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REVIEW ARTICLE

Contributions of the Alzheimer's Disease Neuroimaging Initiative to advancing AD research: a targeted review of recent publications

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Abstract

The Alzheimer's Disease Neuroimaging Initiative (ADNI) recently celebrated its 20th anniversary, reflecting two decades of major contributions to Alzheimer's research through open data sharing and longitudinal multimodal assessments. This review synthesizes 122 high-impact studies using ADNI data or biospecimens from 2023 to mid-2025 to clarify mechanisms of Alzheimer's disease (AD) progression. Studies describe impairment of glymphatic clearance and the impact of cerebral small vessel disease, trajectories of amyloid beta and tau deposition, inflammation, metabolic disturbances, synaptic dysfunction, and neurodegeneration, leading to cognitive impairment and neuropsychiatric symptoms. Multifactorial contributions from genetic and epigenetic influences, co-pathologies and comorbidities, and mechanisms of resilience modulate disease progression. Finally, heterogeneity of clinical presentation and disease course is described in the context of multiple contributing factors, highlighting the complexity of AD. By integrating imaging, fluid biomarkers, genetics, and clinical measures, ADNI provides a comprehensive research dataset for unraveling mechanisms underlying AD progression.

KEYWORDS

Alzheimer's disease, Alzheimer's Disease Neuroimaging Initiative (ADNI), amyloid, amyloid beta, bioenergetic disturbances, cerebrovascular disease, disease progression, genetic variants, glymphatic system, gut microbiome, heterogeneity, Lewy body disease, multimodal data integration, neuroimaging and biomarkers, neuroinflammation, neuropsychiatric symptoms, synaptic dysfunction, tau, vascular risk

Highlights

- ADNI studies define AD as a multifactorial and heterogeneous disease.
- Vascular and glymphatic dysfunction influence Aβ and tau dynamics.
- Neuroinflammation and synaptic failure drive disease progression.
- Genetic risk, co-pathologies, and resilience contribute to disease heterogeneity.

1 | INTRODUCTION

The Alzheimer's Disease Neuroimaging Initiative (ADNI) recently celebrated its 20th anniversary, marking two decades of major contributions to Alzheimer's disease (AD) research. Established in 2004, ADNI's primary objective was to identify and validate biomarkers for the early detection and monitoring of AD.[1,2] Over time, it has evolved into a global research resource that continues to inform disease progression, clinical trial design, and more.

ADNI's open-data framework has set a benchmark for collaborative science. To date, more than 26,000 investigators across 169 countries have accessed ADNI's database, which includes longitudinal clinical, cognitive, imaging, genetic, autopsy, and biomarker data from more than 2400 participants.[3] This resource comprises over 185,000 imaging datasets and has supported more than 405 million data downloads.[4]To date, over 7000 publications have used ADNI data and/or samples. ADNI's continued commitment to open science and unrestricted data sharing has led to rapid advancements in biomarker validation, informed development of disease-modifying therapies such as aducanumab, lecanemab, and donanemab,[2–9] and inspired similar efforts worldwide.[10]

The latest phase of the ADNI study, termed ADNI-4, has improved recruitment of a more generalizable cohort,[11] digital screening strategies,[12] and technical approaches in positron emission tomography (PET) quantification and magnetic resonance imaging (MRI) harmonization and includes newly validated plasma AD biomarker data using the Fujirebio Lumipulse platform, autopsy results, genetics, and biostatistical integration.[2,7,13,14] The inclusion of a recently developed seed amplification assay for detecting cerebrospinal fluid (CSF) α-synuclein (α-Syn), the misfolded pathological protein in Lewy body disease (LBD), has allowed in vivo investigation of the role of this co-pathology in AD disease progression. These innovations position ADNI data and samples as key resources for understanding the complex interactions among amyloid beta (Aβ), tau, vascular, inflammatory, and synaptic processes that drive AD progression.

From early 2023 to mid-2025, 1830 peer-reviewed publications used ADNI data or biospecimens as a primary resource or for validation studies (hereafter termed "ADNI studies"). This review offers an overview of influential publications with a research focus and serves as a companion to a review of those publications with a predominantly clinical focus.[15] Whereas this work examines evidence for the mechanistic underpinnings of disease progression, our companion review focuses on how ADNI has contributed to the development of plasma biomarkers, diagnostic and prognostic methods, and improvements to clinical trials and clinical management. These twin reviews are the latest in a sequence of approximately biannual reviews since 2012[16–21] that describe the impact of ADNI data and sample sharing and are distinct from recent ADNI overviews or reviews from ADNI Cores[2,3,5–9,11,22] in their breadth and unbiased assessment of studies.

For the last several decades, the prevailing view of AD pathophysiology has been the amyloid cascade hypothesis, which suggests that Aβ accumulation is an initial event leading to tau deposition, synaptic dysfunction, and neurodegeneration, ultimately causing cognitive decline. However, this model does not fully account for individual variability in AD and other factors that influence disease progression. Recent analyses using ADNI data suggest that vascular and glymphatic dysfunction, neuroinflammation, and synaptic failure interact with classical Aβ and tau pathology in complex ways that are often synergistic rather than additive. Here, we integrate recent ADNI studies that describe the evolving sequence of pathological events in AD and describe how multiple biological processes interact to promote disease progression and neurodegeneration, resulting in the substantial heterogeneity of AD clinical presentations.

2 | RESEARCH METHODOLOGY

We searched PubMed, Web of Science, and Google Scholar using the terms "ADNI" or "Alzheimer's Disease Neuroimaging Initiative" within the EPUB timeframe of January 1, 2023 to June 30, 2025. Publications were reviewed by DV and SK and were excluded if they were reviews, conference proceedings, or preprints or did not use ADNI data/samples. We identified a total of ~1830 ADNI publications, of which 403 focused primarily on clinical improvements and are covered in our companion review. In addition, 1426 were research-oriented publications describing either research methods or focusing on the sequence of pathological events across one or more biological processes and their link to disease progression and neurodegeneration. We excluded 765 publications primarily describing methods and 57 publications on non-AD topics. From the remaining 604 publications, we selected 158 ADNI papers published in journals with a 2024 Journal Impact Factor of 6 or above for inclusion in the main text. We acknowledge that the arbitrary choice of cut point, designed to include major studies while limiting the total publications for inclusion, may have excluded other studies of note. The remaining research-focused ADNI studies are listed in the Supplementary Table, and studies with a

RESEARCH IN CONTEXT

1. **Systematic review**: We searched PubMed, Web of Science, and Google Scholar, identifying ~1830 publications from January 2023 to June 2025 using ADNI data or biospecimens. Our search resulted in 1426 research-focused publications being screened after excluding clinically oriented studies. Of these, 122 studies published in journals with a Journal Impact Factor of >6 were selected for detailed review, focusing on the biological mechanisms of AD progression.
2. **Interpretation**: ADNI studies during this period suggest the linear amyloid cascade model is insufficient to explain AD progression; instead, they support a more integrated view, emphasizing contributions from vascular and glymphatic dysfunction, neuroinflammation, synaptic and metabolic changes, and genetic factors, alongside Aβ and tau pathology. These findings highlight the roles of co-pathologies and resilience in shaping heterogeneous clinical presentation and disease course.
3. **Future directions**: Future studies should clarify how these processes interact and identify earliest changes. Priorities include identifying modifiable pathways (e.g., vascular and inflammatory), defining biologically meaningful AD subtypes, and validating findings in more diverse populations using multimodal biomarkers.

clinical focus are described in our companion review.[15] Exceptions to these criteria were limited to a small number of foundational studies relevant to some of the described studies and several review publications from the recent ADNI Special Issue of Alzheimer's and Dementia, briefly mentioned in the introduction.

3 | A "CANONICAL" AD TRAJECTORY AND BEYOND

Jack et al.[23] proposed a model for the temporal progression of AD biomarkers, positing that Aβ biomarkers become abnormal around two decades before the onset of cognitive symptoms. ADNI longitudinal data, now reaching two decades, represents a unique opportunity to investigate changes observed in disease progression. This framework describes the relative timing of biomarker changes. A study of 90 ADNI participants who transitioned to Aβ positivity within 20 years used the onset of Aβ positivity rather than the onset of cognitive symptoms as a biological disease clock to investigate trajectories of AD biomarkers.[24] Both Aβ PET uptake and CSF Aβ42 began to change substantially around 5 years before the threshold for Aβ positivity (≥20 Centiloid [CL]) on Aβ PET was reached (Figure S1A). Around a year later, hippocampal volume and cortical thickness measures began to decrease significantly, followed by increases in CSF phosphorylated tau at threonine 181 (p-tau181) and total tau (t-tau) just before the onset of Aβ positivity. Significant changes in global cognition and subjective cognitive decline began shortly after the threshold and persisted for the next 2 years (Figure S1B). The authors concluded that these results largely recapitulated the expected biomarker order except for the emergence of neurodegeneration prior to increases in CSF tau. Similarly, the use of positivity thresholds for amyloid and tau PET as an anchor point for assessing the timing of changes in AD blood biomarkers showed the earliest abnormalities in plasma Aβ42/Aβ40 almost 8 years before the threshold for amyloid PET positivity and 14 years before the onset of clinical symptoms.[25] This was closely followed by glial fibrillary acidic protein (GFAP), reflecting astrocytic activation, phosphorylated tau, and, finally, neurofilament light (NfL), reflecting neurodegeneration. Together, these findings refine and test the temporal ordering proposed in the original biomarker curve framework.

In 2024, the Alzheimer's Association (AA) published revised criteria for the diagnosis and staging of AD.[26] The criteria identified a "canonical" trajectory through both biological and clinical stages that individuals who had only or predominantly AD pathology would follow. However, because most elderly individuals do not have only AD pathology but also other pathologies, the AA working group expected that many individuals would not follow this canonical "AD-only" trajectory. In addition, the strength of reserve/resilience mechanisms varies widely from person to person, which again confers interpersonal variance in the relationship between AD biological stage and clinical manifestations as individuals progress through the disease. This was expected and was described extensively in the 2024 AA criteria. Only around a third of ADNI participants staged using the AA working group revised criteria for AD diagnosis (AA-2024),[26] which uses both clinical and biological dimensions to operationalize AD progression, followed the AD-only trajectory.[26,27] This is represented by a diagonal sequence of events from cognitively unimpaired (CU) with Aβ deposition to dementia with Aβ deposition and severe neocortical tau deposition (Figure 1). Most participants deviated from this expected trajectory, having either a better or a worse clinical stage than that predicted by biological stage. A better-than-expected clinical trajectory given someone's AD biological stage can be attributed to cognitive and brain resilience, whereas a worse-than-expected clinical trajectory may be due to a variety of factors such as genetic, epigenetic and sex differences, lifestyle factors, environmental exposures, and the presence of co-pathologies and comorbidities.

