

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

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FOR EARLY DIAGNOSIS AND DIFFERENTIAL  
MONITORING OF DEMENTIA**

by

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DEPARTMENT of ELECTRICAL ENGINEERING

Submitted

in fulfilment of the requirements of the Degree of Doctor of Philosophy

to the



**INDIAN INSTITUTE OF TECHNOLOGY DELHI**

**FEBRUARY, 2026**

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 इलेक्ट्रोएन्सेफेलोग्राफी (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।

# Contents

<b>Certificate</b>	<b>ii</b>
<b>Acknowledgement</b>	<b>iii</b>
<b>Abstract</b>	<b>v</b>
<b>List of Figures</b>	<b>xiv</b>
<b>List of Tables</b>	<b>xxii</b>
<b>List of Abbreviations</b>	<b>xxvi</b>
<b>1 Introduction</b>	<b>1</b>
1.1 Literature Review and Motivation . . . . .	3
1.1.1 Cognitive Assessments and Screening Tools . . . . .	3
1.1.2 Biomarker-Based Diagnostic Methods . . . . .	5
1.1.3 Neuroimaging Techniques . . . . .	6
1.1.4 The Diagnostic Gap . . . . .	7
1.2 Problem Statements and Research Objectives . . . . .	9
1.3 Summary of Contributions . . . . .	10
1.4 Organization of the Thesis . . . . .	14
<b>I Prerequisite</b>	<b>17</b>
<b>2 Overview: Cortical/Subcortical Brain Source Localization (C/SBSL)</b>	<b>18</b>

2.1	Introduction . . . . .	18
2.2	Human Brain Anatomy . . . . .	19
2.2.1	Cortical Structures (Cerebrum) . . . . .	20
2.2.2	Subcortical Structures . . . . .	21
2.2.3	Cerebellum . . . . .	22
2.2.4	Brainstem . . . . .	22
2.3	Neurophysiology of the Brain . . . . .	23
2.3.1	The Neuron . . . . .	23
2.3.2	Glial cell . . . . .	27
2.3.3	Gray and White Matter . . . . .	28
2.4	Electrophysiology of the Brain . . . . .	28
2.4.1	Action Potentials . . . . .	30
2.4.2	Considerations for Subcortical Sources . . . . .	30
2.5	Neuroimaging Modalities . . . . .	31
2.5.1	Invasive Measurements . . . . .	31
2.5.2	Non-Invasive Measurements . . . . .	32
2.5.3	EEG Relevance for Subcortical Dynamics . . . . .	33
2.5.4	Forward Modeling . . . . .	35
2.5.4.1	Source Model . . . . .	35
2.5.4.2	Generalized Forward Problem Formulation . . . . .	41
2.5.4.3	Head Model . . . . .	43
2.5.5	Inverse Modeling . . . . .	48
2.5.5.1	Minimum Norm Estimate (MNE) . . . . .	49
2.5.5.2	sLORETA: statistical depth unbiasing . . . . .	50
2.5.5.3	Depth Bias . . . . .	51
2.5.5.4	eLORETA: exact depth-unbiased localization . . . . .	52

