

BENG 485: Fundamentals of Neuroimaging
Professor Fahmeed Hyder

By submitting this essay, I attest that it is my own work, completed in accordance with University regulations. —Vasilisa Malenkiy

An Optimal Multimodal Biomarker Pipeline for the Classification and Diagnosis of Alzheimer's Disease
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Abstract

Accurate and early diagnosis of Alzheimer's disease (AD) is challenging due to its complex and heterogeneous pathology. Incorporating multiple biomarkers - including hippocampal atrophy (sMRI), amyloid- β (AV45-PiB-PET) and tau tangles (FTC-PET, SNP, & CSF), and temporoparietal hypometabolism (FDG-PET) - alongside genetic (APOE ϵ 4), demographic (sex, age), and clinical data within machine-learning-based classification models yields the highest diagnostic accuracy. This multimodal approach enables early detection and differentiation of AD from normal cognition (NC), mild cognitive impairment (MCI), and non-Alzheimer's disease dementia (nADD). Evidence supports the inclusion of the broadest possible set of neuroimaging and clinical data for early-stage diagnosis, while sMRI and clinical data alone may suffice in later-stages. Beyond diagnosis, multimodal neuroimaging may guide the development and assessment of emerging AD therapies, such as 40 Hz gamma-wave stimulation. Ultimately, the optimal AD diagnostic pipeline adapts its neuroimaging modality selection to each disease stage, incorporating complementary demographic and clinical data points for precise and timely AD differentiation and diagnosis.

1. Introduction

An increasingly common and devastating neurodegenerative disorder, Alzheimer's disease (AD) impacts millions worldwide, yet its early detection and accurate diagnosis continuously challenge the medical community. Misdiagnosis and delayed detection reduce the

efficacy of treatments, worsen patient and caretaker outcomes, and contribute to a growing global disease burden projected to reach \$2 trillion by 2030 (Venugopalan et al. 2021). The current diagnostic criteria for AD consists of three characteristic biomarkers: structural hippocampal atrophy, cortical amyloid- β depositions, and temporo-parietal hypometabolism (Chételat et al. 2018, Zhang et al. 2011). However, current diagnostic approaches often rely on singular neuroimaging modalities which fail to fully capture the complicated pathology of AD.

Multimodal neuroimaging combines multiple data sources to enhance diagnostic precision, accuracy, and the ability to distinguish AD from other neurodegenerative dementias, which may present similarly to AD from a uni-modal perspective, but exhibit observable distinctions from a multimodal point of view. Multimodal neuroimaging significantly outperforms unimodal imaging approaches in classifying Alzheimer's Disease (AD) and differentiating it from cases of normal cognition (NC), mild cognitive impairment (MCI), and non-Alzheimer's Disease Dementia (nADD). Classification models striving to achieve the highest diagnostic accuracy must integrate a wide variety of neuroimaging techniques and clinical data points including structural MRI (sMRI), PET imaging (with PiB, AV45, FTC, and FDG radiotracers), cerebrospinal fluid (CSF) biomarkers, and single nucleotide polymorphism (SNP) data. Furthermore, the best models employ deep learning techniques such as 3D convolutional neural networks (3DCNN) and enhanced transformers to fuse the multimodal neuroimaging data into a comprehensive AD classification scheme. Given the additive nature of neuroimaging biomarkers (Chételat et al. 2018), the most robust diagnostic pipeline for AD takes advantage of multiple modalities for early diagnosis, while later-stage classification, in efforts to avoid subjecting patients to unnecessary tests, may prioritize sMRI and clinical data alone due to the more pronounced structural atrophy in advanced AD. However, further intel into the refinement of sMRI-based

classification methods to reliably distinguish severe AD-related atrophy from nADD is needed to ensure accurate differential diagnosis in the later stages of AD disease progression.

2. Background

2.1 Alzheimer's Disease Biomarkers

Three different biomarkers of AD provide distinct yet complementary information for its accurate and differential diagnosis, distinguishing it from similar neurodegenerative conditions including MCI and nADD. **Hippocampal atrophy** is a foundational biomarker of AD but lacks specificity, also being observed in many other neurodegenerative conditions including frontotemporal dementia (FTD), vascular dementia (VD), Lewy body dementia (LBD), and even normal aging (Chételat et al. 2018). Hippocampal subfield volumetry, performed with a high-resolution proton density MRI, uncovers distinct, differential patterns of hippocampal subfield atrophy in the subiculum, CA1-4, and dentate gyrus across different neurodegenerative conditions, providing a criterion upon which to distinguish AD from MCI, SD, and normal aging (Chételat et al. 2018).

