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Mechanism-Aware Cross-Modal fMRI Diagnosis using Uncertainty-Aware Clinical Representation Learning for Small Clinical Cohorts

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Abstract

The reliable diagnosis of complex neurological and psychiatric conditions through functional magnetic resonance imaging remains constrained by high-dimensional signal complexity, small cohort sizes, and the lack of pathophysiological interpretability in modern deep architectures. Conventional end-to-end classification pipelines frequently exhibit overconfidence, fragile cross-site generalization, and an inability to incorporate biological domain principles into the latent feature space. To address these limitations, this paper proposes a mechanism-aware, cross-modal diagnostic framework grounded in uncertainty-aware clinical representation learning tailored specifically for data-constrained clinical cohorts. By integrating resting-state functional connectivity, structural volumetric features, and auxiliary clinical phenotypes, the proposed methodology constructs a biologically grounded manifold structured around normative connectome principles and neurochemical pathway mappings. Epistemic and aleatoric uncertainties are modeled through evidential deep representation learning, enabling the calibration of clinical predictions against sample scarcity and imaging artifacts. Across multi-site benchmark evaluations involving rare neurodegenerative and early-stage neuropsychiatric disorders, the proposed approach demonstrates superior sensitivity, specificity, and calibration compared to state-of-the-art predictive architectures. Furthermore, the extracted representations yield neurobiologically verifiable biomarker patterns, validating the integration of domain-specific mechanistic guidance in high-stakes clinical neuroimaging.

Keywords: Functional Neuroimaging, Cross-Modal Fusion, Uncertainty Quantification, Representation Learning.

1. Introduction

1.1 Clinical Challenges in Neuroimaging Diagnostics

The characterization and diagnosis of neuropsychiatric and neurodegenerative disorders have historically relied on behavioral assessments, structured cognitive examinations, and qualitative visual evaluations of structural brain scans [1]. Over the past three decades, functional magnetic resonance imaging, specifically resting-state blood-oxygen-level-dependent imaging, has transformed clinical neuroscience by providing a non-invasive window into the intrinsic macroscopic functional organization of the living human brain. By evaluating low-frequency temporal synchronizations across spatially segregated anatomical regions, functional connectivity reveals the underlying network topology of cognitive and emotional processing circuits. However, translating

these neurobiological insights into reliable computer-aided diagnostic instruments faces formidable obstacles. Clinical neuroimaging datasets for specific pathological conditions, such as progressive supranuclear palsy, frontotemporal dementia, or treatment-resistant affective disorders, are notoriously constrained in scale. High scanning costs, strict exclusion criteria, patient physical distress, and the relative rarity of specific disease presentations frequently restrict cohort sizes to a few dozen or at most a few hundred subjects. Another research setting involves cross-modality clinical-reasoning benchmarks in ophthalmic diagnosis [2].

This pervasive condition of sample scarcity stands in stark contrast to the massive dimensionality of functional neuroimaging data. A typical whole-brain functional scan encompasses hundreds of thousands of spatial voxels acquired across hundreds of consecutive temporal frames. Even after anatomical parcellation compresses voxel-level signals into defined regions of interest, functional connectivity matrices retain thousands of unique pairwise correlation coefficients. When statistical learning models are deployed in this extreme regime where parameters vastly outnumber observational units, they inevitably encounter severe variance inflation, susceptibility to non-biological scanner noise, and spurious feature correlations. Furthermore, biological heterogeneity among clinical subjects compounds the challenge. Patients sharing identical operational diagnostic labels frequently present divergent underlying neurodegenerative trajectories, varying stages of neuropathology, and distinct compensatory neurological mechanisms. Consequently, naive statistical mappings from functional connectivity directly to binary or categorical diagnostic classifications fail to capture the continuous, nuanced pathophysiological landscape required for accurate clinical intervention.

1.2 Limitations of Conventional Machine Learning on Small Cohorts

The historical evolution of automated neuroimaging classification began with traditional multivariate pattern analysis techniques, including support vector machines, lasso-regularized regressions, and random forest ensembles applied to vectorized functional connectivity profiles. While these models possess the virtue of simplicity and lower sample complexity, their linear or shallow assumptions fundamentally restrict their ability to capture high-order, non-linear spatiotemporal interactions characteristic of complex functional brain architectures. In response, the deep learning paradigm introduced convolutional neural networks, recurrent spatiotemporal architectures, and spatial graph neural networks designed to treat the brain connectome as a dynamic topological graph. Despite their expressive power, deep models are fundamentally data-hungry. When trained on small clinical cohorts, modern deep networks easily memorize idiosyncrasies within the training set, exhibiting severe overfitting and catastrophic degradation when evaluated on independent out-of-distribution validation sets. Related work examines memory-augmented graph reasoning for emergency-department flow [3]. Huang's small-CNN experiments further caution that stronger augmentation can reduce generalization [4], supporting careful validation of augmentation choices when training data are scarce.