Resilience to cognitive decline has been studied using education as a proxy. In ADNI and the Amsterdam Dementia Cohort, higher educational attainment was significantly associated with greater resilience.[28] Higher educational attainment is associated with a slower decline in global cognition and language abilities, along with a median delay of 1.9 years in the onset of brain atrophy.[29]

Social determinants of health may affect cognition, and it is important to consider the adverse impact of socioeconomic factors. In participants from several cohorts, including ADNI, across Latin America and the United States, lower educational attainment was linked to reduced gray matter (GM) volume and functional connectivity in key regions, including the hippocampus and orbitofrontal cortex.[30] Education explained 24.6% to 98.7% of regional differences in brain measures.

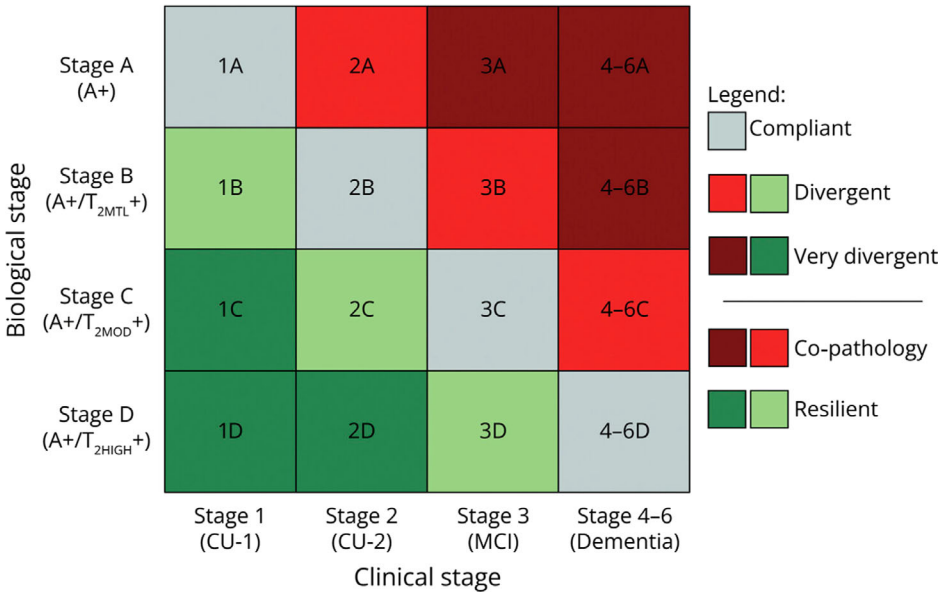

FIGURE 1 Biological and clinical staging framework aligned with the AA-2024 diagnostic criteria. Stages that follow the predicted sequence of the amyloid cascade (main diagonal) are shown in gray. Stages that diverge moderately from this trajectory (the diagonals adjacent to the main diagonal) appear in light red and light green. The most pronounced deviations, found in the corner cells of the matrix, are shown in dark red and dark green. Regions in the upper off-diagonal portion indicate co-pathological stages (light or dark red), whereas the lower off-diagonal region highlights resilient phenotypes (light and dark green), influenced by genetic, epigenetic and sex-related factors. A+, Aβ positive; CU, cognitively unimpaired; MCI, mild cognitive impairment; T+, tau positive. Reproduced under open access from Mendes et al.[27]

High neighborhood disadvantage, including factors like housing quality, employment, education, and income, was associated with worse performance in several cognitive domains and with frontal and temporal cortical morphological disorganization.[31] However, it remains unclear whether any of these social determinants directly cause these effects.

A wide range of processes has been implicated in AD through genetic studies. For example, 17 common and rare variants with functions including transcription, microglial response, and neural development were identified in the *OARD1/NFYA/TREML1*, *JAZF1*, *FERMT2*, *SLC24A4*, and *KAT8* regions, some of which were implicated in other neurodegenerative disorders.[32] Interactions between RNA modifications and programmed cell death also implicate processes such as neuroinflammation and synaptic dysfunction in AD.[33] The complex picture emerging of AD, summarized in Figure 2, shows a sequence of events in disease progression determined not only by the amyloid cascade but also by multiple factors that can both increase disease susceptibility and provide resilience against decline. In the following sections, we will describe ADNI studies that shed light on this progression and explain the heterogeneity in AD clinical presentation and disease course resulting from these multifactorial contributions.

4 | AD DISEASE PROGRESSION

4.1 | Perturbation of Aβ clearance mechanisms and the blood–brain barrier

Impairment of the glymphatic system, which clears AD pathological proteins and metabolic waste products from brain interstitial fluid via the venous perivascular space to lymphatic drainage vessels, has been proposed to contribute to the accumulation of Aβ and tau in their pathological forms early in disease progression. A diffusion tensor imaging (DTI) measure of glymphatic activity, termed the Analysis along the Perivascular Space (ALPS) index, has been used to explore how dysfunction in this clearance pathway affects disease progression.[34,35] In ADNI, with replication in the UK Biobank cohort, the ALPS index increased in Aβ-positive (A+) individuals across disease stages and predicted worsening clinical status[34] (Figure S2). Notably, the ALPS index became abnormal prior to the CSF Aβ42 positivity threshold, then plateaued at the same time as Aβ PET and Preclinical Alzheimer's Cognitive Composite (PACC) scores started to decline. Moreover, the association of the ALPS index with PACC was fully mediated by Aβ PET and brain atrophy. An additional measure, the freewater fraction of the choroid plexus, along with the ALPS index, was higher in A+ compared to Aβ-negative (A−) ADNI participants and predicted Aβ status.[36]

The glymphatic system may be damaged by cerebral small vessel disease (CSVD) in the perivascular pathways. The ALPS index was associated with choroid plexus volume and cognition, and both CSVD and Aβ burden were independently associated with the ALPS index and choroid plexus volume.[35] Similarly, ischemic heart disease was associated with cognitive decline and increased risk of conversion to AD in non-demented ADNI participants.[37] The freewater metric derived from DTI mediated 14% of the relationship between ischemic heart disease and ADNI executive function (EF), suggesting that glymphatic dysfunction partially mediated the link between ischemic heart disease and cognitive dysfunction.[37]

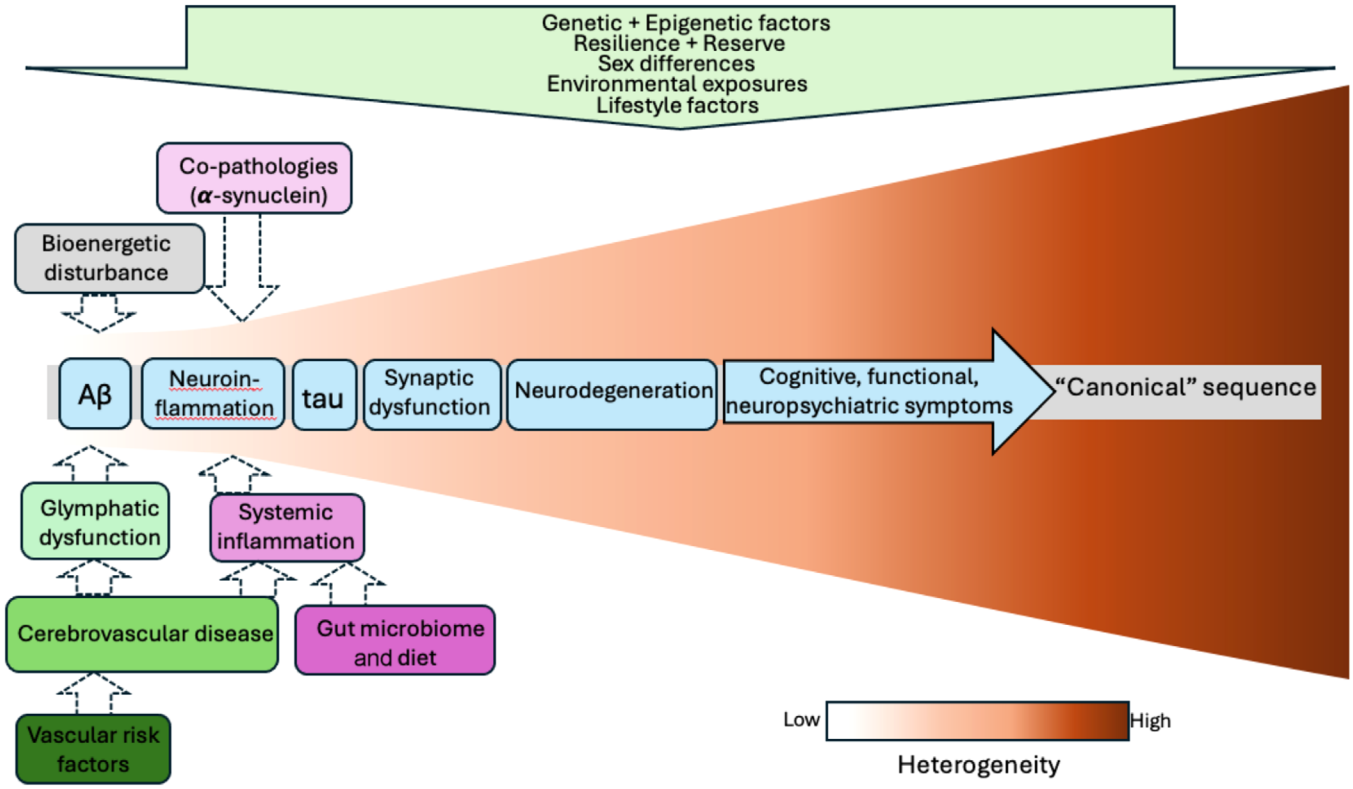

FIGURE 2 Review outline summary. Recent ADNI studies showed that a minority of individuals followed a "canonical" AD-only sequence of disease progression. Different pathways of progression are also observed. Heterogeneity increases over disease progression, influenced by co-pathologies, vascular disease, genetic and epigenetic factors, environmental exposures, lifestyle factors, and brain resilience, resulting in a wide variety of presentations. The overall picture emerging from ADNI studies is as follows: Glymphatic dysfunction, influenced by cerebrovascular disease, impedes the clearance of Aβ, resulting in neuroinflammation and tau deposition. Bioenergetic disturbances may play a role in initiating the amyloid cascade. Microbiome and vascular risk factors exacerbate systemic immune response and neuroinflammation. Co-pathologies such as α-synuclein interact synergistically with early pathology. Synaptic dysfunction follows, leading to tau spread and eventually neurodegeneration, observed as hypometabolism, disruption of brain networks, and atrophy. Finally, clinical symptoms appear as cognitive and functional decline and neuropsychiatric conditions. Every individual has a unique set of factors that define their individual course of progression. Heterogeneity is reflected in distinct patterns of Aβ and tau spread, hypometabolism, and atrophy. These are manifested clinically in the impairment of specific cognitive domains and the appearance of different neuropsychiatric conditions. These studies provide new ideas for future therapies and illustrate the need for personalized medicine approaches to clinical care.