In addition to hippocampal atrophy, **amyloid- β ($A\beta$) deposition and tau neurofibrillary tangles** are two fundamental pathophysiological markers of AD. Intracellular neurofibrillary tangles, composed of hyperphosphorylated tau proteins, quantified through cerebrospinal fluid collection, and extracellular amyloid plaques, detected via amyloid PET, are key indicators of AD pathology.

However, the exact relationship between $A\beta$ accumulation, tau pathology, and neurodegeneration remains complex (Chételat et al. 2018). Lastly, **temporoparietal**

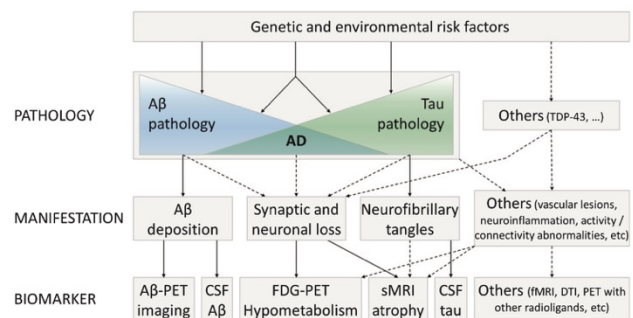


Figure 1: Relationship between AD pathology, manifestation, and biomarkers detected with imaging and clinical data outlined in section 2.2 (Chételat et al. 2018)

hypometabolism detected via FDG-PET is associated with the onset and progression of AD. Particularly, a declining cerebral metabolic rate of glucose (CMR_{glc}) in the temporo-parietal lobes, critical to memory and cognition, correlates with neuronal death and cognitive decline. FDG-PET studies consistently demonstrate reduced glucose uptake in individuals with MCI, early AD, and in those with genetic risk factors for AD (Raut et al., 2019). Despite advances in identifying AD pathology, the relationships between its three biomarkers - structural atrophy, $A\beta$ pathology, and hypometabolism - remain complex. While each biomarker contributes to AD diagnosis, none offer definitive results alone. Neuroimaging techniques enable the detection and characterization of these biomarkers forming the foundation for a robust multimodal classification pipeline that captures the full spectrum of AD pathology.

2.2 Neuroimaging Techniques for AD Biomarker Identification

2.2.1 MRI

Magnetic resonance imaging (MRI) is rooted in Nuclear Magnetic Resonance (NMR), a technique which detects electromagnetic radiation emitted by atomic nuclei probed by radiofrequency pulses (RF) in an external magnetic field. MRI reconstructs high resolution images of neural structures by measuring the relaxation of the bulk magnetization vector (M) of proton (1H) signals in water. T1-weighted images track longitudinal M relaxation times, reflecting the time it takes protons to realign with the external magnetic field while T2-weighted images measure transverse relaxation time, or the time for spinning protons to lose phase coherence in the transverse plane. **Structural MRI (sMRI)** generates images to examine the morphology, size, and topography of different brain structures. T1-weighted sMRI optimally distinguishes gray from white matter, measuring changes in volumes and cortical thickness in the assessment of neurodegeneration. T2-weighted images provide better measures of water content

in various disease pathologies (Preston 2016). For AD, structural MRI is well-suited to evaluate areas of brain atrophy and degeneration, particularly in hippocampal subfields and structures.

2.2.2 PET

Positron emission tomography (PET) tracks metabolic activity with radioactive tracers introduced intravenously or through inhalation. PET tracers accumulate in regions of high metabolic activity, granting insights into AD pathophysiology. Key AD radiotracers include PiB-PET (Pittsburgh compound B) and AV45-PET (florbetapir AV45) for amyloid detection, FTC-PET (flortaucipir) for measurements of tau accumulation (Mares et al. 2024), and FDG-PET (fluorodeoxyglucose) for assessing glucose metabolism (Castellano et al. 2024). Enabling observations of amyloid deposition, tau pathology, and hypometabolism, PET provides a route to identifying the characteristic deficits of AD, with PET studies noting increased A β deposition and reduced glucose metabolism particularly in the parietal, posterior, and temporal regions of AD patients (Zhang et al. 2011). Increased tau deposition is observed in the temporal, frontal, parietal, and occipital regions of AD APOE ϵ 4 carriers (Mares et al. 2024).