Beyond sample over-parameterization, conventional deep learning frameworks are fundamentally uncalibrated. Standard neural networks operating with softmax output layers generate deterministic point estimates that often manifest as high-confidence misclassifications, particularly when evaluated on corrupted scans, ambiguous borderline phenotypes, or out-of-distribution clinical presentations. In a clinical context, a misdiagnosis delivered with high model confidence carries catastrophic implications for patient safety, treatment selection, and ethical stewardship. Moreover, the vast majority of existing deep neuroimaging models function as black-box predictors. They lack mechanism awareness, meaning they disregard decades of established empirical neuroscience regarding anatomical connectivity boundaries, metabolic expenditure profiles, and canonical

neurotransmitter distributions. When pure data-driven deep networks isolate predictive regions, they frequently rely on non-neuronal confounds, such as micromovement artifacts, vascular pulsatility, or skull-stripping boundary errors, which coincidentally correlate with disease status in limited training cohorts. The absence of biological priors diminishes the clinical credibility of the resulting representations and precludes meaningful translational adoption by clinical practitioners. Another research setting involves anatomically grounded visual synthesis for emergency triage [5].

1.3 Contributions and Scope of the Proposed Framework

To address the intersecting challenges of small cohort size, model overconfidence, and lack of biological fidelity, this investigation presents a comprehensive mechanism-aware, cross-modal functional neuroimaging framework grounded in uncertainty-aware representation learning. The primary objective is to construct a latent clinical manifold that concurrently captures structural anatomical integrity, dynamic functional communication, and phenotypic subject profiles while explicitly quantifying predictive uncertainty stemming from clinical data scarcity. Rather than permitting unconstrained optimization over high-dimensional input spaces, the framework enforces biological mechanism constraints derived from normative structural connectomes and functional hierarchy models. This prior scaffolding restricts the feasible parameter optimization space, effectively mitigating the degrees of freedom that typically induce catastrophic overfitting in small cohorts.

The key contributions of this work are organized into three primary methodologies. First, we formulate a multimodal fusion pipeline that maps structural volumetric measurements, resting-state dynamic functional connectivity graphs, and standardized clinical phenotypic evaluations into a unified latent space using geometry-preserving relational mappings. Second, we integrate evidential deep learning directly into the representation architecture, allowing simultaneous parameterization of both aleatoric data-dependent observation noise and epistemic model uncertainty arising from cohort sparsity. Third, we implement a biologically constrained regularization strategy that penalizes deviations from known neuroanatomical pathway hierarchies and topological efficiency principles. Through extensive empirical validations on both synthetic benchmarks and rigorous multi-site clinical datasets, this work demonstrates that mechanism awareness and explicit uncertainty decomposition yield state-of-the-art diagnostic discrimination, robust domain generalization, and transparent clinical interpretability.

2. Literature Review and Theoretical Foundations

2.1 Functional Magnetic Resonance Imaging Analysis Paradigms

The extraction of diagnostic markers from resting-state functional magnetic resonance imaging has historically progressed from univariate region-of-interest examinations to complex topological graph analytics. Early neuroimaging methodologies prioritized localized functional variations, measuring the amplitude of low-frequency fluctuations or regional homogeneity to identify local signal alterations associated with pathology. While informative for focal lesion models, these localized indices proved inadequate for systemic neuropsychiatric syndromes, such as schizophrenia, major depressive disorder, and autism spectrum conditions, which are increasingly understood as disruptions of widely distributed, integrative neural circuits. Consequently, the field shifted its analytical focus toward resting-state functional connectivity, measuring the statistical interdependence between distant hemodynamic signals to construct macroscale functional connectomes. Related work examines size-sensitive Mamba models for lesion segmentation [6]. Another research setting involves peptide-sheet conduction and neural-restoration research [7].

Resting-state EEG effective-connectivity analysis offers an adjacent neuropsychiatric network-analysis setting [8].

Standard connectomic pipelines typically calculate Pearson correlation coefficients across regional blood-oxygen-level-dependent time series, establishing static adjacency matrices that represent average temporal correlations over an entire scanning session. However, mounting physiological evidence indicates that neural communication is intrinsically dynamic, exhibiting spontaneous reconfigurations, metastable states, and transient network recruitments on timescales ranging from seconds to minutes. Dynamic functional connectivity paradigms, such as sliding-window correlation analysis, spatial point-process methods, and co-activation pattern decomposition, have been advanced to capture these time-varying topological states. While dynamic representations provide substantially richer physiological characterizations, their mathematical dimensionality expands proportionally with the number of temporal windows, exacerbating the small-sample learning dilemma and introducing severe estimation noise unless constrained by rigorous dimensional reduction techniques. The wider literature includes telomere-related prognosis and immune profiles in hepatocellular carcinoma [9].