The glymphatic system is most active during deep sleep, and sleep disorders are a risk factor for AD. ADNI participants who reported chronic sleep disturbances had worse baseline cognition and greater cognitive decline.[38,39] In ADNI participants, sleep disturbances interacted with Aβ positivity to disrupt salience network functional connectivity, suggesting exacerbation of an early Aβ-dependent step in disease progression.[40] Sleep disturbance-related cognitive decline may also be associated with a high tau-mediated neutrophil inflammatory response[38] and axonal damage.[39] Treatment of sleep difficulties has been proposed as a means of slowing AD progression; however, some sleep medications have been associated with an increased risk of AD. In ADNI participants as well as in a meta-analysis of 26 longitudinal studies, there was a dose-dependent relationship between the use of benzodiazepines and Z-drugs (e.g., zopiclone, zolpidem), but not melatonin, with an increased risk of AD.[41]

Perturbation of the blood–brain barrier (BBB) can lead to the entry of neurotoxic substances from the blood into the brain, which can induce an inflammatory response and result in Aβ accumulation around cerebral vasculature.[42] In ADNI AD participants, upregulation of *SMAD* expression in pericytes and a downregulation of its molecular partner, *VEGFA*, in astrocytes of the BBB gliovascular unit were associated with lower brain Aβ, less regional atrophy in the temporal, parietal, and frontal lobes, and decreased brain infarcts.

Taken together, these studies suggest that dysfunction of the glymphatic system may occur before Aβ levels reach abnormal thresholds and can predict cognitive decline, mediated by Aβ and neurodegeneration. Glymphatic system dysfunction may partially exacerbate the deleterious effects of ischemic heart disease on cognition. CSVD may contribute to disease progression in an additive manner with Aβ deposition. Sleep disturbances may impede Aβ clearance. However, the cause-and-effect relationship between the glymphatic system and the integrity of the BBB in the development of neurodegeneration and symptoms remains unclear. Changes in the glymphatic system and BBB function may directly influence processes leading

to neurodegeneration, or they may be caused by early pathological changes, or both. Given its clear importance in early-stage disease progression, the glymphatic system has been targeted recently with therapies using pharmacological modulation or non-invasive tools such as phototherapy. Similarly, additional approaches are addressing BBB permeability. ADNI genetics studies may provide additional targets for drug development.

4.2 | Aβ deposition and the influence of the *APOE* ε4 allele and other genetic loci

Recent ADNI studies have yielded insights into the meaning of the discordance of Aβ measures and the underlying genetic and epigenetic factors associated with Aβ deposition. These factors influence the stereotypical pattern of Aβ spread and differ across racial and ethnic groups. CSF Aβ42 and Aβ PET are both used to determine Aβ status but reflect different forms of Aβ: soluble versus fibrillar aggregates, respectively. An imbalance between soluble and fibrillar Aβ species may represent distinct pathways to Aβ abnormality, influenced by apolipoprotein E ε4 (*APOE ε4*), the chromosome 19 allele associated with the highest AD risk.[43] A lower Aβ aggregation score, reflecting relatively more soluble Aβ, was associated with *APOE ε4* homozygosity, male sex, and worse cognition across all clinical stages, whereas a higher score was linked to increased CSF p-tau181 and t-tau and slower cognitive decline (Figure S3).

APOE ε4 strongly impacts Aβ processing and deposition. The *APOE ε4* allele strongly influenced the early transition from A−T− to A+T− in ADNI participants.[44] It was associated with greater Aβ deposition in a dose-dependent manner but not with a significantly different rate of Aβ accumulation compared with *APOE ε3/ε3* homozygotes.[45] *APOE ε4* carriers had greater memory impairment after a shorter period of Aβ positivity than *APOE ε3/ε3* homozygotes, with the most severe effect on memory reported in *APOE ε4/ε4* homozygotes. However, this effect was specific to episodic memory, and *APOE ε4* carriers did not differ from *APOE ε3/ε3* homozygotes in other cognitive domain trajectories. The authors suggest that the *APOE ε4* allele may confer a greater susceptibility to Aβ deposition in the hippocampus, resulting in earlier deficits in episodic memory.

Additional genetic variants likely account for some portion of the heterogeneity in the association between Aβ load and subsequent atrophy and cognitive decline. Regional expression of the Aβ metabolism-related genes, *CLU*, *APP*, *CNTNAP2*, and *TMEM106B*, was associated with regional Aβ deposition in the medial frontal cortex and medial parietal cortex within the Default Mode Network (DMN) and with cognitive impairment, suggesting that expression of these genes contributes to regional vulnerability to Aβ deposition.[46] Different biochemical forms of apolipoprotein E (apoE) and Aβ (insoluble, soluble, and membrane-bound fractions) that result from complex processing were used as endophenotypes in a study that identified eight novel variants.[47] *SCIN* and *NPAS3* were associated with increased membrane-bound apoE and lower AD risk, *SLC9A9*, *RFX7*, *STRN4*, and *KCNN2* were associated with increased membrane bound Aβ40 and higher AD risk, and *ITGB4* was associated with increased soluble Aβ40 and lower AD risk. Pathway analysis of these novel variants implicated synaptic function and immune response among other biological functions, and these variants were functionally related to neuropsychiatric disease and brain health.

A genome-wide methylation analysis of *APOE* genotypes in ADNI, Religious Orders Study/Memory and Aging Project (ROS-MAP), and Framingham Heart Study (FHS) cohorts found seven CpG sites in the *APOE* region (including *TOMM40*, *APOE*, and *APOC1*) that were differentially methylated between *ε4* carriers and non-carriers, affecting expression in brain and blood.[48] Co-methylation network analysis identified networks that included estrogen response pathway genes perturbed by estradiol. This suggests a mechanism of action for the lowering of AD risk in postmenopausal women by hormone replacement therapy with estradiol via differential methylation of the *APOE* locus. However, it should be emphasized that gene methylation studies are conducted on genetic material from peripheral blood, and the extent to which these reflect changes in the brain remains to be determined.

Racial and ethnic differences in the prevalence of Aβ positivity and genetic susceptibility to Aβ deposition are factors to be considered in AD treatment strategies. The prevalence of Aβ positivity differed between Korean (K-ROAD) and non-Hispanic White (NHW) cohorts (ADNI).[49] In CU participants, but not those with mild cognitive impairment (MCI) or AD, Koreans had a significantly lower prevalence of Aβ positivity compared to NHWs, even after adjusting for AD risk factors. However, A+ non-demented Koreans had faster cognitive decline than A+ non-demented NHWs (Figure S4).

In summary, novel genetic variants influence biochemical forms of Aβ and apoE. Relatively more soluble Aβ was linked to *APOE ε4* homozygosity and worse cognition, whereas more insoluble Aβ was associated with a more favorable disease trajectory. The *APOE ε4* allele was associated with greater Aβ deposition and, specifically, with episodic memory impairment, indicating Aβ-related hippocampal atrophy. Differential methylation in the *APOE* region may be related to estrogen response and contribute to the greater prevalence of AD in women. Multiple factors likely contribute to racial and ethnic differences in prevalences of Aβ positivity that should be taken into consideration in management and treatment.

4.3 | Interaction of vascular risk factors with Aβ deposition

Cerebrovascular disease (CVD), which is associated with vascular risk factors, has a profound effect on the human brain. CVD may impede cerebral blood flow, causing ischemia and infarction, leading to white matter hyperintensities (WMHs), cerebral microbleeds (CMBs), and lacunar infarcts and strokes. Recent ADNI studies have begun to unravel the effects and mechanisms of vascular dysfunction, supporting an evolving view that systemic vascular risk may initiate the cascade, leading to the development of Aβ pathology, which in turn becomes the dominant driver of WMHs in later stages. Vascular

changes may affect amyloid/tau/neurodegeneration (ATN) progression and certainly affect development of symptoms caused by the ATN cascade.

Metabolic syndrome is a constellation of vascular risk factors (obesity, hypertension, insulin resistance, and dyslipidemia). A marker of metabolic syndrome, a higher ratio of plasma triglycerides to high-density lipoprotein cholesterol, was associated with faster decline in cognition and function and with type 2 diabetes mellitus (T2DM) in ADNI MCI and AD participants.[50] T2DM, in turn, was associated with accelerated atrophy of the nucleus accumbens, cognitive decline, and progression to dementia in MCI ADNI participants.[51] In a cohort of CU participants from 10 neuroimaging studies including ADNI, hypertension, smoking, obesity, hyperlipidemia, and T2DM were associated with distinct signatures of neuroanatomical change and with worse cognition and greater Aβ deposition.[52] Patterns of neurodegeneration associated with obesity, likely attributable to CVD, inflammation, hypertension, diabetes, and insulin resistance, partially overlapped with patterns of AD-associated neurodegeneration.[53] WMH burden was associated with progression of both A+ MCI to AD and A− MCI to other forms of dementia.[54] Although these studies suggest an association between vascular disease and AD-specific neurodegeneration, the cause-and-effect nature of this association is unclear.

