Received: 16 March 2025 | Revised: 25 June 2025 | Accepted: 30 July 2025

DOI: 10.1002/alz.70648

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

REVIEW ARTICLE

Recent advances in neuroimaging of Alzheimer's disease and related dementias

Julie Ottoy[1,2,3] | Nicole Owsicki[1] | Murat Bilgel[4] | Alexa Pichet Binette[5,6,7] | Gemma Salvadó[6,8] | Min Su Kang[1,2] | David M. Cash[9,10] | Michael Ewers[11,12] | Renaud La Joie[13] | Laura E. M. Wisse[14] | Maged Goubran[1,2,15] | Tobey Betthauser[16,17]

[1]Black Centre for Brain Resilience & Recovery, Sunnybrook Research Institute, University of Toronto, Toronto, Ontario, Canada

[2]Physical Sciences, Sunnybrook Research Institute, University of Toronto, Toronto, Ontario, Canada

[3]Department of Medicine (Neurology), University of Toronto, Toronto, Ontario, Canada

[4]Laboratory of Behavioral Neuroscience, National Institute on Aging, Baltimore, Maryland, USA

[5]Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, University of Montréal, Montréal, Quebec, Canada

[6]Department of Clinical Sciences in Malmö, Clinical Memory Research Unit, Lund University, Lund, Sweden

[7]Department of Physiology and Pharmacology, Université de Montréal, Montréal, Quebec, Canada

[8]Barcelonaβeta Brain Research Center (BBRC), Pasqual Maragall Foundation, Barcelona, Spain

[9]Dementia Research Centre, UCL Queen Square Institute of Neurology, London, UK

[10]UK Dementia Research Institute at University College London, London, UK

[11]Institute for Stroke and Dementia Research, University Hospital, Ludwig-Maximilian-University LMU, Munich, Germany

[12]German Center for Neurodegenerative Diseases (DZNE), Munich, Germany

[13]Department of Neurology, Memory and Aging Center, Weill Institute for Neurosciences, University of California San Francisco, San Francisco, California, USA

[14]Department for Clinical Sciences Lund, Lund University, Lund, Sweden

[15]Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada

[16]Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA

[17]Department of Medicine, University of Wisconsin–Madison School of Medicine and Public Health, Madison, Wisconsin, USA

Correspondence
Julie Ottoy, Sunnybrook Research Institute, University of Toronto, Toronto, Ontario, Canada.
Email: Julie.Ottoy@sri.utoronto.ca

Julie Ottoy, Nicole Owsicki, Maged Goubran, and Tobey Betthauser share first and senior authorship.

Funding information
Canadian Institutes for Health Research, Grant/Award Numbers: CIHR-PJT-190220, CIHR-187890; Alzheimer Society of Canada, Grant/Award Numbers: ALZ23-05, ALZ26-021; Alzheimer's Association,

Abstract

This review covers recent advances (2023–2024) in neuroimaging research into the pathophysiology, progression, and treatment of Alzheimer's disease (AD) and related dementias (ADRD). Despite the rapid emergence of blood-based biomarkers, neuroimaging continues to be a vital area of research in ADRD. Here, we discuss neuroimaging as a powerful tool to topographically visualize and quantify amyloid, tau, neurodegeneration, inflammation, and vascular disease in the brain. We examine the utility of neuroimaging for (1) tracking the spatiotemporal progression of pathology, (2) serving as the reference standard for validating novel fluid biomarkers, (3) characterizing disease heterogeneity, (4) exploring the role of brain networks in ADRD progression, and (5) evaluating biomarkers for better individualized estimates of treat-

Grant/Award Numbers: 24AARF-1242638, 22AARF-972612, SG-666374-UK, AARG-22-926899; Alzheimer's Society Dementia Research Leaders Fellowship, Grant/Award Number: AS-DRL-23-005; National Institute for Health and Care Research University College London Hospitals Biomedical Research Centre; European Union's Horizon 2020 Research and Innovation Program, Grant/Award Number: 101061836; Strategic Research Area MultiPark; BrightFocus Foundation, Grant/Award Numbers: A2024012F, A2024007F; National Institutes of Health National Institute on Aging, Grant/Award Numbers: R01AG080766, P30AG062715, R01AG027161, P30AG062422; Brain Canada, Grant/Award Number: 24AARF-1242638; Alzheimerfonden, Grant/Award Numbers: AF-980942, AF-994514, AF-1012218; ERAPerMed, Grant/Award Numbers: BMBF, 01KU2203; Alzheimer's Society Research Program

ment benefit. Finally, we discuss advances in radiotracer development and AD risk factors. By reviewing the most promising breakthroughs in the neuroimaging field, we hope to spark new ideas for future discoveries that will deepen our understanding of ADRD.

KEYWORDS
Alzheimer's disease, amyloid, cerebrospinal fluid biomarker, cerebrovascular disease, clinical trials, co-pathology, connectivity, disease staging and subtyping, heterogeneity, inflammation, neuroimaging, plasma biomarker, positron emission tomography, risk factors, tau

Highlights

- The diagnostic and staging criteria for Alzheimer's disease (AD) were updated in 2024.
- Despite robust harmonization methods for amyloid beta positron emission tomography (PET), parallel efforts for tau PET remain challenging.
- Larger anti-amyloid drug effects were seen at lower levels of amyloid and tau PET.
- Phosphorylated tau217 (p-tau217) is currently the most promising plasma biomarker to detect AD pathology.
- There are new tracer developments for alpha-synuclein, primary tauopathies, and inflammation.

1 | INTRODUCTION

The last few years of research in Alzheimer's disease (AD) have been marked by exciting milestones and discoveries, including newly approved disease-modifying therapies and sensitive blood-based biomarkers. These breakthroughs are finally giving individuals and their families living with AD and related dementias (ADRD) renewed hope and the possibility that previous estimates of the global burden of AD exceeding 150 million by 2050 might be changed.[1] Various neuroimaging techniques have been at the heart of many of these breakthroughs, giving us tremendous insights into the start and spread of core pathophysiological processes as well as downstream neurodegenerative processes. Central to the pathophysiology of AD are amyloid beta (Aβ) plaques and neurofibrillary tangles (NFTs) of hyperphosphorylated tau aggregates. However, the pathogenesis of AD is multifaceted, involving a complex interplay of co-pathological, genetic, environmental, and lifestyle factors.[2] Recent advances in neuroimaging and fluid biomarkers, alongside the development of biological staging frameworks, have markedly pushed the field forward to achieve more effective detection, differential diagnosis, and patient stratification for clinical trials. Large-scale multi-site and multi-cohort studies have been particularly instrumental in advancing these efforts, offering new avenues to characterize and treat AD. As we are now making treatment decisions based on neuroimaging data, it is more important than ever to standardize imaging protocols, quantification methods, and positivity thresholds.

This perspective review, drafted in collaboration with the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART) Neuroimaging Professional Interest Area (PIA) following the Year-In-Review talk at the 2024 Alzheimer's Imaging Consortium, aims to contextualize the current status of human neuroimaging research in relation to the pathophysiology, progression, and treatment of ADRD. The Neuroimaging PIA includes 1693 members from 64 countries, including 15.4% from low- and middle-income countries (LMICs). The review includes published manuscripts from peer-reviewed journals solicited from Neuroimaging PIA members via an online survey request and additional literature review with a prespecified keyword string (Methods S1 in supporting information) and date range (2023–2024) in PubMed. Key themes of our review (Figure 1) include: the role of neuroimaging in characterizing Aβ and tau within the revised diagnostic & staging framework, imaging findings from clinical trials of disease-modifying therapies, fluid biomarker validation, biological staging and subtyping, connectomics, neuroinflammation and cerebrovascular contributions, novel positron emission tomography (PET) radiotracers, and prominent risk factors. We conclude our review by highlighting key limitations and future needs. Figure 2 illustrates the connections between these key themes, along with the frequency of word occurrences in the included abstracts. Neuroimaging continues to be a cornerstone of ADRD research as it provides essential in vivo topographical mapping for neuropathologically defined AD subtypes, fluid biomarker validation, and efficacy estimates of emerging disease-modifying therapies.

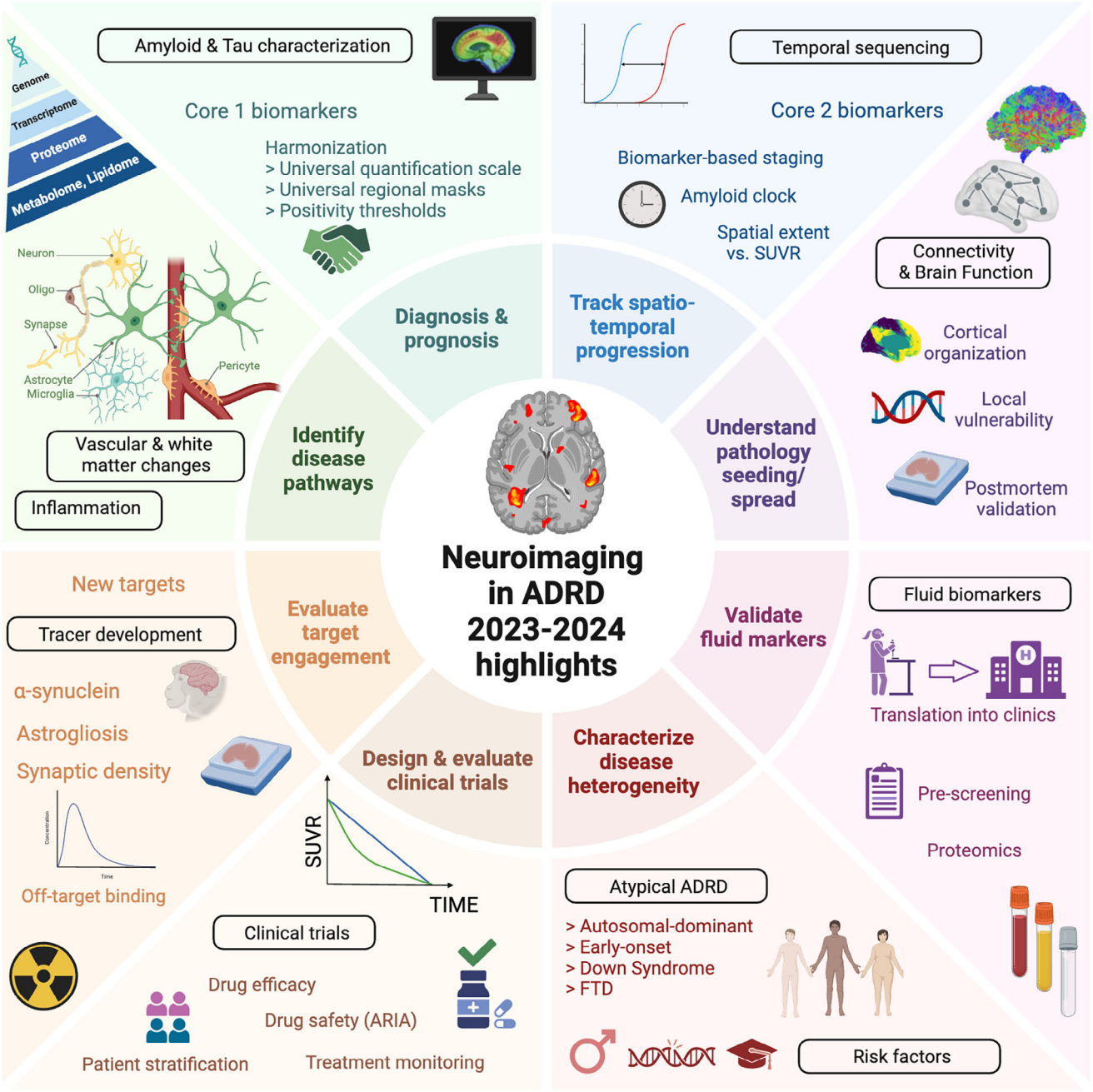

FIGURE 1 Recent highlights (2023–2024) of neuroimaging research in ADRD. Inner circle (colored text) represents the applications of imaging in ADRD research; outer boxes represent the main themes (black text) and subtopics (colored text) discussed in this review. Figure created with BioRender. ADRD, Alzheimer's disease and related dementias; ARIA, amyloid-related imaging abnormality; FTD, frontotemporal dementia; SUVR, standardized uptake value ratio.

2 | AMYLOID AND TAU PET IN DIAGNOSIS AND CLINICAL TRIALS

2.1 | A/T characterization and quantification

The 2024 revised criteria for the diagnosis and biological staging of AD incorporates the latest advances in biomarker research.[3] In the 2018 version, the biological stages included amyloid, tau, and neurodegeneration (A/T/(N)); instead, the revised version focuses on A or T biomarkers to diagnose AD and incorporates recent evidence from tau PET to develop an updated biological staging system. For AD diagnosis, the revised framework requires biomarker evidence of AD pathology from so-called Core 1 biomarkers (Aβ PET/fluid or phosphorylated tau [p-tau] fluid). For biological staging, the framework now includes four stages from Core 2 biomarkers based on the spatial extent and amount of tau PET (none→ medial-temporal only→ neocortex moderate→ neocortex high), reflecting increasing severity presumed to have prognostic value. The strongest evidence for bio-

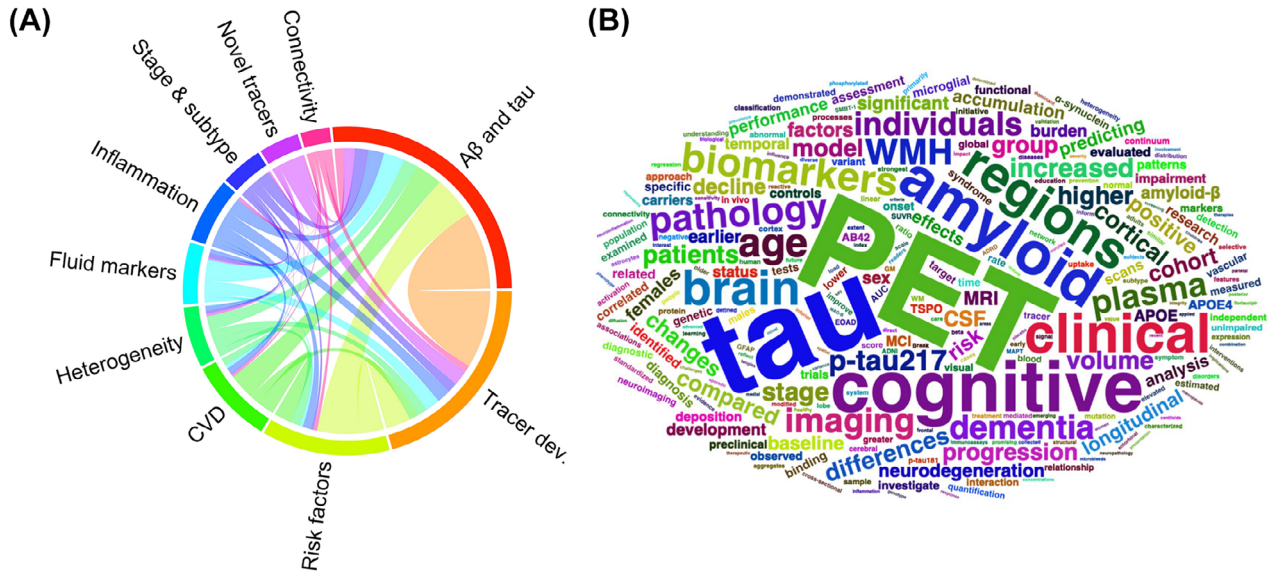

FIGURE 2 Connectivity and frequency of key themes in ADRD neuroimaging research. A, Connectogram indicating how the different themes of our review are connected across abstracts. B, Frequency table of words in the abstracts, depicted as a word cloud in which font size reflects word frequency. Methods are outlined in Methods S2 in supporting information. Aβ, amyloid beta; ADRD, Alzheimer's disease and related dementias; CVD, cerebrovascular disease; dev., development.

logical staging based on tau PET is summarized in a recent review.[4] Efforts to operationalize this biomarker-driven system are underway, focused on defining the regions of interest (ROIs) for different stages, tau tracer harmonization, and positivity cutoffs.

