COMPUTER-AIDED EARLY DETECTION OF PARKINSON'S DISEASE THROUGH MULTIMODAL DATA ANALYSIS

R. PRASHANTH

DEPARTMENT OF ELECTRICAL ENGINEERING

INDIAN INSTITUTE OF TECHNOLOGY DELHI

AUGUST 2015

COMPUTER-AIDED EARLY DETECTION OF PARKINSON'S DISEASE THROUGH MULTIMODAL DATA ANALYSIS

by

R. PRASHANTH

DEPARTMENT OF ELECTRICAL ENGINEERING

Submitted

in fulfilment of the requirements of the degree of

DOCTOR OF PHILOSOPHY

to the

INDIAN INSTITUTE OF TECHNOLOGY DELHI

AUGUST 2015

CERTIFICATE

This is to certify that the thesis entitled, "**Computer-Aided Early Detection of Parkinson's Disease through Multimodal Data Analysis**", being submitted by **Mr. R Prashanth** for the award of the degree of **Doctor of Philosophy** is a record of bonafide research work carried out by him in the Department of Electrical Engineering of the Indian Institute of Technology Delhi.

Mr. R Prashanth has worked under our guidance and supervision and has fulfilled the requirements for the submission of this thesis, which to our knowledge has reached the requisite standard. The results obtained here, have not been submitted to any other University or Institute for the award of any degree.

Dr. Sumantra Dutta Roy	Dr. Shantanu Ghosh	Prof. Pravat K. Mandal
Associate Professor, Dept. of Electrical Engineering, Indian Institute of Technology Delhi	Research Fellow, Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Massachusetts, USA	Professor, National Brain Research Center, India & Associate Professor (Adj.), Dept. of Radiology Johns Hopkins Medicine, USA

Dated:

To my family and friends

Acknowledgements

I express my sincere thanks to my PhD supervisors Dr. Sumantra Dutta Roy, Dr. Shantanu Ghosh and Dr. Pravat Mandal for their able guidance, and also to my other research committee members, Dr. Santanu Chaudhury, Dr. Prem Kalra and Dr. Brejesh Lall, for their valuable comments and feedback which helped to improve the work.

My heartfelt thanks to Dr. Senthil Kumaran of the All India Institute of Medical Sciences (AIIMS), New Delhi, for his most valuable discussion which culminated in the selection of my PhD topic.

My gratitude to Dr. Jyotirmoy Chatterjee and Dr. Pranab Kumar Dutta of IIT Kharagpur, and Dr. Sambuddha Ghosh of Regional of Ophthalmology, Kolkata who were the real inspiration for me to continue in research after my masters.

I thank the reviewers of the manuscripts, that were communicated to peer-reviewed journals, for providing constructive comments that improved the quality of the thesis.

Many thanks to my friends Jitesh Joshi, Pratik Shah, Yogesh T. Piolet, Teesta Naskar, Nikhil Anto Ponnor and Apurva Agrawal who helped me in getting journal papers that were inaccessible at IIT.

I thank my other friends Jeevanand Seshadrinath, Sabyasachi Gupta and other people who were a constant support throughout my PhD study. I thank my fellow lab mates and lab staff in the Multimedia Lab for their help during the study. I thank Dr. Rajesh of the IIT Hospital, Delhi, Dr. Subash Babu and Dr. Bindu of the Ayurveda College

Hospital, Trivandrum, Dr. Pravin Haribakti and Dr. Monal Shah, Ahmedabad, for providing medical help when I got sick. I also thank Drs. Haraja, Aswathy, Maya, Neetu, Parvathy and Vishnu Prasad for their encouragements. My heartfelt thanks to Baiju sir for his help in a spiritual way and my childhood friends Dr.Vishnu and Vineesh for their amazing friendship. I also thank Richard uncle for his important help.

Most importantly, I thank the Parkinson's Progression Marker's Initiative (PPMI) study for publicly sharing their database without which this thesis would not have been possible. I also thank the industry partners and mainly, the Michael J. Fox Foundation (MJFF) for Parkinson's Research for funding the PPMI study. I thank the Data & Publication Committee (DPC) of the PPMI for providing timely administrative reviews of the manuscripts which was a requirement prior to submission to a journal/conference. I thank Vanessa Arnedo, Reena Vanjani, Sohini Chowdhury, Susan Mendick, Shirley Lasch and other members of the PPMI team for their assistance with regard to manuscript submission to DPC, administrative reviews and clearing my queries regarding the PPMI study.

I am grateful to my family members who have helped me by taking care of my mother during my stay away from home.

Last but not the least, I thank the Almighty who gave me the much necessary endurance to tackle hardships that came upon during the study and life.