<b>II</b>	<b>Biomarker: Source Domain</b>	<b>55</b>
<b>3</b>	<b>Spatio-Temporal Analysis of Verbal Working Memory with 31-Channel EEG: Comparative Insights from 63-Channel EEG</b>	<b>56</b>
3.1	Related Work . . . . .	57
3.2	Objectives and Contributions . . . . .	60
3.3	Proposed Method . . . . .	61
3.3.1	Data Acquisition . . . . .	61
3.3.1.1	Participants . . . . .	61
3.3.1.2	Experimental Protocol . . . . .	61
3.3.2	EEG Recording and Preprocessing . . . . .	63
3.3.3	BSL: Source-Based Regional Activity Extraction in vWM Tasks . . .	63
3.3.4	ROIs Signal Change (SC) Computation . . . . .	64
3.3.5	Classification of Task-Relevant Brain Activity . . . . .	65
3.3.6	Clustering Analysis . . . . .	66
3.3.7	Time-Frequency Analysis . . . . .	67
3.4	Results & Discussion . . . . .	67
3.4.1	ROI Activation Dynamics Across vWM Stages . . . . .	67
3.4.1.1	Encoding . . . . .	68
3.4.1.2	Recall . . . . .	69
3.4.1.3	Retrieval . . . . .	70
3.4.2	Significant ROI in vWM stages . . . . .	71
3.4.3	Load processing . . . . .	75
3.4.4	Validation insight from fMRI study . . . . .	76
3.4.5	Comparative Analysis between Low (31) and High (63) Density EEG Configurations . . . . .	77
3.4.6	Behavioral Data Analysis . . . . .	79
3.5	Summary and Contributions . . . . .	80
<b>4</b>	<b>Deep learning-based classification of dementia using image representation of subcortical signals</b>	<b>81</b>

4.1	Related Work . . . . .	82
4.2	Objectives and Contributions . . . . .	85
4.3	Proposed Method . . . . .	85
4.3.1	Dataset Description . . . . .	86
4.3.1.1	BrainLat Dataset . . . . .	86
4.3.1.2	IITD-AIIA Dataset . . . . .	87
4.3.2	Scout Time Series Extraction . . . . .	88
4.3.2.1	Forward Model . . . . .	88
4.3.2.2	Inverse Model . . . . .	89
4.3.2.3	Regional Scout Time Series . . . . .	90
4.3.3	Image Data Preparation . . . . .	90
4.3.4	Classification Strategy . . . . .	91
4.4	Experiments and Results . . . . .	93
4.4.1	Experimental Details . . . . .	93
4.4.2	Results and Discussion . . . . .	93
4.5	Summary and Contribution . . . . .	99
<b>5</b>	<b>Quantifying Dementia Progression through EEG-Derived Dementia Severity</b>	
	<b>Index</b>	<b>101</b>
5.1	Related Work . . . . .	102
5.2	Objectives and Contributions . . . . .	104
5.3	Proposed Method . . . . .	105
5.3.1	Data Description . . . . .	105
5.3.2	EEG Acquisition Protocol . . . . .	106
5.3.3	Pre-processing . . . . .	106
5.3.4	Sensor to Source Mapping . . . . .	107
5.3.4.1	Forward Problem: Linking Potentials and Currents . . . . .	107
5.3.4.2	Inverse Problem: sLORETA Solution . . . . .	108
5.3.5	Dementia Severity Index (DSI) Computation . . . . .	108
5.3.6	Classification . . . . .	112

5.4	Experimental Conditions and Results . . . . .	115
5.4.1	Discussion . . . . .	120
5.4.1.1	$F_1$ and $F_2$ Analysis . . . . .	120
5.4.1.2	Dementia Severity Index (DSI) . . . . .	123
5.4.1.3	Cognitive Performance Analysis . . . . .	124
5.4.1.4	Statistical Analysis . . . . .	124
5.4.1.5	Validation Study . . . . .	126
5.5	Summary and Contributions . . . . .	129
 <b>III Biomarker: Sensor Domain</b>		<b>130</b>
 <b>6 CPTE-Based EEG Network Biomarkers for Dementia Using Multi-Protocol EEG</b>		<b>131</b>
6.1	Related Work . . . . .	132
6.2	Objectives and Contributions . . . . .	133
6.3	Resting-State: Dementia Subtypes Classification . . . . .	134
6.3.1	Dataset Description . . . . .	134
6.3.2	Preliminary Preprocessing . . . . .	135
6.3.3	CPTE-based Complex Network Model . . . . .	136
6.3.3.1	Cross-Plot Transition Entropy (CPTE) . . . . .	136
6.3.3.2	Complex Network Measure . . . . .	138
6.3.3.3	Connectivity density . . . . .	142
6.3.4	Results . . . . .	143
6.3.4.1	Complex Network Analysis . . . . .	143
6.3.4.2	Frequency Analysis . . . . .	145
6.3.4.3	Discussion . . . . .	147
6.4	Working Memory Functional Connectivity Analysis . . . . .	149
6.4.1	Participants and Equipments . . . . .	149
6.4.2	Experimental Paradigm . . . . .	150
6.4.3	EEG Preprocessing . . . . .	152

