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Alzheimer's Disease Forecasting: Evolution from Classical Methods to Multimodal Foundation Models

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ABSTRACT

This review traces the evolution of the last two decades of computational forecasting models for Alzheimer's disease progression, where the field has evolved from early linear methods to advanced multimodal and foundation models. Therefore, the paper highlights the computational importance of early disease prediction through longitudinal cohorts (e.g., ADNI, OASIS-3) and multimodal data architectures, which include structural, functional, clinical, biofluid, and genomic biomarkers. The review discusses the trajectory of predictive modelling from initial cognitive and structural pairing techniques to the deep learning era, where automated feature extraction and temporal tracking were introduced. Importantly, this review addresses a significant "Credibility gap" in recent deep learning research, which occurred due to data leakage and improper data-splitting techniques. So, the paper advocates a strict "Methodological Triad", in which subject-level data separation and external validation are essential.

Furthermore, this review analyses the state-of-the-art paradigms of 2024-2026, where Transformer-based architectures, tabular foundation models, and Agentic AI frameworks are integrating, which are shifting the field from black-box prediction to explainable clinical intelligence.

This review examines XAI techniques such as SHAP, Grad-CAM, LIME, and LRP. Along with this, Graph Neural Networks(GNNs) are discussed as a framework of a brain connectivity model, where cortical regions are nodes and their anatomical and functional connections are edges. Because of this, network-level disruptions can be captured that cannot be detected by scalar biomarkers.

Keywords: Alzheimer's Disease Forecasting; Multimodal Deep Learning; Longitudinal Cohorts; Foundation Models; Data Leakage; Methodological Triad; Agentic AI; Neuroinformatics; Decentralized Learning; Explainable AI (XAI); Graph Neural Networks; Brain Connectivity.

I. INTRODUCTION

Memory loss is often the result of gradual brain network changes over time [26], [31] Alzheimer's unfolds differently in each individual, where protein pathology and hidden inflammation symptoms begin before clinical symptoms appear, and a long delay exists between early damage and clinical decline. Some stay stable in gray zones, and recovery is also seen in rare cases. To understand the conversion of chaotic neural aging into structured progression, researchers analyze the longitudinal shifts to predict who will progress and who will remain stable [2], [4], [36].

Most past drug trials were not effective, mainly because the intervention started at a late stage. Because of this, predicting the disease became necessary so that action can be taken on time [23], [24]. This helps to identify high-risk patients so they can receive treatment at the right time. From a computational point of view, there are generally 3 main methods to solve this progression prediction [9], [12].

In this approach, the subjects are classified in 2 groups: stable ones and those whose condition changes in a defined time (usually 2 years). Tracking can be started from baseline or mid-term data. Outcome is evaluated at the end of the time period, and final labels are assigned after observing the entire timeline [9].

This technique uses time-to-event analysis, where the time to conversion is measured by continuously tracking risk signals, such as through Random Survival Forest models [8].

Continuous outcomes, like ADAS-Cog13 scores and brain ventricle volumes, are first predicted using statistical models that estimate their future values [3].

The work started with linear methods in 2008, and by 2026, it reached up to autonomous systems [1], [4],[7]. These new models depend on large global datasets, and progress is not possible without this huge amount of data. Each phase was systematically built upon previous developments.

II. LITERATURE REVIEW

An analysis of 43 sources on computational forecasting of Alzheimer's disease from 2007 to 2026 is presented, organized across three themes: disease overview, computational models and their performance in forecasting, and emerging paradigms.

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A. Alzheimer's Disease: Overview and Progression:

Alzheimer's disease (AD) is a progressive neurodegenerative disease that is a major cause of dementia cases worldwide [12],[13]. AD progression-caused by the buildup of amyloid-beta plaques and tau tangles (which lead to brain inflammation, loss of connections, and shrinkage of the cortex, especially in the hippocampus and entorhinal cortex)-begins years before symptoms appear. Disease follows a linear pathway: from Cognitively Normal to Mild Cognitive Impairment and then up to full dementia, which is measured by MMSE, ADAS-Cog13,CDR-SB scores, and structural and biofluid markers(like hippocampal volume, CSF p-tau217) [9], [14] In the past, most drugs failed because treatment started too late, so predicting AD progression early has become a major computational challenge [23], [24].