In non-demented (CU and MCI) ADNI participants, interactions between hypertension and Aβ were observed at a low Aβ positivity threshold of 12 CL, indicating that the synergistic interaction between vascular disease and Aβ deposition may occur early in disease progression, consistent with early perturbation of Aβ clearance mechanisms.[55] The AD-associated and independent effects of vascular risk factors may be mediated by regional differences in WMH burden. ADNI participants with preclinical AD (CU A+) had WMHs in predominantly posterior periventricular white matter (WM) regions.[56] Hypertension was associated with deep frontal WMH burden, reduced entorhinal cortex (EC) thickness, and impaired episodic memory in A− non-demented ADNI participants, but with occipital and medial temporal lobe (MTL) WMH burden, increased EC tau deposition, reduced EC thickness, and impaired episodic memory in A+ participants.[55] These effects of hypertension may be mediated by regional hypoperfusion, with Aβ positivity associated with reduced cerebral blood flow in occipital and MTL regions, but lack of Aβ positivity associated with reduced cerebral blood flow in frontal regions.[55] Regional patterns of WMH burden also differed by Aβ status in participants from the Meta VCI Map consortium project of 11 cohorts, including ADNI.[57] Arteriolosclerosis was associated primarily with WMHs in frontal regions, whereas Aβ positivity was associated primarily with WMHs in posterior regions. These studies are consistent with previous work suggesting an independent effect of vascular risk factors on cognition mediated by frontal WMH burden and an AD-associated effect mediated by Aβ and WMH accumulation in posterior regions. The latter appears to be the predominant pathway and affects memory.

ADNI AD participants had greater WMH expansion in frontal regions, suggesting that frontal WMH burden may also be a characteristic of widespread Aβ deposition observed in AD dementia.[56] MCI A+ ADNI participants who progressed to dementia also had widespread WMH accumulation across total, frontal, and temporal regions compared to A− progressors, suggesting that Aβ contributes to WMH beyond posterior regions.[54]

The Aβ-mediated effect on WMH volume may be partly attributed to the presence of cerebral amyloid angiopathy (CAA), which preferentially affects small vessels in posterior brain regions.[57] Longitudinal increases in total WMH volume were greater in ADNI participants with CMBs, indicative of CAA, than in those without, and these increases were associated with GM atrophy and Aβ positivity.[58] In contrast, systemic vascular risk was not associated with baseline or longitudinal WMH volume after accounting for CMBs, Aβ burden, GM atrophy, or age. The authors concluded that WMH volume in AD was primarily related to vessel and parenchymal amyloidosis and neurodegeneration rather than vascular risk factors. Further studies are needed to resolve these inconsistencies.

Given the relationship between Aβ and vascular risk, and the association between the *APOE ε4* allele and Aβ, it might be expected that *APOE ε4* carriers with vascular risk factors would have a greater risk of cognitive decline than non-carriers. Indeed, vascular risk was associated with plasma Aβ42/40 and cerebral Aβ burden in CU *APOE ε4* allele carriers but not in non-carriers from ADNI and the University of California, Davis Alzheimer's Disease Research Center study.[59]

In summary, recent ADNI studies support the effects of vascular risk factors as being an integral part of symptom progression, strongly associated with Aβ deposition. Figure 3 illustrates how systemic vascular risk factors may initiate early pathology, while amyloid pathology becomes the dominant driver of WMH burden in later disease stages. These risk factors can result in hypoperfusion and ischemic injury, impairing glymphatic clearance of Aβ, resulting in Aβ accumulation. Aβ accumulation, in turn, can result in microglial activation and neuroinflammation that exacerbate WMH burden in posterior regions, further impeding Aβ clearance in structurally linked cortical regions. The initial involvement of posterior regions in presymptomatic patients may reflect the preferential localization of CAA in the small vessels of posterior brain regions. Carriage of the *APOE ε4* allele exacerbates this feedforward loop. This process is linked to a unidirectional process of increased MTL tau, MTL atrophy, and memory impairments. Later in disease progression, more widespread WMHs in frontal regions may lead to further cognitive deficits. Vascular risk factors may also affect cognition independently of Aβ via frontal WMHs, but this appears to be the minor pathway. The clinical implications of these studies suggest that managing vascular risk factors such as hypertension, T2DM, and dyslipidemia, for example, is likely to slow disease progression and are discussed in our companion clinical review. It remains unclear whether vascular risk factors or CVD influences the ATN pathway, whether there is a statistical interaction between risk factors and CVD, and what role the ATN pathway itself plays.

4.4 | Immune response and inflammation

Neuroinflammation in response to pathological AD proteins appears to play a role in AD progression. The genetic architecture of brain

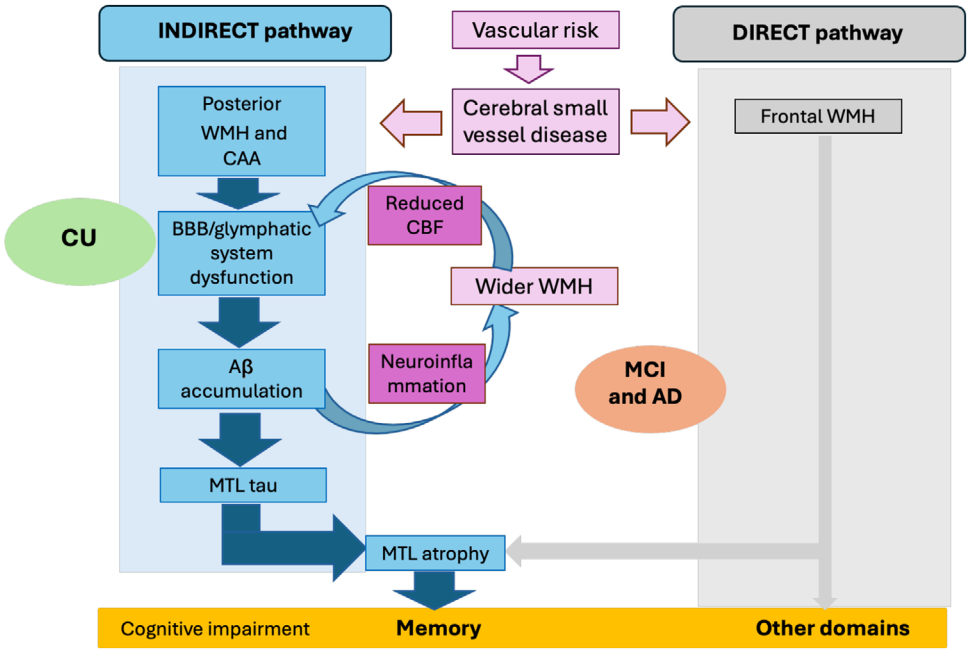

FIGURE 3 Summary of vascular influences in AD. This figure summarizes findings from several studies. Vascular risk factors (obesity, hypertension, insulin resistance, dyslipidemia, and type II diabetes mellitus) are associated with cerebral small vessel disease (CSVD) and the risk of cognitive impairment.[50–52,70] This may occur either directly[53,54] via predominantly frontal WMHs [55] that may lead to MTL atrophy and memory impairment[55] or other cognitive deficits, or indirectly[53,55,58] via predominantly posterior WMHs[55,56,111,112] or CAA,[58] which may perturb the glymphatic system, resulting in Aβ accumulation.[67,70] Neuroinflammation[67] may mediate the effect of Aβ accumulation on increases in WMH burden. Wider WMH burden can lead to reduced regional cerebral blood flow[55,113] and axonal damage, which results in further Aβ accumulation. This synergistic interaction between CSVD and Aβ creates a feedback loop that exacerbates Aβ accumulation even before the onset of clinical symptoms (CU)[56] and is worse in *APOE* ε4 carriers.[59] This may lead to a unidirectional pathway[55] of tau deposition in the MTL, subsequent MTL atrophy, and AD-typical memory deficits.[55] Widespread CSVD develops in MCI and AD, including frontal WMH.[56] The synergistic interaction between CSVD and Aβ appears to be the predominant pathway in AD, with the direct effect of CSVD, with frontal WMH playing a lesser role.

amyloidosis overlapped substantially with that of amyotrophic lateral sclerosis, frontotemporal dementia, and inflammatory disorders such as Crohn's disease, possibly suggesting shared mechanisms between AD and neuroinflammatory disorders.[60] Recent ADNI studies have begun to elucidate the associations between different neuroinflammatory processes, AD pathological biomarkers, and disease progression, suggesting that these associations may be stage-dependent and nuanced.

The Triggering Receptor Expressed on Myeloid Cells (TREM) protein family is involved in microglial activation and neuroinflammatory responses to AD pathology. A key biomarker of microglial activation is soluble TREM2 (sTREM2), which is formed by the cleavage of the extracellular domain of TREM2 and is released into CSF. sTREM2 increased with age across all diagnostic groups but more rapidly after the onset of Aβ deposition early in disease progression.[61] In early Aβ accumulators (A+ on CSF Aβ42 but not Aβ PET), higher but still subthreshold CL was associated with increases in both CSF sTREM2 and p-tau181, and higher CSF sTREM2 was associated with glucose hypermetabolism[62] (Figure S5). In contrast, in late Aβ accumulators (A+ on both CSF and PET), there was no association between CL and sTREM2, and higher sTREM2 was associated with higher CSF p-tau181 and hypometabolism[62] (Figure S5).

CSF progranulin (PGRN) is an additional biomarker of neuroinflammation. It is expressed predominantly in microglia in the brain and regulates lysozyme function. Like elevated CSF sTREM2, higher levels of CSF PGRN were associated with higher levels of CSF p-tau181 and t-tau in participants from the Chinese Alzheimer's Biomarkers and LifEstyle study and ADNI,[63] suggesting both proteins may be neuroinflammatory biomarkers in the context of tau-related neurodegeneration. However, in earlier disease stages, PGRN and sTREM2 interacted synergistically to alleviate Aβ pathology. The association between higher CSF PGRN and higher CSF Aβ42 was partially mediated (~30%) by sTREM2, and conversely, the association between CSF sTREM2 and CSF Aβ42 was partially mediated (~15%) by CSF PGRN (Figure 4). The mechanism for this synergistic protective effect is unknown.