2.2.3 CSF Biomarkers & Genetic Factors

Lastly, the Apolipoprotein E (APOE) ϵ 4 allele is the strongest known genetic risk factor for AD, exhibiting a modulatory influence on the other biomarkers. Studies using sMRI, FDG-PET, and Florbetapir-PET have demonstrated accelerated A β accumulation with age in APOE ϵ 4 carriers, but not in noncarriers (Chételat et al. 2018). Additionally, APOE ϵ 4 levels and tau concentrations may be quantified in cerebrospinal fluid (CSF) and FTC-PET measurements, complementing neuroimaging techniques for enhanced accuracy in AD diagnosis. In contrast, the ϵ 2 allele confers protection against AD pathology by attenuating A β deposition and neurotoxicity in carriers, also being associated with reduced tau pathology in A β -positive individuals (Li et al. 2020). A class of AD treatments support the conversion of APOE ϵ 4 to ϵ 2 via CRISPR (Li et al.

2020). The widely common APOE $\epsilon 3$ allele is considered to have a neutral effect on the risk of AD development. Further complexity emerges when considering the heterogeneity of APOE $\epsilon 4$'s influence on common AD biomarkers. These effects vary across age, sex, genetic carrier status, and disease state (CN, MCI, and AD) (Mares et al. 2024). Integrating multimodal data to track regional and group-level differences enables more accurate predictions of conversion from CN to MCI or AD in both APOE $\epsilon 4$ carriers and non-carriers. Understanding how APOE $\epsilon 4$ carriers and non-carriers differ in their pathological presentation at various stages of the AD continuum promotes early detection and personalized interventions.

sMRI, FDG and amyloid (PiB/AV45) + tau (FTC) PET, fMRI, and CSF analysis enable the detection of AD biomarkers - including hippocampal atrophy, A β deposition, and temporoparietal hypometabolism - along with genetic risk factors like APOE $\epsilon 4$. While each imaging modality provides detailed insights into each biomarker, relying on a single imaging technique overlooks the full scope of AD progression and prohibits differentiation from NC, MCI, and nADD. A multimodal approach improves diagnostic accuracy, early detection, and disease monitoring by integrating the complementary information provided by each biomarker. A proposed multimodal neuroimaging pipeline based on machine learning optimizes this balance, addressing both the use of multiple biomarkers and genetic data for early AD diagnosis and differentiation, and minimizing unnecessary tests in later stages of the disease's progression.

3. Proposing an Optimal Multimodal Neuroimaging Pipeline for Diagnosis and Monitoring of AD

A collection of neuroimaging research studies conducted over the years has demonstrated the increasingly superior nature of multimodal approaches over single-modality methods in AD

diagnosis and its differentiation from cases of NC, MCI, and nADD. Across all AD classification pipelines, models incorporating multimodal data consistently outperformed uni-modal approaches relying on single imaging, clinical, or genetic data types.

For instance, Zhang et al. (2011) employed a multiple-kernel support vector machine (SVM) to fuse MRI, FDG-PET, and CSF biomarkers, reaching a 93.2% accuracy in distinguishing AD from healthy controls and 91.5% in predicting MCI-to-AD

conversion (Zhang et al. 2011). Expanding on his foundational fusion approach, Tang et al. (2024) implemented a 3DCNN equipped with an enhanced transformer to extract key deep feature representations of AD from sMRI and PET scans, improving classification accuracy to 98.1% on the Alzheimer’s Disease Neuroimaging Initiative (ADNI) dataset. The transition from a single-modality approach to a multimodal one led to a 6.19% improvement over sMRI alone and a 10.96% improvement for PET (Tang et al. 2024). Several other studies also reported improved classification accuracy in fusion-based approaches including combining MRI, SNPs, and electronic health records (EHR) in a deep-learning framework (DLF) (Venugopalan et al. 2021); MRI and non-imaging data in a DLF in multiple sequential diagnostic steps (Qiu et al. 2022); and 2D and 3D T1-weighted MRI along with amyloid PiB and AV45-PET data in a CNN (Castellano et al. 2024). Given the overwhelming improvement of AD classification accuracy and differentiation from NC, MCI, and nADD across a series of multimodal studies, any successful AD classification pipeline must include sMRI and PiB-AV45-PET neuroimaging, complemented