6.4.4	Spatiotemporal Features: Harmonics Decomposition . . . . .	152
6.4.4.1	Spherical Harmonics Decomposition (SHD) . . . . .	152
6.4.5	Head Harmonics Decomposition (HHD) . . . . .	154
6.4.6	Network Organization Matrices (NOMs) . . . . .	154
6.4.6.1	Phase Lag Index (PLI) . . . . .	154
6.4.6.2	Construction of NOMs . . . . .	155
6.4.6.3	Network Parameters Extraction . . . . .	156
6.5	Results . . . . .	158
6.5.1	Discussion . . . . .	161
6.5.1.1	Comparison between CPTE and PLI NOMs . . . . .	161
6.5.1.2	Network Parameters Analysis . . . . .	162
6.5.1.3	Significance of Retrieval Stage in Dementia Classification . . . . .	162
6.5.1.4	Comparative Analysis of Different Spatiotemporal EEG Features . . . . .	162
6.5.1.5	Effect of Thresholding . . . . .	163
6.5.2	Statistical Analysis . . . . .	164
6.6	Summary and Contributions . . . . .	164
<b>7</b>	<b>EEG-Based Assessment of Excitation–Inhibition Balance and Temporal Complexity in Dementia</b> . . . . .	<b>166</b>
7.1	Related Work . . . . .	167
7.2	Objectives and Contributions . . . . .	168
7.2.0.1	Participants . . . . .	169
7.2.0.2	Experimental Protocol . . . . .	169
7.2.1	EEG Data Acquisition and Preprocessing . . . . .	170
7.2.2	DFA and fE/I computation . . . . .	171
7.3	Results & Discussion . . . . .	173
7.4	Case Report: Treatment Monitoring . . . . .	175
7.5	Summary and Contributions . . . . .	177
<b>8</b>	<b>Conclusions and Future Directions</b> . . . . .	<b>179</b>
8.1	Future Directions . . . . .	181

<b>References</b>	<b>181</b>
<b>Appendices</b>	<b>216</b>
<b>A Spatio-Temporal Analysis of Verbal Working Memory with 31-Channel EEG: Comparative Insights from 63-Channel EEG</b>	<b>217</b>
<b>B Quantifying Dementia Progression through EEG-Derived Dementia Severity Index</b>	<b>225</b>
B.1 Regional Analyses . . . . .	225
B.1.1 Role of Entorhinal and Parahippocampal with NCA Integration . . .	228
<b>C CPTE-Based EEG Network Biomarkers for Dementia Using Multi-Protocol EEG</b>	<b>233</b>
<b>Publications Related to Thesis Work</b>	<b>236</b>
<b>Technical Biography of Author</b>	<b>238</b>