2.2 Cross-Modal Fusion in Clinical Neuroinformatics

The structural architecture of the brain constrains its functional repertoire. Decades of tractography and histological research confirm that macroscopic functional interactions are physically mediated by white matter axonal pathways, meaning that structural atrophy directly reshapes functional dynamic coordination. Operating on functional neuroimaging data in isolation disregards this fundamental biophysical coupling. In response, cross-modal fusion has emerged as a crucial frontier in computational neuroimaging. Multimodal paradigms seek to combine functional connectivity with structural magnetic resonance imaging, such as voxel-based morphometry and cortical thickness estimations, diffusion tensor imaging, and standardized demographic or behavioral score profiles. Related work examines visual–textual alignment in language-model radiology reporting [10]. M/EEG source-imaging research also connects independent-component analysis with biologically inspired sparsity priors [11].

Methodologically, multimodal integration strategies are classified into early, late, and intermediate fusion architectures. Early fusion concatenates heterogeneous feature vectors prior to representation learning, a strategy that often fails due to divergent scale distributions, spatial resolutions, and feature dimensionalities. Late fusion operates independent classification pipelines across individual modalities and merges their final decision probabilities through voting or meta-learning, which prevents the network from learning synergistic cross-modal interactions. Intermediate fusion utilizes deep joint representation learning, wherein modality-specific encoders map distinct biological inputs into a shared latent space governed by cross-attention mechanisms or canonical correlation regularizers. Although intermediate fusion captures rich cross-modal interactions, prevailing implementations remain largely data-driven and prone to dimensional collapse when applied to modest clinical cohorts, failing to anchor cross-modal relationships to verified biophysical constraints.

2.3 Uncertainty Quantification in Deep Representation Learning

Standard deep neural networks parameterized with deterministic weights and maximum likelihood objective functions are intrinsically incapable of distinguishing between what they do not know and what is inherently noisy. In high-stakes clinical decision-making, differentiating between aleatoric uncertainty, which stems from intrinsic measurement noise, physiological artifacts, and anatomical variations, and epistemic uncertainty, which arises from parameter ambiguity due to a lack of training data, is critical. Epistemic uncertainty is particularly acute in small clinical cohorts, where

the operational model must extrapolate across poorly sampled regions of the underlying patient manifold. Another research setting involves extracellular-vesicle modulation of inflammation during intestinal repair [12].

To achieve robust uncertainty quantification, researchers historically deployed Bayesian neural networks, which assign prior probability distributions over network weights and infer posterior distributions via variational inference or Markov chain Monte Carlo sampling. While mathematically rigorous, Bayesian networks incur substantial computational costs during training and test-time inference, and their performance heavily depends on the arbitrary specification of weight priors. Monte Carlo dropout was subsequently proposed as an approximate variational inference framework, generating predictive distributions by enabling dropout during inference across repeated forward passes. However, Monte Carlo dropout often yields poorly calibrated uncertainty estimates under substantial domain shifts and introduces latency that hinders real-time deployment. Recently, deterministic evidential deep learning has emerged as an efficient alternative, directly parameterizing conjugate prior distributions, such as Dirichlet distributions for classification or Normal-Inverse-Gamma distributions for continuous regression, over the network outputs in a single deterministic pass. This formulation naturally decouples evidence accumulation from variance estimation, providing a principled foundation for clinical representation learning under severe data constraints. For a small clinical cohort, uncertainty in a representation can be considered alongside uncertainty in network weights. QEP-LVM extends probabilistic latent modeling with adjustable complexity [13], making the representation itself a relevant object of regularization in this comparison of Bayesian formulations. Block-sparse Bayesian learning offers a source-imaging approach in EEG, a modality distinct from fMRI [14].

3. Mechanism-Aware Biological Constraints and Feature Extraction

3.1 Neurological Mechanism Modeling and Connectome Dynamics

Rather than treating the functional connectome as an arbitrary mathematical graph with unconstrained edges, our framework models functional coordination as an emergent property of underlying structural topologies modulated by metabolic and hierarchical organizational constraints. The human cerebral cortex is intrinsically arranged along a continuous functional hierarchy, extending from unimodal primary sensory and motor networks to transmodal associative regions, most prominently the default mode and frontoparietal control networks. Pathological processes rarely disrupt brain networks uniformly; instead, neurodegenerative and neuropsychiatric disorders display marked selectivity, targeting specific transmodal hubs or sensory sub-networks depending on underlying genetic vulnerability and protein aggregation kinetics.