Harmonization and robust positivity thresholds have been developed for Aβ PET through the tracer-independent "Centiloid" scale.[5] By harmonizing across Aβ tracers, Centiloids are a valuable adjunct to visual reads, as they provide information on Aβ-based disease staging beginning early in disease and are used extensively across clinical trials for patient selection and treatment arm assignment as well as treatment monitoring. Compared to Aβ PET, harmonization of tau PET remains challenging due to the more focal and region-specific nature of tau deposition, the lack of a clear reference tracer (e.g., [^{11}C]Pittsburgh compound B for Aβ), and differences in tracer off-target binding. Tau PET harmonization efforts are ongoing, including developing the "CenTauR" scale, which has previously defined standardized ROIs, including a "universal" mask and individual ROIs for mesial temporal, meta-temporal, tempo-parietal, and frontal regions.[6] More recently, a joint propagation model (JPM) was proposed to harmonize quantitative tau PET values across tracers through head-to-head tracer comparisons.[7] This JPM eliminates the need for a reference tracer by directly comparing all tracers head to head. Efforts are underway to compare JPM to other models being developed, such as the "Unit" scale in the Head-to-Head Harmonization of Tau PET Tracers in Alzheimer's Disease (HEAD) study.[8] Comparing tracer outcomes, some clear distinctions exist. For example, [^{18}F]MK6240 has a larger dynamic range compared to other tracers. This dynamic range may contribute to the plateauing of tracer binding in high-uptake regions for the other tracers, leading to poorer correspondence with [^{18}F]MK6240. Additionally, methods for harmonizing Aβ and tau PET outcomes across multi-site cohorts, such as the Alzheimer's Disease Neuroimaging Initiative (ADNI), have been developed.[9] Such an image harmonization approach across tracers and scanners represents a great effort toward accessibility and generalizability of study outcomes.

Efforts in determining tau PET positivity are also ongoing, showing high agreement between quantitative and visual read methods.[10–12] With regard to visual reads, several methods were developed for [^{18}F]MK6240 PET. The first method focuses on rapid clinical reads based on four phenotypes ("no uptake," "medial temporal lobe [MTL] only," "MTL and neocortical," and "outside MTL").[13] Another visual rating method focuses on more detailed regional scoring based on an intensity score in eight bilateral regions and an extent score per region (% of the region with increased uptake).[14] A recent paper has now developed the first visual rating method for [^{18}F]PI-2620 PET in diagnosing 4R-tauopathies.[15] While a visual rating is currently the only US Food and Drug Administration (FDA)-approved method for tau PET interpretation in clinical settings, adding semi-quantitative PET measures to visual ratings could further enhance the sensitivity to the early tau deposition. For example, because tau deposition patterns can differ at the individual level and are often more focal, recent methods, including spatial extent metrics (% supra-threshold regions or voxels) have been proposed to capture this spatial heterogeneity.[16–18] These studies suggest that the spatial extent metric may be more sensitive to detect early Aβ and tau compared to the intensity of regional tracer uptake, such as standardized uptake value ratios (SUVRs).

A separate working group convened by the Alzheimer's Association and the Society of Nuclear Medicine and Molecular Imaging updated the appropriate use criteria for Aβ and tau PET imaging in clinical practice.[19] In addition, research efforts aim to identify robust fluid biomarker correlates of tau PET (see section 3), which could potentially serve as Core 2 staging biomarkers as conceptually presented within the new framework.

2.2 | Imaging in clinical trials

There have also been major advances in clinical trials, wherein outcomes related to Aβ and tau PET yielded insights into AD pathophysiology and clinical progression. Evidence for the higher efficacy of anti-amyloid therapies before pathology is too advanced comes from the successful TRAILBLAZER-ALZ 2 phase 3 trial testing donanemab in early symptomatic AD patients.[20] Participants with low/medium tau PET binding showed greater slowing of clinical progression compared to the combined group that also included high-tau participants.

Solanezumab, an antibody that recognizes monomeric Aβ, was tested in the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) trial and did not slow cognitive decline nor reduce Aβ plaques on PET over ≈ 4.5 years.[21] Subsequent analyses of openly available data from A4 and Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN) clearly showed how elevated baseline Aβ PET and plasma p-tau217 are strongly related to cognitive decline and clinical progression.[22] Stratifying by Aβ-based tertiles, all groups, even the lowest tertile (< 46.1 Centiloids), showed cognitive decline measured by the Preclinical Alzheimer Cognitive Composite (PACC), with the steepest decline in the highest tertile (> 77.2 Centiloids). This latter group also showed the steepest functional decline, with >50% progressing to a Clinical Dementia Rating (CDR) of ≥ 0.5. Similar results were observed when stratifying by p-tau217 instead of Aβ PET. In a subset of participants with tau PET, cortical uptake in early tau regions was also strongly associated with cognitive decline, providing an additional independent contribution beyond p-tau217. Such results support intervening earlier during preclinical stages of biomarker-defined AD and support the ongoing A3 and A45 sister trials testing lecanemab in cognitively unimpaired elderly individuals with intermediate Aβ (≈ 20–40 Centiloids) and elevated Aβ (>40 Centiloids), respectively.[23]

Among tau therapies, an antisense oligonucleotide decreasing the synthesis of tau protein (BIIB080) showed reduced tau PET uptake, particularly in the temporal lobe, in a phase 1b trial,[24] and a phase 2 trial is currently ongoing in patients with mild symptoms and elevated Aβ (NCT05399888). A recent anti-tau antibody targeting the mid-region epitope, bepranemab, for the first time showed significantly reduced tau PET binding in prodromal/mild AD after 80 weeks, but this result did not translate to clinical benefit.[25] Interestingly, participants with low tau responded better than those with high tau. While preliminary, these results support previous evidence that early intervention (i.e., low/moderate pathology) is crucial for maximizing clinical benefit.

3 | VALIDATION OF FLUID BIOMARKERS WITH IMAGING

Recent fluid biomarker developments, particularly in blood, have revolutionized AD research, with neuroimaging often used as the reference standard for validation and clinical utility comparisons. Plasma p-tau217, or its ratio to the non-phosphorylated form (%p-tau217), has emerged as one of the most promising biomarkers, demonstrating high A+/− agreement with Aβ PET (area under the curve >0.9).[26,27] Remarkably, plasma p-tau217 performs non-inferior to FDA/European Medicines Agency-approved cerebrospinal fluid (CSF) biomarkers that are used in the clinic, with Aβ and tau PET positive scans as the reference.[28] Plasma p-tau217 has also shown utility in primary and secondary care settings[29] and across diverse populations from different ethno-racial backgrounds,[30,31] underscoring its real-world clinical utility. Furthermore, plasma p-tau217 alone or combined with Aβ42/40 has shown promise in predicting Aβ PET accumulation, even in Aβ-negative individuals.[32,33]

In addition to detecting Aβ pathology, plasma p-tau217 can identify tau PET–positive (T+) individuals with a positivity rate of ≈ 70%, enabling pre-screening for subsequent tau PET referral in memory clinics[34] and clinical trials.[35] Despite these advancements, tau PET remains a better predictor of cognitive decline in symptomatic patients,[36] although this may be different in earlier stages.[22,37]

Beyond p-tau217, novel biomarkers are emerging to assess aggregated tau pathology in AD. CSF microtubule-binding region containing residue 243 (MTBR-tau243) has shown the strongest association with tau PET compared to other biomarkers, including p-tau181 and p-tau217.[38] Further, MTBR-tau243 exhibited the largest longitudinal increases in PET-derived A+T+ individuals, while p-tau217 plateaued after early increases in A+T− individuals. However, MTBR-tau243 currently requires mass spectrometry for measurement, which raises logistical and cost barriers. Efforts are underway for blood-based testing. Another biomarker, CSF p-tau205, has a high correlation with tau PET[39] and a stronger association with tau PET versus Aβ PET, but a weaker association with tau PET compared to MTBR-tau243 in mass spectrometry studies. Analyses comparing p-tau205 and MTBR-tau243 measured by immunoassays remain unavailable. Additionally, a new blood assay of N-terminal-containing tau fragments (NTA-Tau) has shown correlations with tau-aggregated pathology, cognitive decline, and brain atrophy.[40,41]

While p-tau217 is currently the most established and accessible plasma AD biomarker, integration of blood-based biomarkers into the clinic remains challenging due to the diverse analytical platforms and the uncertain ability for differential diagnosis in diverse patient populations with varying comorbidities and confounding factors.[42]

4 | TEMPORAL SEQUENCING, SUBTYPING, AND MACHINE LEARNING APPLICATIONS

With the growing availability of biomarkers and treatments for AD, accurately identifying personalized windows for therapeutic intervention is critical. While traditional longitudinal studies depict a stereotypical progression from Aβ deposition to cognitive decline, there is substantial variability in both the timing of biomarker positivity and symptom onset. Given the lack of real-world clinical cohorts with longitudinal data spanning a full lifespan, understanding the subject-level progression trajectories requires novel modeling approaches that move beyond traditional methods anchored to chronological age. As such, alternative time axes have been developed. One approach is to

calculate time to an anchoring disease event, such as a clinical symptom or brain Aβ onset. For example, sampled iterative local approximation (SILA)[43] has been applied to construct an "Aβ clock" relative to A+ onset age estimated from longitudinal PET data. A recent study applying this approach demonstrated that the earliest tau pathology in the entorhinal cortex is detectable within a decade of A+ onset and that tau tends to spread to the neocortex by the 10-year mark.[44] As such, the first decade after A+ onset appears to be the crucial time window for intervention, when tau is still limited. Another approach for constructing an alternative time axis is to temporally align individuals based on their similarity across multiple biomarkers, as summarized in a recent review.[45] In this respect, recent studies leveraged advanced statistical and unsupervised machine learning (ML) techniques to identify AD phenotypes (subtypes) and pseudo-temporal biomarker progression (stages), based on cross-sectional brain atrophy,[46,47] tau,[48] CSF,[49] and cognition.[50] Many of these studies have particularly used the Subtype and Stage Inference (SuStaIn) algorithm or relied on deep learning (DL) networks (e.g., conditional variational autoencoder) and/or a clustering method.[51] Estarellas et al.[52] adapted SuStaIn to handle missing data for multi-modal datasets and identified five unique AD subtypes (using magnetic resonance imaging [MRI], PET, CSF, and cognitive tests from ADNI), each of which was associated with distinct biomarker trajectories, cognitive profiles, and risk factors, which in turn may assist with patient stratification in clinical trials and patient management in the clinic.

A recurring finding in the temporal sequence of imaging and fluid biomarker changes is that Aβ42/40 is the earliest to show change,[49,53–55] and it may plateau prior to the development of mild cognitive impairment (MCI).[55] This early plateau of Aβ42/40 suggests that Aβ42/40 may be unsuited for monitoring disease progression beyond MCI. P-tau181 and AD non-specific markers such as glial fibrillary acidic protein (GFAP) and neurofilament light chain (NfL),[55] which are more dynamic post-amyloid onset,[56] may be better for monitoring progression later in disease. Several longitudinal studies, two of them spanning more than two decades, confirmed that the earliest changes in Aβ (fluid then PET) were followed by tau and neurodegeneration,[53,54,57] and with the earliest decline in cognition at 0.2 years after A+ onset.[57] Regarding early AD changes, a recent method aiming at estimating tau-related processes in small structures indicated that changes in an MRI-based proxy of locus coeruleus integrity even preceded changes in tau PET uptake in the MTL.[58]

Neuroimaging-based ML/DL models are increasingly pivotal in advancing ADRD research, offering novel tools for diagnosis, prognosis, risk assessment, and biomarker discovery. In recent studies, ML specifically has been applied to neuroimaging and fluid biomarkers for patient subtyping, early detection, predicting disease progression, and synthesizing clinically inaccessible imaging modalities. Besides the use of SuStaIn, previous work has investigated the neuroanatomical heterogeneity of AD using a semi-supervised DL-based generative adversarial network (GAN). Their findings identified two continuous latent dimensions of brain atrophy: "diffuse-AD" and "MTL-AD."[59] These dimensions were associated with various pathological mechanisms beyond the sporadic AD genetic risk factor apolipoprotein E (*APOE*) ε4, including inflammation, cardiovascular diseases, and hormonal dysfunction, suggesting potential systemic involvement even in the early asymptomatic stages. Another study[60] focused on the heterogeneity of tau PET patterns in particular and created an ML-based summary measure, called the Tau Heterogeneity Evaluation in Alzheimer's Disease (THETA) score, to identify tau PET positivity in AD. Subsequent validations showed that THETA was associated with Braak staging similar to the traditional meta-ROIs but mapped better onto clinical diagnostic and cognitive indices.