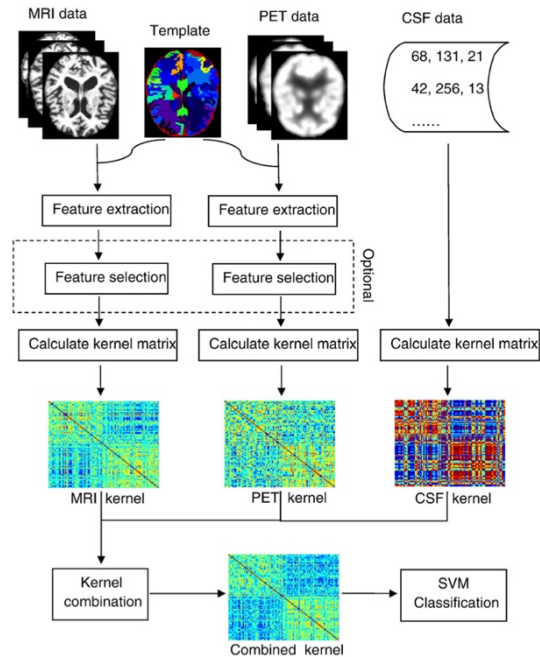


Figure 2: Schematic illustration of multimodal data fusion and classification pipeline (Zhang et al. 2011)

by clinical data like CSF and SNP markers to improve classification accuracy and enable the early prediction and differential diagnosis of various stages of AD-related cognitive decline. Additionally, the success of Venugopalan et al. (2021) and Tang et al. (2024) suggests that the optimal pipeline harnesses deep-learning by employing 3DCNNs equipped with enhanced transformers to fuse neuroimaging data across multiple modalities and extract key, common neuroimaging features for AD classification.

However, even the most robust multimodal pipelines risk misclassification without accounting for the nuances of a key biological factor - the APOE $\epsilon 4$ allele. APOE $\epsilon 4$ carrier status drives measurable heterogeneity in the regional distributions and concentrations of AD biomarkers - differences that vary not only between carriers and non-carriers, but also across sex, age, and disease progression - calling for multimodal neuroimaging approaches tailored to these intersecting sources of variation. Combining multiple imaging modalities as before, with a focus on genotype, including florbetapir-PET ($A\beta$), flortaucipir-PET (tau), structural MRI (volume), and FDG-PET (glucose metabolism) enables critical analysis of APOE $\epsilon 4$'s impact across the AD continuum, with stratification by genotype, disease stage, age, and sex.

Mares et al. (2024) demonstrated that APOE $\epsilon 4$ carrier status correlates with increased $A\beta$ accumulation across CN, MCI, and AD, with widespread deposition in the temporal, frontal, parietal, and cingulate cortices and precuneus, nucleus accumbens, and insula. No significant age or sex-specific regional or level differences arise in $A\beta$ between $\epsilon 4$ carriers and non-carriers, except for more affected regions in CN female carriers and larger effect sizes in female MCI carriers. Additionally, $A\beta$ levels significantly increased in the anterior cingulate cortex, nucleus accumbens, and superior frontal cortex of CN carriers who later converted to MCI/AD (Mares et al. 2024). Tau pathology in APOE $\epsilon 4$ progresses with disease advancement, beginning in the amygdala and entorhinal cortex (CN), spreading to the temporal, frontal, and parietal cortices in

MCI/AD, with AD showing most the widespread involvement. Female CN carriers show more tau in the entorhinal cortex and amygdala and younger carriers suffer greater tau burden than older ones, especially during MCI. Non-carrier converters display tau increases in the amygdala and temporal cortex while carrier converters show in broader regions (Mares et al. 2024).

