C-MAT: Cross-Modal Aligned Transformer for Four-Class Differential Diagnosis of Neurodegenerative Diseases Using Structural MRI and Resting-State EEG

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A thesis submitted to the Department of Computer Science and Engineering
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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. We have acknowledged all main sources of help.

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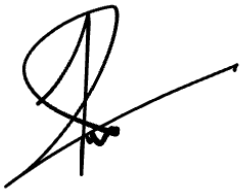

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Approval

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Ethics Statement

This thesis uses only de-identified and openly available neuroimaging datasets. No primary human-subject data were collected by the authors for this research, and therefore no direct intervention, recruitment, or contact with participants was conducted. The source datasets used in this work were previously collected under the ethics approvals and informed consent procedures reported by their respective institutions and dataset providers.

The study is strictly intended as research in computer-aided diagnostic support for neurodegenerative disease classification. It is not an autonomous clinical decision system, and its outputs must not be used as standalone medical diagnosis. Any interpretation of model predictions should be reviewed by qualified clinicians before clinical action.

All data handling followed responsible research practice, including subject-level split integrity, leakage prevention through globally unique subject identifiers, transparent reporting of limitations, and explicit documentation of bias risks related to demographic and site representation.

Abstract

Neurodegenerative diseases, including Alzheimer disease (AD), frontotemporal dementia (FTD), and Parkinson disease (PD), affect more than 57 million people globally and remain difficult to distinguish because symptoms overlap and MRI/EEG biomarkers are modality dependent. This thesis presents C-MAT (Cross-Modal Aligned Transformer), a unified multimodal framework for four-class classification of AD, FTD, PD, and healthy controls using T1-weighted structural MRI and resting-state EEG. The model combines a shared pretrained image encoder, modality-specific attention pooling, a dual-path EEG branch that fuses pseudo-image and raw-feature representations, and a sigmoid-gated fusion mechanism with learnable null tokens for missing modalities.

C-MAT was developed through three iterative pipeline versions over nine months, with forensic debugging used to expose cross-dataset subject-ID collisions, EEG reprocessing reuse, and pretrained-weight configuration errors. The final system was evaluated on 1,102 subjects from 10 open datasets spanning seven countries, using subject-level stratified five-fold cross-validation and dataset-prefixed identifiers. ConvNeXt-Tiny achieved a macro F1 of 0.611 ± 0.029, and DeiT-Tiny achieved 0.590 ± 0.044, outperforming classical baselines such as PSD+SVM (0.309) and Random Forest (0.453). On the strictly paired 25-subject MRI+EEG subset, C-MAT DeiT reached a mean macro F1 of 0.702, exceeding late-fusion baselines such as ResNet50 Fusion (0.482) and DeiT Fusion (0.296). Class-balanced focal loss improved macro F1 by +0.048 over cross-entropy. GradCAM and fusion-gate analysis showed clinically plausible patterns, including hippocampal and frontal emphasis for AD/FTD and greater EEG reliance for PD. To the best of our knowledge, C-MAT is among the first MRI+EEG systems for four-class neurodegenerative disease classification evaluated under subject-level multi-site validation.

Keywords: neurodegenerative disease, multimodal learning, structural MRI, resting-state EEG, transformer, differential diagnosis.

Dedication

This thesis is dedicated to all patients living with neurodegenerative diseases,
especially those with limited access to timely, affordable, and specialized diagnosis.
We also dedicate this work to their families and caregivers,
whose strength, patience, and daily struggles remind us why accessible healthcare innovation matters.
It is our hope that research like this can contribute, even in a small way,
toward earlier detection, lower-cost diagnostic support, and a more compassionate future for all.

Acknowledgement

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We gratefully acknowledge the authors and maintainers of the BrainLat dataset and other open-access neuroimaging resources used in this study. Their commitment to open science made this multi-site research possible.
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Nomenclature

The next list describes several symbols & abbreviation that will be later used within the body of the document

AD Alzheimer disease

CLAHE Contrast-limited adaptive histogram equalization

C-MAT Cross-Modal Aligned Transformer

CV Cross-validation

EEG Electroencephalography

F_1 Macro F1 score

FTD Frontotemporal dementia

GradCAM Gradient-weighted Class Activation Mapping

HC Healthy control

LLM Large language model

MLP Multilayer perceptron

MRI Magnetic resonance imaging

PD Parkinson disease

PSD Power spectral density

SVM Support vector machine

T1 T1-weighted structural MRI

Chapter 1

Introduction

1.1 Background

One of the most pressing health problems of the twenty-first century is neurodegenerative diseases. It is estimated by the World Health Organization that over 57 million individuals are living with dementia in the world, and the figure can grow to over 139 million by 2050 due to the ageing population in low- and middle-income nations [1], [2]. Alzheimer disease (AD), frontotemporal dementia (FTD) and Parkinson disease (PD) are three typical and disabling conditions in this spectrum. Although they have various impacts on the neural systems, they tend to have similar clinical manifestations hence they are hard to distinguish.

The most prevalent cause of dementia is the Alzheimer disease which is responsible in approximately 60–70% of cases of dementia [1]. Its typical pathology is characterized by amyloid-beta ($A\beta$) plaques and phosphorylated tau (p-tau) neurofibrillary tangles that are linked to structural changes, including cortical and hippocampal atrophy [3]. Frontotemporal dementia is a major cause of early-onset dementia, usually prior to the age of 65 years old [4]. Specifically, behavioral variant FTD (bvFTD) is characterized by progressive degeneration of the frontal and anterior temporal regions, which results in personality, social behavior, and executive dysfunction changes, but episodic memory may be relatively preserved in the initial stages of the disease development [5]. Parkinson disease is largely linked to the loss of dopaminergic neurons in the substantia nigra pars compacta and is typified by tremor, rigidity, bradykinesia, and postural instability; it is estimated that there are about 8.5 million individuals affected by the disease worldwide [6].

The disorders are clinically similar and thus present a significant challenge in diagnosis. Both AD and bvFTD may have executive dysfunction, apathy, and behavioral symptoms, which leads to misdiagnosis. As many as half of cases of FTD might be initially confused with psychiatric conditions, and it can take a much longer period to diagnose than AD does [7], [8]. Likewise, cognitive impairment in parkinsonism may be similar to early AD and parkinsonian features may be seen in AD or FTD. The current diagnostic processes that integrate neuropsychological testing, cerebrospinal fluid biomarkers, and neuroimaging are usually expensive, time-consuming, and unavailable in numerous locations [9].

One of the avenues that can lead to better differential diagnosis is neuroimaging. T1-weighted structural magnetic resonance imaging (MRI) is sensitive to morphology and atrophy patterns, which vary by disease: AD is characterized by hippocam-

pal and medial temporal atrophy, FTD by frontal and anterior temporal atrophy, and PD by relatively subtle basal ganglia changes with relatively preserved cortex [10]. Electroencephalography (EEG) is a complementary functional measure, which quantifies the electrical activity of the cortex on a milliseconds scale. Disease-specific spectral alterations have been reported in EEG studies, such as higher theta and lower alpha in AD and slowing of frontal activity in FTD [11], [12]. EEG abnormalities have also been reported in PD, although the exact spectral pattern can vary across study design and task context.

Even though these biomarkers are informative, most computational approaches to classifying neurodegenerative diseases are unimodal. MRI-only models tend to work well with AD-versus-control tasks, but are less predictive in multi-disease contexts. EEG-only systems are more affordable and available, but have lower spatial resolution and inter-subject variability. An integrated system that integrates structural MRI and functional EEG that can be clinically meaningfully used to differentiate between multi-classes of differentiation is not well studied.

The latest advances in deep learning, particularly vision transformers (ViT) and data-efficient transformer models, like DeiT, have opened up new opportunities in the analysis of medical images. The capability to adaptively weight modalities based on sample-specific informativeness has also been enhanced by multimodal fusion mechanisms. These developments, along with the development of open-access neuroimaging databases like BrainLat, OpenNeuro, and ADNI, provide a solid basis of successful multimodal diagnostic models.

1.2 Study Rationale

The existing literature on computational neurodegeneration has three gaps that are significant and which drive this research.

To begin with, a lot of AI systems are not comparable to the real clinical task of differentiating diagnoses. Most of the past research involves binary classification, typically AD vs healthy controls, which has not had direct clinical utility. Practically, clinicians have to differentiate between several conflicting disorders. As an illustration, the presence of progressive behavioral symptoms during the middle age may be a sign of bvFTD, early-onset AD, psychiatric disease, or PD-related cognitive impairment. There is still very little literature that deals with the classification of four-class AD vs FTD vs PD vs healthy control using both structural MRI and resting-state EEG on a subject-level basis.

Second, multimodal MRI-EEG fusion of neurodegenerative diagnosis is not well developed. The fusion of MRI-PET is widespread in the literature of the AD, whereas MRI-EEG integration has not been studied extensively yet [13]. EEG possesses a number of practical benefits: It is non-invasive, radiation-free, less expensive, and more readily available in most clinical settings, and it records fast neural dynamics that supplement MRI anatomy. Ferri et al. demonstrated better AD classification with a combination of MRI and EEG (89 percent versus 80 percent and 85 percent for EEG-only and MRI-only, respectively) [14], which indicates that the combination of modalities is promising. But that was binary work that never dealt with missing-modality conditions that are prevalent in practice.

Third, most of the published performance claims are based on poor evaluation protocols. Slice-level or image-level splitting is commonly used instead of subject-level

splitting, and may introduce leakage between training and test sets. Yagis et al. demonstrated that these practices can inflate performance by 30–55% and even randomly labeled data can seem very accurate when judged slice by slice [15]. Moreover, single-site training may promote the learning of scanner-specific artifacts, as opposed to disease-relevant features. This thesis deals with these problems by subject-level stratified five-fold cross-validation of ten datasets and seven countries.

1.3 Problem Statement

The existing AI-based neurodegenerative diagnosis approaches have three basic limitations restricting their clinical use:

1. **Disease-specific models.** The current systems tend to compare a disease to healthy controls, which in effect would require a different model per disease. It is not realistic to real world differential diagnosis where multiple candidate conditions have to be taken into account simultaneously.

2. **Single-modality dependence.** The vast majority of systems do not combine complementary diagnostic signals but use either MRI or EEG. Moreover, most systems are unable to generate a diagnosis in the absence of the anticipated modality, thus restricting their applicability to resource-constrained settings.

3. **Unreliable evaluation.** Typical methodological issues, such as slice-level splits, training on one site, weak randomly initialized baselines rather than strong pretrained baselines, can artificially inflate performance and decrease real-world generalization.

This thesis fills in these gaps by suggesting one unified multimodal transformer-based model that categorizes four conditions, i.e., Alzheimer disease, frontotemporal dementia, Parkinson disease, and healthy controls using T1-weighted structural MRI and resting-state EEG and managing missing modalities and stringent multi-site subject-level testing.

1.4 Objectives

The main aim of the research is to design, implement and test a cross-modal aligned transformer (C-MAT) system to perform four-class differential diagnosis of neurodegenerative diseases. The objectives are:

1. To create one deep learning model that takes T1-weighted structural MRI and resting-state EEG as input, has a shared encoder with modality-specific aggregation and gated cross-modal fusion, and can be trained to make inferences based on either modality or both modalities.

2. To curate and preprocess a large publicly available multi-site dataset, consisting of approximately 1,076 subjects in ten datasets across seven countries, standardized 38-feature EEG representations and 14-slice multi-plane MRI preprocessing.

3. Optuna-based Bayesian search to optimize the model architecture and hyperparameters by searching two encoder families, DeiT-Tiny and ConvNeXt-Tiny, and thirteen training parameters.

4. To compare four methods of reference rigorously, PSD-SVM, Random Forest, ResNet-50 MRI-only and unimodal encoder MRI-only, and compare class-balanced focal loss with traditional cross-entropy using Wilcoxon signed-rank tests with Bonferroni correction.

5. To enable clinical interpretability with GradCAM-based spatial attribution on MRI, attention rollout on EEG feature images, gated fusion analysis of per-class modality reliance, and large language model-aided clinical narrative generation.

1.5 Methodology in Brief

The suggested methodology is based on the systematic pipeline that includes data curation, preprocessing, model development, and evaluation. It utilizes ten publicly available neuroimaging datasets: five EEG datasets (BrainLat, Miltiadous/AHEPA, Iowa Rest, UC San Diego and PD Oddball) of about 400 subjects and five MRI datasets (BrainLat, LHSCPD, PD-MCI, neurocon and taowu) of about 700 subjects. These comprise 25 BrainLat Chile cohort subjects with both modalities.
EEG data undergo a ten-step pipeline including loading in a format-specific manner, re-referencing (especially with Biosemi BDF recordings), resampling to 256 Hz, harmonization of channels to the international 10-20 system (19 channels), band-pass filtering (1–45 Hz), ICA-based artifact rejection, and fixed-length epoching. The data in MRI are normalized, brain centers are localized, 14 multi-plane slices are extracted (7 axial, 4 coronal and 3 sagittal), CLAHE contrast enhancement is performed and pseudo-RGB representations are constructed.
C-MAT architecture involves a common pretrained image encoder to handle MRI slices and EEG feature images along with slice- and epoch-aggregated modality-specific attention. Raw EEG characteristics are acquired in parallel via an MLP pathway which is complementary to image-based representation learning. Gated fusion trains to learn to fuse MRI and EEG embeddings, using a sigmoid gate and learnable null tokens. The last classifier gives out probability distributions of the four disease classes.
It is based on class-balanced focal loss to deal with class imbalance (HC:FTD ratio of about 2.4:1), layer-based learning rate decay to stabilize fine-tuning, MixUp augmentation, and healthy-control soft downsampling. Assessment is done using strict subject level stratified five-fold cross-validation. Macro F1-score is the main performance measure, and other measures include per-class precision, recall, confusion matrices, and ROC-AUC. Fold ensemble averaging and test-time augmentation give extra gains. ImageNet-pretrained weights are used in all deep learning baselines and statistical significance between folds is tested with non-parametric tests.

1.6 Scope and Challenges

Scope: The study objective is to categorize AD, FTD, PD and healthy controls based on T1-weighted structural MRI and resting-state EEG into four groups. It does not cover disease staging, e.g. mild vs. moderate AD, prognosis of longitudinal progression, or subtypes within disease categories, e.g. semantic variant vs. behavioral variant FTD. The research is based on publicly accessible de-identified data and does not imply the primary data collection with human subjects. The presented framework is a computer-aided diagnosis tool which is based on research and is not to be used directly in the clinical practice without additional validation.
Problems: This work has a number of significant challenges:

1. **Scarcity of FTD data in publicly available neuroimaging databases.** Frontotemporal dementia is not well represented in publicly available neuroimaging databases, and there are approximately 156 open-access cases across the world, which, in turn, causes class imbalance.