Date:

Place: New Delhi R. Prashanth

Abstract

Early detection of Parkinson's disease (PD) is an important and challenging problem for effective management and treatment. There are no definitive diagnostic tests for PD and the clinical diagnosis relies on presence of classic symptoms, and by the time a patient shows these symptoms, more than 60% of dopaminergic neurons are lost. In this thesis, approaches based on multimodal data analysis and machine learning for early detection of PD are presented.

Recent neuroimaging techniques, such as SPECT, have shown to be sensitive in discriminating PD from healthy normal even at the early stages of the disease. Striatal Binding Ratio (SBR) values are well-established and clinically used quantification measures obtained from SPECT. This work carries out a novel use of these features in developing classification and prediction models for discriminating early PD from healthy controls. A high accuracy is achieved in classification.

Along with discriminating PD from normal, SPECT imaging have also indicated their usefulness in detecting a group of subjects, called Scans Without Evidence of Dopaminergic Deficit (SWEDD) who show normal scans who otherwise were clinically misdiagnosed as PD. This work carries out analysis of SPECT images, for segmenting and quantifying the high activity regions that correspond to striatal uptake, for extracting discriminatory features that eventually are used for classifying degenerative parkinsonism such as PD from healthy normal and non-degenerative conditions such as SWEDD. These computed features show good variation in PD as

compared to normal and SWEDD, and they are statistically significant as well. The classification accuracy is also observed to be very high.

Research studies show that there exist a phase called the premotor or the prodromal phase before the motor phase in PD and that this phase is mostly dominated by non-motor symptoms such as smell loss and REM sleep behavior disorder. This work carries out a novel use of these features along with other relevant features such as imaging and cerebrospinal fluid measurements to classify early PD from healthy normal. A very high accuracy is obtained in classification using an SVM classifier.

As of now, there exists no standard screening procedures for detecting PD, and patient questionnaire are easy tools that might have the potential for a screening instrument. This work carries out the novel use of using the patient questionnaire portion of the widely-used Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) to classify early PD from healthy normal. We observe a very high accuracy in classification.

Therapeutic options in PD depend on the stage and severity of the disease. This work carries out estimation of stage and severity of PD using MDS-UPDRS which evaluates the most pertinent features in PD. The AdaBoost-based classifier ensemble gave a high accuracy in classification. We infer from the study that such models have the potential to aid clinicians in the diagnostic process.

Table of Contents

List of Figures

List of Tables

List of Important Abbreviations

^{123}I-FP-CIT	^{123}I-2-carbomethoxy-3-(4-iodophenyl)-N-(3-fluoropropyl)nortropane
^{18}FDG-PET	^{18}F-fluoro-2-deoxyglucose PET
AD	Alzheimer's Disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
AUC	Area Under the ROC curve
Aβ1-42	amyloid beta peptide 1-42
BOLD	Blood Oxygenation Level-Dependent
CSF	Cerebrospinal Fluid
DAT	Dopamine Transporter
DLB	Dementia with Lewy bodies
DRT	Dopamine Replacement Therapy
DTI	Diffusion-Tensor Imaging
DWI	Diffusion-Weighted imaging
ET	Essential Tremor
FA	Fractional Anisotropy
fMRI	Functional MRI
FN	False Negative
FP	False Positive
GA	Genetic Algorithm
HC	Healthy Control
HY scale	Hoehn and Yahr scale
ICA	Independent Component Analysis
LRRK2	leucine-rich repeat kinase 2
MAO-B	Monoamine Oxidase B
MCI	Mild Cognitive Impairment
MD	Mean Diffusivity
MDS-UPDRS	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
MLR	Multivariate Logistic Regression

MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
MSA	Multiple System Atrophy
NMS	Non-Motor Symptoms
PCA	Principal Component Analysis
PD	Parkinson's Disease
PET	Positron Emission Tomography
PPMI	Parkinson's Progression Markers Initiative
PQ	Patient Questionnaire
PS	Parkinsonian Syndrome
P-tau181	tau phosphorylated at threonine 181
RBD	REM sleep Behavior Disorder
RBDSQ	RBD Screening Questionnaire
RBF	Radial Basis Function
REM	Rapid Eye Movement
RF	Random Forests
ROC	Region Operating Characteristic
ROI	Region of Interest
RUS	Random Undersampling
SBR	Striatal Binding Ratio
SBR_{LC}	SBR value of the left caudate
SBR_{LP}	SBR value of the left putamen
SBR_{RC}	SBR value of the right caudate
SBR_{RP}	SBR value of the right putamen
SPECT	Single Photon Emission Computed Tomography
SVD	Singular Value Decomposition
SVM	Support Vector Machine
SWEDD	Scans Without Evidence of Dopaminergic Deficit
TN	True Negative
TP	True Positive
T-tau	Total tau
UPDRS	Unified Parkinson's Disease Rating Scale
UPSIT	University of Pennsylvania Smell Identification Test

VMAT2	Vesicle Monoamine Transporter
α-syn	α-synuclein