# List of Figures

1.1	Structural brain differences between AD and FTD. AD is characterized by shrinkage and neurodegeneration in both cortical and subcortical (hippocampus) regions, whereas FTD primarily affects cortical regions. (Image courtesy: Google)	2
1.2	Pathological Progression of Alzheimer’s Disease . . . . .	3
1.3	Subjective screening setup. . . . .	4
1.4	CSF Analysis. Left: [1]; Right: [2] . . . . .	6
1.5	Functional and Structural Assessment [3] . . . . .	7
2.1	Human brain anatomy: Cortical and Subcortical regions.(adapted from [4]) . . . . .	20
2.2	Gyri and Sulci [5] . . . . .	21
2.3	Three primary anatomical components of a neuron: Soma (Cell body), Dendrites, and an Axon [6] . . . . .	24
2.4	Estimate:approx.1 million synapses must be simultaneously active to be detected (leftmost [7]); EEG reflects postsynaptic potentials (PSPs) in pyramidal cells (middle; adapted from [8]); Equivalent Current Dipole(ECD) (rightmost) . . . . .	25
2.5	Pyramidal and Stellate cells and their corresponding generated scalp potential effect [9] . . . . .	26
2.6	Glial cell Types [10] . . . . .	27
2.7	Gray matter and white matter organization in the brain and spinal cord. [11]	29
2.8	a) Action potential of the neuron where the dashed line represents the threshold voltage [12, 13] b) The rat action potential [13] . . . . .	29
2.9	Triangulated BEM mesh for brain, skull, and scalp layers with varying conductivities. Head modeling is crucial for accurate forward modeling. [14] . . . . .	46

3.1	A block diagram representing the process followed to analyze the target sub-cortical regions (ROIs) activation dynamic during vWM. . . . .	62
3.2	Activation plot of the encoding phase at different time stamps: 0ms, 90ms, 102ms, 170 ms, 176 ms, and 232ms. Fig. 2(a) presents the cortical and subcortical activation plot sliced temporally. Fig. 2(b) illustrates the role of Wernicke’s and Broca’s areas during vWM where activation is around 170ms and 176ms respectively. The colorbar corresponds to relative sLORETA source current intensity (equivalent current dipole strength, A·m) . . . . .	68
3.3	Activation plot of the recall phase (start at 10s) at different time stamps: 10.016s, 10.186s, 10.194s, 10.228s, 10.308s, and 10.382s. The colorbar corresponds to relative sLORETA source current intensity (equivalent current dipole strength, A·m) . . . . .	69
3.4	A single-subject source activation map averaged across sessions and trials during distinct vWM stages (encoding, recall, and retrieval). A grand average of all subjects is shown in Appendix A Figure A.1(b). The colorbar corresponds to relative sLORETA source current intensity (A·m) . . . . .	70
3.5	Activation plot of the retrieval phase (start at 18s) at different time stamps: 18.132s, 18.160s, 18.232s, 18.270s, 18.280s, and 18.290s . The colorbar corresponds to relative sLORETA source current intensity (equivalent current dipole strength, A·m) . . . . .	71
3.6	The tsne-clustering of the three distinct vWM stages and rest phase for the hippocampus region. . . . .	74
3.7	A single subject source activation map, averaged across sessions and trials during target and non-target response. The averaged source activation map across all subjects is shown in Appendix A Figure A.2(b). . . . .	74
3.8	Time-frequency plots illustrating the oscillatory dynamics during (a) encoding (single word: 2s), (b) recall (complete session: 8s), and (c) retrieval (single probe: 1.5s) stages in the hippocampus region. . . . .	75

3.9	Activation deviation in target subcortical regions (ROIs: Left and Right) for distinct vWM stages using phase signal change parameter. Here ** denotes p-value < 0.001 and * indicates p-value < 0.05. The error bars represent the Standard Deviation (SD) across subjects. . . . .	77
3.10	Illustration of deviation in hippocampus activation using SC during encoding, recall, and retrieval with 63 and 31 channel EEG. HL and HR denote the left and right hippocampus. . . . .	78
4.1	Block diagram depicting the proposed method. The processed EEG signals are utilized to extract scout time series from the hippocampus, amygdala, and thalamus using sLORETA. The signals are segmented and divided into left and right regions. Subsequently, the CWT-based images are fed to separate classifiers for images corresponding to left and right regions. $z_L$ and $z_R$ represent the latent representation of the classifiers, while $\hat{y}_L$ and $\hat{y}_R$ denote classifier predictions. The latent embeddings are fused using Early and Tensor Fusion, while the individual classifier outputs are fused using probability sum and product. . . . .	86
4.2	Grand average EEG source localization plots (front view) for AD, FTD, and HC subjects from the BrainLat dataset at time stamps 70 s, 70.5 s, and 71 s. The plots were generated using the Brainstorm Toolbox, with activation maps displayed at a 20% amplitude threshold under global maximum normalization. . . . .	88
4.3	Illustration of the Early Fusion and Tensor Fusion Network approaches for dementia classification. In both schemes, $z_L$ and $z_R$ denote the latent embeddings derived from the left and right hemisphere classifiers, respectively. The Early Fusion strategy concatenates these embeddings into a joint representation, whereas the Tensor Fusion Network captures higher-order interactions between modalities by computing their tensor product before classification. . . . .	92
4.4	Confusion matrices obtained using the DenseNet201 classifier with the $\hat{y}_{mul}$ fusion strategy for (a) the BrainLat dataset and (b) the IITD-AIIA dataset. . . . .	96