DL was leveraged to predict PET-determined ATN status directly from MRI scans and readily available clinical data, identifying key temporal, parietal, frontal, and occipital cortical regions on MRI, along with age, cognitive scores (Alzheimer's Disease Assessment Scale 13-item subscale and Mini-Mental State Examination [MMSE]), hippocampal volumes, and *APOE* status as important predictive features (areas under the receiver operating characteristic curve [AUC] of 0.79 for A, 0.73 for T, and 0.86 for N status).[61] Similarly, Cai et al.[62] demonstrated that the MRI-based Alzheimer's disease resemblance atrophy index (AD-RAI), an ML-derived marker, outperformed plasma NfL and traditional hippocampal measures in predicting a 4-year cognitive decline risk of A+T+ cognitively unimpaired or MCI subjects, particularly when combined with plasma p-tau181, *APOE* ε4 genotype, and clinical features (age, sex, education, and baseline Montreal Cognitive Assessment; AUC of 0.83 for cognitively unimpaired and 0.85 for MCI). Complementing these approaches, Lee et al.[63] developed a convolutional neural network (CNN) to synthesize tau PET images from more widely available imaging modalities (T1-weighted MRI, fluorodeoxyglucose [FDG] PET, or Aβ PET), with FDG-based models showing significantly improved classification of T+ and diagnostic groups compared to the original input data. Artificial intelligence–imputed (synthetic) tau PET may extend the clinical value of existing scans and reduce reliance on costly or less accessible imaging.

Despite the promise of ML on standardized research datasets like ADNI, MRI-based ML models for dementia detection were found to perform considerably lower on real-life clinical data from hospital settings.[64] This performance drop was largely attributed to classifiers being heavily biased by irrelevant characteristics such as image quality or contrast agent use, a phenomenon termed shortcut learning, which underscores the challenge of translating these models to clinical practice and the need for robust validation and bias mitigation. Future work should therefore prioritize developing unbiased models, effective image homogenization techniques, and integrating multimodal data to enhance the generalizability of these algorithms to real-world data. Additionally, model validation in larger, out-of-distribution (unseen), and more diverse cohorts, including underrepresented ethnic groups, is essential for developing clinically relevant and scalable imaging-derived models.

5 | BRAIN FUNCTION AND CONNECTOMICS

The brain's network, or connectome, may be a promising therapeutic target biomarker in ADRD. Specifically, neuromodulation or

stimulation interventions that target brain networks could prove useful as adjuvant therapies in reducing early-stage hyperactivity as well as blocking tau seeding or progression (or cell-to-cell transmission) along the brain networks. Recent studies have reinforced the critical role of functional connectivity in AD pathological progression. Functional connectivity is a measure of between-region synchronicity that can be derived from functional imaging techniques, including magnetoencephalography (MEG) and functional MRI (fMRI). fMRI studies in cognitively unimpaired individuals consistently showed increased fMRI blood oxygenation level-dependent signal ("hyperactivity") in the MTL together with greater tau PET signal (see review in Corriveau-Lecavalier et al.[65]). Using a task-based fMRI paradigm to simulate a shift toward excitatory/inhibitory imbalance, it was shown that MTL hyperexcitability in A+ individuals was linked to hyperexcitability of the default mode network (DMN), and that the degree of MTL hyperexcitation by the DMN was further associated with MTL tau PET accumulation.[66] Early tau deposition in the MTL in preclinical stages was also associated with high-frequency neurophysiological activity (via task-free MEG), shifting it toward slower waves, a process linked to later neurodegeneration and cognitive decline.[67] Collectively, these works suggest that neuronal hyperactivity, potentially driven by Aβ-mediated excitatory–inhibitory imbalances, may be a key link between early Aβ deposition in the DMN and subsequent neocortical tau accumulation.

Regional susceptibility has also emerged as a putative factor influencing tau seeding and spread. For example, integrating functional connectivity with Aβ PET and *MAPT* gene expression increased the proportion of explained variance in tau PET binding potential compared to using either fMRI, Aβ PET or *MAPT* expression alone.[68] This notion of regional vulnerability was further supported by Ottoy et al.,[69] demonstrating that pathologic tau tends to accumulate in regions that have more similar brain-wide functional connectivity patterns (referred to as "functional connectome gradient"), particularly regions within the higher-order transmodal cortex. The observed contraction of this functional gradient in symptomatic AD likely reflected a dedifferentiation of the functional networks, which in turn correlated to cognitive decline. Beyond functional connectivity, the study also highlighted how tau PET patterns were shaped by structural brain organization (via tractography) and by microglial reactivity (via translocator protein [TSPO] PET, see section 7) in a disease stage–dependent manner, following a posterior-to-anterior pattern. Together, it is likely that structural–axonal pathways, (hyper-)synchronicity, and intrinsic local vulnerability influence Aβ-related tau seeding/spreading in a disease stage- and region-dependent manner; a recent overview of connectome-based modeling in AD was published by Vogel et al.[70]

6 | CEREBROVASCULAR DISEASE AND MICROSTRUCTURAL INJURY

Cerebrovascular and AD pathology frequently co-occur, with bidirectional effects that can accelerate cognitive decline and contribute to mixed dementia phenotypes. Vascular brain lesions visible on MRI, specifically infarcts and white matter hyperintensities (WMHs), are now included as biomarkers of non-AD co-pathology in the revised criteria of AD.[3] However, these lesions merely capture end-stage results of diverse biological processes, involving both AD-specific and vascular origins, with cardiovascular risk factors alone accounting for < 15% of the variance in WMHs.[71] Thus, there is a need to decipher region- and stage-specific markers of vascular pathology in AD.

Potential AD-specific mechanisms of vascular pathology encompass Aβ (parenchymal and/or cerebral amyloid angiopathy [CAA]), tau, tau-related neurodegeneration, and inflammation, all of which can be studied in vivo with imaging and fluid biomarkers. For instance, CSF or PET measures of Aβ have been associated with (posterior-dominant) WMHs both cross-sectionally[72,73] and longitudinally,[74,75] supporting an additive or synergistic AD-driven pathway toward lesion formation.

Beyond direct associations, synergistic interactions between Aβ and vascular imaging have also been documented, impacting subsequent tau, atrophy, and cognitive changes. In cognitively unimpaired individuals, neocortical Aβ PET and lobar microbleeds synergistically interacted on trajectories of temporal tau PET accumulation.[76] Also in cognitively unimpaired individuals but in relation to cognition, neocortical Aβ PET interacted with white matter injury to accelerate PACC decline over time,[77] while no interaction effect was observed on baseline PACC.[78] These studies suggest that vascular (V) mechanisms are already at play in the preclinical stage. In contrast to the findings in the early disease stage, two independent studies in combined unimpaired and impaired A+ cohorts indicated cerebrovascular burden did not further exacerbate cognitive decline, with similar MMSE decline observed in both A+V− and A+V+.[79,80] This suggests that, during clinical stages, cognition is primarily impacted by the AD pathology. Nevertheless, WMH progression and cortical thinning have demonstrated a mutually reinforcing (rather than parallel) relationship across the AD spectrum,[81,82] and cognition may be impacted by WMHs indirectly through cortical atrophy.[73] This suggests that multiple pathways contribute to the neurodegeneration and cognitive decline observed in AD.

Microstructural changes such as free water and mean diffusivity, assessed via diffusion-weighted MRI (dMRI), can precede MRI-visible lesions, offering a potential early and predictive marker for disease progression. Even when Aβ PET was still negative, greater free-water levels were observed in the temporo-occipital tracts of individuals with abnormal plasma Aβ42/40.[83] Both free water and mean diffusivity exhibited early increases in the temporo-parietal regions of A+T− individuals.[84,85] Both metrics were also positively associated with plasma GFAP, possibly indicating an astrocytic response around damaged gray and white matter tissue.[83,84] The entorhinal cortex was found to show the earliest microstructural abnormalities, with lower neurite density in *APOE* ε4 presymptomatic individuals.[86] Accordingly, cortical mean diffusivity interacted with Aβ to accelerate tau PET in the entorhinal cortex.[87] A recent ex vivo high-field (11.7T) dMRI and tractography study of *post mortem* AD tissue confirmed that microstructural damage via fractional anisotropy emerges early in the entorhinal–hippocampal pathway.[88] Importantly, free water, mean diffusivity, and fractional anisotropy are all non-specific markers of microstructural changes. More advanced multi-compartment dMRI

models, such as neurite orientation dispersion and density imaging (NODDI), combined with A and T biomarker status, hold promise for further enhancing diagnostic prediction accuracy.[89]

ML-based methods applied to brain MRI scans can also provide a scalable and more precise approach to predicting vascular lesions. For example, recent DL-based tools have been applied on brain MRI scans in clinical populations to automatically derive the radiographic severity of Aβ-related imaging abnormalities (ARIAs)[90] or to more robustly segment WMHs from heterogeneous populations with varying degrees of cerebrovascular disease.[91]

7 | BIOMARKERS REFLECTING INFLAMMATORY PROCESSES

Brain inflammation is increasingly recognized as an early feature in AD, with microglia and astrocytes as key cellular mediators. Neuroimaging has been instrumental in establishing this early role, particularly through observed correlations between inflammatory markers and Aβ PET signal, suggesting a positive feedback loop between the two. Accordingly, inflammatory biomarkers can help to advance our understanding of AD progression, identify new targets for immunomodulation, as well as evaluate response to clinical trials. Radiotracers and ongoing clinical trials targeting brain inflammation in AD were recently summarized.[92]

PET imaging of the 18 kDa TSPO remains the most widely used in vivo technique for mapping the spatiotemporal distribution of reactive microglia across the AD continuum. Recent reviews highlighted the advancements in the development and application of TSPO PET in ADRD research.[93,94] In the largest TSPO PET meta-analysis to date, conducted across 11 distinct neurological and neuropsychiatric disease categories, AD exhibited the most pronounced cortical TSPO PET increases compared to controls.[95] Notably, TSPO PET correlated with tau PET more so than with Aβ PET, both in primary and secondary tauopathies and early-onset AD (EOAD).[96–98] The weaker TSPO–tau association within early Braak stages, however, may reflect an atrophy-[97] or *APOE*-dependent effect,[99] with *APOE* ε4 carriers exhibiting higher TSPO PET in the MTL, irrespective of global Aβ burden, that further worsened tau PET in this region. Importantly, the TSPO PET signal is intrinsically complex, with factors related to cell state, disease stage, and brain region all playing a role.[94] Additionally, the genetic variability in microglial responses to Aβ deposition affects the disease onset and progression. Further complicating its interpretation, a cross-species study suggested that TSPO PET may not reflect a phagocytic microglial phenotype ("activation state") per se but rather the density or recruitment of TSPO-expressing cells in human AD.[100] However, these authors also identified a weak association between human TSPO and CD68 expression (a marker reflective of reactive phagocytic microglia), in line with the TSPO–CD68 correlation noted in another neuropathology study.[101] This points to TSPO being related to a phagocytic profile of microglia in AD. A promising complementary technique to increase both the cell type and state specificity may be circulating microglial extracellular vesicles and their cargo as blood-based biomarkers. Apart from microglia, TSPO expression has also been detected in endothelial cells but was not detected in astrocytes or perivascular macrophages in a recent study,[101] a finding that remains controversial within the current body of literature.

Current PET radiotracers for quantification of reactive astroglia primarily target monoamine oxidase-B (MAO-B;[102] see section 8). For example, [^{11}C]D2-deprenyl (DED) PET was elevated in temporo-occipital areas in presymptomatic autosomal-dominant AD (ADAD) mutation carriers and MCI A+.[103] Similarly, [^{18}F]SMBT-1 PET was already elevated in parieto-occipital areas in presymptomatic sporadic AD.[104] These studies suggest early astrogliosis as Aβ levels rise.[102] Regional vulnerability may stem from local disruptions in astrocytic clearance mechanisms, including impaired aquaporin-4 function, potentially exacerbating AD pathology regionally.[105] Interestingly, in ADAD mutation carriers relative to non-carriers, the between-group differences in [^{11}C]DED PET followed opposite trajectories from plasma GFAP, another marker of astrogliosis. Specifically, plasma GFAP started to increase above the mean non-carrier level after [^{11}C]DED started to decline, and GFAP peaked close to symptom onset while [^{11}C]DED peaked in the very early presymptomatic stage. This suggests that GFAP being released from astrocytes is detected later temporally compared to detection of MAO-B overexpressing astrocytes.[103] PET versus fluid markers may thus represent distinct states or subtypes of astrogliosis, as not all GFAP+ astrocytes overexpress MAO-B. Other studies have also presented significant associations between fluid glial activation markers (i.e., GFAP, sTREM2, YKL-40) and brain structure and function that may flip direction depending on the disease stage.[84,106]

8 | ADRD PET TRACERS BEYOND Aβ, TAU, AND TSPO

Beyond Aβ and tau PET in AD, there remains great interest in developing and characterizing PET tracers for other brain proteinopathies and targets associated with neurodegenerative diseases such as TAR DNA-binding protein 43 (TDP-43), alpha-synuclein, non-AD primary tauopathies, synaptic density, and brain inflammation beyond TSPO. For PET tracers to be viable for brain imaging, they need to (1) be able to cross the blood–brain barrier (e.g., peak standardized uptake value [SUV] >1), (2) be devoid of brain-penetrant radiometabolites, (3) show high affinity (low nanomolar range) and high selectivity to their designated brain target over other central nervous system targets, (4) have a sufficiently fast kinetic profile including peripheral metabolism, and (5) have relatively low non-specific binding. In addition, tracers can ideally be quantified with reference tissue methods and can be radiolabeled with F-18 to improve tracer distribution over shorter lived radioisotopes that require an on-site cyclotron. Developing PET tracers for proteinopathies like TDP-43 and alpha-synuclein is particularly challenging because the density of these protein aggregates is considerably lower than Aβ or AD tau pathology.