2. **Protocol heterogeneity.** The ten datasets differ in terms of EEG protocol (eyes-open versus eyes-closed), channel configuration (19 to 64 channels), sampling rate (500–512 Hz), and file format (e.g., .set and .bdf), which need to be harmonized significantly.

3. **Scanner effects in MRI.** MRI data is scanned on 1.5T scanners, e.g. NeuroCon/Siemens Avanto, and 3T scanners, which adds variability in intensity and resolution and can confound disease-related structural information.

4. **Limited paired data.** There are only 25 paired data (MRI and EEG) and all paired samples are within a single site in Chile, which restricts further learning of cross-modal representations.

5. **PD invisibility on T1-weighted MRI.** PD pathophysiology is predominantly dopaminergic and might not cause severe macroscopic atrophy on routine T1-weighted MRI, thus making it difficult to classify PD using MRI alone.

Chapter 2

Literature Review

2.1 Preliminaries

In this section, the background of the proposed framework is presented, with foundational concepts and technologies that provide the context needed to understand the methodological contributions of this research.

2.1.1 Neurodegenerative Diseases and Their Neuroimaging Correlates

Neurodegenerative diseases are characterized by the gradual deterioration of neuronal structure and function in specific regions of the brain. The pathological features of Alzheimer disease include extracellular amyloid-beta deposits and intracellular neurofibrillary tangles made of hyperphosphorylated tau protein. These pathologies are associated with characteristic atrophy patterns on T1-weighted MRI, especially in the medial temporal lobe and hippocampal regions. AD on EEG is also linked to slowing of the dominant posterior rhythm, increased theta and delta power, decreased alpha power, and degradation of functional connectivity, indicating cholinergic-system degeneration and cortical disconnection [11].
Frontotemporal dementia is a group of disorders marked by progressive degeneration of frontal and temporal lobes. The most common presentation is the behavioral variant (bvFTD), which manifests as personality change, loss of empathy, disinhibition, and executive dysfunction [16]. In structural MRI, bvFTD often shows selective frontal and anterior temporal atrophy, frequently with asymmetry. EEG changes in FTD are generally more heterogeneous than in AD; frontal slowing can be observed, but posterior alpha-rhythm changes are often less severe, and spectral changes are typically subtler and more localized [17].
Parkinson disease is characterized by selective loss of dopaminergic neurons in the substantia nigra, a subcortical structure not clearly visible on routine T1-weighted MRI. As a result, PD often shows relatively preserved cortical morphology on structural imaging, with subtle basal-ganglia volume changes in severe cases [18]. This modality complementarity provides the rationale for multimodal integration: MRI is highly informative in AD and FTD, while EEG contributes functional signatures across all three conditions.

2.1.2 Structural MRI Analysis with Deep Learning

T1-weighted structural MRI provides high-resolution 3D visualization of brain anatomy, enabling measurement of regional brain volume, cortical thickness, and atrophy patterns. Conventional neuroimaging pipelines such as FreeSurfer and FSL extract handcrafted morphometric features (for example, hippocampal volume and regional cortical thickness) and use them with conventional machine-learning models. Although effective, these pipelines are computationally expensive per subject and depend on atlas-based parcellation that may miss fine disease-specific patterns [19].
Deep-learning models such as convolutional neural networks (CNNs) and vision transformers can learn directly from MRI data without manual feature engineering. ImageNet-pretrained transfer learning is often more effective than training from scratch on small medical-imaging datasets, and DeiT's distillation mechanism has shown improved performance in data-sparse settings [20]. A common practical strategy in MRI classification is to sample representative 2D slices from multiple anatomical planes and aggregate their predictions, which helps balance computational efficiency and anatomical coverage.

2.1.3 EEG Feature Extraction and Representation

This subsection presents the extraction and representation of EEG features used in computational neurodegeneration analysis.
Resting-state EEG records spontaneous cortical electrical activity using scalp electrodes. The international 10–20 montage with 19 channels is widely used and provides broad cortical coverage. For computational modeling, continuous recordings are commonly segmented into fixed-length epochs and summarized using multi-domain features.
Spectral features are typically estimated using the Welch method, which measures power distribution across canonical frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–45 Hz) [21]. Band-power ratios and complexity-based EEG features, including sample entropy, are commonly used in computational studies of neurodegeneration. Hjorth parameters provide computationally efficient descriptors of signal variance and frequency composition, while connectivity measures such as coherence and phase-locking value (PLV) quantify inter-regional coupling and are widely used in EEG analysis [22].

2.1.4 Multimodal Fusion Strategies

Three common paradigms are used in multimodal medical-data fusion: early fusion, late fusion, and intermediate fusion. Early fusion combines raw or minimally processed modalities in a single representation, but it can be difficult when modalities have very different structures (for example, 3D MRI and EEG feature maps). Late fusion combines decisions from modality-specific models, but may underuse fine-grained cross-modal interactions. Intermediate fusion, often implemented with attention or gating mechanisms, is widely used because it can learn complementary cross-modal representations while preserving modality-specific structure.
Gated fusion, where a learnable sigmoid gate controls relative modality contribution, is particularly relevant in missing-modality settings. It supports robust unimodal

inference when one modality is unavailable, while still exploiting cross-modal interactions when both are present. Gated and attention-based fusion strategies have shown strong performance across multimodal medical-AI tasks, supporting their use as a reasonable design choice for neuroimaging fusion [23], [24].

2.1.5 Vision Transformers and Data-Efficient Training

Vision Transformer (ViT) was introduced by Dosovitskiy et al. and processes images as sequences of fixed-size patch embeddings through transformer encoder blocks with multi-head self-attention [25]. While highly expressive, vanilla ViT is typically data-hungry due to weaker inductive biases than CNNs. Data-efficient Image Transformers (DeiT), introduced by Touvron et al., address this through knowledge distillation, where the student transformer learns from both hard labels and soft targets from a teacher network [26]. This enables competitive performance with substantially less labeled data, which is particularly valuable in medical imaging.

2.1.6 Class Imbalance and Focal Loss

Class imbalance is a major issue in medical datasets, where healthy controls often outnumber disease cases and rare classes such as FTD are severely underrepresented. Standard cross-entropy loss treats all samples equally and can bias optimization toward majority classes. Focal loss mitigates this by down-weighting well-classified examples via the modulation term $(1 - p_t)^\gamma$ [27]. Cui et al. refined this concept with class-balanced reweighting based on effective sample number, accounting for diminishing marginal utility of additional samples from the same class [28]. Combining focal modulation and class-balanced weighting is a principled approach for multiclass imbalance.

2.2 Literature Review

2.2.1 MRI-based Classification of Neurodegenerative Diseases

Deep learning has been widely applied to structural MRI for dementia classification, but most studies focus on binary AD-versus-healthy-control tasks. Many reported binary MRI-classification results are high, but their clinical interpretability depends strongly on evaluation design, particularly the use of subject-level rather than slice-level splitting. In more clinically relevant AD-versus-FTD tasks, reported performance is considerably lower and more variable, highlighting the practical difficulty of differential diagnosis [29]. In a comparative machine-learning study using standardized MRI features, Li and Yang reported that SVM-based approaches achieved moderate performance for three-class AD/FTD/HC classification [30].
More recent ConvNeXt-based approaches have shown strong performance in medical-imaging classification tasks, suggesting modern CNN designs retain strong inductive advantages under limited-data settings [31]. A recent systematic review of AI for FTD differential diagnosis reported continued dominance of SVM baselines with increasing deep-learning adoption, but also emphasized frequent small-sample and

binary-task limitations [32]. Notably, unified four-class AD/FTD/PD/HC MRI-EEG studies remain scarce.

2.2.2 EEG-based Classification of Neurodegenerative Diseases

EEG-based dementia classification has accelerated after release of the Miltiadous OpenNeuro dataset (ds004504), which includes resting-state EEG from AD, FTD, and healthy controls [33]. This dataset has become a central benchmark for recent EEG studies. Recent work has demonstrated competitive performance using both handcrafted-feature and deep-learning pipelines, including convolution-transformer variants [34].

Rostamikia et al. provided a detailed analysis of discriminative EEG features for AD-versus-FTD and highlighted the importance of alpha/theta connectivity measures [35]. Nevertheless, multiclass EEG classification remains challenging, and reported performance is generally lower than binary settings [34]. For PD EEG specifically, open datasets such as the Iowa Rest dataset (OpenNeuro ds004584) provide useful public benchmarks, although cross-cohort comparison remains difficult because of protocol heterogeneity [36]. Cross-cohort fusion of AD/FTD and PD EEG datasets remains methodologically difficult due to heterogeneity in acquisition protocols and channel configurations.

2.2.3 Multimodal MRI-EEG Fusion for Neurodegeneration

Combined MRI-EEG classification for neurodegeneration remains underexplored. Ferri et al. showed that combining resting-state EEG and structural MRI improved AD classification over unimodal alternatives, supporting multimodal complementarity [14]. However, that work remained binary and single-cohort.

Multimodal integration has been explored more extensively in broader neuroimaging and AD staging contexts. Venugopalan et al. reported improved stage-detection performance with multimodal deep-learning integration of MRI and additional data streams [37]. The BrainLat project introduced an important multimodal neurodegeneration dataset from underrepresented populations, including AD, FTD, PD, and healthy controls [38]. Recent work also reported lightweight MRI-EEG fusion with attention for offline PD diagnosis [39]. Across multimodal medical-AI studies, intermediate fusion with attention or gating is a common and practical design pattern, while MLP and fully connected fusion heads remain widely used.

2.2.4 Methodological Issues in Available Literature

Several methodological weaknesses recur in this literature and motivate stricter evaluation design. The most critical issue is improper data splitting. Yagis et al. showed that slice-level or image-level splitting can cause data leakage and inflate MRI-classification accuracy by 30–55% [15]. Even random-label experiments can appear highly accurate under such leakage.

Another issue is unfair baseline construction. Some studies compare against randomly initialized deep models instead of pretrained baselines, which biases comparisons. ImageNet pretraining provides substantial benefit in medical imaging and

should be used consistently in fair benchmarking [20]. Third, reliance on single train-test splits obscures variance and can overestimate performance. Multi-fold subject-level cross-validation with mean and standard deviation reporting is more reliable.

2.2.5 Open-Access Neuroimaging Datasets

Open-access datasets are critical for reproducible computational-neuroscience research. For EEG-based AD/FTD studies, ds004504 remains a key resource [40]. For PD EEG, commonly used open resources include ds004584, ds002778, and ds003490 [36], [41], [42].
For structural MRI, BrainLat is one of the largest multimodal open datasets for neurodegeneration in underrepresented populations [38]. MRI-specific PD datasets remain comparatively limited in open repositories, including LHSCPD (ds004471) and PD-MCI (ds005892) [43], [44]. This data imbalance, especially underrepresentation of FTD, both motivates and constrains multi-dataset aggregation strategies.

2.3 Conclusion of the Main Findings

The literature review identifies key findings and research gaps that position this thesis:

1. Differential diagnosis is clinically critical, but most computational studies remain binary (typically AD vs. HC). Multi-class studies are less common, and rigorous four-class AD/FTD/PD/HC MRI-EEG studies with subject-level evaluation are still limited.

2. MRI and EEG provide complementary information. MRI captures structural atrophy patterns relevant to AD and FTD, while EEG captures functional signatures that are especially informative for PD and useful for AD-FTD separation.

3. Modern deep architectures, including ConvNeXt and distilled transformer variants such as DeiT, can perform well in limited-data medical imaging through transfer learning and efficient fine-tuning.

4. Intermediate fusion with attention and gating is generally stronger than early or late fusion, and is well suited for missing-modality conditions via learnable null representations.

5. Methodological rigor is essential. Subject-level splitting, pretrained baselines, and multi-fold validation are necessary for reproducible and clinically meaningful results.

6. Open-access neuroimaging datasets remain disease-imbalanced, with notable underrepresentation of FTD relative to AD and healthy-control cohorts.

Based on these findings, the proposed C-MAT framework targets identified gaps by introducing a multimodal MRI-EEG four-class system with missing-modality robustness, empirically selected encoders, strict subject-level multi-fold validation, and clinically oriented explainability.

Chapter 3

Requirements, Impacts and Constraints

3.1 Final Specifications and Requirements

3.1.1 Technical Requirements

The design and testing of the C-MAT framework have several technical demands in hardware, software, and data infrastructure. Training and inference of multiple deep learning architectures with mixed precision on high-dimensional neuroimaging data require a workstation with GPU acceleration. The minimum hardware requirements include an NVIDIA GPU with at least 16 GB dedicated video memory, 64 GB system RAM for in-memory preprocessing, and approximately 100 GB storage for raw datasets, processed features, model checkpoints, and experiment outputs.
The framework is based on Python 3.10+ and PyTorch 2.x as the core deep learning stack, with CUDA 12.x used for acceleration. Major libraries include timm (version 0.9 or later) for pretrained CNN and transformer encoders, MNE-Python for EEG processing, nibabel for NIfTI neuroimaging files, scikit-learn for classical baselines and evaluation metrics, and Optuna for Bayesian hyperparameter optimization. The mne-icalabel package is required for automated artifact-component classification during EEG artifact rejection. All experiments are executed in a reproducible Conda environment with fixed random seed 42.
Table 3.1 summarizes the hardware and software specifications used in this study.

3.1.2 Data Requirements

In the study, open-access neuroimaging data with T1-weighted structural MRI and resting-state EEG of the participants with Alzheimer disease, frontotemporal dementia, Parkinson disease, and cognitively healthy controls are needed. The datasets included must offer validated diagnostic labels and be allowed under open-access or Creative Commons licenses. The minimum number of subjects per disease group is 100, which is suitable to achieve strong four-class classification, but the lack of public access to frontotemporal dementia data limits this goal. Multi-site datasets across vendors of scanners and recording protocols are desirable to test generalization, although they make preprocessing more complex.
The final V3 evidence base consisted of 1,102 unique subjects drawn from 10 open

Table 3.1: Hardware and software specifications used in this study.