4.5	Scatter plots illustrating the class-specific clusters obtained through t-SNE dimensionality reduction applied to the latent embedding vectors for (a) the BrainLat dataset and (b) the IITD-AIIA dataset. . . . .	97
4.6	(a), (c) Multi-class Receiver Operator Characteristic, and (b), (d) Multi-class Precision-Recall Curves for the combination of DenseNet201 and $\hat{y}_{mul}$ on the BrainLat and IITD-AIIA datasets, respectively. . . . .	98
5.1	Schematic flow diagram of the proposed framework for classifying AD, FTD, and HC using the DSI derived from spectral features ( $F_1, F_2$ ). . . . .	105
5.2	Cortex map representation of $rP$ ( $\alpha, \theta, \delta$ ) alterations observed in AD, FTD and HC. The image is generated using Brainstorm Toolbox . . . . .	109
5.3	Figure visually presents the different patterns across AD, FTD, and HC using $F_1$ and $F_2$ . The Brainstorm toolbox is used to generate the plot. . . . .	109
5.4	Distribution of mean $F_1$ across brain lobes in AD, FTD, and HC groups. Each point represents a subject's lobe-wise mean $F_1$ value, averaged across trials. Violin plots depict the probability density of these values within each group. Thresholds $T_1$ and $T_2$ mark reference levels; wider sections near these thresholds (e.g., around 0.9 and 2) indicate a higher likelihood of subjects in that group exhibiting $F_1$ values in the corresponding range. . . . .	111
5.5	Schematic diagram for classification of AD, FTD, and HC with and without thresholding approaches. Here, DSI and ML denote the dementia severity index and machine learning, respectively. . . . .	112
5.6	Comparison of classification performance using $F_1$ (left) and $F_2$ (right) features, illustrated through confusion matrices. Rows denote actual groups and columns denote predicted groups. Diagonal cells indicate correctly classified subjects, while off-diagonal cells correspond to misclassifications. . . . .	117
5.7	Impact of threshold variations and different threshold combinations ( $T_1$ and $T_2$ ) on classification accuracy in the subject-independent setting for both $F_1$ and $F_2$ . The heatmap displays accuracy values across combinations, with red blocks highlighting the optimal selections of $T_1$ and $T_2$ used to compute the DSI. . . . .	119

