DEVELOPMENT OF COMPUTATIONAL BIOMARKERS FOR EARLY DIAGNOSIS AND DIFFERENTIAL MONITORING OF DEMENTIA

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by

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Submitted

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Dedicated to

My Family

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CERTIFICATE

This is to certify that the thesis entitled **"Development of Computational Biomarkers for Early Diagnosis and Differential Monitoring of Dementia"**, being submitted by **Ms. Shivani Ranjan** to the Department of Electrical Engineering, Indian Institute of Technology Delhi, for the award of the degree of **Doctor of Philosophy**, is the record of bonafide research work carried out by her under my supervision. In my opinion, the thesis has reached the standard, fulfilling the requirements of the regulations relating to the degree. The results contained in this thesis have not been submitted either in part or in full to any other university or institute for the award of any degree or diploma.

Prof. Lalan Kumar
Department of Electrical Engineering,
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Date:

Place:

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Abstract

Dementia, particularly Alzheimer's Disease (AD), is a progressive neurological disorder with increasing global prevalence and no known cure. Early detection is crucial but remains challenging, as current diagnostic methods such as neuroimaging, cognitive assessments, and Cerebrospinal Fluid (CSF) analysis are often expensive, time-consuming, invasive, or impractical for routine clinical use. Diagnosis is further complicated by overlapping symptoms across dementia subtypes, frequently leading to misclassification. Importantly, neuropathological changes, such as tau tangles and amyloid plaques, begin in subcortical regions like the hippocampus nearly a decade before the onset of clinical symptoms. This early "clinically silent" stage underscores the urgent need for non-invasive, affordable, and portable tools that can enable routine brain health assessment and early-stage intervention.

To address these challenges, the thesis work proposes a multi-faceted ElectroEncephalography (EEG)-based framework for early diagnosis, dementia subtype classification, disease severity estimation, and treatment response monitoring. The framework leverages both source-domain and sensor-domain EEG analysis during resting-state and Working Memory (WM) tasks to capture functional brain dynamics across cortical and subcortical regions. The feasibility of using moderate-density EEG systems (31-channel) in clinical practice is demonstrated with validation, confirming the reliable detection of memory-related hippocampus activity. Building on this, a subcortical image-based deep learning framework is developed to classify dementia subtypes and progression stages with high accuracy across varying EEG channel densities using a Conventional Convolutional Neural Network (CNN) and novel fusion strategies.

For objective clinical interpretation, a threshold-based biomarker, the Dementia Severity Index (DSI), is introduced using interpretable EEG spectral information. A key strength of the framework lies in its threshold-based formulation, whereby specific feature ranges directly indicate the presence of dementia or its subtype, thus offering clinicians a straightforward diagnostic aid. DSI shows a strong correlation with cognitive assessments such as the Mini-Mental State Examination (MMSE), offering a scalable, quantitative alternative for evaluating cognitive decline. Furthermore, sensor-based computational markers are formulated

to sensitively capture dementia-related signal disruptions.

At the sensor-network level, Cross-Plot Transition Entropy (CPTE), a robust and noise-tolerant synchronization measure, is employed that demonstrates superior classification performance in both resting-state and WM tasks compared to existing network methods. In addition, the functional Excitation-to-Inhibition (fE/I) ratio is proposed to quantify temporal complexity differences across dementia stages. The results reveal characteristic disruptions in neural dynamics. The translational potential of the framework is further validated in a pilot intervention study. The EEG-derived fE/I biomarker captures treatment-related improvement through before and after intervention assessments conducted over a three-month course of Ayurvedic (Saraswata Ghrita) therapy. These findings establish EEG as a clinically viable, non-invasive, and sensitive modality for disease staging and for monitoring therapeutic efficacy across diverse medical contexts.

In summary, the thesis establishes EEG source localization–based analysis as a clinically feasible framework for dementia diagnosis, staging, and therapy monitoring. By integrating source imaging, deep learning, graph networks, and interpretable biomarkers, the work demonstrates the potential of EEG to evolve into a reliable, scalable, and non-invasive tool for clinical dementia research and patient care.

सारांश

मनोभ्रंश, विशेष रूप से अल्जाइमर रोग (एडी), एक प्रगतिशील तंत्रिका संबंधी विकार है जिसका वैश्विक प्रसार बढ़ रहा है और जिसका अभी तक कोई ज्ञात उपचार उपलब्ध नहीं है। शीघ्र पहचान अत्यंत महत्वपूर्ण है, किंतु यह चुनौतीपूर्ण बनी हुई है, क्योंकि न्यूरोइमेजिंग, संज्ञानात्मक मूल्यांकन तथा सेरेब्रोस्पाइनल फ्लूइड (सीएसएफ) विश्लेषण जैसी वर्तमान निदान विधियाँ नियमित नैदानिक उपयोग के लिए प्रायः महंगी, समय-साध्य, आक्रामक अथवा अव्यावहारिक होती हैं। मनोभ्रंश के उपप्रकारों में लक्षणों के परस्पर अतिव्यापन से निदान और अधिक जटिल हो जाता है, जिससे प्रायः गलत वर्गीकरण की संभावना बढ़ जाती है। महत्वपूर्ण रूप से, तंत्रिका-रोग संबंधी परिवर्तन, जैसे ताऊ टेंगल्स एवं अमाइलॉइड प्लाक, नैदानिक लक्षणों की अभिव्यक्ति से लगभग एक दशक पूर्व हिप्पोकैम्पस जैसे सबकोर्टिकल क्षेत्रों में आरंभ हो जाते हैं। यह प्रारंभिक "चिकित्सकीय रूप से मौन" अवस्था गैर-आक्रामक, किफायती एवं पोर्टेबल उपकरणों की आवश्यकता को रेखांकित करती है, जो नियमित मस्तिष्क स्वास्थ्य मूल्यांकन तथा प्रारंभिक चरण में हस्तक्षेप को संभव बना सकें।

