model and places them into a much broader framework for understanding health and well-being (Kitwood, 1997, p: 40).

Core Values followed in social model:

1. Maximizing personal control.
2. Enabling choice.
3. Respecting dignity.
4. Preserving continuity (of lived experience and care provision).
5. Promoting equity.

Kitwood (1997) identified a culture of care that can arise when a narrow view of dementia dominates. He termed this culture of care 'malignant social psychology' and it is important to emphasize that it can

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arise even where care staff are behaving in ways that they believe to be kind and altruistic. According to Kitwood the most important elements of malignant social psychology includes:

1. **Imposition:** Forcing a person to do something overriding desire or denying the possibility that they may have a choice.
2. **Disempowerment:** Not allowing a person to use whatever abilities they may have
3. **Infantilization:** i.e. treating an adult like a child; patronizing them.
4. **Intimidation:** Inducing fear through the use of threats, either explicitly or implicitly.
5. **Objectification:** Treating someone as if they were a piece of dead matter, an object to be moved, lifted, etc, without proper reference to the fact they are human beings.
6. **Banishment:** Sending a person away or excluding them, either physically or psychologically.
7. **Invalidation:** Failing to acknowledge the subjective reality of a person's experience and how they may be feeling.
8. **Withholding:** Refusing to meet evident need or give asked-for attention.

4.3. Personal Care Model

Person Centred Care reflects the related concepts of dignity, worth and human rights. These ideas are enshrined in national and international documents that govern the way health care is provided.[10]There is still debate about an exact definition of person centred care. Person centred care offers hope and support to the person living with dementia. It values the person's experiences and makes him or her, the focus of care delivery not their disease (Edvardsson, 2010, pp: 834-46). Person centred care:

- Recognizes and maintains person hood,
- Recognizes uniqueness and individuality, and acknowledges this in care plans and care pathways,
- Is professional care that respects autonomy, dignity, privacy and the rights of the person,
- Identifies strengths and positive aspects, rather than weaknesses and problem. Acknowledges the person's lived world (Slater, 2006, p: 135-44),
- Person centred care has been promoted as best practice in dementia care, but the concept is still poorly defined and lacks an empirical base (Brooker, 2003, p: 215-222),
- A positive social environment in which the person living with dementia can experience relative wellbeing. (www.caresearch.com.au/caresearch).

4.4. Risk Enablement and Safeguarding Model

Risk enablement Social Model of Dementia Care is based on the idea that the process of measuring risk involves balancing the positive benefits from taking risks against the negative effects of attempting to avoid risk altogether (Derbyshire Department of Health, 2010). It involves:

1. The development of systems for enabling and managing risk which allow people with dementia to retain as much control over their lives as possible.
2. Recognizing the strengths that each person with dementia possesses and builds on the abilities that he or she has retained.

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3. Taking a tailored approach to risk by acknowledging that dementia affects different people in different ways.
4. Identifying less restrictive alternatives – those interventions that cause less disruption or change in the circumstances of the person with dementia and which maximize their independence and freedom, with due attention to the safety of others.
5. The recognition that people with dementia's perceptions of risk are likely to be influenced by events and decisions that have occurred during the course of their lives, as well as by the impact of any changes that can be attributed to the effects of dementia.
6. Acknowledgement that a shared agreement about risk will not always be possible but it is important that everyone involved in reaching decisions about risk reaches a shared understanding of the viewpoints of all those who are affected by decisions involving risk.
7. Strike a good balance between the protection of residents and the quality of life gains that come from taking some risks.

Risk assessments need to consider the impact on people with dementia's wellbeing and autonomy as well as the possible risks to their physical safety and Effective practice to combat and prevent abuse. Potential risks to be minimized include (Mukherjee, 2015):

- Overcrowding.
- Lack of privacy.
- Lack of activities.
- Inadequate staff attention.
- Poor communication between the person with dementia and staff.
- Conflicts between staff and carers.

4.5. Community Support Model

People with dementia and their care givers do not always receive the health and social care interventions required to support them to live in the community. The prevalent construct of care provided fails to recognize community support as a resource to facilitate resilience and promote independence. Poor quality community services can increase the challenges of living with dementia. The integration of health and social care provides an opportunity to create a structured, coordinated and strategic approach to community support for people with dementia and their care givers (Kinnaird, 2012, pp:13-15). This will help to enable the person with dementia to remain in the community for as long as possible.

The integration of health and social care provides an opportunity to create a structured, coordinated and strategic approach to community support for people with dementia and their care givers to ensure their dignified stay in the community for long (Kinnaird, 2012, pp:13-15). According to Lindsay Kinnaird, the 8 pillars of the model of community support for dementia incorporates:

1. **Dementia Practice Coordinator:** A skilled practitioner who will lead the care, treatment and support for the person and their carer on an ongoing basis, coordinating access to all the pillars of support and ensuring effective intervention across health and social care.
2. **Therapeutic Interventions to Tackle Symptoms of the Illness:** Dementia-specific therapies to delay deterioration, enhance coping, maximize independence and improve quality of life.

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3. **Support for Care Givers:** A proactive approach to supporting people in the caring role and maintain the care givers own health and wellbeing.
4. **Personalized Support:** Flexible and person-centred services to promote participation and independence.
5. **Community Connections:** Support to maintain and develop social networks and to benefit from peer support for both the person with dementia and the care givers.
6. **Environment:** Adaptations, aids, design changes and assistive technology to maintain the independence of the person and assist the carer.
7. **Mental Health Care and Treatment:** Access to psychiatric and psychological services to maintain mental health and wellbeing.
8. **General Health Care and Treatment:** Regular and thorough review to maintain general wellbeing and physical health.

5. PSYCHOLOGICAL THERAPIES

5.1. Cognitive Stimulation Therapy

It is a process of intervening people with dementia that offers a range of enjoyable activities providing general stimulation for thinking, concentration and memory, usually in a social setting such as a small group. 'Cognitive Stimulation Therapy', or CST, is a brief treatment for people with mild to moderate dementia (CST, n.d.).

- Play music or sing song as per the likings of the individuals (dementia patients).
- By keeping tools and patterns for art and crafts for making painting and knitting.
- Clean around the house by sweeping, wiping the table, chair, or folding cloths and other household task to make the person feel a sense of accomplishment.
- Read the newspaper.
- Cook or bake simple recipes together.
- Work on puzzles.
- Watch family videos.
- Look at books the person used to enjoy.
- Tend the garden or visit a botanical garden.

5.2. Music Therapy

Music Therapy is a target-oriented activity. Therapists work with individuals or groups. John Carpenter, a music therapist says that "Meeting individually and within a group, elder clients express themselves and recall the memories that music sparks and stimulates. By listening to live music and being involved in live music-making experiences, a greater quality of life is possible." By this it empowers the dementia patients to come out of isolation (**Schaeffer, n.d.**).

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5.3. Reality Orientation Therapy

It is a progressive treatment for confused elderly patient's i.e. disturbances in the clinical level of memory, executive functioning, and self-directed behaviour to help them focus on their immediate surroundings. Reorientation therapy works by presenting orientating information, such as time, place, and person (Study, n.d.).Reality orientation therapy (ROT) is a psychosocial intervention widely used in the care of people with dementia.

5.4. Recreational Activities

It give an opportunity for people with dementia to engage in meaningful activity and are often used as a way of facilitating the individual's need for communication, self-esteem, sense of identity and productivity. Activities used range from self-expression through drawing, music, arts and crafts, to cooking, games and interacting with pets (Beck, et al 2002). The most successful activities for individuals with dementia utilised strengths from the individuals current functioning, and previous interests. Individualised activities adapted to maximise the person's remaining abilities and based on previous interests may be more beneficial to people with dementia than generic activities.

5.5. Validation Therapy

Validation is a method of communicating with and helping disoriented very old people. It is a practical way of working that helps reduce stress, enhance dignity and increase happiness. Validation theory explains that the people who are in the last stage of life of dementia trying to resolve unfinished issues in order to die in peace (https://vfvalidation.org/web). This is developed by Naomi Feil. Using Validation techniques disoriented elderly can be given an opportunity to express what they wish to express whether it is verbal or non-verbal communication.

5.6. Reminiscence Therapy

It aims to stimulate memory and mood in the context of the patients' life history. Reminiscence therapy involves helping a person with dementia to relive past experiences, especially those that might be positive and personally significant, for example family holidays and weddings. The aim of reminiscence therapy is to strengthen cognitive memory components, and to encourage either intrapersonal development or interpersonal development (Hsieh& Wang, 2003).

5.7. Home Remedies

Some of the home remedies used for the dementia patients is as follows (Mayo Clinic, n.d.):

1. **Enhance Communication:** While communicating with the loved one, the dementia patients should be encouraged to maintain eye contact, speak slowly in simple sentences, and don't rush the response.
2. **Encourage Exercise:** Exercise benefits everyone, including people with dementia. The main benefits of exercise include improved strength and cardiovascular health. Physical activity may slow

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the progression of impaired thinking (cognitive) function in people with dementia. Exercise can also lessen symptoms of depression, help retain motor skills and create a calming effect.

3. **Encourage Participation in Games and Thinking Activities:** Participating in games, crossword puzzles and other activities in which people are using thinking (cognitive) skills may help slow mental decline in people with dementia.
4. **Establish a Night-Time Ritual:** Behaviour of the patient is often worse at night. Care givers should try to establish going-to-bed rituals that are calming and away from the noise of television, meal clean-up and active family members. Leave night lights on to prevent disorientation. Limiting caffeine during the day, discouraging daytime napping and offering opportunities for exercise during the day may help prevent night-time restlessness.
5. **Encourage Keeping a Calendar:** Keeping a reminder calendar may help the loved one remember upcoming events, daily activities and medication schedules. Consider sharing a calendar with your loved one.
6. **Plan for the Future:** Developing a plan with the loved one that identifies goals for care in the future. Several support groups, legal advisers, family members and others can help you. You'll need to consider financial and legal issues, safety and daily living concerns, and long-term care options.

6. CONCLUSION

The best way we can show our gratitude to our previous generations is through the creation of dementia friendly society and by making dementia a national public health and social care priority worldwide. We have to improve public and professional attitudes and understanding of dementia. A welfare state needs to invest health and social systems to improve care and services for the people with dementia and their caregivers;

The Action Plan for Dementia must emphasize on: [11].

1. Early diagnosis (compulsory dementia testing after 50 years of age), timely diagnosis and quality in diagnosis.
2. Physician training and improving access to diagnosis and care pathways (development of specialised dementia care services in general hospitals).
3. Coordinated specialized diagnosis and support.
4. Dementia Behaviour Management Advisory Service and psycho geriatric consulting resources.
5. Develop services (ambulatory e.g. day-care, home visit, short stay and residential e.g. intensive care homes services, including "community-based long-term care services" such as group homes or networking of families and small-scale multifunctional in-home care services which are designed to support users to remain in their familiar environments) to assist people in living well with Dementia.
6. Support and information for individuals with dementia and families(Following Goa model appointment of Home care advisors HCA's at Taluka[12] level)[13].
7. Research funding and need for National level.
8. Community support grants, Staff education and training, training for aged care staff.
9. Increased public awareness, information and education.
10. Planning for appropriate, safe and secure environments.

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11. Respite services for caregivers, research on caregiver needs and advance directives on care choices.
12. Intergenerational volunteer initiative and preparing future caregivers.
13. improved interdisciplinary communication.
14. Enabling patients and their families to choose support at home.
15. Advice regarding existing government schemes for elders.

In countries like India where different section of the society experience discrimination based on caste, class gender, religion and so on. Thus social protection is essential to improve access to services and ensuring that people do not experience financial hardship as a result of paying for them. Social protection strategies consist of policies and programmes designed to reduce poverty and people's vulnerability.

Social protection in old age is fragile and depends on the interaction of many factors – such as health, living arrangements, family support, and sources and levels of income. Women, often due to their multifarious intersectional vulnerabilities are stand at the bottom of the care tree. Some supports are available through financial benefits for older people, particularly in high-income countries. However, many people in lower and middle income countries cannot access financial benefits such as aged or retirement benefits, disability pension or compensatory benefits for caregivers, and have to rely on out-of-pocket payments for health care and other essential services. This leads to barriers to the access to services for the poor and may result in severe financial difficulties.

We can emulate Dementia –care policies of Japan. With the world's highest ageing rate, Japan established the public long-term care insurance system in April 2000. The insurance aims to support those who are facing the need for long-term care; clarify the relationship between benefits and burdens by way of introducing a social insurance approach; enable service users to receive comprehensive services from a variety of facilities of their choice; and separate long-term care from coverage of health care insurance. Insurers are primarily municipalities.[14] The insurance covers 90% of the service charge and users pay the rest out-of-pocket. The insurance covers both ambulatory and residential care. The long-term care insurance system has now become indispensable in supporting people, including people over the age of 40 years with dementia. It is never too late to begin with a comprehensive National Action Plan to tackle the situation. Our challenge for change has just began.

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ENDNOTES

1 60+ years.

2 Extended family: A family that includes people of different generations who are related by blood or marriage or who otherwise regard themselves as a large family in one household near relatives (such as grandparents, aunts, or uncles) in addition to a nuclear family. The extended family enjoy certain advantages, such as a greater sense of security and belonging due to sharing a wider pool of members to shoulder responsibilities and resources during a crisis.

3 Lower house of Indian parliament.

4 Lok Sabha Unstarred Question No. 5826, dated on 11.5.2012.http://14.139.155.5:2106/table/health/16/disabledpopulation/76/65...retrievedon25/5/2015

5 One of the Indian state.

6 Capital of Tamilnadu-an Indian State.

7 Traditional Indian joint family according to Ross is a kind of entity of those related to each other as some type of kindred. Co-residence, common property and commensality, co-worship as well as the observance of certain rights and obligations are some of the essential features of the Indian joint family.

8 In a highly stratified Indian society with interlocking inequalities based on caste, class, gender, physical ability and so on, the concept of social inclusion means the encompassing of the entire population in the performances of the individual function systems. On the one hand, this concerns access to these benefits and, on the other, dependence of individual modes of living on them. To the extent that inclusion is achieved, groups disappear that do not or only marginally participate in social living (Luhman 1990: 34).

9 dementia and old age are considered to be as disability.

10 The International Declaration of Human Rights, professional ethics documents, The Aged Care Act (1997) and other related documents, The ICN code of ethics for nurses says “Inherent in nursing is respect for human rights, including cultural rights, the right to life and choice, to dignity and to be treated with respect” (The ICN Code of Ethics for Nurses, 2006),The Australian Code of Ethics for Nurses states “nurses recognize the vulnerability and powerlessness of people in their care” and must “actively manage the power differential”.

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[11] As it exists in various developed countries. Source: Dementia: A public Health Priority,2012, WHO Report, United Kingdom.

[12] Country> State> District> Sub division> taluka.

[13] The HCA were trained in key skills including listening and counselling skills, bereavement counselling, stress management, and health advice. The HCA applied a flexible home-care program tailored to the needs of the individual and the family (Dias etal, 2004).

[14] The insurance is financed from public funds – government and prefectures (37.5%), municipalities (12.5%) – and premiums of the insured (50%).Persons over 40 years of age pay monthly premiums according to their age, income and the area in which they live. The average premium paid per month is 4160 JPY (approximately US$ 54 or Indian Rs 3575). When citizens require services covered by the long-term care insurance, they are certified and classified into one of seven eligibility levels by the local certification committee. Standards for certification are uniformly and objectively determined nationwide.

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Chapter 28
Environmental Landscape Design for Alzheimer's

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ABSTRACT

People suffering from Alzheimer's may feel anxious or unsettled as a result of these symptoms – in particular the decrease in their cognitive abilities and in their ability to take into account new information or external stimuli – as well from the effects of their medications. Because of their sensitivity, such individuals find it difficult to keep up a positive attitude and remain emotionally stable for long: they experience mood swings, and are unable to keep their negative emotions in check. For this reason, the best practice in treatment is to help them maintain a positive view of their lives and balance their emotions, both personally, in terms of keeping their sense of self, and in social environments, where they have to recognize and interact with others. In this way, good environmental landscape design will have an important role to play in improving their quality of life.

INTRODUCTION

The disorder known as Alzheimer's disease falls into the general category of dementia, which refers to various symptoms of progressive cognitive deterioration that have an impact on daily life. It is characterized by loss of memory, a decline in cognitive, commmunicative and decision making abilities, loss of orientation in time and space, and an inability to tolerate intense, or even moderate sensory stimuli. As such, it may lead to other neurodegenerative disorders, the inability to function normally; and to behavioral problems, for example, if the environment provides too many stimuli to process, or if the intervention poses a cognitive challenge (Detweiler et al., 2012; Chong & Hermreck, 2011).

In cognitive terms, the progress of the disease may lead to the individual's having confused or fragmented memories, ideas and feelings; these may be accompanied by the frustrations of short-term amnesia, problems in processing or using language, impaired judgment and spatial disorientation. Yet despite these difficulties, Alzheimer's patients are typically able to carry out such functions as walking,

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gesturing, and responding to environments that are mildly stimulating. Thus older patients may develop a modicum of control and a feeling of familiarity with their environment by exercising their long-term memories, along with engaging in gentle physical activities outdoors (Garcia, 2014).

This places various restrictions on designing environments for individuals with Alzheimer's, because both their specific needs and their daily routines must be taken into account. In the first place, they may be living their lives in particular contexts. Patients in the early stages tend to stay in their own homes, but eventually may require support from friends, family members, or carers. Or they may move from an assisted living apartment to a home providing personal care. Such facilities may or may not have specialized healthcare services, depending on the philosophy of their programs, which should both clarify the purposes of the care and explain how it is related to the physical environment provided (Brawley, 1997).

Indeed, one of the characteristics of people with Alzheimer's is that it becomes more and more difficult for them to relate to their environment. A setting that feels familiar also feels more easily controllable, so patients do not feel the stress or fear associated with a sense of alienation. It is therefore essential that in designing for such people, environments are made to feel more familiar and more like home (Nord, 2004); in addition, there should be recognition of Alzheimer's sufferers as people who wish to be independent, and to keep their self-respect and dignity. The environment should therefore provide familiarity and a feeling of comfort and confidence; for elderly patients, or others with advanced cognitive or perceptual problems, care should also be taken to see that safety is ensured. This is, of course, a rather complex problem.

Depression, stress, and some of the symptoms of Alzheimer's, may be reduced by engaging in activities outdoors (Kuo & Taylor, 2004; Mooney & Nicell, 1992). Alzheimer's sufferers tend to become disoriented more easily in complex environments, where they both lose their way and lose the concept of where they were intending to go or what they were trying to find; they often react to such situations by acting out their frustration and being aggressive. The incidence of such situations can be decreased if information that can help a person move around in an environment is embedded in it in the form of clear paths, markers, and signs (Ziesel, 2003); in some cases, prosthetic aids can be made available at clearly indicated locations to help people orientate themselves. One study has indicated that Alzheimer's patients in care facilities with access to gardens experience fewer negative reactions and less anger than those in environments without access to gardens (Mooney & Nicell, 1992). Gardens are a useful feature in residential environments, as they provide Alzheimer's patients with a sense of tradition and cultural memories, as well as natural images; they are removed from the cold, clinical atmosphere that many longterm care facilities have.

Well-designed outdoor spaces may help to offset some of the behavioral problems of patients as they become weaker and less in control of their environment; and that poorly designed spaces will exacerbate the confusion, disorientation and frustration of the cognitively impaired. Yet it is only recently that healthcare settings for Alzheimer's sufferers have begun to be designed with a focus on the salutary effects of the outdoors, sunlight and fresh air; there is a real need to create spaces responsive to climate that are simple to negotiate, and still provide a wealth of meaningful associations (Brawley, 2002). This simply requires recognition that Alzheimer's sufferers have, besides specific conditions related to the disease, the same basic physical and psychological needs as other people: to have a sense of security, social relations, external stimulation, and to be valued as individuals. Thus the main aims in designing interventions for people with Alzheimer's should be focused on maintaining their dignity and their quality of life (including the experience of nature), and providing comfort.

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Symptoms Affect the Design Process

The symptoms of Alzheimer's vary from case to case; they may first appear when an individual is in his or her fifties, but may not be recognized as such until much later, and will eventually affect them in nearly every aspect of life. In general, they may be categorized as cognitive, behavioural and physical.

Cognitive Symptoms

In its early phases, the disease begins to affect an individual's thought processes, memories, and ability to make judgments. The patient finds it difficult to make rational decisions or judgments, to connect visual images with their meanings, and may have problems with visual perception, particularly perceiving depth. He or she becomes less able to learn new things, react to information and follow everyday routines. Language and reasoning skills deteriorate; there is a sense of disorientation in terms of time and space; and the patient has an increasing tendency to forget recent events.

But although people with Alzheimer's do have problems with remembering recent events, they often retain clear long-term memories of past experiences; and these can be stimulated in an outdoor setting – Brawley (1997), for example, suggests this can be done through basic activities like mowing, raking leaves, gardening, or hanging clothes out on a line. An Alzheimer's patient's age is a factor that should also be taken into account in the design process; the landscaping around a facility should reflect the long-term memories of residents: gardens they remember from their childhoods, flowers they remember from earlier times, or plants that were important or meant something personal to them in the past (Dixon, 2002).

Behavioral Symptoms

Various behavioral symptoms are associated with the progression of Alzheimer's. The 1987 National Medical Expenditure Survey found that 59% of cases diagnosed with dementia exhibited symptoms such as wandering aimlessly, hurting themselves or others, dressing inappropriately, extended periods of crying, hoarding, becoming upset, making no effort to avoid danger, stealing, and inappropriate sexual behaviour (U.S. Congress, 1992). Another common symptom is "sundowning," where patients become confused or disturbed when the sun is setting; this is because as the disease progresses, changes in the brain are affected by environmental changes.

In general, patients' defensive or aggressive behavior is the result of fear or confusion caused by their difficulty in understanding their surroundings: they need to distance themselves from environmental situations that may be causing tension or discomfort such as noise or crowds. For this reason, both individual and group situations need to be planned for in designing their environments (Dixon, 2002). Interestingly, garden environments have been shown to generally improve morale, but to have negligible effects on patients' behavior (Mather, Nemecek & Oliver, 1999).

Physical Symptoms

Patients in advanced stages of Alzheimer's, frequently remain quite fit; however, physical changes may include weakened muscles and problems in perceiving depth, so some patients may have a tendency to trip and fall and may require walking support or wheelchairs. In general, outdoor activities such as regular

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walks can provide structured daily routines and contribute to patients' health and feeling of well-being (Cedervall & Aberg, 2010).

The Benefits of Environmental Design

Studies have shown that Alzheimer's patients' stress and blood pressure levels may be lowered and they may recover faster from illnesses if they can both see and physically experience natural surroundings. For example, patients diagnosed with stroke and dementia have been shown to have better social skills, be more self-confident, and have better mobility and dexterity if they are engaged in working in gardens (Hartig at all., 2003; Kaplan, 1993; Rappe, 2005; Ulrich, 2002, Ulrich at al., 1991). The garden may connect them to experiences, objects, interests or thought processes from before the onset of the disease, and so create a "sense of normality" (Whear at all., 2014). Thus one patient in a study commented:

Resident – "I like it all. The fountain, the fish, the memory boxes – everything. The table and chairs in the sunroom came from my lounge room at home, you know. We all sit around it and talk." (Edwards et al, 2013).

In general, being in or having access to outdoor environments helps stabilize patients' circadian rhythms and sleeping and waking cycles; and has the added benefit, if there is exposure to sunlight, of promoting vitamin D absorption, which is critical for bone strength. Alzheimer's patients should also be able to continue to engage in their previous outdoor activities in a safe and comfortable environment. Being able to see elements of nature, for example, from a window (Figure 1), can have a positive effect on their sense of being comfortable in the setting of their neighborhood, as well on their general sense of well-being (Kaplan, 2001; Traynor, Fernandez & Caldwell, 2013; Bechtel & Churchman, 2003).

Figure 1. Alzheimer' respite center, Temple road, Blackrock, Dublin, Fotography Nick Kane/Joanna Karatzas
Source: Niall McLaughlin Architects Bedford House, 2012

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LITERATURE REVIEW

Jackson (2005) suggests that older patients feel freer, and less limited by the physical spaces of a room when they can see natural settings and the expanse of the sky, because these refer them back to memories of their personal lives. In this connection, "healing gardens" can be designed for Alzheimer's patients which provide both a comfortable space for physical activities and sensory stimuli that help them recall positive events and feelings (HCNDACRSP 2004; Hartig and Cooper-Marcus 2006). Studies indicate that such gardens help make patients more independent; Zeisel's (2007) research, for example, showed that in a healing garden at an assisted-living facility for Alzheimer's patients in Massachusetts, 36% of the patients would visit the garden of their own accord, and 59% were able to return without assistance (Zeisel, 2007).

Activities related to horticulture have also been shown to help reduce behavioral issues and problems of insomnia in patients with Alzheimer's or other types of dementia (Cohen-Mansfield & Werner, 1998); a study of green day activities for psychogeriatric patients in several care institutions in the Netherlands suggests that activities of this type help improve quality of life for these patients (Andreoli, 2003). Using plants that vary with the seasons is aesthetically pleasing, and also has a salutary effect on mental activity, maintaining interest and providing a sense of time as well as cues that stimulate memories of past home environments in the elderly (Browne, 1992). Horticultural activities help generate more positive emotions, more of a sense of wellbeing, and decreased agitation, in comparison with other activities (Gigliotti et al., 2004; Lee & Kim, 2007; Bomalaski, 2011); and making use of wander gardens over a year has been found to decrease not only the number of falls recorded among individuals with dementia, but also their "use of high-dosage anti-psychotic medications" (Detweiler et al., 2008, 2009).

In a pilot study of nursing-home residents with dementia conducted over a year, Cornell et al. analyzed the relation of indoor and outdoor activities to these patients' behavior and sleep patterns. In both cases the total amount of sleep increased, but there was a significant increase in the maximum length of sleep, and increased verbalization in those engaged in outdoor activities (Connell, Sanford & Lewis, 2007). And a longitudinal study by Mooney and Nicel (1992) comparing five facilities with and without outside environments showed that over time, the incidence of episodes of violence in patients living in the former decreased, while in the latter they increased.

Various outdoor design solutions have been suggested by Randall et al. (1990), making use of ideas from both nurses and landscape architects. These solutions are intended to supplement other approaches, and to focus on creating safe outdoor environments where Alzheimer's patients can feel comfortable. They therefore take into account specific symptoms of the disease exhibited by patients, including amnesia, apraxia (deterioration of motor skills), frailty, agnosia (problems processing sensory data), disorientation and wandering, eating plants, sundowning, and delusions or hallucinations. (Randall, Burkahrdt & Kutcher, 1990). As we have seen, physical exercise can improve these patients' cognitive abilities; purpose-designed gardens can provide colors, odors and textures that evoke positive feelings and recollections (Elings, 2006); and there is also evidence to suggest that patients in advanced stages of Alzheimer's become calmer in the presence of simulations of nature, such as recordings of birdsong or flowing brooks, or pictures of natural scenes (Whall et al., 1997).

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DESIGN

The principles of design that are appropriate for Alzheimer's patients should be based on primordial and basic concepts of healing and well-being, such as feelings of safety and freedom, understanding the surroundings, being aware of social norms and expectations; being able to get away and relax, to see a destination and enjoy the process of approaching it; taking pleasure in nature, the weather and the seasons; and feeling confident and comfortable in acting, accepting failures and celebrating achievements (Volicer & Charette,1999).

Environmental Perceptions

In designing for Alzheimer's patients, the primary aim is to create an environment that accentuates positive and reduces negative stimuli as far as possible. The critical elements are (Figure 2):

- **Color:** A general problem experienced by such patients is distinguishing surfaces, planes, and objects from each other; one consideration must therefore be to provide strong light-dark, textural and color contrasts, which can help them find their way. As these patients often become disorientated and get lost; the use of color can help patients to find their way: floors and areas of a space should be color-coded for this purpose (Bissell, 2010); and successful techniques include using colored inlays, varying the flooring material in different areas, and using patterns to provide guidance and facilitate movement.

It should be borne in mind, however, that perception of contrast varies with individuals: aspects of color such as hue, brightness and saturation can be affected by visual disorders, and some patients are unable to distinguish an object from others nearby if they are similar in color; the redder colors of the spectrum appear to be perceived more easily than the blues. Colors used in design should therefore generally be calm and soothing, evoking comfort and a sense of healing; the addition of some bright accents may contribute to a sense of pleasurable excitement and youth.

- **Taste, Smell and Touch:** A roughly circular space can be designed which attracts patients, where they can engage in various activities, including gardening, and enjoy themselves; here they should have the opportunity to touch and smell plants, herbs and flowers, and perhaps pick fruit, if they so choose.
- **Hearing:** One way of providing pleasant auditory experiences is to set up an aviary in the center of the garden; this is a traditional concept, and may may also serve as a visual landmark by which patients can orient themselves (Nord, 2004).
- **Acoustics:** In general, gardens provide a range of pleasant auditory stimuli, such as the sound of wind in the trees or leaves, that can have a soothing and healing effect on Alzheimer's patients.

Location

In designing gardens, care should be taken to ensure that they can adapt to seasonal changes in temperature; a garden with an ideal microclimate in one season may not feel pleasant in another.

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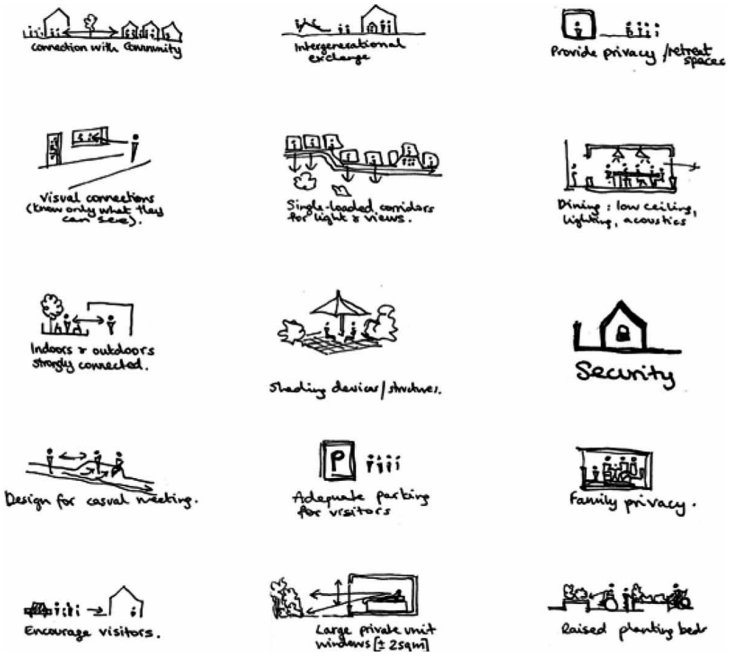
Figure 2. Design for dementia: A visual snapshot
Source: Willatt, 2011



In addition, the choice of location and vegetation should take into account the problem of sundowning: patients need to feel that they are in a comfortable and familiar environment, and effort should be made to reduce shadows that might have a frightening effect. For this reason, a garden space at the southeast of the facility's building is recommended, so that the only shadow cast in it by the sun will be that of the recognizable form of the building (Randall, Burkhardt & Kutcher, 1990).

Designing for Other User Groups

Designing an external environment that is appropriate for Alzheimer's patients and suitable for facility staff and visitors as well presents a challenge, but one which is not insurmountable. Research shows that all users can appreciate garden environments that enable relaxation, bring back memories, and encourage and facilitate outdoor activities (Whear at all., 2014); and that all benefit from the stress relief provided by the access and connection to nature facilitated by gardens, window views, and nature-themed artworks (Ulrich & Gilpin, 2003).

Staff

The role of care facilities for Alzheimer's patients is to maintain a pleasant environment, where there is sufficient space for activities, areas where residents can get away from stress, and where staff can take a break. Staff should be able to modify the environment as the need arises; and they should be able to surveil and monitor the entire area from a distance, so as to minimize the need to accompany patients, and instead enable them to use it as independently as possible.

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Family and Visitors

Staff should also ensure that the care provided is of a high standard, and that the environment provides patients with a feeling of home, where they can have privacy as well as a normal social life and engage with visitors and family.

Design Elements

Exit Control

Alzheimer's patients often forget how to return to their homes, because they lack the ability to maintain and negotiate cognitive maps; for this reason, they should always be accompanied when they leave home. As a protective and preventive measure, exit doors that lead out into broader public areas should be controlled, and signals that tell staff they have been opened should be discreet – for example, doorbell chimes may be used, rather than harsh alarm sounds that would clash with the ambience. Less noticeable exits and more discreet signal systems will be less disturbing, and enable residents to feel less confined and more free and independent within the safety of their environment (Ziesel, 2003).

Enclosing Walls

Enclosed areas have the effect of creating a refuge for Alzheimer's patients. Well-designed walled or fenced-off spaces open up interior spaces by allowing views of the outside: a courtyard, for example, can offers views that change during the day and with night lighting, and also vary according to seasonal or weather conditions; perceiving these changes is especially valuable for patients whose capacity for recalling events is reduced. The enclosed space is safe and provides a sense of privacy; and in addition, looking out at a natural environment can provide a pleasant and aesthetic experience (Wells, 2014).

Walking Paths

For the elderly, an active lifestyle helps to maintain the functions of the brain, and it may also delay the advancement of Alzheimer's *(*Rolland, Abellan van Kan & Vellas, 2008). One symptom of the disease is for a patient to wander in search of something, although without knowing exactly what that thing is. This may pose a problem in facilities without suitable spaces for wandering in; so a pathway, if it is designed to be interesting and leads somewhere, may help turn this activity into the physical exercise of walking (Figure 3). The pathway does not have to take the form of a circular track; instead, it can be created simply by connecting corridors and common spaces leading in a particular direction, and interest can be maintained by ensuring that it has visible goals that can be reached at strategic points, such as pictures, plants, or a new view (Volicer & Charette, 1999). Pathways should have a minimum width of 90cm so they are safe for patients to use on their own or with walkers or wheelchairs. A feature at the end, such as the entrance to a garden, a social area or a hearth can serve as a destination that can be achieved and make the wandering meaningful (Ziesel, 2003).

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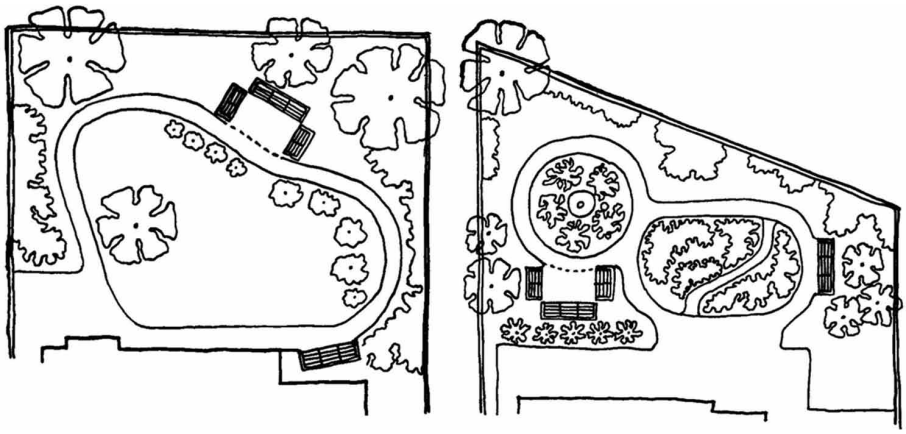
Figure 3. Possibilities for pathway designs
Source: Cave & Brown, 1992



Steps and Ramps

Sloping gardens may require steps or ramps. For ease of use, steps should be level and regular, with a minimum tread of 28cm and a maximum height of 15cm. Flights larger than eight steps should have level rest areas at least 150cm deep. Ramps should have a maximum gradient of 1:20, and should ideally have rest areas every 10 meters (Harris, Dines & Brown, 1998).