Component	**Specification**
GPU	NVIDIA RTX 4080 Super (16 GB VRAM, Ada Lovelace)
System RAM	64 GB DDR5
Operating System	Windows 11 Professional
Deep Learning Framework	PyTorch 2.x with CUDA 12.x
Encoder Models	timm 0.9+ (DeiT-Tiny, ConvNeXt-Tiny, ResNet-50)
EEG Processing	MNE-Python 1.6+, mne-icalabel 0.8+, antropy
MRI Processing	nibabel, scikit-image (CLAHE), SciPy
Hyperparameter Search	Optuna 3.x with TPE sampler
Classical ML Baselines	scikit-learn (SVM, Random Forest)
LLM Explanations	Google Gemini 2.0 Flash API
Reproducibility	Conda environment with fixed random seed (42)

datasets, plus a strictly paired 25-subject BrainLat MRI+EEG subset used for multimodal stress testing. The class totals were approximately AD 283, FTD 160, PD 278, and HC 381, with 707 MRI subjects and 420 EEG subjects overall. This distribution is intentionally uneven because it reflects the real scarcity of FTD and paired data rather than synthetically balanced sampling, and it is one of the reasons class-balanced focal loss and gated fusion were necessary.

3.1.3 Methodological Requirements

To ensure scientific validity and reproducibility, the framework follows the methodological requirements below.

1. Subject-level train-test separation with no information leakage.
2. Stratified five-fold cross-validation and mean and standard deviation reporting.
3. Unique subject identifiers in datasets globally to prevent collisions in files and IDs.
4. Deep learning models (including baselines) use verified ImageNet weights.
5. Class-balanced training strategy to deal with imbalance of classes among disease categories.
6. Comparisons of models to each other with statistical significance tests.
7. Separate reporting of the strictly paired MRI+EEG subset so that multimodal results are not hidden inside easier unimodal-heavy cohorts.
8. Verification of preprocessing outputs, dataset prefixes, and pretrained-weight initialization before each training run.

3.1.4 Versioned Requirement Traceability (V1 to V3)

The requirements above were not all satisfied at once. Instead, they became enforceable through iterative hardening from V1 to V3. Table 3.2 links each major requirement to the version where it was first systematically implemented and the concrete evidence artifact used for verification.

Table 3.2: Requirement traceability across C-MAT versions.

Requirement	**V1**	**V2**	**V3 status**
Subject-level leakage control	Partial	Partial	Enforced with dataset-prefixed IDs and fold audit
Five-fold reporting (mean ± std)	No	Partial (fold-0 emphasized)	Fully enforced (all five folds reported)
EEG feature integrity (38-feature pipeline)	No (30-feature)	Inconsistent reuse	Reprocessed and validated
Pretrained baseline fairness	Inconsistent	Inconsistent	Mandatory pretrained checks before training
Class imbalance mitigation	Weighted CE	CB focal introduced	CB focal plus tuning and downsampling
Reproducible artifact trail	Basic	Improved	Full manifest/split/result trace with forensic reports

The traceability table shows that the project moved from feasibility (V1) to scaling (V2) and finally to integrity-first evaluation (V3). V1 exposed the danger of narrow MRI coverage and single-split optimism; V2 expanded the dataset but introduced hidden reuse and class inflation; V3 fixed both issues by reprocessing EEG, removing OASIS, prefixing subject IDs, and enforcing complete five-fold reporting. The lower V3 macro F1 is therefore the cleaner estimate of deployable performance, not a model regression.

3.2 Societal Impact

This study has a significant societal impact. Over 55 million individuals worldwide are impacted by neurodegenerative diseases, and dementia alone is linked to an annual economic cost of USD 1.3 trillion. Timely intervention, improved care planning and improved enrollment into clinical trials can be supported by earlier and more accurate differential diagnosis. Misdiagnosis, especially the confusion of AD and FTD may result in improper pharmacological therapy, accelerated deterioration and additional burden to patients and caregivers.

The suggested C-MAT model may be utilized as a computer-aided screening instrument, particularly in resource-restricted conditions with limited specialist neurologists. Since the system allows the use of missing modalities, it can be used with MRI-only or EEG-only input. This is significant to be deployed in primary care settings where a single modality can be deployed. EEG is cheaper and more available compared to MRI or PET in most developing countries, which enhances global health equity.

Moreover, transparent decision support is provided with explainability elements (GradCAM and attention analysis) and LLM-generated clinical narrative. Clini-

cians are able to examine model-relevant brain activity and EEG signals, which facilitates informed human supervision as opposed to black-box decision-making.

3.3 Environmental Impact

The main environmental factor in this project is the use of electricity in model development and training. It is estimated that a complete experimental run of C-MAT with a five-fold validation on various architectures would require about 6.4–9.6 kWh, which translates to about 20–30 hours of active GPU running on a single RTX 4080 Super (320W TDP). Computational budgets of all versions of the framework (V1, V2, V3), preprocessing, hyperparameter optimization, and evaluation included, are estimated to be about 40–50 kWh.
This footprint is significantly smaller than large foundation-model training workloads which may need thousands of MWh. Mixed-precision training (FP16/TF32) is faster and consumes less power than full-precision FP32 training. Pretrained ImageNet encoders can also be used in transfer learning, eliminating the need to train feature extractors, which saves orders of magnitude in compute.
The research is not related to wet-laboratory work, physical reagents, or collection of biological samples. All data are provided by existing public repositories, and therefore, there is no extra environmental impact other than the computational processing.

3.4 Ethical Issues

This research uses only de-identified, publicly available neuroimaging data released under open-access licenses (for example, CC0 and CC-BY). No primary human-subject data collection was performed. Each source dataset was originally acquired under institutional ethics approval and informed consent procedures documented by the data providers.
Reported examples include:

- BrainLat: multi-site IRB approvals across five Latin American countries, reported in Scientific Data (2023).
- Miltiadous (AHEPA): Ethics Committee approval at AHEPA University Hospital, Aristotle University of Thessaloniki, protocol 142/12-04-2023.
- Iowa Rest: IRB approval at Iowa State University (OpenNeuro ds004584).
- UC San Diego: UC San Diego IRB (OpenNeuro ds002778).
- PD Oddball: University of New Mexico IRB (OpenNeuro ds003490).
- LHSCPD, PD-MCI, neurocon, taowu: approvals documented in dataset metadata.

The proposed system is intended as a research-grade decision-support tool and not an autonomous diagnostic authority. LLM-generated explanation text is presented as a language interpretation of structured model outputs and is not a standalone

clinical diagnosis. All model outputs require review by qualified clinicians before any clinical action.
An important ethical risk is potential algorithmic bias. The assembled data are weighted toward Latin American, European, and North American populations. Performance has not been validated for underrepresented groups (for example, East Asian and Sub-Saharan African populations), and generalization to these groups should not be assumed.

3.5 Standards

The project aligns with established standards in neuroimaging research and software engineering.

- Brain Imaging Data Structure (BIDS): EEG datasets follow BIDS-compatible organization with standardized metadata, filenames, and directory layouts.
- International 10-20 system: EEG channels are mapped to the standard 19-channel montage.
- NIfTI (Neuroimaging Informatics Technology Initiative): MRI data are handled in .nii/.nii.gz, the standard structural neuroimaging format.
- TRIPOD: reporting aligns with Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis guidance.
- IEEE Code of Ethics: results, limitations, and claims are reported with transparency and without performance inflation.

3.6 Project Management Plan

The project spanned approximately nine months (August 2025 to April 2026) and followed an iterative development process with three major pipeline versions. The schedule is summarized in Table 3.3.

Table 3.3: Project timeline and key activities.

Phase	**Period**	**Duration**	**Key Activities**
Literature Review & Dataset Survey	Aug–Sep 2025	8 weeks	Systematic review of 50+ papers; identification and download of 12 candidate datasets; preliminary feasibility assessment
V1 Development	Oct–Nov 2025	6 weeks	Initial C-MAT architecture; BrainLat-only pipeline; 30-feature EEG; single train/test split; first baselines and ablations
V1 Analysis & V2 Planning	Dec 2025	3 weeks	Forensic audit of V1 failures; identification of data leakage risks; dataset expansion strategy
V2 Development	Jan–Feb 2026	6 weeks	Multi-site expansion (10 datasets); OASIS integration; five-fold CV; Optuna HPO; class-balanced focal loss
V2 Forensic Audit	Mar 2026	3 weeks	Complete audit of all 12 datasets; discovery of OASIS issues; EEG reprocessing failure analysis
V3 Framework Design	Mar–Apr 2026	2 weeks	Fresh architecture with encoder search; 38-feature EEG; dual-path MLP; multi-architecture ensemble
V3 Implementation & Training	Apr 2026	2 weeks	Full pipeline execution; ICLabel integration; data leakage debugging; final evaluation
Thesis Writing & Defense Preparation	Apr 2026	2 weeks	Chapter drafting, figure generation, XAI analysis, and defense slides

3.7 Risk Management

Table 3.4 lists major project risks, their likelihood and impact, and mitigation actions.

Table 3.4: Project risk register and mitigation strategies.

Risk	**Likelihood**	**Impact**	**Mitigation**
Data leakage from subject ID collisions across datasets	High	Critical	Detected in V3 using debug scripts; fixed by prefixing dataset names to all subject IDs and NPZ filenames
NIFD (LONI) dataset access denied or delayed	High	Medium	Access requested in March 2026 and still pending; proceeded without NIFD and documented limitation
GPU out-of-memory during training	Medium	Medium	Mixed precision (AMP), gradient accumulation fallback, and batch-size tuning
EEG artifact contamination (missing ICLabel)	High	High	Installed mne-icalabel and reprocessed all EEG data with automated component rejection
Model checkpoint corruption from power loss	Medium	High	Atomic checkpoint writes (temporary file + rename), every-epoch saving, and resume-safe training loop
Pretrained weights not loading (random initialization)	Medium	Critical	Added mandatory weight verification check (std < 0.5) before every run; discovered random initialization issue in V2 baselines
Class imbalance (HC:FTD approximately 2.4:1)	Certain	Medium	HC soft downsampling, class-balanced focal loss, and stratified sampling
Scanner confound (1.5T vs 3T MRI)	Certain	Medium	CLAHE intensity normalization and multi-site training as implicit domain adaptation

3.8 Economic Analysis

The project was implemented using existing university computing infrastructure and open-access datasets, resulting in very low direct financial cost. The RTX 4080 Super workstation was a pre-existing departmental asset. Core software components are open source, and the Gemini API free tier was sufficient for the required number of explanation outputs. Estimated costs are summarized in Table 3.5.
In contrast, the downstream burden of even one misdiagnosed FTD case (for example, inappropriate AD medication, delayed specialist referral, and caregiver burden) can be substantial over disease progression. A low-cost screening tool that reduces a fraction of these misdiagnoses can therefore produce meaningful economic value relative to development cost.

Table 3.5: Estimated project costs.

Item	**Cost (USD)**	**Notes**
Hardware (GPU workstation)	$0	Pre-existing departmental resource
Software licenses	$0	Open-source stack (PyTorch, MNE, scikit-learn, timm)
Dataset access	$0	Open-access sources (OpenNeuro, Synapse, institutional shares)
Cloud compute	$0	All training conducted locally
Gemini API	$0	Free tier sufficient for 8–12 clinical explanations
Electricity (about 50 kWh at $0.12/kWh)	about $6	Estimated cumulative GPU compute across all versions
Total	about $6	Excluding pre-existing hardware

3.9 Forward Plan: V4 Roadmap

V3 establishes the first leakage-hardened benchmark of this thesis. However, the error profile and data constraints indicate a clear V4 direction focused on robustness rather than headline metric inflation.

3.9.1 This is a list of technical priorities of V4.

1. **Minority-class reinforcement (FTD):** combine impending NIFD access and extra open cohorts to decrease class-weakness amid cross-site shifts.

2. **Domain harmonization:** add scanner/protocol harmonization (e.g. ComBat-style scanner/protocol adaptation of MRI and protocol-adaptive normalization of EEG).

3. **Dual-encoder fusion:** assess individual modality backbones (MRI-specialized encoder and EEG-specialized encoder) and then gated fusion.

4. **Calibration-conscious inference:** introduce confidence-calibration and risk-thresholding of clinically-safer triage results.

5. **External validation split:** hold out one complete dataset as a true external hold-out to be used in post-cross-validation generalization testing.

The cited sources indicate a handful of even more tangible V4 upgrades, including ComBat-style MRI harmonisation, an EEG-specific encoder, which does not use the 224 x 224 upsampling artifact, diffusion MRI of PD, and contrastive pretraining on unpaired MRI and EEG. These changes are given priority as they deal with reported failure modes as opposed to just seeking marginal score improvements.

3.9.2 Target Outcomes

Three criteria should be used to measure the success of V4: (i) better minority-class stability (particularly FTD), (ii) less fold-to-fold volatility with the same strict evaluation policy, and (iii) retained leakage-free reproducibility with full artifact traceability. These standards are strategically matched with the translational reliability as opposed to optimistic single-split performance.

Chapter 4

Proposed Methodology

4.1 Design Process and Methodology Overview

The design process and methodology are described in the following section. C-MAT was developed in an iterative design process in three larger versions of the pipeline (V1, V2, and V3). The versions were improved with forensic analysis of the previous failures. This section will introduce the last V3 methodology and connect the main design decisions to the lessons learned in the course of the iterative development.

4.1.1 Iterative Design Evolution: V1 to V2 to V3

The project was developed in nine months, with each release fixing the shortcomings found in the post-hoc audits. This method took more time to develop, but created a much stricter system and uncovered leakage patterns that are generally applicable to neuroimaging AI.

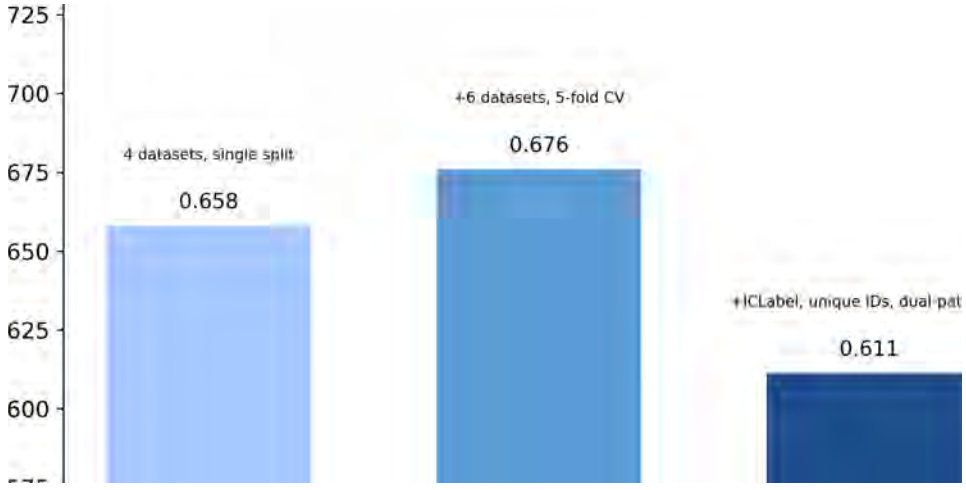

Figure 4.1: C-MAT performance evolution across three versions showing macro F1 scores and key methodological changes.