APOE $\epsilon 4$ carriers exhibit downregulated glucose metabolism in the posterior cingulate, angular gyrus, inferior temporal gyrus across CN, MCI, and AD groups. Female MCI $\epsilon 4$ carriers show greater reductions in FDG signal than male counterparts. Younger and older $\epsilon 4$ carriers show decreased FDG uptake compared to non-carriers and glucose hypometabolism occurs across both carrier and non-carrier converters (Mares et al. 2024). Lastly, APOE $\epsilon 4$ carriers in MCI and AD exhibit atrophy in specific regions, including the hippocampus, amygdala, entorhinal cortex, fusiform gyrus, middle temporal gyrus, and inferior parietal cortex. Female MCI carriers show more widespread atrophy while male carriers show primarily left hippocampal atrophy. Younger carriers display prominent hippocampal atrophy which later progresses to the entorhinal cortex and other regions in older MCI carriers (Mares et al. 2024).

Taken together, APOE $\epsilon 4$ exhibits a differential effect on AD pathology producing distinct patterns of amyloid deposition, tau pathology, glucose hypometabolism, and structural atrophy, its impact modulated by sex, age, and disease stage (CN, MCI, AD). This heterogeneity is evident not only in carriers and non-carriers, but also within carrier subgroups. These effects show up differently across the AD continuum highlighting the temporal evolution of AD biomarkers. Thus, a single-modality approach, or one that

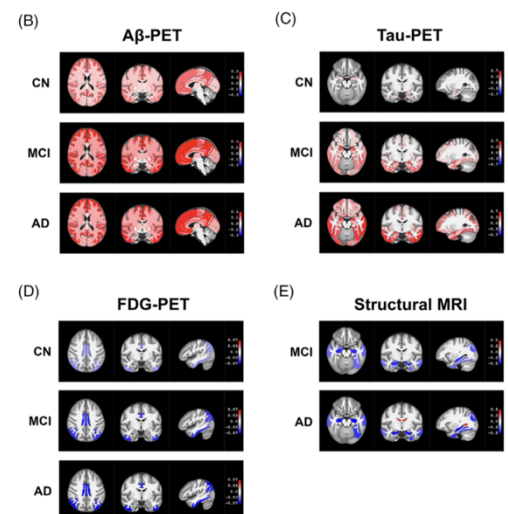


Figure 3: APOE $\epsilon 4$ associated differences by diagnostic group. Red (upregulated in carriers) and blue (downregulated in carriers) represent regions w/ significantly different biomarker levels between carriers and noncarriers. Translucency corresponds with the magnitude of statistical difference between groups (Mares et al. 2024).

overlooks the paramount importance of APOE ϵ 4, risks missing key regional or demographic patterns in diagnosis. A multimodal imaging strategy - integrating A β -PET, FTC-PET, FDG-PET, and sMRI - remains optimal for AD classification. However, incorporating granular clinical stratification by APOE ϵ 4 genotype, age, sex, and disease stage into the classification architecture (via. machine learning) further enhances diagnostic accuracy.

In designing the optimal multimodal approach, one must also consider the relative strengths of different imaging techniques, as well as the degree of their informativity at various stages of AD progression. In earlier stages of AD progression, a successful multimodal pipeline not only includes sMRI to monitor regions of hippocampal atrophy, PiB and AV-45 PET to track A β deposition, FTC-PET, CSF, and SNP biomarkers to identify the presence of APOE ϵ 4, and clinical data, but additionally, the inclusion of FDG-PET for insights into regions of hypometabolism that enable successful differential diagnosis. In particular, an sMRI, FDG-PET, and florbetapir-PET imaging study revealed that atrophy and hypometabolism exhibit an additive, rather than sequential relationship in AD and since cognitively normal elderly exhibit either neurodegeneration or A β deposition, but not both, neuroimaging biomarkers function as partly independent evidences which each increase the likelihood of AD development (Chételat et al. 2018). Thus, for early stages where AD may be more readily mistaken for other forms of neurodegenerative decline (e.g. NC w/ APOE ϵ 4 carrier status, MCI, nADD) a fully robust multimodal pipeline includes all the possible neuroimaging methods and clinical data to capture each of the AD biomarkers, each contributing to an additive probability of AD development.