Handrails

Some patients may need handrails for support when using outdoor areas; they help the patient balance and move, and also reduce patients' fear of falling. Handrails should not prevent patients from interacting with the vegetation; they should always be comfortable to hold, and also suitable for patients who have difficulties using their hands because of arthritis (Figure 4).

Figure 4. The Lodge at Broadmead, Victoria, BC, Canada
Source: Marcus, 2005

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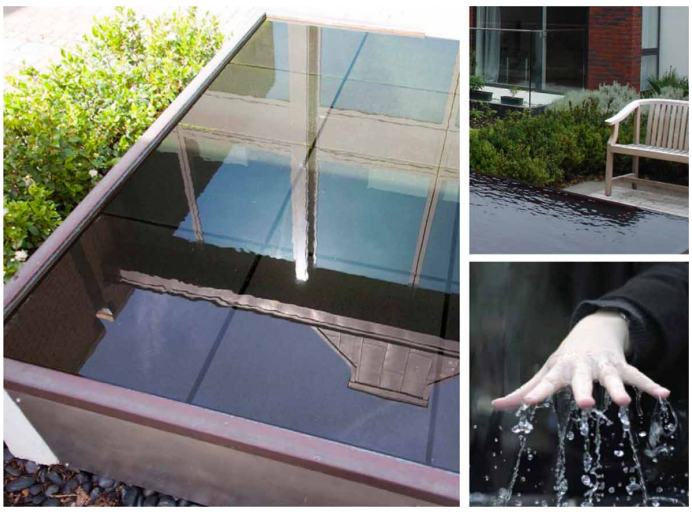
Paving

For outdoor areas, paved surfaces are the most suitable; they should have fine texture, help resist slipping, and not create a glare when reflecting light (this is an important consideration for older patients); and there should also be enough space for walkers and wheelchairs to pass. The aesthetics of paved surfaces plays a significant role in shaping the emotional response to a space, so their color, texture and other characteristics should be taken into account in the design process (Wells, 2014).

Water

Water features can have particular significance for Alzheimer's patients. In early, mild phases of the disease, it may play only a symbolic cognitive role, as its sound has a calming effect and it is aesthetically pleasant to see. However, in more advanced stages of cognitive decline, the patient may have a pre-cognitive, pleasurable aesthetic response to the sight of water, arising from deep memories; it has been suggested that this may be of genetic origin. In addition, the tactile experience of touching or dipping a hand in water can create a positive physical experience (Figure 5) (Wells, 2014).

Figure 5. Shallow reflective pools or bublers pose have the least risk for Alzheimer's
Source: PRP Landscape, 2013



Mount or Hill

Hills may also have therapeutic value as visual elements in gardens designed for Alzheimer's patients. Hills should be subtle, with a low gradient, and as different configurations of space, should help to define the flat and level areas of a garden. If they are near a seating area, hills may serve as metaphors of both places of refuge and areas to wander in.

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Sitting Areas

Garden furniture for Alzheimer's patients should be designed so it is heavy and stable; a seating height of 45cm is recommended. There should be alternative types of seating areas at various places: one important area is on the way out from the building into the garden; others should be situated near entrances, areas where activities are done, on routes that patients typically take, and also in quiet, private areas. (Cohen & Weisman, 1991).

Artwork

Studies on patients being treated for psychiatric problems as well as others not undergoing such treatment have shown that their being exposed to abstract art causes negative emotions and stress, and may lead to aggressive behavior. For this reason, artworks used should be representational in character (Ulrich, Bogren & Lundin, 2012).

Planting

Different types of vegetation should be considered when designing outdoor areas for Alzheimer's patients. Elderly patients may slip on fallen leaves, so the most appropriate choices would be non-deciduous plants, and plants whose fallen leaves will not be slippery or slide on walking surfaces. Trees and bushes give a structure to a garden, and the movement of tree branches and leaves can express aspects of climate such as the strength of the wind, and attract patients' interest. Choosing vegetation, including flowering plants, that show seasonal changes in color, will continually provide a diverse and interesting environment; plants that are visited by insects, birds and other animals will add to the interest.

Patients may be stimulated to recall past memories in gardens featuring herbs, vegetables and traditional flowers; such elements have pleasurable and calming effects (Wright, 2014). Care should be taken, however, that non-toxic plants are used, since patients in the advanced stages of Alzheimer's often put things in their mouths. Herbs such as lavender and other aromatic plants release their odor when they are touched (Kennard, 2006); and research has shown that olfactory stimulation, such as the scent of flowers, can have an immediate positive effect on the psychological state of people patients in the advanced stages of Alzheimer's (Witucki & İwibell, 1997).

Patients have easy access to plants which are in elevated planters or containers that can be moved; this enables them to interact by seeing, touching or smelling the plants (Figure 6). The "elevated garden" is especially useful for people who cannot bend easily or are confined to a wheelchair. Containers should be set about 6-85cm above the ground, and to make access easier, the arms of chairs or wheelchairs should be able to fit under them (Dixon, 2002).

Wayfinding

Depending on how advanced the symptoms of dementia are, a patient may have difficulties with short-term memory recall. This often leads to problems in direction-finding, because memories of paths or routes travelled recently may be forgotten. Because of this, design for people with dementia should emphasize "wayfinding." Research shows that these individuals perform poorly in wayfinding tasks even in spaces they are familiar with, but do pay the same attention as those who are not affected by the

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Figure 6. Portland Memory Garden, Portland, OR
Source: ERIN Research Inc., 2010

disorder, to similar architectural features and wayfinding features such as signage (Sheehan, Burton & Lynne, 2006). Athough some care facilities for patients with impaired memory focus on other factors, it seems clear that wayfinding should be prioritized as the most important aim in designing environments for Alzheimer's patients (Bissell, 2010). Outdoor areas in particular should have clear points of reference and landmarks – flowerbeds, water features, sculptures, etc. – so the patients can locate themselves (Nord, 2004).

Signage

Signs help patients to orient themselves, and indicate their present location as well as possible destinations that can serve as meaningful goals (Clayton, 2012). The fonts used on signs should be simple, large, and contrasted with the background, so as to be read clearly, particularly by older patients whose eyesight may be weak.

Lighting

Gardens should be accessible to patients as much as possible, and lighting makes them available in the evenings (Figure 7). Good lighting makes patients feel safer, and since they can see others, this creates an informal interaction which also helps staff to monitor other patients (McBride, 1999). Lighting can also be used for effect or to dramatize certain features of the garden so they are visible both from the garden and inside the building (Dixon, 2002). Typical problems encountered with lighting are either that there is not enough, so the surroundings become even darker; that it is uneven, so it creates shadows that may be frightening; that it may be too strong, so it creates a glare; or that it is insufficent to provide safety and security in transition areas (Brawley, 2001).

Personal Places

Patients in Alzheimer's care facilities see a lot of each other, so they need spaces where they can be on their own, away from social pressure; in this respect they are no different from anyone else. For this purpose, individual spaces can be made available in the garden (Ziesel, 2003).

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Figure 7. Illuminated outdoor areas are particularly important for residents experiencing acute sensitivity to sunlight
Source: PRP Landscape, 2013

Social Space

While time alone is a necessary requirement for Alzheimer's patients, social interaction is no less important, as it contributes to well-being and helps individuals to function in daily life; it is thus crucial that patients interact with others, be it other patients, or staff, or relatives (Figure 8) (Dixon, 2002). Thus two or more common spaces should be available where patients can alleviate the boredom and agitation that might result from their being alone (Ziesel, 2003). Engaging in outdoor physical activities with others contributes to psychosocial well-being, and also encourages commitment to these activities. There are various possibilities for social spaces: these may be intimate areas for two people, or areas where groups of different sizes can meet. Clusters of tables and chairs encourage spontaneous interactions; a chair by a window with a view of a bird feeder, for example, can motivate a patient to engage in bird watching (Alzheimer's Association, 2007).

Figure 8. Movable seating for converstaion
Source: Marcus, 2008

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Healing Gardens

The ideal Alzheimer's care facility would have a safe outdoor area next to the residential building; however, in practice this is not always the case, although the importance of such a feature is unquestionable. As these patients live from day to day, the freedom of being outside and relaxing is an essential part of life; but the healing garden, beyond this, serves therapeutic functions and as a refuge.

Potential Risks in the Alzheimer's Garden

Designers of gardens for Alzheimer's patients should follow principles that maximize their benefit to the patients, and also take into account potential risks or dangers that may be encountered.

For example, for patients who tend to put flowers and other plant material or soil in their mouths, types of activities other than gardening should be considered. In selecting vegetation for the garden, it should be remembered that many bulbs and plants, like the philodendron or, for instance, the leaves of the tomato plant, are toxic; and chemical pesticides are used on plants sold by garden centers. If ingested, particularly by the elderly, these may affect their health or cause problems if they interact with medications. Organically grown plants would thus seem to be the safest option.

In terms of the environment to be created, potential hazards include rough, uneven or slippery surfaces; glare produced by the materials used; patients' experiencing problems of balance caused by visually confusing patterns and dark colors; and unsafe transitions between different areas (Brawley, 2001). In addition to these risks of falling, patients may also incur injury when using gardening tools that are not adapted to their safety needs. Patients in advanced stages of Alzheimer's will forget to care for their adopted plants, so for practical reasons, the personal "pet plant" may have to be abandoned in favor of a community garden.

Finally, exposure to too much sunlight or heat can negatively affect elderly patients and others taking some medications; and dehydration may also be a problem. It should therefore be ensured that shaded and sitting areas are available, that patients have readily acccessible drinking water, and that activities in the garden are monitored constantly (Bruce, 2014).

CONCLUSION

Well-designed landscaped gardens can meet many of the needs of Alzheimer's patients; these include design elements such as unobtrusive monitoring systems; handrails, ramps, steps and rest areas; a simple looped pathway, clear signage, and landmark features to facilitate way-finding; lighting elements to accentuate landscape features and encourage use of the garden throughout the day; dark or tinted walking surfaces that do not create glare and are not slippery; non-toxic and accessible vegetation that evokes pleasant memories, other vegetation that evokes seasonal changes and attracts fauna; and seating and recreational areas that provide opportunities for both solitude and socialization.

For Alzheimer's patients there are significant therapeutic benefits to be gained from such purpose-designed environmental landscapes, which also help reduce the load of staff at care facilities. Such landscapes provide calming views and experiences of nature, help lower stress and tension, offer opportunities for exercise and physical activity, stimulate patients to remember positive events and situations, create opportunities and spaces both for escaping or having time alone and for socialization; and in contrast

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to the stress of clinical spaces, give patients a feeling of safety, security and control in a familiar setting (Ulrich at all., 2004). A well-designed outdoor environment has a positive effect on these patients' thought processes and behaviors; it enables them to live actively and independently, and maintain their sense of wellbeing and quality of life.

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KEY TERMS AND DEFINITIONS

Alzheimer's Disease: A degenerative disease of the brain that causes people to forget things, including the people in their lives, and which eventually leads to death.

Behavioral Measure: Overt actions and reactions that are observed and recorded, exclusive of self-reported behavior.

Environment Landscape: The physical and interpersonal surroundings landscape that can affect mood and behavior in people with Alzheimer's.

Environmental Perception: The way in which an individual perceives the environment; the process of evaluating and storing information received about the environment.

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Chapter 29
Monitoring System for Persons With Alzheimer's Disease via Video-Object Tracking

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ABSTRACT

This article presents a framework for a food intake monitoring system intended for use with persons with Alzheimer's disease and other dementias. Alzheimer's disease has a significant impact on the individual's ability to perform their daily activities including eating. Providing assistance with feeding is a major challenge for caregivers, including a significant time commitment. We present a vision-based system that tracks moving objects, such as the hand, using a combined optical flow and skin region detection algorithms. Skin detection is implemented using two different methods. Hue, saturation, and value (HSV) color space, which is on separation of the illuminance component from chrominance one as the first method and skin color information is extracted from subject's face detected using Viola-Johns algorithm for the second method. Once face and other moving skin regions are detected, bounding boxes are created and used to track all moving regions over the video frames, recognizing eating behavior or the lack of it. Based on experimental results the proposed method using optical flow and skin regions segmentation using HSV color detects the hand to mouth eating motion with 92.12% accuracy. The optical flow and skin region segmentation based on face color information achieves a higher accuracy of 94.29%.

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INTRODUCTION

Globally 50 million people are diagnosed with Alzheimer's disease. This number is expected to rise to 152 million by 2050. During this period, the number of affected people age 65 or older in the US will expand from 5.8 to 13.8 million (Alzheimer's Disease, 2019; Women contribute, 2018). One of each 10 people of the age of 65 or older has Alzheimer's disease. Every 65 seconds a person in the United States develops Alzheimer's disease. In 2018, the cost for Alzheimer's and dementia's care was estimated to be $1 trillion globally and $290 billion in the US. In 2050 the cost is projected to be more than 1.1 trillion (World Alzheimer Report 2018; Alzheimer's Disease, 2019).

One of the most significant challenges for persons with the disease relates to nutritional intake. Overall, 81.4% of Alzheimer's patients showed eating disorder compared to 26.7% in normal elderly people (Kai et al., 2015). Individuals with cognitive impairments may forget to eat and equally problematic, may not recognize how to eat. The use of simple utensils, such as fork, may be not understood, thus requiring intensive assistance from a family or staff member caregiver. Persons with Alzheimer's are considered at high risk for malnutrition resulting from decreased appetite, attention deficits and an increasing inability to recognize food.

Research has documented that care providers are most heavily involved in feeding (Vaingankar et al., 2016). Finding effective ways to support these feeding activities is essential because malnutrition is linked to premature disability and diminished quality of life (Rasheed & Woods, 2013). One approach for improving nutritional intake among persons with Alzheimer's is to provide feeding assistance. However, providing the appropriate level of feeding assistance can be complicated. Johanssen and colleagues' qualitative study (Johansson, Christensson, & Sidenvall, 2011) illustrated that persons with Alzheimer's, particularly in the early stages, have a desire to be as independent as long as possible in eating. Excessive assistance with feeding when unnecessary may lead to learned helplessness. Independence in eating may be preserved longer with interventions that support both the person with dementia and care provider. To this end, assistive technologies may play an important role. A recent systematic review indicates that assistive technologies have the potential to reduce care provider burden, reduce levels of assistance and increase the independence of the user (Marasinghe, 2016).

In this paper, we present a food intake monitoring system with the potential to help persons with Alzheimer's to eat independently. In addition to the monitoring function, our system is also designed to prompt the participants to continue eating using pre-recorded audio prompts or videos from caregivers.

BACKGROUND

Food intake detection methods have been also studied by other researchers. Some of these methods used motion sensors for food intake monitoring, like the work presented in (Farooq & Sazonov, 2016; Doulah et al., 2017; Mendi et al., 2013; Dong & Biswas, 2016; Kalantarin et al., 2015). Swallowing and chewing sounds are features that can be also used effectively to detect an eating event. These sounds can be collected using microphones usually mounted on subject's body close to the mouth. Some researchers worked on this topic like the work presented in (Farooq et al., 2014; Kalantarian et al., 2016; Turan & Erzin, 2018; Shengjie et al., 2017; Makeyev et al., 2017; Paßler et al., 2012). These sensors are usually

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attached to subject's body, this is not applicable for some cases. People with Alzheimer's for instance may simply forget and remove these sensors since they may perceive them as obtrusive. Therefore, designing and using a vision-based monitoring system could be the best scenario.

Vision-based food intake monitoring has been also proposed in (Al-Anssari & Abdel-Qader, 2016) for Alzheimer's patients by detecting skin regions using a combination of YCbCr and YIQ color spaces. The tracking was performed using controlled bounding boxes and reported accuracy at 90.82%. Gao et al. also proposed a food intake monitoring system based on hidden Markov model (HMM) to track certain features such as the physical distance between moving objects and reported 77% accuracy (Gao, Hauptmann, Bharucha, & Wactlar, 2004). Villalobos et al. (2011) designed a platform for calculating the number of calories in the food aimed to reduce obesity. In this study, they asked participants to take pictures of their food before eating using a smart phone and their thumbs as size calibration reference to be able to determine the size of the food portions in the plate and estimating caloric intake. Similarly, Sun et al. (2008) proposed a method for food intake monitoring by collecting information about people nutrition in their daily life. In their work, a card is used to determine portion size for food size calibration and determine food quantity. The Microsoft Kinect (MSK) sensor was developed by Cunhaa et. al. (2014) to monitor food intake for older persons. The participant's head and hands were detected and recognized from the seated skeleton imported from the MSKinect.

Optical flow has been applied in many of the computer vision applications like object tracking, motion segmentation, motion estimation, and image compression (Stanisavljevic, Kalafatic, & Ribaric, 2000). The combination of the optical flow algorithm with skin color detection has been proposed by others like Lyu, Yang, and Ru (2015) developed a gesture motion detection algorithm for human-computer interaction based on optical flow and the skin regions segmentation based on skin color. They used Lucas-Kanade optical flow method and the ellipse skin model based on YCbCr color space for the gesture motion detection. Optical flow motion vectors are used to determine the direction of the moving hand. In every four consecutive frames, optical flow Lucas-Kanade method is implemented to determine the direction of movement on the first and second frames, next on the third and fourth frames, if the directions are consistent, then hand movement direction is detected.

Similarly, Ali and Morris (2011) combined skin color detection with optical flow algorithm for the detection and the tracking of skin regions. This work was proposed for gesture recognition. Normalized red and green color spaces were used for skin regions detection and these results are combined with optical flow information to determine moving skin regions. For skin regions tracking, Bayesian framework was used.

Also, Park and Lee (2011) use optical flow algorithm combined with skin regions detection based on YCbCr color model in hand posture recognition. For hand gesture recognition they used Fourier descriptor to describe hand features, Principal Component Analysis (PCA) for hand features extraction, and Hidden Markov Model (HMM) to examine the extracted feature and determine whether this is a hand gesture or not. In this work, we present a method for food intake monitoring aiming for higher accuracy and system's reliability by combining skin detection and optical flow measurements with the bounding box tracking algorithm and the capability of prompting the user in case of lack of eating. Prompting can be achieved in a variety of techniques based on experts and family input.

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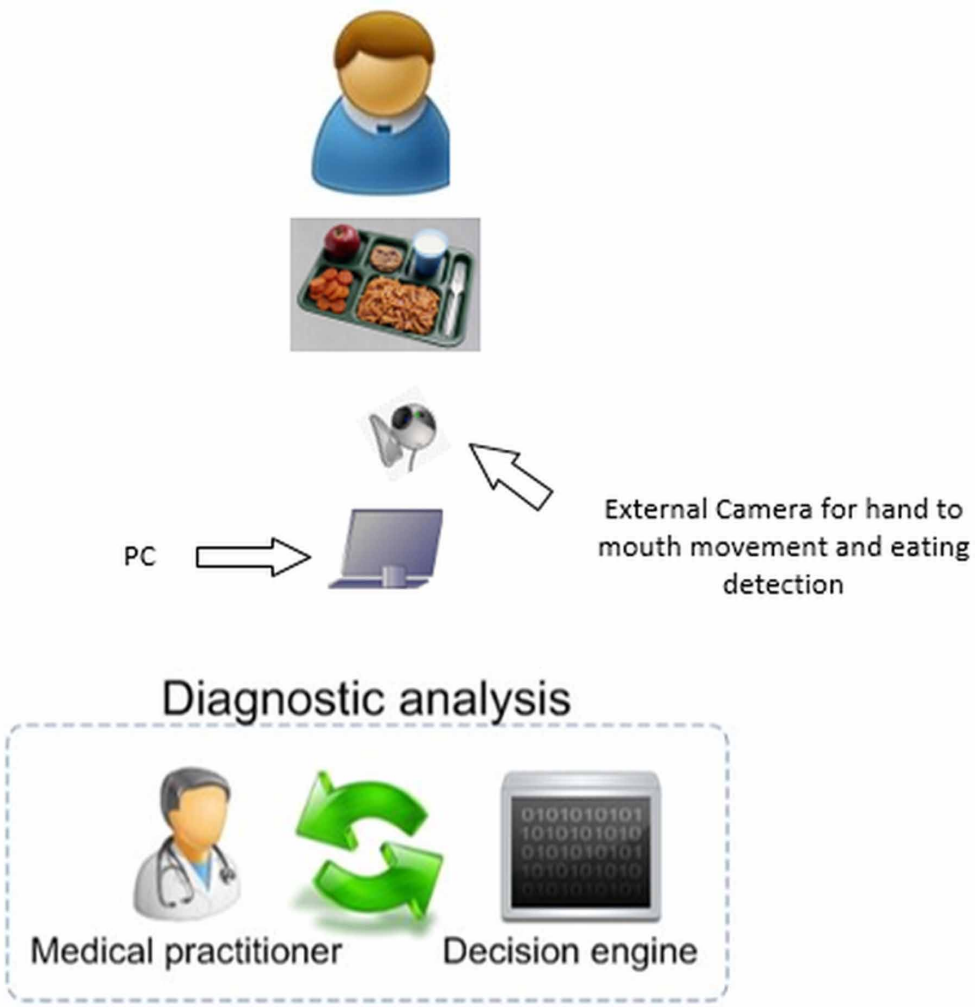
Figure 1. Schematic for the food intake monitoring proposed system



PROPOSED FRAMEWORK SYSTEM

The purpose of this framework is to develop an automated alert system to detect food intake activity for people with Alzheimer's disease. The system will monitor food intake behavior of the participants, using skin detection and optical flow. This information is valuable to the care provider and lays the groundwork for a related prompting function. Figure 1 represent the schematic for the proposed framework. To be able to track the hand movement in real time and decide whether the participant is eating once the system is turned on (when the food is served), we need to detect and segment the hands accurately. We detect skin regions using two different methods, one is based on HSV color space and the second is based on color information extracted from subject's detected face.

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Skin Region Segmentation

Skin regions segmentation based on skin color is a very common method used in many applications such as face detection, hand gesture recognition, and human computer interaction. This method has the advantage of being invariant to scale and rotation; however, changes in illumination and the cluttered background are the main factors that affect its performance (Kakumanu, Makrogiannis, & Bourbakis, 2007).

To enhance skin detection, several color models such as HSV, YCbCr, and CIElap have been used rather than using RGB color space, which is very sensitive to illumination changes. The main advantage of these models is that the illumination component is separated from the chrominance component and so skin regions can be processed independently from illumination (Kakumanu et al., 2007). We proposed two methods for skin region segmentation, the first method is based on the HSV color space while the second is based on the color information extracted from detected face. A comparison on the performance between them is presented in the experimental results section.

Method 1: Skin Segmentation Based on HSV Color Space (SS-HSV)

In this work, HSV color model is used for the skin regions segmentation in which hue and saturation components are separated from the illumination component. The conversion from RGB color space to HSV color space is performed using Equations (1) to (3) (Liu & Peng, 2010):

$$H = \begin{cases} \left(6 + \dfrac{G-B}{MAX-MIN}\right) * 60^{\circ}, & if \quad R = MAX \\ \left(2 + \dfrac{B-R}{MAX-MIN}\right) * 60^{\circ}, & if \quad G = MAX \\ \left(4 + \dfrac{R-G}{MAX-MIN}\right) * 60^{\circ}, & if \quad B = MAX \end{cases} \tag{1}$$

$$S = MAX - MIN \tag{2}$$

$$V = MAX \tag{3}$$

where MAX = maximum(R,G,B) and MIN = minimum(R,G,B).

Skin regions segmentation based on the HSV color model is done as follow (Sawicki & Miziolek, 2015; Chen, Wang, Jiang, & Li, 2016), where a pixel $P(x,y)$ is considered to be a skin pixel if the hue and the saturation values for this pixel are within the range:

$$P\left(x,y\right) = \begin{cases} skin & 0^{\circ} \le H\left(x,y\right) \le 50^{\circ} \; AND \\ & 0.2 \le S\left(x,y\right) \le 0.69 \\ non-skin & otherwise \end{cases} \tag{4}$$

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Method 2: Skin Segmentation Based on Face Color Information (SS-FCI)

Face detection based on the Viola-Jones algorithm (Viola & Jones, 2001) is used to extract skin color information from the face and use it to develop a color model to detect other skin regions specifically the hands. After face detection, K-mean clustering algorithm is implemented on the face region to cluster the pixels based on their color as shown in Figure 2. Three clustered regions are shown in Figure 2 (b), (c), and (d) respectively. The region with the highest number of ON pixels, nonblack-color pixels, is selected as the sample of the face skin, in this example Figure 2 (d). Three-color vectors for red (Rv), green (Gv), and blue (Bv) will be then generated from this region and used for color filter by first generate the histogram for each color vector, the mean for each color vector histogram is calculated and used to determine the minimum and maximum values for each color vector where the minimum is the lowest value above the mean, while the maximum is the maximum value for the color component. The three color components for each pixel is tested by the designed color filter as in Equation (5). Figure 3 is an example of the highest number of ON pixels, color components histograms, and the mean value for each of the color components:

$$P\left(x,y\right)=\begin{cases} & Rmin\le R\left(x,y\right)\le Rmax\,AND \\ skin & Gmin\le G\left(x,y\right)\le Gmax\,AND \\ & Bmin\le B\left(x,y\right)\le Bmax \\ non-skin & otherwise \end{cases} \tag{5}$$

Detection of Moving Objects

Optical flow is the estimation of the apparent motion in consecutive video images, it is the measure of the velocity for each pixel in the image (Chen & Wu, 2015).

The optical flow method allows for estimating of the motion between two frames extracted from a onsistency assumption, which is:

$$I\left(x,y,t\right)=I\left(x+\Delta x,y+\Delta y,t+\Delta t\right) \tag{6}$$

where *I* is the image intensity and Δx and Δy are the changes in pixel location between the two frames (Horn & Schunk, 1981). From Equation 6, we can write:

$$I_x u+I_y v=-I_t \tag{7}$$

where $u=\dfrac{\partial x}{\partial t}$ and $v=\dfrac{\partial y}{\partial t}$ are the change in *x* and *y* locations with respect to time, respectively. Equation 7 has two unknowns and cannot be solved; therefore, other constraints were proposed to solve it. Horn and Schunck (1981) proposed to use the neighbouring regions information which resulted in the following iterative scheme:

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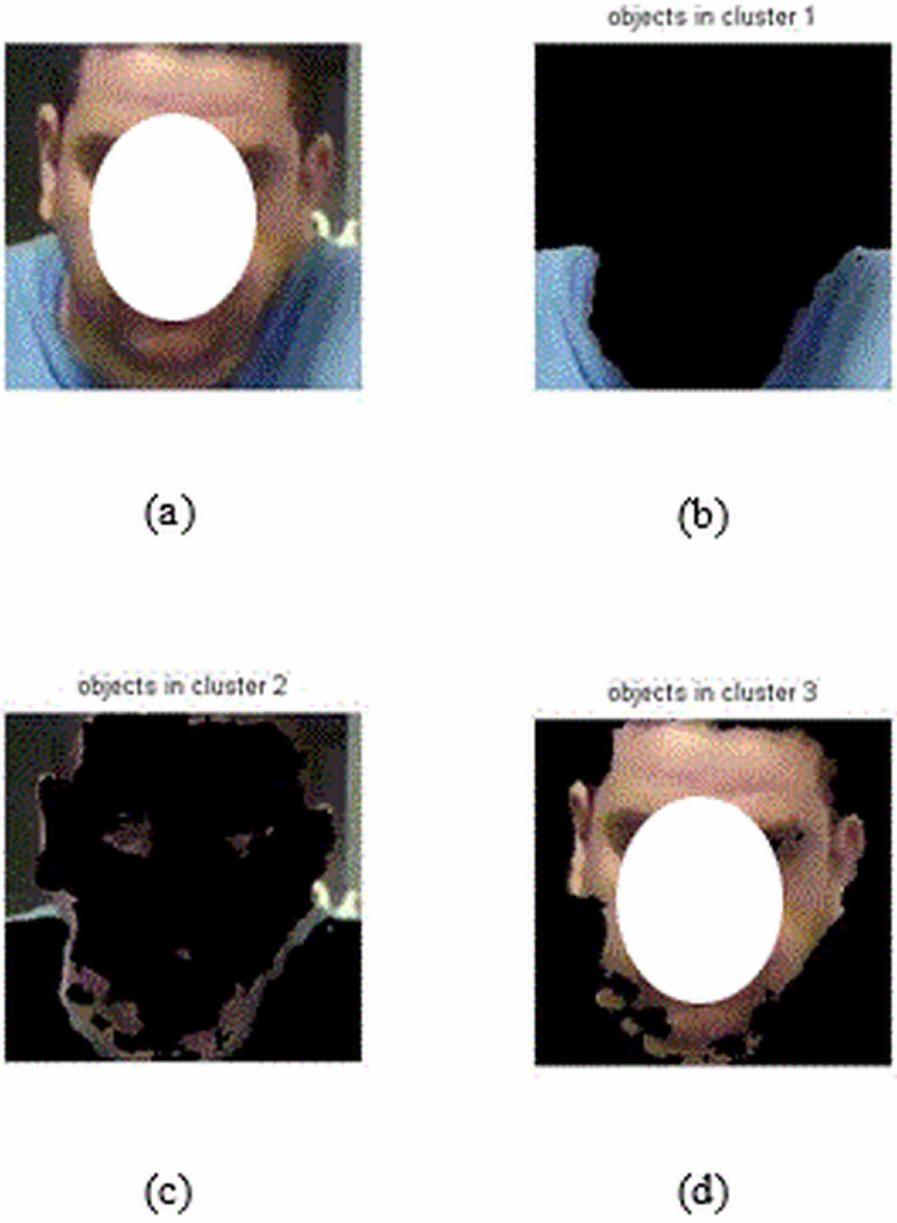
$$u^{k+1} = \overline{u}^k - \frac{I_x\left(I_x\overline{u}^k + I_y\overline{v}^k + I_t\right)}{\propto^2 + I_x^2 + I_y^2} \tag{8}$$

$$v^{k+1} = \overline{v}^k - \frac{I_y\left(I_x\overline{u}^k + I_y\overline{v}^k + I_t\right)}{\propto^2 + I_x^2 + I_y^2} \tag{9}$$

Figure 2. (a) is the detected face, (b), (c), and (d) are color based clustered regions using K-mean clustering



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Information Fusion

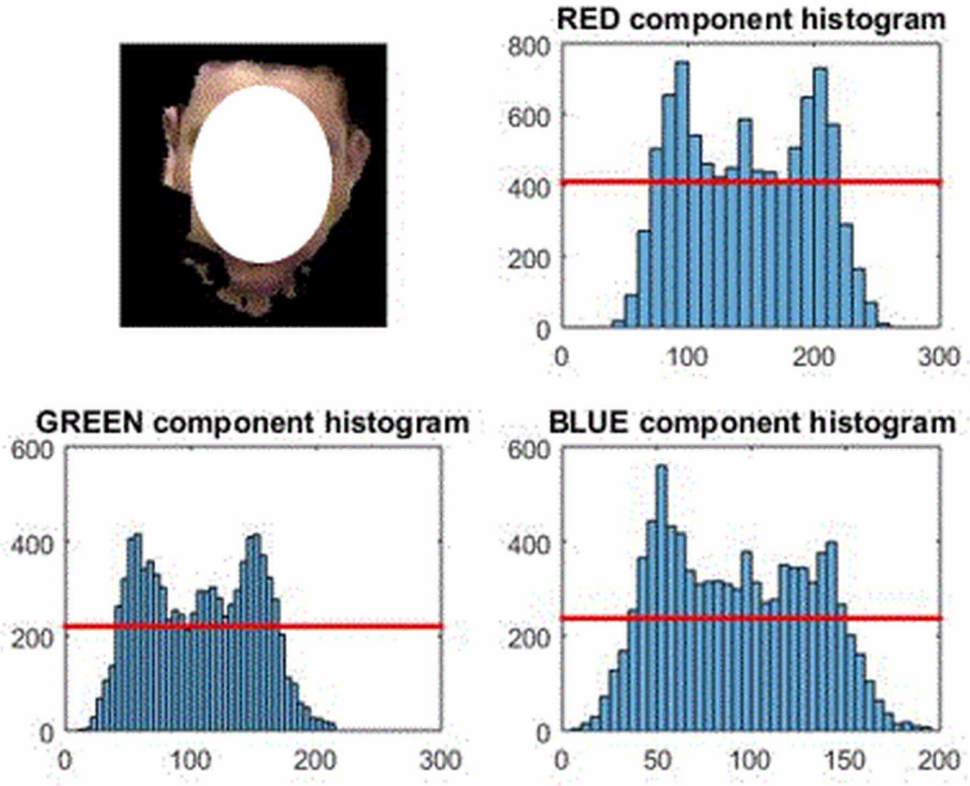
Skin regions segmentation based on either SS-HSV or SS-FCI is not enough by itself because of the skin-like color objects. Similarly, motion information can detect all the moving objects into video frames including non-skin moving objects. We integrate motion detection with the regions of skin color. The benefit of this fusion is to detect moving skin regions and discard other false detected regions. Each pixel of the input frame will be classified as a moving skin-color pixel or not as shown in Equation (10):

$$P\left(x,y\right)=\begin{cases}1 & \left(P\left(x,y\right)is\,skin\right)AND\ \left(P\left(x,y\right)is\,moving\right)\\ 0 & otherwise\end{cases} \tag{10}$$

Figure 4 shows the proposed method components. The systems can be described as follows:

- Subject's face detection using Viola-Jones method;
- Optical flow algorithm is then applied to detect moving objects in each frame;
- Apply thresholding, and morphological operator to the image to define moving object's blobs;
- Skin regions segmentation is applied using either SS-HSV or SS-FCI methods;
- Bounding boxes are created around moving skin color objects;
- Eating event tracking procedure is then initiated to detect the eating or the lack of it.

Figure 3. Example of the selection of the minimum and maximum values for each of the color components



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The tracking procedure for eating, which can be custom design, occurs when a certain sequence of hand movements is detected. Figure 5 shows an example of the eating process tracking schematic description, where the cyan circle is the face, the red box is the hand, the large green box is denoted by (fbext) which is bigger than the detected face bounding box (fb), where fb is a vector contains face bounding box coordinates:

fb = (top right corner y coordinate, top right corner x coordinate, width of face bounding box, height of face bounding box)

$$fbext = [fb(1,1)-\alpha, fb(1,2)- \alpha, fb(1,3)+ \beta, fb(1,4)+ \beta] \quad (11)$$

for frame size of 192*256, α and β are chosen to be 10 and 15 respectively, which represent how many pixels, wider and higher, fbext is bigger than fb. The blue line is denoted by the tracking reference line (cntln) which is located below the bottom line of the face bounding box, the location of this line is determined using the following equation:

$$cntln = fb(1,2) + 2*fb(1,4)-\gamma \quad (12)$$

γ is chosen to be 18 pixels. The difference between the cntln and the x coordinate of the top bounding box in the current frame is determined and denoted by (dist):

$$dist(nFrames) = cntln\text{-}centroids(1,2) \quad (13)$$

where centroids refer to the array of the centroids data of the bounding boxes, nFrames is the number of the current frame, and centroids (1,2) returns the height of the first bounding box. The overlap between the fbext and the top bounding box is determined in each frame. Eating process is detected when the following sequence takes place:

- The top box, which is usually the hand, is first located below the tracking reference line;
- The box movement is recognized, as moving up crossing the cntln;
- Then, check if there is an overlap between the top bounding box and the fbext;
- Finally, this bounding box moves back below the cntln.