B. Computational Models and Performance in AD Forecasting:

From early methods, AD forecasting models have shifted from linear and kernel methods to transformers and foundation models [13]. In State-of-the-art approaches, NeuroNetAD achieved about 98.68% multiclass accuracy [10], while SMMT achieved about 97.05% accuracy with around 40.4% less energy use [5]. BrainFound was trained on 49,000 brain scans and achieved the highest zero-shot AUROC in low-data settings [6]. MAGNETAD achieved a concordance index of 0.858 for predicting MCI-to-AD conversion time [8] , and L2C-TabPFN achieved an MAE of 0.1577 for predicting ventricular volume using structured clinical data [3]. Together, these approaches show that the field is now moving from simple models to multimodal and time-based forecasting systems [18].

C. Emerging Paradigms

In AD models, XAI approaches like SHAP, Grad-CAM, and LIME are used, which consistently extract important predictors like hippocampus volume, ADAS-Cog13, CSF markers, and focus attention on the temporal pole and entorhinal cortex [14], [15]. Federated Learning enables privacy-preserving multi-site training by encrypted weight sharing instead of raw patient data [11], [38] and GANs generate synthetic scan data to solve the problem of limited data[22] Graph Neural Networks model brain regions as nodes and connections as edges to study network problems that cannot be seen with simple biomarkers[26], [27]. Recent approaches use Multimodal LLMs (like AD-LLaVA-3D), which moves beyond black-box models toward clinical intelligence [21].

III. RESEARCH GAP AND CHALLENGES

Even after 20 years of development, studies show that there are 5 main problems in computational AD forecasting that limit the clinical use, reliability, and fairness of models:

1) ***Widespread data leakage and lack of subject-level validation:***
   Many studies report high accuracy because they use a visit-level split in longitudinal data instead of a subject-level split. This causes "information leakage", because multiple visits of the same patient come in both train and test, which increases the accuracy artificially. When the subject-level split is applied correctly, then accuracy drops from 94% to 66%. Even after knowing this problem, many research works do not follow the Methodological Triad [23], [24].

2) ***Limited external validation across diverse cohorts:***
   Almost every AD forecasting model is trained and validated on the ADNI dataset, which is mainly developed from the high-education non-Hispanic white population. So, the validation is very rare on diverse datasets like OASIS-3, NACC, and AIBL, which reduces the generalization ability of models across different demographics, scanners, and imaging biases [18], [38].

3) ***Disconnection between molecular biomarkers and imaging-based models:*** Even after valuable, fluid biomarkers (like plasma p-tau217) and genetic biomarkers(like APOE4 status) are not used in the deep learning pipelines properly [16]. Also, there is no single model that can predict disease progression by fully integrating molecular, genetic, and neuroimaging data [18].

4) ***Absence of prospectively validated Agentic AI and Digital Twin models:*** New methods like AD-LLaVA-3D and neural ODE simulators perform better on retrospective data, but they are not tested in clinical trials. These models depend on continuous wearable and EHR data, which are not usually available in standard clinics. Due to this, there is a significant gap between lab results and real clinical practice [21].

5) ***Insufficient standardization of XAI evaluation and regulatory compliance:*** In XAI, there is a lot of work done on technical fidelity, and research is mostly focused on how XAI affects the decisions of doctors. There is no standard benchmark defined for neuroimaging AI explanations. Regulations such as EU AI act have not set any requirements for AD diagnostic systems [25].

Because of these problems, future work should focus on clear rules, better testing of explanations, diverse data, combining molecular and imaging data, and proper clinical testing so that AD prediction can be used in real practice.

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IV. DETAILED TECHNICAL ANALYSIS

A. Data infrastructure: the scaffolding of neuroinformatics

TABLE I:
MULTI-MODAL DATA ARCHITECTURE

Modality	Specific Biomarkers	Computational Role
Structural [7], [9]	T1-weighted MRI; cortical thickness; ventricular volume.	Quantifies macro-scale gray matter atrophy and irreversible neurodegeneration.
Functional [29], [31]	FDG-PET; AV45-PET; Tau-PET radioligands.	Detects metabolic hypofunction and protein accumulation years before structural decay.
Clinical [9]	MMSE; ADAS-Cog13; CDR-SB; FAQ.	Provides objective measures of cognitive decline; used as both input features and predictive targets.
Biofluid [9], [14]	CSF (Aβ42, tau) and plasma (p-tau217).	Provides molecular-level signatures; p-tau217 acts as a specific "Alzheimer's clock."
Genomics [16], [27]	SNPs; APOEε4 allele; mRNA expression.	Establishes immutable genetic risk and enables subtyping via Polygenic Risk Scores (PRS).

Mathematical modeling of neurodegenerative velocity fundamentally depends on high-quality longitudinal datasets [2], [9]. High-depth repositories allow disease progression to model in the form of dynamic velocity, instead of relying on static snapshots [4], [32].