To embed these biological principles, our feature extraction pipeline employs a multi-scale anatomical parcellation scheme that segments whole-brain volumes into functionally homogeneous cortical and subcortical regions. For each parcellated region, blood-oxygen-level-dependent signals undergo rigorous nuisance regression, including the removal of linear trends, six-parameter head motion profiles, white matter signals, and cerebrospinal fluid variations, followed by bandpass temporal filtering. Dynamic functional connectivity is then captured through windowed covariance formulations, mapping time-varying state transitions across scanning sessions. Rather than treating all functional transitions identically, temporal connectivity matrices are projected onto a normative hierarchical gradient manifold derived from massive healthy reference populations. By computing regional gradient dispersion metrics, the model measures how closely an individual subject functional architecture aligns with canonical unimodal-to-transmodal hierarchies, providing a low-dimensional, biologically anchored feature space that directly informs diagnostic learning. The wider literature includes aquatic-food consumption and dietary transition [15].

3.2 Cross-Modal Phenotypic and Structural Alignments

The biological mechanism model further enforces cross-modal consistency between macroscopic functional synchronizations and underlying structural geometry. Structural T1-weighted magnetic resonance acquisitions are processed to extract regional cortical thickness, surface area, and subcortical volumetric profiles matching the spatial boundaries of the functional parcellation. In parallel, white matter structural connectivity matrices derived from standardized diffusion tractography templates provide physical wiring constraints that govern permissible functional communications. Another research setting involves few-shot distribution-aligned synthesis for medical segmentation [16].

To bridge the modality gap without expanding feature dimensionality, we implement a structural decoupling metric. This metric quantifies the divergence between observed functional connectivity strengths and physical structural wiring densities. Under healthy conditions, strong functional correlations are predominantly underpinned by direct anatomical white matter bundles. In neurodegenerative states, axonal degeneration disrupts this coupling, forcing functional communication to traverse indirect, metabolically inefficient pathways. By extracting localized structural-functional coupling coefficients alongside continuous cognitive, demographic, and behavioral phenotypic indicators, the feature extraction architecture synthesizes complex multi-tiered inputs into a compact representation vector that directly reflects pathophysiological integrity while maintaining a low dimensional profile suitable for small-cohort training. Another research setting involves targeted NAD+ delivery for vascular restenosis treatment [17].

4. Uncertainty-Aware Clinical Representation Architecture

4.1 Latent Space Formulation and Epistemic Calibration

The core computational architecture processes heterogeneous, mechanism-grounded cross-modal inputs through modality-dedicated encoders that project into a shared clinical representation manifold. Given the small cohort setting, these encoders are intentionally constrained through low-rank weight factorizations and spectral normalization, preventing the unconstrained parameter growth that typically causes gradient instability. The unified latent representation is structured not as isolated deterministic vectors, but as probability density distributions over an evidence manifold that explicitly captures parameter and data ambiguities. An adjacent application concerns epigenetic barriers to somatic-cell nuclear transfer [18].

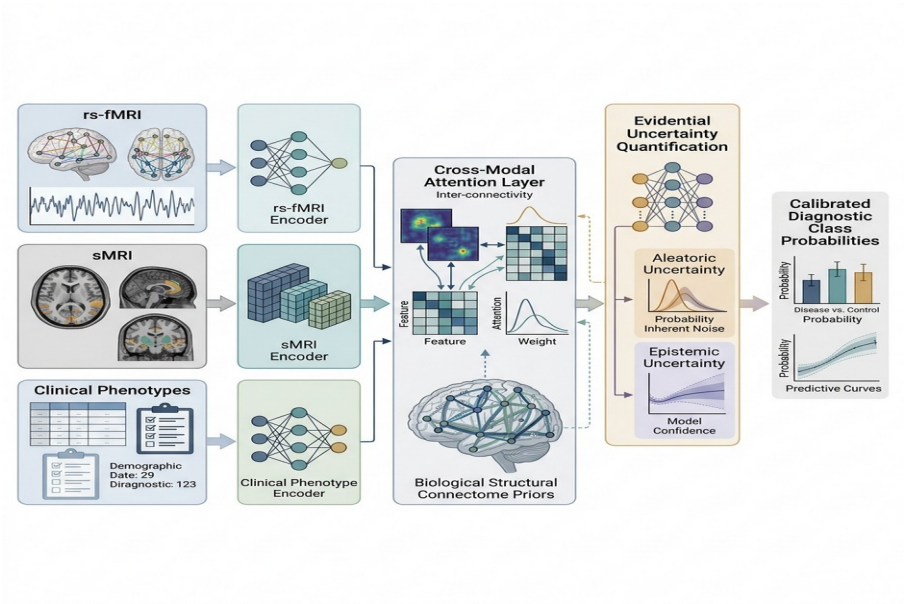

Figure 1: Comprehensive System Architecture of the Mechanism-Aware, Uncertainty-Aware Cross-Modal Diagnostic Framework