EXPERIMENTAL RESULTS

The proposed method was implemented using a set of 27 videos. Some videos were recoded in different locations with different subjects and under different conditions of activity and persons. Additionally, the MOBISERV-AIIA dataset (Iosifidis, Marami, Tefas, Pitas, & Lyroudia, 2015) was used in which participates were recorded while they were eating, drinking, talking, and reading a book. Other variations of specific interest, naturally, is in clothing, which were considered such as wearing long and short sleeves. Eating and drinking events were captured with a variety of scenarios such as consuming hot and cold drinks, with and without straws, use of a fork, a spoon, and using each hand separately or both hands.

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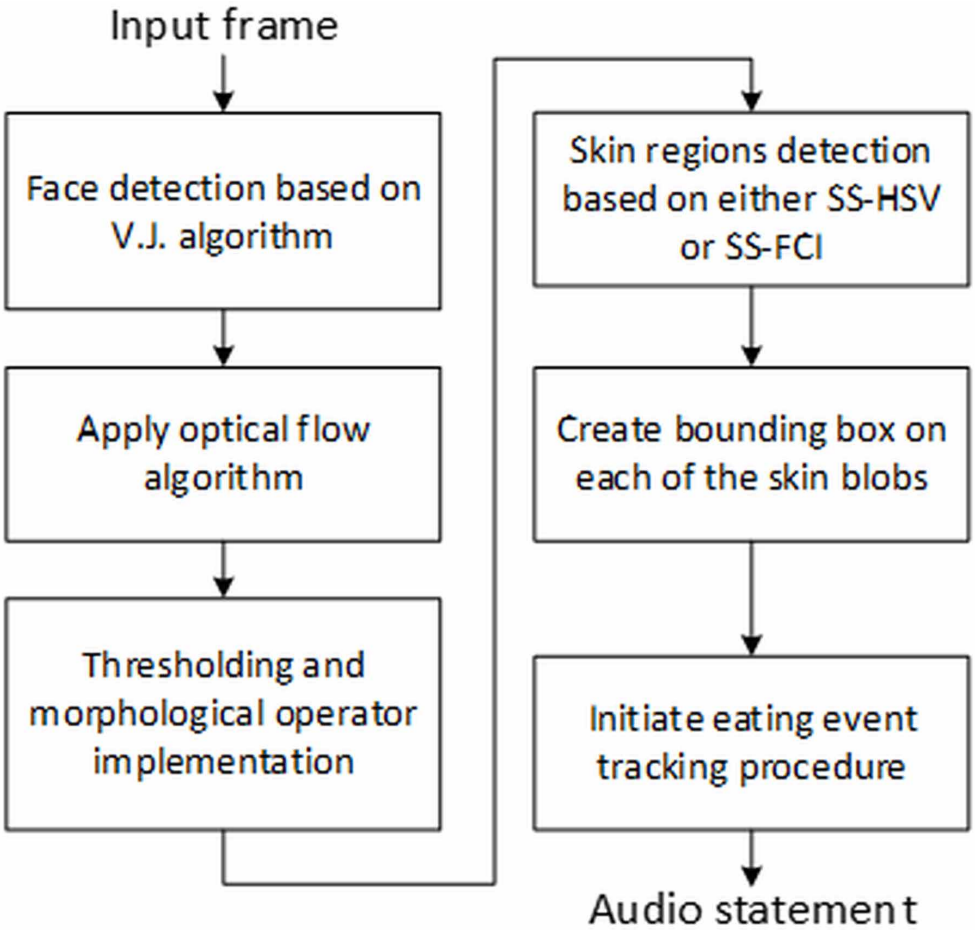
Skin segmentation using SS-HSV method is shown in Figure 6 where skin regions are detected based on the HSV color space. However, pixels and objects with skin-like color can affect the performance of HSV color-based skin detection algorithm as shown in Figure 7.

Alternatively, SS-FCI skin segmentation method based on color information extracted from detected face also performs well as shown in Figure 8. Similar to SS-HSV, skin-like color objects are challenging this method.

Optical flow is a well-known method for moving object detection. Figure 9 is an example of the implementation of optical flow algorithm on a video sequence for a person who is dinning. Unfortunately, optical flow alone resulted in poor regions detection since optical flow is very sensitive to noise. To enhance our results, we proposed to employ morphological operators to the resulting regions to better define moving-object blobs and thus enhance the results. Bounding boxes are created around each of the moving objects, as shown in Figure 9 (c).

The bounding boxes might include the hands, the face, and other parts from the background which makes it difficult to track the hands for eating purposes. Therefore, we present the combination of the segmented skin regions and the optical flow segmented blobs to allow for the detection of the moving skin regions only, specially the hands.

Figure 4. Proposed food intake monitoring system components



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The combination of the optical flow algorithm and skin regions detection based on SS-HSV and SS-FCI methods show a good moving skin regions detection as shown in Figure 10. SS-HSV method was implemented on the recorded videos to detect eating processes, the successful detection rate was high at 92.12%, wrong detections occurred when subject's face is moving a lot and there were more than one bounding box resulting from this movement, and in the case of short sleeves.

The combination of optical flow and our hand localization proposed method based on face color also shows good results with 94.29% success rate. Wrong detection occurs mainly because sometimes the hand illumination became inconsistent when the hand is moving in addition to the case of short sleeves where hand segmented region will be bigger and affected detection rate.

Table 1, we present a summary of the results for the two proposed frameworks. In Figure 11, we show samples of the implementation of our proposed method to track the eating process for a person who is dining using spoon, bare hands, and drinking using a mug, eating events were successfully detected.

To make the system a user-friendly for the caregiver whether at a nursing home or at the family home, we have created a Graphical User Interface (GUI), which makes it easier to run, stop, change the display, and or listen to the audio messages. Also, this GUI provides the number of detected eating sequences and time consumed. Figure 12 includes some snapshots for this GUI. This will allow caregivers to have a food intake history recorded and used for analysis or share with the physician.

Figure 5. Proposed method for the tracking of an eating process illustration, (a) the hand is below the cntln, (b) the hand is crossing the cntln, (c) the hand is above the cntln and overlap occurred, and (d) the hand is going back down

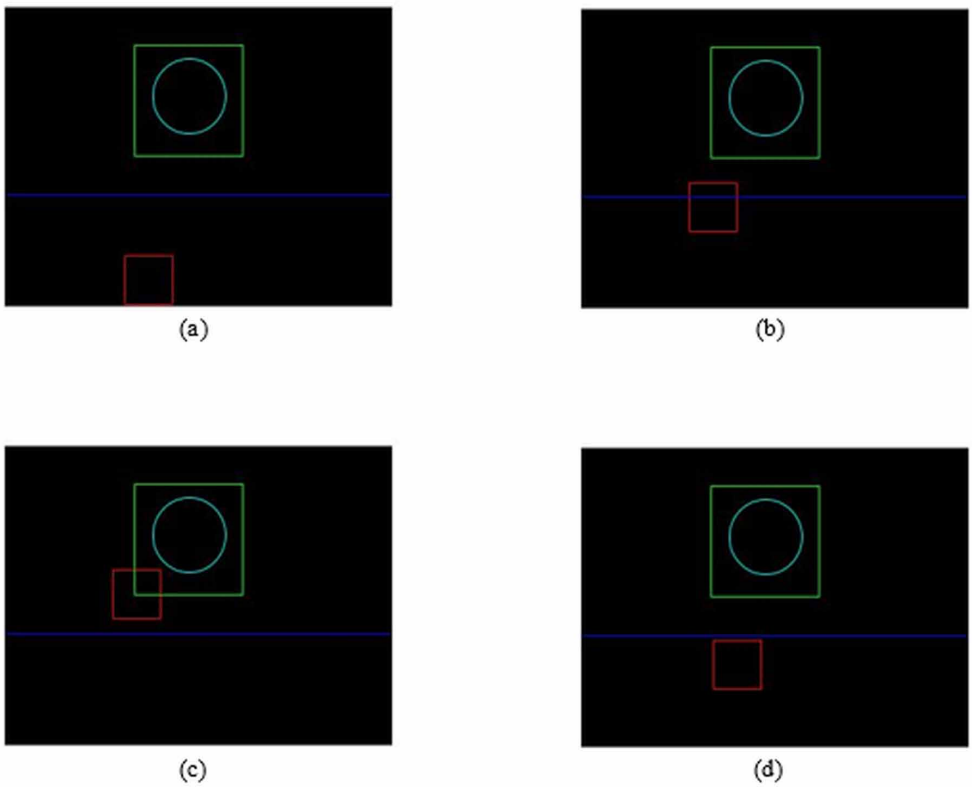

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Figure 6. (a) is the original image, and (b) is resulting image after HSV color-based skin regions detection

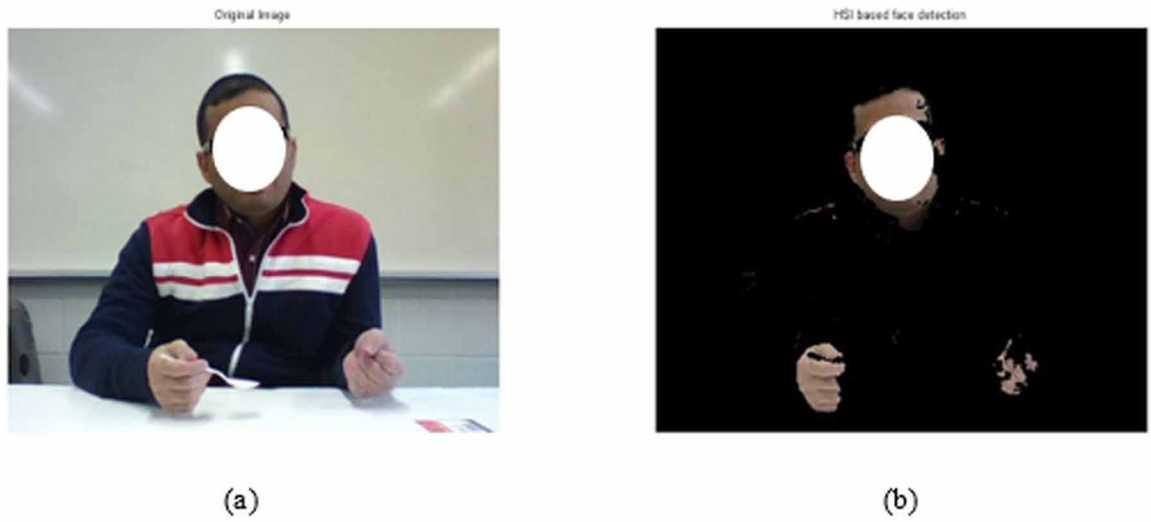

Figure 7. Left side images are original images while right side are resulting images after implementing SS-HSV method

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Figure 8. Left side images are original images while right side are resulting images after implementing SS-FCI method

Figure 9. (a) and (b) object flow representation, (c) bounding boxes created around moving objects based on optic flow algorithm

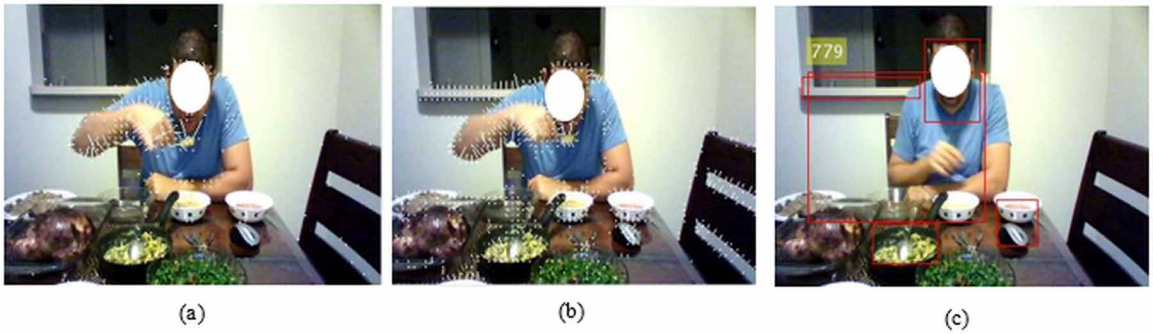

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Table 1. Implementation results summary

Implemented Method	No. of Processed Videos	No. of Processed Frames	No. of Success Detections	Missed and Wrong Detections	Recording Time (hh:mm:ss)	Success Rate
SS-HSV	27	147702	841	71	2:53:00	92.12%
SS-FCI			860	52		94.29%

Figure 10. Results from the combination of optical flow and skin detection showing successful moving hand detection methods

CONCLUSION

In this paper, we have presented a new algorithm for detecting and tracking food intake processes as a care instrument for persons with Alzheimer's disease or other types of dementia problems. Our method is based on detecting moving skin regions based on either skin regions detection using HSV color model, or based on detected face extracted color information, combined with optical flow algorithm. Specifically, the system hinges on face location, moving skin regions, and bounding boxes tracking. The experimental

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results show that the proposed methods can achieve an accuracy of 92.12%, with the hybrid system of optical flow and SS-HSV. A higher accuracy of 94.29% is achieved when combining optical flow and the SS-FCI method. Eating events were successfully detected and tracked using our proposed algorithm with a very low failure rate. Errors occur when wearing very short sleeves where hand segmented region is big and affected detection rate. This is being addressed in future work by including some hand shape features to enhance the hand localization and tracking.

The number of persons with Alzheimer's disease and other related dementias continue to increase rapidly. This growth, combined with severe workforce shortages to care for this population, present serious challenges. Our monitoring system can be used to track eating behavior with interaction plans that includes an audio-visual prompting feature in the future. This technology is a promising strategy for providing support to care providers and maintaining independence for persons with Alzheimer's disease and other dementias.

Figure 11. Samples of the eating process tracking showing successful eating event detection for a person who is dinning using bare hand and drinking using a mug

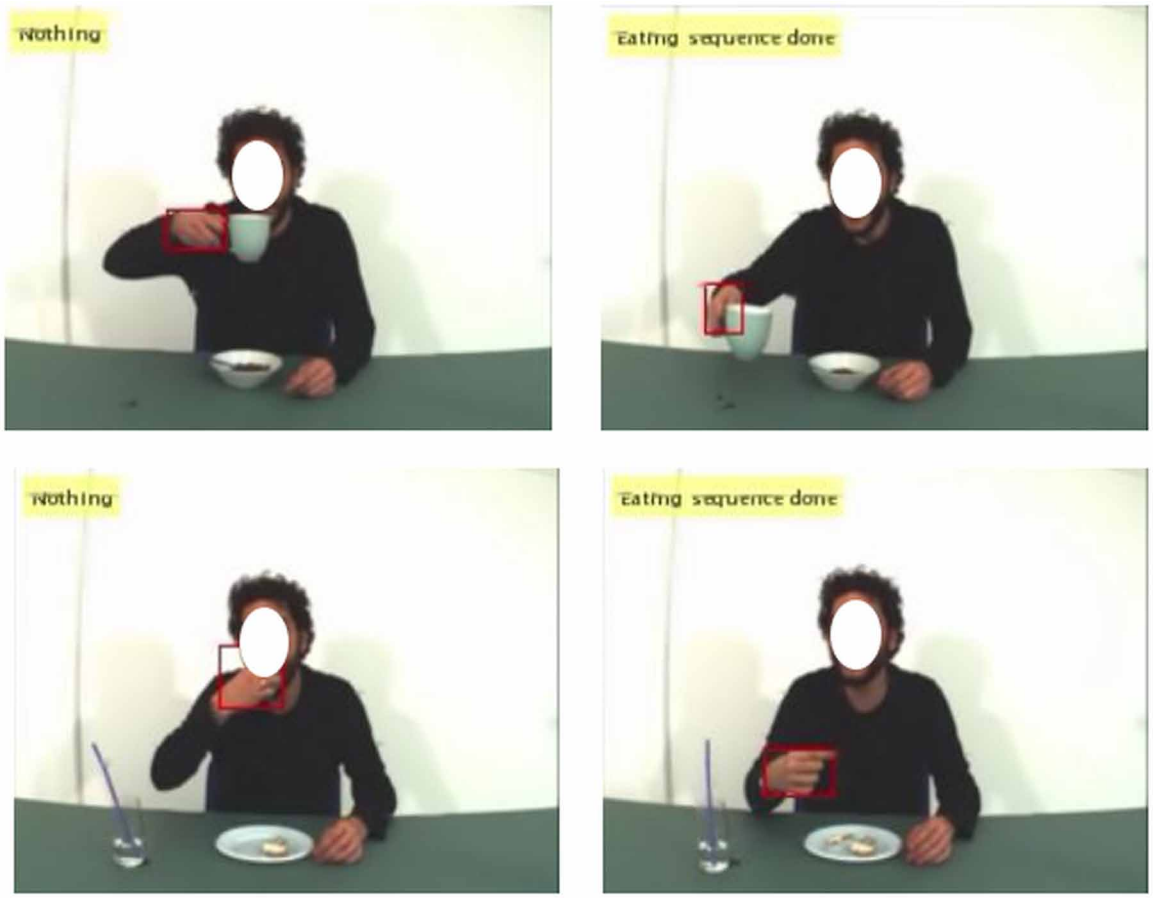

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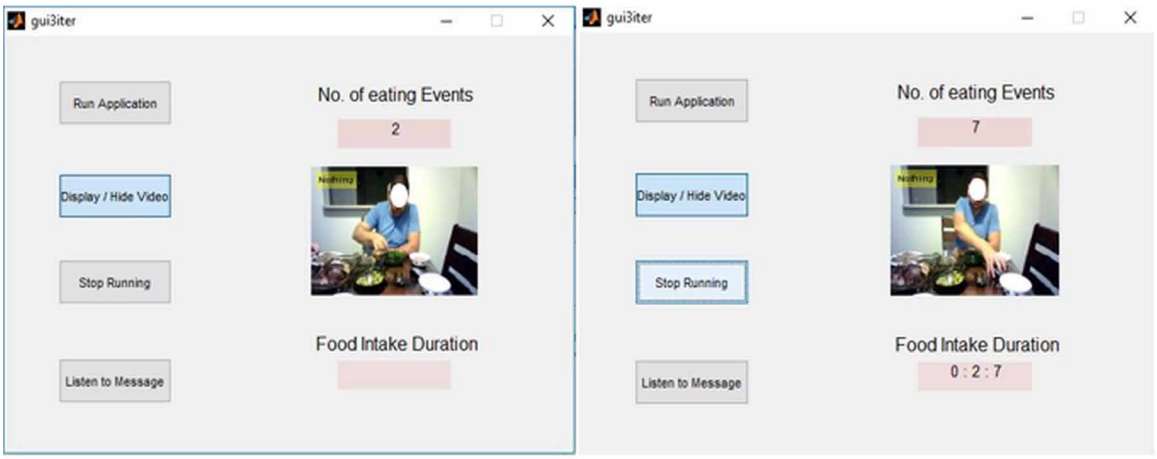
Figure 12. Snapshots from the GUI designed for the proposed method with interactive custom design choices to suit the needs of the patients and their care givers



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Women contribute over 58 billion hours globally per year to caring for people with dementia yet receive no wage. (2018). *Alzheimer's disease International*. Retrieved from https://www.alz.co.uk/media/180704

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Chapter 30
Assessment of Graph Metrics and Lateralization of Brain Connectivity in Progression of Alzheimer's Disease Using fMRI

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ABSTRACT

Alzheimer's disease (AD) is a progressive brain disorder which has a long preclinical phase. The beta-amyloid plaques and tangles in the brain are considered as the main pathological causes. Functional connectivity is typically examined in capturing brain network dynamics in AD. A definitive underconnectivity is observed in patients through the progressive stages of AD. Graph theoretic modeling approaches have been effective in understanding the brain dynamics. In this article, the brain connectivity patterns and the functional topology through the progression of Alzheimer's disease are analysed using resting state fMRI. The altered network topology is analysed by graphed theoretical measures and explains cognitive deficits caused by the progression of this disease. Results show that the functional topology is disrupted in the default mode network regions as the disease progresses in patients. Further, it is observed that there is a lack of left lateralization involving default mode network regions as the severity in AD increases.

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1. INTRODUCTION

Alzheimer's disease (AD) is a prominent cause of dementia that gradually eradicates memory and other cognitive functions (Ballard, Gauthier, Corbett, Brayne & Aarsland, 2011; Brookmeyer, Johnson, Ziegler-Graham & Arrighi, 2007). In its early stages, loss of, episodic memory, motor and language skills are recognized symptoms. Mild cognitive impairment (MCI) is the preliminary stage of AD, where the memory deterioration is greater than the normal cognitive subjects but not worse than the AD subjects. Also, the probability of becoming cognitively impaired increases with age (Huang, Matsushita, Kawagoe & Yasuda, 2016). As the disease progresses cognitive deficiency manifest leading to death eventually. Thus, Alzheimer's disease represents a most important public health apprehension and has been recognized as a research priority (Matthews, Filippini & Douaud, 2013; Carr, Goate, Phil & Morris, 1997).

Neuroimaging techniques provide promising potentials in diagnosis of Alzheimer's disease (AD) (Huang et al., 2009). The various imaging modalities in analysing AD include magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), positron emission tomography (PET), functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI). Structural imaging studies have shown that the specific brain regions such as hippocampus of people with AD shrink significantly as the disease progresses. The micro-anatomy integrity of white matter tracts has been analysed using DTI (Nestor, Scheltens & Hodges, 2004). MRS provides crucial information about AD pathology due to induced alteration in various neurochemical levels. MRS demonstrates changes in neurochemistry due to increased oxidative stress and altered lipid metabolism with the progression of the disease (Mandal, 2007). In order to identify brain genes related to Late-Onset Alzheimer's Disease (LOAD) Classification models have been identified with statistical accuracy (Coelho, Goertzel, Pennachin & Heward, 2009). Cognitive methods have been successful in investigation AD related genes using microarray data (Nishiwaki, Kanamori & Ohwada, 2017).

Functional magnetic resonance imaging (fMRI) procedure has been used to evaluate the functional integrity of brain networks involving memory regions through the stages of AD. It is a non-invasive practice that permits the indirect measurement of neuronal activity and imaging of activated cortical regions. Mathews measured function and connectivity using MRI, for classification of genetic aids to determine the neuropathology of AD (Matthews, Filippini & Douaud, 2013) fMRI has also been used to observe spontaneous inherent activity during rest and constant performance of a segmented two-back working memory test (Fransson, 2006).

The existence of spontaneous intrinsic low frequency BOLD (blood oxygen level dependent) signal fluctuations during rest have attracted attention in neuroscience community in recent times. An automated technique that helps in the diagnosis of Alzheimer's disease has been developed by Tripoliti (Tripoliti, Fotiadis, Argyropoulou & Manis, 2010). The method also supports in observing the progression of the disease. fMRI and multivariate analytic procedures have been employed to examine memory related fMRI activity among the normal ageing, mild cognitive impairment (MCI) and mild AD subjects. Independent component analysis showed exact memory related networks that activated or deactivated throughout an associate memory paradigm. As the cognitive task may not be effectively performed by AD patients; resting state fMRI study has been identified to be more feasible (Tie et al., 2014).

Resting state fMRI has been proved to be an appropriate approach for finding pathophysiological changes in more severely impaired patients (Wang et al, 2006). The changes in hippocampal connectivity have been scrutinized with the resting state fMRI. Studies compared mild AD with healthy age-matched controls. The functional connectivity between right hippocampus and set of regions like medial prefron-

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tal cortex (MPFC), ventral anterior cingulate cortex (vACC), right infero-temporal cortex, right cuneus extending into precuneus, left cuneus, right superior and middle temporal gyrus and posterior cingulate cortex (PCC) were found to be interrupted in AD (Wang et al, 2006). Much has not been reported on understanding progression of AD through each stage after its onset.

Default-mode network (DMN) regions (posterior cingulate cortex, medial prefrontal cortex, and lateral temporal parietal junction, among other areas) in brain gets activated when the individual is idle and at wakeful rest. DMN regions actively distinguish AD from normal. The rs-fMRI data in the DMN has been used to examine the functional connectivity in autism spectrum disorder (Vidhusha, & Anandan, 2016). Researchers have investigated the dynamic behavior of resting state connectivity across the course of single scan, performing a time frequency coherence analysis using the wavelet transforms. They focused on PCC which is the primary node of the default mode network of the brain evaluating its relationship with both the anti-correlated (task –positive) networks as well as other nodes of the DMN (Chang & Glover, 2010; Greicius, Srivastava, Reiss & Menon, 2004).

Graph theoretical analysis is a potential tool in the field of connectomes (Bullmore & Sporns, 2009; Wang & Adewumi, 2012) and brain network analysis based on neuroimaging data (Rubinov & Sporns, 2010). A complex brain network can be represented as a graph G in which N nodes denote brain area and K edges denote connections between brain regions (Jaime, Torres, Ramos & Garcia-Aguilar, 2014). The various parameters derived from graph theory are used to quantify different characteristics of the network organization (Simpson, Bowman & Laurienti, 2013). Graph theoretical measures are employed to resting-state fMRI data, to enhance the understanding of resting-state network (RSN) dynamics (Damoiseaux et al., 2006). Recent studies in neurophysiological and neuroimaging have used advanced graph theoretical network analysis techniques to show that structural and functional integrity is diminished in AD patients, underlying high-level cognitive functions. Currently, distinct regions of DMN were used in particular to understand AD more effectively (Boccaletti et al, 2006; Watts & Strogatz, 1998).

Lateralization of brain structure and function occurs due to developmental neurological disorders (Nielsen et al., 2014). The lateralized brain function is classified into two broad networks - a right- and left lateralized network. The left-lateralized network is associated for intrahemispheric network consolidation while the right-lateralized network is involved between hubs of the network and brain regions in both hemispheres (Nielsen et al., 2014; Keller & Kell, 2016). The regions from dorsal and ventral attention networks and the frontoparietal executive network constitute the right-lateralized network. The thrust regions of language (Broca and Wernicke areas) together with the regions of default mode network form the left-lateralized network (Nielsen et al., 2013). In AD; however, effect of lateralization in brain atrophy is less clear.

The present work focuses on analysis of whole brain and inter-hemispheric connectivity patterns of AD subjects, through three progressive years of scan or stages using resting state fMRI. The results are analyzed using Functional connectivity maps, which are discussed in detail. The comprehensive analysis using various measures is done on default mode network regions, known to be the most crucial to the neurodegenerative processes. The altered network topology is analysed by graph theoretical measures. Further, functional lateralization of left hub DMN regions is also analysed.

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2. MATERIALS AND METHODS

2.1. Image Acquisition

Resting state fMRI images of three progressive stages of AD (N=10) were acquired from Alzheimer's Disease Neuroimaging Initiative (ADNI) database (Petersen et al., 2010). The mean age of subjects during each stage and other demographic information are shown in Table 1.

The images have been acquired using Philips Medical system 3 Tesla with Echo Time (TE) of 30.00ms, Repetition Time (TR) of 3000.0ms with the number of Slices equal to 6720 and a slice thickness of 3.313 mm. The groups did not differ significantly on age or gender composition as shown in Table 1. Figure 1 shows the general block diagram of the methodology followed in the current work.

Table 1. Demographic details

Parameters	STAGE 1	STAGE 2	STAGE 3
Age (years)	75 .2± 0.5	76.2 ± 0.56	77 ± 0.7
MMSE	28 (3.36)	25 (4.16)	23 (4.5)
N	10	10	10
Gender (male/Female)	3/7	3/7	3/7

2.2. Preprocessing

Preprocessing includes extraction of fMRI voxel time series signals from the raw data. The artifacts in the fMRI signal are mainly because of subject motion, fluctuation in the blood oxygenation level and the amplifiers in the equipment. Preprocessing removes the additional variation in the fMRI signals and enhances the area of interest (Tripoliti, Fotiadis, Argyropoulou & Manis, 2010; Strother, 2006).

Slice timing correction estimates the signal that would have been obtained if the slices had been acquired at the beginning of each scan. This is done by a shift of the phase of the sinusoids which make up the signal (Strother, 2006). The signal is convolved with a shifter filter to apply the phase shift and the correction is computed using sinc interpolation as shown in (1).

$$sinc\left(x\right) \equiv \frac{sin\pi x}{\pi x} \,.\, \sin c(x) = \frac{\sin \Pi x}{\Pi x} \tag{1}$$

Patient movement is one of the most important artifacts in fMRI. Motion correction has been achieved by a rigid body transformation of the whole time series of the image to the image picked first. Six variable parameters (three translations and three rotations) are involved in rigid body transformation (Strother, 2006).

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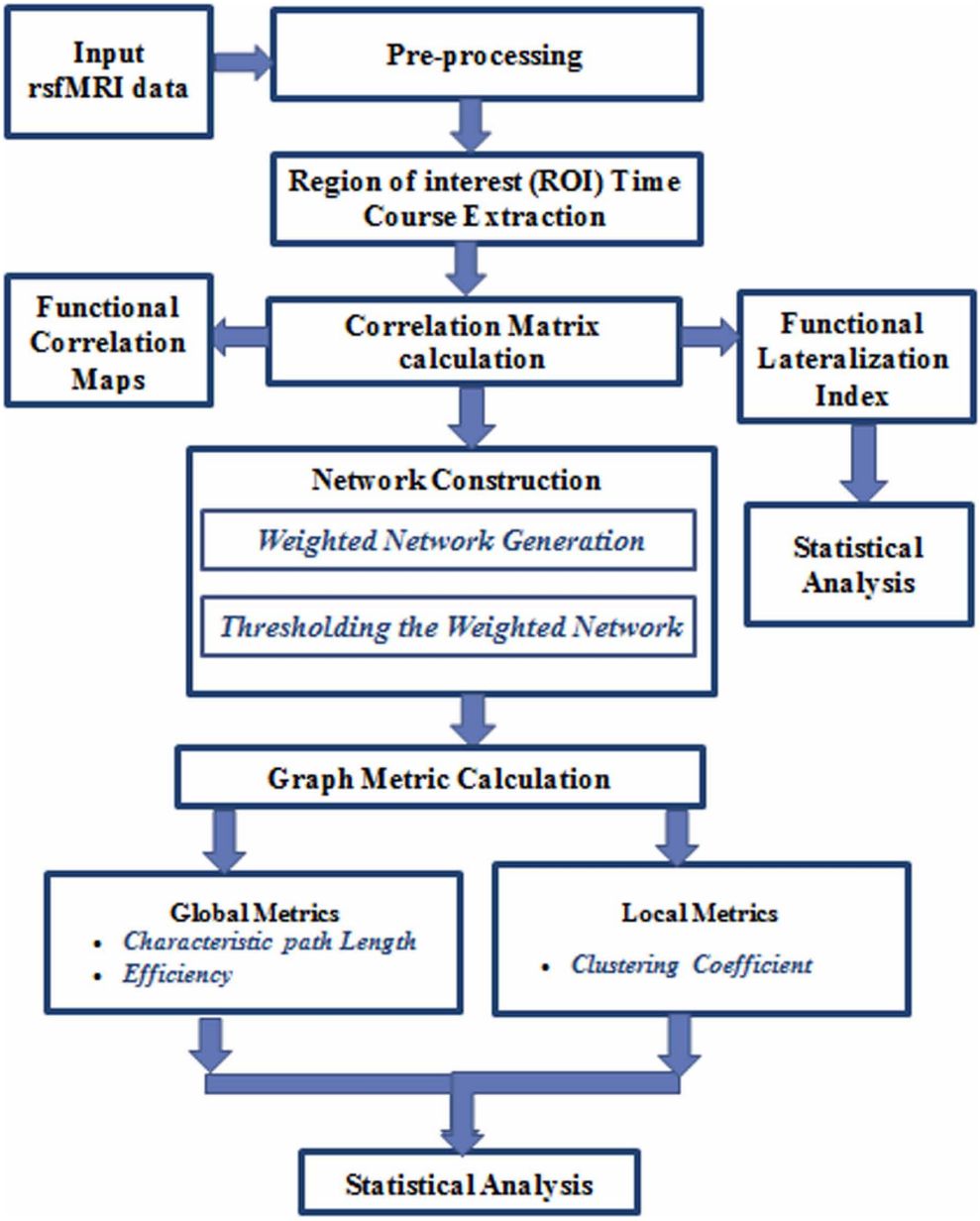
Figure 1. Framework for analysis of progression of Alzheimer's disease



Anatomical and functional images are overlaid to maximize the mutual information which is shown in Figure 2(a) and Figure 2(b). The mean functional image is co-registered to a high resolution anatomical image [MRI], and all of the other functional images are then re-sliced to align with the reference image (Strother, 2006). Normalised Mutual information (NMI) given in (2) is used as cost function

$$NMI = \frac{(H(a) + H(b))}{H(a,b)} \tag{2}$$

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where $H(a)$ and $H(b)$ are individual entropies and $H(a,b)$ is the joint entropy obtained from P(a) and P(b), the probabilities of anatomical and functional images from histogram are given in equations (2.1), (2.2) and (2.3).

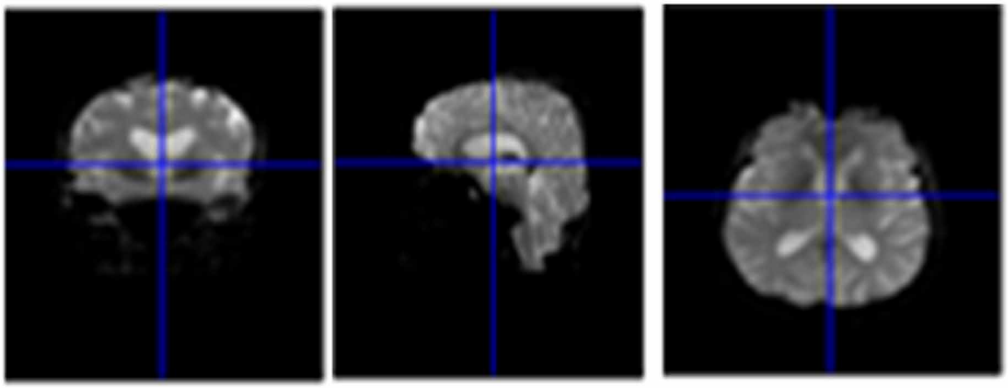
$$H(a) = -\int aP(a)\log_2 P(a) \tag{2.1}$$

$$H(b) = -\int bP(b)\log_2 P(b) \tag{2.2}$$

$$H(a,b) = -\int aP(a,b)\log_2 P(a,b) \tag{2.3}$$

Anatomical differences between different individuals are diminished by spatial normalization technique (Strother, 2006; [26]. It also enables localization of different cortical regions and allows group comparison. Normalization as shown in Figure 3(b) is performed using two steps. First step encompasses the determination of affine registration expressed in (3) between the object image and the standard template Montreal Neurological Institute (MNI) shown in Figure 3(a) (Roebroeck, Formisano & Goebel, 2005). The second step is for correcting the unrefined changes in the head shape. Nonlinear distortion is necessary to plot a brain in one space to brain in another space and this is modeled using linear combination of brain function (Matthews, Filippini & Douaud, 2013; Strother, 2006).

Figure 2. (a) A representative functional MRI after motion correction (a) Coronal View (b) Sagittal View (c) Axial View



(a) **(b)** **(c)**

The affine transformation can be expressed as

$$x' = Ax \tag{3}$$

Where A is the affine matrix that includes the translation, rotation, and scaling transformation parameters.