TABLE II:
PRIMARY LONGITUDINAL COHORTS AND GLOBAL DATASETS

Dataset Name	Primary Characteristics	Strategic Utility in ML Validation
ADNI (1, GO, 2, 3, 4) [40]	Public-private partnership tracking subjects longitudinally for up to 10 years, including ADNI-GO/2 (early/lateMCI subdivision) and ADNI4 (remote and underrepresented cohorts).	Considered the gold standard for model training; provides the required longitudinal depth for multi-year forecasting and time-to-event analysis.
OASIS-3 [41]	A retrospective dataset comprising 1,379 subjects and 2,842 MRI sessions collected over a 30-year time span.	Indispensable for validating long-term prognostic models and assessing cross-dataset generalization.
NACC [42]	A large-scale repository compiled by ADRCs, including tens of thousands of participants with deep phenotyping data	Vital for evaluating algorithmic robustness against site-specific imaging bias and demographic heterogeneity.
AIB [43]	A longitudinal Australian cohort featuring 144+ follow-up data points.	Crucial for validating blood-based biomarkers, multi-omics integration, and amyloid-PET tracking.

B. Genesis of modeling: pioneering approaches (2007–2013)

Early researchers relied on statistical methods applied to cognitive scores to characterize disease progression, and it was initially unclear whether neuroimaging could meaningfully improve accuracy beyond psychometric assessments. Fleisher et al. [7] set an initial benchmark weight held by cognitive scores; still, the prediction accuracy pushed up to 78.8% by pairing the scores with structural markers like right entorhinal cortex thickness and hippocampal volume. Subsequent findings confirmed that structural brain measurements, particularly hippocampal volume and entorhinal cortex thickness, could predict cognitive decline well before overt clinical symptoms appeared.

Initially the researchers faced the problem which was later called "concatenation flaw", incorrectly combining features led to increased dimensionality and slowed progress. Zhang and team [20] proposed a multimodal kernel combination method using a linear SVM in 2011, where MRI, FDG-PET, and CSF biomarkers were each mapped into separate kernel spaces and combined into a single mixed kernel. Modality weights were optimized via cross-validation grid search under the constraint that their sum equals 1. All features were manually extracted from 93 pre-defined anatomical ROIs — no automatic feature learning was involved— and the method achieved a classification accuracy of 93.2% for AD versus healthy controls.

C. The Deep Learning Era and The TADPOLE Standardization (2014–2020)

Around 2015, deep learning began replacing classical kernel and SVM-based approaches, marking a fundamental methodological break [12], [24]. Unlike the previous era, which depended on manually extracted features from pre-defined anatomical regions [20], deep neural networks automatically extracted hierarchical representations directly from raw 3D volumetric data, eliminating the need for expert-guided feature engineering.

Later on, researchers focused on temporal modeling because Alzheimer's worsens over time, and a single snapshot does not reflect the progression speed. Instead of simple stacking, recurrent networks like LSTMs and GRUs tracked the pattern across the longitudinal visits, which led to capturing the current state along with the rate of change. In 2019, Cui and team showed the improved performance by achieving 0.750 AUC by repeated scans and test results [2].

A Major shift happened during the Tadpole Challenge, where models had to predict the long-term outcomes without time limits [9]. Surprisingly, the winning system was "Frog" based on the XGBoost instead of deep nets. The reason for its success was the L2C (Longitudinal-to-

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Cross-sectional) technique, in that irregular patient histories were converted to fixed-sized data chunks [3], [9]. This showed that deep learning is strong in image, but tree-based methods still dominate in handling the irregular and incomplete medical records.

D. The credibility gap: identifying research gaps and vulnerabilities

When deep learning systems started reporting an accuracy above 95%, this raised doubts about the reliability. Klingenberg and Fristed highlighted the flaws in the data splitting process, where the results were artificially inflated by hidden data leakage.

In longitudinal studies, a patient gives multiple brain scans over the years. If a data split occurs based on the slices or visits, then instead of actual disease patterns, the model learns the individual skull features or scanner-specific artifacts. True validation is only reported when subject-level splitting is done. After this proper separation, the performance significantly drops from an inflated 94% to realistic 66%. This clears that the high accuracy reported was due to personal traits, not by real generalization [23], [24].

To ensure clinical readiness, the field adopted a structured framework, formalized as "Methodological Triad":

1) In this approach, each subject appears in just one part of the study. Training and test data are kept separately, where no individual is repeated in both sets. Each subject

is assigned only to one group, ensuring subject-level separation across the dataset [12], [23].

2) Validation is necessary through external validation, where results are verified on independent cohorts such as OASIS-3, AIBL, and NACC [18], [38].