These results support an initial microglial activation, reflected in the observed hypermetabolism and sTREM2 increases, that occurs in response to early Aβ deposition. Increased sTREM2, possibly acting synergistically with PGRN, may initially attenuate Aβ deposition, likely by enhancing microglial phagocytosis of Aβ.[63] Later in disease progression, overactivation of microglia in response to extended exposure to amyloid plaques may elevate pro-inflammatory cytokines, impairing their phagocytosis, and result in the release

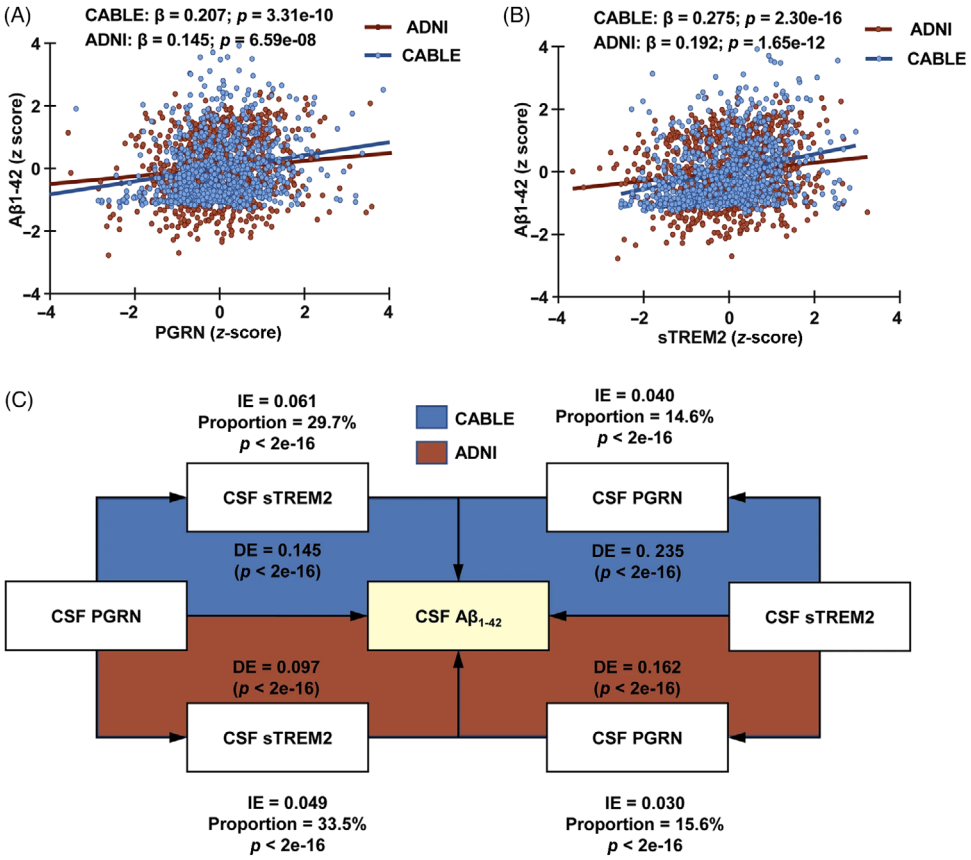

FIGURE 4 Associations between CSF PGRN, CSF sTREM2, and amyloid pathology. (A) Higher CSF progranulin (PGRN) levels were associated with increased CSF A$\beta_{1\text{-}42}$. (B) Higher CSF sTREM2 levels were similarly related to increased CSF A$\beta_{1\text{-}42}$. (C) Mediation analyses showed that PGRN may influence CSF A$\beta_{1\text{-}42}$ partly through its effects on sTREM2, and sTREM2 may likewise affect the relationship between PGRN and A$\beta_{1\text{-}42}$. Data from the CABLE cohort are shown in blue and data from ADNI in red. A$\beta_{1\text{-}42}$, amyloid beta 1-42; ADNI, Alzheimer's Disease Neuroimaging Initiative; CABLE, Chinese Alzheimer's Biomarker and Lifestyle study; CSF, cerebrospinal fluid; PGRN, progranulin; sTREM2, soluble triggering receptor expressed on myeloid cells 2. Reproduced under open access from Huang et al.[63]

of p-tau, ultimately resulting in hypometabolism and cognitive decline.

One potential mechanism for the higher prevalence of AD in women compared to men may be greater reactivity to Aβ, mediated by microglial activation. Female ADNI participants were reported to have a stronger association between sTREM2 and p-tau181 than men,[64] and the deleterious effect of *APOE ε4* carriage on p-tau181 levels was greater in women than in men.[64] Conversely, the *APOE ε2* allele protected against cognitive decline in male carriers only.[65] ApoE4 may have greater neuroinflammatory effects in women than men, and apoE2 may not be protective.

A protective haplotype within the *SORL1* locus (Hap1), involved in the modulation of immune function, was identified in three East Asian cohorts but was rare in European cohorts.[66] Hap1 was protective against abnormal ATN plasma biomarkers, atrophy, and cognitive decline in both *APOE ε4* allele carriers and non-carriers.[66]

Factors that promote inflammation have been associated with increased AD risk. In ADNI CU and MCI participants with hypertension, homozygotes for a risk allele in the innate immune pathway (rs386-5444-C, upstream of CD33) had elevated expression of genes related to BBB dysfunction compared to those without hypertension.[67] The study suggests that genetic variants associated with inflammatory response may influence the association between hypertension and cognitive decline by altering the expression of genes involved in BBB dysfunction. Elevated levels of CSF ferritin, a biomarker of brain iron burden, were associated with inflammatory response proteins in ADNI and BioFINDER CU participants, but with higher CSF p-tau181 and the *APOE ε4* allele in A+ T+ participants, implying that effects of iron on cognition may be mediated by distinct pathways across disease progression.[68] Osteoarthritis, which releases pro-inflammatory cytokines known to promote neuroinflammation,[69] was associated with accelerated Aβ and tau deposition in the precentral and postcentral cortices in ADNI A+ participants.[69]

This influence of systemic inflammation on AD progression may be a common mechanism that links many chronic diseases to AD. A high multimorbidity burden, indicating the co-occurrence of multiple chronic conditions, was associated with a faster rate of brain Aβ accumulation across the cognitive spectrum of ADNI participants.[70] This finding held true for both multimorbidity of the central nervous system (acute injury, depression, anxiety, insomnia, CVD) and

for the peripheral system (including T2DM, hypertension, hyperlipidemia, atrial fibrillation, gastrointestinal disorders, cancer, and hearing loss) (Figure S6). Although individually only eight chronic conditions were reported to be associated with longitudinal Aβ deposition, the study suggests that the cumulative effect of multiple chronic diseases worsens Aβ deposition. The authors suggest that mechanisms for these synergistic effects may include neuroinflammation, neurodegeneration, and perturbation of energy metabolism. However, other explanations are possible. First, factors that increase susceptibility to other diseases may increase susceptibility to AD. Second, conditions that elevate risk for other diseases, such as poor diet, exposure to toxins, and less access to health care, may similarly increase the risk for AD. Consequently, effective management of individual chronic conditions may play an important role in delaying or preventing AD.

These studies emphasize the key role of the neuroinflammatory response in exacerbating disease progression. Microglial activation response to early Aβ deposition may initially be protective, enhancing Aβ phagocytosis, before sustained activation leads to deleterious effects such as tau phosphorylation, hypometabolism, and cognitive decline. These effects appear to be greater in women and in *APOE ε4* allele carriers. Factors involved in immune function and inflammatory response such as genetic variants and brain iron burden can be protective against or heighten the risk of disease progression. Chronic diseases involving systemic inflammation may increase AD risk via increased Aβ deposition and neuroinflammation.

4.5 | Synaptic dysfunction

The synaptic loss that precedes neuronal death may be a common point at which different processes converge to affect AD disease progression. Recent ADNI studies have helped characterize the progressive disruption of synaptic transmission across disease progression, the association between AD pathology and microglial activation, and how presynaptic dysfunction predicts subsequent neurodegeneration and cognitive decline.

Microglial and astrocytic reactivity are associated with synaptic dysfunction, linking neuroinflammation to subsequent neuronal loss and cognitive impairment.[71] Astrocytes, microglia, the pre-synapse, and the post-synapse together form the quad-partite synapse, in which these glial cells modulate synaptic transmission in complex ways that change in aging and in response to AD pathology. Using CSF biomarkers of microglia (sTREM2) and astrocyte (GFAP) reactivity, and of the pre-synapse (Growth Associated Protein 43 [GAP43]) and post-synapse (neurogranin [Ng]), a study in the TRIAD cohort with replication in ADNI examined the associations between glial reactivity and synaptic dysfunction over aging and in association with CSF Aβ42 and p-tau181.[71] Independently of Aβ status, GFAP was associated with both biomarkers of synaptic dysfunction across the cognitive spectrum, suggesting that astrocyte reactivity results in synaptic dysfunction in both aging and AD. In contrast, sTREM2 was associated with only presynaptic dysfunction biomarkers in A+ individuals across the cognitive spectrum. P-tau181 mediated the association between both glial reactivity biomarkers and both synaptic dysfunction biomarkers (Figure 5).

Increased Aβ deposition has been proposed to lead to increased presynaptic inhibition and reduced postsynaptic excitation, progressively disrupting the excitation–inhibition (E–I) balance across CU, MCI, and AD participants in the ADNI.[72] Regional analysis of alterations to the E–I balance identified the greatest progressive impairment in key limbic and cingulate regions associated with AD disease progression, and these alterations correlated with cognitive impairment. Inhibitory connections were more consistently impaired than excitatory connections, possibly reflecting the role of GABAergic dysfunction in AD.[72]

In ADNI CU, MCI, and AD participants stratified by their ATN profiles, abnormal tau but not Aβ pathology was associated with higher baseline and longitudinal CSF GAP43 levels.[73] In ADNI participants stratified by CSF Aβ status alone, CSF GAP43 levels were higher in A+ than A− participants, regardless of diagnostic status, but CSF p-tau181 and t-tau had a far greater effect on these levels than Aβ pathology.[74] Higher baseline levels of CSF GAP43 were associated with greater hypometabolism and atrophy[73] and with greater hypometabolism, atrophy, cognitive decline, and clinical progression in A+ participants.[74] These associations were observed even in CU participants. Abnormal levels of CSF GAP43 were reported in ADNI participants with abnormal CSF p-tau181, regardless of cognitive status.[75] The transition from A+(TN)− to A+(TN)+ was associated with increased CSF Ng, a synaptic biomarker, suggesting synaptic dysfunction plays a role in this transition.[76] Taken together, these studies support the hypothesis of a tau-mediated effect on presynaptic dysfunction that may be Aβ-dependent, occurring as early as preclinical AD but preceding neurodegeneration and cognitive impairment. This is likely mediated by neuroinflammation and microglial phagocytosis of synapses. However, microglial activation may also result in synaptic elimination independently of AD pathology.[77] In ADNI participants and a Chinese cohort, elevated CSF sTREM2 was associated with higher levels of CSF GAP43 independently of Aβ PET and CSF p-tau181 status.