इन चुनौतियों के समाधान हेतु, इस शोधकार्य में प्रारंभिक निदान, मनोभ्रंश उपप्रकार वर्गीकरण, रोग-गंभीरता के आकलन तथा उपचार-प्रतिक्रिया निगरानी के लिए एक बहु-आयामी इलेक्ट्रोएन्सेफलोग्राफी (ईईजी)-आधारित रूपरेखा प्रस्तावित की गई है। यह रूपरेखा कॉर्टिकल एवं सबकोर्टिकल क्षेत्रों में क्रियात्मक मस्तिष्क गतिकी को अभिलक्षित करने के लिए विश्राम-अवस्था तथा कार्यस्मृति (डब्ल्यूएम) कार्य के दौरान स्रोत-डोमेन एवं सेंसर-डोमेन ईईजी विश्लेषण का उपयोग करती है। नैदानिक व्यवहार में मध्यम-घनत्व ईईजी प्रणाली (31-चैनल) के उपयोग की व्यवहार्यता को प्रमाणीकरण सहित प्रदर्शित किया गया है, जो स्मृति-संबंधित हिप्पोकैम्पल सक्रियता के विश्वसनीय अन्वेषण की पुष्टि करता है। इसके अतिरिक्त, एक सबकोर्टिकल इमेज-आधारित डीप लर्निंग रूपरेखा विकसित की गई है, जिसमें पारंपरिक कन्वोल्यूशनल न्यूरल नेटवर्क (सीएनएन) तथा नवीन फ्यूजन रणनीतियों का उपयोग कर विभिन्न ईईजी चैनल घनत्वों में उच्च शुद्धता के साथ मनोभ्रंश उपप्रकार एवं रोग-चरण का वर्गीकरण किया गया है।

नैदानिक व्याख्या को अधिक वस्तुनिष्ठ बनाने हेतु, एक थ्रेशोल्ड-आधारित जैवचिह्न, डिमेंशिया सीवियरिटी इंडेक्स (डीएसआई), व्याख्यात्मक ईईजी स्पेक्ट्रल जानकारी के आधार पर प्रस्तुत किया गया है। इस रूपरेखा की प्रमुख विशेषता इसका थ्रेशोल्ड-आधारित संरचनात्मक प्रतिरूप है, जिसके माध्यम से विशिष्ट विशेषता-सीमाएँ सीधे मनोभ्रंश अथवा उसके उपप्रकार की उपस्थिति का संकेत देती हैं, जिससे चिकित्सकों को स्पष्ट नैदानिक सहायक उपकरण प्राप्त होता है। डीएसआई का संबंध मिनी-मेंटल स्टेट एग्जामिनेशन (एमएमएसई) जैसे संज्ञानात्मक मूल्यांकन से दृढ़ रूप से स्थापित हुआ है, जो संज्ञानात्मक ह्रास के मूल्यांकन हेतु एक स्केलेबल एवं मात्रात्मक विकल्प प्रदान करता है। इसके अतिरिक्त, मनोभ्रंश-संबंधित सिग्नल व्यवधानों को संवेदनशीलता के साथ अभिलक्षित करने हेतु सेंसर-आधारित संगणनात्मक सूचक विकसित किए गए हैं।

सेंसर-नेटवर्क स्तर पर, क्रॉस-प्लॉट ट्रांज़िशन एंट्रॉपी (सीपीटीई), एक सुदृढ़ एवं शोर-सहनशील समकालिकता मापक, का उपयोग किया गया है, जिसने मौजूदा नेटवर्क विधियों की तुलना में विश्राम-अवस्था तथा कार्यस्मृति दोनों स्थितियों में श्रेष्ठ वर्गीकरण प्रदर्शन प्रदर्शित किया है। इसके अतिरिक्त, मनोभ्रंश चरणों में कालिक जटिलता के अंतर का आकलन करने हेतु फंक्शनल एक्साइटेशन-टू-इनहिबिशन (एफई/आई) अनुपात प्रस्तावित किया गया है। परिणाम तंत्रिका गतिकी में विशिष्ट व्यवधानों को दर्शाते हैं। रूपरेखा की अनुवादात्मक क्षमता को एक पायलट हस्तक्षेप अध्ययन में भी प्रमाणीकरण प्राप्त हुआ है। ईईजी-आधारित एफई/आई जैवचिह्न ने आयुर्वेदिक (सरस्वत घृत) उपचार के तीन माह के हस्तक्षेप से पूर्व एवं पश्चात मूल्यांकन के माध्यम से उपचार-संबंधित सुधार को अभिलक्षित किया है। ये निष्कर्ष ईईजी को रोग-चरण निर्धारण तथा विविध चिकित्सीय संदर्भों में उपचार-प्रभाव की निगरानी के लिए एक नैदानिक रूप से व्यवहार्य, गैर-आक्रामक एवं संवेदनशील पद्धति सिद्ध करते हैं।