3) By statistical methods, age and sex differences are adjusted, and scanner field strength is also included in the adjustments. The interpretation of results is influenced by these individual factors [6], [38].

Reviewing 2024–2026 papers against these criteria, compliance remains uneven: NeuroNet-AD[10] and SMMT[5] lack external cohort validation; BrainFound[6] partially satisfies this through cross-dataset generalization; MAGNET-AD[8] applies subject-level splitting but omits covariate corrections; L2C-TabPFN[3] is validated within ADNI[40] only. Explicit reporting of all three Triad criteria should become standard practice [23], [24].

E. State-of-the-art paradigms (2024–2026): transformers and foundation models

Current research is now shifted towards Transformer-based architectures that are designed to handle the extreme multi-modality and long-range temporal dependencies [17].

TABLE III:
COMPARATIVE ANALYSIS OF STATE-OF-THE-ART ARCHITECTURES (2025–2026)

Model Name	Core Innovation	Key Metrics	Clinical Advantage
NeuroNet-AD (2025) [10]	Meta Guided Cross Attention (MGCA)	98.68% Multiclass Accuracy	Perfectly aligns biological imaging with genetic and demographic risk factors.
L2C-TabPFN (2025) [3]	L2C Transform + Tabular Foundation Model	MAE: 0.1577 (Ventricular Vol)	Superior for forecasting physical brain atrophy trajectories over time.
SMMT (2025) [5]	Cluster-Based Sparse Multi-Modal Transformer	97.05% Accuracy; -40.4% Energy	Resource-aware deployment; handles missing modalities (e.g., missing PET).
MAGNET-AD (2025) [8]	Spatiotemporal GNN (STGNN)	0.858 C-index	Excels at predicting the exact time of conversion (PACC/Conversion time).
BrainFound (2026) [6]	BrainIAC core (pre-trained on 49k scans)	Highest AUROC (Zero-shot)	Unmatched generalization in label-scarce environments via self-supervision.

Note: Models address distinct tasks- multiclass classification, volume regression, survival analysis, and zero-shot generalization. And therefore, report incomparable metrics so cross-row numerical comparison is not meaningful.

Going beyond accuracy, Field is transitioning towards Multimodal LLM frameworks, like AD-LLaVA-3D [1]. This system interprets 3D volumetric sequences in video form and captures the continuous temporal dynamics to generate natural language clinical reports. So, the paradigm is shifting from "black-box" prediction to explainable clinical intelligence[14].

F. Emerging frontiers: privacy, synthesis, and decentralization

While developing better prediction methods, researchers faced some real challenges, like fragmented data systems and privacy concerns. To address these issues, three key approaches emerged. First, shared learning where models are trained without any data transfer[38]. Second, privacy-preserving models that work on limited or hidden information. Third, intelligent imputation techniques that reconstruct the incomplete data [22].

In 2026, synthetic image generation systems like pg-GAN create realistic brain scans from population-level patterns [22]. This reconstructs the missing follow-up scans effectively. With these variations of different scanners, like 1.5T and 3T machines, also harmonize [38]. Layered learning architectures adapt temporal outputs smoothly, where population trends guide the formation of detailed patterns [4].

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Model training across hospitals now occurs locally. Instead of sensitive data transfer, each site locally updates the model and only shares the encrypted summaries [11], [38]. Due to this system, the results are comparable to centralized systems, whereas raw data remains in the original site. This maintains the privacy, and the collective model knowledge becomes stronger, ensuring global utility without compromising individual security.

Edge-based systems, which operate near the data source, efficiently perform the health signal computations on specialized chips. These models achieve 89% precision and generate the results in about 0.061 seconds. They consume low power (35–39 mW). By this approach, dependency on remote servers reduces, enabling fast and energy-efficient local processing of physiological markers.

G. Explainable ai (xai) towards clinical translation

Predictive accuracy is only not sufficient for clinical use; models also need to explain why it took this decision. XAI solves this problem by making the model behaviour transparent and auditable. Methods are divided in two types, post-hoc techniques which explain black-box models after training, and ante-hoc designs which are interpretable from starting. SHAP, LIME, Grad-CAM, and LRP AD are the most used post-hoc tools in the literature.

i. Feature Attribution and Spatial Saliency

In tabular models, top predictors of Alzheimer's are consistently identified through SHAP, such as ADAS-Cog13, MMSE, CSF biomarkers (Aβ -42, p-tau), and hippocampal volume [14]. Abdelaziz et al. showed that SHAP based selected features transfer effectively from ADNI to OASIS-3 datasets, which suggests simple harmonization methods.