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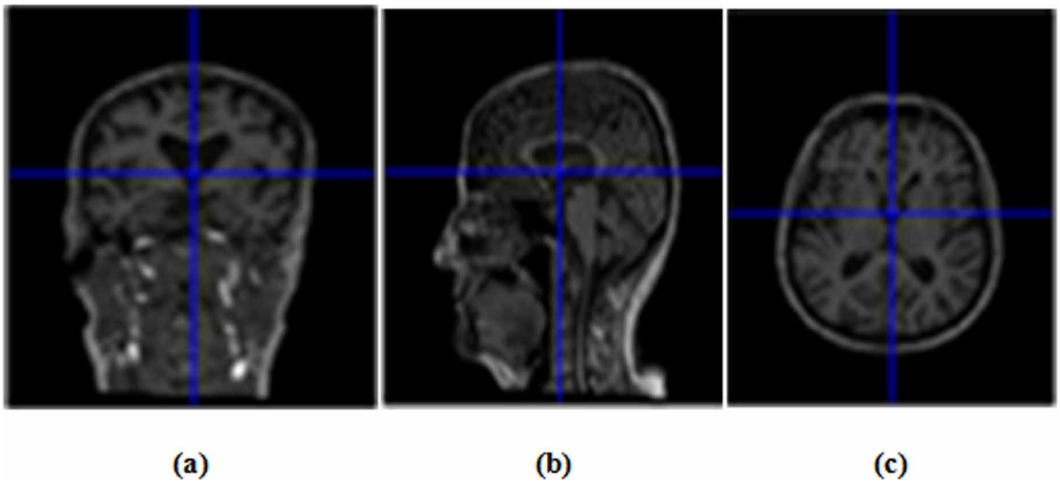
Figure 3. (a) Montreal Neurological Institute (MNI) Template(a) Coronal View (b) Sagittal View (c) Axial View



After pre-processing, the images are subjected to further analysis of functional connectivity (Song et al., 2011). Linear detrending and temporal band pass filtering (0.01–0.08 Hz) have been applied to decrease the effect of low-frequency drifts and high-frequency physiological artifacts (Watanabe et al., 2013).

2.3. Functional Connectivity: Region-to-Region Connectivity

In this work, regions-of-interest-based functional connectivity approach has been employed to assess the intra and interhemispheric resting state functional connectivity. The integration of information between the two hemispheres is quantitatively measured by computing correlation between mean voxel time series extracted from ROI. The spherical ROIs of 3mm radius in DMN regions have been chosen to analyze both inter intra hemispheric connectivity (Leech et al., 2011 ; Brier et al., 2014). Figure 4 shows location of the 20 DMN areas and the regions included in the study are given in Table 2.

2.4. Graph Theoretical Approach

In this work, the connectivity matrix has been generated by calculating Pearson correlation coefficients for time courses extracted from each of 20 DMN regions or nodes (Leech, Kamourieh, Beckmann & Sharp, 2011; Brier et al, 2014). The connectivity matrix is converted into a weighted connection matrix by deriving weighted adjacency matrix. The weighted undirected graphs are constructed over a range of connection densities or costs, from 10% to 40%, at 10% intervals (Zhao et al., 2012). Connection densities are defined as the fraction of present connections to possible connections.

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Table 2. Default Mode Network regions

ANATOMICAL AREA	Montreal Neurological Institute (MNI) Coordinates in (mm)		
	X	Y	Z
Ventral medial prefrontal cortex vMPFC (AH)	6	70	14
Superior Frontal gyrus (SFG)	8	50	38
Ventral Posterior Cingulate (v_PC)	-6	-48	26
Dorsal Posterior Cingulate (d_PC)	0	-24	38
Precuneus (Pre)	-8	-60	14
Left Inferior Parietal Lobe (L_IPL)	-56	-66	24
Right Inferior Parietal Lobe (L_IPL)	50	-62	30
Anterior Medial Pre-frontal cortex (aMPFC)	1	55	26
Ventro-medial Prefrontal cortex (vMPFC)	-3	40	0
Left Superior Frontal Gyrus (L_SFG)	-14	36	59
Right Superior Frontal Gyrus (R_SFG)	17	35	58
Left ITG (L_ITG)	-62	-33	-20
Right ITG (R_ITG)	66	-17	-19
Left Parahippocampal gyrus (L_PH)	-22	-26	-21
Right Parahippocampal gyrus (R_PH)	25	-26	-18
Posterior Cingulate Cortex (PCC)	-2	-29	39
Left Lateral Parietal (L_LP)	-47	-71	35
Right LP (R_LP)	54	-61	36
Posterior Cingulate (PC)	3	-53	6

2.5. Graph Properties

The graph network properties can be classified in two categories as global and local. The global network properties give an overall view of the network. Local network properties give more detailed network descriptors (Watts & Strogatz, 1998).

The characteristic path length and clustering coefficient are two vital measures that can be used to distinguish different types of networks such as regular and small-world. Regular networks have a greater clustering coefficient but a longer characteristic path length due to the lack of long-distance connections. In a small-world network, the nodes usually have greater local interconnectivity characterized by a high clustering coefficient and a low characteristic path length (Watts & Strogatz, 1998).

In this work the global network properties have been evaluated statistically and visualized over the range of 10–40% connection densities (Xia, Wang & He, 2013; Kruschwitz, List, Waller, Rubinov & Walter, 2015).

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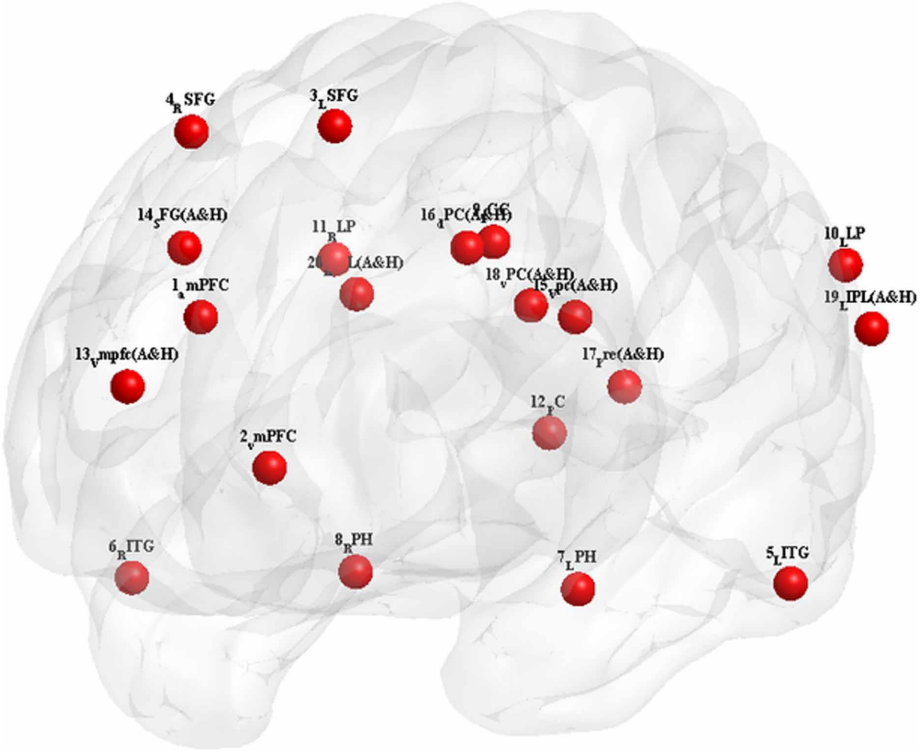
Figure 4. Graph theoretical nodes representing the DMN regions



2.5.1. Characteristic Path Length

The mean of the path lengths between all possible pairs of vertices and is the most commonly used measure of functional integration stated in (4). It quantifies the extent of cliquishness of information transfer of a network (Rubinov& Sporns, 2010; Watts & Strogatz, 1998; Latora, & Marchiori, 2001).

$$L = \frac{1}{N(N-1)} \sum_{i,j \in N, i \neq j} dij \tag{4}$$

where d_{ij} is distance between two vertices *i* and *j* (shortest).

2.5.2. Efficiency

The average inverse shortest path length is a related measure known as the global efficiency given in (5) (Latora, & Marchiori, 2001). It is a measure of how efficiently the two vertices exchange information.

$$E(G) = \frac{2}{N(N-1)} \sum_{i<j \in G} \frac{1}{dij} \tag{5}$$

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Table 3. Core DMN regions

ANATOMICAL AREA	ABBREVIATION	X (MNI)	Y (MNI)	Z (MNI)
Anterior medial prefrontal cortex	aMPFC	6	-52	2
Posterior cingulate cortex	PCC	-8	56	26
Dorsal medial prefrontal cortex	dMPFC	0	52	26
Temporal pole junction	TPJ	-54	-54	28
Lateral Temporal cortex	LTC	-60	-24	-18
Temporal pole	Tempp	-50	14	-40
Ventral medial prefrontal cortex	vMPFC	0	26	-18
Posterior inferior parietal lobe	pIPL	-44	-74	32
Retrsospinal cortex	Rsp	-14	-52	8
Para-hippocampal cortex	PHC	-28	-40	-12
Hippocampal Formation	HF+	-22	-20	-26

2.5.3. Clustering Coefficient

The fraction of triangles around an individual node and is specific measure of functional segregation as in (6) (Latora, & Marchiori, 2001).

$$C_i = \sum\sum \frac{2t_i}{k_i(k_i - 1)} \tag{6}$$

Where t_i is the number of triangles at the i^{th} vertex.

And k_i is degree at the i^{th} vertex, defined as the number of edges connected to a particular node

2.6. Lateralization

Functional lateralization index (LI) was defined as the difference (unflipped - flipped) between Fisher-transformed correlation coefficients (Nielsen et al., 2013). The left lateralized regions were taken excluding the Wernicke and Broca's area which is associated with speech. The LI was analyzed for all the 20 DMN regions (Watanabe et al., 2013; Leech, Kamourieh, Beckmann & Sharp, 2011). Besides here handedness of the subject was not taken into account.

3. RESULTS

The Mini Mental Status Exam (MMSE) scores estimated for the subjects showed a significant difference between all the three years of scan and the progression of AD was associated with decreasing MMSE as shown in Table 1. The functional correlations between various DMN regions have been calculated. Figure 5 show the mean correlation maps of all the ten subjects obtained for DMN regions through the three progressive stages or years of scan. The region to region connectivity has been studied using cor-

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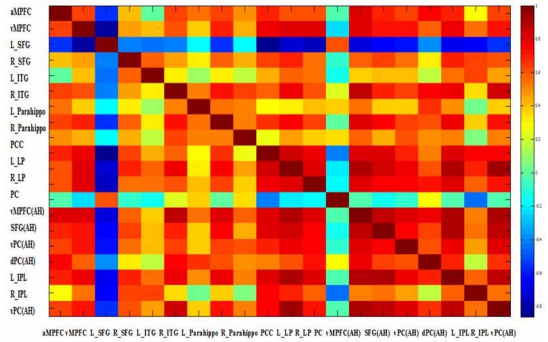
relation analyses of voxel (or ROI) time series. The time course was calculated as the average across all voxels within the ROI. The clear decreasing trend in correlation maps was observed indicating the reduced integrity in the DMN regions of the brain. Positive and strong correlation indicated by red color, negative correlation in blue and correlation near zero by green color in the resting state functional correlation maps between all DMN pairs. This analysis of functional correlation maps thus shows the disruptive nature of brain connectivity through the progressive stages of AD.

Figure 5. Mean functional correlation map of ten subjects for all anatomical areas obtained in the first stage



The anterior and dorsal regions of medial prefrontal cortex, posterior cingulate cortex regions of DMN show strong intrahemispheric connection. The strong interhemispheric connectivity between left and right inferior temporal gyrus, superior frontal gyrus is observed in first stage of AD as seen in Figure 5.

In the second stage of AD the regions of default network, which include inferior temporal gyrus, show reduced strength of inter hemispheric connectivity as seen in Figure 6. Figure 7 shows the function correlation map in the third stage of AD. The anterior and dorsal regions of medial prefrontal cortex, lateral parietal, posterior cingulate cortex, and para-hippocampus have weak intra and inter hemispheric correlation.

Figure 6. Mean functional correlation map of ten subjects obtained for all anatomical areas in the second stage

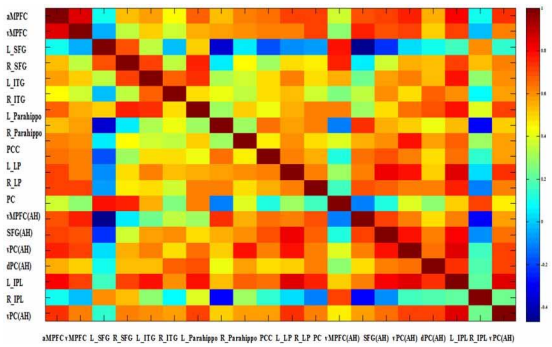


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Figure 7. Mean functional correlation map of ten subjects obtained for all anatomical areas in the third stage

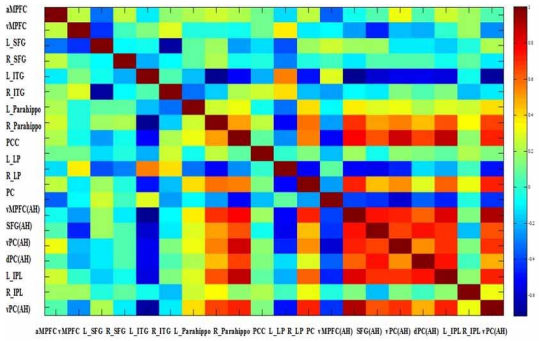

Figure 8, 9 and 10 represent the network visualization of mean functional connectivity of the core DMN regions listed in Table 3 for the three progressive stages of tensubjects. The thickness of the lines reflects the strength of the correlation between regions.

During the first stage, it is observed that all the nodes of DMN regions are highly connected as shown in Figure 8. The anterior and dorsal part of medial prefrontal cortex is observed to have the strongest interconnection between them and also with other DMN regions.

Figure 9 shows the network visualization in the second stage of AD. The anterior, ventral and dorsal regions of medial prefrontal cortex are found to be highly connected while the temporal pole (TP) and lateral temporal cortex regions of DMN are moderately interconnected in the second stage. In the third stage of AD the regions of default network, which include dorsal and anterior medial prefrontal cortex, temporal pole, and posterior cingulate cortex, show reduced strength of interconnectivity as seen in Figure 10.

Figure 8. Network visualization of mean functional connectivity of Core DMN regions during stage 1

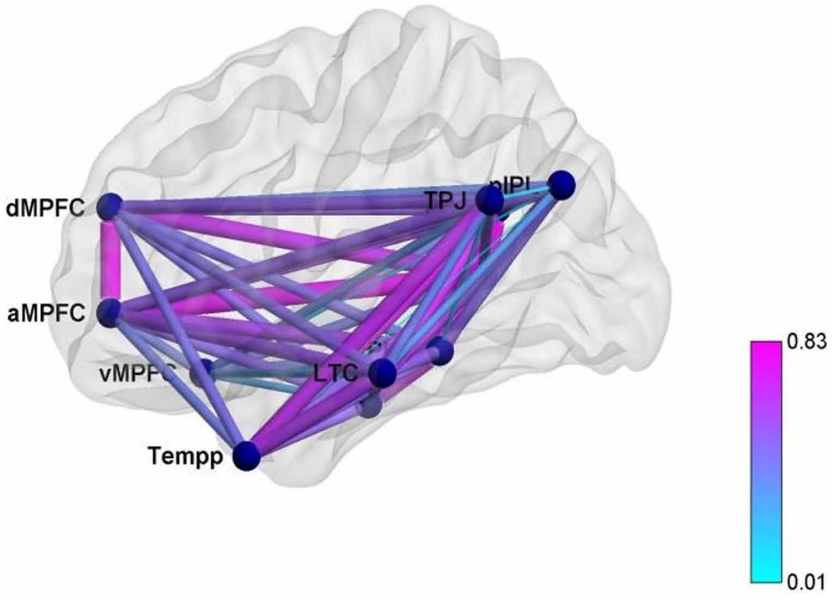

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Figure 9. Network visualization of mean functional connectivity of Core DMN regions during stage 2

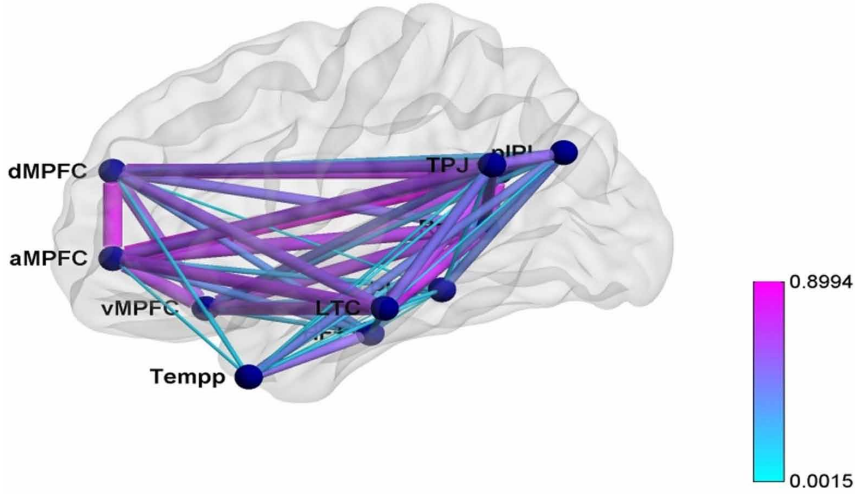
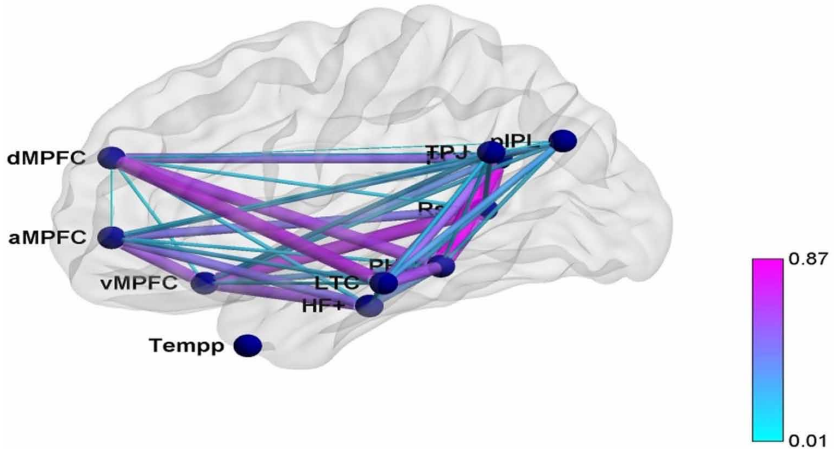


Figure 10. Network visualization of mean functional connectivity of Core DMN regions during stage 3



The graph theory parameters are plotted for all three progressive stages of AD and are statistically analyzed. Figure 11 shows the variations of characteristic path length with network density for all three progressive stages. Results showed an increase in global characteristic path length in the DMN regions for a range of thresholds, during progression of AD. This indicates ineffective deterioration of the small-world network properties as the disease progresses (Zhao et al., 2012).

Since the data is not normally distributed, non-parametric Friedman test has been performed to evaluate the overall significance and the Wilcoxon signed ranks have been estimated to determine the significant difference across the related groups.

For a network density of 0.3, significant difference has been observed in the mean characteristic path length between the initial and third year of scan ($p<0.05$) by Wilcoxon signed rank test. By increasing the network density to 0.4, significant differences between all the three progressive years of scan in Characteristic path length of AD ($p<0.05$) have been observed.

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Figure 11. Global mean characteristic path length for all three stages of AD with varying network densities

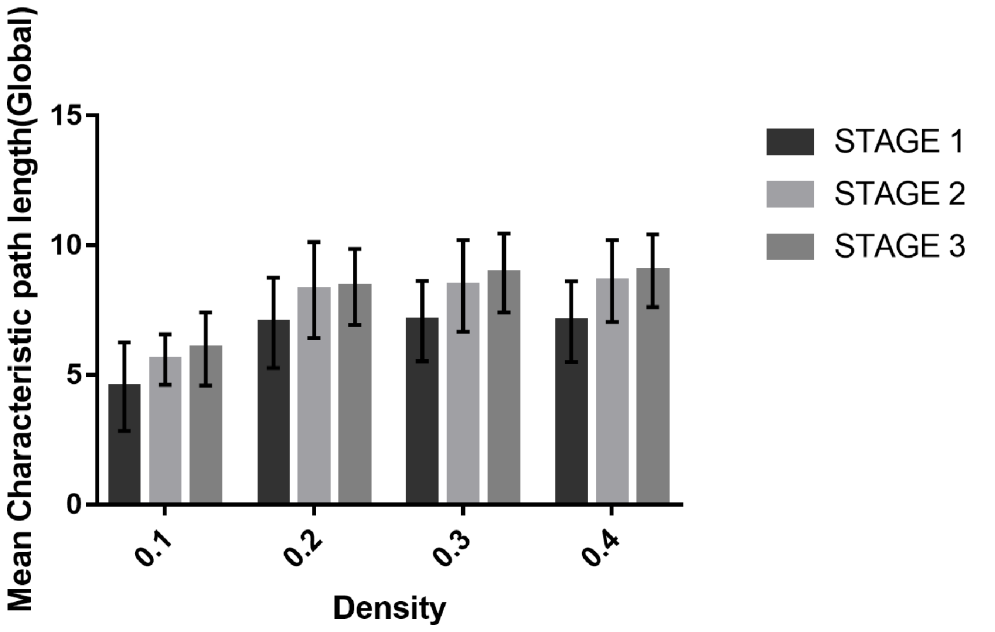
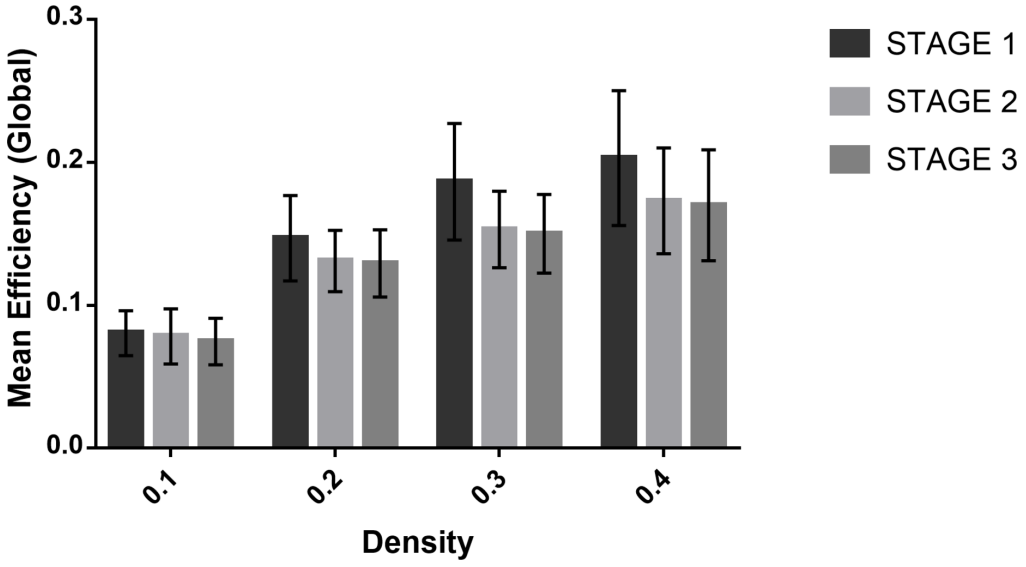


Figure 12 indicates the decreasing trend in global mean efficiency for a range of thresholds through progressive stages of AD indicating the deterioration global characteristics. Global efficiency of network with density of 0.2 ($p<0.05$) showed significant differences between the initial and third year of scan. For network density of 0.4, significant differences ($p<0.05$) have been observed between stages 1 and 2, and stages 1 and 3, for global efficiency of AD.

Figure 12. Variation of mean global efficiency with various network densities for all three stages



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Figures 13, 14 and 15 show the changes in clustering coefficient with 0.1, 0.2 and 0.3 network densities respectively for all the three progressive stages of AD. Though no statistically significant differences with regard to clustering coefficient between the stages of AD have been observed by Wilcoxon signed ranks Test ($p > 0.05$), mean values showed a considerable decrease in the clustering coefficient for densities ranging from 0.1 to 0.4. Also, the local network analysis at density of 0.1 suggests that posterior cingulate cortex comprising ventral and dorsal regions form the major hubs.

Figure 13. Variation of Mean clustering coeficient for all three stages at density 0.1

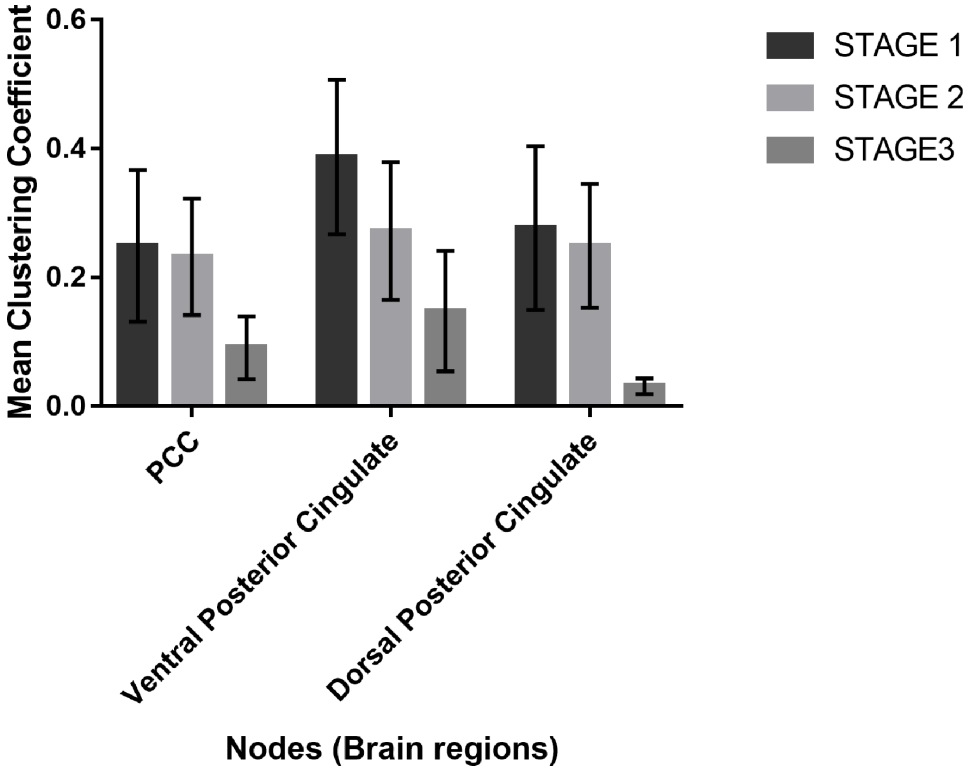

Figure 16, Figure 17 and Figure 18 represent the lateralization for different DMN regions during the first, second and third years of fMRI recordings respectively. Red colour represents the regions are left lateralized with a positive LI and blue regions are right lateralized representing negative LI. The mean lateralization index for first year of scan shown in Figure 14 indicates the laterality of left hub DMN regions. During the second stage, the laterality of regions are disrupted as shown in Figure 15 and Figure 16 shows the laterality of left hub regions is totally disrupted in the third stage of AD.

To validate the differences in degree of lateralization each subject's average functional lateralization has been estimated for all the 14 DMN regions. Then a paired sample t test for the three stages comparing mean functional lateralization for all the DMN regions has been performed. A significant difference in LI has been observed in Medial Temporal gyrus, PCC ($p<0.05$) in the paired t test. Although no statistically significant differences between the stages of AD has been obtained by paired t test ($p > 0.05$), mean values showed considerable differences in lateralization index for rest of the DMN regions.

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Figure 14. Variation of Mean clustering coeficient for all three stages at density 0.2

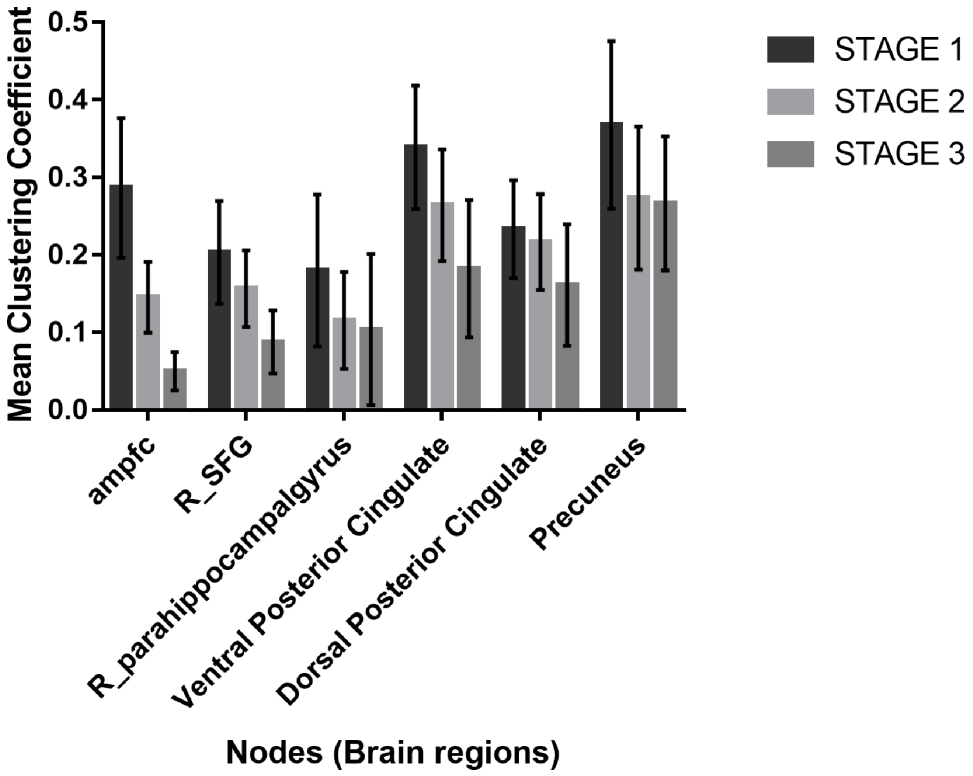

Figure 15. Variation of Mean clustering coeficient for all three stages at density 0.3

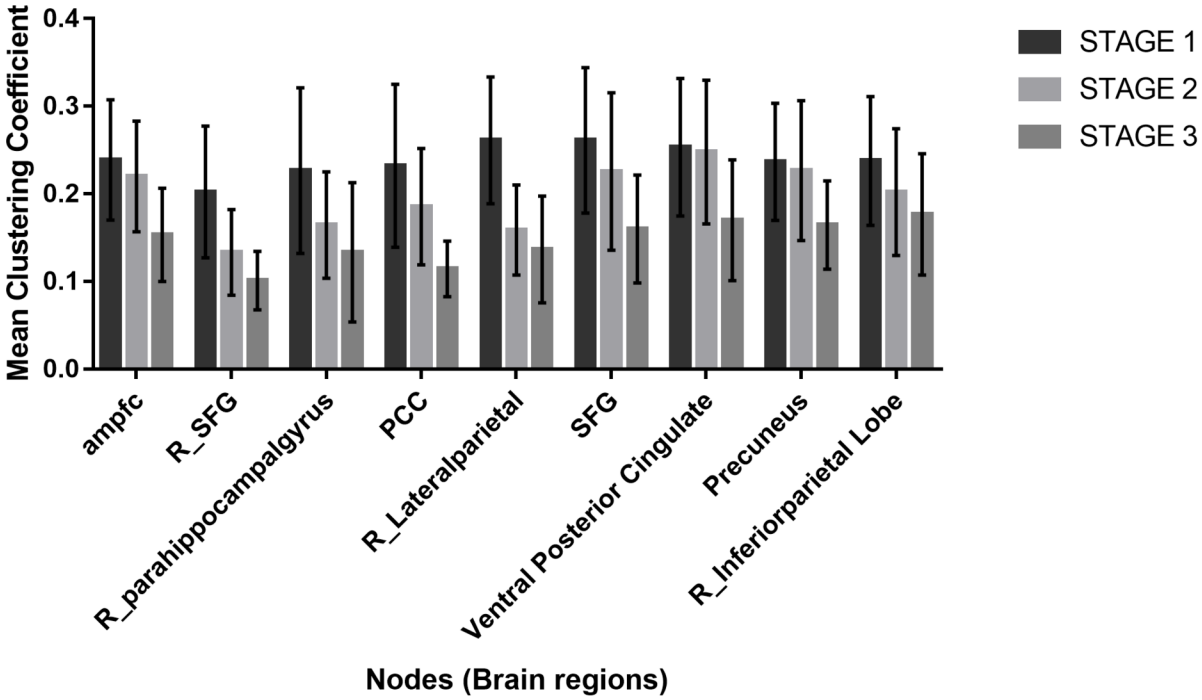

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Figure 16. Average LI of all the subjects obtained in the first stage

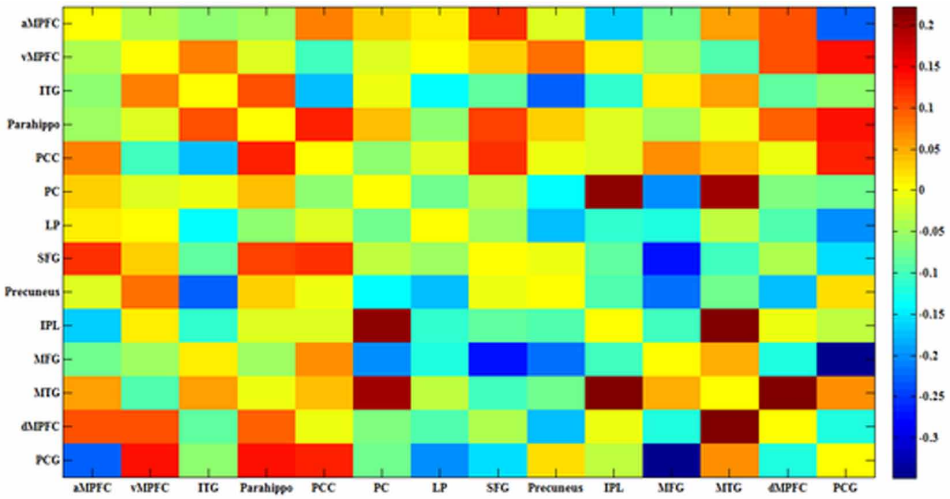

Figure 17. Average LI of all subjects obtained in second stage

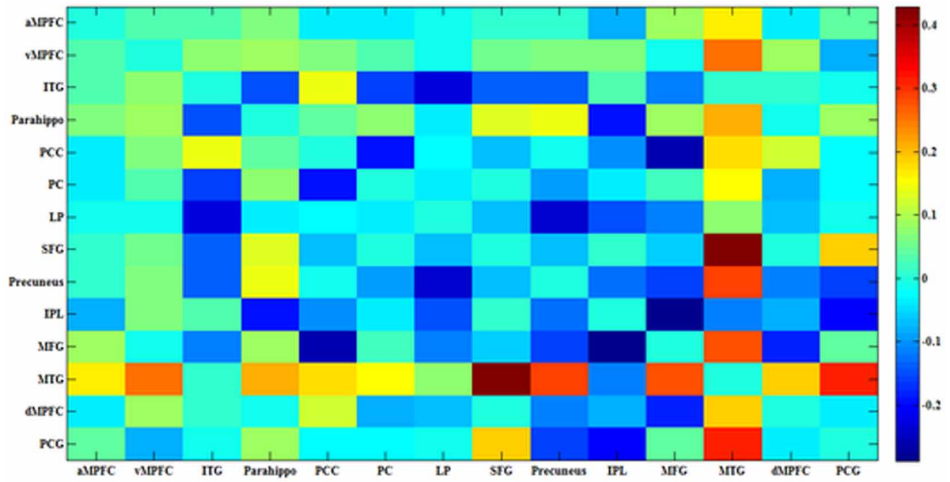

Table 4 shows the lateralization index values for progressive stages of AD found in the medial Prefrontal cortex (mPFC), Para hippocampal gyrus (PH), Inferior Parietal Lobe, Superior Frontal Gyrus, ITG. As the disease progresses (LI < 0), the left lateralized regions are disrupted. During Stage 2 the initially left lateralized regions (LI > 0) are bi-lateralized. During stage 3 the left laterality of the regions is lost. This clearly indicates the severity of progression of the disease in the three stages.