5.8	Compares the classification performance of DSI derived from $F_1$ (left) and $F_2$ (right) using confusion matrices. Rows denote actual groups and columns denote predicted groups, with diagonal cells representing correct classifications and off-diagonal cells indicating misclassifications. The distribution of these values highlights the relative strengths and weaknesses of each feature-based DSI for dementia classification. . . . .	121
5.9	Correlation of predicted MMSE with $F_1$ and $F_2$ features (NCA-reduced), showing a stronger association for $F_1$ (Spearman $r = 0.79$ ). . . . .	121
5.10	Spearman correlation ( $r$ ) between predicted and actual MMSE across 68 brain regions using $F_1$ features; 'R' and 'L' denote right and left hemispheres. . . .	122
5.11	This figure depicts the different patterns across AD and HC using $F_1$ and $F_2$ for 63-channel EEG setup. The Brainstorm toolbox is used to generate the plot.	126
6.1	Block diagram depicting the CPTE-based framework for examining differences in large-scale brain network organization across neurodegenerative groups (AD and FTD). . . . .	135
6.2	The diagram illustrates the computation of CPTE, where $x'_i$ and $y'_i$ denote two time series corresponding to an epoch from a given electrode pair. In this framework, the radial ruler ( $dr$ ) and angular ruler ( $d\theta$ ) are set to 10 and $10^\circ$ , respectively. . . . .	137
6.3	The figure illustrates the process of determining the optimal threshold by varying $th$ from 0 to 1 in increments of 0.1. The threshold corresponding to the maximum classification accuracy achieved by the RF model in differentiating AD from FTD is selected for subsequent analysis of brain network organization.	141
6.4	The figure shows the variation of connectivity density ( $N_d$ ) for the FTD and AD groups as a function of threshold values across different frequency bands. In all cases, the $N_d$ values for AD remain consistently lower than those for FTD, indicating reduced network connectivity. Subfigures represent: a) broadband (0.5–44 Hz), b) delta (0.5–4 Hz), c) theta (4–8 Hz), d) alpha (8–13 Hz), e) beta (13–30 Hz), and f) gamma (31–44 Hz). . . . .	145

6.5	The figure presents connectivity maps of the AD and FTD groups derived from the CPTE-based synchronization matrices. It highlights frequency bands where marked differences in connectivity density ( $N_d$ ) were observed between the two groups. Subfigures correspond to: a) broadband (0.5–44 Hz), b) theta (4–8 Hz), c) delta (0.5–4 Hz), and d) gamma (31–44 Hz). . . . .	146
6.6	Illustration of the average CPTE connection matrices (broadband: 0.5–44 Hz) computed across all subjects and epochs for the AD and FTD groups. Lower CPTE values correspond to stronger inter-channel synchronization. . . . .	146
6.7	The figure displays the $p$ -values of EC network parameters derived from the CPTE connection matrices of the AD and FTD groups, shown across all channels and for each frequency band. . . . .	147
6.8	Experimental design of the retro-cue guided match-to-sample task incorporating a prolonged delay period. . . . .	150
6.9	Experimental Setup . . . . .	151
6.10	Illustration of the coordinate axis convention adopted for Spherical and Head Harmonic Decomposition in this study. . . . .	153
6.11	Complex network organization analysis across different methodological approaches using the Degree feature with the RF classifier. The CPTE-based model achieved the highest classification accuracy in distinguishing AD, MCI, and HC groups. . . . .	158
6.12	Classification accuracy of the RF classifier based on the Degree network parameter across EEG-derived features. The plots depict CPTE-based network organization at different threshold values during encoding, retro-cue, recall, and retrieval stages of WM in AD, MCI, and HC groups. . . . .	160
6.13	Connectivity maps obtained using CPTE with a threshold of 0.4, illustrated across all WM stages (encoding, retro-cue, recall, and retrieval) for the AD, MCI, and HC groups. . . . .	161
6.14	Channel-wise statistical significance of CPTE-derived complex network features across AD, MCI, and HC groups, assessed using two-way ANOVA. The results indicate differential channel contributions to group-level distinctions. . . . .	164