In Gene expression analysis, SHAP classifiers correlate outputs with known AD molecular pathways [16]. Also, Grad-CAM and LRP heatmaps converge on the regions such as temporal pole, hippocampus, entorhinal cortex,

parahippocampal gyrus, which are affected by AD pathology.

Transformer-based models (ViT/BEiT) show high classification performance and automatically generate accurate attention maps. Saqib et al. [19] achieved clinical level diagnostic performance with LIME, while Anzum et al. [17] combined MRI and RNA data to achieve disease stage classification with 99% accuracy.

ii. Progression Modelling, Challenges, and Regulation

Longitudinal prediction using counterfactual explanations helps the clinicians to query potential biomarker changes delaying MCI to AD conversion [21]. Based on the success of GAMs, EBMs and tree ensembles with LIME and SHAP post hoc explanation, these methods will be applied on tabular representation of data from cardiac imaging and clinical data [20], [28]. Of the 46 PET-MRI imaging studies evaluated, eight that included Shapley values confirmed attention on amyloid- and tau-sensitive areas [29]. There are still many challenges: the computational cost of SHAP for 3-D CNNs, the spatial dispersion of Grad-CAM activations, and the lack of a standardised benchmark for explanation quality. The European Union Artificial Intelligence Act is a new regulatory pressure that poses greater urgency on the standardisation of evaluation. Increased use of XAI in speech-based cognitive decline detection indicates a growing recognition that explainability is now a must-have [25].

H. Graph neural networks for brain connectivity modelling

Traditional brain imaging treats regions as isolated and ignores the topological organization of neural circuits. GNNs solve this problem by modeling the regions as nodes, and their anatomical or functional connections as edges. Because of this, models can learn network-level disruptions that cannot detect scalar features[27].

i. Graph Construction and Classification

There are two common approaches to building GNNs. In subject-level graphs, each ROI is treated as a node, where edges are based on DTI or rs-fMRI connectivity. While in population graphs, subjects are nodes, not ROI; here, edges represent non-imaging similarities(like demography) or imaging similarities(like brain connectivity networks). Lei et al. [38] focused on improving robustness in the presence of noisy data, and for this, local weighted clustering is used to strengthen the structural features. At the classification level, Wang et al. [31] treated metabolic-functional coupling indices of ROI as a graph and applied GCN; due to this, AUC=0.992 was achieved for SCD detection. The DEG-BRIN-GCN model used transcriptomics data from 19 brain regions to identify 329 differentially expressed genes that may be involved in AD progression. GNN-based brain age estimation of Gao et al. showed a significant age difference between the hippocampus of Alzheimer's patients and controls, which was also significant in the parahippocampal gyrus and amygdala, and was consistent with previous studies [27].

ii. Temporal GNNs, Multimodal Fusion, and Challenges

Static GNNs are not effective for AD because they cannot capture temporal variability. To solve this time-based extension is used, where graph representations are coupled with recurrent layers or temporal message passing is applied [32]. A spatiotemporal GNN called MAGNET-AD

[8] achieves 0.858 concordance index while predicting GNN MCI-to-AD conversion time. Zhang et al. [32] made longitudinal heatmaps by improving spatiotemporal GCN with Grad-CAM, which show which regions are

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becoming more discriminative near the time of conversion.

For MCI and AD separation, two feature extraction channels and population-level cluster pooling are used(Prasath & Sumathi). Embedding DTI and rs-fMRI in a graph variational autoencoder led to better subtyping than single-modality approaches [34]. Wiener, Szeged, and Graovac-Ghorbani network invariants were used as interpretable graph-features, which maintained an average accuracy of 89.45% and a good precision-recall tradeoff [35]. Attention-based GCN identified the putamen and palladium as key discriminating regions in 3-class classification(CN, MCI, AD) [30], [37].

V. CONCLUSION

Earlier Alzheimer's research mainly depended on basic statistical patterns, but now multi-modal intelligent functions as active decision support tools. Instead of traditional mathematical stacking, researchers are developing temporal-spatial networks that map the changes in the brain with time. By jointly linking the space and timing, these architectures capture the subtle patterns which earlier used to miss out. Now it's essential to strictly follow three core methodological rules, missing out any can lead to misleading results. Explainable AI techniques such as SHAP, Grad-CAM and LIME have strengthened the clinical trust by linking predictions with neuroanatomically meaningful regions, while Graph Neural Networks have improved the field by treating brain regions as connected nodes, because of this network-level disruptions are captured that cannot reveal biomarker methods. Recent systems take autonomous decisions in the testing phase, acting more like advisors than calculators. This transition has the potential to make early dementia detection routine, enabling timely clinical intervention before severe neurodegeneration.

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