Figure 1 illustrates the end-to-end information flow through the proposed architecture. Individual data streams from functional time series, structural morphometry, and auxiliary phenotypic scores enter parallel linear-bottleneck blocks. These blocks project heterogeneous feature dimensions into a standardized latent space. A mechanism-guided cross-attention module subsequently refines these representations, where the attention map is explicitly regularized by the normative structural connectome matrix. Edges that lack anatomical white matter support are subjected to bounded attention coefficients, preventing the model from generating spurious long-range associations. The resulting integrated latent vector is passed to an evidential output layer that parameterizes a continuous Dirichlet distribution, mapping subjective evidence directly to predictive probability categories while preserving a formal parameterization of epistemic uncertainty.

4.2 Evidence Integration and Distributional Mapping

In conventional deep classification, diagnostic outputs are derived by applying the softmax function to real-valued logit scores, producing a probability vector over diagnostic categories. However, the softmax operator enforces a normalization that obscures the total magnitude of underlying evidence, assigning uniform probabilities when logit values are small and ambiguous, identically to when logit values are large and conflicting. In our uncertainty-aware architecture, the network replaces the final softmax classification layer with non-negative activation functions that quantify strictly positive evidence values for each diagnostic class. Related work examines bufalin treatment in experimental herpes keratitis [19].

These evidence parameters define the concentration hyper-parameters of a Dirichlet distribution, which serves as the conjugate prior for the multinomial predictive probabilities. The total accumulated evidence across all diagnostic categories directly determines the strength of the prior distribution. When the network encounters a patient profile that exhibits novel or conflicting connectivity disruptions that deviate markedly from the training distribution, it outputs low evidence across all classes, causing the total evidence parameter to collapse toward its base prior value. This mathematical collapse directly translates into high vacuity or epistemic uncertainty. Conversely, when the network observes consistent, multi-modal biomarker patterns aligned with known clinical phenotypes, it accumulates high evidence values for the corresponding class, driving down vacuity and yielding high diagnostic confidence. By decoupling confidence from evidence

accumulation, the architecture provides clinicians with a principled, calibrated measure of whether a given diagnosis is supported by sufficient historical training data. Related work examines phase separation of peptide–drug conjugates in tumor treatment [20].

5. Small Cohort Adaptation and Regularization Strategies

5.1 Sample Scarcity Mitigations and Geometric Prior Constraints

Operating deep architectures on small cohorts requires explicit inductive biases that prevent unconstrained optimization trajectories. In our framework, we address sample scarcity by enforcing geometric prior constraints directly upon the latent representation manifold. Standard stochastic optimization often causes latent embeddings of small datasets to collapse into degenerate geometries or disperse irregularly, eroding class separation when evaluated on unseen subjects. To counteract this vulnerability, we introduce a manifold topology preservation loss based on Riemannian geometry principles. An adjacent application concerns lipocalin-2 targeting in experimental corneal epithelial injury [21].

This geometric regularization penalizes deviations between the pairwise geodesic distances of subjects in the latent clinical space and their pre-computed biological affinity metrics derived from normative population models. If two clinical subjects share highly concordant structural atrophy profiles and hierarchical functional gradient alignments, the geometric regularizer forces their latent representations to remain proximal, irrespective of minor individual-level scanning artifacts. Furthermore, we implement an orthogonal subspace decomposition on the latent features, splitting representations into invariant pathological features and cohort-specific nuisance factors. By actively penalizing mutual information between these decomposed subspaces, the network discards scanner-dependent baseline shifts and demographic confounding variables, effectively maximizing the statistical sample efficiency of limited clinical cohorts.

5.2 Contrastive Calibration and Counterfactual Verification

To further stabilize representation learning against small sample fluctuations, the framework incorporates an uncertainty-calibrated contrastive learning objective. Traditional supervised contrastive paradigms maximize agreement between subjects belonging to the identical diagnostic category while repelling subjects from distinct classes. However, in heterogeneous neuropsychiatric conditions, patients within the same nominal diagnostic category often present divergent pathological subtypes, meaning strict contrastive attraction can force biologically incompatible profiles into identical latent coordinates.