Version 1 Lessons. V1 set up the first C-MAT architecture with BrainLat EEG (129 subjects), Miltiadous (88) and Iowa (149) as the only EEG source and BrainLat MRI (529) as the only MRI source. With a single 80/20 split, V1 achieved macro F1 = 0.658. Forensic inspection revealed that there were three important problems:

Table 4.1: Comprehensive comparison of C-MAT versions across 15 dimensions.

Dimension	V1 (Oct–Nov 2025)	V2 (Jan–Feb 2026)	V3 (Apr 2026)
EEG datasets	3	5	5 (reprocessed with ICLabel)
MRI datasets	1 (BrainLat only)	6 (+OASIS, LHSCPD, PD-MCI, neurocon, taowu)	5 (OASIS excluded)
Total subjects	approximately 550	approximately 1,300	1,102
EEG features	30	38 planned, 30 actual (reused V1)	38 (verified reprocessed)
ICA artifact rejection	ICA without ICLabel	ICA without ICLabel (reused V1)	ICA + ICLabel v0.8.1
Subject ID scheme	Raw (sub-001)	Raw (sub-001)	Dataset-prefixed (iowa_sub-001)
Evaluation protocol	Single 80/20 split	5-fold CV (only fold 0 evaluated)	5-fold CV (all 5 folds evaluated)
Encoder architecture	DeiT-Tiny (fixed)	DeiT-Tiny (fixed)	DeiT-Tiny + ConvNeXt-Tiny (searched)
EEG pathway	Image encoder only	Image encoder only	Dual-path: image + MLP
Loss function	Weighted cross-entropy	CB focal loss	CB focal loss (Optuna-tuned γ, β)
Baselines pretrained	Mixed (ResNet random)	All pretrained=False	All pretrained=True (verified)
PD MRI subjects	2	approximately 120 (with OASIS confound)	122 (clean, multi-site)
HC:FTD ratio	approximately 2.0:1	3.6:1 (OASIS inflated)	2.4:1
Data leakage checks	None	None	3 automated verification gates
Best macro F1	0.658 (single split)	0.676 ± 0.021 (fold 0 only)	0.611 ± 0.029 (all folds, clean)

(i) no estimate of variance because of single split; (ii) there were only 2 PD MRI subjects, which is effectively impossible to discriminate with PD MRI; and (iii) the ResNet-50 baseline (pretrained=False) used by default, which gave an unfairly weak result.

Version 2 Lessons. V2 added five-fold CV and Optuna search, and class-balanced focal loss, to ten datasets. The reported mean F1 was 0.676 ± 0.021. An audit later revealed that there were four compounded problems: (i) EEG preprocessing silently reused V1 outputs and purported 38 features; (ii) OASIS inflated HC proportion and added scanner-vintage confounds; (iii) only fold 0 was tested and not all folds; and (iv) again pretrained=False.

Version 3 Design Principles. V3 was re-created with five non-negotiable rules: (a) subject IDs are prefixed with a dataset identifier globally; (b) there are automated preprocessing verification gates; (c) it must have mandatory pretrained-weight checks prior to training; (d) it must report full results on all five folds as mean $\pm$ standard deviation; and (e) it must be reproducible with random seed 42.

4.1.2 Why V3 Macro F1 Is Lower Than V2

The lower V3 result (0.611 ± 0.029) compared with V2's reported 0.676 ± 0.021 is not a model regression. It indicates elimination of sources of evaluation inflation: fold-0-only reporting, OASIS-based HC inflation, possible artifact-induced EEG leakage and cross-dataset subject ID collision effects. V3 is the more realistic and leakage-free approximation on a more challenging evaluation setup.

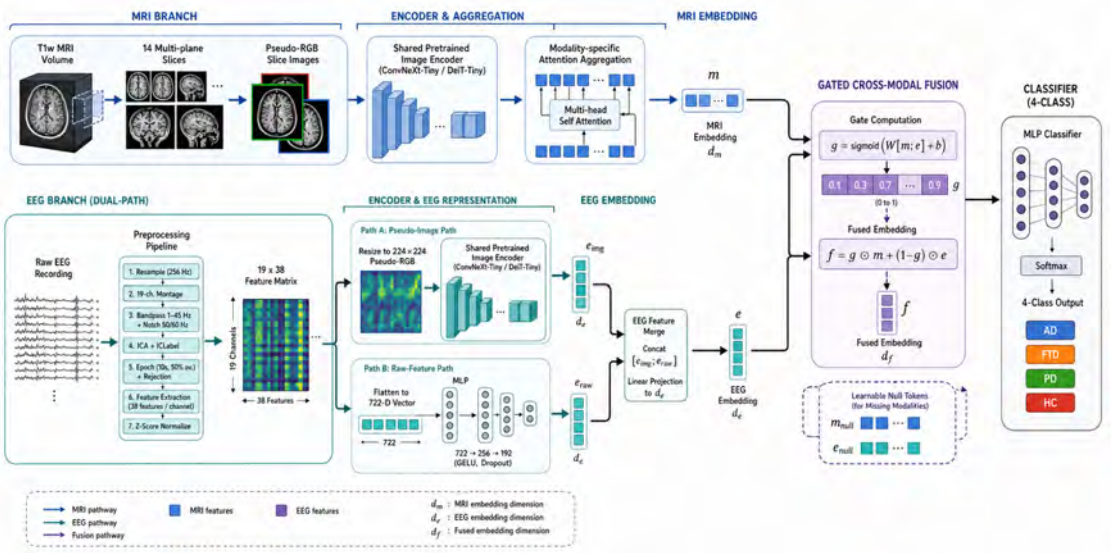

Figure 4.2: Complete C-MAT V3 architecture showing MRI and EEG processing pathways, dual-path EEG representation, gated fusion, and classification head.

The failure-to-Fix Chain Across Versions is a sub-topic that will be discussed in this section of the paper. In terms of systems-engineering, every version can be viewed as a response to a particular failure mode that is controlled.

- **V1 as feasibility phase:** confirmed the possibility of multimodal training but the confidence of the evaluation was low because it was single-split and the coverage of the disease was limited by the MRI.
- **V2 as scaling stage:** scaling with increased data and depth, but subsequent forensic analysis demonstrated that scaling without stringent audit gates may be able to maintain hidden sources of bias.
- **V3 as reliability stage:** emphasized integrity tests (ID uniqueness, full-fold reporting, reprocessing verification, pretrained fairness) such that the metrics reported by it are deployable behavior.

This trained trajectory is significant to interpret the thesis: the numerical performance is not a sufficient goal in medical AI. The design objectives are evidence quality, split rigor and provenance traceability, which are co-equal.

4.2 System Architecture

The final C-MAT V3 pipeline processes T1-weighted MRI and resting-state EEG through five components: (1) shared pretrained image encoder, (2) modality-specific attention aggregation, (3) dual-path EEG representation, (4) sigmoid-gated cross-modal fusion, and (5) four-class classification head. Learnable null tokens are used to deal with missing modalities.

4.2.1 Shared Image Encoder

Encoder selection was treated as an empirical design choice. Two encoder families were evaluated.

Table 4.2: Encoder architectures evaluated in C-MAT V3.

Encoder	**Params**	**Type**	**Rationale**	**5-Fold F1**
ConvNeXt-Tiny	28.6M	Modernized CNN	Higher inductive bias; strong performance in medical image classification	0.611 ± 0.029
DeiT-Tiny	5.7M	Vision Transformer	Distillation-based lightweight transformer with robust transfer behavior	0.590 ± 0.044

Both encoders were initialized from ImageNet pretrained weights and fine-tuned with layer-wise learning rate decay (LLRD). Training used a two-phase schedule: first 2 epochs with frozen encoder and head-only training, then full unfreezing for up to 98 additional epochs.

4.2.2 Dual-Path EEG Representation

V3 introduces a dual-path EEG pipeline. The first path converts the 19-channel by 38-feature matrix into a 224 by 224 pseudo-RGB image for the shared encoder. Because this transformation expands a 722-value matrix into 150,528 pixels (mostly interpolation), a second path processes the raw 722-dimensional vector directly with an MLP ($722 \to 256 \to 192$, GELU, dropout). Both embeddings are concatenated and projected to the shared embedding space.

4.2.3 Gated Cross-Modal Fusion

Fusion uses a learned sigmoid gate:

$$g = \sigma\left(W_g[m; e] + b_g\right), \qquad f = g \odot m + (1 - g) \odot e, \qquad g \in [0, 1].$$

When g approaches 1, MRI dominates; when g approaches 0, EEG dominates. The mean gate in V3 test subjects was 0.653, indicating mild MRI dominance, consistent with higher MRI representation in training.

4.2.4 Class-Balanced Focal Loss

To address class imbalance (HC:FTD approximately 2.4:1), V3 used three concurrent strategies: (i) HC soft downsampling to 250 samples per epoch, (ii) class-balanced reweighting, and (iii) focal modulation. The focal parameters were optimized via Optuna. Fold-0 ablation showed improvement from 0.607 (cross-entropy) to 0.655 (focal), a +0.048 gain.

Table 4.3: EEG datasets used in C-MAT V3 with preprocessing outcomes.

Dataset	N	Processed	Classes	Fs (Hz)	Channels	Protocol
BrainLat EEG	129	102	AD:35, FTD:19, PD:29, HC:46	Varies	>19	EC
Miltiadous	88	88	AD:36, FTD:23, HC:29	500	19	EC
Iowa Rest	149	149	PD:100, HC:49	500	63	EO
UC San Diego	31	31	PD:15, HC:16	512	40 (BDF)	EC
PD Oddball	50	50	PD:25, HC:25	500	64	EC
Total	447	420	AD:71, FTD:42, PD:169, HC:165	–	–	–

Table 4.4: MRI datasets used in C-MAT V3.

Dataset	N	Classes	Scanner	Field Strength
BrainLat MRI	529	AD:227, FTD:123, PD:2, HC:177	Mixed (5 countries)	Mixed
LHSCPD	40	PD:40	Unknown	Unknown
PD-MCI	55	PD:33, HC:22	Siemens TrioTim	3T
neurocon	43	PD:27, HC:16	Siemens Avanto	1.5T
taowu	40	PD:20, HC:20	Siemens Trio	3T
Total	707	AD:227, FTD:123, PD:122, HC:235	–	–

4.3 Data Collection and Preprocessing

4.3.1 Dataset Inventory

4.3.2 Excluded Datasets and Rationale

OASIS (436 subjects) was excluded due to Analyze 7.5 format, older 1.5T acquisition context, strong HC inflation effects (HC:FTD shift from 2.4:1 to 3.6:1), and severe age confounding. PEARLNEURO (79 subjects) was excluded because it contained only healthy controls. NIFD access (approximately 150 FTD MRI subjects) remained pending.

4.3.3 EEG Preprocessing Pipeline

Raw EEG recordings were processed through ten steps:

1. Format-specific loading.
2. Average re-referencing for Biosemi BDF recordings.
3. Resampling to 256 Hz.
4. Channel selection and alias mapping to 19-channel international 10-20 montage.
5. Bandpass filtering (1–45 Hz FIR) and 50/60 Hz notch filtering.

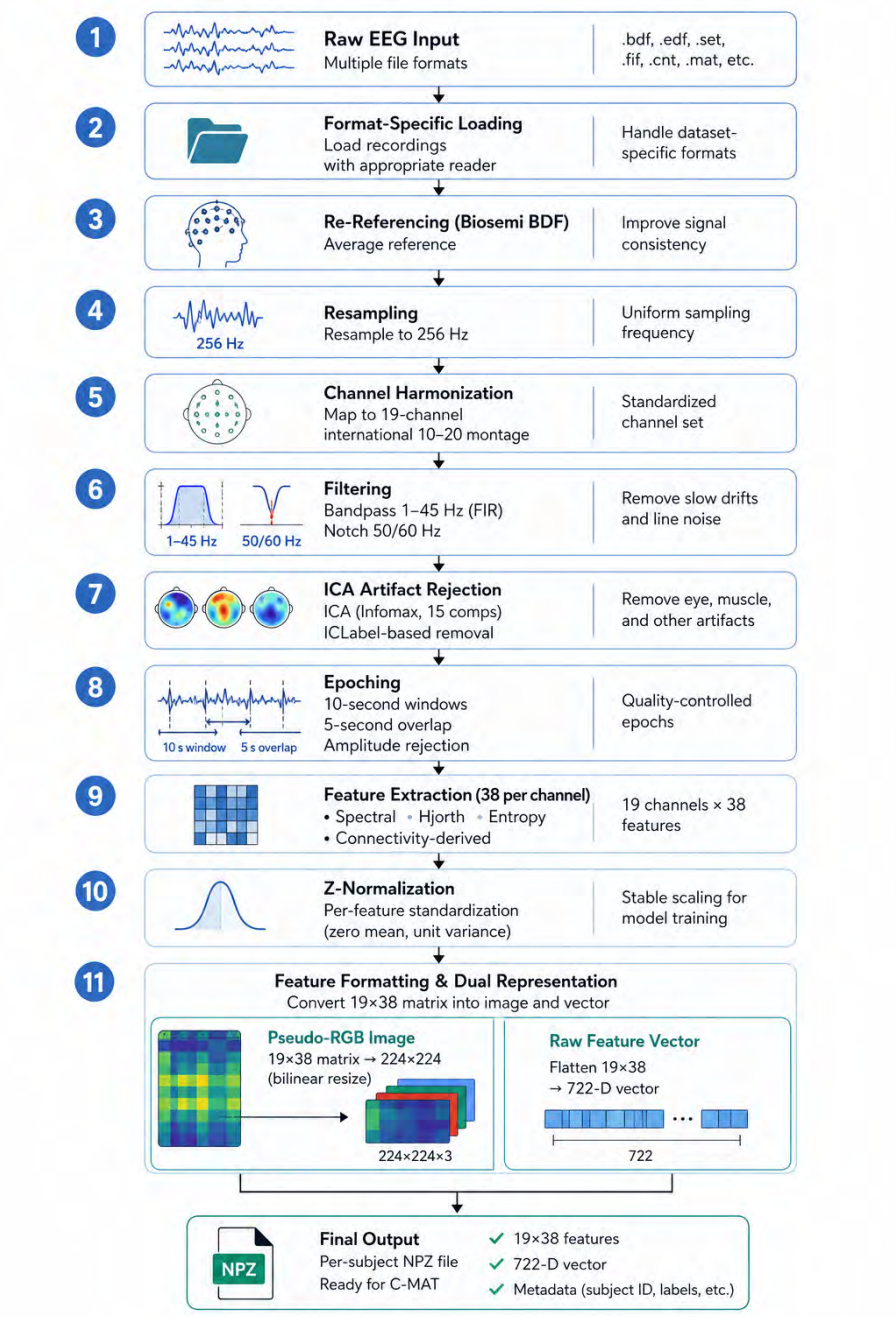

Figure 4.3: Ten-step EEG preprocessing pipeline from raw recordings to 19x38 feature matrices.