4. DISCUSSIONS

The current work throughout examines the correlation maps and graph metrics of the DMN regions in AD patients during progression of the disease. The results show a decreased connectivity in the DMN

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Figure 18. Average LI of all subjects obtained in third stage

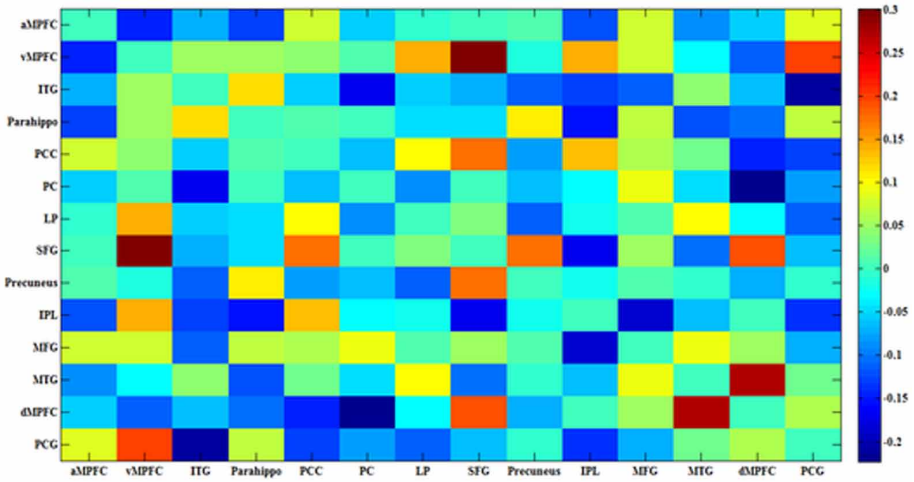

Table 4. Lateralization Index Values

ROI Pairs	STAGE 1	STAGE 2	STAGE 3
mPFC and Vmpfc	0.0294	0.001	-0.35
L_ITG and R_ITG	0.0017	-0.01	-0.055
L_Superior Frontal Gyrus and R_ Superior Frontal Gyrus	0.021	-0.001	-0.04
L_Inferior Parietal Lobe and R_ Inferior Parietal Lobe	0.0304	-0.011	-0.0159
L_Para hippocampal gyrus (PH) and R_ Para hippocampal gyrus	0.0191	0.0101	0.008

regions as the disease progresses, thereby representing decreased activity of the default mode network and contribute to episodic memory impairment in AD. Graph theoretical measures have provided quantitative measurements for each node that incorporate connectivity information from the complete network. Also, this technique has enabled for a direct comparison of data through visualization of graphs. Rubinov & Sporns (2010) described a set of measures that quantify local and global properties of complex brain networks in order to investigate more about structural and functional network connectivity plus to contrast the network parameters across subjects. This work analyses three measures- characteristic path length, efficiency and clustering coefficient stating functional integration and functional segregation for three progressive stages using resting state fMRI. With increasing connection density, global efficiency, clustering coefficient decrease and characteristic path length increased (Zhao et al., 2012). The decrease clustering coefficient and global efficiency is analogous to the result obtained by (Brier et al., 2014; Zhao et al., 2012). The shortest characteristic path ensure effective transfer of information to distinct brain regions. Our results show an increase in characteristic path length with progression of AD indicating information transfer reduces in AD as disease progresses. Previous researchers (Brier et al., 2014; Watanabe et al., 2013; Zhao et al., 2012) found decrease in whole brain connectivity, efficiency and have also found decrease in DMN connectivity with age which is well correlated with the present study.

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From the LI estimation, it is evident that the laterality of left hubs gets disturbed. The loss of hubs in AD might be explained by atrophy of particular areas and that network in AD being selectively vulnerable (Nielsen et al., 2013). The lateral asymmetries between three progressive stages of AD were found in the DMN regions suggesting the neurological disruptions. In particular, we found lateral differences in the medial Prefrontal cortex (mPFC), Para hippocampal gyrus (PH), Inferior Parietal Lobe, Superior Frontal Gyrus, ITG. From a clinical perspective, the distinct progressive stages of AD and heterogeneity of data are vital factors that can affect the results of AD studies as the behavioural symptoms vary with different stages.

5. CONCLUSION

Resting state fMRI has been effective in analyzing functional connectivity in patients with mild and moderate Alzheimer's disease (Wang et al., 2006). But the alterations in functional connectivity have not been tracked in patients as the disease progresses. Further, the raw functional MR imaging data acquired does not reveal much information about the brain's integrity. The results obtained significantly depend on time course extraction upon the preprocessing techniques and time course extraction. Brain network analysis is a new multidisciplinary approach to study the multipart system of brain networks with significant neurobiological measures (Rubinov & Sporns, 2010). This work aims at understanding the pattern in the variations of functional connectivity, in memory associated brain regions, using appropriate preprocessing as well as image processing routines. In conclusion; a novel technique of applying graph theoretical measures seems to be a promising framework for understanding functional network topology in DMN regions during AD progression. Further, during progression of AD the left lateralization of DMN regions is observed to diminish. The results obtained in this work contribute to a better understanding of the relationship between functional changes and cognitive dysfunction in Alzheimer's disease. This takes it closer to an overall goal in the field of Alzheimer's research to detect the onset, determine when and how to intervene to decelerate the progression, and evaluate the treatment response. This work thus proves to be clinically significant in demonstrating the effects of disease progression specifically in terms of functional connectivity and network metrics among the memory associated regions of interest thereby leading to more powerful understanding towards quantum of personal assistance required for AD patients.

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Chapter 31
IoT in the Field of Healthcare

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ABSTRACT

The chapter at first focuses on IoT being used in healthcare in general and then it moves to Parkinson's disease, specifically, and how people with it can be benefitted by IoT.

INTRODUCTION

Technology, over the years has always brought about a revolutionary change in the history of mankind. Be it good or bad, it has always influenced us in a large way and has shaped the modern 21st century world. Though it has led to war and destruction, it has also helped keep world peace and unity. Over the years, mankind has seen many interesting and breathtaking discoveries which have revolutionized the different aspects of everyday life. The Internet of Things is one such topic which has evolved or rather come across a long way since its discovery in the 90's. It has pioneered the way for headway and development. It has connected various people across the globe and has led to path breaking discoveries and countless inventions which aims to provide a better future for all of us. It has conquered many fields including science, medicine. Smart objects inspired by IoT are found in each and every walks of life such as Smart Homes, Smart Parking System, Smart Agriculture etc. The IoT is an ideal technology which has played a key role in communication. We have seen that through the years how internet became the base for various programs. In this world of IoT, each object which has been connected, be it a phone or a room etc is considered to be smart. It has been programmed in such a way that it can be used to its utmost capabilities with the help of existing technologies such as RFID etc.

Smart Healthcare is very important in various health related applications through various sensors in patients and their medicines for seeing upon them. The IoT is used by clinical care to take care of the physiological and neurological conditions of the unhealthy through sensors by amassing their existing status and then passing this information to the required centers so that the doctors can check upon these affected people and take necessary steps in order to prevent deterioration of the patient's condition. For example, if the blood pressure of a heart patient is varying rapidly, this can easily be detected by certain

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important sensors which will then process this information and send it to the concerned authorities who can take immediate action to prevent any mishaps and ensure the safety of the person. Various patients in hospitals require proper attention and they can be checked upon using IoT inspired monitoring. This method deploys sensors to accumulator important physiological information and uses gateways to get the job done. When you go to your medical exam, The doctor not only has general clinical / laboratory testing was based on static dimensions of your biological and metabolic, but also abundant better data from sensors. Using presented data, and assisted by verdict support schemes also will be having admittance to a large amount of observational data for other people have, your neurologist can make a much superior prognosis of the health and advise on treatment. Such a troublesome expertise with a transformational influence on could have worldwide fitness schemes and a radical decrease in healthcare costs and recover the haste and precision of analysis. In day to day life where everyone is busy, where we don't have much span to check and to keep a watch on everything. How do we intend to keep our health good? Sensors offer us with correct and proper output and it's a much better selection than ancient medical instruments like thermometers like they may have optical phenomenon errors. For endlessly sending message from person's location to medical informative GSM electronic equipment is used. Now days, heart diseases are exceeds up to dangerous level which results in death of such a large amount of individuals. Observance of patient anytime is tough or doctors also are unable to observe explicit patient for total operating hours. In several important conditions like patient is found remote from hospital or conjointly just in case of old patient who suffering with heart condition and physical disorders, continuous observance of patient isn't potential (Ufoaroh, Oranugo, & Uchechukwu, 2015).

These days, the health care sensors are assuming an essential part in our everyday life. Health care checking frameworks is one of the real upgrades in view of its advanced innovation. So we are essentially interfacing the temperature sensor and heart rate sensor so that at the same time we can observe the state of person who have been suffering and subsequently discounting the utilization of the thermometer and different devices to check the present state of the person who have been suffering.

A heart rate sensor is an individual measuring device for individuals and it enables the subject to check his/her present heart rate for further examination. Prior Systems were included a container that contains terminal leads which are connected to the chest. Grown-ups show at least a bit of kindness rate roughly around 72 beats for every moment (bpm) and for children it's around 120bpm. A few more seasoned kids have heart rates around 90 bpm. The heart rate rises step by step amid activities and backs off to rest an incentive after exercise (Jubadi, & Sahak, 2009). In the event that the rate at which the beat comes back with the ordinary estimation of heart rate, then it implies that the specific individual is fit. Individuals with heart rates lower than the typical are generally confronting a condition known as bradycardia, while the general population with higher face a condition which is known as tachycardia. Heart rate is basically figured by keeping the fingertip to the LDR sensor and afterward assessing and including the beats for the most part a 30 seconds of a specific time period (Jadhav, Devkatte, & Dhumal, 2015; Kale, A. V., Gawade, Jadhav, & Patil, 2015). The specific domain name for this application would be: It would be used to detect heart rate and body temperature. It would be used to detect fever and help us to state how much stressed up we are and how much exercise we need.

In a broader context it would be a part of "MEDICAL SCIENECE". The main Moto is to develop a Heart Rate and Temperature Monitoring System which could help those people who have been suffering from heart rate and physical disorder. This paper deals with solving above problems. Module consist of wireless sensor which measures the heart rate and body temperature and sends the value of heartbeat and temperature to the android phone with the help of Bluetooth module. If there is any abnormalities

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then SMS will be send through GSM module to the medical advisory for the precautions so that patient can be prevented from serious health problem or serious situation before reaching to the hospital. For display the measured values of heart beat and body temperature, LCD is used. From android phone, it will be also sent to the cloud database.

The evolution of technology has been inching towards a more integrated, connected environment and society. Each new invention, discovery or development is leading to an overall improvement in the quality of life for each human being. There is an increase in the life expectancy of each person and consequently, the progressive ageing of the human race. There are several side effects and drawbacks of this whole process as well. The swift upsurge in the number of people affected by chronic diseases has been the topic of several conversations. Additionally, the increase in life expectancy also means there is an upsurge in the number of elderlies who require palliative care and attention from caregivers or doctors. As more and more people have begun to live alone, not only is regular monitoring and nursing difficult for each person, personal support and care is progressively challenging to provide one to one upkeep for all. In the case of any emergency, the first responders can only respond only after the victim raises an alarm that he is in distress. This is not a very proactive approach for a technology driven world. To ensure a decent quality of life, we must ensure remote access of such health data and vital signs of a person to adopt an active tactic in observing and maintaining the personal health of anybody. By integrating IoT-enabled devices in medical equipment, healthcare professionals are able to monitor their patients very effectively. They can also and the data collected from these devices to determine which patients require the most active attention. In different words, by making the most of this network of devices, healthcare specialists may use data to create a system of pre-emptive management – as is often said by a lot of people, the prevention is better than the cure.

IoT based remote monitoring tools have hence become central to a shift in paradigm in the healthcare industry to adapt to these new upcoming needs of people. The quantification of human health conditions can be done discretely by now inexpensive, wearable sensors that can measure various vital signs of any human being and transmit over short or long range to the appropriate medical personnel who can interpret this data and immediately respond. In many cases, systems are also designed to perform actuation on the basis of recorded signs. These new, cheap, wearable sensors have the potential to establish the Smart-health systems for various classes and categories of patients like those suffering from chronic fatal and non-fatal diseases, the elderly and even more so for people who want to monitor their health on a regular basis. The sensors are attached to various parts of the body of a person to monitor vitals such as heartbeat, blood glucose levels, body temperature, blood pressure, etc. and transmit the data for statistical analysis so as to deduce behavioral patterns of a person and enable professional to advice and guide them on how to improve health practices. Besides, such systems can also set off alarms and prompt for remote action and provide adequate help at the right time to all those who need it in times of emergency. This shall go a long way in improving life expectancy and is also a cost-effective way of maintaining regular patient records in hospitals and health centers.

The greater part of the budding countries has exceptionally bad healthcare transportation. There are very less doctor's facilities in contrast with blasting population. That couple of doctor's facilities is insufficiently prepared and not many specialists are available for the essential diagnostic equipment used for finding of life frightening diseases is missing. On the off chance that if we can construct cheaper convenient health sensing device, including a few sensors, fit for measuring the key traits of a human body, and can speak with the hospital database, we could furnish with excellent medicinal counsel.

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The health check is given after the authority specialists from the gathering of specific specialists there throughout the world assess those health constraints on clinic database. It acts as private cloud. Besides, if healthcare sensing gadget is made to speak among convenient PC like a tab or cell phone which have default capacity of speaking with the clinic database, in that case, the entire framework will be considerably extra financially suitable. This is on the grounds that these days a great many people have entry to convenient communication devices and these gadgets have turned out to be very cost effective. The framework can likewise has prepared IoT empowered and M2M friendly.

This paper displays the usage of healthcare monitoring system. In this manner, we can possibly profit a vast population. Every sensor ought to timely compute the information taking after the approved sampling time of the constraint, and information ought to be sending to the information processor with no overlap used for healthcare monitoring system to become dependable. Every sensor has differing prerequisites regarding information length and sampling speed the sensor information gathered without overlap by information processor we can replace notepad at patient bed with smart device by utilizing NFC technology and patient's information can be extricated from smart gadget consequently by utilizing NFC.

IoT is the next era of human life (Free Scale and Emerging Technologies, ARM, 2016), IoT is no more a hype it has started to become a reality (Evans, 2011; Zanella, Bui, Castellani, Vangelista, & Zorzi, 2014), IoT has changed the human thinking in all the aspects of life (ITU-T Technology Watch Report, 2013), IoT is converting normal cities to smart cities (Borodin, Zavyalova, Zaharov, & Yamushev, 2015; La, Kim, & Kim, 2015), IoT uses a lot of RFID tags, sensors and cloud servers for its functioning.

In (Catarinucci, De Donno, Mainetti, Palano, Patrono, Stefanizzi, & Tarricone, 2015) *ecg* and heart rate are monitored with the help of a app where the data's are stored in local storage and in cloud memory and can keep an eye on the patients' health progress. In (Rahmani, Thanigaivelan, Gia, Granados, Negash, Liljeberg, & Tenhunen, 2015) we are monitoring diseases like hypertension, diabetes and *ecg* they are integrated in a sensor kit. The outcome values can be monitored on desktop. The introduction of a smart gateway where the data from the sensors are stored in the cloud *db* and user *db*. All the data's are received from the sensors through wireless medium (Seales, Do, Belyi, & Kumar, 2015). Data's are stored in the cloud server through internet web clients can use smart phones and laptops to see the data of the accelerometer and *ecg* are made in this paper (Gope & Hwang, 2016) but a power efficient one. With the help of *phinet*as the cloud service we integrate all the actions performed values from the sensors like accelerometer, temperature,*ecg* and air flow sensor can be visualizes by healthcare professionals (Chiuchisan, Chiuchisan, & Dimian, 2015). BSN body sensor network where we monitor details of sensor like *eeg*, *emg*, Blood Pressure, Motion Detection, *ecg* and temperature with the help of internet to the *bsn* care server where the local physicians and emergency team will take care of them (Serdaroglu, Uslu, & Baydere, 2015). In (Gupta, Patchava, & Menezes, 2015) we monitor the blood pressure, pulse and oxygen, electrocardiogram, patient position and body temperature with the help of the microcontroller to the clients like doctor, family, friends and emergency team with the help of internet and also as implementation of mobile app. Activity recognition has been implemented for the patients to monitor whether the elderly persons are taking pills or the medications at the right time prescribed by the physicians with the help of *rfid* tag and reader. If the person is inactive during the prescribed time an alert will be sent to the admin. Electrocardiogram is used to sense the health of the patient and monitor it updates the values at regular intervals to the website. Forwarding the values as a message to the doctor if any abnormal value is found and also turning on the buzzer. This new technology with advantages brings in a lot of disadvantages along with it.In this paper we discuss the advantages and disadvantages involved by getting IoT into our day to day life and conclude if IoT is a boon or curse to healthcare.

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BACKGROUND

Over the years, several papers have focused on the healthcare benefits in general. They have mentioned various cases about how IoT has played about a major role in the betterment of the sick, diseased and the unhealthy.

One of the papers written in the IEEE Conference on Overhaul Computing spoke about Health Nursing and Administration using the Internet of Things. The writers enlightened us as to how Networked sensors make it possible to gather large amount of data which tells us about the psychological and corporeal health. Apprehended on an extensive period basis, combined, and successfully administered, such data could transmit about a sole and delightful alteration in the vigor care domain. In specific, the handiness of figures at impossible balances and chronological length attached with a first-hand cohort of bright procedures can: (a) ease an development in the recurrence of therapeutic stadium, from the contemporary pole facto diagnose-and treat sensitive example, to an astounding practice for analysis of these various ailments, coupled with discouragement, cure, and the slow development of fitness instead of syndrome; (b) empower personalizing of conduct and administration options beleaguered chiefly to the particular conditions and wanting of the separate; and (c) help substantiate the fee of health care while concurrently refining aftermaths. In this paper, the icing on the cake will be the chances and encounters with IoT in seeing this revelation of the forthcoming health care regions.

The IoT plays a important role in a comprehensive range of healthcare solicitations, from managing chronic diseases to avert diseases. Here are some examples of how its role is already being seen:

Clinical

Hospitalized people whose biological status necessitates close care can be frequently monitored using IoT driven, noninvasive observing. This type of answer employs antennae to collect ample physiological statistics and uses posterns and the cloud to scrutinize and store information to caregivers for additional analysis and evaluation. It substitutes the procedure of consuming a health professional come by at steady intermissions to check the patient's vigorous signs, instead if a continuous automated flow of evidence. In this way, it instantaneously advances the superiority of care through thoughtfulness and depresses the cost of maintenance by eradicating the need for a caregiver to energetically engage in info assembly and anaysis.

Remote Checking

There are folks all over the realm whose health may agonize because they don't have complete access to current health observing. But small, authoritative wireless solutions connected over the IoT are now building it possible for watching to come to these patients instead of vice versa. These resolutions can be castoff to steadily imprisonment patient data. A variation of sensors and apply composite algorithms in order to examine the data. The progress achieved in this field has been mind-boggling and has helped ease the pain endured due to lack of proper healthcare facilities.

Figure 1 shows us one of the current trends used in the field of healthcare with the help of the various components of IoT such as sensors (temperature, humidity, vibration etc).

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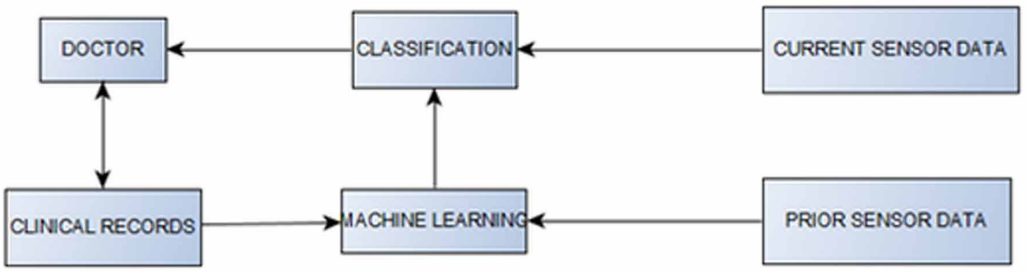
Figure 1.



- **Parkinson's Disease:** Parkinson's disease (PD) is a continuing and broadminded program ailment, meaning that indicators endure and deteriorate over period. Nearly around two million individuals in the country of India are bodily with Parkinson's disease. The origin is strange, and even though nearby is presently no remedy, there might be management options for example prescription and surgery to cope its indications. Parkinson's begins with the diminishing of vivacious nerve cells in the cerebrum, called neurons. Parkinson's to a great extent influences these particular nerve cells in a zone of the mind named the substantianigra. As PD upgrades, the condition of the person deteriorates over time which leads to a person not able to control his movements.

Effects of Parkinson's include:

1. Quiver of the hands and feet,
2. Not able to perform day to day activities.

The choice of PD be represented by upon the being of at least one of the four most mutual engine side effects of the sickness. In including, there are other minor and teetotaler proposals that touch numerous people and are logically familiar by clinicians as crucial to giving Parkinson's.

By definition, Parkinson's is a dynamic sickness. Albeit a few people with Parkinson's just have markers on one side of the figure for innumerable years, in the long run the signs start on the extra side. Signs on the additional side of the frame regularly don't change over as unembellished as signs on the early transversely.

The aim of this paper, is on the heartbeat rate monitoring and to alert the person and it is also able to observe the heart rate abnormality of a person. The system concludes and then sends an alert text to the mobile phone. It is compact and cost effective. It is very efficient system thus easy to handle and hence provides greater flexibility and serves as an improvement over other customary monitoring and alert systems. Biomedical engineering (BME) it has two angles: the design and the problem resolving techniques of engineering combined with medical sciences to enhance patient's wellbeing and the quality of life of individuals. The primary and a very common reason to ultimate death in the world are the cardiovascular diseases. The only feasible tool for the diagnosis is the heart beat readings that could aid early detection of cardiac events. We can measure one's heart rate through fingertip by this method.

The essential wireless technologies that as of now are used for social insurance frameworks are RFID, Bluetooth, ZigBee and remote sensor network which gives creative medium for information transmission in the field of medicine. WBAN ordinarily utilizes Zigbee. The smart sensors dealt with by patients

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transmit fundamental signs and flags to individual server consecutively; the information is transmitted from individual server to servers of the healthcare framework, similar to weather forecast, medical database or crisis server over Internet. Calculations might be executed on the healthcare framework servers to give moment and patient-particular proposals.

In the paper, the existing research is evaluated on wireless body area network in Healthcare framework. By utilizing wban health related medicinal services, framework will build up their performa and will be helpful for decreasing death rate. This give Quality of Service, low power utilization, consistent wellbeing observing and portability. In proposed framework they are processing the heart rate and body temperature variables by utilizing key elements of wireless body area network. In which data are taken from sensors which are sent on to android cell phone and subsequent to figuring down those data, heart assault can be normal. With the goal that versatility is achieved, and telemedicine framework is additionally implemented (Mazidi, McKinlay, & Causey, 2008).

In this paper, Patient Monitoring System using wireless technology strengthens the capabilities of doctors and medical authorities to track patient's vital conditions and determine their health condition. Persistent screen are the most essential symptomatic gadgets in basic care units of healing facilities that gives ceaseless show and translation of the patient's crucial parameters. Patient monitoring system measures physiological condition either continuously or at regular interval. The patient's monitoring requirements includes periodic detection of routine vital parameters and transmission of alerting signals when vital parameter indicates any type of threats or danger. PMS has resulted in stronger bedside patient monitors which are adequate of complex bio-signal processing.

In this paper, 12V and 5V power supply given to GSM modem and different gadgets individually. At the point when framework will begin, all devices are initialized. At that point heart rate sensor and temperature sensor measures heart rate and body temperature individually and both yields are given to the PIC controller. By means of GSM modem with the assistance of AT-Commands this data sends to medical authority. In the middle of PIC controller and GSM level converter is utilized to change over TTL to CMOS level and the other way around. For level changing over reason, we utilized MAX232 IC. In this module, we are given limit level for heart rate and body temperature. When heart rate and body gets temperature exceeded abnormally then the buzzer will turns ON (AmolGosavi, Dnyaneshwar Kandekar, Ghadge, Behere, & Patil) Pic controller gets easy program updates and it is small in size. Machinery and control system are the major use of PICI6F877A (Pounraj, Winston, Christabel, & Ramaraj, 2016).

When we placed a finger on heart rate sensor, it gives its output. The led sensor will blink up on each heartbeat. The sensor output is directly associated to PIC controller to calculate the heart beat rate. It is based on the phenomenon of blood flowing through fingertip at each pulse. LED is use in to detect the blood flowing through the vessels (Sundaram, 2013).

Advancement in the field of Micro Electro Mechanical Systems (MEMS) has led to a lot of imminent progression in the study of WSNs. There is a lot of existing research in the field of wireless sensors networks used in various applications. They have several uses in many different industries. Some of them include military applications, security and health. in the military, they have been used for various specific purposes such as battlefield surveillance and battle damage assessment. Existing research in collection of physiological data from wireless sensors nodes to transmit to doctors or medical personnel has been exhaustive. Several applications have been designed for various purposes such as patient tracking, drug administration and tele monitoring of patient's data over the web. WSNs have been very convenient in usage for ambient assisted living applications as well. WSNs can also been used to check chemical levels and water purity levels in pollution check systems. They aid in detecting amount of pol-

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lutants and chemicals in water or air. They can also be used to check the amount of nutrients in the soil which is extremely useful and beneficial in agricultural applications as well. Other applications also include home automation and home security systems. Wireless sensor nodes have been deployed in a wide variety of applications. They have been widely researched. One the major advantages of wireless sensors are their low power consumption compared to other modes of communication. According to several researchers, these systems are also largely fault tolerant. They also solve the issue of wiring and restricting the mobility of the systems they are attached.

The following aspect would clarify about the proposed smart health monitoring and alert system. There are such a variety of places where this system is utilized. This is for the most part utilized as a part of the places where medical centre are far away.

This paper describes the health monitoring system for PV array of 2×2 . This method is used for finding the health position of patient in 30 mins. from 6.00 am to 6.00 pm. This method is used for improvement of extraction of energy, it detects the fault accurately and it is extendable for any kind of arrays. It can implement the reconfigured control switch for the increase of power generation of the faulty conditions of this system (Spencer Jr, Ruiz-Sandoval, & Kurata, 2004).

This paper describes the monitoring of ECG, heart rate, SpO2, pulse rate and temperature by using a patient's health monitoring system. The values are uploaded in a web server by storing them in a database In future; it can be uploaded in a database automatically. The doctor who is sitting abroad can also get the full report of patient's medical history so that they can see and advice the patient that what they can do for the treatment of the disease (Navya, & Murthy, 2013).

This paper gave a prologue to smart sensing technology, recognizing various occasions, and a portion of the related difficulties. Smart sensors which are on the Mote worldview will give the capacity to improvement of the up and coming era of structural health monitoring frameworks and opens new prospects for innovative work. Multi-specialist system innovation presents a computational structure for new calculations execution (Setyowati, Muninggar, & NA, 2017).

The paper describes a Wireless Sensor Network (WSN) used for observing patient's physiological circumstances continually utilizing Zigbee. In this paper, the physiological values, for example, body temperature, heart rate, body effect and saline level are observed. Low-control arranged intensifiers were utilized to limit battery utilization. The design of the IR sensors could be upgraded to diminishing its acceptance to buzz, to a point where it could be moved onto the wrist unit. The unit is intended for use by the develop, inside the house, where a caretaker is available yet is not ready to be always in visual contact with the patient (Perera, Liu, & Jayawardena, 2015).

In this paper, the healthcare monitoring is prepared by utilizing remote sensor gadgets and reports all the sensor information to the doctor. Throughout the healthcare monitoring if any patient wellbeing condition is severe, then it sends a crisis notice message to the doctor by utilizing GSM innovation. Utilizing four sensors connected to healthcare monitoring, for example, beat sensor, Accelerometer, breathing sensor and blood Pressure sensor which is controlled by microcontroller and get information from sensors. The work left will be intended to utilize Zigbee to send information from sensor gadgets to PC and they will utilize GSM innovation to send crisis notice messages to the doctor's mobile (Arpan Pal, Innovation Lab, 2016).

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Proposed Approach

For many persons breathing with Parkinson's disease, the performance of mastication and believing can be a test. One way to contract with this is to mixture foods up to minimalist the essential to portion. But what if it's problematic just bringing the serve to one's mouth without dropping its fillings? In order to target this, I have thought of a few devices that not only help to counter Parkinson's disease but also make the lives of those affected much easier with the help of this.

Smart Pen/Spoon

Smart Pen is the first tremor stopping pen that syndicates software and hardware to make a clever resolution to the extensively knowledgeable problematic of script tremors. It uses dynamic steadying to counterbalance tremors much more meritoriously than key snow on the market. Inside, a gimbals instrument and a equipoise regulator procedure work in tandem to mollify the pen. Make the calligraphy tremor-free. The pen is also malleable. By substituting the insert with any inscription utensil, all kinds of doings can advantage from the pen's single soothing skills.

Figure 2. IMU: An inertial measurement unit (IMU) is an electrical device that processes and reports a body's exact force, angular rate by means of able no. of accelerometers

A servomotor is a rotary actuator that countenances for detailed control of angular or linear position, velocity and acceleration.

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Figure 3. Tilt and Accelerometer Sensors: Orientation sensing

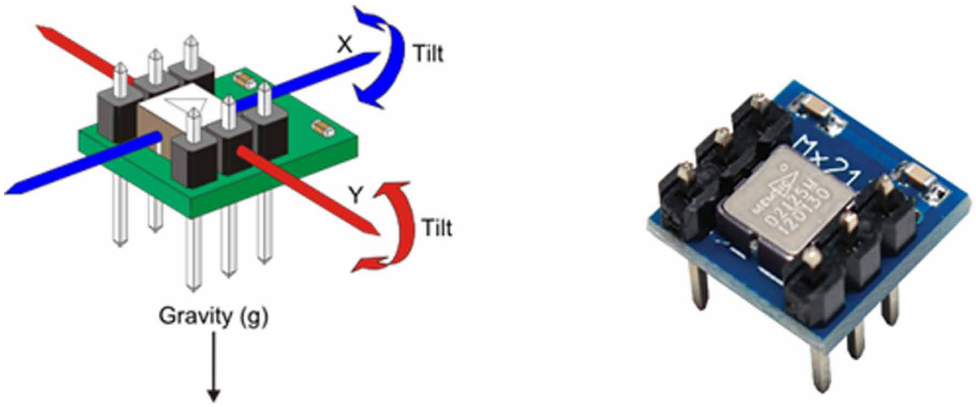
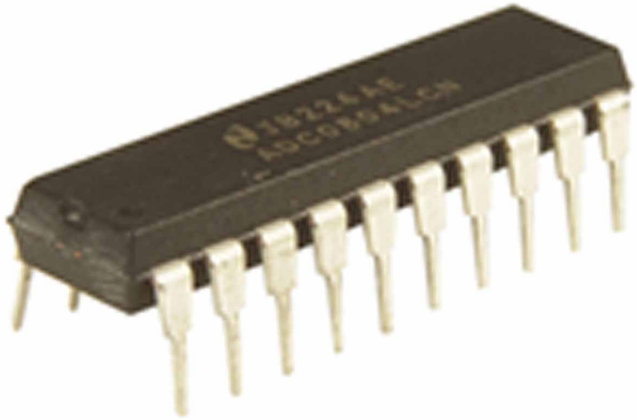


Figure 4. 8 Bit AVR Microcontroller



Working

The person's tremors are checked upon by the system which goes as an acceleration data which is taken from the IMU and then passes through (AVR) which executes guesstimate on the data assimilated from the acceleration sensor. In order to make sure that the system will go in an opposite directional electromagnetic (a servo) drive is premeditated to function with an embedded micro-controller based application. Every time there is a change in acceleration data the servo is actuated in a direction opposite to the recorded value from the person's hand tremor. This device uses six-point based sensor data calibration (Ufoaroh, Oranugo, & Uchechukwu, 2015).

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Figure 5. Servo Motor

Smart Devices to Improve Voice

Apps and devices can give individuals more control over the choice of therapy plans. The idea is to create an app that changes the frequency of the voice of the person suffering from Parkinson's disease. It is highly suitable for improving loudness or for normalizing speech rate.

Walking Device

(Smart) Falls are an intermittent and perilous inconvenience of Parkinson's infection. Understanding reviews show that the rate of PWPs who learning falls can keep running as high as 68 percent. Parkinson's patients are at an expanded danger of dropping due to the signs of Parkinson's sickness - strong solidness, solidifying, rearranging stride, adjust debilitation or stooped stance - and in uncommon cases thus of the reactions of anti-parking son meds. Indeed, even a minor fall can starting point wounds and sprains. More mindful falls can reason genuine wounds, for example, destroyed bones or electronic stun. In totaling, the fear of decreasing can likewise touch PWP enthusiastic, which unwillingness to authorization the family unit. In this way, Fall Deterrence is a huge guideline for giving Parkinson's sickness, extraordinarily exposed to the harsh elements months, when even garages and walkways require additional safety measures. Here we plot a portion of the proposals would come. In order to counter this, a smart walking device can be formed which senses the movement of the person and prevents him from falling by tilting in a particular direction.

Smart Room

Equipping the room to an ambient temperature and ensuring that the patient is taken care of properly.

Figure 6 provides the working of the Smart Spoon.

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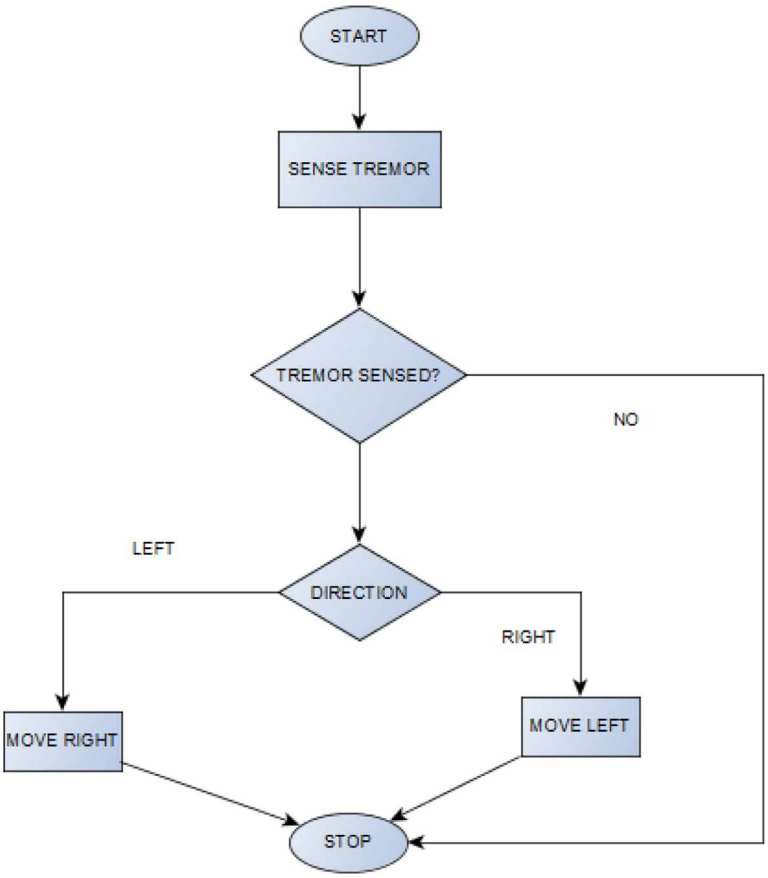
Figure 6.