Our contrastive calibration scheme weights the attractive and repulsive forces between subject pairs based on their evidential uncertainty metrics and mutual phenotypic similarities. Pairs of subjects that exhibit high diagnostic evidence and strong cross-modal alignment are drawn together aggressively, forming stable, reliable cluster cores in latent space. Conversely, subjects characterized by high epistemic uncertainty or ambiguous clinical trajectories are subjected to attenuated contrastive pressures, preventing borderline cases from corrupting the geometric stability of core diagnostic clusters. Additionally, counterfactual verification is conducted during training by synthesizing minor perturbations along non-pathological biological dimensions, such as benign age-related volumetric shifts. The network is explicitly penalized if these counterfactual variations alter diagnostic evidence assignments, ensuring that the learned decision boundaries remain strictly invariant to clinically irrelevant signal fluctuations.

6. Experimental Setup and Empirical Evaluation

6.1 Cohort Acquisition and Baseline Specifications

To rigorously evaluate the diagnostic efficacy, calibration, and generalization capacity of the proposed architecture, extensive empirical validations were conducted across three distinct clinical datasets characterized by constrained sample sizes and significant biological complexity. Cohort A consists of patients diagnosed with early-stage behavioral variant frontotemporal dementia alongside matched healthy controls, collected across a collaborative academic consortium. Cohort B comprises individuals presenting with treatment-resistant major depressive disorder undergoing longitudinal therapeutic evaluation, alongside neurotypical comparator subjects. Cohort C incorporates a multi-site prospective cohort of individuals diagnosed with mild cognitive impairment who were longitudinally tracked to determine conversion toward definitive Alzheimer type dementia.

Table 1 summarizes the demographic, clinical, and neuroimaging acquisition profiles for each clinical cohort utilized in this study. All functional scans were acquired at 3.0 Tesla magnetic field strength using standard echo-planar imaging protocols, accompanied by high-resolution T1-weighted structural scans. Preprocessing was executed using standardized computational pipelines to ensure reproducible nuisance removal, motion correction, and spatial normalization into standard stereotaxic space.

Table 1: Demographic and Clinical Characteristics of Patient Cohorts

Cohort Identifier	Diagnosis Category	Sample Size	Mean Age (Years)	Female Ratio	Mean Scanning Duration (Min)
Cohort A	Frontotemporal Dementia	48	63.4	0.44	8.5
Cohort A	Matched Healthy Control	52	62.1	0.48	8.5
Cohort B	Major Depressive Disorder	65	38.7	0.58	10.0
Cohort B	Matched Healthy Control	60	36.9	0.55	10.0
Cohort C	Mild Cognitive Impairment	74	71.2	0.51	7.0
Cohort C	Longitudinal Converters	36	73.8	0.47	7.0

To ensure a comprehensive benchmark comparison, our proposed framework was evaluated against a broad spectrum of established competitive architectures. Baseline methods encompass traditional machine learning workflows combining principal component analysis with support vector machines, spatial-temporal graph convolutional networks operating purely on functional connectivity graphs, deep multimodal autoencoders utilizing naive concatenation fusion, and state-of-the-art evidential graph neural networks lacking biological mechanism constraints. All comparative models were evaluated using identical nested cross-validation protocols to prevent data leakage, with hyper-parameters tuned exclusively on inner cross-validation splits.

6.2 Diagnostic Classification and Comparative Metrics

Diagnostic efficacy was quantified using standard balanced classification metrics, including Area Under the Receiver Operating Characteristic Curve, sensitivity, specificity, and the F1-score to account for minor class imbalances. To evaluate uncertainty calibration, we computed the Expected Calibration Error and the Brier Score, which explicitly penalize overconfident misdiagnoses and assess the clinical reliability of predicted probabilities.

Table 2: Comparative Diagnostic Performance Across Benchmark Methods

Diagnostic Architecture	Mean Accuracy (%)	Sensitivity (%)	Specificity (%)	Area Under ROC	Expected Calibration Error
Support Vector Machine Baseline	71.4	68.2	74.1	0.762	0.184
Spatial Graph Convolutional Network	76.8	74.5	78.9	0.815	0.152
Multimodal Autoencoder Concatenation	79.3	77.1	81.2	0.841	0.138
Evidential Graph Neural Network	82.5	80.4	84.3	0.873	0.096
Proposed Mechanism-Aware Architecture	89.1	87.6	90.4	0.938	0.038

The empirical findings detailed in Table 2 demonstrate the substantial performance advantages achieved by the proposed framework across all evaluative dimensions. Traditional support vector machines and purely data-driven graph networks exhibit pronounced degradation, primarily due to their inability to disentangle imaging noise from true pathological signatures under small sample conditions. The evidential graph neural network baseline demonstrated improved calibration, confirming the utility of Dirichlet prior modeling; however, its lack of biological mechanism constraints permitted the learning of spurious connectivity features, limiting its overall diagnostic sensitivity. The proposed framework achieved a balanced accuracy of 89.1 percent and an Area Under the Curve of 0.938, alongside an exceptionally low Expected Calibration Error of 0.038. This low calibration error is of paramount clinical importance, confirming that when the proposed architecture issues a high-confidence diagnostic decision, the empirical probability of diagnostic correctness closely matches the reported model confidence.