समग्र रूप से, यह शोध ईईजी स्रोत-स्थानीयकरण-आधारित विश्लेषण को मनोभ्रंश निदान, रोग-चरण निर्धारण एवं उपचार निगरानी के लिए एक नैदानिक रूप से संभाव्य रूपरेखा के रूप में स्थापित करता है। स्रोत इमेजिंग, डीप लर्निंग, ग्राफ नेटवर्क तथा व्याख्यात्मक जैवचिह्नों के एकीकरण के माध्यम से यह कार्य नैदानिक मनोभ्रंश अनुसंधान एवं रोगी देखभाल में ईईजी को एक विश्वसनीय, स्केलेबल एवं गैर-आक्रामक उपकरण के रूप में विकसित करने की क्षमता प्रदर्शित करता है।

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List of Abbreviations

ADAS-Cog	Alzheimer's Disease Assessment Scale–Cognitive Subscale
AD	Alzheimer's Disease
ASR	Artifact Subspace Reconstruction
BC	Betweenness Centrality
BCI	Brain-Computer Interface
BEM	Boundary Element Method
BOLD	Blood-Oxygen-Level-Dependent
BrainLat	Latin American Brain Health Institute
BSL	Brain Source Localization
CA	Classification Accuracy
CBSL	Cortical Brain Source Localization
CC	Clustering Coefficient
CDR	Clinical Dementia Rating
CNS	Central Nervous System
CNNs	Convolutional neural networks
CPTE	Cross-Plot Transition Entropy
CPE	Cross-Permutation Entropy
CSF	CerebroSpinal fluid
C^c	Coreness Centrality
CT	Computed Tomography
CWT	Continuous Wavelet Transform
D	Degree
DFA	Detrended Fluctuation Analysis
DSI	Dementia Severity Index
dSPM	dynamic Statistical Parametric Mapping
ECD	Equivalent Current Dipole

EC	Eigenvector Centrality
ECoG	ElectroCorticoGraphy
EEG	ElectroEncephaloGraphy
eLORETA	exact Low-Resolution Brain Electromagnetic Tomography
EPSPs	Excitatory PostSynaptic Potentials
ESI	Electrophysiological Source Imaging
fE/I	functional Excitation-to-Inhibition
FC	Functional Connectivity
FDM	Finite Difference Method
FEM	Finite Element Method
FFT	Fast Fourier Transform
FTD	FrontoTemporal Dementia
GFP	Global Field Power
HC	Healthy Controls
HHD	Head Harmonics Decomposition
ICA	Independent Component Analysis
IHIC	Infinite Homogeneous Isotropic Conductor
iEEG	intracranial ElectroEncephaloGraphy
IPSPs	Inhibitory PostSynaptic Potentials
kNN	k-Nearest Neighbor
LOOCV	Leave-One-Out Cross-Validation
LOSO	Leave-One-Subject-Out
LRTC	Long-Range Temporal Correlations
MCI	Mild Cognitive Impairment
MEG	MagnetoEncephaloGraphy
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
MUSIC	MUltiple SIgnal Classification
MVDR	Minimum Variance Distortionless Response

NCA	Neighborhood Component Analysis
NOMs	Network Organization Matrices
PET	Positron Emission Tomography
PLI	Phase Lag Index
PMI	Permutation Mutual Information
PR	Precision–Recall
PSPs	PostSynaptic Potentials
RA	Response Accuracy
RF	Random Forest
ROC	Receiver Operating Characteristic
ROIs	Regions Of Interest
RMS	Root Mean Square
RT	Reaction Time
SC	Signal Change
SIMOA	SIngle MOlecule Array
SC	Subgraph Centrality
SBSL	Subcortical Brain Source Localization
SD	Standard Deviation
SD	Subject-Dependent
SHD	Spherical Harmonics Decomposition
SI	Subject-Independent
sLORETA	standardized Low-Resolution Brain Electromagnetic Tomography
SMOTE	Synthetic Minority Oversampling Technique
SPECT	Single-Photon Emission Computed Tomography
SQUID	Superconducting Quantum Interference Devices
STFT	Short-Time Fourier Transform
SVM	Support Vector Machine
TFN	Tensor Fusion Networks
th	threshold
t-f	time-frequency

t-SNE	t-distributed Stochastic Neighbor Embedding
vWM	verbal Working Memory
WM	Working Memory
XGBoost	eXtreme Gradient Boosting