CONCLUSION

In this chapter, we have seen how the evolution of healthcare under the influence of IoT has helped the greater humanity at large and what the current trends are. It particularly focuses on the Parkinson's disease and how it can be tackled if not cured with the help of the Internet of Things.

Feature Enhancement

Mobile cloud computing (mcc) is able to save energy, improve application and experience of the users. All frameworks mentioned above have their own benefits and issues but still not up to level to address all issues related to security, energy and user experience. Security issues are key problem in mcc, they need to be focused more compare to other issues.

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Chapter 32
Assessment of Gait Disorder in Parkinson's Disease

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ABSTRACT

Neurological disorders are some of the leading chronic disorders that impose a massive burden on low-income and developing countries. The disability resulting from the neurological disorder increases the severity and costs during the primary healthcare and for entire lifetime. Parkinson's disease (PD) is the second most common chronic neurodegenerative disorder which is slowly progressive with decrease in the motor and non-motor function of the nervous system due to cognitive impairment leading to gait abnormality. PD is most common in the age group of 40-65years leading to increase in gait disorders associated with slowing down of the movement, balance instability, rigidness in the muscles, and difficulty in performing everyday tasks. The assessment of gait plays a significant role in maintaining the balance disorders in Parkinson's disease. In patients with PD, the neurons present in substantia nigra region of the brain get injured, and they progressively decline during their lifetime. Therefore, the patients lose their ability to perform movement and also lose their stability. The symptoms of PD can be monitored and controlled by assessing gait parameters based on gait disorder.

INTRODUCTION

Neurodegenerative disorder primarily affects the neurons present in the human brain leading to the loss or death of the neurons. Aging is one of the greatest risk factor of neurodegenerative disorder. The WHO (World Health Organization) has estimated that the neurological disorder affected more than one billion

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people worldwide leading to disability and suffering. Gait and balance disorders usually occurs in all major neurological diseases. Parkinson's Disease is the second most progressive neurological disorder which affects the elderly and its prevalence is predicted to increase with respect to the growth of the elderly population. Dr. James Parkinson, a surgeon and physician gave an essay describing the Shaking Palsy which is familiar in the western world. The birthday of Dr. James Parkinson has been chosen as the "World Parkinson's Day" and red tulip flower has been selected as its symbol. The clinical features of the PD combine four major parts of the human body namely changes in the motor function, changes in the cognitive function of the brain, changes in the behaviour and symptoms leading to failure in autonomic nervous systems. Every portion of the brain plays a different and critical role in the human body. The PD develops because there is a loss in the cells present in the basal ganglia portion of the brain. The basal ganglia control the basic human activity like walking and other movements. The abnormality in this portion results in irregulated movements of the human. Normally there are certain specific cells present in the basal ganglia which are responsible for the production of dopamine. The dopamine is one of the neurotransmitters produced in the brain which releases a chemical to communicate with different parts of the brain. Therefore, the progression of PD over many years makes these brain cells to die and there will be reduction in the dopamine level of the brain leading to more complication like resting tremor, bradykinesia, rigidity in the body and balance disorders. The symptom related to PD are unilateral which means one side of the body is more affected than the other side. The disease later progresses to the bilateral findings. Tremor usually occurs during the beginning of the PD and limited to one side of the arm or leg for many years. Bradykinesia which is described as the peculiar and most disabling characteristic of PD leads to slow or absent of movement. Rigidity is the resistance to the movement of the individual. Balance disorder is one the major problem in PD patients leading to frequent falling and postural abnormalities. There are also several minor motor and non-motor functions associated with PD patients namely speech impairment, cognitive impairment and psychological disorder. There are variety of medications available to treat the symptom of PD. At the initial stage the individual has already developed disability and therefore pharmacological treatment is required. The second stage is the development of complications and the third stage is the dopamine deficiency treated using dopamine agonists. Gait Rehabilitation are recommended for PD patients who have speech and mobility problems. The economic cost for the PD patients is high and PD reduces the quality of life of the individual and caregivers. The current research focus on building animal models based on gene therapy and stem cell transplantation.

BACKGROUND

Parkinson's disease (PD) is a neurodegenerative disease which mainly affects the human motor system (Rodriguez-Martin, Sama, Perez-Lopez, Catala, Moreno Arostegui & Cabestany, 2017). PD has many symptoms in which the freezing of Gait (FoG) is one among them. In recent years, the classification systems with several classifiers such as Linear Discriminate Analysis, K-nearest neighbour, K-means, Random forest, Naïve Baiyes, Support Vector Machine (SVM), Artificial Neural Network (ANN) etc. are utilized as an automated decision support tools for the early detection of diseases of human body. Eventhough, the Naive Bayes classifier is one of the oldest classifier, it is very simple to implement and needs fewer amounts of training data. This simple and efficient classifier is adopted by several researchers on biomedical and other fields for classification (Sarkar, Goswami, Agarwal & Aktar 2014;

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Wolfson, Bandyopadhyay, Elidrisi, Vazquez-Benitez, Musgrove, Adomavicius, Johnson & O-Connor 2014;Ahmed, Shahjaman, Rana, Mollah & Haque 2017).

Principal Component Analysis (PCA) is a dimensionality reduction technique which is used in various fields such data analytics, bio-signal, image processing etc. where the original dimensionality is too large to process (Chen, Lin, Liao, Lai, Pei, Kuo, Lin, Chang, Chen, Lo & Chen, 2011; Kim, Shin, Shin & Lee, 2009; Hsieh, Lin, Te, Lo, Wu, Chung, Chang, Lin, Lo & Hu, 2017). In bio-signal or image processing, the PCA is used to improve the accuracy of the classifiers. Kikkert et al. (2017) have utilized PCA and extracted 11 gait variables to determine the gait properties. Also, the authors have developed a model using Partial Least Squares-Discriminant Analysis for the assessment of fall risk in geriatric patients. Matsushima et al. (2017) have analysed the characteristics of ataxic gait which is recorded with the help of triaxial accelerometer. Further, the authors have adopted PCA and extracted four principal components in the control subjects and two principal components in the abnormal patients.

Zhao et al. (2013) have designed an ECG identification system using ensemble empirical mode decomposition. Further, the authors have used PCA to reduce the dimensionality of feature space and the K-nearest neighbors (KNN) classifier is utilized as the classification tool.

Feng at al. (2013) have proposed a Naive Bayes based method for the prediction of phage virion proteins. Further, the authors have concluded that the proposed method has a classification accuracy of 79.15% which is superior than other state-of-art classifiers. Sambo et al. (2012) have proposed a Bag of Naive Bayes (BoNB) classification algorithm for the analysis of genome-wide SNP data. Further, the authors have concluded that the proposed BoNB classifier has good classification accuracy which can be used as both classifier and genetic biomarker.

Miranda et al. (2016) have discussed about the detection of risk levels of cardiovascular disease for adults using naive bayes classifier. Further, the authors have assessed three different classifier's performance such as accuracy, sensitivity and specificity. Also, the authors have concluded that the proposed model has the prediction rate of 80%.

SVM is based on statistical learning theory which is highly suitable for semi-structured or unstructured data such as text or images. Also, the SVM with appropriate kernel function can solve any type of complex problems. The various kernel functions are Linear, Quadratic, sigmoid, Gaussian, radial kernel etc (Saberioon, Cisar, Labbe, Soucek, Pelissier&Kerneis, 2018; McDermott, O'Halloran, Porter & Santorelli, 2018). Due to the technological advancements, the SVM classifiers with different kernels are used in wide fields such as image processing, optical text recognition, bio-signal classification etc. McDermott et al. (2018) have discussed about the detection of brain haemorrhages using Electrical Impedance Tomography (EIT) measurement frames and Linear SVM classifiers. Also, the authors have demonstrated that the performance parameter such as sensitivity and specificity of Linear SVM classifier is 90%.

Wu and Xu (2016) have proposed a method in which the block sparse Bayesian learning (BSBL) algorithm is presented to reconstruct an acceleration data. Further, the authors have validated the feasibility of the proposed method for gait telemonitoring application with three different gait classification models such as support vector machine (SVM), multilayer perception (MLP) and KStar.

Nukala et al. (2016) have developed a Wireless Wearable Gait Sensor for the classification of patients with balance disorders and normal subjects. Further, the authors have extracted the features from gait signals which is acquired using gyroscopes and accelerometers and have adopted four different classifiers such as SVM, binary decision trees (BDT), k-nearest neighbours (KNN) and back propagation artificial

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neural network (BP-ANN) for the classification process. Also, the authors have reported that the SVM has overall classification accuracy of 98%.

Saberioon et al. (2018) have adopted four different classification methods such as Random forest (RF), Support Vector Machine, Logistic regression and KNN to evaluate fish diets. Further, the authors have concluded that the SVM with radial based kernel has highest classification rate of 82% and it is superior to other adopted classifiers.

Wu and Wu (2015) have proposed a novel method for assessment of gait symmetry using advanced statistical learning algorithm. Further, the authors have recorded gait signals from 60 participants using a strain gauge force platform. Also, the authors have designed an advanced statistical learning algorithm such as SVM for binary classification and are utilized to quantitatively evaluate gait symmetry. The authors have reported that the proposed algorithm using SVM can be used as a tool for early identification of the elderly gait asymmetry in the clinical diagnosis.

Simila et al. (2017) have proposed a novel method to detect early stage of shortfalls in balance from gait. Further, the authors have collected gait acceleration data using waist-mounted accelerometer. Also, the authors have concluded that the gait features can be considered for the assessment and prediction of early signs of balance shortfalls. Zhou et al. (2018) have discussed about the impacts of hemodialysis process on gait and balance beyond aging and diabetes condition.

Raknim and Lan (2016) have proposed a Pedestrian dead reckoning based method for continuous assessment of patient's gait signals using smartphone. Also, the authors have concluded that the binary classification-based support vector machine is more significant on classifying walking patterns of a PD patient with overall accuracy of 94%. Thiede et al. (2016) have quantified gait and balance using wearable sensors. Further, the authors have assessed the group differences in frailty using analysis of variance whereas the authors have determined the independent connections within gait and balance using logistic regression models.

Backstrom et al. (2018) have examined mortality and associated risk factors in a community-based population with incident parkinsonism and Parkinson disease. Maqbool et al. (2016) have discussed about the real-time rule based gait event detection for lower limb amputees using shank mounted inertial measurement unit. Further, the authors have stated that the proposed system is highly capable of detecting temporal gait events with detection accuracy of 99.78%. Lee et al. (2014) have analysed the videos which is taken from patients having Parkinson disease. Further, the authors have classified the parameters associated to posture and gait into three classes namely standing, gait and associated symptoms. Also, the authors have concluded that the visual inspection of gait and posture gives reliable information for the diagnosis of Parkinson disease.

Laske et al. (2014) have discussed various diagnostic tools for early detection of Alzheimer's disease. Pistacchi et al. (2017) have investigated an abnormal gait pattern in early Parkinson disease patients. Further, authors have stated that there are some distinguishing characteristics of gait namely ambulation disorders are present in early Parkinson disease patients and they suggested it can be mitigated by proper rehabilitation process.

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METHODOLOGY

Assessment of Gait in Healthy Individuals

The neurological condition in which a person slowly develops difficulty in controlling the activities related to movement is termed as movement disorder or gait disorder (Levine, Richards & Whittle, 2012). The ability of the body to maintain stability related to gait and posture with respect to the centre of gravity is defined as balanced gait (Baker, 2018). The analysis of gait can be carried out in two ways namely standard laboratory-based gait analysis or new upcoming methods like wearable and non-invasive measurement methods. The standard laboratory-based measurement is a golden standard for performing gait analysis using EMG(Electromyography) sensor attached to the body motion of the patient or by using optical measurement system and force sensor (Chen, Wang, Liou & Shaw, 2013).The results produced by this method are accurate but only for shorter distance. The wearable and non-invasive measurements use portable digital based equipment which are light, small and less expensive compared to standard method. This type of measurements is used for long term monitoring of patients.

Walking is a most complicated task involving various changes in the gait patterns which is performed by precisely controlling the limb and posture movements. In the brain, cerebral cortex receives input from the visual part, vestibular and proprioceptive part of the brain stream, basal ganglia, cerebellum and integrates it with the neurons which carry signals from muscle stretch receptors. The gait cycle is often assessed during two phases namely swing phase and strike phase. Further, the complexity of walking phase increases the risk of losing stability among elderly people due to age and motor function disorder. Depending upon this, the assessment of gait can be classified into four main stages of the gait cycle (Smulders, Dale, Carlson-Kuhta, Nutt & Horak, 2016). They are

1. First Stage: Walking straight on a flat surface
2. Second Stage: Initiation of gait movement
3. Third Stage: Ability to walk during turning and other rotations
4. Fourth Stage: Adaptability of gait to walk on irregular surface

First Stage: Walking Straight on a Flat Surface

In first stage the motor behaviour is performed automatically in healthy subjects because this stage requires only minimal attention and less cognitive part while walking straight (Hawkes, Del Tredici & Braak, 2010). The stability of gait is determined by calculating the variability in the stride length from step phase to stride phase. This stage does not require much attention because the sensorimotor striatum provides an automatic control to the brain and the operation is performed.

Second Stage: Initiation of Gait Movement

In the second stage, the attentional control gives instruction to the motor cortex because it involves shifting of the posture and balance. The initiation of gait is a goal generated movement which involves more strain to the cortical part. The length of each step and the duration and amplitude are studied during this stage.

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Third Stage: Ability to Walk During Turning and Other Rotations

The third stage requires more cognitive control of the attentional and automatic control of the brain for performing the turning action which in turn requires both change in the posture and balance. The turning phase involves uneven rotation of the foot and the upper body. The number of steps taken for rotation, gait speed postural stability with respect to the centre of mass and co-ordination of the feet-head are studied to quantify the turning phase.

Fourth Stage: Adaptability of Gait to Walk on Irregular Surface

The fourth stage is mostly dependent on the cognitive control for adaptability of the gait over obstacles. The obstacles involve walking on an irregular surface, uneven terrain and crowded areas. The output measures of gait adaptability are studied by measuring the success rate in obstacle avoidance, distance measured between the obstacle and the foot and the stability while crossing the obstacle (Xu, Hunt, Foreman, Zhao & Merryweather, 2018).

The recent advances in analysing gait disorder includes portable wireless monitoring of the patient's data, data gathering with the help of intelligent systems by the patient and also wireless sensor monitoring. The portable wireless technology will be the future of gait assessment since it reduces the time complexity and easy for measurement. Further, the force-plate sensors can be fixed into the footwear for measurement which also helps in long-term monitoring of gait irrespective of the stages of the patient. Quantitative measurement makes more accurate measurement of duration, gait speed, stability in gait and gait rhythmicity. Therefore, the advantages of wireless and non-invasive monitoring provide a way to integrate huge number of data depending on the task performed by the individual compared to laboratory based measurement.

Assessment of Gait Disorder in Parkinson's Disease

Parkinson disease is mainly characterised by disability in the motor functions leading to different stages of bradykinesia, cogwheel rigidity, parkinsonian tremor and gait abnormality. The pathology of PD is loss in the energy level of dopamine neurons. Since PD is a chronic and highly progressive disease it has both the motor and non-motor symptoms (Mouradian, 2001). Motor automaticity is associated with the changes in the motor and non-motor function of the PD patients. The PD patients lose the automatic skills or new motor skills due to the impaired function of the sensorimotor striatum. The motor automaticity is usually evaluated during the dual-task paradigm where the secondary action requires equal level of attention as that of the first action (Wu, Hallett & Chan, 2015). When the patients perform dual task in parallel, the attentional resources are limited and divided. An automatic action of this task is accompanied by increased efficiency, minimal attentional demands and little resources to perform the task. The first action includes tasks like getting up from the bed in the morning, eating breakfast, holding a fork/spoon all these requires minimal cognitive action whereas the secondary action requires little attention to the motor function like counting numbers task which requires more cognitive action compared with the first action. The first motor task is said to be automatic if it is performed correctly without any sort of interference. If the performance of any one task lags during the dual task paradigm then the motor action is not performed automatically.

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In healthy patients if the motor skills are automatic then (1) the neural functioning of the patient becomes more efficient (2) There will be no need for attentional network (3) The interference will be resisted during the automatic task (4) The support for sensorimotor striatum is critical. If the motor skills are not automatically performed whereas in case of PD patients, they tend to perform all the daily behaviours slower with smaller amplitude than healthy patients. Therefore, the PD patient have difficulty in performing automatic task like arm swing, modulation in speech, facial expression, blinking even during the early stage of the disease. The gait disorder is an early symptom of people with PD and it increases with age leading to disability.If the motor skills are not automatic in PD patients then (1) the movement of the neural coding is less efficient (2) there is a failure in shifting the automated motor skills to the sensorimotor striatum (3) the automatic mode is not stable and it can be disturbed within the striatum (4)mostly they rely on the attention control to execute the movements which are automatically performed by the healthy patients.

First Stage of PD Patients

Bradykinesia, the first stage of symptom in the analysis of PD subjects where they experience smaller steps than usual, and the imbalance associated with it making the people double the time to perform any specific action. The shorter steps at this stage reflects the difficulty in controlling the Centre of Mass (CoM) of the body. The bradykinesia in the upper part of the body results in reduced movement of the arm and reduction in the velocity and range of motion. Further, the changes are also observed during the postural instability which will results in increased risk of falling in PD subjects. Also, there will be at least 50% loss in the level of dopamine(neuron) present in the substantia nigra where these symptoms lead to the starting of PD. Cell loss in this region causes low level of dopamine neurons.

Second Stage of PD Patients

Anticipatory Postural Adjustments (APA) or Akinesia, the second stage of the symptom shows difficulty in APA during the initiation of the gait cycle. The first step length is short, and the movement is also performed slowly by repetitive movements in PD subjects compared to healthy subjects. Depression defined as the premotor symptom plays a major role in the PD patients. The severity of the disease is correlated with the decreased functional connectivity and reduced function of the basal ganglia. Therefore, the automatic control of the PD patient becomes disable and there is no action performed by the sensorimotor to initiate the movement and therefore the attentional control performs the action leading to more time and less force.

Third Stage of PD Patients

Sequential movement, the third stage of the symptom shows difficulty in the co-ordination of eyes and head movement. The turning can be performed only when both cognitive and neural functions of the body work in co-ordination with each other. Therefore, this task of turning and rotating which requires the action of eyes, legs and head simultaneously can only be performed by additional turning and jerky rotational steps sometimes leading to imbalance and increases the risk of instability. The obstacle hit experienced by the PD patients will be more when compared to the healthy patients.The impaired and decreased function of the basal ganglia followed by reduction in the level of dopamine reduces the

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movement in PD patients. The PD patients performs simple repetitive task with high timing variability compared to the healthy patients.

Fourth Stage of PD Patients

Gait Adaptability, the fourth stage where the patient with PD experience higher number of hit and they are less stable compared with healthy subjects. Sometimes they also experience a breakdown in their motor planning part which makes their situation even worse. The placement of foot relative to that of the obstacle is also smaller and therefore there are more chances of collision. During this stage, the pathology of the disease is widespread, and it is difficult to predict the correlation in the clinical data. A small portion of the PD patients develop changes in the behaviour mainly due to the dopaminergic therapy.

Freezing of Gait

Freezing of gait (FoG), the last stage of PD eventually develops to majority of patient where they have a feeling that their feet are attached to the ground. FoG usually occurs during the dual task paradigm where multiple attention is needed to perform a task like talking or using a device while walking. Therefore, the FoG patients perform these tasks very slowly compared with the PD patients and FoG patients have a shorter stride length and step length. Further, the defective motor functioning in PD patients are also a reason for contributing to FoG. Initiation of gait is usually performed internally in healthy patients. In FoG patients the connectivity of the basal ganglia cortex motor functioning loop is disrupted, and they have difficulty in performing the gait cycle. During the turning phase, FoG patients takes more time to perform the action than PD patients. These patients face a severe cortical damage at the last stage. The damage further results in the impaired taste pathway. Also, the loss of dopaminergic neuron induces a difficulty in executing automatic action in FoG patients. Typically, in this phase the patient is unable to move from a position leading to the advanced stage of the disease.

Comparison of Gait Disorder Between Healthy and PD Patient

Figure 1 shows the assessment of gait in both healthy and PD patients by collecting input from the force sensors that where placed on both the foot of the patient. The old age patients above 60years where considered for assessment. PCA is used for extracting highly correlated features from raw input data obtained from the force sensors. After feature extraction, classification of the healthy and PD patients is performed based on two classifiers namely Naive Bayes (NB) and Linear Support Vector Machine (LSVM). Further, the evaluation of the classifier performance parameters is calculated by considering the accuracy, sensitivity, specificity, positive predictive value and negative predictive value of both the classifiers.

DATA ACQUISITION AND ANALYSIS

In this study, the gait rhythm dataset (Hausdorff, Lertratanakul, Cudkowicz, Peterson, Kaliton & Goldberger, 2000) from the Physiobank was utilized for analysis of gait in PD patients (Zeng, Liu, Wang, Ma & Zhang, 2016). This is one of the large extensively used physiological data for public research

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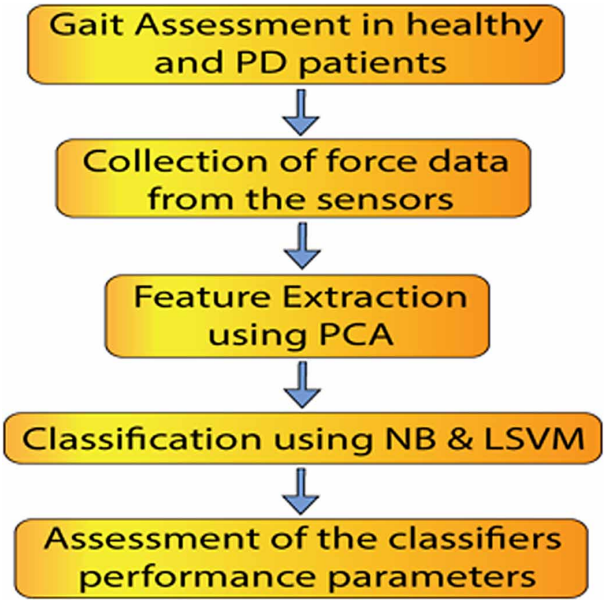
Figure 1. Flowchart for assessment of gait order using classification algorithms



purposes founded by Harvard- MIT institutes. This dataset contains both healthy and PD patient in the age of 66.3 years with 63%men. In the experiment, the patient is required to walk continuously in a flat level ground for a period of two minutes. Under each foot there were 8 sensors that measure the force (in newtons) as a function of time. The output from the sensors are digitized and recorded at 100 samples per second. The stride time (initial contact of one foot to the time taken for the subsequent contact from the same foot), swing time (time taken when one foot is in air with respect to the stride time) and also the centre of pressure can be calculated as a function of time. The stride to stride measurement output can also be calculated from the force sensors. This database also provides information about the severity of the disease and dual task while walking on the flat surface and treadmill. Further, the feature extraction is carried out by transforming the input data obtained from the Physiobank into a set of features which may represent the input data in a well-defined form for performing further analysis of the gait rhythm.

Principal Component Analysis (PCA)

PCA is extensively used in large number of applications in healthcare and industry due to its simplicity and extracting meaningful information from a complex dataset. PCA is easy to understand since it simplifies the confusing dataset to lower dimension (De Maesschalck, Estienne, Verdu-Andres, Candolfi, Centner, Despagne, Jouan-Rimbaud, Walczak, Massart, De Jong & De Noord, 1999). The principle of PCA is to transform the maximum possible number of correlated variables into smaller variables known as principal components. The dimensionality of the PCA is reduced with the help of vector transformation. The reduced dataset makes the interpretation much more clear and easier. The algorithm steps for PCA are as follows:

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Step 1: Identify a set of orthogonal coordinate axis from the input data. The new axis obtained is called as first principal component of the data.
Step 2: The interpretation of the first principal component is represented in the form of score plot to identify the correlation in the data.
Step 3: Identify the second principal component axis which is orthogonal to the first principal component and the best direction to approximate the input data.
Step 4: The interpretation of the second principal component is represented in the same above score plot and the loading plot gives the eigen vector values.
Step 5: Covariance is used to measure the correlation between the two variables in the data.

Using these steps, the feature extraction using PCA is carried out for the gait rhythm database. PCA is used for many applications in neuroscience, quantitative analysis of risk management and multivariate calibration in spectroscopy. Next step is the classification of gait rhythm of patients with PD using machine learning algorithms.

Naive Bayes (NB)

The NB classifier is a probabilistic classification method based on the Bayes theorem. Each features of the NB classifier provide independent assumptions. The principle of NB classifier assumes that the particular feature present or absence in a class is unrelated to the presence or absence of the other feature in the same class (Leung, 2007).The Bayesian classifier are based on statistical classifiers which can predict the probability of the data from the given dataset. The algorithm steps involved in NB classifier are as follows:

Step 1: Consider an n-dimensional vector space with a set of training samples, measured values and their class labels.
Step 2: Now given a sample X the classifier will predict the class of X based on the highest probability.
Step 3: In order to reduce the computation steps an assumption is made in the naive classifier by making the value of the attribute independent to one another.
Step 4: The probabilities can be easily calculated with the help of the training data.
Step 5: In case the value of the attribute is categorical, the number of samples in the training data is divided by the number of samples of the original data
Step 6: In case the value of the attribute is continuous, then the values are calculated based on the gaussian distribution with respect to mean and standard deviation.

Some common application of NB classifier is useful in the field of multi-class prediction, real-time prediction, text classification, sentimental analysis and also in automatic medical diagnosis.

Linear Support Vector Machine (LSVM)

SVM is a non-probabilistic linear binary classifier developed from the statistical learning theory and have been applied in numerous numbers of application from time series to biomedical data processing. The principle of SVM are defined by a subset of feature vectors which are known as support vectors.

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SVM is based on a set of supervised algorithms which is used for prediction, classification and regression based on optimization theory to increase the prediction accuracy and avoid over fitting of the data. The special feature of SVM are (1) the generalization of the matrix is made high by maximizing the margin (2) the non-linear functions are learned efficiently using kernel function. The steps followed in the SVM algorithm are:

The initial form of the LSVM classifier a linear binary classifier where the output obtained from the learned function may be either positive or negative (Yu & Kim, 2012). A multiclass problem can also be computed by means of LSVM by combining multiple binary classifiers together. The main steps are maximization of the margin data and kernel function.

Step 1: Each data point is represented by means of a n dimensional vector. The data points are divided into two categories in case of binary classifier.
Step 2: Linear classifier is used to correctly classify the data in the two-dimensional space with respect to the hyperplane.
Step 3: The LSVM finds the hyperplane with larger margin and maximum separation between the classes.
Step 4: The margin obtained shows the shortest distance separating the hyperplane to the data point nearer to both the categories
Step 5: Similarly, to do mapping of the feature set of the input of the non-linear classification problem kernel function is used.

SVM are used for solving huge number of real-world problems in hand-written characters, classification of images in different fields and also in text and hypertext categorization.

RESULTS AND DISCUSSION

In this chapter, two main events are considered for the recording of force data namely normal walk and Treadmill walk. Also, the individuals of two different groups such as normal or control subjects and PD patients are considered for this study. The force data from both the control subjects and PD patients during normal walk and Treadmill walk are recorded for analysis.

Figure 2 (a) and (b) shows the Total force recorded from control subject during normal walk under the right and left foot, respectively. Further, the total force is given in newtons with respect to time. Figure 3 (a) and (b) shows the Total force recorded from PD patients during normal walk under the right and left foot, respectively. It is seen that there is no significant difference by visually observing the force data's recorded from control subject and PD patient during normal walk.

Figure 4 (a) and (b) shows the Total force recorded from control subject during Treadmill walk under the right and left foot, respectively. Further, the total force is given in newtons with respect to time. Figure 5 (a) and (b) shows the Total force recorded from PD patients during Treadmill walk under the right and left foot, respectively.

In this chapter, the Principal component analyses feature extraction technique is utilized to extract the features from recorded force data. Further, these extracted features are utilized by LSVM and Naïve Bayes classifiers for the classification of normal and PD force data. The standard performance parameters of two different classifiers such as LSVM and Naïve Bayes were obtained using the following equations:

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$$Accuracy = (TP+TN) / (TP+FP+TN+FN) \quad (1)$$

$$Sensitivity = TP/ (TP+FN) \quad (2)$$

$$Specificity = TN / (TN+FP) \quad (3)$$

$$Positive\ predictive\ value = TP / (TP+FP) \quad (4)$$

$$Negative\ predictive\ value = TN / (TN+FN) \quad (5)$$

Figure 2. Total force recorded from control subject during normal walk under the (a) right foot (b) left foot

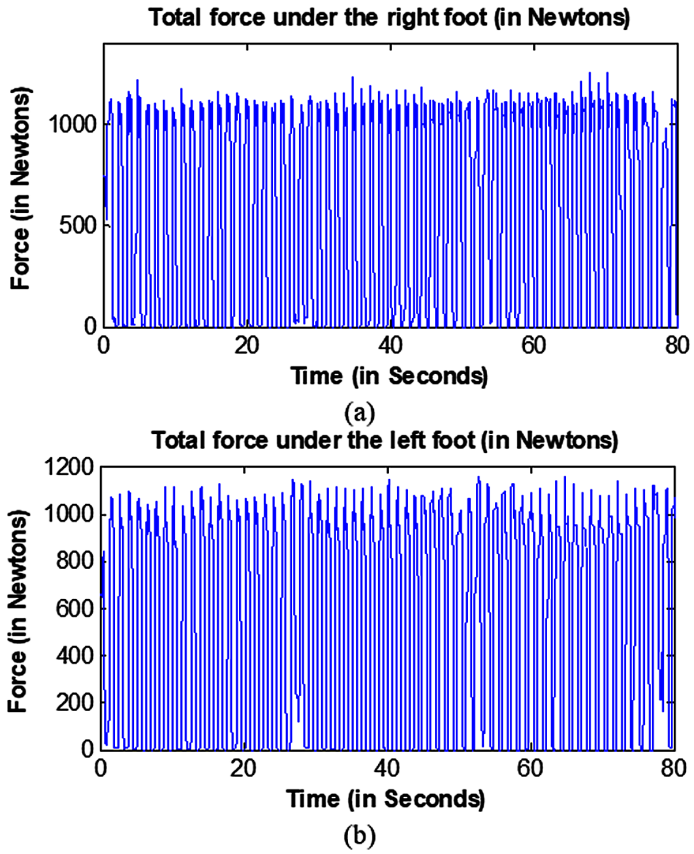

Figure 6 (a) and (b) show the five different performance parameters such as accuracy, sensitivity, specificity, Positive Predicted Value (PPV) and Negative Predicted Value (NPV) for LSVM and Naïve Bayes classifiers during normal walking event, respectively. Usually, from the output of the classifiers the parameters such as true positive (TP), true negative (TN), false positive (FP) and false negative (FN) are used to assess the standard performance parameters. Further, it is seen that the accuracy of LSVM classifier is 91% and the accuracy of the Naïve Bayes classifier is 73%. It is observed that the Positive Predictive Value of Naïve Bayes is 55% and the Negative Predicted Value is 91. It is seen that the per-

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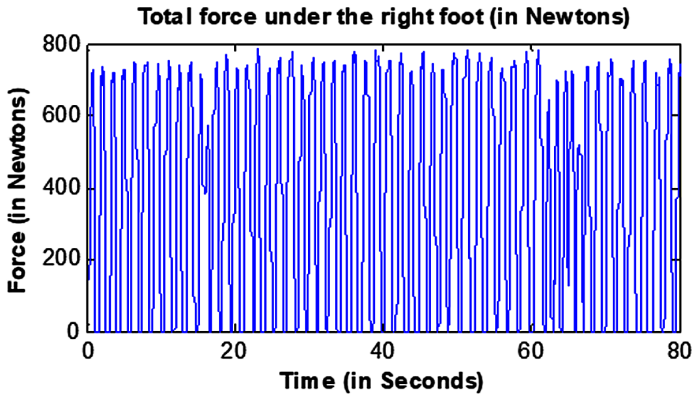
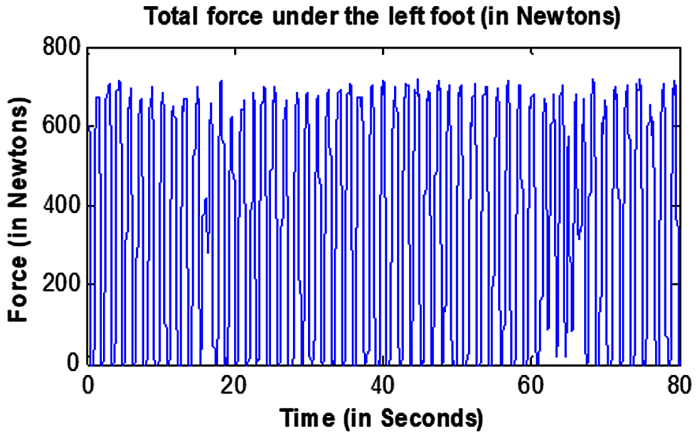
Figure 3. Total force recorded from PD patient during normal walk under the (a) right foot (b) left foot



(a)



(b)

formance of LSVM classifier is good when compared to Naïve Bayes classifier during normal walking. Table 1 presents the performance parameters of LSVM and Naïve Bayes classifiers during normal walking.

Figure 7 (a) and (b) show the performance parameters such as accuracy, sensitivity, specificity, PPV and NPV for LSVM and Naïve Bayes classifiers during Treadmill walking event, respectively. It is seen that the accuracy of the LSVM classifier is 86% and the accuracy of the Naïve Bayes classifier is 77%. Further, the sensitivity and specificity of LSVM classifier is 83% and 90% respectively. Also, it is inferred that the performance of LSVM classifier is superior to the performance of Naïve Bayes classifier. Table 2 presents the performance parameters of LSVM and Naïve Bayes classifiers during Treadmill walking.