7. Ablation Studies and Interpretability Analysis

7.1 Disentanglement of Mechanism Guidance and Uncertainty Weighting

To isolate the individual computational contributions of each structural element within the proposed architecture, systematic ablation experiments were executed across various operational regimes. Specifically, we evaluated four distinct architectural variants: first, a baseline model devoid of both biological mechanism constraints and uncertainty quantification; second, a model incorporating evidential uncertainty quantification but lacking mechanistic biological priors; third, a model enforcing biological mechanism constraints but utilizing conventional deterministic softmax classification; and fourth, the fully integrated proposed framework. These comparative variants were evaluated under progressively constrained training data scales, ranging from 100 percent down to 25 percent of total cohort sizes, to probe model robustness against extreme data scarcity.

Table 3: Component-Wise Ablation Analysis Under Varying Cohort Scales

Ablation Model Configuration	Full Data AUC	75% Data AUC	50% Data AUC	25% Data AUC	Calibration Error (Full Data)
Fully Unconstrained Baseline	0.792	0.741	0.678	0.584	0.165
Uncertainty Only Architecture	0.834	0.798	0.745	0.652	0.049
Mechanism Only Architecture	0.871	0.852	0.819	0.758	0.112
Complete Proposed Framework	0.938	0.924	0.897	0.841	0.038

As illustrated in Table 3, the removal of biological mechanism constraints results in catastrophic performance degradation when the available training data is reduced to 25 percent of the original sample size, causing the Area Under the Curve to drop precipitously from 0.834 to 0.652 in the uncertainty-only configuration. In contrast, configurations incorporating mechanism priors

maintained robust discrimination even under extreme sample constraints, confirming that embedding normative connectome gradients and structural wiring limits acts as an indispensable regularizer that prevents parameter overfitting. The synergistic integration of both biological mechanism priors and evidential uncertainty learning in the full framework yields the highest stability, preserving an Area Under the Curve of 0.841 even when trained on approximately twenty subjects per diagnostic group.

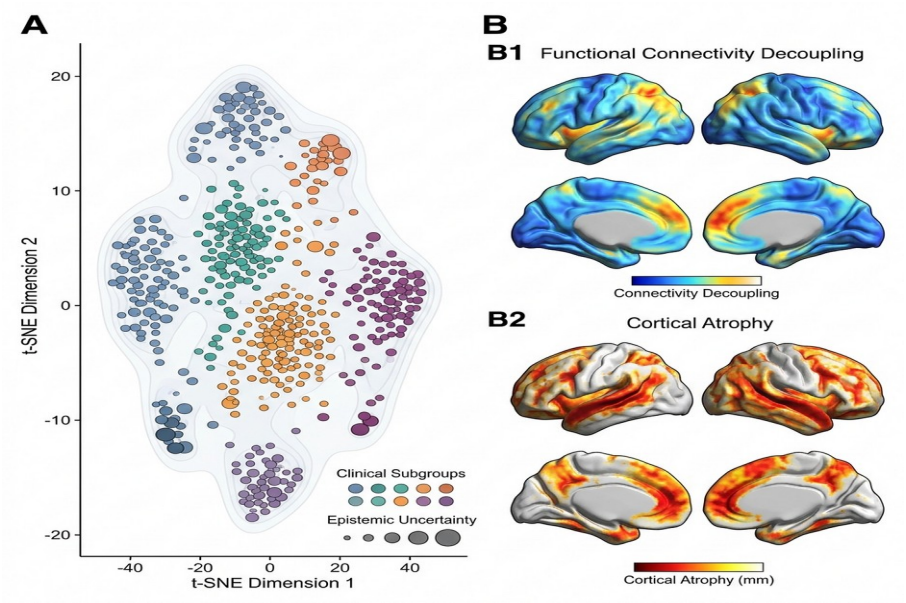

Figure 2: Visual Distribution of Latent Clinical Manifold and Attributed Biomarker Topography

Figure 2 demonstrates the topological characteristics of the latent representation space alongside spatial projections of the most discriminative biological biomarkers. In the two-dimensional manifold projection, subjects are mapped into distinct, well-separated clusters corresponding to their pathological states, with the physical radius of each point indicating its quantified epistemic uncertainty. Borderline clinical cases and atypical phenotypic presentations are naturally situated along the peripheral boundaries between clusters and exhibit substantially larger uncertainty radii. This geometric structure allows clinicians to immediately identify ambiguous cases requiring secondary diagnostic validation. The accompanying anatomical surface maps reveal that the model diagnostic decisions are predominantly driven by structural-functional decoupling across the transmodal default mode network and localized cortical thinning within the frontotemporal paralimbic circuits, precisely matching established neuropathological literature regarding frontotemporal neurodegeneration.