Perturbation of synaptic function may be the point at which the cascade of events beginning with abnormal Aβ deposition intersects with Aβ-independent factors that result in inflammation and neuronal injury. Five principal components (PCs)[1] derived from CSF Aβ42, p-tau181, t-tau, Ng, YLK-40, and NfL that reflect different processes related to AD[78] were used as endophenotypes in a genome-wide association study (GWAS) followed by a transcriptome-wide association study in ADNI and EMIF-AD cohorts.[79] The study identified two novel loci in the *GRIN2D* region that were strongly associated with the PC "non-AD synaptic functioning," driven primarily by CSF Ng. *GRIN2D*, which encodes the GluN2D subunit of the N-methyl-D-aspartate (NMDA) glutamate receptor (NMDAR) and is involved in

[1] Principal components were named (1) "tau pathology/neurodegeneration" loading on p-tau181, tau and, to a lesser extent, Ng (synaptic dysfunction), and YKL-40 (neuronal inflammation); (2) "amyloid pathology" loading on CSF Aβ42; (3) "injury/inflammation" loading on NfL and YKL-40; (4) "non-AD inflammation" loading on YKL-40; and (5) "non-AD synaptic function" loading primarily on Ng.

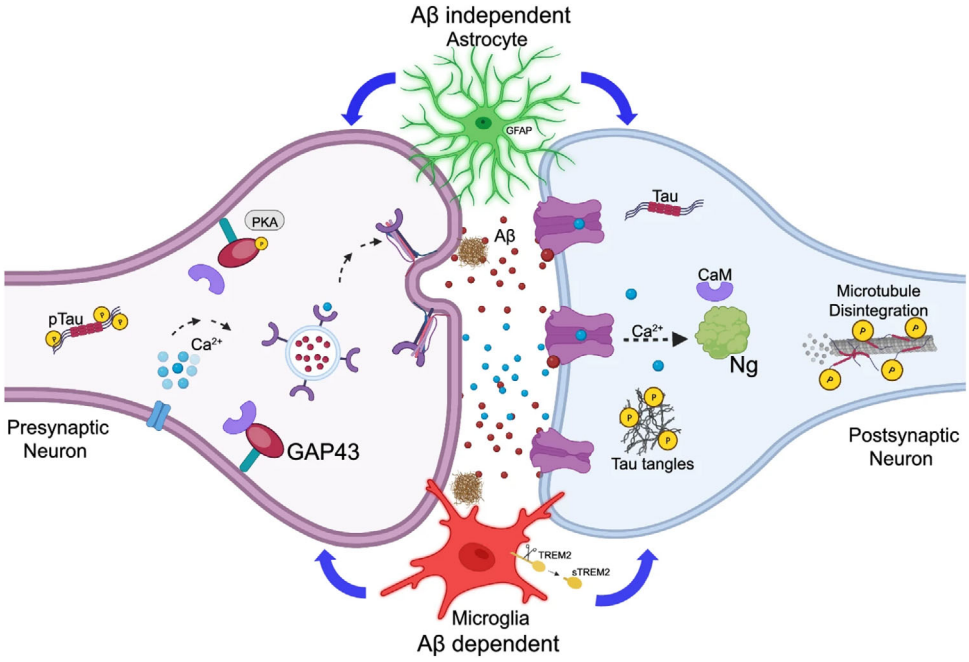

FIGURE 5 Schematic representation of associations between astrocytic and microglial abnormalities and synaptic dysfunction. Astrocyte reactivity, reflected by elevated CSF GFAP levels, is associated with both presynaptic (GAP43) and postsynaptic Ng markers, independent of Aβ pathology. In contrast, microglial activation, represented by sTREM2, shows an Aβ-dependent relationship with synaptic dysfunction, linking to presynaptic dysfunction (GAP43) only in Aβ+ individuals and to postsynaptic dysfunction (Ng) only in the presence of cognitive impairment. The schematic highlights key molecular processes, including p-tau accumulation, Ca^{2+} signaling, and microtubule disintegration, that contribute to neurodegenerative mechanisms. Aβ, amyloid beta; Aβ+, amyloid beta-positive; Ca^{2+}, calcium ion; CSF, cerebrospinal fluid; GAP43, growth-associated protein 43; GFAP, glial fibrillary acidic protein; Ng, neurogranin; p-tau, phosphorylated tau; sTREM2, soluble triggering receptor expressed on myeloid cells 2. Reproduced under open access from Rohden et al.[71]

learning and memory, was previously associated with AD risk but not synaptic function. The authors suggest that *GRIN2D* may exert its effect on AD risk via non-AD-associated synaptic dysfunction. The study also identified known *APOE* loci associated with the amyloid pathology PC, which captures the sequence of Aβ and tau deposition, inflammation, and synaptic dysfunction. In contrast, known loci in *TMEM106B* and *CHI3L1* were associated with the Aβ- and tau deposition-independent injury/inflammation PC and the non-AD inflammation PC, respectively. Mediation analysis suggested the existence of a non-AD-specific neurodegenerative pathway, driven by variants in *GRIN2D*, *TMEM106B*, and *CHI3L1* and involving inflammation, synaptic dysfunction, and neuronal injury, that is distinct from the *APOE*-driven AD-specific pathway. *TMEM106B* is a risk gene for TAR DNA-binding protein 43 kDa (TDP-43) proteinopathy, suggesting that co-pathologies may contribute to the non-AD specific pathway.

Early changes in neuronal activity related to Aβ deposition were also reported within the cholinergic system of the basal forebrain, a site known to be selectively vulnerable to AD pathology.[80] Atrophy of cholinergic neurons in the basal forebrain has long been implicated in AD pathogenesis. The cholinergic pathway in the basal forebrain is essential for utilizing the neurotransmitter acetylcholine, targeted by the acetylcholinesterase inhibitors donepezil, rivastigmine, and galantamine for the treatment of AD symptoms. The cholinergic system also regulates neuronal E–I in the prefrontal cortex. Both Aβ and tau have been shown to disturb this balance and increase neuronal excitability.[81,82] Aβ binds to nicotinic acetylcholine receptors to decrease nicotinic signaling. *CHRNA5* encodes an auxiliary subunit of the high-affinity nicotinic acetylcholine receptor expressed in chandelier cells of the prefrontal cortex. A single-nucleotide polymorphism (SNP), rs197990A, that increases *CHRNA5* expression, predicted reduced cortical Aβ load, suggesting that CHRNA5 has a neuroprotective effect via reduced Aβ binding and reduced excitability of chandelier cells.[83]

These studies support synaptic dysfunction as a key link between neuroinflammation and neuronal loss and as a point of convergence between Aβ-dependent and Aβ-independent disease mechanisms. Perturbation of the function of the quad-partite synapse by Aβ-induced microglial and astrocytic reactivity and subsequent tau phosphorylation has been documented using CSF biomarkers. This perturbs the E–I balance across the synapse in key AD-related regions such as the cholinergic system of the basal forebrain and limbic and cingulate regions. Aβ-independent genetic risk variants involved in inflammation may also result in synaptic dysfunction. Maintenance of synaptic plasticity and prevention of synaptic loss are therefore a major focus of AD therapy programs. ADNI studies may provide additional targets for drug development.

4.6 | Tau deposition and spread

The accumulation of successive tau PET scans of ADNI participants since its introduction in 2015 has increasingly enabled the exploration of questions such as the spatiotemporal pattern of tau pathology spread, what determines this pattern, the connection between tau spread and subsequent brain atrophy, and cognitive and functional decline. Recent ADNI studies have contributed to a more nuanced understanding of this critical step in disease progression.

Aβ and tau interact synergistically to exacerbate neurofibrillary tangle (NFT) formation.[84] Aβ deposition appears to influence tau deposition, primarily in early disease progression. A+T+ CU participants from four cohorts, including ADNI, had greater neurodegeneration and cognitive decline than A+T− participants.[85] For each increase of one CL of Aβ PET binding, there was a 4% increase in the odds of having at least one brain region with abnormal tau deposition.[86] Regional Aβ was associated with tau staging in an inversely proportional manner, being most strongly associated with MTL tau abundance.[87] Furthermore, in A+ ADNI participants with subthreshold levels of tau, baseline Aβ deposition in the EC was associated with faster MTL tau accumulation.[88] However, in A+T+ ADNI participants, tau accumulation beyond the MTL was not predicted by regional Aβ but by entorhinal tau.[88]

The interaction between Aβ and tau deposition may differ between males and females. Greater tau phosphorylation for the same level of Aβ deposition has been reported in A+ females from two studies.[64,84] Females from both ADNI and the TRIAD cohort had higher CSF p-tau181 levels and faster tau deposition for the same level of Aβ deposition[84] (Figure S7). A three-way interaction between female sex, Aβ, and p-tau181 significantly predicted faster NFT accumulation.[84]

In addition to its effects on Aβ deposition, the *APOE ε4* allele also affects tau deposition. MCI *APOE ε4* allele carriers had greater levels of tau deposition.[86] These carriers showed a greater increase in tau binding, leading to greater neurodegeneration and cognitive decline. In participants from ADNI and AVID-A05, *ε4* carriers had faster Aβ-mediated tau spread across early Braak stages, occurring at lower levels of Aβ compared to non-carriers.[89] The trajectories of Aβ-related tau deposition diverged between *ε4* carriers and non-carriers at approximately 12 to 15 CL, considerably below the typical cutoff for Aβ positivity of 26 CL, and later converged. This *APOE ε4*-associated increase in tau binding may be due to both direct and Aβ-mediated effects of *APOE ε4*. In preclinical participants from the A4 study and ADNI, Aβ mediated only between 22% and 39% of the total effect of *APOE ε4* on MTL tau, implying that this allele has a substantial direct effect on tau deposition in this region (Figure S8).[90] *APOE ε2* had both Aβ-mediated and direct effects on neocortical tau whereas *APOE ε4* had only Aβ-mediated effects in this region.