Several candidate ligands (e.g., [^{18}F]ACI-12589, [^{18}F]C05-05, and [^{18}F]F0502B) targeting synucleinopathy showed promise in preclini-

cal models and in vitro studies but have been less optimal in initial human studies. For example, ACI-12589 showed increased midbrain binding in patients with multiple system atrophy (MSA), but not dementia with Lewy bodies (DLB) nor Parkinson's disease (PD).[107] C05-05 showed elevated binding in PD/DLB but also exhibited elevated binding in healthy controls, potentially limiting its diagnostic utility.[108] F0502B appeared selective to synucleinopathy fibrils over other brain targets in vitro and showed differences in binding in rhesus macaque alpha-synuclein models compared to controls despite somewhat low brain uptake (SUV ≈ 1), but is yet to be tested in humans.[109] In addition, several other studies have identified and tested lead compounds for alpha-synuclein PET in preclinical and in vitro studies, with most of these suffering from slow metabolism, poor selectivity, and/or showing similar selectivity to MSA versus DLB or PD alpha-synuclein aggregates.[110–114] Overall, these studies suggest that current alpha-synuclein tracers may have some limited utility for MSA but likely not for detecting Lewy body pathology observed in PD or DLB.

Most currently available tau PET tracers bind with high affinity to AD-type tau aggregates, but there remains a need to develop tau tracers that are sensitive and selective to primary tauopathies observed in other neurodegenerative diseases. Primary tauopathies are prominent features of several neurodegenerative diseases, such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), primarily comprised of 4R tau, and Pick's disease with aggregates primarily comprised of 3R tau. These tau aggregates differ structurally from each other and those observed in mixed 3R/4R AD tauopathy, which likely affects the accessibility of tau tracer binding sites. Two recent studies using [^{18}F]florzolotau (aka [^{18}F]PM-PBB3) demonstrated group differences between healthy controls and CBD and PSP patients in subcortical structures but also observed considerably higher binding in A+ AD patients.[115,116] A [^{18}F]PI-2620 study showed high accuracy and high inter-rater reliability for AD versus controls and suggested using earlier 20 to 40 minute frames with intensity scaling improved inter-rater reliability and discrimination of PSP and CBD from controls.[15] In a separate study, [^{18}F]OXD-2314 demonstrated nanomolar affinity to AD, PSP, CBD, and Pick's disease brain tissue, with ≈ 10-fold higher affinity in CBD and Pick's disease tissues compared to [^{18}F]PI-2620 and [^{18}F]florzolotau.[117] OXD-2314 also showed brain uptake (peak SUV ≈ 2.4) and fast washout in rats and suggested ≈ 1.5 to 2.5 times higher target density in AD frontal cortex compared to PSP, CBD, and Pick's disease. These studies highlight the challenges in developing selective primary tauopathy tracers, and it is likely that future iterations of these tracers will be needed to overcome the relatively low target density of 3R and 4R tauopathies compared to AD.

Reactive astrocytes overexpress MAO-B, positioning MAO-B as a potential target for non-invasive, in vivo imaging of astrogliosis. Relatively recent discoveries of [^{18}F]SMBT-1, a reversibly bound MAO-B PET tracer, and [^{11}C]BU99008 targeting imidazoline-2 binding sites (I_2BS) on astrocytes, have spurred research characterizing the nuances of reactive astrogliosis. Recent in vitro binding and autoradiographic examination of cognitively normal and AD tissue demonstrated that SMBT-1 and L-deprenyl bind to similar binding sites but that BU99008 likely binds to additional sites, with SMBT-1 (at high concentrations of 1 μM) displacing >90% of L-deprenyl binding but only ≈ 50% of BU99008 binding.[118] These differences in binding profiles may reflect the complex changes of reactive astrocytes and support a multi-tracer approach to characterize astrocytic changes in neurodegenerative diseases. MAO-B as a target for reactive astrogliosis in AD and other neurodegenerative diseases is further supported by recent detailed pathologic characterization of MAO-B in relation to other brain pathology in human brain tissue[119] and in preclinical mouse models (5XFAD, rTg4510).[120]

Beyond brain inflammation, synaptic dysfunction/loss is an important pathological feature of AD. However, the impact of AD on brain synapse diversity remains poorly understood.[121] Synaptic vesicle protein 2A (SV2A), a ubiquitously expressed synaptic vesicle membrane protein, represents a putative marker of synaptic density, though earlier human SV2A studies in AD have yielded mixed findings. One study comparing control and AD brain tissue indicated minimal differences in UCB-J binding (SV2A) in neocortical brain regions except for the middle frontal gyrus, which was lower in AD.[122] A separate in vitro study using cellular and subcellular fractions from human tissue recapitulated the high specificity of UCB-J for SV2A in brain homogenates but also suggested possible off-target binding of UCB-J to p-tau species, though it remains unclear to what extent tau phosphorylation may impact in vivo UCB-J binding.[123] Another study with detailed pathologic characterization of SV2A density in several brain regions and neurodegenerative diseases showed reductions in SV2A density for disease versus controls for all regions evaluated, and some disease- and region-specific reductions in SV2A density.[124] These studies demonstrate the complex nature of SV2A as a biomarker of synaptic density and inform the ability of SV2A as a target and current SV2A tracers to quantify synaptic density in vivo with PET imaging.

9 | IMAGING BIOMARKERS IN ATYPICAL FORMS OF ADRD

9.1 | EOAD and ADAD

The young onset of pathobiological changes in individuals with EOAD reduces the confounding effects of age-related changes, thus allowing for a more direct association between pathology and known AD biomarkers.[2,125] The Longitudinal Early-Onset Alzheimer's Disease Study (LEADS) cohort in sporadic EOAD[126] developed a novel atrophy signature involving the inferior parietal, precuneus, posterior cingulate, and caudal lateral temporal cortices. In addition to greater posterior temporo-parietal atrophy, A+ EOAD patients in LEADS showed greater tau PET signal in a parietal-predominant pattern[127] associated with female sex and younger age of onset.[127,128] Seventy-two percent of clinical EOAD were A+T+ based on PET, while 25% did not show biomarker evidence for underlying AD, warranting further study.[127]

Cerebrovascular-related pathologies also show distinct patterns in the LEADS cohort. They have higher WMH burden relative to early-onset non-AD and controls,[129] in line with a previous study in ADAD that showed elevated parietal and occipital WMHs as early as 22 years

before estimated disease onset.[130] This greater burden of WMHs was associated with elevated meta-ROI tau PET but not with neocortical Aβ PET, after adjustment for clinical diagnosis.[129] Mechanistically, it has been suggested that WMHs in EOAD are potential reflections of genotypic variability[131] or CAA progression. With regard to the latter hypothesis, microbleeds (a late-stage imaging marker linked to probable CAA) only weakly mediated the relationship between AD mutation carriership and WMH.[132] Other mechanisms that link WMH to AD at the level of the neurovascular unit are currently being explored, including angiogenesis, inflammation, blood–brain barrier breakdown, and clearance. For example, a recent study pointed at impaired perivascular clearance and glymphatic dysfunction in EOAD using a diffusion tensor imaging-based approach along the perivascular space (DTI-ALPS).[133] Notably, brain atrophy mediated the relationship between lower DTI-ALPS and cognitive dysfunction both in EOAD and late-onset AD,[133,134] suggesting a protective role of the glymphatic system on cognition indirectly through the preservation of gray matter integrity.

9.2 | Down syndrome

Individuals with Down syndrome (DS) typically develop AD neuropathological changes before the age of 40, primarily due to trisomy 21, which results in the triplication of amyloid precursor protein production and subsequent overproduction of Aβ fibrils, similar to genetic forms of AD. Neuroimaging studies revealed a younger onset of AD pathology in DS compared to ADAD.[135] The younger onset of AD in DS may be, in part, explained by higher levels of tau prions with older age at death (a pattern opposite to that seen in AD patients), suggesting a more aggressive form of tau seeds in DS.[136] The regions most prominently affected on tau PET in DS are subcortical and MTL regions, compared to the precuneus, fusiform gyrus, and other MTL regions in ADAD.[135] Interestingly, DS individuals exhibited delayed global Aβ accumulation relative to presenilin-1 ADAD carriers[137] but the magnitude of tau PET for a given level of Aβ PET was higher.[135] This compression of Aβ and tau buildup at nearly the same time in DS was also supported by the longitudinal findings from Lao et al.[138] Here, the earliest age-associated changes in DS corresponded to vascular changes (MRI-visible perivascular spaces and infarcts) at age 31, followed by global Aβ PET, early Braak stage tau PET, and frontoparietal WMH increases at age 35, and later Braak stage tau at age 37. Together, these findings reveal an accelerated disease course in DS relative to ADAD despite their overlapping genetic risks, likely further influenced by DS-specific comorbidities such as oxidative stress, metabolic dysregulation, and inflammation.[135]

Despite a low incidence of systemic vascular risk factors in DS, neuroimaging studies have identified changes in cerebrovascular-related pathology. WMHs appeared a decade before symptom onset[139] and are directly and indirectly associated with p-tau217 levels through astroglial reactivity (GFAP).[140] This astroglial reactivity, in turn, promoted tauopathy in presymptomatic stages of AD-DS pathology.[140] Another marker of cerebrovascular pathology, cortical microinfarcts, displayed a parietal-dominant posterior pattern in DS dementia with a prevalence of ≈ 12%, which is comparable to sporadic AD but notably higher than controls.[141] Given the overall lesser involvement of vascular risk factors in AD-DS, the comparable microinfarct rates between DS dementia and sporadic AD may suggest a role for non-hemorrhagic CAA contribution in AD-DS.[141] Together, these findings underscore the critical role of cerebrovascular pathology in clinical trial design for this population.

9.3 | Variants of atypical AD and frontotemporal dementia

Atypical clinical phenotypes, accounting for 6% to 14% of all AD cases,[142] present distinct imaging features that distinguish them from typical AD, as discussed in a recent review.[143] For example, primary progressive aphasia (PPA) presented with greater impairment in emotion processing than typical AD, which was linked to frontal and temporal atrophy in the non-fluent and logopenic variants of PPA, respectively.[144] Another atypical AD variant, that is, posterior cortical atrophy (PCA), demonstrated slower rates of tau PET accumulation in the right temporoparietal and occipital regions compared to logopenic variant PPA.[145] Vascular contributions to PCA variants were also distinct relative to typical AD, with lower frequencies of lobar microbleeds in PCA.[146] Regional inflammation further distinguished PCA from AD, with elevated parietal GFAP and activated myeloid cells (MHC-II) in the fusiform gyrus in PCA, contrasting hippocampal-dominant MHC-II and complement factor (CD68) in AD.[147]

Among frontotemporal dementia (FTD) variants, Planche et al.[148] observed a "radiological" prodromal phase of 8 to 10 years, with amygdalar and striatal atrophy consistently preceding degeneration of the more typical language and behavioral networks. In behavioral variant FTD (bvFTD), a novel MRI-based atrophy signature spanned large-scale prefrontal and temporal networks, extending well beyond the traditionally proposed salience network.[149] The left anterior insula and supplementary motor area are known disease epicenters in bvFTD and non-fluent variant PPA, respectively, and exhibited widespread decreased functional connections to bilateral cortical regions.[149] These studies suggest alterations of multiple large-scale networks at play in FTD. Future work should investigate the relationship between connectivity and abnormal protein spread among atypical AD and FTD subtypes. Moving forward, the use of AD biomarkers, together with better recognition of atypical and FTD phenotypes, can refine differential diagnostic accuracy and better guide individual treatment.[143]

10 | RISK FACTORS

10.1 | Sex

Females are disproportionately affected by dementia-related disease burden in terms of disability-adjusted life years globally.[150] Susceptibility to AD-related pathology also differs by sex, with A+ females

showing higher CSF p-tau181 concentrations and faster NFT accumulation in AD signature regions compared to males.[151] Notably, the relationship between greater CSF p-tau181 and Aβ PET was modulated by female sex, a three-way interaction that predicted faster tau-PET accumulation across all Braak regions at 2-year follow-up.[151] The sex differences in tau PET were not attributed to off-target extracerebral retention or partial volume effects.[152] In preclinical AD, greater meta-temporal tau PET was related to lower cognition (PACC score) in females but not males.[153] Consequently, tau mediates female-specific cognitive decline in AD—an observation linked to several tau-interacting X-linked escapee genes, such as *USP11*, which drives tau acetylation, impeding its degradation.[154] Other studies have tied the higher tau burden in A+ females to earlier age-at-menopause and late initiation of hormone therapy.[155] Another theory poses a female-driven vascular pathway in AD, with females showing greater burdens of WMH[74] and MRI-visible perivascular spaces[156] with stronger negative impacts on cognition.[157] These results emphasize the necessity of using sex-stratified analyses and provide important prognostic insights into AD pathophysiology based on sex.

There are also critical sex-specific divergences in brain inflammatory processes, including microglia responses. In parallel with prior studies noting greater TSPO PET in healthy females,[158] Aβ plaque–independent TSPO PET uptake was associated with higher Braak II tau PET uptake exclusively in females.[159] Mechanistically, crosstalk between peripheral and central immune cells may contribute to tauopathy differently between sexes, as interleukin 17–signaling neutrophils were shown to interact with microglia to suppress their response to pathology, particularly in female *APOE* ε4 carriers.[160] These findings highlight the role of sex-moderated inflammation and potential complexities of immunomodulation in AD.

10.2 | APOE

Among the growing number of identified genetic risk factors, *APOE* ε4 remains the strongest and most prevalent in sporadic AD. A recent study in > 7000 predominantly White individuals with Aβ PET (included datasets: ADNI, A4, Alzheimer's and Families [ALFA], Wisconsin Registry for Alzheimer's Prevention [WRAP], Open Access Series of Imaging Studies [OASIS-3]) and 1000 individuals with *post mortem* data (dataset: National Alzheimer's Coordinating Center [NACC]) revealed near-full penetrance of AD pathological markers with *APOE* ε4 homozygosity.[161] Symptom onset was predictable in these carriers, similar to that seen in DS and ADAD.[161] In support of this, cortical morphology was found to change over 30 years prior to AD pathological onset in cognitively intact young adult *APOE* ε4 carriers, as they exhibited a thinner and more convoluted cortex as well as lower functional connectivity in the right angular gyrus and DMN.[162,163]

Aβ is associated with neocortical tau PET in the presence of *APOE* ε4 carriership.[164] Compared to a comprehensive genetic risk score for AD (AD-GRS) of 83 genome-wide significant variants omitting *APOE*, only *APOE* ε4 status was linked with higher Aβ PET composite scores as well as more volume loss of AD-signature regions longitudinally.[165] This faster disease progression seen with *APOE* ε4 carriage may be explained by its ability to accelerate Aβ-driven cortical tau spreading across functionally connected regions, particularly at the lower levels of detectable Aβ.[166] Also at low Aβ, another study supported a potential vascular-driven pathway to AD progression in *APOE* ε4 carriers, with widespread cortical blood–brain barrier breakdown based on dynamic contrast-enhanced MRI.[167]

The rare *APOE* ε3 Christchurch (*APOE3*^{Ch}) variant (R136S) has been identified as protective in ADAD,[168,169] delaying neurodegeneration and tau PET uptake, even in the presence of Aβ PET positivity.