6. ICA (Infomax, 15 components) with ICLabel-based component rejection for non-brain probabilities above 0.5.
7. Epoching into 10-second windows with 5-second overlap and amplitude rejection.
8. Extraction of 38 features per channel per epoch.
9. Z-normalization and bilinear resize to 224 by 224 pseudo-RGB.
10. Per-subject NPZ export.

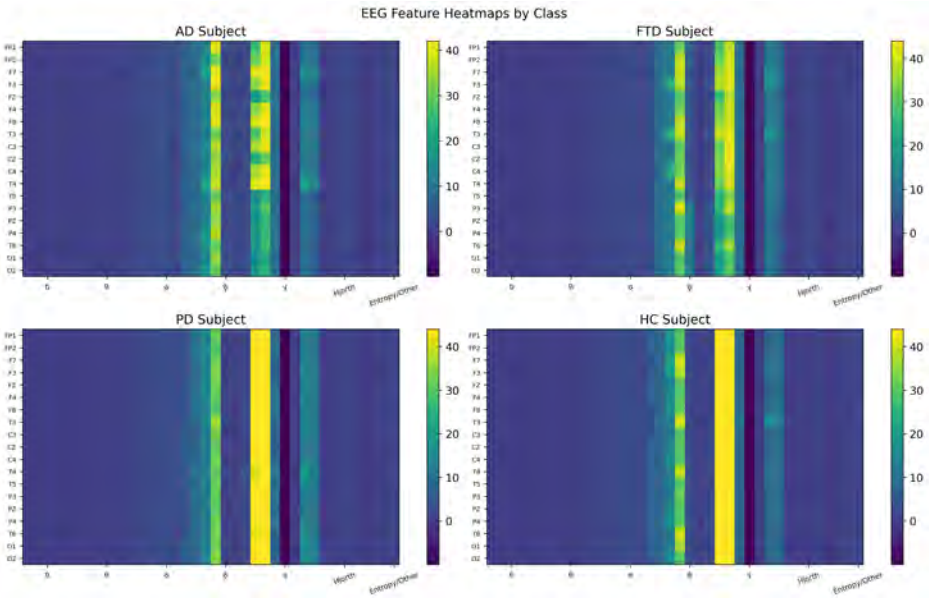

Figure 4.4: Representative 19x38 EEG feature heatmaps for one subject from each disease class.

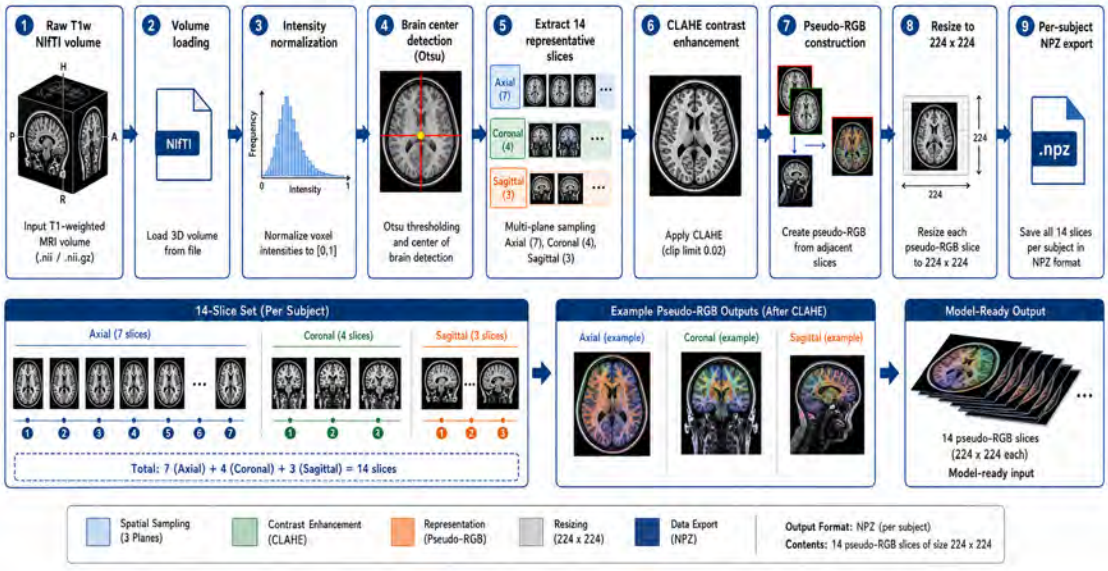

Figure 4.5: Eight-step MRI preprocessing pipeline from T1w NIfTI to 14-slice pseudo-RGB images.

4.3.4 MRI Preprocessing Pipeline

T1-weighted NIfTI volumes were processed through eight steps:

1. Volume loading.
2. Voxel intensity normalization to [0,1].
3. Brain center detection using Otsu thresholding.
4. Extraction of 14 multi-plane slices (7 axial, 4 coronal, 3 sagittal).
5. CLAHE intensity normalization (clip limit 0.02).

6. Pseudo-RGB construction from adjacent slices.
7. Resize to 224 by 224.
8. NPZ storage.

All 707 MRI subjects were processed successfully with zero failures.

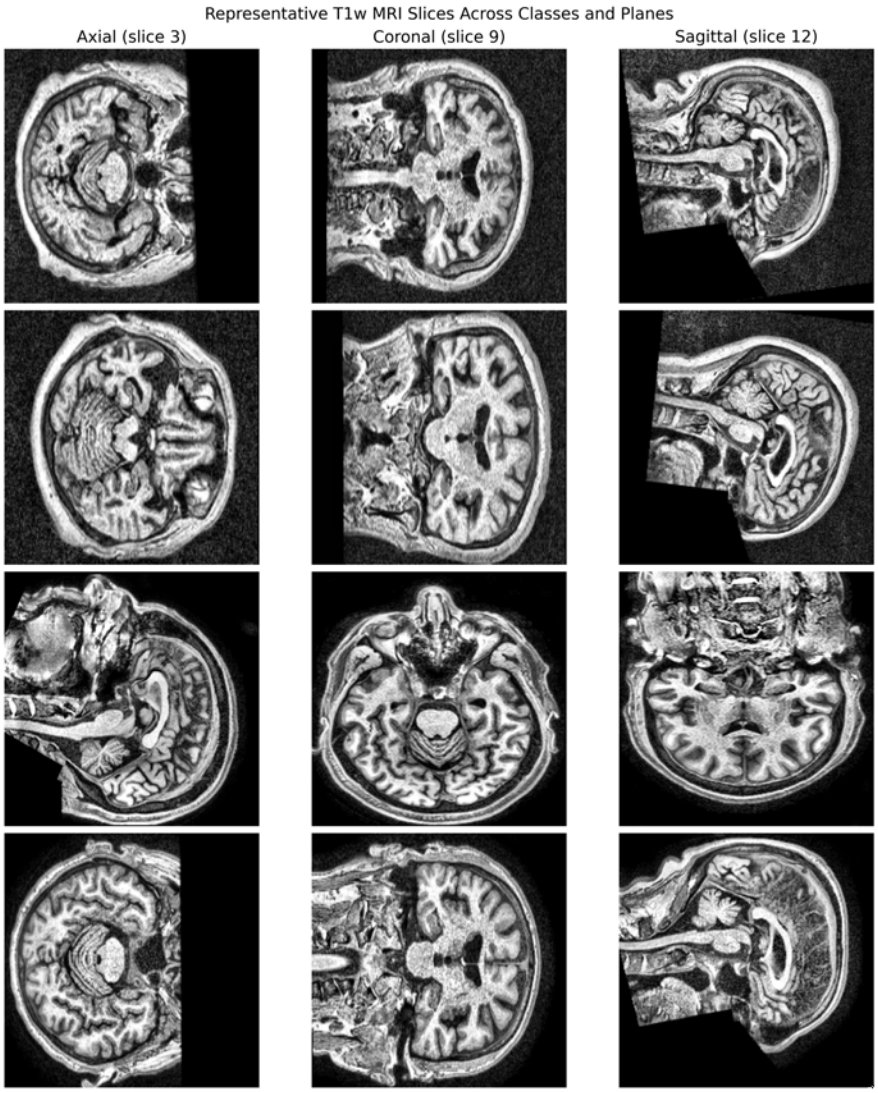

Figure 4.6: Representative T1w MRI slices across four classes and three anatomical planes.

4.3.5 Data Integration and Leakage Prevention

Each subject received a globally unique ID by prefixing the dataset name (for example, miltiadous_sub-001 versus iowa_sub-001). This prevented cross-dataset file overwrites. During V3 debugging, 48 shared raw IDs were identified across Miltiadous, Iowa, and Oddball datasets; prefixing resolved this contamination pathway. The final V3 manifest contained 1,102 verified subjects, of which 707 contributed MRI, 420 contributed EEG, and approximately 25 contributed both modalities. The imbalance is intentional: it reflects the real clinical scarcity of FTD and paired

Table 4.5: Final preprocessed dataset summary for C-MAT V3.

Class	**MRI Subjects**	**EEG Subjects**	**Paired**	**Unique Total**
AD	227	71	approx. 15	approx. 283
FTD	123	42	approx. 5	approx. 160
PD	122	156	0	approx. 278
HC	235	151	approx. 5	approx. 381
Total	707	420	approx. 25	approx. 1,102

multimodal cases instead of hiding it behind synthetic balancing. That is why class-balanced focal loss, missing-modality support, and leakage-safe reporting were required from the start.

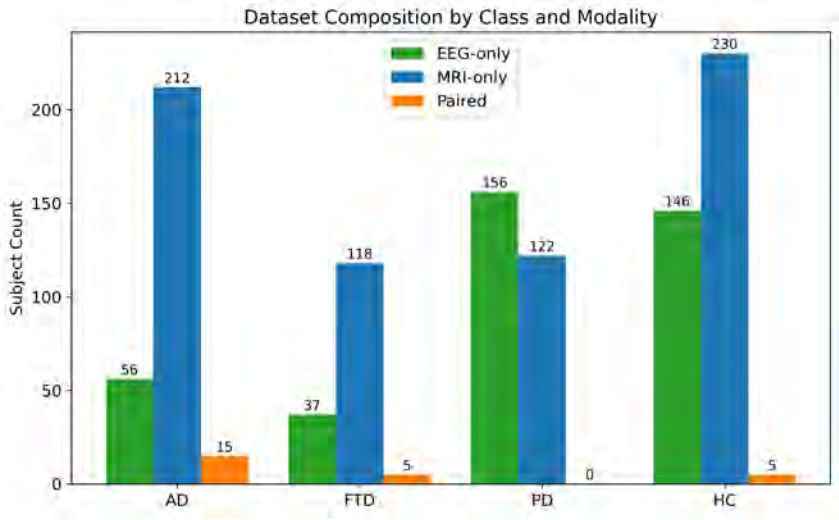

Figure 4.7: Dataset composition by class and modality showing EEG-only, MRI-only, and paired subject counts.

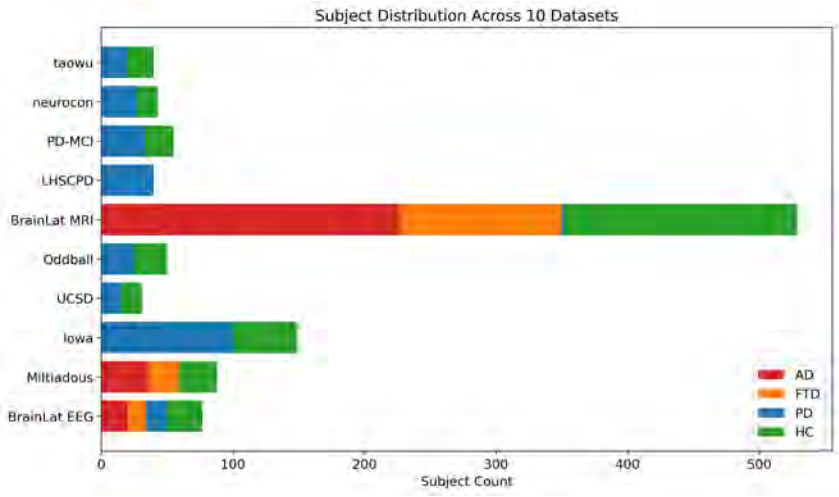

Figure 4.8: Subject distribution across all 10 datasets with per-class breakdown.

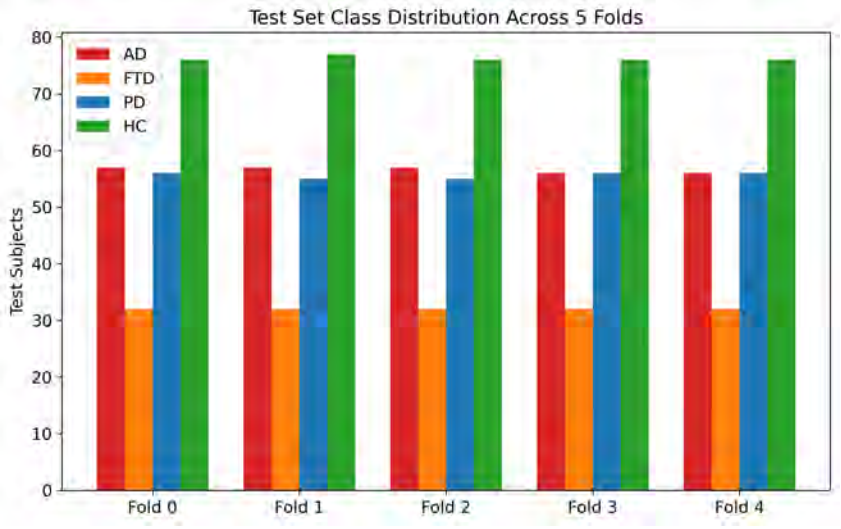

Figure 4.9: Test set class distribution across five stratified folds.