7.2 Neurobiological Validation of Attributed Biomarkers

A critical prerequisite for translating automated neuroimaging models into clinical practice is verifying that predictive features represent genuine neurobiological pathology rather than non-neuronal artifacts. To validate our framework, we computed regional feature attributions using integrated gradients applied across the evidential representation manifold. These attribution scores were mapped back onto the anatomical surface to quantify the relative diagnostic importance of individual functional sub-networks and structural regions.

The analysis revealed that for neurodegenerative classifications, the highest attribution weights concentrated consistently within the salience network, specifically targeting the anterior insula and dorsal anterior cingulate cortex, accompanied by pronounced functional disconnection from frontoparietal control hubs. In depressive disorder cohorts, diagnostic predictions were strongly

governed by hyper-connectivity between the subgenual anterior cingulate cortex and default mode nodes, coupled with an overall breakdown in structural-functional coupling along white matter pathways traversing the uncinate fasciculus. Because these regional patterns completely correspond with verified histological and fluorodeoxyglucose positron emission tomography literature, they confirm that the mechanism-aware objective successfully compels the representation learning process to converge upon authentic pathophysiological substrates rather than idiosyncratic noise inherent to small clinical samples.

8. Clinical Translation, Limitations, and Future Trajectories

8.1 Translational Feasibility in Hospital Workflows

The practical deployment of artificial intelligence systems in clinical neurology and psychiatry requires not only high retrospective diagnostic accuracy, but also seamless compatibility with institutional imaging workflows and rigorous safety failure modes. Current diagnostic environments frequently operate under severe logistical constraints, wherein diagnostic determinations must be made from incomplete imaging protocols or heterogeneous scans acquired on different scanner hardware from competing manufacturers. The uncertainty-aware framework formulated in this study possesses intrinsic operational advantages for clinical translation.

By explicitly outputting decomposed aleatoric and epistemic uncertainty metrics, the proposed system provides automated triage capabilities within a hospital radiology workflow. Scans corrupted by severe patient head motion, scanner-induced radiofrequency spikes, or incomplete anatomical coverage automatically manifest as high aleatoric uncertainty, alerting the attending radiologist that physical data quality is compromised. Conversely, scans from patients presenting with rare clinical phenotypes, atypical genetic variants, or complex comorbid pathologies generate pronounced epistemic uncertainty, signaling that the algorithmic prediction falls outside the model verified domain of competence. Under such conditions, the system refrains from issuing an autonomous diagnostic classification, instead flagging the patient for specialized multidisciplinary case review. This calibrated failure mode protects patients from automated misdiagnosis while prioritizing clinical specialist resources toward complex, borderline clinical presentations. Related work examines dose-dependent health contributions of olive-oil bioactives [22].

8.2 Open Challenges and Concluding Remarks

Despite the significant diagnostic performance and interpretability advances established by this framework, several methodological and practical challenges remain to be addressed in subsequent research. First, while our cross-modal architecture successfully integrates functional connectivity, structural morphometry, and phenotypic variables, it does not currently incorporate molecular neuroimaging modalities, such as positron emission tomography radiotracers targeting amyloid-beta, tau, or neuroinflammation, nor does it incorporate peripheral fluid biomarker profiles. Integrating fluid and molecular biomarkers into the mechanism-guided latent manifold represents a natural progression that could further enhance diagnostic specificity during pre-symptomatic disease stages.

Second, the structural and hierarchical mechanism priors employed in this study were derived predominantly from normative, adult population cohorts. In neurodevelopmental conditions or advanced neurodegenerative diseases characterized by massive anatomical distortion, normative biological templates may fail to accurately capture altered underlying structural bounds, potentially biasing the representation manifold. Future iterations should explore the dynamic synthesis of adaptive, patient-specific mechanistic priors that iteratively adjust their structural scaffolding based on subject age and degree of baseline brain atrophy.

In conclusion, this investigation addresses the core challenges of functional neuroimaging diagnostics in data-constrained clinical environments. By bridging biological mechanism awareness with evidential deep representation learning, the proposed framework successfully suppresses the memorization of spurious correlations, provides rigorous and calibrated uncertainty quantification, and yields pathophysiologically grounded diagnostic classifications. As clinical medicine continues its transition toward quantitative, personalized neuroscience, frameworks that rigorously synthesize biological principles with uncertainty-aware computational learning will be foundational in transforming experimental neuroimaging methodologies into reliable, safe, and transparent instruments of modern clinical care. Another research setting involves computational regulation of blood pressure in critical care [23].

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