In contrast to the A− to A+ transition, which was dominated by the *APOE ε4* allele, the transition from A+T− to A+T+ was influenced to a greater extent by a polygenic risk score (PRS), suggesting additional loci are more influential at this later stage in disease progression.[44] A GWAS using tau PET as an endophenotype across 12 studies, including ADNI, identified rs2113389, a locus between *RMDN2* and *CYP1B*. The minor T allele of this variant was associated with higher CSF p-tau181 and t-tau, and higher MTL and cortical tau in AD-typical regions.[91] This locus explained 4.3% of the variation in cortical tau, compared to 3.6% for *APOE ε4* rs429358, and was additive to the effects of diagnosis, *APOE ε4*, and Aβ positivity on tau PET binding (Figure S9). CYP1B1 belongs to the cytochrome P450 family, which is involved in oxidative, fatty acid, and cholesterol metabolism, among other functions. Tau levels may also be modulated by epistatic interactions. A genome-wide epistasis study of CSF p-tau181 in ADNI identified five pairwise interactions between previously identified AD-related genes that explained a significant amount of p-tau181 variance.[92]

Tau spread may be associated with underlying gene expression patterns. Regional MAPT gene expression explained around 8% of the variance in tau PET region of interest (ROI) values across three cohorts, including ADNI.[93] Regional expression of established AD risk alleles, including *APOE ε4*, *CD33*, *APH1B*, *SORL1*, and *TREM2*, was strongly positively associated with MTL tau binding, while others were strongly negatively associated with later tau binding stages.[87] Similarly, regional expression of *APOE ε4*, *MAPT*, *AGRN*, and *PLD3* was positively associated with tau spread, whereas *ADAMTS4 and CD2AP* were negatively associated with tau spread.[46] Gene sets related to tau spread included proteins with synaptic and post-synaptic functions.[46] Pre- and post-synaptic proteins, brain-derived neurotrophic factor, neurexin, and NMDARs were also implicated in gene set enrichment and protein–protein interaction analyses of regional transcriptomics related to tau spread.[94] These studies suggest that regional expression of major AD risk alleles and genes involved in synaptic function contributes to patterns of regional tau spread and support the importance of transsynaptic spread of tau fibrils as a major pathomechanism.

Changes in gene expression regulation across disease progression have been linked to tau accumulation. DNA methylation changes in *HOXA5* were associated with tau PET and CSF p-tau181 in AD but not in CU participants.[95]

Properties of brain functional and structural networks may influence tau propagation. Resting state functional MRI (rs-fMRI) detects dynamic networks based on interregional synchronous correlations of blood oxygen level-dependent sequences. Changes in functional brain network organization were associated with spatial patterns of tau propagation and neurodegeneration. Aβ deposition and plasma p-tau217 and p-tau181 were independently associated with lower functional connectivity, and the association between Aβ deposition and perturbations of functional connectivity was fully mediated by plasma p-tau217 across continuous Aβ stages of AD.[96] Myelination of WM tracts may impact the spatial pattern of progression of fibrillar tau along axonal connections.[97] In A+ ADNI participants, lower levels of myelination were associated with higher rates of cortical tau accumulation in Braak stages III–IV and with tau accumulation in connected GM regions.[97] These effects were more pronounced in *APOE ε4* carriers. Lower levels of myelination were also associated with faster decline in memory and global cognition, mediated by tau accumulation. As cholesterol, transported by apoE, is a major component of myelin,

the deleterious *APOE ε4* allele may lead to demyelination and higher rates of tau accumulation in connected regions, ultimately resulting in cognitive decline.

Combinations of these factors likely drive tau spread. Combined connectomic and gene-expression models predicted tau spread[98] and key genes such as *MAPT* and *BACE1* were linked to vulnerability or resilience to tau spread, respectively. In A+ CU ADNI participants, with replication in the A4 study, a multimodal model comprising gradients of gene expression, functional connectivity, myelination, and neurotransmitters explained 76.8% of regional tau PET.[94] In A+ MCI and AD ADNI participants, these predictors, along with Aβ PET, explained 77.4% of regional tau PET variance (Figure S10). The model also explained around 30% to 40% of the variance in individual tau PET levels. In contrast to the studies described above,[86–88] these results suggest that Aβ deposition underlies regional tau spread later rather than earlier in disease progression.

It is well established that tau deposition is closely linked to neurodegeneration and changes in cognition and function. Local tau deposition in the initial seeding regions of the MTL and lateral inferior temporal gyri was significantly associated with remote glucose hypometabolism in neocortical regions, after accounting for the remote effect of spatially distributed Aβ and was not affected by *APOE ε4* genotype in ADNI MCI participants.[99] ADNI preclinical A+T+ participants (stratified by CSF biomarkers) had greater cortical thinning in AD signature regions, greater hippocampal and whole-brain atrophy, an increased risk of progression to MCI or AD, and worse cognitive decline (PACC) compared to A−T− controls.[100] In ADNI CU participants, greater baseline inferior temporal and entorhinal tau were associated with a decline in function (Functional Activities Questionnaire [FAQ]), after adjusting for global Aβ burden,[101] whereas in cognitively impaired (CI) participants, particularly MCI, this functional decline was predicted by broader tau binding in temporal, parietal, and frontal brain regions. Similarly, in ADNI CU participants, baseline tau, particularly in the EC, inferior temporal, and supramarginal regions, was associated with worsening financial capacity (Financial Capacity Instrument – Short Form), whereas in MCI, more widespread tau binding was associated with this loss of function.[102] These results are consistent with the association of initial tau binding within the MTL in preclinical AD with memory and functional decline, the strong association of more widespread tau binding in MCI with impairment of several cognitive domains and functions, and a weaker association in dementia as tau deposition plateaus.

Recent longitudinal tau PET studies support an initial Aβ-dependent tau accumulation in the MTL, a process that was accelerated in women and associated with regional expression of established AD risk alleles. Later in disease progression, tau deposition and spread beyond the MTL were predicted by entorhinal tau in addition to Aβ and influenced by genetic variants involved in synaptic function. These studies support the transsynaptic spread of tau fibrils, which may also be influenced by properties of brain networks such as demyelination and functional connectivity. Regional tau deposition was associated with functional and specific cognitive impairments.

4.7 | Bioenergetic disturbances

Dysregulation of mitochondrial bioenergetic pathways has been implicated in AD as a potential biological basis of cognitive deficits, as it leads to disturbed energy metabolism and increased oxidative stress.[103] This, in turn, is reflected as glucose hypometabolism, often observed in presymptomatic patients. Recent ADNI studies provide further evidence for the effects and mechanisms of bioenergetic disturbances and their relationship to resilience or susceptibility to AD, suggesting targets for clinical interventions.

Mitochondrial dysfunction is reflected in a reduced copy number of mitochondrial DNA (mtDNA).[104] Decreased blood-derived mtDNA copy number was associated with an increased risk of AD and a higher risk of MCI to AD conversion. Reduced copy number was also associated with hypometabolism, worse CSF biomarkers (Aβ42, p-tau181, and t-tau), and plasma NfL, while higher copy number was associated with the *APOE ε2* allele, suggesting this allele may protect against mitochondrial dysfunction. The effect of mtDNA copy number on AD risk was partially mediated by acylcarnitines, which reflect mitochondrial metabolism of fatty acids and proteins. Fasting blood acylcarnitine levels were used to derive a "bioenergetic age" metric in ADNI participants, which showed strong correlations with AD biomarkers, cognitive function, and disease progression.[103] Individuals with a "younger" bioenergetic profile showed slower cognitive decline over 5 years, even when they were chronologically older than their counterparts. Bioenergetic age was influenced by both genetic and environmental factors (Figure 6), and a simulated clinical trial indicated that targeting bioenergetic age with interventions such as ketogenic diets, physical activity, and drugs like Metformin could lead to clinical improvements comparable to anti-amyloid treatments like lecanemab.

Genetic changes contribute to bioenergetic disturbances and result in oxidative stress. A GWAS in ADNI, with replication in UK Biobank, that used time to clinical conversion of non-demented participants as an endophenotype identified loci near *APOE* and a novel locus in *PARL*, encoding a mitochondrial rhomboid protease involved in mitochondrial homeostasis.[105] The minor (A) risk allele of rs6795172 in *PARL* was associated with higher CSF p-tau181 and t-tau levels, regional atrophy, and cognitive decline. AD's link to oxidative stress may involve variation at the *TNIP1/GPX3* locus.[106] *GPX3* encodes glutathione peroxidase 3, which reduces hydrogen peroxide and helps combat rising oxidative stress in the early pathophysiological processes of AD. The minor allele of rs34294852 at the *TNIP1/GPX3* locus was associated with decreased CSF glutathione peroxidase 3 levels and worsening CSF Aβ42 and p-tau181.