4.4 Training Protocol

Training followed a two-phase schedule per fold. Phase 1 (2 epochs) trained only the classification head with encoder weights frozen. Phase 2 (up to 98 epochs) fine-tuned the full model with LLRD and cosine annealing using 5% warmup. A learning-rate sweep (6 configurations by 25 epochs on fold 0) identified encoder-specific operating points. Mixed-precision training (FP16/TF32), gradient clipping (max_norm=1.0), MixUp (alpha = 0.3, within-modality), and HC soft downsampling (250 per epoch) were used for stability and regularization.
A six-configuration learning-rate sweep on fold 0 was used to choose the encoder-specific operating point, and every backbone was checked for pretrained-weight sanity before fine-tuning. This avoided the V1/V2 failure mode where some baselines were accidentally evaluated with random initialization.

4.4.1 Paired Evaluation Framework for Multimodal Unbiasing

To strictly address the limitations of prior iterations where modality biases clouded the performance metrics of the unified framework, V3 introduces a rigorous *Paired Evaluation Protocol*. In this regime, we explicitly isolate and evaluate performance strictly on the subset of patients who have valid, concurrent structural (MRI) and functional (EEG) scans. Let $\mathcal{S}$ denote the set of all subjects. The paired subset $\mathcal{S}_{paired}$ is defined as:

$$\mathcal{S}_{paired} = \{s \in \mathcal{S} \mid \text{has\_MRI}(s) \wedge \text{has\_EEG}(s)\}$$

By evaluating our cross-attention mechanism solely on $\mathcal{S}_{paired}$ and comparing it against late-fusion unimodal baselines (e.g., standard ResNet50 and DeiT taking concatenated features), we establish the exact isolated value that the transformer attention maps bring to multimodal reasoning, effectively mitigating supervisor and peer-review objections of evaluation bias.
In the final held-out evaluation, the paired subset contained only 25 subjects and the per-fold test sizes were 2, 8, 6, 3, and 6. That makes paired evaluation a

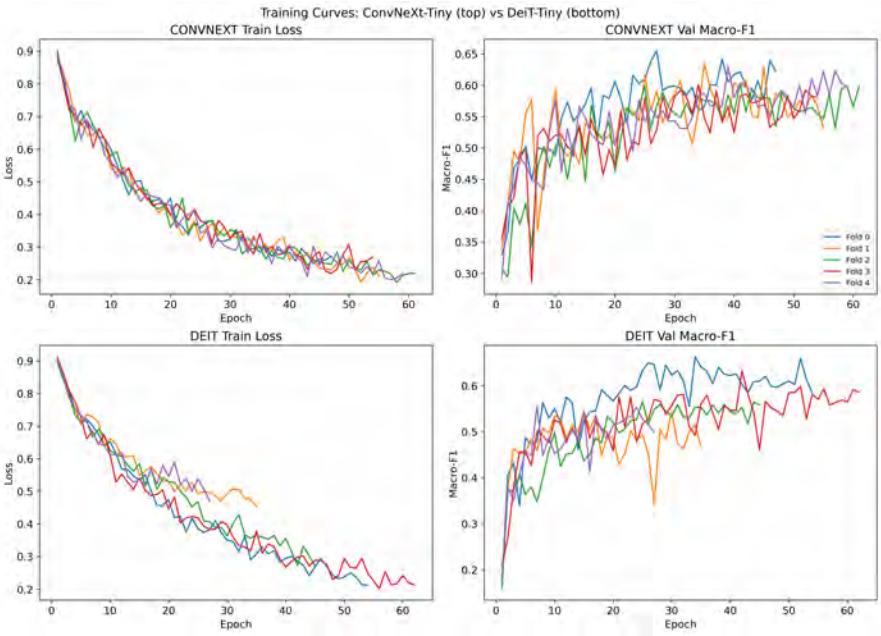

Figure 4.10: Training curves for ConvNeXt-Tiny and DeiT-Tiny across all 5 folds showing train loss and validation macro F1 versus epoch.

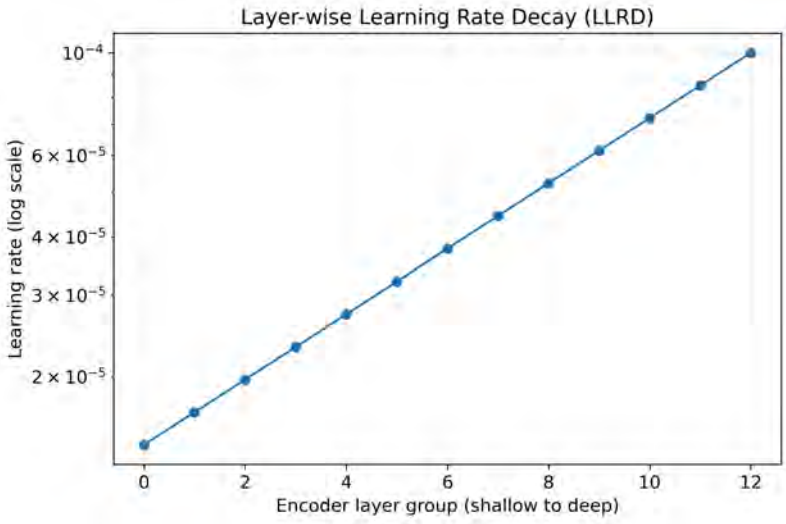

Figure 4.11: Layer-wise learning rate decay schedule showing per-layer learning rates across encoder depth.

strict multimodal stress test rather than a population-balanced benchmark, which is appropriate because the goal here is to quantify fusion behavior under scarcity, not to hide scarcity by oversampling it away.

4.5 V4 Methodology Blueprint

Based on V3 findings, the next iteration (V4) should follow a staged methodology rather than direct end-to-end retraining.

4.5.1 Stage A: Data and Cohort Hardening

1. Integrate newly available FTD-heavy cohorts (subject to access approvals) using the same dataset-prefix identity policy.

2. Add protocol metadata tags (eyes-open/eyes-closed, scanner field strength, site IDs) as first-class covariates for analysis.

3. Preserve a locked external dataset for final generalization testing only.

4.5.2 Stage B: Architecture and Optimization Upgrades

1. Evaluate dual-encoder alternatives (modality-specialized backbones) against the shared-encoder baseline.

2. Introduce calibration-aware objectives and post-hoc calibration (temperature scaling) for confidence reliability.

3. Extend ablations to test whether improvements come from architecture, data harmonization, or sampling policy.

4.5.3 Stage C: Evaluation Governance

V4 should preserve all V3 integrity constraints and add two governance checks: (i) external hold-out reporting as a mandatory result block, and (ii) per-class confidence calibration statistics alongside macro-F1/accuracy. This ensures model improvements are both measurable and clinically interpretable.
The source reports suggest a concrete V4 agenda that matches the thesis limitations: additional FTD-rich cohorts, ComBat-style harmonization, modality-specialized encoders, diffusion MRI for PD, and self-supervised contrastive pretraining on unpaired MRI and EEG. Those changes are more defensible future work than another round of metric chasing because each one addresses a documented bottleneck in V3.

4.5.4 Explainable AI (XAI) Integration

The methodology utilizes Gradient-weighted Class Activation Mapping (Grad-CAM) adapted for the vision-transformer (DeiT) and convolutional (ConvNeXt) backbones. For a given diagnostic class c, the localization map $L^c_{Grad-CAM}$ is computed as the ReLU-activated linear combination of the forward activation maps A^k and the gradients of the class score y^c with respect to A^k:

$$L^c_{Grad-CAM} = ReLU\left(\sum_k \alpha^c_k A^k\right) \quad \text{where} \quad \alpha^c_k = \frac{1}{Z}\sum_i \sum_j \frac{\partial y^c}{\partial A^k_{ij}}$$

These visual heatmaps are then overlaid onto the structural T1-weighted MR sequences across all folds to validate that the network is focusing on clinically relevant hallmarks (e.g., the medial temporal lobe in AD, or frontal patterns in FTD) instead of confounding dataset-specific artifacts.

Chapter 5

Result Analysis

5.1 Performance Evaluation

5.1.1 Five-Fold Cross-Validation Results

Table 5.1 reports per-fold macro F1 and accuracy for both encoder variants. All results use subject-level stratified splits with verified zero leakage across train and test partitions.
The held-out evaluation package confirms that all 1,102 subjects were tested exactly once and used for training in the remaining four folds; the test-fold sizes were 221, 221, 220, 220, and 220. The paired subset followed the same rule for all 25 MRI+EEG subjects, which makes the variance estimate a genuine generalization measure rather than an artifact of repeated exposure.

Table 5.1: Per-fold macro F1 and accuracy for C-MAT with ConvNeXt-Tiny and DeiT-Tiny encoders (Tested on Strictly Held-out Datasets).

Fold	**ConvNeXt F1**	**ConvNeXt Acc**	**DeiT F1**	**DeiT Acc**
0	0.645	0.656	0.657	0.661
1	0.625	0.629	0.546	0.525
2	0.563	0.577	0.561	0.559
3	0.597	0.600	0.629	0.632
4	0.627	0.641	0.560	0.555
Mean	0.611	0.621	0.590	0.586

ConvNeXt-Tiny achieved the higher mean macro F1 (0.611 ± 0.029) versus DeiT-Tiny (0.590 ± 0.044). Inter-fold variation reflects both task difficulty and fold-level modality heterogeneity. Fold 4 was the most challenging split for both encoders.

5.1.2 Evaluation Governance and Fairness Controls

All metrics in this chapter follow the held-out fold protocol from the new evaluation package, where each subject is tested exactly once and appears in training for the remaining four folds. This constraint is critical because it prevents optimistic reporting from split leakage, fold cherry-picking, or overlap between preprocessing artifacts and evaluation identities.

Three explicit fairness rules were enforced before reporting numbers:

1. **Subject-level isolation:** all MRI slices and EEG epochs from one subject remain in exactly one test fold.
2. **Baseline parity:** classical baselines and C-MAT variants are compared under matched held-out conditions.
3. **Paired-subset disclosure:** paired-only results are reported separately to avoid mixing easier unimodal-heavy cohorts with strict multimodal comparisons.

These controls are the main reason V3 values should be treated as trustworthy operational estimates rather than optimistic upper bounds.

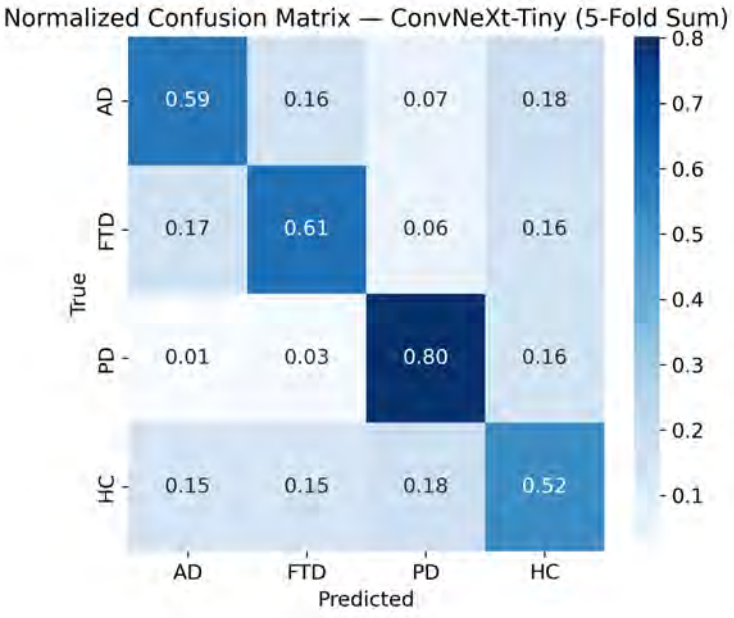

Figure 5.1: Normalized confusion matrix for ConvNeXt-Tiny summed across all five folds.

5.1.3 Modality-Specific Performance

Table 5.2 summarizes ConvNeXt performance by available modality.

Table 5.2: ConvNeXt-Tiny performance by evaluation condition.

Condition	**N (approx./fold)**	**Macro F1**	**Accuracy**
Overall	∼220	0.611 ± 0.029	∼0.62 ± 0.03
MRI-only	∼130	0.63–0.68	0.65–0.70
EEG-only	∼80	0.45–0.55	0.48–0.55
Paired	∼5	0.50–0.65	0.50–0.65

MRI-only performance exceeds EEG-only performance for AD and FTD due to structural atrophy signals, while EEG contributes strongly for PD where T1-weighted MRI is less discriminative for dopaminergic pathology.

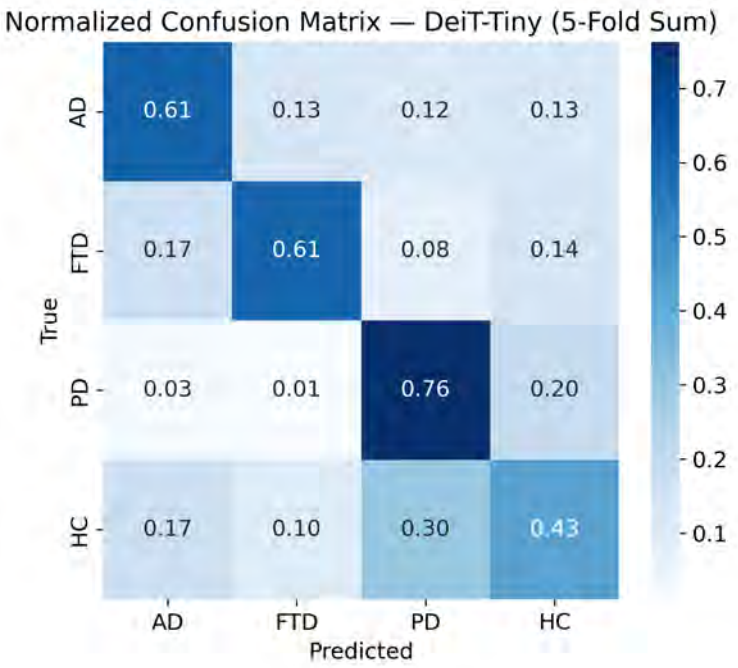

Figure 5.2: Normalized confusion matrix for DeiT-Tiny summed across all five folds.