10.3 | Education

Higher levels of education contribute to cognitive reserve by promoting brain network adaptability and engendering interindividual differences in neural compensation and AD susceptibility. High school education and occupational complexity independently predict prolonged dementia-free survival time.[170] However, education appears to impact cognition differently depending on the disease stage. In A+ cognitively unimpaired adults, longer education was associated with lower fusiform and left lateral occipital cortical volumes. This underscores that, even with cortical atrophy, higher educational attainment is associated with a greater tolerance to Aβ-related cognitive dysfunction.[171] By contrast, in individuals with subjective cognitive decline, this relationship became inverted such that higher education was associated with a lower tolerance to the effects of Aβ on cognition, potentially related to more subjective awareness.[172] In relation to tau pathology in the clinical stage, education modified the impact of temporal tau PET on AD-signature cortical thinning and cognitive decline, such that there was a protective effect on cognition only at lower levels of tau.[173] However, with increasing tau burden, higher education adversely modified the impact of tau pathology, accelerating cognitive decline and cortical thinning.[173] Importantly, while education seems to be a consistent modifier of the Aβ–tau relationship, effect sizes in research studies remain overall small.

11 | LIMITATIONS

This article followed the Year-In-Review talk at the 2024 Alzheimer's Imaging Consortium, which is hosted annually in North America or Europe. While this consortium consists of experts in the AD neuroimaging field, it also introduces a geographic and community bias that may have skewed the selection of included articles. A recent manuscript by the Alzheimer's Association highlighted that two-thirds of individuals with dementia reside in LMICs, yet the majority of research is centered in high-income countries.[174] Similarly, only 11.6% of the disease-modifying therapies tested in ADRD clinical trials were conducted in LMICs, of which 2% were in low-income countries specifically.[175] In the Global South, despite having achieved notable progress in plasma, neuroimaging, and genetic studies, critical chal-

FIGURE 3 Continent and sex of first/last author for the papers included in this review. A, World map corresponding to the first author's affiliation (figure created with Datawrapper) and bar plots of the first and last authors' affiliations. B, Sex of first and last author. The data were not verified with the authors.

lenges in the form of funding scarcity, infrastructure, and sociocultural barriers remain.[176] Moving forward, it will be critical to ensure the growth of LMIC-focused research and global collaboration.

12 | FUTURE RESEARCH PRIORITIES

We encourage the imaging community in ADRD research to further refine and apply the revised diagnosis and staging framework to improve our understanding of the clinicopathological trajectory of AD. We require longer follow-up studies, longitudinal data from ongoing clinical trials, and multi-site (replication) cohorts extracted from memory clinics, communities, *post mortem* data, racially diverse older adults, and mixed dementia populations. In light of such multi-site/multi-cohort studies, efforts are already underway to harmonize tau PET quantification akin to the established Centiloid scale for Aβ PET and to further develop more sensitive quantitative metrics, universal imaging masks, and positivity cut-offs, particularly at the earlier disease stages.

Based on the papers cited in this review, we observed a significant difference in sex between the first and last author, such that the last author was more frequently male (M/F/Unassigned, first author: 42.1%/53.0%/4.9%, last author: 70.8%/28.7%/0.6%; $P < 0.001$; Figure 3A). With regard to the continent of the first author's affiliation, North America had the most publications (51.3%), followed by Europe (37.2%), and the rest of the world (11.5%; Figure 3B). Last, we also calculated the reporting frequency of race/ethnicity in cohort-based studies and found that race/ethnicity went unreported in 75.2% of the included papers. Of those that reported race/ethnicity, the majority of the study participants were White (78.6%). The consequences of study underrepresentation across strata such as sex, race, ethnicity, and geography can be far reaching, including limited generalizability of results, disparate acceptance of research and trial findings across population groups, and inequitable access to accurate dementia and disease diagnoses.[177–179] Similarly, underrepresentation in clinical research, such as the lower number of female senior authors observed in this review, may affect publication numbers, grant success, promotion opportunities, and leadership appointments. Moving forward, we encourage the ADRD imaging community to collect and report data on race/ethnicity and other demographic characteristics (e.g., education, rurality, socioeconomic status) when establishing new cohorts and replicating their findings within diverse ethnoracial groups. For example, in Latin American and Caribbean countries, risk factors arising from social and health disparities (social determinants of health, cardiometabolic, and mental health risks) were significantly more consequential on cognition and functional ability than classical risk factors such as chronological age and sex.[180] A critical goal will be to advance dementia research in LMICs to be able to achieve a more equitable and globally representative understanding of the disease.[174] In this

regard, research programs such as Africa-FINGERS are essential to implement dementia risk reduction strategies and ensure capacity and infrastructure building and development in these regions.[181]

Now that AD is increasingly recognized as a disease of multiple pathogenic pathways, neuroimaging will be imperative to integrate, through multi-modal and multi-omic approaches, the many factors at play that predict disease development, progression, and clinical phenotype in each individual. While the therapeutic field will be moving toward combinational and more personalized treatment strategies, there is a need to consider which outcome biomarker should be applied for various subtypes and co-pathologies, including those for atypical AD and non-AD dementia, while also considering the intended use of each biomarker (e.g., safety, diagnostic, trial endpoint, patient stratification). For example, despite an urgent need for more region- and stage-specific markers to represent the vascular (V) and inflammatory (I) categories in the revised criteria on AD diagnosis & staging, identifying such V and I markers remains challenging due to heterogeneity. For the "V" contributions, deciphering heterogeneity is needed not only in terms of the biological and genetic pathways involved but also in terms of imaging-derived lesion size and location, vessel dysfunction, and related cognitive deficits, which often manifest with temporal delays relative to lesion appearance. For the "I" contributions to AD, more research is urgently needed to understand the selectivity of PET radioligands for the distinct inflammatory cell states/phenotypes within their local environmental and clinicopathological context. Similarly, PET ligands that detect other targets, including alpha-synuclein, TDP-43, and 4R tauopathies, are underway.

Together, it is clear that different proteins and cell types mutually interact to accelerate AD pathophysiology, and this notion makes it unlikely that a one-size-fits-all *ante mortem* biomarker for AD will ever suffice. This current review presents recent developments and advances in ADRD research and can help generate new avenues of brain imaging research to identify novel biomarkers and pathobiological mechanisms underlying modifiable phenotypes.

ACKNOWLEDGMENTS

This manuscript was facilitated by the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART), through the Neuroimaging Profession Interest Area (PIA). The views and opinions expressed by authors in this publication represent those of the authors and do not necessarily reflect those of the PIA membership, ISTAART, or the Alzheimer's Association. The authors would like to thank the Alzheimer's Association and our survey responders: Anders Fjell, Beau Ances, Brian Gordon, Emma Coomans, Junhao Wen, Ludmila Kucikova, Luiza Santos Machado, Mario Torso, Pulkit Khandelwal, Rik Ossenkoppele, Rosaleena Mohanty, Samuel Lockhart, and anonymous responders. J.O. is supported by the Alzheimer's Association (24AARF-1242638), BrightFocus (A2024012F), and the Alzheimer Society of Canada (ALZ26-021) and the Canadian Institutes for Health Research (CIHR). M.B. is supported by the Intramural Research Program of the National Institutes of Health, National Institute on Aging. M.G. is supported by the Canada Research Chairs program (CRC-2021-00374), the Canadian Institutes for Health Research (CIHR-PJT-190220), and the Alzheimer's Society (ALZ23-05). L.E.M.W. was supported by MultiPark—A Strategic Research Area at Lund University. D.M.C. is supported by funding from the Alzheimer's Society Dementia Research Leaders Fellowship (AS-DRL-23-005), UK Dementia Research Institute which receives its funding from DRI Ltd, funded by the UK Medical Research Council, Alzheimer's Society and Alzheimer's Research UK, Alzheimer's Association (SG-666374-UK BIRTH COHORT), and the National Institute for Health and Care Research University College London Hospitals Biomedical Research Centre. G.S. received funding from the European Union's Horizon 2020 Research and Innovation Program under Marie Sklodowska-Curie action grant agreement number 101061836, an Alzheimer's Association Research Fellowship (AARF-22-972612), the Brightfocus Foundation (A2024007F), the Alzheimerfonden (AF-980942, AF-994514, AF-1012218), Greta och Johan Kocks research grants and travel grants from the Strategic Research Area MultiPark (Multidisciplinary Research in Parkinson's Disease) at Lund University. R.L.J. is funded by the NIH/NIA (P30AG062422) and the Alzheimer's Association (AARG-22-926899). M.S.K. is supported by the CIHR-187890 and the Alzheimer's Society Research Program. M.E. is supported by the ERAPerMed (BMBF, 01KU2203). T.J.B. is supported by National Institutes of Health National Institute on Aging (NIH/NIA; R01 AG080766, P30 AG062715, R01 AG027161).

CONFLICT OF INTEREST STATEMENT

R.L.J. consulted for GE Healthcare. G.S. has received speaker fees from Springer and Adium. J.O., N.O., M.B., A.P.B., M.S.K., D.M.C., M.E., L.E.M.W., M.G., and T.B. have nothing to disclose. Author disclosures are available in the supporting information.

CONSENT STATEMENT

Because this is a review article, no human subjects provided informed consent.

ORCID

Julie Ottoy https://orcid.org/0000-0002-9879-7497

REFERENCES

1. Nichols E, Steinmetz JD, Vollset SE, et al. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health*. 2022;7:e105-e125. doi:10.1016/S2468-2667(21)00249-8
2. Korczyn AD, Grinberg LT. Is Alzheimer disease a disease?. *Nat Rev Neurol*. 2024;20:245-251. doi:10.1038/s41582-024-00940-4
3. Jack CR, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimers Dement*. 2024;20:5143-5169. doi:10.1002/alz.13859
4. Therriault J, Schindler SE, Salvadó G, et al. Biomarker-based staging of Alzheimer disease: rationale and clinical applications. *Nat Rev Neurol*. 2024;20(4):232-244. doi:10.1038/s41582-024-00942-2
5. Collij LE, Bollack A, La Joie R, et al. Centiloid recommendations for clinical context-of-use from the AMYPAD consortium. *Alzheimers Dement*. 2024;20:9037-9048. doi:10.1002/alz.14336