CONCLUSION

The assessment of gait should be performed as a basic initial examination and follow-up for future treatment in every PD patient. The effective treatment of gait reduces the need for medication and further helps in improving the quality of life of PD patients. Further, the symptoms corresponding to the clinical test,

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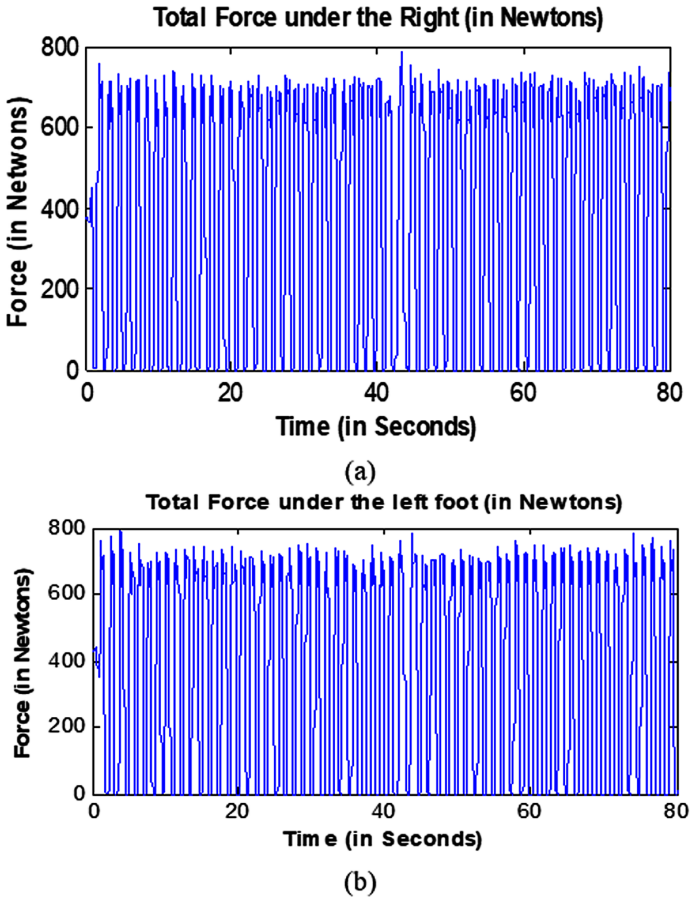
Figure 4. Total force recorded from control subject during Treadmill walk under the (a) right foot (b) left foot



neuro-imaging, molecular genetic data and laboratory data should be considered for future diagnosis of the PD patients during the different stages of the disease. Walking test which requires dual task reflect more challenges in the study of PD patients. The patients with PD find it difficult to perform the basic day to day activities and face lot of obstacles. Therefore, the gait rehabilitation can be carried out by increasing the level of dopamine which becomes more effective method for controlling the gait-based disorders in PD patients.

FUTURE WORK

For future analysis,

- The motor automaticity can be analysed by focusing on the attentional control, automatic control and motor cortex networks.

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- The reason for bradykinesia can be further investigated by focusing on the non-motor symptoms such as facial movement deficits, micrographia and sleep disorder associated with PD.
- The advances in analysing the gait technology helps in improving the facility by designing intelligent gait system using wearables and wireless data transfer.
- In-vivo and in-vitro studies for diagnostic biomarkers helps in reducing the morbidity and mortality of PD patients (Sharma, Moon, Khoali, Haidous, Chabenne, Ojo, Jelebinkov, Kurdi & Ebadi, 2013).
- Finally, the research on gait rehabilitation can be performed for future diagnosis and long-term assistance of the patients suffering with PD.

Figure 5. Total force recorded from PD patient during Treadmill walk under the (a) right foot (b) left foot

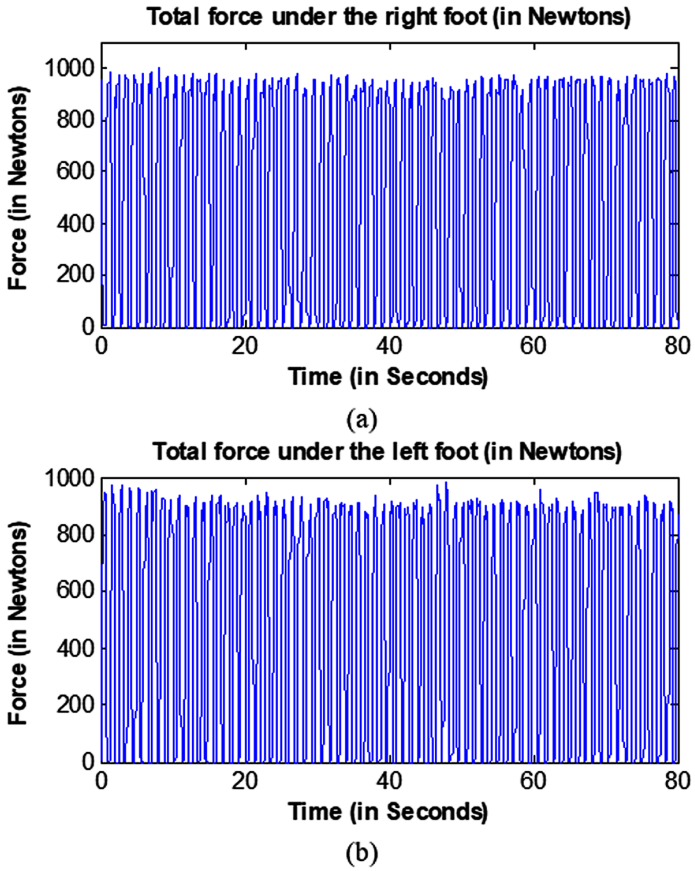

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Figure 6. Performance parameters of (a) LSVM and (b) Naïve Bayes classifier during normal walking event

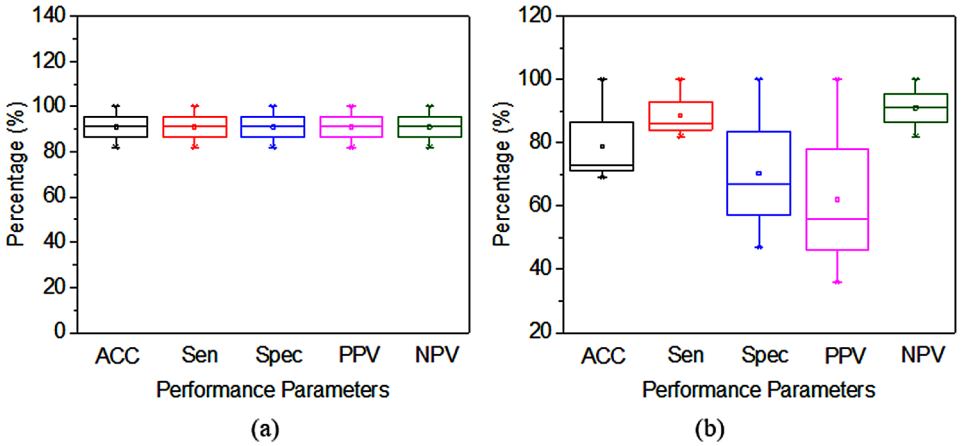

Figure 7. Performance parameters of (a) LSVM and (b) Naïve Bayes classifier during Treadmill walking event

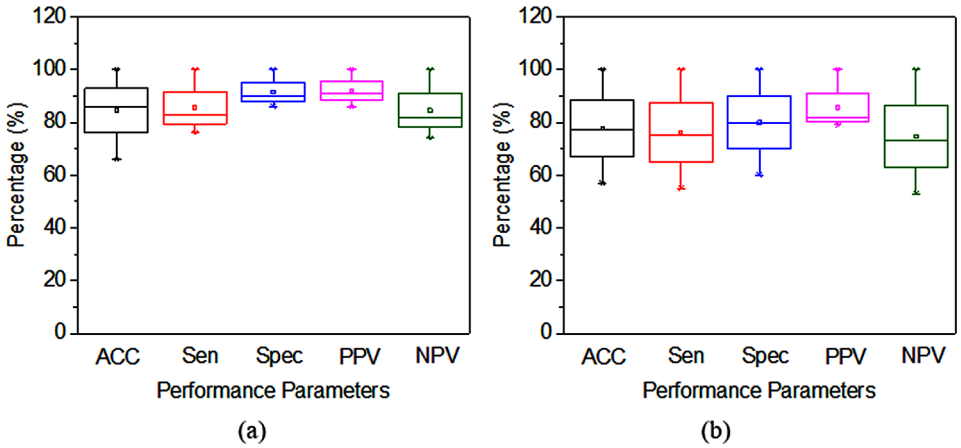

Table 1. Performance parameters of LSVM and Naïve Bayes classifiers during normal walking

Performance Parameters	Normal Walk	
	LSVM classifier (%)	Naïve Bayes classifier (%)
Accuracy	91	73
Sensitivity	91	86
Specificity	91	67
PPV	91	55
NPV	91	91

Table 2. Performance parameters of LSVM and Naïve Bayes classifiers during treadmill walking

Performance Parameters	Treadmill Walk	
	LSVM classifier (%)	Naïve Bayes classifier (%)
Accuracy	86	77
Sensitivity	83	75
Specificity	90	80
PPV	91	82
NPV	82	73

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Chapter 33
Using Technology to Empower People With Multiple Sclerosis (MS) to Make Shared Decisions About Managing Their Own Healthcare:
A UK Case Study

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ABSTRACT

In 2014, the UK National Health Service (NHS) 'Five Year Forward View' plan set out key objectives to reform the NHS, which included empowering the population as a whole (particularly those with long-term health conditions) to take more responsibility for managing their own healthcare and introducing initiatives to use technology to improve services and reduce costs. The "Long Term Plan" explains how the 2014 initiatives will be further developed. This chapter presents a review of literature on digital health information and information usability. It presents the key findings from a mixed methods study that explored how people with MS (PwMS) access and use health digital information when trying to manage their MS. While the study found that there is much good quality digital health information available for PwMS, and that this facilitates shared decisions, some necessary information is still missing. The chapter concludes with recommendations for digital health information providers.

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INTRODUCTION

The Internet has changed the way many people around the world search for information about healthcare. Governments, healthcare providers, and agencies have been quick to move to providing a range of digital health services and resources, which continue to expand at a rapid pace. Eysenbach (2001, para. 3) offered the following definition of e-health:

e-health is an emerging field in the intersection of medical informatics, public health and business, referring to health services and information delivered or enhanced through the Internet and related technologies.

Rapid developments since Eysenbach's definition mean that there is now a confusing array of seemingly interchangeable terms used to describe health information that is provided on a digital platform (examples include telemedicine, digi-health, health informatics, and e-health). The increasing use of mobile devices has itself generated several new terms (such as health-app and m-health).

In this chapter, the term "digital health information" is used to refer to health information that can be accessed online or in some other electronic format.

This chapter will provide some background to multiple sclerosis (MS) and to various National Health Service (NHS) policies and initiatives, before discussing some literature on digital and health literacies and the usability of information. Finally, the chapter will present findings from a case study that explored if, and how, people with MS (PwMS) use technology to access health information and engage in shared decision making with clinicians. The chapter will conclude with recommendations for digital health information providers and suggestions for future research.

BACKGROUND TO MULTIPLE SCLEROSIS

MS is a neurological condition of the central nervous system. The name derives from the scars (sclerosis) that usually form in multiple sites of the nerves in the brain and spinal cord. It is an autoimmune disease, which means that the body's immune system attacks itself instead of attacking germs or infections. In MS, these attacks damage myelin, which coats the nerves in the central nervous system. The damaged nerves cause a wide range of physical and cognitive symptoms in people with MS (PwMS).

There is no universally accepted theory defining the cause of MS and there is no cure for it. MS is not hereditary, contagious, or infectious. Worldwide, there are many clinical studies and trials researching potential causes of and treatments for MS.

Twice as many women have MS than men (MS Trust, 2019). The typical age of onset and diagnosis is 20-40. It is rare in children, but childhood cases have increased in recent years (perhaps due to better diagnostic technology).

There is no universal consensus on how many different types of MS there are, and neurologists continue to debate the criteria for diagnosing the different types of MS, particularly benign MS. However, the National Health Service (NHS), MS Trust, and MS Society in the UK agree that there are four types of MS: relapsing remitting (RR), secondary progressive (SP), primary progressive (PP), and benign MS.

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Although there are some patterns and trends in MS and its progression, the unique and diverse course of MS for each individual means that providing relevant information and services to support PwMS can be a challenge.

MS is a long-term health condition. The life expectancy of those with MS is improving as new drugs and treatments for it are developed. This means that many people will live with MS for most of their adult lives and need different types of information to help them understand and manage their MS as it changes, they grow older, and new treatments emerge.

The MS International Federation's (MSIF) 2013 Atlas of MS recorded that 2.3 million people around the world have been diagnosed with MS. This shows a 2.4% increase in the number of cases of MS since the previous record was published in 2008. The MSIF findings show that MS is most prevalent in North America and Europe.

The UK has one of the highest prevalence rates of MS per level of population in the world (MS Trust, 2019). Despite this prevalence, there is no mandatory NHS register for MS and no comprehensive data on the exact number of people living with MS in the UK and the types of MS that they have. The lack of accurate data has serious implications for healthcare planning and provision, policy making, and assessing the economic impact of MS in the UK. The MS Society and University of Swansea established a UK register in 2011 as part of a collaborative study. Although the data has grown since its establishment, some PwMS and clinicians are unaware of it, or prefer not to register details in it.

McKenzie et al. (2013) conducted a descriptive study based on the General Practitioner's Research Database (GPRD) to determine the number of people living with MS in the UK between 1990 and 2010. They concluded that in 2010, 126,669 people in the UK had MS. The study also reported a 2.4% increase in the number of people diagnosed each year and that people with MS were living longer. In 2016, the MS Society conducted further research using the McKenzie et al. methodology and incorporated new population data from the Office of National Statistics. Their 'MS in the UK' report concluded that in January 2016, 107,740 people in the UK had MS and 89,030 lived in England. The MS Society's totals are lower as the McKenzie et al. report included *possible* as well as confirmed cases of MS. However, the Society's data also confirms the number of people diagnosed and living with MS is increasing each year in England.

HEALTH POLICIES IN THE UK

The NHS was one of the early adopters of digital health information and continues to pioneer and trial a wide range of digital health projects. The NHS has ambitious plans to increase the use of technology in healthcare (NHS, 2014). In 2014, the UK's House of Commons Health Select Committee advised that the management of long-term health conditions (LTCs) was one of the greatest challenges to the NHS in England. Their 2014 report found that 70% of healthcare expenditure in England was on the 15 million people living with LTCs (House of Commons, 2014). With the expectation that this number would rise to 18 million by 2025, the Committee called for an urgent review of the co-ordination and management of this care and called for a systematic and cultural shift towards greater personalization of healthcare and services.

Consequently, NHS England established its 'Five Year Forward View' (2014) project to implement the required changes. The project set many targets for the NHS including targets for improving and integrating health and social care models, reducing hospital and particularly accident and emergency

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admissions, and ensuring availability of sufficient staff in the NHS trained to support the significant changes that the plan will introduce.

A key provision in the plan was to empower people with LTCs to manage their healthcare by:

- Improving both the information, and access to information, for those with ltcs
- Improving education for those with ltcs to help them manage their condition, make treatment choices, and use technology in healthcare
- Increasing the use of technology to allow all patients to access (and input into) their own digital health records.

Simultaneously, NHS England was charged with making significant financial savings across its services and reducing expenditure on LTCs. It believed the targets it set out (in 'Five Year Forward View') would change the management and care of people with LTCs, lead to improved services, and reduced costs. For example, people with diabetes would spend less time in hospital if they learned to recognize and deal with their insulin problems quickly.

The MS 'Forward View' (MS Trust, 2016a, p. 6) acknowledged that the success of the 'Five Year Forward View' project relies on organizations for specific LTCs (e.g. the MS charities) supporting the targets to make them a reality. The report identified a number of MS specific issues that must be addressed to *empower all people with MS* to access information and contribute to managing their care. The MS Trust argues that the current provision of funding, information, care and services for PwMS is heavily biased to relapsing remitting MS (RR), to the detriment of other types of MS (secondary progressive SP, primary progressive PP, and benign MS). Worryingly, a survey undertaken by the MS Trust (2016b) found that "people with progressive MS, *who make up almost half of the total MS population in the UK*, are seeing their key specialist health professionals far less often than people with relapsing remitting MS, and often failing to receive the proactive, continuing care that can make all the difference to living well with the disease" (p.2, emphasis added). There is no typical course of MS, but many people move from RR to SP and PP over time. PwMS are now living longer, so more of them are likely to develop one of the progressive forms of the disease and will need to make decisions about managing the changes it brings. During the progressive stages of MS, there are less relapses, but disability increases, which means that people with progressive forms of MS have vastly different information, care and treatment needs to those with RR MS. The bias towards RR MS results in unequal access to the personalized information needed to meet the 'Five Year Forward View' objectives, and limits the potential for people with *other* types of MS to engage in shared decision making, as the authors will explore later in this chapter.

In 2017, the NHS 'Next Steps on the Five Year Forward View' interim report provided a "balanced but not comprehensive" summary of progress towards the objectives in the original 'Five Year Forward View' plan (NHS, 2017, p. 9). The report (favorably) summarized a number of successful initiatives that were underway to meet some of the financial targets and improvements in integrating health and social care services to provide more individualized care to patients.

The interim report also set out the next steps in the phased technology program of work aimed at "simplifying access to care, in the most appropriate location, while supporting people in managing their own health" (2017, p. 64). It focused on making more services available online to patients, increasing patients' access to their own medical records online, and the introduction of NHS approved library of health apps to help patients manage their own conditions. Many of the technology and digital projects,

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set out in the 2014 and 2017 reports, have been taken forward by NHS Digital, a public body in the Department of Health, which was launched in April 2017.

The 'Long Term Plan' (LTP) provides examples of some of the successful digital projects that have been completed since 2014 (NHS, 2019). However, it acknowledges that there is still much work to do to reach the 'digital first' options it plans to implement for all types of patient contact with the NHS. Eventually, NHS patients will be provided with digital options for everything from booking a GP appointment, accessing their own records, ordering prescriptions, to consultations with specialists. The 'digital first' agenda will reduce costs, take much of the complex administration out of the NHS, and better enable staff to focus on clinical care.

Since 2014, NHS Digital has driven technology projects, which are now embedded in the NHS. It has:

- Led on improvements to the NHS website (formerly known as NHS Choices and NHS Direct)
- Introduced Artificial Intelligence (AI) into the NHS to help with clinical decision making and triage activities
- Led on integrating patient NHS records and care plans to ensure healthcare professionals and patients have access to their full records
- Overseen the development of the NHS apps library. The library, now part of the NHS website, hosts 70 approved apps targeting a range of conditions (e.g. anxiety) and general topics (e.g. how to access health data). There are no MS specific apps in the library, but some apps may help to manage some of the symptoms of MS (e.g. anxiety). Many apps have been developed in association with charities and patient organizations, which has been welcomed by the Patient Information Forum (PIF, 2019).

The LTP contains bold statements setting out the ambition to transform health and social care by improving access to NHS digital tools. It aims to become a "trustworthy" source of information and health apps (p. 93). Perhaps because of previous criticisms from the Kings Fund, Patient Information Forum, and health charities, the LTP plan includes a new objective to work with the wider health sector and voluntary groups and individuals as it takes forward the digital agenda. This objective has been welcomed by the PIF (2019) and Kings Fund (2019), although both organizations express concerns about the lack of funding and resources needed to deliver the work to schedule.

The commitment to involve patients, their carers, and lay members of the public in NHS projects was initiated in 2014, and continues to expand across a range of projects and technology developments to ensure products better meet user needs. The LTP states that by 2020, every person with a long-term health condition will be supported to manage it, by interoperability of data, monitoring devices, and home use technology. Furthermore, all secondary care providers must be fully digitized by 2024 to support their patients and ensure health and social care records are seamlessly integrated.

The Patient Information Forum and the Kings Fund have long criticized the Government's record on delivering health technology reform projects on time and within budget. The Kings Fund (2019) believes there are still a number of risks that will affect delivery of the LTP digital objectives, which include:

- The end of the technology funding in 2021
- The ongoing delay of deadlines for digitization (for health and care organizations, the deadline has moved from 2020 to 2024)
- Severe staff shortages across the NHS

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- High dependence on the digital infrastructure (also acknowledged in the LTP itself)
- Lack of training and capacity building for staff and patients to use and understand technology.

PwMS now have access to a vast range of regulated and unregulated digital healthcare information on the internet (a Google search for 'multiple sclerosis information' on March 6, 2019 gave about 41, 000,000 results). Given the unprecedented pace of change, PwMS face significant choices about the quality, validity, and reliability of information available and need to determine if it can empower them to participate in making decisions about their healthcare.

DIGITAL HEALTH INFORMATION

This section will present some relevant literature on digital and health literacies, the usability of digital health resources, the information and communication needs of patients and healthcare providers, and technology for patient empowerment and shared decision making.

Digital and Health Literacies

It is important to consider the impact of making more health information available online to all potential users. 'The Real Digital Divide?' (Good Things Foundation, 2017) analyzed the level of access to the internet in the UK and found that 15.2 million people are either non-users or limited users of the internet. 11.5 million users lack basic digital skills. The report's sociodemographic data shows that those with limited or no access to the internet are likely to be from disadvantaged groups, with lower levels of employment, income, and education. 47.7% of the low or non-user group had a disability or long-term health condition.

There is no universal definition of health literacy. However, Health Literacy UK (2019) describe it as "the personal characteristics and social resources needed for individuals and communities to access, understand, appraise and use information and services to make decisions about health".

The ability to not just understand, but to act on information about health, is becoming increasingly important as the NHS (and other providers) implement policies that require the population at large to be active participants in their own healthcare. Health Literacy UK report that England has very poor levels of functional health literacy, and that 43% of the adult population cannot understand much of the health information provided. If the health information includes numerical information, this rises to 61%. This figure is significant as it implies that 61% of people may not be able to follow a prescription dosage correctly, which is not only a danger to health, but costs the NHS millions of pounds in wasted medications each year. As health information is increasingly provided in digital format, the population needs to become digitally literate to access and search for information.

Moccia et al. (2015) found that people with MS are very active users of digital health information. However, their study analyzing the readability of 10 MS websites in the UK and US found that most websites failed to meet the US Institute of Health Readability Guidelines and were therefore difficult for PwMS to read and use. They concluded that PwMS would need help from clinicians to interpret some of the complex MS digital information provided. By contrast, Lejbkowicz et al. (2010) found that many PwMS do not use the internet at all and argued that other forms of health information must be provided to avoid disadvantaging this group. Marrie et al. (2014) conducted literacy tests with 13,020 PwMS and

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concluded that most (68%) performed well in both digital health and functional literacy tests. They noted that there is a need to expand research to cover the less literate PwMS. Importantly, they also state that research is needed to establish links between health literacy and adherence to healthcare treatment plans.

Patients will only make use of new NHS services, such as information sent by email and telephone support lines, if it is presented in a format that is appropriate for their needs and clearly signposted to them (Patient Information Forum, 2018). The Patient Information Forum (PIF) report stresses that the literacy issues identified by Health Literacy UK must not be ignored if the benefits of new NHS digital services are to be accessible to all.

The Usability of Digital Health Resources

At a time when traditional healthcare systems struggle to cope with demand for services, providing digital health information and data can be an effective cost-saving strategy for governments and a source of revenue for commercial providers. However, as websites become larger and more complex, the cost of building, testing, and maintaining their infrastructure also increases, and the complexity of some products means they can fail to meet their users' needs. In addition, many users now expect to access digital health information from different types of devices at any time of day and from phones when mobile (m-health). Additional usability testing is required to ensure information design for m-health meets user expectations and engages the audience.

Usability and readability are particularly important for digital health information, as there is potential for harm, and even danger, if users cannot locate and understand information about their healthcare.

Studies by Chaudhry et al. (2006) and Hinchcliffe and Mummery (2008) found that lack of user engagement in the design of health websites reduced their effectiveness as they failed to provide relevant information to users.

Powell et al. (2011) agreed website designers must understand how and why users search for digital health information. A mixed method survey of 792 users categorized reasons for using the NHS Direct website (the forerunner of the current NHS Choices), and found that people wanted to find trustworthy information that they could use to develop their own understanding and to prepare for discussions with clinicians. Powell et al. concluded the NHS Direct website could attribute its high usability satisfaction to the NHS commitment to user engagement in the design.

Changes in both technology and the type of information presented on health websites means users now have more choice of information than ever. Ziebland et al. (2016) conducted an extensive study examining whether usability of websites is improved if they include patient experience (Pex) information. Although their study concluded Pex information was valuable to many (and it is indeed now a common feature on many health websites), the MS sub-group within the study reported major concerns that sharing such information could frighten many PwMS and provide a very negative user experience. This study, in particular, highlights how different users may have very different preferences for information. Dennison et al. (2016) conducted a small qualitative study of PwMS and identified that some PwMS prefer not to know about their full prognosis or likely outcomes. Thorne (2009) questions the trend for using experience narratives to explain health issues. She notes it can be an effective communication method, but needs to be used carefully with qualitative research into the validity of the narrative and its potential impact on readers.

Synott et al. (2016) found that relatively little research had been conducted to establish what exactly MS users need from digital health information. They conducted a qualitative research project investigating

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how PwMS find and use information. They noted that while some PwMS felt empowered to search for information, others could find the search results upsetting. Participants expressed a need for information about the *practicalities* of living with MS (which was not always available) as well as medical data. Over time, participants developed strategies for identifying trustworthy sources of information, and became more selective in their searches than they were at diagnosis.

Kopke et al. (2014) carried out a study reviewing the importance and preferred formats of information for PwMS in 10 different treatment trials. They found that the information provided resulted in PwMS learning and retaining more about MS medical *issues* than managing the practical aspects of life with MS. Unlike studies by Synott et al. (2014), Thorne (2009), and Ziebland (2016), Kopke et al. found that information for PwMS did not cause any negative or upsetting reactions.

Marrie et al. (2013) also studied the information preferences of 8,464 PwMS in a review of MS projects around the world. Their study found that the three most trusted sources of MS specific information in the cohorts of PwMS were doctors, the internet, and patient advocacy groups. Preferences for the format and perceived quality of the information varied, with the age and sociodemographic of the participants affecting their preferences.

Colombo et al. (2014) conducted qualitative research into how PwMS and their families search for and use online information. They reported an increase in use of social media sites (e.g. Facebook, YouTube, and MS Association Discussion Forums) to find information, particularly among the younger cohorts of PwMS. They noted participants trusted sources affiliated to MS associations more than other sites (these sources were often moderated) and included links to further relevant information endorsed by the associations. Riel et al. (2017) studied the impact of internet searches carried out by 936 patients and their GPs and found that two thirds of patients search the internet to prepare for consultations with clinicians, and often did so to be better informed and to facilitate discussions with their clinicians. In this study, clinicians did not feel threatened by internet information and some clinicians reported that relatives' opinions had more impact on patients than online search results.

Sbaffi and Rowley (2017) conducted a systematic literature review of health information to identify factors that affect users' perception of the trustworthiness and credibility of web-based information. They found that the authority of the website owner and content authors, clear design, and interactive features had a positive impact on the user, and that advertisements had a negative impact. This study, and those by Colombo et al. (2014) and Marrie et al. (2014), agree that there is merit in conducting more research into understanding how PwMS select, use, and evaluate the credibility of online information.

The Information and Communication Needs of Patients and Healthcare Providers

The PIF report (2018) identifies key times when patients need good communication with their healthcare professionals and information to help them manage their long-term condition. The report stresses that information at diagnosis is crucial, yet notes that many patients were not provided with any information at diagnosis. Others were given information they could not understand. Diagnosis can stress and overwhelm patients but the combination of patient appropriate information and strong communication from healthcare professionals can mitigate this to some extent.

Edwards et al. (2008) carried out a qualitative study of PwMS in the UK and found that 43% of PwMS had not been given any information at diagnosis. However, when PwMS were provided with information and clinicians explained it to them, it reduced patient anxiety and depression. Furthermore, not only

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did support from healthcare professionals help PwMS through the often-lengthy diagnosis stage, it set the tone for how many people coped with MS in the longer term and how they sought information and communicated with their healthcare professionals in future.

Solari (2014) conducted an informal literature review of the experiences of people at the time of their MS diagnosis. She also noted that the process for making a definitive MS diagnosis can be lengthy and cause anxiety and stress for the patients. In interventions where PwMS were provided with additional clinical communications, stress and anxiety were reduced.

Thorne et al. (2004) also reported that communications with healthcare professionals can shape the way PwMS perceive treatment options and self-management. In their qualitative study, PwMS felt dependent on healthcare professionals for information. When information was too generalized, further communications with healthcare professionals were crucial to relate it to the specific needs of each person – this was particularly important to manage fear at diagnosis.

The PIF report explains that over time information needs change for those living with long-term conditions, to the point where patients often consider themselves experts on their condition. Corrie and Finch (2015) report that the expert patient will demand better information and communication from the NHS in future and is willing to use technology to both seek information and communicate with healthcare professionals. Bodeheimer et al. (2002) recognized there is a paradigm when both the patient and doctor are both experts: the doctor is an expert in medicine, but the patient is the expert in how their medical condition affects their life. Good communication between both parties with doctors adding information to the knowledge the patient has already gained, can lead to good shared decision making, better adherence to treatment plans, and patient empowerment.

Technology for Patient Empowerment and Shared Decision Making

Shared decision making (SDM) is driving health authorities to introduce SDM-specific programs and initiatives and is shaping the ways clinicians are trained to communicate with patients. In some countries (notably the US), technology is enabling clinicians and patients to use new communication and monitoring applications to share decision making and to empower patients to take more responsibility for their own healthcare.

The European MS Platform's Code of Good Practice in MS (2014) calls for MS organizations in all European states to provide appropriate information to empower PwMS to take part in the decision making "that ultimately affects their lives" (p. 9). Increasing SDM between patients and clinicians is one of the key objectives of the NHS 'Five Year Forward View' (2014).

There are many benefits and challenges associated with shared decision making. Corrie and Finch (2015) found that patients engaged in shared decisions are more likely to adhere to treatment plans and need less urgent care, thus contributing to cost savings. Ruddell et al. (2016) recommended the use of an MS SDM healthcare app, which helped PwMS monitor and track aspects of living with MS. The app facilitated communication between clinicians and PwMS and led to improved management of fatigue, as PwMS and clinicians could identify and manage fatigue triggers.

Heesen et al. (2007) noted the potential for good health outcomes and improved patient clinician relationships, *provided* decisions were made jointly. McMullan (2006) found that some clinicians felt threatened by the SDM process as it enables patients to challenge their decisions; other clinicians felt frustrated that patients brought digital health information to meetings, which contradicted their clinical decisions. The 'Implementing Shared Decision Making' report (Health Foundation, 2013) recommends

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ensuring staff buy in to the SDM projects so that they do not feel threatened if their decisions are challenged and concludes that most patients need support from healthcare staff to make decisions; in other words, information alone is not enough. Kvedar et al. (2015) reviewed the impact of a wide range of apps and telemedicine products in the US and noted that successful products ensure patient and clinician input in design and support communications for SDM, rather than trying to replace face-to-face appointments and meetings.

Heesen et al. (2007) reviewed the role preferences of PwMS when making decisions with doctors. They found that the majority (79%) of PwMS wanted to make shared and informed decisions, and have an active role in the decision. However, others did not want to take part in SDM at all; some preferred to have an autonomous role and make their own decision, and others wanted their doctors to have a paternalistic role and make decisions for them. Heesen et al. found that PwMS were more likely to adhere to treatment plans when their preferences were accommodated.

There are also times when PwMS prefer not to know at all about prognosis and likely outcomes of their MS, particularly if the outcomes are deteriorating health and disability (Dennison et al. 2006). Although, prognostication techniques offer opportunities for shared decision making about future beneficial management and treatments, there are complex ethical concerns for healthcare staff working with PwMS who do not want to know about prognosis, let alone share decisions about it. For some PwMS, the prognosis forecasting can be emotionally distressing or have negative psychological effects.

Furthermore, the 'Falling Short' report (Neurological Alliance, 2017) notes fewer people with neurological conditions feel they can contribute to making choices about their own healthcare (63% of the 3,328 surveyed in 2016, compared to 71% in the same study in 2014). They attribute lack of access to neurological specialists, particularly clinical nurse specialists, and barriers to accessing information, to some of this dissatisfaction. The report recommends that NHS trusts and staff should work closely with patient groups, particularly at diagnosis, to ensure better access to condition specific information. It further recommends clinicians work with patient groups to ensure letters and patient information includes signposting to sources of help and information, rather than leaving patients to conduct their own research into information that they can find frightening and confusing.

A reliance on providing information over the Internet can create barriers for PwMS (Lebjkowicz et al., 2010), as they might not have Internet access and/ or the necessary digital skills, as discussed earlier. However, when PwMS and clinicians *jointly search* for web-based information, it can overcome some of these barriers, by increasing user search confidence and directing PwMS to reliable and patient specific sources of information.

The 'Acute Neurology Survey' (Association of British Neurologists, 2017) reports that a serious shortage of neurologists means there are huge regional variations in access to specialist neurology centers and support for all neurological patients across England. The 'Long and Winding Road' report (Marie Curie, 2016) found that, even though the NHS has many digital and non-digital SDM tools and resources at its disposal, the NHS is struggling to implement SDM in many regions of England, as some staff have not received adequate training to support it. The report also notes that the fall in number of clinical specialist nurses across many disciplines is having a detrimental effect, as they are often the experts in SDM and the key link between patients, other clinicians, and community service providers. The 'Forward View' report confirms that the staff shortages and reduced patient access to neurology specialists are having a detrimental effect on both PwMS, and the staff working with them, to make shared decisions (MS Trust, 2016a). The NHS has acknowledged that its staff and those working with the NHS need more training in communications to support SDM. The 'Person Centred Approaches Framework' will support

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training and development for staff working towards SDM in future (Health Education England, Skills for Health, and Skills for Care, 2017).

CASE STUDY

This case study presents the findings from a mixed methods study conducted between June and August 2017. The purpose of the study was to determine if technology and digital health information empowers PwMS to make shared decisions about managing their own healthcare.

The study received approval from the University of Limerick (UL) Research Ethics Committee.

Data Collection

Participants for the PwMS cohort were recruited from a small number of online and face-to-face support groups for PwMS in England. Two of the support groups were established by national MS charities and both groups are moderated by charity staff and have clear terms of reference. The other group is an informal Facebook group originally established as a self-help forum, which is administered by two PwMS. Participants in the PwMS cohort were from a number of different Clinical Commissioning Groups in England. The participants had different types of MS, and had lived with MS for different lengths of time.

Six information providers from the two major MS charities, as well as one NHS clinician, also participated in the study. Table 1 summarizes the methods used to collect primary data for the case study and how many people participated in each stage of the research.

Table 1. Summary of data collection methods and participants

Data Collection Methods	Notes
Qualitative semi-structured interviews with PwMS	Six interviews were conducted with PwMS (either face-to-face or by Skype). Interviews were audio recorded and transcribed for analysis.
Focus group for PwMS	One focus group was attended by three PwMS. A record of the key themes discussed at the meeting was produced.
Online questionnaire for PwMS	A further 17 PwMS completed an online questionnaire. This method provided a broader sample of PwMS in the short time permitted for the study. It allowed further perspectives to be collected on the key topics identified during the literature review.
Online questionnaire for clinicians working with PwMS	One MS clinician completed a questionnaire.
Online questionnaire for information providers	Six staff at charities producing MS information completed questionnaires.

Data Analysis

Given the small scale of the study, data from the interviews and focus group was transcribed and coded into themes using a simple coding system, as recommended by Mason (2002). Curry (2015) suggests using an integrated method for coding to produce a starter list of themes derived from the literature review, and adding sub-codes to the starter list as the researcher becomes more familiar with the data content,

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and when an extra level of coding would be helpful to the analysis. In this case study, a starter list of themes was produced from the literature and sub-codes were added to the themes. The coding system was then tested and amended after the first interview and focus group. Table 2 presents the themes and sub-codes discussed in this chapter.

Table 2. Themes and sub-codes from data analysis

Theme	Sub-codes
Health and digital literacy	Sources of digital health information Accessibility Proactive use of information
Information usability	Trustworthiness Currency Importance of other PwMS experiences Missing information

Results

This section presents the results from our case study, focusing specifically on health and digital literacy and information usability.

Health and Digital Literacy

NHS Digital continues to upgrade existing digital information (e.g. the NHS Choices website) and introduce new online healthcare initiatives to meet the objectives of the 'Five Year Forward View' plan (NHS, 2014).

Although the nine participants from the interviews and focus groups said they have reliable internet connections and consider themselves regular and proficient users of technology, they were largely unaware of the current and future changes to NHS services. None of them had access to their own online healthcare records or knew how to request access to online services. Only one participant was aware of the plans to digitize services such as booking appointments, requesting prescriptions, and obtaining test results.