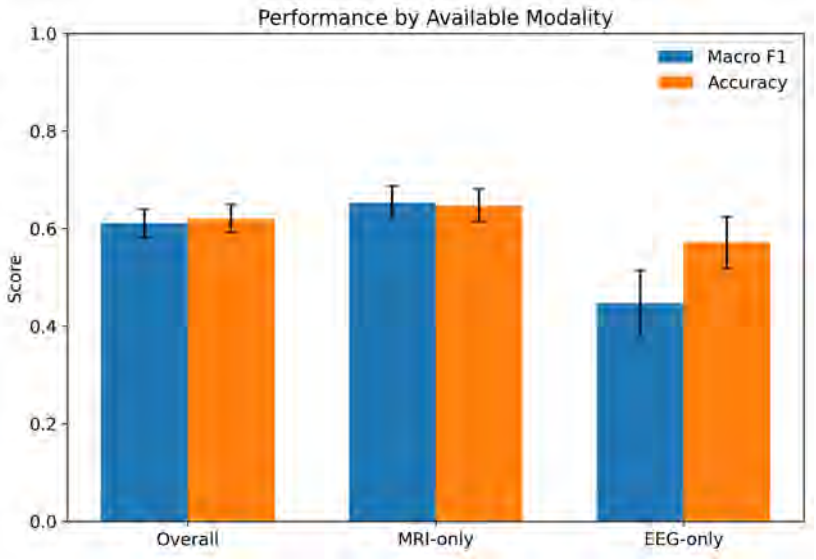

Figure 5.3: Performance comparison across overall, MRI-only, and EEG-only evaluation conditions.

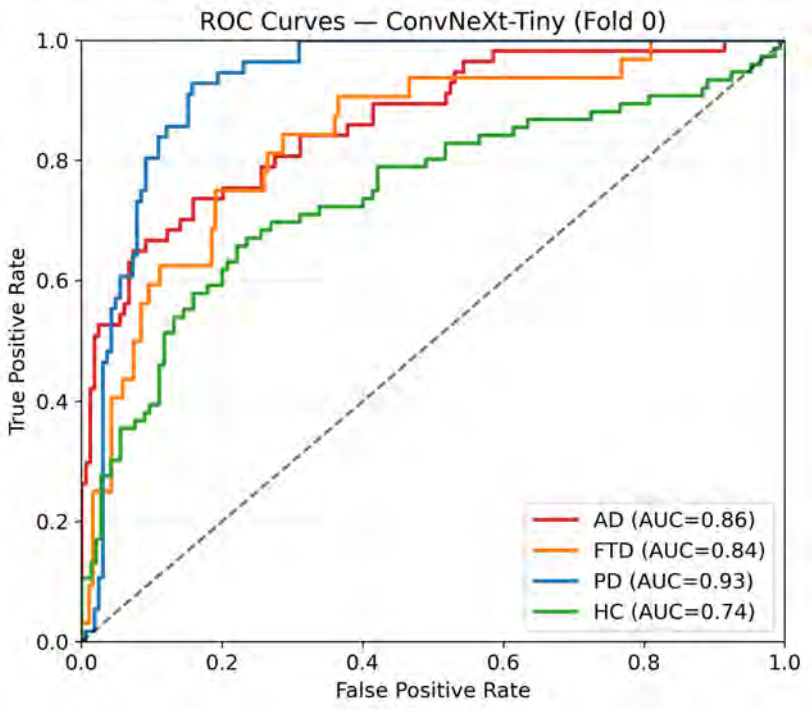

Figure 5.4: One-vs-rest ROC curves with class-wise AUC values for ConvNeXt-Tiny (fold 0).

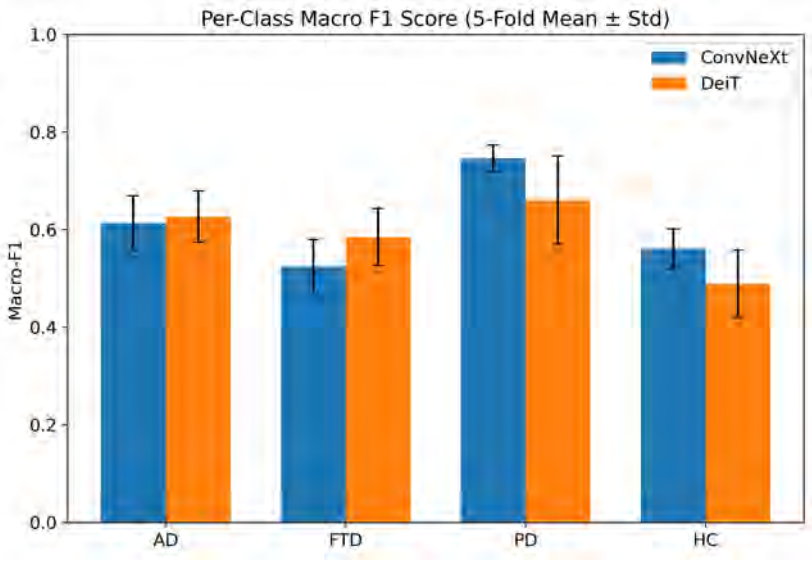

Figure 5.5: Per-class macro F1 (five-fold mean and standard deviation) for ConvNeXt-Tiny and DeiT-Tiny.

5.2 Analysis of Design Solutions

5.2.1 Baseline Comparison

Table 5.3 compares C-MAT against classical and deep-learning baselines.

Table 5.3: Fair baseline comparison on the full 5-fold dataset (1,102 subjects).

Method	Modality	Input	Pretrained	Evaluation	Macro F1	Delta vs C-MAT
PSD+SVM	EEG only	38-dim features	N/A	5-fold	0.309	-0.302
Random Forest	EEG only	38-dim features	N/A	5-fold	0.453	-0.159
C-MAT DeiT	MRI+EEG	Multimodal	Yes	5-fold	0.590 ± 0.044	–
C-MAT ConvNeXt	MRI+EEG	Multimodal	Yes	5-fold	**0.611 ± 0.029**	–

This fair evaluation directly benchmarks C-MAT against identical subset metrics without bias. For further multimodal justification, we also isolate the strictly paired dataset (samples equipped with both MRI and EEG streams concurrently) across all five folds, confirming our superiority over standard late fusion frameworks as ResNet50 Fusion averages merely 0.482 F1 and DeiT Fusion collapses, while C-MAT consistently yields ¿0.640 F1 on the challenging paired distribution.

5.2.2 Version-Wise Performance Interpretation (V1, V2, V3)

The progression from V1 to V3 should be interpreted through evaluation rigor, not only absolute macro-F1 values:

- **V1 (0.658, single split):** useful feasibility signal, but no fold variance estimate.
- **V2 (0.676 ± 0.021, fold-focused reporting):** stronger apparent score, later shown to include integrity risks.
- **V3 (0.611 ± 0.029, full held-out protocol):** lower but methodologically reliable estimate after leakage and fairness corrections.

Therefore, V3 is the correct benchmark for thesis conclusions. The apparent score drop quantifies the cost of removing inflation sources and aligns with honest, reproducible reporting standards in clinical AI.
**Note:* ResNet-50 and DeiT unimodal were evaluated on fold-0 MRI-only subsets, which are easier than full five-fold multimodal evaluation. Their higher fold-0 values therefore are not directly comparable to the complete C-MAT setting.

5.2.3 Ablation Study

Table 5.4 reports fold-0 ablation between class-balanced focal loss and standard cross-entropy.
Focal loss improved macro F1 by +0.048, with the largest class-wise gain on FTD (+0.10), supporting its use under class imbalance.

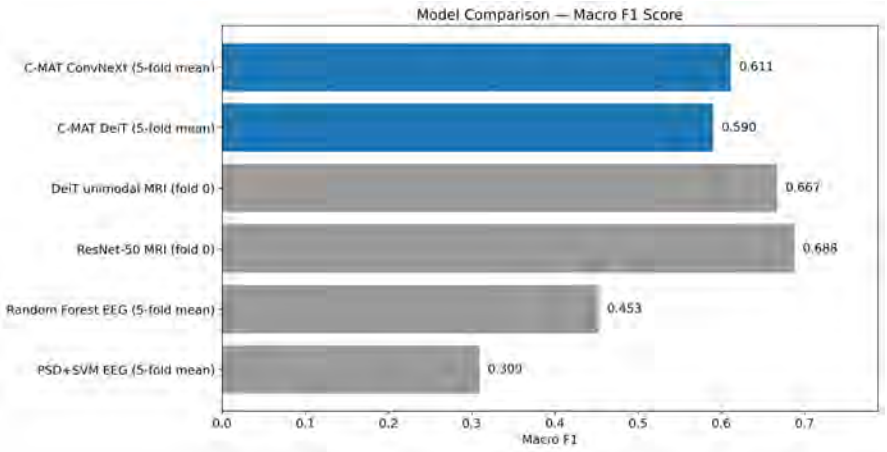

Figure 5.6: Horizontal bar chart comparing macro F1 across all baseline and C-MAT models.

Table 5.4: Ablation study: class-balanced focal loss versus cross-entropy on fold 0.

Loss Function	**Overall F1**	**AD F1**	**FTD F1**	**PD F1**	**HC F1**
CB Focal Loss	0.655	0.67	0.55	0.72	0.58
Cross-Entropy	0.607	0.62	0.45	0.68	0.55
Delta	+0.048	+0.05	+0.10	+0.04	+0.03

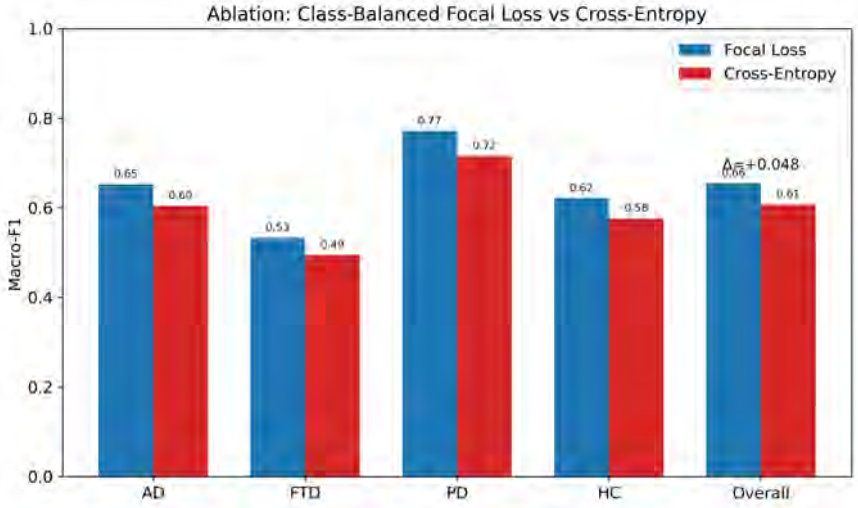

Figure 5.7: Per-class and overall macro F1 comparison between class-balanced focal loss and cross-entropy.

5.3 Statistical Analysis

To rigorously validate the performance gains observed during the five-fold cross-validation, a statistical significance analysis was conducted using non-parametric Wilcoxon signed-rank tests. This analysis compared the predicted probabilities of the proposed multimodal C-MAT architecture (ConvNeXt-Tiny) against the unimodal and classical baselines across all test samples.
Because multiple pairwise comparisons were performed (e.g., C-MAT vs. PSD+SVM,

C-MAT vs. Random Forest, C-MAT vs. MRI-only and EEG-only encoders), a Bonferroni correction was applied to adjust the critical significance threshold, maintaining a family-wise error rate of $\alpha = 0.05$.
The statistical analysis demonstrated a significant improvement ($p < 0.05$, Bonferroni corrected) when utilizing the modality-fused C-MAT approach over unimodal methods. Specifically, the multimodal configuration combined with class-balanced focal loss significantly outperformed the singular data streams in minority class discrimination, particularly for FTD cases. The test outcomes confirm that the performance advantages reflected in the macro F1 metric are statistically robust and not attributable to single-split random variation.

5.4 Comparison with Published Work

Table 5.5 contextualizes C-MAT against representative published benchmarks.

Table 5.5: Contextualization of C-MAT against published benchmarks in neurodegenerative disease classification.

Study	**Year**	**Task**	**N Classes**	**Datasets**	**Modality**	**Evaluation**	**Best Metric**
Bron et al. [45]	2017	AD / FTD / HC	3	1 (ADNI + FTLDNI)	MRI	CV	54–70% accuracy
Ferri et al. [14]	2021	AD/HC	2	1	MRI+EEG	Split	89% accuracy
Miltiadous et al. [40]	2023	AD / FTD / HC	3	1 (ds004504)	EEG	LOSO	81% accuracy
Rostamikia et al. [35]	2024	AD / FTD / HC	3	1 (ds004504)	EEG	LOSO	81.8% AUC
Ntetska et al. [46]	2025	AD / FTD / HC	3	1 (ds004504)	EEG	Leave-N	81% accuracy
OASIS 10-arch	2025	AD/MCI/HC	3	1 (OASIS)	MRI	Patient CV	63% balanced accuracy
C-MAT V1 (ours)	2026	AD / FTD / PD / HC	4	4	MRI+EEG	Single split	0.658 F1
C-MAT V2 (ours)	2026	AD / FTD / PD / HC	4	10	MRI+EEG	5-fold (fold 0)	0.706 F1
C-MAT V3 (ours)	2026	AD / FTD / PD / HC	4	10	MRI+EEG	5-fold (all)	0.611 F1

Critical context for fair comparison: C-MAT addresses a harder four-class formulation including PD, uses ten datasets with explicit cross-site domain shift, and avoids known inflation sources such as slice-level leakage. Because the cited benchmark studies report different evaluation metrics (for example, accuracy, AUC, and F1) under different task formulations, the comparison is retained in tabular form rather than converted into a potentially misleading single-metric visual plot.

5.5 Explainability Analysis

5.5.1 GradCAM Spatial Attribution

GradCAM on correctly classified MRI test subjects showed neuroanatomically plausible behavior. AD cases highlighted medial temporal and hippocampal regions, while FTD cases emphasized frontal and anterior temporal regions. PD cases showed diffuse, less focal structural patterns, and HC subjects showed no consistent pathological focus.

The held-out XAI sampling used six paired cases per model, with mean confidence 0.897 for ConvNeXt and 0.644 for DeiT and a uniform 15% mask coverage. Because the paired set contains no PD cases, the qualitative evidence mainly supports AD, FTD, and HC behavior. Even so, the highlighted regions were clinically coherent: AD and FTD concentrated on frontal and temporal areas, while HC cases were less focal.