In later stages of AD progression however, a reliance on sMRI and clinical data may be sufficient for accurate classification, reducing the need for invasive imaging techniques such as PET. Both MRI and PET identify the left parahippocampal region as a consistently abnormal area in AD pathology (Tang et al. 2024). Unimodal MRI scan approaches also outperform unimodal

amyloid PET by an 8-10% classification accuracy, emphasizing the greater significance of structural degeneration over amyloid deposition (Castellano et al. 2024). These findings support the idea that while amyloid PET may offer minor improvements in accuracy, it may not be necessary when high-confidence classification is achieved using sMRI focused on structural degeneration in the left parahippocampal region and non-imaging data. For example, the success of Qiu's et al. (2022) MRI and clinical data fusion model that achieved a 95% classification accuracy for NC, MCI, AD, and nADD highlights the feasibility of bypassing PET to alleviate patient testing burden. Additionally, Zhang's et al. (2011) SVM approach merging CSF, MRI, and FDG-PET, identified MCI classification as requiring more brain regions than AD, suggesting that since atrophies increase with AD progression, a smaller subset of brain regions with greater neurodegeneration are needed for AD classification further along in the disease progression (Zhang et al. 2011). Such results offer additional support for the prioritization of sMRI in the late-stage AD pipeline. Although one may argue that atrophy and clinical data alone fails to provide a holistic framework capable of differentiating AD from MCI or nADD, 3D hippocampal volumetry mapping studies (Chételat et al. 2018) alleviate this concern by identifying CA1 atrophy as a distinguishing feature of AD compared to MCI and normal aging. The same study claimed that functional connectivity influenced the propagation of AD biomarkers, with intrinsic connectivity disruption in MCI spreading in AD (Chételat et al. 2018). These insights suggest that sMRI alone provides sufficient diagnostic power by evaluating structural CA1 atrophy and functional connectivity degeneration. Furthermore, since APOE ϵ 4 primarily influences A β accumulation rather than neurodegeneration (Chételat et al. 2018), and differentially impacts all AD biomarkers across various demographic groups, carrier statuses, and disease stages (Mares et al. 2024), CSF biomarkers provide additional, complementary information, in the spirit of a multimodal approach, about A β and tau deposition without requiring radioactive PET scans.

A multimodal approach not only enhances AD diagnosis, but also supports the development of targeted AD treatments, such as non-pharmacological brain stimulation therapies targeting gamma rhythms (Traikapi and Konstantinou 2021). The disruption of hippocampal and entorhinal cortex gamma oscillations, central to memory formation, may form the foundation for an additional early biomarker of AD, prior to plaque formation. Gamma-based therapies employing 40 Hz sensory stimulation (via. transcranial or magnetic stimulation) reduce key AD neuropathologies, including A β plaques and tau tangles (Murdock et al. 2024). Multimodal imaging and clinical biomarkers may identify key AD brain regions to target (e.g. hippocampus) or further promote the development of gamma-based therapies - like employing two-photon microscopy to demonstrate the promotion of glymphatic clearance of amyloid by optogenetic stimulation (Murdock et al. 2024).

4. Conclusion and Future Research

Ultimately, the proposed optimal multimodal neuroimaging pipeline for the diagnosis of Alzheimer's disease (AD) is adapted based on the stage of disease progression. In early stages, a comprehensive multimodal approach must integrate sMRI, PiB/AV45/FDG-PET, CSF, FTC-PET, and SNP biomarkers of APOE ϵ 4, along with other clinical data to achieve a high classification accuracy by capturing independent yet complementary AD biomarkers, accounting for their heterogeneity across patient APOE genotype, age, sex, and disease stage. This combination rules out other forms of neurodegeneration like MCI and nADD due to the additive contribution of atrophy, hypometabolism, and amyloid deposition on the probability of AD development (Chételat et al. 2018). However, in later stages, sMRI and CSF clinical biomarkers alone may be sufficient to identify extreme CA1 subfield degeneration and significant A β deposition characteristic of AD, bypassing the need for invasive PET imaging. Given the overwhelming success of deep learning based multimodal fusion approaches, future research

should focus on expanding computational power to accommodate larger training datasets for improved classification accuracy, as many current studies restrict neuroimaging dataset sizes used for model training due to efficiency constraints (Castellano et al. 2024). Additionally, computational models must incorporate the variability of biomarkers across disease stage, age, sex, and genetic groups in conjunction with other imaging and clinical data. Further investigation into the differentiation of AD and MCI or nADD related atrophy in earlier stages may allow AD diagnosis with solely sMRI with clinical data, enabling the omission of radioactive PET earlier in the AD diagnostic pipeline. Finally, multimodal neuroimaging techniques may be applied to evaluate the efficacy of and support the development of emerging AD treatments including non-invasive gamma-wave stimulation to attenuate AD pathology (Murdock et al. 2024).

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