These nine participants used a range of devices to access digital health information—nine used a laptop or desktop computer; three of them also used a tablet. One participant said that she did not like to use a smartphone, as her MS meant that she sometimes had problems with her grip and a static larger keyboard was easier to use than a phone.

All the PwMS in this study (n=26) confirmed that they use digital health information. When asked to list the sources they use, they reported as follows (see Figure 1).

Each participant used several different types of digital health information. Use of MS apps was low, with only one participant using an app to record taking medications.

Five of the six information providers reported that they provide information to PwMS in a range of formats that include hard copy information leaflets, websites, blogs, and social media sites. "We sometimes have to print out webpages to send to those PwMS that have no access to the internet." (IS5) One clinician said she only provided hard copy information leaflets from the MS Trust and MS Society charities, to PwMS.

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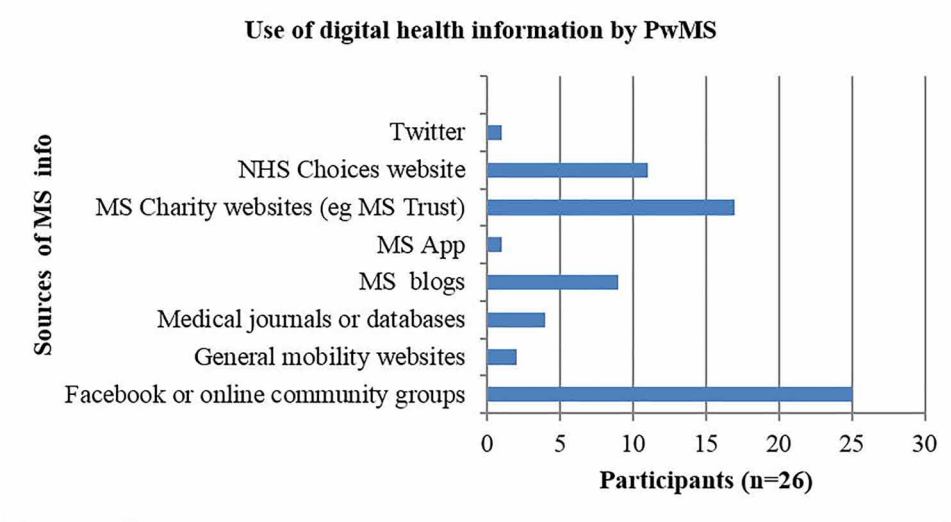
Figure 1. Sources of digital information used by PwMS in this study



A number of participants gave examples that demonstrated their ability to act on health information and how they use it to help manage their MS. One participant described a long struggle with an MS nurse, as she tried to withdraw from a drug that made her feel worse.

It was a really big research job for me, but eventually, I had enough evidence and my GP accepted I was right. Even then, the MS nurse was still dismissive, saying my side effects were very rare. I told her winning the lottery was rare but someone wins every week! But seriously, it was so frustrating that so many people just wouldn't listen to me. (P5)

Others felt they had to be proactive and use information to resolve problems to influence the outcomes of decisions about managing their care. Further examples included using funding information for an appeal when (successfully) re-applying for aids a doctor had refused to authorize (P1, P8) and taking information to appointments to make the most of time with healthcare staff: "doctors expect you to do some research before you arrive and to be prepared these days." (P2)

Information Usability

Nine participants indicated why they use digital health information, by selecting all applicable reasons from a list of options (see Table 3).

Three PwMS said the currency of digital health information was important. They thought that digital health information was more likely to be up to date than hard copy information sheets available in health-care centers. One participant (P3) noted that her local neuroscience center was issuing an old edition of an information sheet about types of MS that had been updated several times by the charity that produced it. "And that's what our hospital was giving to people who had just been told they've got MS." (P2)

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Table 3. Reasons why PwMS use digital information

Reasons for using digital health information	Participant responses (n=9)
To keep myself informed about new MS developments.	7
To help me make shared decisions about how to manage my MS with healthcare professionals and others (e.g. family).	3
If my MS changes and I need advice.	7
To feel as if I am being proactive in managing my MS.	6

PwMS use digital sources not only to search for facts about MS and treatment options, but also to learn about the experiences of others living with MS. This partly accounts for the high use of social media sites. "I like to see how other people manage and if their ideas can help me." (P2); "Facebook can be a great and quick way to get advice from others." (P1) The convenience of being able to find information when travelling and at any time of day from social media was important to some. (P6, P9) "*Social media is the way now and the NHS just isn't there so I use the MSS site*."(P9) Three participants (P3, P5, P8) said they did not like to use Facebook, but felt it was becoming an important source of MS information so they would need to use in future.

Reduced access to healthcare professionals also increases the use of social media, as PwMS search for answers to questions they would have previously directed to their healthcare team. "People start to rely on social media more if you can't find out what you are supposed to do and need help between appointments." (P4)

Eight of the nine participants felt that their methods for searching for information to help to manage their MS had changed since they were diagnosed. They had become more proactive in using the internet and social media to find information about treatments and living with MS. "I mostly look online now rather than wait to be given information. I know what I am looking for now and what works for me." (P6)

Participants also described how they decide whether health information is trustworthy and reliable. The reasons they provided are summarized in Table 4.

Table 4. Reasons for deciding information is trustworthy and reliable

Reasons given by PwMS for deciding whether information is trustworthy and reliable	Participant responses (n=26)
Use information recommended by healthcare staff	2
Trust and use the NHS information	2
Use own personal judgement/ want to make own decisions	3
Look for information based on personal experience from other PwMS	3
Use official sources (sources not specified)	2
Conduct own research	5
Use information from the MS Trust or MS Society	9

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One comprehensive response on how to decide if information is trustworthy summarizes several reasons (some also offered by other PwMS) for determining if information is reliable:

I look at the content and decide the value and authenticity by looking at what authority the source has in putting forward MS information. I look at the history of the source and feedback from others. A biggie for me is that the source is speaking from an understanding viewpoint (experience of or personally or emotionally invested in MS) rather than a knowledge of MS. (P15)

Several participants preferred information that included experience of other PwMS: "I tend to trust people that have it [MS] more than general health websites." (P7); "I value sites where other people with MS can advise me and personal experience of it is very important." (P6)

Five participants said that they carry out their own research before deciding if a source is trustworthy or not. This included following links from MS website data to the corresponding full research reports and medical databases: "I do my own academic research and follow up more than most people do. I read the full reports and it's better than stuff on the general websites." (P7); "I look for evidence based and accredited sources." (P18) Research experience also helps PwMS decide when not to use a source: "I am sceptical (sic.) about a lot of it as I know the research is just based on case notes." (P8)

Nine of the 26 participants said that they trust information provided by the MS Society and MS Trust more than other sources. "I probably shouldn't say this, but I never look at the NHS MS info! I trust the MS Trust and MS Society info as I know it is peer reviewed, professionally written, evidence based and up to date. I've never been given any NHS info or directed to the website by my healthcare team so now I just go straight to the MS Trust and MS Society stuff." (P4)

Four participants commented that moderated social media sites (particularly the MS Trust forum) were helpful as they combine personal experience of others with MS with suggestions from the forum moderators and links to more detailed reliable information.

Over time, some PwMS become more confident in choosing sources of information that they trust and think are relevant to their own needs: "I know a great deal about my condition and that helps me recognise information that is not trustworthy. This was not always the case!" (P12); "I have learned to choose trusty websites and now stay away from the strange ones - you know, the (sic.) you can be cured if you only drink goats' milk sites." (P8)

The staff at the charities providing information (used by the clinician and PwMS) refer to a number of sources to ensure the information they produce is evidence based and reliable. One charity uses the Oxford Centre for Evidence-based Medicine levels for assessing and weighing evidence before it is incorporated into information given to PwMS (IS2). Staff also refer to peer reviewed scientific and medical sources (IS5, IS4) and involve clinicians and PwMS in their authoring and editing process. (IS3)

Despite the wealth of MS information available online, nine participants reported that they had been unable to find information on some topics that they believe hinders them when trying to manage their MS. Some felt that there is not enough information about local services (n=2/9) and others wanted information on aids and equipment for living with MS (n=4/9): "I need info about adaptations and equipment and things that would make life easier, safer and better for me and my career." (P5) They felt that there is little information about making life changing decisions about moving home due to disability (n=2/9) and opportunities for respite care. Others (n=3) felt there is a lack of information about places accessible to disabled people, but noted that this did not just apply to PwMS. There is less information available about SP and PP than RR MS (n=4/9), "It's all about DMDs and RR, and it's so unfair!" (P7)

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Some participants (n=3/9) said they thought information specifically for carers and relatives of PwMS is needed. "There's stuff written for children, but nothing to tell other relatives about how MS will impact on everyone - not just the one that gets the MS, and how to cope with all that." (P1)

Information staff generally thought there was a good range of information available, but did identify some gaps. They agreed more information about how local services could help PwMS would be useful (n=2/6). Information on coordinating symptomatic treatments (n=1/6) and explanations of how to access healthcare staff (n=2/6) could reduce the number of queries they receive on these topics. "We take a number of calls from PwMS who don't want to trouble the MS team, or know who to contact for help between appointments." (IS5)

Asked how healthcare staff could help to improve the use of digital information to make shared decisions, nine PwMS felt that the healthcare team could signpost them to information about local MS services (n=2) and reliable digital information (n=3) "so that I don't spend two hours searching MS information that can scare me to death." (P4)

Some participants suggested that providing digital information in shorter, bite-sized easy to read formats, podcasts, and infomercials would be helpful. Some (n=3) thought the NHS was lagging behind in using technology to improve access to healthcare staff and that NHS staff should consider offering forums for questions from PwMS and Skype or smartphone appointments with clinicians.

DISCUSSION

The majority of PwMS described in our case study have access to the internet and are capable of searching for their own digital information. However, the results from charity staff and volunteer participants concur with a study by Lebjkowicz et al. (2010), which found that some PwMS do not use the internet at all and need information in other formats. Indeed, in our study, the focus group felt that providing information in different formats (such as podcasts and infomercials) would be helpful. This finding aligns with the 'Perfect Information Journey' report (PIF, 2018) that says information should be provided in a variety of formats to meet all users' needs (recommendation #1).

Our study also found the majority of PwMS (including those who are proactive users of health information) had little knowledge of plans to digitize many services (e.g. online health records) that may affect how they communicate with healthcare staff and manage their MS in future. For example, NHS Digital is currently developing an NHS Apps Library, and other healthcare apps are already available for purchase. While the participants in this study stated that they are not interested in using many of the apps that are on offer, some participants had experience of technology-based reviews or appointments with healthcare staff (e.g. Skype and conference telephone calls with doctors and MS nurses) and believed expanding this provision could improve use of staff resources. However, the NHS (and other providers) should be mindful of the analyses by Rudell et al. (2016) and Kvedar et al. (2015) that show that PwMS and clinicians will only engage with and use new technology if the benefits of using it are clearly outlined to them (recommendation #2).

On a positive note, our study aligns with the results of previous studies by Powell et al. (2011) and Riel et al. (2017) that found people use digital healthcare information as they want to both improve their understanding of their condition and to prepare for discussions with clinicians. On a negative note, however, our findings suggest that lack of access to, and perceptions of poor support from, healthcare specialists left some PwMS feeling that they had no choice but to be proactive and search for their own

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health information. Echoing findings in the 'Long Winding Road' (Marie Curie, 2017), 'Forward View' (MS Trust, 2016a) and 'Falling Short' (Neurological Alliance, 2017) reports, our study found almost a quarter of participants do not have access to neurology experts that can help them make decisions to manage their MS. As discussed earlier in this chapter, there is a bias towards providing people with RR MS with access to healthcare specialists, at the detriment of people with other types of MS (MS Trust, 2016b). Consequently, people with other types of MS will have fewer opportunities for SDM. If the NHS is serious about empowering everyone to engage in SDM, it will need to readdress this imbalance (recommendation #3).

Our study found that participants value health information that includes experiences of other PwMS. These findings correlate with previous studies by Ziebland et al. (2016), Marrie et al. (2013), and Colombo et al. (2014) attributing the use of social media sites to the need to learn from and communicate with other PwMS but also the need for communication forums moderated by trusted MS organizations. Several participants in this study expressed serious concerns about the ability of other PwMS to understand information to manage their MS. In addition, they expressed concerns about advice from non-clinicians (to PwMS) about medications and treatments that could be dangerous. Those expressing such views sometimes contribute to social media forums, discussions and blogs as a way of helping the PwMS that they are concerned about. Given the NHS plans to develop additional digital services, associated social media forums will need to be moderated by experts (recommendation #4).

Although there is a vast range of MS information available, the results of our study concur with others by Synott et al. (2014) and Kopke et al. (2014) who found that PwMS perceive there is far more *clinical* information available than guidance about the *practicalities* of living with MS and its impact on PwMS, their carers, and families. However, once the participants in the study find sources of information they trust, they tend to return to those sources again, which could mean they miss updates from, and improvement to, other sources. For example, most interviewees in our study did not know that the NHS Choices site includes a searchable (by postcode) directory of MS health, care and mobility services that provides some of the practical information they believe is missing. To fully engage PwMS with digital health information, there needs to be appropriate guidance, signposting to, and orientation for users of that information (recommendation #5).

FUTURE RESEARCH DIRECTIONS

Future research could review the impact of digitization of the NHS with larger cohorts of PwMS to determine whether technology really does empower people to make shared decisions. The proposed study could also analyze which particular tools and technologies empower PwMS and which tools they find useful. As the NHS digital programme expands, the study could review the full impact of the new digital service model on PwMS and wider aspects of their care and management.

It would also be interesting to study the needs of PwMS who are not digitally literate or are less digitally literate, and consider the implications of shared decision making for this cohort of PwMS. While younger "digital natives" are familiar with using technology in their day-to-day lives, there is still a large cohort of people who do not have access to technology, or who do not possess skills to use technology to manage their healthcare effectively.

Finally, researchers could examine digital healthcare initiatives in other countries, to determine best practice for using technology for shared decision making.

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CONCLUSION

This chapter presented a review of literature on digital health information and information usability. It presented some findings from a mixed methods study that explored how people with MS (PwMS) access and use health digital information when trying to manage their MS. While our study found that there is much good quality digital health information available for PwMS, and that this facilitates shared decisions, PwMS report that some necessary information is still missing, such as practical details about living with MS (for PwMS, their carers, and families). The chapter concludes with some recommendations for providers of digital health information for PwMS and suggestions for future research.

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KEY TERMS AND DEFINITIONS

Digital Health Information: Health information that can be accessed in electronic form.

E-Health: Health services and information delivered using digital technologies.

Health Literacy: Personal characteristics and social resources needed by an individual to access, evaluate, and use health-related information.

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Long-Term Condition (LTC): Term used to describe chronic health conditions.

Multiple Sclerosis (MS): A neurological condition of the central nervous system.

National Health Service (NHS): The body responsible for policies, priorities and directions of health and care in England.

Person or People With MS (PwMS): A neutral (and non-offensive) term used to describe someone who has MS.

Shared Decision Making (SDM): An initiative to encourage patients and their healthcare staff to share responsibility for health decisions.

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Index

3D image 170

A

Acetylcholine 1, 3, 25, 154, 164, 226, 247, 510, 515-516, 524
Adni Images 281-282, 284
Alpha secretase 1, 6, 10
Alpha-synuclein 18, 20, 40, 83, 298, 382-383, 387-388, 403-404, 406-409
Alzheimer Disease 12-15, 32, 34, 88, 90-91, 95-96, 100, 103, 106-107, 117, 125, 139-140, 143, 149, 155-156, 158, 168, 170, 176, 187-189, 192, 207, 221-222, 239-241, 265, 267, 280, 424, 497, 502, 550, 565-566, 568, 608
Alzheimer's Disease (AD) 1, 3-4, 9-17, 29, 34, 37-38, 43, 62, 89-90, 95-97, 100-101, 104-107, 109-115, 118-120, 133, 139-141, 145, 147-160, 162-165, 167-177, 186-193, 198, 200, 202, 207, 220-225, 239-246, 263-267, 269, 280, 287, 290, 292, 294, 347, 367, 382, 388, 393, 405, 411-412, 420, 423, 425, 428, 453, 497, 507-510, 513, 516, 518-520, 522-525, 527-529, 545, 550, 564-571, 573, 583-584, 586, 588-590, 592-593, 607-610, 629
Amyloid Plaques 4, 52, 81, 147, 149-150, 159, 166, 225
Amyloid precursor protein 1, 5, 7, 12-17, 153, 159, 171
Amyloid β (Aβ) 1, 8, 10, 12, 15, 96, 147, 158-159, 171, 173, 388, 510, 513
ANOVA 464-465
Antioxidants 89, 425, 453, 508, 511, 513-514, 521
Artificial Intelligence (AI) 165, 182-183, 349, 649
Artificial Neural Networks 161, 224, 242-243, 265, 301, 327, 358
Augmented Reality (AR) 492, 499
Autism 94, 492, 494, 498-499, 518, 523, 591, 609
Autistic Spectrum Disorder 492
Automatic Diagnosis System 191

B

Behavioral Measure 550, 569
Beta secretase 1, 6, 10
Bilingual / Multilingual 120
Biomarkers 119, 153, 156, 160, 162-165, 167-169, 226, 240-243, 297, 302, 323, 326, 331, 367, 382, 384, 426, 503, 640, 643
Blood Brain Barrier 367, 502, 504, 524
Bounding Boxes 570, 572, 577-579, 582-583, 585
Bovine 42-43, 46, 48, 50-51, 53, 58, 424, 452
Bradykinesia 82, 295, 297, 299, 327, 344, 346, 390, 396, 627, 631-632, 640
Brain Tissues Classification 267
Brain-Computer Interfaces 475-476, 482
Brainstem 19-21, 23-26, 39, 61, 93, 102, 343, 389, 391, 393
BSO 329, 331

C

Capability Approach 526, 536-538, 546-547
Care givers burden 526
Central Nervous System 12, 43, 60, 82, 91, 93, 95, 100, 133, 188, 296, 327, 329, 344, 359-360, 367, 388, 405, 474, 504, 509, 646, 666
Chaperones 44-45, 52, 55
Cinnamic Acid 411-413, 420
CNN 160, 165-166, 327
Cognition 2, 22, 24, 26, 31, 39, 117-119, 123, 125, 129-130, 137-139, 142-144, 146, 211, 243, 265, 329-330, 393, 408, 506-507, 524, 531, 566
Cognitive Reserve 109, 115, 119-120, 135, 145, 147, 189, 212
Cognitive-Communicative disorders 211
Creutzfeldt-Jakob 42-43, 45-51, 53-58
CSF 62, 65, 140, 152-153, 160, 163-165, 167, 192, 213, 241, 268-270, 277-280, 283-284, 288

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D

Data Imbalance 295, 297-298, 300, 302-303, 310, 313-314, 317-318, 323-324, 327
Deep Learning 160-162, 164-169, 241, 363
Default Mode Network 165, 589, 591, 596, 606, 609
Delirium 132-133, 146
Dementia 2, 11, 14, 17-19, 21, 23-26, 28-41, 46, 48, 50, 60, 89, 94-96, 98-99, 104-106, 109-113, 115-121, 123-125, 128-148, 150-151, 155-157, 159, 162, 169-171, 173-174, 176-177, 187, 189-192, 210-223, 225-226, 235, 240-243, 245-247, 264-266, 296, 298-300, 362, 367, 388-394, 398, 402-407, 410, 412, 423-424, 428, 453, 492-493, 495-499, 513, 516, 522, 526-531, 533-550, 552-554, 556, 560, 564-569, 571, 583, 585-586, 588, 590, 608
Dementia of Alzheimer's Type (DAT) 210-212, 214, 219, 223
Dementia with Lewy bodies 18, 21, 23-24, 26, 29-41, 106, 129, 133, 367, 387, 402-403, 405, 407, 410, 528
Design Of Experiments 456, 460, 462
Detection 40, 54, 58, 119, 121, 125, 135, 143, 147, 150, 152-153, 159-161, 163, 165, 167, 169-170, 180, 182, 192, 207-208, 222, 224, 241, 243, 245, 256, 262-263, 265, 272-273, 277, 295, 297-298, 301-304, 307, 309-311, 313, 315-318, 321-330, 332, 335-336, 338-340, 354, 360, 365-366, 382, 456-458, 460, 470-472, 475, 479, 481-482, 485, 488-489, 491, 503, 509, 569, 571-575, 577, 579-581, 583-587, 609, 614, 616-617, 627-629, 643-644
Diagnosis 12, 19, 26, 28, 31, 36-37, 39, 42-43, 50, 53-54, 56-58, 65, 71, 81, 98, 101, 108, 111-112, 118-119, 123-125, 132-133, 137-139, 141-143, 147, 149-153, 155-160, 162-168, 174-175, 177-178, 181-183, 186-187, 189, 191-193, 200, 202, 208, 210-213, 215, 219-220, 222-226, 235, 237, 239-241, 243, 245, 247, 262-264, 268, 286, 295, 297-298, 300-303, 323-327, 330-331, 336, 339, 361, 381, 390, 392, 395, 403-405, 407-408, 447, 470, 492, 496-497, 503, 521, 529-531, 539, 544, 590, 610, 616, 624, 629, 635, 639-640, 646, 652-654, 665
Digital Health Information 645-647, 650-651, 653, 655-657, 661-662, 665
Digital Literacy 656
Disability Paradox 526, 537-538
Disease diagnosis 167, 174, 181, 189, 191, 193, 200, 202, 325-327, 341
Dopamine 23, 26-27, 32, 68, 71-73, 78, 82, 85-87, 102, 105-106, 295-298, 300, 323, 327, 341, 345-346, 391, 393-394, 408, 456-457, 477, 513, 627, 631-632, 639

E

Early Detection 119, 160-161, 192, 222, 224, 241, 243, 245, 262, 265, 295, 297-298, 301-302, 318, 321, 323-324, 326-329, 340, 365, 509, 609, 616, 627, 629, 644
Early Diagnosis 147, 149-150, 152-153, 155, 159-160, 165-166, 168, 189, 208, 224, 226, 237, 239, 241, 263, 326, 330, 531, 544
EEG Early Event 266
EEG Event 266
E-Health 623-624, 645-646, 663, 665
Electroencephalogram 224, 245, 247, 265-266, 475
Electroencephalogram Signals 224, 265
Electromyography 345, 359-360, 478, 630
Encephalopathies 42-43, 46, 58
Energy variation 245
Environment Landscape 550, 569
Environmental Perception 550, 569
EOAD 160, 163
Epidemiology 43, 48, 53, 57, 74, 78-79, 82, 88, 97, 101, 103, 105, 107, 140-141, 362
Etyology 79
Executive Function 114, 123, 125, 129-131, 138-139, 146, 212-213, 223, 393, 404
Extreme Learning Machine 295, 298, 303, 317, 325, 327, 642

F

Face Detection 570, 574-575, 577, 585-586
Features Extraction 183, 193, 476, 481, 572
Features Selection 191, 193, 195, 202, 232, 248, 253
Flower Pollination Algorithm 192, 196, 209
fMRI 112, 151-152, 157, 159, 170, 178-179, 183-184, 490, 589-592, 603, 606-610
Food Fortification 502
Food Intake Detection 570-571, 585-587
Food Supplements 502
Freesurfer 170, 183-185, 188
Freezing Of Gait 456-457, 459, 469-472, 626-627, 633, 643
Functional Connectivity 421, 448, 589-591, 595, 600-601, 607, 609-610, 632
Functional Electrical Stimulation 473-475, 490
Fuzzy Classifier 329-331, 339

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Fuzzy C-Means Algorithm 267, 291, 294
Fuzzy Possibilistic C-Means Algorithm 267

G

Gait Disorder 626, 630-633
Gamma secretase 1, 6, 10-11, 14
Gaucher's disease 395, 405
Genetic Algorithms 208, 254, 269
Graph Theory 589, 591, 601, 607
Grey Wolf Optimizer 192, 195, 208

H

Havy metals 79
Head-Mounted Display 499
Health Literacy 650-651, 663, 665
Healthcare 80, 160-162, 168, 182, 184, 212, 266, 393, 471-472, 493, 513, 529, 551, 566, 589, 611-615, 617-618, 622-626, 634, 643, 645-661, 663, 665-666
heavy metals 59-60, 62, 64, 68, 70, 75, 79-82, 86, 89, 91-92, 94, 105
Hereditary Parkinson's disease 387, 391-392
Huntington disease 59-60, 71, 73, 75-78, 86, 347

I

Image Processing 169-170, 174, 181, 190, 192-193, 207, 292, 323, 585, 587, 607, 628
Immersive Interactive Simulation System 499
Immersive Reminiscence 496, 499
Impairment 1-2, 4, 8, 10-11, 13, 16, 18, 21, 24-26, 35, 38-39, 50, 66, 93, 97, 107-108, 111, 116, 119, 123-125, 128-135, 138-146, 149, 158, 164-166, 171, 174, 187-188, 191-192, 198, 208-212, 214-219, 221-225, 239-242, 245-246, 264, 294, 330, 340, 389-390, 393-394, 398, 402, 404, 411-412, 428, 453, 456, 483, 488-489, 502, 513, 515-517, 538, 590, 606, 608, 626-627
In Silico 411-413, 415, 417, 420-421, 428, 433, 446, 449
Inhibitor Docking 427
Internet of Things 611, 615, 622-625

L

L36I Mutant 427, 441-442
Lateralization 589, 591, 598, 603, 605-607, 609
Lewy body disease 18, 21-22, 24, 26, 28-29, 31-35, 38-39, 41, 391-392, 398
LOAD 160, 163, 563, 590
Long-Term Condition (LTC) 666
lysosomal storage diseases 387-388, 395, 410

M

Machine Learning 161, 166-167, 169-170, 181-182, 186, 191-192, 208-209, 240, 266, 313, 317, 326, 328-330, 335, 338, 340-341, 349-352, 354, 358-365, 458, 471, 635, 643-644
Machine Learning System 208, 341, 349
MCI patients 124, 129-130, 137, 167, 187-188, 198-199, 226, 232, 245, 247, 253-256, 262-263, 266
Memory loss 88, 92, 120, 125, 146-147, 149, 162, 177-178, 180, 220, 222, 246, 393, 513, 516, 527
Michael Addition 411-414, 417, 419, 427, 430-431, 443-444, 455
Mild Cognitive Impairment (MCI) 13, 119, 123-125, 128, 133, 138-146, 158, 164-166, 171, 174, 187-188, 192, 208-211, 217, 221-223, 225, 239-242, 245-246, 294, 393, 402, 411-412, 428, 453, 590
Mitochondrial Pyruvate Carrier 411-412, 421-425, 427-428, 447-455
Mixed Reality (MR) 499
Moth Flame Optimization 192, 195
Motion Detection 570, 572, 577, 586, 614
MPC1 414-416, 418-419, 427-442, 444-447, 451
MPC2 412, 414, 427-431, 434-436, 438-442, 445-446
MRI 26, 36, 40, 50, 90, 100, 112, 147, 150-151, 156-157, 159-161, 163-165, 167-170, 177-178, 181-184, 187-188, 191-193, 198-200, 202, 207-208, 213, 215, 244, 269-270, 272, 277, 282-283, 287, 292-293, 396, 398, 590, 593-594, 608
Multiple Linear Regression 366, 370
Multiple Sclerosis (MS) 59-60, 70-78, 342-343, 502, 505, 523, 645-646, 650, 662-666
Multiple system atrophy 30, 36, 297, 300, 367, 387, 394, 403-405, 408-410

N

Naive Bayes 298, 301, 318, 326, 358, 626-628, 633, 635, 642-643
Nanotechnology 504-505, 524, 624
National Health Service (NHS) 645-646, 666
Neurodegeneration 6, 9-10, 18-20, 38-39, 42-43, 46, 49, 52, 54, 59, 62, 67, 72-75, 94, 104, 156, 172, 176, 188, 366, 394-399, 401-402, 404-406, 409-412, 422, 446, 449, 502, 518, 522
Neurodegenerative disease 15, 36, 56-57, 79, 90, 147-148, 162, 169-171, 176, 420, 425, 517, 627

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Neurodegenerative Disorder 1, 21, 24, 42, 60, 68, 81, 88, 90, 95, 148, 295, 344, 367, 381, 389, 626
Neurofibrillary Tangles (NFTs) 1, 8, 13, 15, 81, 89-90, 94, 118, 147, 149-150, 152, 159, 225, 232, 246, 367, 392
Neuroimaging 52, 100, 112, 149-151, 160, 163-165, 169-170, 183, 213, 215, 240, 243, 267, 269, 290, 292, 382, 590-592, 608-609
Neurons 1, 5-9, 13-14, 18-19, 22-26, 29, 32, 34, 36, 41-43, 49, 64-65, 67-69, 72, 76, 81-82, 84-89, 91, 93, 97, 99, 102-103, 107, 149, 159, 172-173, 176, 178, 247, 252-253, 266, 296, 318, 345, 367, 389, 391, 394-396, 399, 410, 456, 513, 516, 616, 626, 630-632
Neuro-Nutraceuticals 502
Neuropsychological Rehabilitation 123, 146
Nigrostriatal system 82, 84
Non-Invasive 153, 167, 226, 247, 329-330, 473, 476, 478, 488-489, 590, 630-631

O

Object Tracking 570, 572
One-Class SVM 298, 303-304, 328
Optical Flow 570, 572-573, 575, 577, 579-580, 583-587
Overlapping Cases 295, 297-298, 302-303, 307, 310, 314-315, 317-318, 323-324, 328

P

Parkinson's disease (PD) 18, 21, 23, 26, 29-41, 72, 76, 82, 94-108, 111, 113, 133, 139, 157, 165, 220, 235, 263, 265, 295-302, 323-327, 329-330, 335, 338-341, 343-348, 360, 362-367, 382-384, 387, 389-392, 402-409, 411-412, 422, 427-428, 446, 456, 469-474, 477-478, 480, 482-483, 485-486, 488-491, 502, 508, 510, 523, 611, 616, 619, 621-622, 626-627, 631, 642-644
Parkinson's disease dementia 21, 23, 26, 30-31, 38-40, 387, 404
Parkinsonian Tremor 343, 349, 363, 631
Parkinsonism 18, 21, 24, 26-27, 29-32, 36, 38-40, 71-72, 76, 81, 88, 99-100, 102, 104, 218, 295, 297, 300, 326-327, 364, 390-391, 393-395, 402, 404, 406-408, 472, 629, 642-643
Person or People With MS (PwMS) 666
pesticides 59-60, 64, 69-70, 72, 76, 79-83, 85-86, 89, 91, 93-94, 96-97, 99-100, 102-105, 107, 299, 563
PET Radio Tracer Agent 366
Polyphenols 433, 449, 514-516, 519-520, 524
Possibilistic C-Means Algorithm 267-268
Presenilin 2, 6-7, 153, 163
Principal Component Analysis 164-165, 192, 302, 331, 572, 626, 628, 634, 642-643
Prion 42-58, 403
Processing Speed 124-126, 128, 131, 146
Propagation Time 245, 256, 263
Protein Homology Modeling 411, 413
Protein Protein Docking 427
Proteinopathies 42, 44-45
Pseudo-Dementia 125, 132, 142, 146, 216
Pyruvate 411-412, 415, 418, 421-425, 427-455

Q

QAAR 366-368, 371-373, 375-376, 382, 384
QSAR 367-368, 370-373, 375-376, 382-384

R

Random Forest 166, 331, 341, 350, 358, 456-458, 460, 462, 464, 467-469, 609, 627, 629, 643
Real Images 281, 284
Rule Based Learning 329

S

Scalp 178, 227, 232, 247-248, 256, 266, 277, 488
Self-Organized Maps 245, 247, 252
Sensorimotor Feedback Loop 473-474
sequences 10, 40, 174, 245, 256-257, 259, 262-263, 391, 427-428, 431, 580
Serotonin 40
Shared Decision Making (SDM) 645-646, 648, 650, 653-654, 661, 663, 665-666
Shift-to-the-Left 229, 247, 250, 266
Signal Processing 227, 239, 242-243, 248, 264-266, 292, 340, 361, 476, 478, 482, 489, 585-587
Single Nucleotide Polymorphism 167
Skin Detection 570, 572-574, 579, 583, 587
Speech Analysis 329-330, 338
Sporadic Creutzfeldt-Jakob Disease 47, 54, 57
Stroke Rehabilitation 473-474, 476, 483, 488-490
Support services 526, 536-537
Support Vector Machine 166, 192, 202, 298, 301-302, 317, 326, 335-336, 338, 341, 358, 361-362, 420, 459, 482, 488, 626-629, 633, 635, 643
Swarm Optimization Algorithms 191

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Symptoms 2-3, 11, 18-19, 21-28, 38-39, 42, 46, 48, 50-51, 60, 65, 69, 82, 88-89, 111-112, 120, 124-125, 130, 135, 137-138, 140, 143, 146-149, 153-155, 162, 165, 168-169, 171, 173, 176-177, 180, 191, 211-213, 216, 225-226, 237, 246-247, 266, 297-300, 323, 327, 329-330, 338, 340-341, 343-347, 359-360, 367, 389-391, 396, 398, 402, 406, 408-409, 457, 473-474, 477, 493-495, 503-504, 508, 517, 527-528, 530-531, 539, 541, 544, 550-552, 554, 560, 590, 607, 611, 626-627, 629, 631-632, 638, 640, 646, 649

T

Tau Protein 2, 16, 81, 89, 147, 152-153, 159, 167, 172, 376
temporal events 245, 248, 263, 265
Therapeutic 3, 6-7, 9-11, 17, 27, 51-52, 58, 72-73, 160, 384, 387, 399, 403, 406, 410-411, 427-428, 431, 492, 494-497, 502, 504-505, 523, 541, 559, 563-568, 615
Thiazolidinedione 411-412, 432-433, 448
Thiohemiacetal 411, 414, 417-418, 429-431, 437, 442-444, 449
Tomek-Link 295, 298, 303, 307, 309, 315, 317, 323-324, 328
Treatment 6-7, 9, 26-28, 33, 35-36, 41-43, 51-54, 90, 93, 99, 105, 108, 110, 112, 119, 121, 129, 135, 140-143, 146-147, 149, 153, 157-159, 162, 165-166, 168, 176, 181-182, 208, 215, 219, 225-226, 241, 247, 264, 268, 297, 299-300, 302, 314, 323, 330, 363, 387-388, 390, 394, 399-401, 404-405, 409, 428, 465, 471, 492-493, 496-497, 500, 502-505, 507, 510-511, 513-518, 521-524, 529-530, 534-535, 539, 541-543, 546, 550, 560, 566, 569, 607, 612, 618, 627, 638, 643, 648, 651-654, 658, 665
Tremor 24, 26-27, 82, 297, 299-300, 327, 341-344, 346-349, 358-364, 390, 396, 405, 457, 477-478, 480, 482-483, 485-488, 490-491, 619-620, 627, 631
Tremor Reduction 480, 483, 485, 488

U

Ubiquitin proteasome system 1
UK-5099 412, 414, 417, 430, 432, 442-444
Unsupervised Classification 252, 266

V

Variant Creutzfeldt-Jakob Disease 48, 54, 56-58
VE 657, 659
Viola-Jones 575, 577
Virtual Environments 492, 494, 496-499
Virtual Reality (VR) 492, 494, 497-500
Virtual Reality Exposure Therapy (VRET) 500
Visuospatial Ability 128, 146

W

Well-water 79, 83
Wild Type 66, 431, 435, 438-442, 444
α-Syn 20, 23, 25, 28
α-Synuclein 30-33, 35-41, 367-368, 370, 373, 376-384, 387-389, 391, 393-410
α-Synucleinopathies 20, 387-388, 401

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