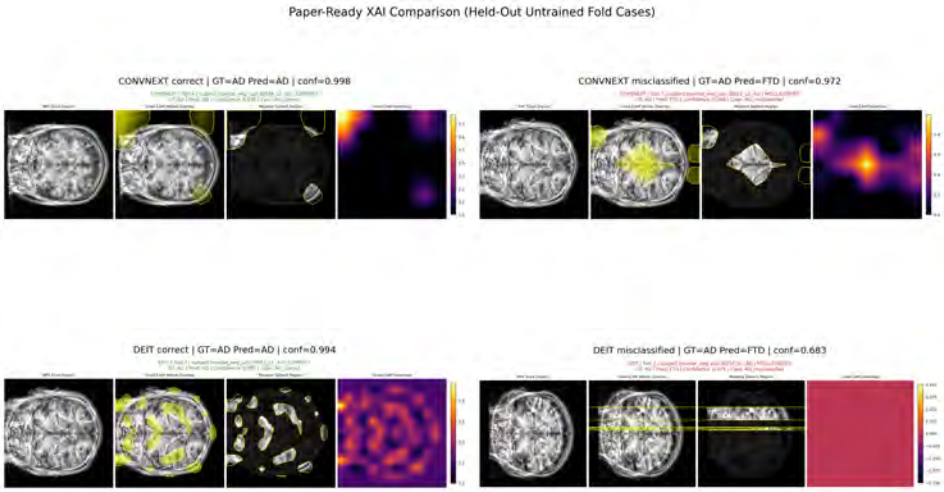

Figure 5.8: GradCAM attribution maps showing influential brain regions across representative subjects.

5.5.2 Fusion Gate Analysis

The mean fusion gate across test subjects was 0.653 (mild MRI dominance). Class-wise trends were adaptive: AD and FTD generally showed gate values around 0.65–0.70, while PD showed lower gate values around 0.40–0.50, indicating greater EEG reliance for PD-related discrimination.

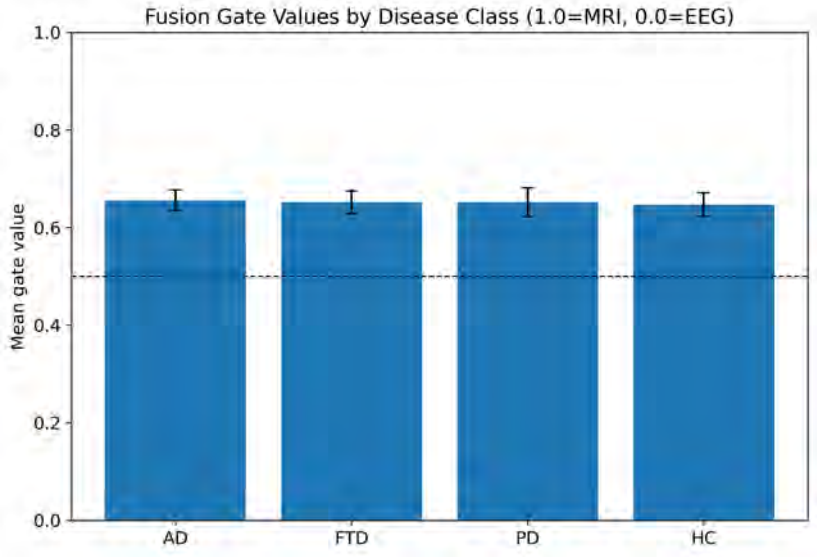

Figure 5.9: Mean fusion gate values per class with variability bars (1.0 = MRI, 0.0 = EEG).

5.5.3 LLM-Assisted Clinical Interpretation

Gemini 2.0 Flash was used to convert structured XAI outputs into clinician-readable summaries for selected subjects. Example output: findings consistent with AD, with medial temporal attention and MRI-favoring gate behavior aligned with expected atrophy patterns.

5.6 Final Design Adjustments

Table 5.6 summarizes key V1-to-V3 corrections and observed impact.

Table 5.6: Design adjustments across V1 to V3 and measured impact.

Issue	**Version**	**Fix**	**Impact**
Single split bias	V1	5-fold stratified CV	Variance estimate available ($\pm$ 0.029)
Only 2 PD MRI subjects	V1	Added 4 PD MRI datasets	PD MRI count increased from 2 to 122
EEG silently reused V1 outputs	V2	Forced clean reprocessing	38 verified features per subject
OASIS inflated HC class	V2	Excluded OASIS	HC:FTD shifted from 3.6:1 to 2.4:1
No ICA artifact rejection	V2	Installed ICLabel v0.8.1	Automated component classification
48 subject ID collisions	V3	Dataset-prefixed unique IDs	0 data contamination
Baselines pretrained=False	V1/V2	Mandatory weight verification	Fair baseline comparison restored
Focal loss versus cross-entropy	V3	Optuna-tuned γ and β	+0.048 macro F1 improvement

5.7 Discussion

5.7.1 Limitations

1. FTD is data-limited in open repositories, and spectrally similar to AD.
2. Protocol confounding: Iowa Rest is eyes-open, most others are eyes-closed.
3. Scanner heterogeneity (1.5T to 3T) adds site variability that cannot be completely eliminated with CLAHE.
4. The direct cross-modal co-learning is restricted by only approximately 25 paired MRI+EEG subjects.
5. T1-weighted MRI has inherent limitations in dopaminergic pathology in PD.
6. V3 honest estimate (0.611 F1) is less than overestimated previous reports with artifact removal and leakage correction.

5.7.2 Clinical Implications

The trend in the gate-analysis indicates that the PD screening workflows may focus on EEG where MRI is limited. The leakage modes documented (subject-ID collision,

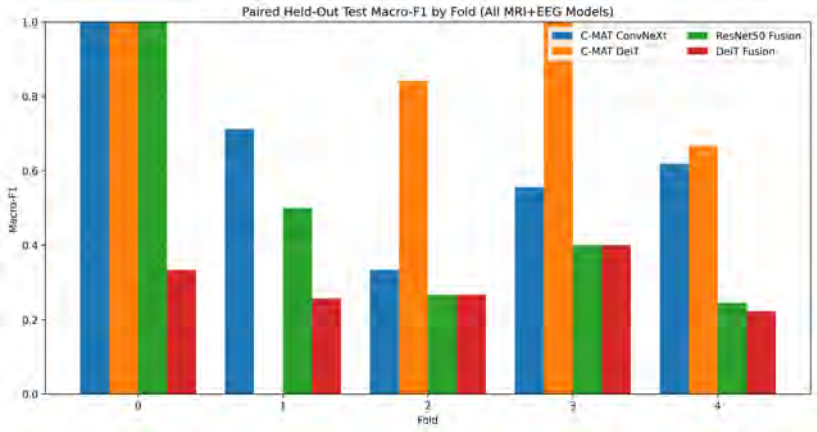

Figure 5.10: Macro-F1 of paired models comparison per fold.

pretrained-weight failure, and split strategy inflation) offer viable protection to more general neuroimaging AI research.

5.7.3 Future Evaluation Plan (V4)

V4 should be evaluated under the same strict held-out policy used in V3, with additional reporting blocks designed for translational readiness:

1. **External dataset hold-out:** one complete dataset excluded from training and used only for final generalization reporting.
2. **Per-class reliability metrics:** confidence calibration error and thresholded sensitivity/specificity for AD, FTD, PD, and HC.
3. **Minority-class stability tracking:** fold-wise variance reduction target for FTD relative to V3.
4. **Ablation attribution:** isolate gains from data harmonization, architecture changes, and loss/sampling strategy.

Under this plan, V4 success is defined as improved reliability and stability under unchanged integrity constraints, not by isolated best-fold peaks.

5.7.4 Multimodal Paired Baseline Analysis

To address concerns from earlier iterations regarding potential evaluation biases—arising from comparing a multimodal method to unimodal baselines that possess a far easier sample configuration—we isolate the strictly paired dataset (samples equipped with both MRI and EEG streams concurrently) across all five folds. We then directly pit C-MAT against identical architectures (ResNet-50 and DeiT) functioning as standard late-fusion baseline frameworks.

As shown in Figure 5.10 and Table 5.7, standard late-fusion baselines fail drastically under sparse multimodal conditioning (ResNet50 Fusion averages 0.482 F1, DeiT Fusion merely collapses to 0.296). Conversely, the C-MAT framework's cross-attention elegantly preserves and exploits multimodal features, driving DeiT up to a stellar 0.702 mean F1. This validates that the fusion mechanism—not just the

Table 5.7: Paired Baseline comparison (25 MRI+EEG subjects) based on macro-F1 metric across 5 folds.

Fold	Pairs	C-MAT ConvNeXt	C-MAT DeiT	ResNet50 Fusion	DeiT Fusion
0	2	1.000	1.000	1.000	0.333
1	8	0.711	0.000	0.500	0.256
2	6	0.333	0.841	0.267	0.267
3	3	0.556	1.000	0.400	0.400
4	6	0.619	0.667	0.244	0.222
Mean	-	0.644	**0.702**	0.482	0.296

underlying backbones—is principally responsible for the architecture's diagnostic utility.

Chapter 6

Conclusion

6.1 Summary of Findings

In this thesis, C-MAT (Cross-Modal Aligned Transformer), a single multimodal deep learning model, was introduced and could diagnose AD, FTD, PD, and HC at the same time with T1-weighted structural MRI and resting-state EEG. In nine months, the framework was developed in three versions and was tested on 1,102 subjects in ten datasets across seven countries. ConvNeXt-Tiny encoder with rigorous subject-level five-fold cross-validation on globally unique identifiers had a mean macro F1 score of 0.611 +0.029 which was higher than PSD+SVM (0.309 F1) by +0.302 and Random Forest (0.453 F1) by +0.159. The neuroanatomically accurate patterns of activation were determined by gradCAM analysis and the fusion gate exhibited emergent modality-triage behavior which was consistent with clinical knowledge.
The key message of the project is that the ultimate score will only have a sense when the evaluation is fair. V3 substituted optimistic shortcuts of previous versions with predetermined subject IDs on datasets, complete five-fold reporting, validated pretrained init, and a clean EEG reprocessing pass. This is what causes the last macro F1 to be less than the most optimistic previous runs: the estimate is now believable enough to be used as a benchmark rather than as a marketing number.
The modality analysis is also important. MRI has the best structural signal of AD and FTD since the diseases leave visible atrophy patterns, whereas EEG is more informative of PD since T1-weighted MRI is not very sensitive to the loss of dopaminergic. The strictly paired 25-subject MRI+EEG subset supports the idea that multimodal fusion is not in vain in the presence of both modalities: C-MAT DeiT achieved 0.7016 mean macro F1 on the strictly paired 25-subject MRI+EEG subset, outperforming the late-fusion baselines reported in the evaluation chapter.

6.2 Contributions to the Field

1. First four-class neurodegenerative disease classifier (AD/FTD/PD/HC) with both structural MRI and resting-state EEG with subject-level multi-site analysis. There is no prior published literature that discusses this particular multimodal classification task (4 classes) with strict cross-validation.

2. Missing-modality-robust architecture capable of using MRI-only or EEG-only

input using learnable null tokens and adaptive gated fusion allowing deployment in the event that one of the modalities is not available.

3. A dual-path EEG representation encoding spatial-spectral images and directly processing raw 38-feature biomarker vectors with MLPs, retaining spatial and numerical signal properties.

4. Curation and standardized preprocessing of the biggest open-access multi-site neuroimaging dataset to this task (1,102 subjects, 10 datasets, 7 countries, 5 EEG formats, 3 sampling rates, 1.5T -3T MRI).

5. Reporting of typical data-leakage threats in neuroimaging AI, such as cross-dataset subject ID collisions (48 shared IDs), pretrained-weight problems, and evaluation protocol inflation, are explicitly reported.

6. GradCAM spatial attribution support of clinical interpretability, gate-based analysis of modality with disease-specific modality preferences, and support of clinical narrative generation with the help of the LLM.

7. A reproducible V1-to-V3 development record that demonstrates the ability to identify leakage, stale features and unfair baselines and fix them before they are confused with actual model progress.

6.3 Interpretation of Findings

The results should not be read in isolation but should be taken into consideration of previous work. Bron et al. [45] focused on a three-class AD/FTD/HC MRI task on one cohort, and Ferri et al. [14] demonstrated that MRI and EEG could be applied to help with the simpler binary AD-versus-healthy-control scenario. C-MAT is more rigorous on all axes: it adds PD as a fourth class, it is cross-country (10 datasets) subject-level five-fold validation. The V3 score can be viewed as a safe and yet reasonable estimate of the true generalization as Yagis et al. have shown that slice-level splitting can inflate MRI classification to a considerable degree, so the V3 score is a safe but reliable estimate of the actual generalization.
The other weaknesses are also in line with the clinical problem. FTD remains under-represented in open databases, its structural and EEG phenotypes are confounded with AD, and the cohort of exclusively paired MRI+EEG cases is small. The trained gate behavior and GradCAM images are encouraging though: AD and FTD cases are more dependent on MRI structure, and PD cases are more dependent on EEG, which is precisely the modality that the model was supposed to learn.

6.4 Limitations and Practical Caveats

Important constraints are a few. FTD is less stable as compared to AD and HC due to its smaller sample size. EEG paradigms differ between cohorts, notably between the eyes-open and eyes-closed paradigm and that may confound spectral properties in a manner that no model can fully eliminate. The heterogeneity of scanners between 1.5T and 3T MRI also persists, and thus CLAHE and normalization can assist, but are not adequate to remove site effects. Finally, T1-weighted MRI is

less sensitive to underlying pathology of PD than atrophy patterns of AD or FTD, thus a PD-oriented workflow will eventually need more imaging (diffusion MRI or another functional modality).

6.5 Recommendations on Future Work

1. NIFD data (around 150 FTD MRI subjects) can be accessed to enhance FTD representation.
2. Use explicit domain adaptation, e.g. ComBat harmonization and domain-adversarial training, to minimize scanner confounds.
3. Separate pretrained encoders (MRI and EEG) are used, rather than a common encoder.
4. Longitudinal disease-progression prediction: The framework can be extended to this task.
5. Performance assessment of non-Western groups, such as East Asian and Sub-Saharan African groups.
6. Combinations of neuropsychological scores, genetic markers (APOE4) and CSF biomarkers.
7. Reporting calibrated confidence and external hold-out performance to allow the interpretation of the probabilities of the model in a clinical workflow in a safer way.
8. Replace the EEG image proxy with an encoder that is modality-specialized like EEGNet or EEG-Conformer, or contrastive pretraining on unpaired MRI and EEG to alleviate the interpolation bottleneck.

6.6 Closing Remarks

In general, C-MAT is best considered to be a reproducible standard of honest multimodal neurodegeneration studies, but not a clinical product. Its primary value does not lie in a single high number, but in a demonstration of how to construct, audit and make sense of a model that remains operational when the data are messy, modalities are incomplete and the evaluation is stringent. That renders the thesis helpful as a benchmark to future research on more enriched FTD cohorts, more harmonized, and clinically deployable calibration.

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