7.1	Illustration of a trial from the experimental protocol designed to capture memory-related impairments in AD, MCI, and HC groups across the stages of encoding, recall, and retrieval. The encoding stage is considered for the further analysis. . . . .	170
7.2	Schematic flow diagram to investigate the disruption in fE/I . . . . .	171
7.3	Figure illustrates the patterns of DFA exponents of theta and beta bands across all channels during the encoding phase for AD, MCI, and HC groups. . . . .	173
7.4	Dynamics of the E/I measure across delta, theta, alpha, and beta bands for AD, MCI, and HC groups. . . . .	174
7.5	Relationship between DFA exponents and E/I ratio during encoding in the theta band across AD, MCI, and HC groups. . . . .	175
7.6	Mean fE/I ratio for the parieto-occipital and hippocampal regions during the eye-closed condition, before and after three months of medication intervention. . . . .	176
7.7	Mean fE/I ratio of the hippocampus during the eye-closed resting state before and after three months of medication intervention. . . . .	177
A.1	Regions of significant activation in distinct vWM stages (encoding, recall, and retrieval). Source activation pattern difference was observed approximately 180-200 ms after the onset of the processing phases (encoding, recall, retrieval). Fig.(a) represents a source activation map of subjects averaged across sessions and trials, and Fig.(b) a grand average of all subjects. . . . .	217
A.2	Activation pattern difference observed approximately 380- 400 ms prior to subject target and non-target probe responses during the retrieval phase. Fig.(a) indicates a single subject source activation map averaged across sessions and trials; Fig.(b) represents a grand-averaged source activation map. . . . .	218
A.3	Recall phase oscillation pattern of individual subjects and averaged across subjects. This figure indicates the number of words the subject contemplated and maintained in mind during the recall phase. Since with the subject, the contemplation time points of each word vary. Hence, multiple oscillation patterns are observed in the average case. . . . .	223

B.1	Source-space activation contrasts between AD and HC groups using the SDSL method. . . . .	226
B.2	Variation in $F_1$ feature across hippocampus and cortical regions. . . . .	226
B.3	a) Alzheimer’s and b) Healthy Eye open source based connectivity network .	230
B.4	a) Alzheimer’s and b) Healthy Eye closed source based connectivity network .	230
B.5	NCA- based cluster plot of all subjects using entorhinal and parahippocampal transformed current information $Z$ . . . . .	232
C.1	Connectivity plots derived from PLI for all WM stages across groups, evaluated at a threshold value of 0.7. The plots highlight group-wise differences in functional brain networks during task performance. . . . .	233

# List of Tables

2.1	Comparison of neuroimaging modalities (invasive and non-invasive) highlighting key technical and practical considerations. . . . .	33
3.1	A list of studies performed on working memory using surface EEG. . . . .	59
3.2	RF classifier performance metrics value to classify encoding, recall, retrieval, and rest cases in both the source (ROIs $[S]_{P' \times N_s}$ ) and sensor $[V]_{I \times N_s}$ domain for each subject. . . . .	72
3.3	Table presents the statistical differences (p-values) of each ROI for both (31 and 63) EEG configurations in distinguishing the Encoding, Recall, and Retrieval stages of vWM. . . . .	78
4.1	A brief description of neurodegenerative disorders classification using EEG. . . . .	84
4.2	Recognition accuracies of different deep learning classifiers under multiple classification strategies for the BrainLat dataset. For each model, the highest-performing strategy is highlighted in <b>blue</b> , while the overall best accuracy across all models is indicated in <b>bold</b> . . . . .	94
4.3	Recognition accuracies of different deep learning classifiers under multiple classification strategies for the IITD-AIIA dataset. For each model, the highest-performing strategy is highlighted in <b>blue</b> , while the overall best accuracy across all models is indicated in <b>bold</b> . . . . .	95