6. Villemagne VL, Leuzy A, Bohorquez SS, et al. CenTauR: toward a universal scale and masks for standardizing tau imaging studies. *Alzheimers Dement*. 2023;15:e12454. doi:10.1002/dad2.12454
7. Leuzy A, Raket LL, Villemagne VL, et al. Harmonizing tau positron emission tomography in Alzheimer's disease: the CenTauR scale and the joint propagation model. *Alzheimers Dement*. 2024;20:5833-5848. doi:10.1002/alz.13908
8. Povala G, Bauer-Negrini G, Bellaver B, et al. Universal tau PET scale (Uniτ)—The HEAD study. *Alzheimers Dement*. 2024;20:e089555. doi:10.1002/alz.089555
9. Landau SM, Harrison TM, Baker SL, et al. Positron emission tomography harmonization in the Alzheimer's Disease Neuroimaging Initiative: a scalable and rigorous approach to multisite amyloid and tau quantification. *Alzheimers Dement*. 2024:alz/14378. doi:10.1002/alz.14378
10. Coomans EM, De Koning LA, Rikken RM, et al. Performance of a [^{18}F]flortaucipir PET visual read method across the Alzheimer disease continuum and in dementia with Lewy bodies. *Neurology*. 2023;101:e1850-e1862. doi:10.1212/WNL.0000000000207794
11. Groot C, Smith R, Collij LE, et al. Tau positron emission tomography for predicting dementia in individuals with mild cognitive impairment. *JAMA Neurol*. 2024;81:845. doi:10.1001/jamaneurol.2024.1612
12. Shcherbinin S, Morris A, Higgins IA, et al. Tau as a diagnostic instrument in clinical trials to predict amyloid in Alzheimer's disease. *Alzheimers Dement*. 2023;9:e12415. doi:10.1002/trc2.12415
13. Shuping JL, Matthews DC, Adamczuk K, et al. Development, initial validation, and application of a visual read method for [18F]MK-6240 tau PET. *Alzheimers Dement*. 2023;9:e12372. doi:10.1002/trc2.12372
14. Seibyl JP, DuBois JM, Racine A, et al. A visual interpretation algorithm for assessing brain tauopathy with 18F-MK-6240 PET. *J Nucl Med*. 2023;64:444-451. doi:10.2967/jnumed.122.264371
15. Bauer T, Brendel M, Zaganjori M, et al. Pragmatic algorithm for visual assessment of 4-Repeat tauopathies in [18F]PI-2620 PET scans. *NeuroImage*. 2025;306:121001. doi:10.1016/j.neuroimage.2025.121001
16. Gérard T, Colmant L, Malotaux V, et al. The spatial extent of tauopathy on [18F]MK-6240 tau PET shows stronger association with cognitive performances than the standard uptake value ratio in Alzheimer's disease. *Eur J Nucl Med Mol Imaging*. 2024;51:1662-1674. doi:10.1007/s00259-024-06603-2
17. St-Onge F, Chapleau M, Breitner JC, Villeneuve S, Pichet Binette A. Tau accumulation and its spatial progression across the Alzheimer's disease spectrum. *Brain Commun*. 2024;6:fcae031. doi:10.1093/braincomms/fcae031
18. Farrell ME, Thibault EG, Becker JA, et al. Spatial extent as a sensitive amyloid-PET metric in preclinical Alzheimer's disease. *Alzheimers Dement*. 2024;20:5434-5449. doi:10.1002/alz.14036
19. Rabinovici GD, Knopman DS, Arbizu J, et al. Updated appropriate use criteria for amyloid and tau PET: a report from the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging Workgroup. *Alzheimers Dement*. 2025;21(1):e14338. doi:10.1002/alz.14338
20. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in Early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA*. 2023;330:512-527. doi:10.1001/jama.2023.13239
21. Sperling Reisa A, Donohue Michael C, Raman R, et al. Trial of solanezumab in preclinical Alzheimer's disease. *N Engl J Med*. 2023;389:1096-10107. doi:10.1056/NEJMoa2305032
22. Sperling RA, Donohue MC, Rissman RA, et al. Amyloid and tau prediction of cognitive and functional decline in unimpaired older individuals: longitudinal data from the A4 and LEARN studies. *J Prev Alzheimers Dis*. 2024;11:802-813. doi:10.14283/jpad.2024.122
23. Rafii MS, Sperling RA, Donohue MC, et al. The AHEAD 3-45 study: design of a prevention trial for Alzheimer's disease. *Alzheimers Dement*. 2023;19:1227-1233. doi:10.1002/alz.12748
24. Edwards AL, Collins JA, Junge C, et al. Exploratory tau biomarker results from a multiple ascending-dose study of BIIB080 in Alzheimer disease: a randomized clinical trial. *JAMA Neurol*. 2023;80:1344-1352. doi:10.1001/jamaneurol.2023.3861
25. Mullard A. Anti-tau antibody stumbles in phase II Alzheimer trial. *Nat Rev Drug Discov*. 2024;23(12):883. doi:10.1038/d41573-024-00180-7
26. Warmenhoven N, Salvadó G, Janelidze S, et al. A comprehensive head-to-head comparison of key plasma phosphorylated tau 217 biomarker tests. *Brain*. 2025;148(2):416-431. doi:10.1101/2024.07.02.24309629
27. Schindler SE, Petersen KK, Saef B, et al. Head-to-head comparison of leading blood tests for Alzheimer's disease pathology. *Alzheimers Dement*. 2024;20(11):8074-8096. doi:10.1101/2024.06.12.24308839
28. Barthélemy NR, Salvadó G, Schindler SE, et al. Highly accurate blood test for Alzheimer's disease is similar or superior to clinical cerebrospinal fluid tests. *Nat Med*. 2024;30:1085-1095. doi:10.1038/s41591-024-02869-z
29. Palmqvist S, Tideman P, Mattsson-Carlgren N, et al. Blood biomarkers to detect Alzheimer disease in primary care and secondary care. *JAMA*. 2024;332:1245. doi:10.1001/jama.2024.13855
30. Mohs RC, Beauregard D, Dwyer J, et al. The Bio-Hermes Study: biomarker database developed to investigate blood-based and digital biomarkers in community-based, diverse populations clinically screened for Alzheimer's disease. *Alzheimers Dement*. 2024;20:2752-2765. doi:10.1002/alz.13722
31. Molina-Henry D, Langford O, Donohue M, et al. Relationship between plasma p-tau217 and amyloid PET in racial and ethnic underrepresented groups (RE-URG) compared with Non RE-URG in LEARN and A4. *J Prev Alz Dis*. 2024;11(4):831-837. doi:10.14283/jpad.2024.124
32. De Meyer S, Schaeverbeke JM, Luckett ES, et al. Plasma pTau181 and pTau217 predict asymptomatic amyloid accumulation equally well as amyloid PET. *Brain Commun*. 2024;6:fcae162. doi:10.1093/braincomms/fcae162
33. Janelidze S, Barthélemy NR, Salvadó G, et al. Plasma phosphorylated tau 217 and Aβ42/40 to predict early brain Aβ accumulation in people without cognitive impairment. *JAMA Neurol*. 2024;81:947. doi:10.1001/jamaneurol.2024.2619
34. Brum WS, Cullen NC, Therriault J, et al. A blood-based biomarker workflow for optimal tau-PET referral in memory clinic settings. *Nat Commun*. 2024;15:2311. doi:10.1038/s41467-024-46603-2
35. Mattsson-Carlgren N, Collij LE, Stomrud E, et al. Plasma biomarker strategy for selecting patients with Alzheimer disease for antiamyloid immunotherapies. *JAMA Neurol*. 2024;81:69-78. doi:10.1001/jamaneurol.2023.4596
36. Smith R, Cullen NC, Pichet Binette A, et al. Tau-PET is superior to phospho-tau when predicting cognitive decline in symptomatic AD patients. *Alzheimers Dement*. 2023;19:2497-2507. doi:10.1002/alz.12875
37. Ossenkoppele R, Salvadó G, Janelidze S, et al. Prediction of future cognitive decline among cognitively unimpaired individuals using measures of soluble phosphorylated tau or tau tangle pathology. medRxiv; 2024. doi:10.1101/2024.06.12.24308824
38. Horie K, Salvadó G, Barthélemy NR, et al. CSF MTBR-tau243 is a specific biomarker of tau tangle pathology in Alzheimer's disease. *Nat Med*. 2023;29:1954-1963. doi:10.1038/s41591-023-02443-z
39. Lantero-Rodriguez J, Montoliu-Gaya L, Benedet AL, et al. CSF p-tau205: a biomarker of tau pathology in Alzheimer's disease. *Acta Neuropathol*. 2024;147:12. doi:10.1007/s00401-023-02659-w

40. Woo MS, Tissot C, Lantero-Rodriguez J, et al. Plasma pTau-217 and N-terminal tau (NTA) enhance sensitivity to identify tau PET positivity in amyloid-β positive individuals. *Alzheimers Dement*. 2024;20:1166-1174. doi:10.1002/alz.13528
41. Lantero-Rodriguez J, Salvadó G, Snellman A, et al. Plasma N-terminal containing tau fragments (NTA-tau): a biomarker of tau deposition in Alzheimer's disease. *Mol Neurodegener*. 2024;19:19. doi:10.1186/s13024-024-00707-x
42. Schöll M, Verberk IMW, Del Campo M, et al. Challenges in the practical implementation of blood biomarkers for Alzheimer's disease. *Lancet Healthy Longev*. 2024;5:100630. doi:10.1016/j.lanhl.2024.07.013
43. Betthauser TJ, Bilgel M, Koscik RL, et al. Multi-method investigation of factors influencing amyloid onset and impairment in three cohorts. *Brain*. 2022;145:4065-4079. doi:10.1093/brain/awac213
44. Cody KA, Langhough RE, Zammit MD, et al. Characterizing brain tau and cognitive decline along the amyloid timeline in Alzheimer's disease. *Brain*. 2024;147:2144-2157. doi:10.1093/brain/awae116
45. Oxtoby NP. Data-driven disease progression modeling. In: Colliot O, ed. *Machine Learning for Brain Disorders*. Springer US; 2023:511-532. doi:10.1007/978-1-0716-3195-9_17
46. Baumeister H, Vogel JW, Insel PS, et al. A generalizable data-driven model of atrophy heterogeneity and progression in memory clinic settings. *Brain*. 2024;147:2400-2413. doi:10.1093/brain/awae118
47. Kim J, Kim J, Park Y-H, et al. Distinct spatiotemporal patterns of cortical thinning in Alzheimer's disease-type cognitive impairment and subcortical vascular cognitive impairment. *Commun Biol*. 2024;7:198. doi:10.1038/s42003-024-05787-5
48. Earnest T, Bani A, Ha SM, et al. Data-driven decomposition and staging of flortaucipir uptake in Alzheimer's disease. *Alzheimers Dement*. 2024;20(6):alz/13769. doi:10.1002/alz.13769
49. Salvadó G, Horie K, Barthélemy NR, et al. Disease staging of Alzheimer's disease using a CSF-based biomarker model. *Nat Aging*. 2024;4(5):1-15. doi:10.1038/s43587-024-00599-y
50. Pommy J, Conant L, Butts AM, et al. A graph theoretic approach to neurodegeneration: five data-driven neuropsychological subtypes in mild cognitive impairment. *Aging Neuropsychol Cogn*. 2023;30:903-922. doi:10.1080/13825585.2022.2163973
51. Yang Z, Wen J, Erus G, et al. Brain aging patterns in a large and diverse cohort of 49,482 individuals. *Nat Med*. 2024;30:3015-3026. doi:10.1038/s41591-024-03144-x
52. Estarellas M, Oxtoby NP, Schott JM, Alexander DC, Young AL. Multimodal subtypes identified in Alzheimer's Disease Neuroimaging Initiative participants by missing-data-enabled subtype and stage inference. *Brain Commun*. 2024;6:fcae219. doi:10.1093/braincomms/fcae219
53. Jia J, Ning Y, Chen M, et al. Biomarker changes during 20 years preceding Alzheimer's disease. *N Engl J Med*. 2024;390:712-722. doi:10.1056/NEJMoa2310168
54. Li Y, Yen D, Hendrix RD, et al. Timing of biomarker changes in sporadic Alzheimer's disease in estimated years from symptom onset. *Ann Neurol*. 2024;95:951-965. doi:10.1002/ana.26891
55. Wojdała AL, Bellomo G, Gaetani L, et al. Trajectories of CSF and plasma biomarkers across Alzheimer's disease continuum: disease staging by NFL, p-tau181, and GFAP. *Neurobiol Dis*. 2023;189:106356. doi:10.1016/j.nbd.2023.106356
56. Bilgel M, An Y, Walker KA, et al. Longitudinal changes in Alzheimer's-related plasma biomarkers and brain amyloid. *Alzheimers Dement*. 2023;19:4335-4345. doi:10.1002/alz.13157
57. Schaap T, Thropp P, Tosun D, Alzheimer's Disease Neuroimaging Initiative. Timing of Alzheimer's disease biomarker progressions: a two-decade observational study from the Alzheimer's Disease Neuroimaging Initiative (ADNI). *Alzheimers Dement*. 2024;20(12):9060-9067. doi:10.1002/alz.14306
58. Bueichekú E, Diez I, Kim C-M, et al. Spatiotemporal patterns of locus coeruleus integrity predict cortical tau and cognition. *Nat Aging*. 2024:1-13. doi:10.1038/s43587-024-00626-y
59. Wen J, Yang Z, Nasrallah IM, et al. Genetic and clinical correlates of two neuroanatomical AI dimensions in the Alzheimer's disease continuum. *Transl Psychiatry*. 2024;14:420. doi:10.1038/s41398-024-03121-5
60. Gebre RK, Rial AM, Raghavan S, et al. Advancing tau PET quantification in Alzheimer disease with machine learning: introducing THETA, a novel tau summary measure. *J Nucl Med*. 2024;65:1473-1480. doi:10.2967/jnumed.123.267273
61. Lew CO, Zhou L, Mazurowski MA, Doraiswamy PM, Petrella JR, Alzheimer's Disease Neuroimaging Initiative. MRI-based deep learning assessment of amyloid, tau, and neurodegeneration biomarker status across the Alzheimer disease spectrum. *Radiology*. 2023;309:e222441. doi:10.1148/radiol.222441
62. Cai Y, Fan X, Zhao L, et al. Comparing machine learning-derived MRI-based and blood-based neurodegeneration biomarkers in predicting syndromal conversion in early AD. *Alzheimers Dement*. 2023;19:4987-4998. doi:10.1002/alz.13083
63. Lee J, Burkett BJ, Min H-K, et al. Synthesizing images of tau pathology from cross-modal neuroimaging using deep learning. *Brain*. 2024;147:980-995. doi:10.1093/brain/awad346
64. Bottani S, Burgos N, Maire A, et al. Evaluation of MRI-based machine learning approaches for computer-aided diagnosis of dementia in a clinical data warehouse. *Med Image Anal*. 2023;89:102903. doi:10.1016/j.media.2023.102903
65. Corriveau-Lecavalier N, Adams JN, Fischer L, Molloy EN, Maass A. Cerebral hyperactivation across the Alzheimer's disease pathological cascade. *Brain Commun*. 2024;6:fcae376. doi:10.1093/braincomms/fcae376
66. Giorgio J, Adams JN, Maass A, Jagust WJ, Breakspear M. Amyloid induced hyperexcitability in default mode network drives medial temporal hyperactivity and early tau accumulation. *Neuron*. 2024;112:676-686.e4. doi:10.1016/j.neuron.2023.11.014
67. Gallego-Rudolf J, Wiesman AI, Pichet Binette A, Villeneuve S, Baillet S. Synergistic association of Aβ and tau pathology with cortical neurophysiology and cognitive decline in asymptomatic older adults. *Nat Neurosci*. 2024;27:2130-2137. doi:10.1038/s41593-024-01763-8
68. Zheng L, Rubinski A, Denecke J, et al. Combined connectomics, MAPT gene expression, and amyloid deposition to explain regional tau deposition in Alzheimer disease. *Ann Neurol*. 2024;95:274-287. doi:10.1002/ana.26818
69. Ottoy J, Kang MS, Tan JXM, et al. Tau follows principal axes of functional and structural brain organization in Alzheimer's disease. *Nat Commun*. 2024;15:5031. doi:10.1038/s41467-024-49300-2
70. Vogel JW, Corriveau-Lecavalier N, Franzmeier N, et al. Connectome-based modelling of neurodegenerative diseases: towards precision medicine and mechanistic insight. *Nat Rev Neurosci*. 2023;24:620-639. doi:10.1038/s41583-023-00731-8
71. Koohi F, Harshfield EL, Markus HS. Contribution of conventional cardiovascular risk factors to brain white matter hyperintensities. *J Am Heart Assoc*. 2023;12:e030676. doi:10.1161/JAHA.123.030676
72. Biesbroek JM, Coenen M, DeCarli C, et al. Amyloid pathology and vascular risk are associated with distinct patterns of cerebral white matter hyperintensities: a multicenter study in 3132 memory clinic patients. *Alzheimers Dement*. 2024;20:2980-2989. doi:10.1002/alz.13765
73. Ottoy J, Ozzoude M, Zukotynski K, et al. Vascular burden and cognition: mediating roles of neurodegeneration and amyloid PET. *Alzheimers Dement*. 2023;19:1503-1517. doi:10.1002/alz.12750
74. Cha W-J, Yi D, Ahn H, et al. Association between brain amyloid deposition and longitudinal changes of white matter hyperintensities. *Alz Res Therapy*. 2024;16:50. doi:10.1186/s13195-024-01417-8