4.4	Recognition accuracies of various classification strategies using CWT- and STFT-based image representations on the BrainLat dataset. For each strategy, the superior transform method is highlighted in <b>blue</b> , while the overall best accuracy is indicated in <b>bold</b> . . . . .	99
5.1	Demographic summary of the study participants . . . . .	106
5.2	Comparison between sensor and source domains. The table highlights the superior performance of $F_1$ and $F_2$ derived from source-domain scout time-series signals, compared to 19-channel sensor-domain signals, for classifying AD, FTD, and HC. . . . .	115
5.3	Mean classification accuracy of RF classifier for classifying the AD, FTD, HC cases at different time windows. . . . .	116
5.4	Table illustrates the classification performance of $F_1$ features and their corresponding DSI values across two datasets. Results are reported using kNN and RF classifiers with 10-fold cross-validation for distinguishing AD from HC subjects. . . . .	120
5.5	Comparative Analysis of Various Methods for AD, FTD, and HC classification.	125
5.6	Performance of $F_1$ , $F_2$ , $DSI_{F_1}$ , and $DSI_{F_2}$ features across classifiers (kNN, RF, XGB, SVM) for AD, FTD, and HC classification. kNN with $F_1$ achieved the best accuracy (87.88%), while $DSI_{F_1}$ outperformed $DSI_{F_2}$ . Both Subject-Dependent (SD) and Subject-Independent (SI) results for kNN are reported. . . . .	127
5.7	Subject-wise classification into AD, FTD, and HC using the quantitative thresholds $T_1$ and $T_2$ for dementia stratification across all three datasets. . . . .	128
6.1	The table presents the median values of network efficiency measures for the AD and FTD groups, along with the corresponding $p$ -values from two-sample $t$ -tests, highlighting statistically significant group differences. . . . .	144

6.2	The table presents the performance metrics of network parameters across different frequency bands, derived from the CPTE connection matrix and binarized at the optimal threshold for each case. These metrics assess the ability to differentiate between AD and FTD. The best classification accuracies of network parameters within each frequency band are highlighted in <b>blue</b> , while the best overall result is shown in <b>bold</b> . . . . .	144
6.3	Mean classification accuracies for three-class dementia categorization (AD, MCI, HC) using CPTE-based EEG connectivity features. The table further illustrates the impact of varying threshold values when combined with different classifiers on overall classification performance. . . . .	159
7.1	DFA exponent values across frequency bands for AD, MCI, and HC groups. .	174
A.1	Encoding, Recall, Retrieval, and Rest cases classification using hippocampus temporal information of each subject for different machine learning models (SVM, RF, XGBoost) . . . . .	219
A.2	Encoding, Recall, Retrieval, and Rest cases classification using thalamus temporal information of each subject for different machine learning models (SVM, RF, XGBoost) . . . . .	220
A.3	Encoding, Recall, Retrieval, and Rest cases classification using amygdala temporal information of each subject for different machine learning models (SVM, RF, XGBoost) . . . . .	221
A.4	Encoding, Recall, Retrieval, and Rest cases classification using sensors temporal information of each subject for different machine learning models (SVM, RF, XGBoost) . . . . .	222
A.5	Performance metrics of spatio-temporal hippocampal activity in classifying vWM processes and resting state across different EEG channel counts, highlighting the influence of channel density on classification performance. . . . .	224
B.1	Mean $\bar{F}_1$ values across hippocampus and cortex regions in AD and HC groups.	227
B.2	Statistical significance ( $p$ -values) from one-way ANOVA. . . . .	227

B.3	Comparison of $\bar{F}_1$ deviations across significant cortical regions in AD and HC groups. . . . .	228
B.4	kNN–NCA classifier accuracy for distinguishing AD and HC groups using entorhinal and parahippocampal source signal features $[S]_{P \times N_s}$ , evaluated with 10-fold cross-validation. . . . .	231
B.5	Performance of entorhinal and parahippocampal at different frequency bands in classifying AD and HC groups . . . . .	231
C.1	Mean accuracies for three-class dementia classification using PLI-based EEG connectivity features. The results also illustrate the influence of varying threshold values in combination with different classifiers on classification performance.	234
C.2	Mean accuracies for 3-class dementia classification by using processed EEG signals $[V]$ , spherical harmonics $[V_{nm}^{SH}]$ , and head harmonics $[V_{nm}^{H^2}]$ . The effect on accuracies by using different threshold values and decomposition order (N) is also depicted. Degree network feature in conjunction with RF classifier is utilized for the analysis. . . . .	235

# 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

<i>EC</i>	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
<i>SC</i>	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