75. Kamal F, Morrison C, Maranzano J, Zeighami Y, Dadar M. White matter hyperintensity trajectories in patients with progressive and stable mild cognitive impairment. *Neurology*. 2023;101:e815-e824. doi:10.1212/WNL.0000000000207514
76. Coomans EM, Van Westen D, Binette AP, et al. Interactions between vascular burden and amyloid-β pathology on trajectories of tau accumulation. *Brain*. 2024;147:949-960. doi:10.1093/brain/awad317
77. Shirzadi Z, Boyle R, Yau W-YW, et al. Vascular contributions to cognitive decline: beyond amyloid and tau in the Harvard Aging Brain Study. *J Cereb Blood Flow Metab*. 2024;44:1319-1328. doi:10.1177/0271678X241237624
78. Morales CD, Cotton-Samuel D, Lao PJ, et al. Small vessel cerebrovascular disease is associated with cognition in prospective Alzheimer's clinical trial participants. *Alzheimers Res Ther*. 2024;16:25. doi:10.1186/s13195-024-01395-x
79. Van Gils V, Ramakers I, Jansen WJ, et al. Contributions of vascular burden and amyloid abnormality to cognitive decline in memory clinic patients. *J Alzheimers Dis Rep*. 2023;7:1299-1311. doi:10.3233/ADR-230040
80. Moonen JEF, Haan R, Bos I, et al. Contributions of amyloid beta and cerebral small vessel disease in clinical decline. *Alzheimers Dement*. 2024;20:1868-1880. doi:10.1002/alz.13607
81. Shirzadi Z, Schultz SA, Yau W-YW, et al. Etiology of white matter hyperintensities in autosomal dominant and sporadic Alzheimer disease. *JAMA Neurol*. 2023;80:1353. doi:10.1001/jamaneurol.2023.3618
82. Bernal J, Menze I, Yakupov R, et al. Longitudinal evidence for a mutually reinforcing relationship between white matter hyperintensities and cortical thickness in cognitively unimpaired older adults. *Alz Res Therapy*. 2024;16:240. doi:10.1186/s13195-024-01606-5
83. DeSimone JC, Wang W, Loewenstein DA, et al. Diffusion MRI relates to plasma Aβ42/40 in PET negative participants without dementia. *Alzheimers Dement*. 2024;20:2830-2842. doi:10.1002/alz.13693
84. Spotorno N, Strandberg O, Stomrud E, et al. Diffusion MRI tracks cortical microstructural changes during the early stages of Alzheimer's disease. *Brain*. 2024;147:961-969. doi:10.1093/brain/awad428
85. Qiu T, Liu Z, Rheault F, et al. Structural white matter properties and cognitive resilience to tau pathology. *Alzheimers Dement*. 2024;20:3364-3377. doi:10.1002/alz.13776
86. Reas ET, Triebswetter C, Banks SJ, McEvoy LK. Effects of APOE2 and APOE4 on brain microstructure in older adults: modification by age, sex, and cognitive status. *Alzheimers Res Ther*. 2024;16:7. doi:10.1186/s13195-023-01380-w
87. Gagliardi G, Rodriguez-Vieitez E, Montal V, et al. Cortical microstructural changes predict tau accumulation and episodic memory decline in older adults harboring amyloid. *Commun Med*. 2023;3:106. doi:10.1038/s43856-023-00324-7
88. Uchida Y, Onda K, Hou Z, Troncoso JC, Mori S, Oishi K. Microstructural neurodegeneration of the entorhinal-hippocampus pathway along the Alzheimer's disease continuum. *J Alzheimers Dis*. 2023;95:1107-1117. doi:10.3233/JAD-230452
89. Gallagher RL, Koscik RL, Moody JF, et al. Neuroimaging of tissue microstructure as a marker of neurodegeneration in the AT(N) framework: defining abnormal neurodegeneration and improving prediction of clinical status. *Alz Res Therapy*. 2023;15:180. doi:10.1186/s13195-023-01281-y
90. Sima DM, Phan TV, Van Eyndhoven S, et al. Artificial intelligence assistive software tool for automated detection and quantification of amyloid-related imaging abnormalities. *JAMA Netw Open*. 2024;7:e2355800. doi:10.1001/jamanetworkopen.2023.55800
91. Gibson E, Ramirez J, Woods LA, et al. segcsvdWMH: a convolutional neural network-based tool for quantifying white matter hyperintensities in heterogeneous patient cohorts. *Hum Brain Mapp*. 2024;45:e70104. doi:10.1002/hbm.70104
92. Bieger A, Rocha A, Bellaver B, et al. Neuroinflammation biomarkers in the AT(N) framework across the Alzheimer's disease continuum. *J Prev Alzheimers Dis*. 2023;10:401-417. doi:10.14283/jpad.2023.54
93. Malpetti M, Franzmeier N, Brendel M. PET imaging to measure neuroinflammation in vivo. *Methods Mol Biol*. 2024;2785:177-193. doi:10.1007/978-1-0716-3774-6_12
94. Ottoy J, De Picker L, Kang MS. Microglial positron emission tomography imaging in vivo: positron emission tomography radioligands: utility in research and clinical practice. In: Tremblay M-È, Verkhratsky A, eds. *Microglia*. Springer International Publishing; 2024:579-589. doi:10.1007/978-3-031-55529-9_32
95. De Picker LJ, Morrens M, Branchi I, et al. TSPO PET brain inflammation imaging: a transdiagnostic systematic review and meta-analysis of 156 case-control studies. *Brain Behav Immun*. 2023;113:415-431. doi:10.1016/j.bbi.2023.07.023
96. Appleton J, Finn Q, Zanotti-Fregonara P, et al. Brain inflammation co-localizes highly with tau in mild cognitive impairment due to early-onset Alzheimer's disease. *Brain*. 2024:awae234. doi:10.1093/brain/awae234
97. Rossano SM, Johnson AS, Smith A, et al. Microglia measured by TSPO PET are associated with Alzheimer's disease pathology and mediate key steps in a disease progression model. *Alzheimers Dement*. 2024;20:2397-2407. doi:10.1002/alz.13699
98. Finze A, Biechele G, Rauchmann B-S, et al. Individual regional associations between Aβ-, tau- and neurodegeneration (ATN) with microglial activation in patients with primary and secondary tauopathies. *Mol Psychiatry*. 2023;28:4438-4450. doi:10.1038/s41380-023-02188-8
99. Ferrari-Souza JP, Lussier FZ, Leffa DT, et al. *APOE* ε4 associates with microglial activation independently of Aβ plaques and tau tangles. *Sci Adv*. 2023;9:eade1474. doi:10.1126/sciadv.ade1474
100. Nutma E, Fancy N, Weinert M, et al. Translocator protein is a marker of activated microglia in rodent models but not human neurodegenerative diseases. *Nat Commun*. 2023;14:5247. doi:10.1038/s41467-023-40937-z
101. Garland EF, Antony H, Kulagowska L, et al. The microglial translocator protein (TSPO) in Alzheimer's disease reflects a phagocytic phenotype. *Acta Neuropathol*. 2024;148:62. doi:10.1007/s00401-024-02822-x
102. Rodriguez-Vieitez E, Kumar A, Malarte M-L, Ioannou K, Rocha FM, Chiotis K. Imaging neuroinflammation: quantification of astrocytosis in a multitracer PET approach. In: Perneczky R, ed. *Biomarkers for Alzheimer's Disease Drug Development*. Springer US; 2024:195-218. doi:10.1007/978-1-0716-3774-6_13
103. Chiotis K, Johansson C, Rodriguez-Vieitez E, et al. Tracking reactive astrogliosis in autosomal dominant and sporadic Alzheimer's disease with multi-modal PET and plasma GFAP. *Mol Neurodegeneration*. 2023;18:60. doi:10.1186/s13024-023-00647-y
104. Villemagne VL, Harada R, Doré V, et al. Assessing reactive astrogliosis with 18F-SMBT-1 across the Alzheimer disease spectrum. *J Nucl Med*. 2022;63:1560-1569. doi:10.2967/jnumed.121.263255
105. Zimmer TS, Orr AL, Orr AG. Astrocytes in selective vulnerability to neurodegenerative disease. *Trends Neurosci*. 2024;47:289-302. doi:10.1016/j.tins.2024.02.008
106. Hayek D, Ziegler G, Kleineidam L, et al. Different inflammatory signatures based on CSF biomarkers relate to preserved or diminished brain structure and cognition. *Mol Psychiatry*. 2024;29:992-1004. doi:10.1038/s41380-023-02387-3
107. Smith R, Capotosti F, Schain M, et al. The α-synuclein PET tracer [18F]ACI-12589 distinguishes multiple system atrophy from other neurodegenerative diseases. *Nat Commun*. 2023;14:6750. doi:10.1038/s41467-023-42305-3
108. Endo H, Ono M, Takado Y, et al. Imaging α-synuclein pathologies in animal models and patients with Parkinson's and related diseases. *Neuron*. 2024;112(15):S0896627324003325. doi:10.1016/j.neuron.2024.05.006

109. Xiang J, Tao Y, Xia Y, et al. Development of an α-synuclein positron emission tomography tracer for imaging synucleinopathies. *Cell*. 2023;186:3350-3367.e19. doi:10.1016/j.cell.2023.06.004
110. Kim HY, Chia WK, Hsieh C-J, et al. A novel brain PET radiotracer for imaging alpha synuclein fibrils in multiple system atrophy. *J Med Chem*. 2023;66:12185-12202. doi:10.1021/acs.jmedchem.3c00779
111. Pees A, Tong J, Birudaraju S, et al. Development of pyridothiophene compounds for PET imaging of α-synuclein. *Chemistry*. 2024;30:e202303921. doi:10.1002/chem.202303921
112. Saturnino Guarino D, Miranda Azpiazu P, Sunnemark D, et al. Identification and in vitro and in vivo characterization of KAC-50.1 as a potential α-synuclein PET radioligand. *ACS Chem Neurosci*. 2024;15:4210-4219. doi:10.1021/acschemneuro.4c00493
113. Di Nanni A, Saw RS, Battisti UM, et al. A fluorescent probe as a lead compound for a selective α-synuclein PET tracer: development of a library of 2-styrylbenzothiazoles and biological evaluation of [18F]PFSB and [18F]MFSB. *ACS Omega*. 2023;8:31450-31467. doi:10.1021/acsomega.3c04292
114. Zeng Q, Zhang X, Li Y, et al. Discovery and evaluation of imidazo[2,1-b][1,3,4]thiadiazole derivatives as new candidates for α-synuclein PET imaging. *J Med Chem*. 2024;67:12695-12710. doi:10.1021/acs.jmedchem.4c00686
115. Liu F-T, Lu J-Y, Li X-Y, et al. ^{18}F-Florzolotau positron emission tomography imaging of tau pathology in the living brains of patients with corticobasal syndrome. *Mov Disord*. 2023;38:579-588. doi:10.1002/mds.29338
116. Liu F-T, Lu J-Y, Li X-Y, et al. ^{18}F-Florzolotau PET imaging captures the distribution patterns and regional vulnerability of tau pathology in progressive supranuclear palsy. *Eur J Nucl Med Mol Imaging*. 2023;50:1395-1405. doi:10.1007/s00259-022-06104-0
117. Lindberg A, Murrell E, Tong J, et al. Ligand-based design of [18F]OXD-2314 for PET imaging in non-Alzheimer's disease tauopathies. *Nat Commun*. 2024;15:5109. doi:10.1038/s41467-024-49258-1
118. Fontana IC, Kumar A, Okamura N, Nordberg A. Multitracer approach to understanding the complexity of reactive astrogliosis in Alzheimer's brains. *ACS Chem Neurosci*. 2024;15:328-336. doi:10.1021/acschemneuro.3c00646
119. Jaisa-aad M, Muñoz-Castro C, Healey MA, Hyman BT, Serrano-Pozo A. Characterization of monoamine oxidase-B (MAO-B) as a biomarker of reactive astrogliosis in Alzheimer's disease and related dementias. *Acta Neuropathol*. 2024;147:66. doi:10.1007/s00401-024-02712-2
120. Kong Y, Maschio CA, Shi X, et al. Relationship between reactive astrocytes, by [18F]SMBT-1 imaging, with amyloid-beta, tau, glucose metabolism, and TSPO in mouse models of Alzheimer's disease. *Mol Neurobiol*. 2024;61(10):8387-8401. doi:10.1007/s12035-024-04106-7
121. Griffiths J, Grant SGN. Synapse pathology in Alzheimer's disease. *Semin Cell Dev Biol*. 2023;139:13-23. doi:10.1016/j.semcdb.2022.05.028
122. Mikkelsen JD, Kaad S, Aripaka SS, Finsen B. Synaptic vesicle glycoprotein 2A (SV2A) levels in the cerebral cortex in patients with Alzheimer's disease: a radioligand binding study in post-mortem brains. *Neurobiol Aging*. 2023;129:50-57. doi:10.1016/j.neurobiolaging.2023.05.003
123. Kumar A, Scarpa M, Nordberg A. Tracing synaptic loss in Alzheimer's brain with SV2A PET-tracer UCB-J. *Alzheimers Dement*. 2024;20:2589-2605. doi:10.1002/alz.13720
124. Shanaki Bavarsad M, Spina S, Oehler A, et al. Comprehensive mapping of synaptic vesicle protein 2A (SV2A) in health and neurodegenerative diseases: a comparative analysis with synaptophysin and ground truth for PET-imaging interpretation. *Acta Neuropathol*. 2024;148:58. doi:10.1007/s00401-024-02816-9
125. McKay NS, Gordon BA, Hornbeck RC, et al. Positron emission tomography and magnetic resonance imaging methods and datasets within the Dominantly Inherited Alzheimer Network (DIAN). *Nat Neurosci*. 2023;26:1449-1460. doi:10.1038/s41593-023-01359-8
126. Touroutoglou A, Katsumi Y, Brickhouse M, et al. The sporadic early-onset Alzheimer's disease signature of atrophy: preliminary findings from the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS) cohort. *Alzheimers Dement*. 2023;19(Suppl 9):S74-S88. doi:10.1002/alz.13466
127. Cho H, Mundada NS, Apostolova LG, et al. Amyloid and tau-PET in early-onset AD: baseline data from the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS). *Alzheimers Dement*. 2023;19(Suppl 9):S98-S114. doi:10.1002/alz.13453
128. Nemes S, Logan PE, Manchella MK, et al. Sex and APOE ε4 carrier effects on atrophy, amyloid PET, and tau PET burden in early-onset Alzheimer's disease. *Alzheimers Dement*. 2023;19:S49-S63. doi:10.1002/alz.13403
129. Eloyan A, Thangarajah M, An N, et al. White matter hyperintensities are higher among early-onset Alzheimer's disease participants than their cognitively normal and early-onset nonAD peers: Longitudinal Early-Onset Alzheimer's Disease Study (LEADS). *Alzheimers Dement*. 2023;19(Suppl 9):S89-S97. doi:10.1002/alz.13402
130. Lee S, Viqar F, Zimmerman ME, et al. White matter hyperintensities are a core feature of Alzheimer's disease: evidence from the dominantly inherited Alzheimer network. *Ann Neurol*. 2016;79:929-939. doi:10.1002/ana.24647
131. Joseph-Mathurin N, Feldman RL, Lu R, et al. Presenilin-1 mutation position influences amyloidosis, small vessel disease, and dementia with disease stage. *Alzheimers Dement*. 2024;20:2680-2697. doi:10.1002/alz.13729
132. Lee S, Zimmerman ME, Narkhede A, et al. White matter hyperintensities and the mediating role of cerebral amyloid angiopathy in dominantly-inherited Alzheimer's disease. *PLoS ONE*. 2018;13:e0195838. doi:10.1371/journal.pone.0195838
133. Chang H, Huang C, Hsu S, et al. Gray matter reserve determines glymphatic system function in young-onset Alzheimer's disease: evidenced by DTI-ALPS and compared with age-matched controls. *Psychiatry Clin Neurosci*. 2023;77:401-409. doi:10.1111/pcn.13557
134. Huang S, Zhang Y, Guo Y, et al. Glymphatic system dysfunction predicts amyloid deposition, neurodegeneration, and clinical progression in Alzheimer's disease. *Alzheimers Dement*. 2024;20:3251-3269. doi:10.1002/alz.13789
135. Wisch JK, McKay NS, Boerwinkle AH, et al. Comparison of tau spread in people with Down syndrome versus autosomal-dominant Alzheimer's disease: a cross-sectional study. *Lancet Neurol*. 2024;23:500-510. doi:10.1016/S1474-4422(24)00084-X
136. Condello C, Maxwell AM, Castillo E, et al. Aβ and tau prions feature in the neuropathogenesis of Down syndrome. *Proc Natl Acad Sci USA*. 2022;119:e2212954119. doi:10.1073/pnas.2212954119
137. Boerwinkle AH, Gordon BA, Wisch J, et al. Comparison of amyloid burden in individuals with Down syndrome versus autosomal dominant Alzheimer's disease: a cross-sectional study. *Lancet Neurol*. 2023;22:55-65. doi:10.1016/S1474-4422(22)00408-2
138. Lao P, Edwards N, Flores-Aguilar L, et al. Cerebrovascular disease emerges with age and Alzheimer's disease in adults with Down syndrome. *Sci Rep*. 2024;14:12334. doi:10.1038/s41598-024-61962-y
139. Morcillo-Nieto AO, Zsadanyi SE, Arriola-Infante JE, et al. Characterization of white matter hyperintensities in Down syndrome. *Alzheimers Dement*. 2024;20:6527-6541. doi:10.1002/alz.14146
140. Edwards NC, Lao PJ, Alshikho MJ, et al. Cerebrovascular disease drives Alzheimer plasma biomarker concentrations in adults with Down syndrome. *Brain Commun*. 2024;6(5):fcae331. doi:10.1101/2023.11.28.23298693
141. Aranha MR, Montal V, Van Den Brink H, et al. Cortical microinfarcts in adults with Down syndrome assessed with 3T-MRI. *Alzheimers Dement*. 2024;20:3906-3917. doi:10.1002/alz.13797

142. Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol*. 2014;13:614-629. doi:10.1016/S1474-4422(14)70090-0
143. Dubois B, Von Arnim CAF, Burnie N, Bozeat S, Cummings J. Biomarkers in Alzheimer's disease: role in early and differential diagnosis and recognition of atypical variants. *Alz Res Therapy*. 2023;15:175. doi:10.1186/s13195-023-01314-6
144. Landin-Romero R, Kumfor F, Ys Lee A, Leyton C, Piguet O. Clinical and cortical trajectories in non-fluent primary progressive aphasia and Alzheimer's disease: a role for emotion processing. *Brain Research*. 2024;1829:148777. doi:10.1016/j.brainres.2024.148777
145. Sintini I, Graff-Radford J, Schwarz CG, et al. Longitudinal rates of atrophy and tau accumulation differ between the visual and language variants of atypical Alzheimer's disease. *Alzheimers Dement*. 2023;19:4396-4406. doi:10.1002/alz.13396
146. Pelak VS, Krishnan V, Serva S, et al. Lobar microbleeds in the posterior cortical atrophy syndrome: a comparison to typical Alzheimer's disease. *Curr Neurol Neurosci Rep*. 2024;24(2):27-33. doi:10.1007/s11910-024-01330-5
147. Boon BDC, Frigerio I, De Gooijer D, et al. Alzheimer's disease clinical variants show distinct neuroinflammatory profiles with neuropathology. *Neuropathology Appl Neurobio*. 2024;50:e13009. doi:10.1111/nan.13009
148. Planche V, Mansencal B, Manjon JV, et al. Anatomical MRI staging of frontotemporal dementia variants. *Alzheimers Dement*. 2023;19:3283-3294. doi:10.1002/alz.12975
149. Agosta F, Spinelli EG, Basaia S, et al. Functional connectivity from disease epicenters in frontotemporal dementia. *Neurology*. 2023;100:e2290-e2303. doi:10.1212/WNL.0000000000207277
150. Patwardhan V, Gil GF, Arrieta A, et al. Differences across the lifespan between females and males in the top 20 causes of disease burden globally: a systematic analysis of the Global Burden of Disease Study 2021. *Lancet Public Health*. 2024;9:e282-e294. doi:10.1016/S2468-2667(24)00053-7
151. Wang Y-T, Therriault J, Servaes S, et al. Sex-specific modulation of amyloid-β on tau phosphorylation underlies faster tangle accumulation in females. *Brain*. 2024;147:1497-1510. doi:10.1093/brain/awad397
152. Scott MR, Edwards NC, Properzi MJ, et al. Contribution of extracerebral tracer retention and partial volume effects to sex differences in Flortaucipir-PET signal. *J Cereb Blood Flow Metab*. 2024;44:131-141. doi:10.1177/0271678X231196978
153. Wang X, Sundermann EE, Buckley RF. Banks SJ, the A4 study team. Sex differences in the association between tau PET and cognitive performance in a non-Hispanic White cohort with preclinical AD. *Alzheimers Dement*. 2024;20:25-33. doi:10.1002/alz.13432
154. Lopez-Lee C, Torres ERS, Carling G, Gan L. Mechanisms of sex differences in Alzheimer's disease. *Neuron*. 2024;112:1208-1221. doi:10.1016/j.neuron.2024.01.024
155. Coughlan GT, Betthauser TJ, Boyle R, et al. Association of age at menopause and hormone therapy use with tau and β-amyloid positron emission tomography. *JAMA Neurol*. 2023;80:462-473. doi:10.1001/jamaneurol.2023.0455
156. Pinho J, Almeida FC, Araújo JM, et al. Sex-specific patterns of cerebral atrophy and enlarged perivascular spaces in patients with cerebral amyloid angiopathy and dementia. *AJNR Am J Neuroradiol*. 2023;44:792-798. doi:10.3174/ajnr.A7900
157. Morrison C, Dadar M, Collins DL. Initiative for the ADN. Sex differences in risk factors, burden, and outcomes of cerebrovascular disease in Alzheimer's disease populations. *Alzheimers Dement*. 2024;20:34-46. doi:10.1002/alz.13452
158. Tuisku J, Plavén-Sigray P, Gaiser EC, et al, Effects of age, BMI and sex on the glial cell marker TSPO — a multicentre [11C]PBR28 HRRT PET study. *Eur J Nucl Med Mol Imaging*. 2019;46:2329-2338. doi:10.1007/s00259-019-04403-7
159. Biechele G, Rauchmann B-S, Janowitz D, et al. Associations between sex, body mass index and the individual microglial response in Alzheimer's disease. *Journal of Neuroinflammation*. 2024;21:30. doi:10.1186/s12974-024-03020-y
160. Rosenzweig N, Kleemann KL, Rust T, et al. Sex-dependent APOE4 neutrophil–microglia interactions drive cognitive impairment in Alzheimer's disease. *Nat Med*. 2024;30:2990-3003. doi:10.1038/s41591-024-03122-3
161. Fortea J, Pegueroles J, Alcolea D, et al. APOE4 homozygosity represents a distinct genetic form of Alzheimer's disease. *Nat Med*. 2024;30:1284-1291. doi:10.1038/s41591-024-02931-w
162. Kucikova L, Zeng J, Muñoz-Neira C, et al. Genetic risk factors of Alzheimer's disease disrupt resting-state functional connectivity in cognitively intact young individuals. *J Neurol*. 2023;270:4949-4958. doi:10.1007/s00415-023-11809-9
163. Huang W, Zeng J, Jia L, et al. Genetic risks of Alzheimer's by APOE and MAPT on cortical morphology in young healthy adults. *Brain Commun*. 2023;5:fcad234. doi:10.1093/braincomms/fcad234
164. Therriault J, Benedet AL, Pascoal TA, et al. APOEε4 potentiates the relationship between amyloid-β and tau pathologies. *Mol Psychiatry*. 2021;26:5977-5988. doi:10.1038/s41380-020-0688-6
165. Saadmaan G, Dalmasso MC, Ramirez A, et al. Alzheimer's disease genetic risk score and neuroimaging in the FINGER lifestyle trial. *Alzheimers Dement*. 2024;20(6):4345-4350. doi:10.1002/alz.13843
166. Steward A, Biel D, Dewenter A, et al. ApoE4 and connectivity-mediated spreading of tau pathology at lower amyloid levels. *JAMA Neurol*. 2023;80:1295-1306. doi:10.1001/jamaneurol.2023.4038
167. Reas ET, Solders SK, Tsiknia A, et al. APOE ε4-related blood-brain barrier breakdown is associated with microstructural abnormalities. *Alzheimers Dement*. 2024. doi:10.1002/alz.14302
168. Quiroz YT, Aguillon D, Aguirre-Acevedo DC, et al. *APOE3* Christchurch heterozygosity and autosomal dominant Alzheimer's disease. *N Engl J Med*. 2024;390:2156-2164. doi:10.1056/NEJMoa2308583
169. Perez-Corredor P, Vanderleest TE, Vacano GN, et al. APOE3 Christchurch modulates β-catenin/Wnt signaling in iPS cell-derived cerebral organoids from Alzheimer's cases. *Front Mol Neurosci*. 2024;17:1373568. doi:10.3389/fnmol.2024.1373568
170. Livingston G, Huntley J, Liu KY, et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. *Lancet*. 2024;404:572-628. doi:10.1016/S0140-6736(24)01296-0
171. Kim H-B, Kim S-H, Um YH, et al. Modulation of associations between education years and cortical volume in Alzheimer's disease vulnerable brain regions by Aβ deposition and APOE ε4 carrier status in cognitively normal older adults. *Front Aging Neurosci*. 2023;15:1248531. doi:10.3389/fnagi.2023.1248531
172. Hönig M, Altomare D, Caprioglio C, et al. Association between years of education and amyloid burden in patients with subjective cognitive decline, MCI, and Alzheimer disease. *Neurology*. 2024;102:e208053. doi:10.1212/WNL.0000000000208053
173. Bocancea DI, Svenningsson AL, van Loenhoud AC, et al. Determinants of cognitive and brain resilience to tau pathology: a longitudinal analysis. *Brain*. 2023;146:3719-3734. doi:10.1093/brain/awad100
174. Kalaria R, Maestre G, Mahinrad S, et al. The 2022 symposium on dementia and brain aging in low- and middle-income countries: highlights on research, diagnosis, care, and impact. *Alzheimers Dement*. 2024;20:4290-4314. doi:10.1002/alz.13836
175. Llibre-Guerra JJ, Heavener A, Brucki SMD, et al. A call for clinical trial globalization in Alzheimer's disease and related dementia. *Alzheimers Dement*. 2023;19:3210-3221. doi:10.1002/alz.12995
176. McGlinchey E, Duran-Aniotz C, Akinyemi R, et al. Biomarkers of neurodegeneration across the Global South. *Lancet Healthy Longev*. 2024;5:100616. doi:10.1016/S2666-7568(24)00132-6
177. Stites SD, Coe NB. Let's not repeat history's mistakes: two cautions to scientists on the use of race in Alzheimer's disease and

Alzheimer's disease related dementias research. *J Alzheimers Dis*. 2023;92:729-740. doi:10.3233/JAD-220507

178. Benson C, Friz A, Mullen S, Block L, Gilmore-Bykovskyi A. Ethical and methodological considerations for evaluating participant views on Alzheimer's and dementia research. *J Empir Res Hum Res Ethics*. 2021;16:88-104. doi:10.1177/1556264620974898
179. Adkins-Jackson PB, Kraal AZ, Hill-Jarrett TG, et al. Riding the merry-go-round of racial disparities in ADRD research. *Alzheimers Dement*. 2023;19:4735-4742. doi:10.1002/alz.13359
180. Santamaria-Garcia H, Sainz-Ballesteros A, Hernandez H, et al. Factors associated with healthy aging in Latin American populations. *Nat Med* 2023;29:2248-2258. doi:10.1038/s41591-023-02495-1
181. Udeh-Momoh CT, Maina R, Anazodo UC, et al. Dementia risk reduction in the African context: multi-national implementation of multimodal strategies to promote healthy brain aging in Africa (the Africa-FINGERS project). *Alzheimers Dement* 2024;20:8987-9003. doi:10.1002/alz.14344

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Ottoy J, Owsicki N, Bilgel M, et al. Recent advances in neuroimaging of Alzheimer's disease and related dementias. *Alzheimer's Dement*. 2025;21:e70648. https://doi.org/10.1002/alz.70648