An association between a member of the mitochondrial solute carrier family, SLC25, and the rate of hippocampal atrophy was discovered using hippocampal-specific transcriptome-wide association study in two discovery cohorts and subsequently validated in ADNI.[107] A mutation (D47N) within the SHMOOSE mitochondrial microprotein was associated with a 56% increased risk of AD in ADNI participants and replicated across three additional cohorts. SHMOOSE D47N levels

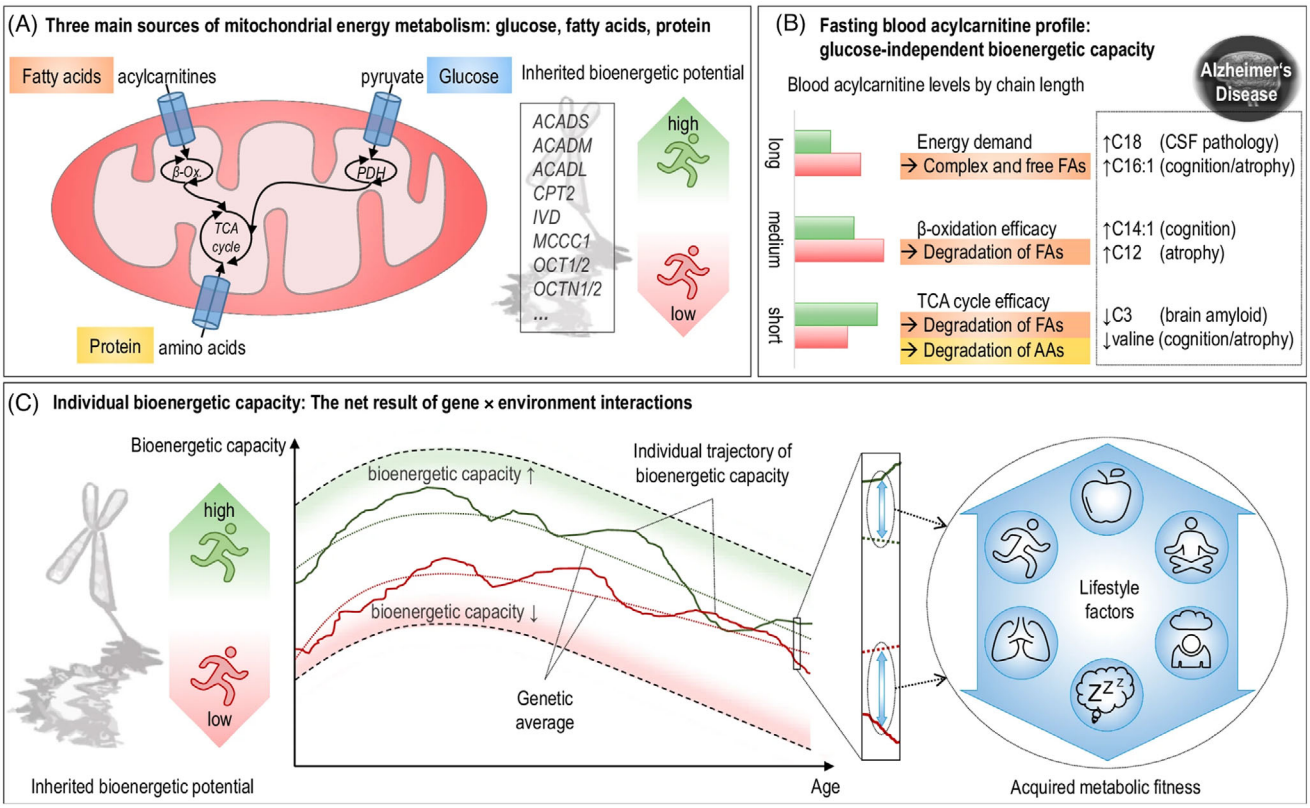

FIGURE 6 Concept of individual bioenergetic capacity mirroring-impaired energy metabolism in the brain. (A) The three main sources of mitochondrial energy metabolism are glucose, fatty acids, and proteins/amino acids, all of which ultimately feed into the TCA cycle. Common genetic variants in mitochondrial transporters and enzymes are assumed to define each individual's inherited bioenergetic potential. The study focuses on fasting individuals, largely removing the effect of dietary glucose and focusing on the fatty acid and protein routes. (B) Chain length-specific role of acylcarnitines as readouts for the bioenergetic capacity through the functionality, activity, and efficiency of mitochondrial energy metabolism, and examples of previously reported acylcarnitine level changes for AD-related phenotypes. (C) Integrated concept of bioenergetic capacity as the age-specific result of inherited bioenergetic potential and acquired modifiable metabolic functionality. Hypothetical trajectories for high and low inherited bioenergetic potential are shown with deviations from the average determined by modifiable lifestyle factors, such as physical activity, diet, health status, and other factors. Deviations from the overall population average are assumed to confer vulnerability or resilience to AD-related pathology and cognitive decline. AD, Alzheimer's disease; FA, fatty acid; AA, amino acid; CSF, cerebrospinal fluid; TCA, tricarboxylic acid; *β*-Ox, beta-oxidation; PDH, pyruvate dehydrogenase complex. Reproduced under open access from Arnold et al.[103]

were correlated with AD-related neuroimaging markers, particularly in limbic regions, as well as CSF p-tau181 and t-tau levels, but not A*β*42, and with WM microstructure. In contrast, expression of wild-type *SHMOOSE*, but not the D47N variant, was increased in AD brains in the temporal cortex and was protective against A*β* pathology. Additional mitochondria-related loci, *IL6ST* (a component of the cytokine receptor complex) and *CTSH* (a lysosomal cysteine proteinase gene), were shown to enhance mitochondrial function and were proposed as candidate biomarkers for resilience.[108]

These studies support mitochondrial dysfunction as a central factor in AD pathogenesis; mitochondrial metabolites such as acylcarnitines may be used to derive a bioenergetic age linked to cognitive decline. Genetic variants related to mitochondrial dysfunction and oxidative stress were associated with susceptibility and resilience to disease progression. Clinical interventions aimed at improving mitochondrial function may have clinical benefits and complement those targeting aspects of the amyloid cascade.

4.8 | Neurodegeneration

Neurodegeneration results from the regional deposition of AD pathology as well as other contributing factors, and leads to cognitive decline. ATN classification uses multiple measures of neurodegeneration, including hypometabolism, CSF t-tau, plasma NfL, and MRI measures of atrophy. Each of these measures reflects slightly different aspects of neurodegeneration and so cannot be considered equivalent. Recent ADNI studies have provided more details on distinct aspects of neurodegeneration. Interestingly, the transition from A+T+N− to A+T+N+ was associated with a marked spike in levels of CSF biomark-

ers reflecting Aβ processing (Aβ38, Aβ40, sAPP) in participants from the ADNI and the BALTAZAR cohorts.[76] This is not predicted by the Jack model of biomarker progression[23] and suggests the existence of a positive feedback loop that augments the amyloid cascade.

4.8.1 | Glucose hypometabolism

Glucose hypometabolism reflects mitochondrial dysfunction and is an early indicator of neurodegeneration. Metabolic networks, constructed from spatial covariance mapping of 18F-fluorodeoxyglucose (FDG) PET images of glucose metabolism, changed throughout disease progression. A characteristic AD-related metabolic pattern comprising reduced glucose metabolism in the precuneus and temporoparietal regions combined with increased metabolism in the primary sensory motor cortex, cerebellum, and pons was expressed most rapidly in progressive MCI followed by progressive CU ADNI participants, but only marginally in stable CU and MCI participants.[109] *APOE ε4* carriage increased the expression of this pattern, which was associated with decline in EF and language composite scores in progressive CU and MCI participants.

4.8.2 | WM microstructural and macrostructural changes

Changes in WM microstructure, such as axonal demyelination, and macrostructure, such as accumulation of WMHs, are important early steps of neurodegeneration. WM microstructural changes are reflected in alterations to fractional anisotropy (FA) measured by diffusion MRI (dMRI). Decreased FA and a faster rate of FA decline were correlated with Aβ deposition and subsequent regional tau deposition.[110] Combined Aβ and tau deposition, and lower FA, each predicted more rapid increases in WMH volume, suggesting a sequence of events comprising initial Aβ deposition, tau aggregation, WM microstructural changes, and finally WM macrostructural changes (i.e., WMHs). However, WM micro- and macrostructural changes may interact to potentiate the effects of each other. Bidirectional causality between FA and WMH was reported in structural subnetworks connected by the inferior longitudinal fasciculus in predominantly posterior medial regions.[111] In addition to microstructural changes in these deep WM fiber tracts, microstructural changes were reported within superficial WM in posterior regions correlating with Aβ and tau deposition.[112] These changes were observed only in A+T+ participants, suggesting they may be triggered by increased tau deposition, consistent with transsynaptic tau spread beginning in these short-range connections directly below the cortex.

Chronic ischemia resulting from CVSD was also linked to axonal degeneration. Long-term elevated blood pressure variability is a risk factor for both AD and CVSD. In ADNI CU and MCI participants, Aβ positivity, in combination with high WMH volume, was associated with the greatest blood pressure variability and the highest levels of plasma NFL.[113] Moreover, plasma NfL mediated the relationship between blood pressure variability, hippocampal atrophy, longitudinal increases in WMH volume, and cognition in these participants, suggesting that the interacting effects of Aβ deposition and blood pressure variability were mediated by axonal damage (Figure S11).

Established AD risk alleles may contribute to alterations in axonal myelination.[114] In participants from seven cohorts, including ADNI, six variants in four genes, *TMEM106B*, *PTK2B*, *WNT3*, and *APOE*, were significantly associated with WM microstructure in the limbic region, with some exerting a protective effect and others being deleterious. An AD PRS and variants in *MS4A6A* identified by interaction analysis were associated with less intact limbic region WM microstructure and cognitive impairment. The genetic risk factors identified in the study were involved in neurodevelopment (*WNT3*), inflammatory mechanisms (*PTK2B*, *MS4A6A*), and lipid metabolism (*APOE*). As perturbations of limbic WM microstructure precede changes in hippocampal microstructure and are associated with early memory dysfunction, these variants may increase AD risk via early disruptions of WM microstructure.

In ADNI participants stratified by ATN, N+ participants had higher levels of NfL, a biomarker of axonal degeneration, regardless of T/N status or levels of CSF GAP43, a biomarker of presynaptic loss.[75] However, levels of plasma NfL and CSF GAP43 interacted to predict MTL atrophy, cortical thinning, hypometabolism, and cognitive impairment, such that participants with high levels of both biomarkers were more likely to experience faster neurodegeneration and cognitive decline.[23,75,76] In summary, changes in WM structure certainly occur as a downstream result of neurodegeneration but may also play a more upstream role to increase risk for developing ATN pathology.

4.8.3 | GM microstructural changes

dMRI measures can be used to explore not only microstructural changes to WM but also GM, such as alterations to cytoarchitecture, neurite loss, and inflammation-associated edema that precede neuronal loss.[115] Cortical microstructure changes reflected by dMRI measures were strongly associated with lower CSF Aβ42 in regions of characterized Aβ deposition such as the EC, isthmus cingulate, and frontal cortex in CU and MCI ADNI participants. Microstructural changes were also associated with higher p-tau181 in frontal and parietal regions of Braak stages V and VI. In contrast, cortical thickness measures were more highly associated with p-tau181 than Aβ42, and only in the EC. The association between CSF biomarkers and cognition (Delayed Logical Memory) was partially mediated by dMRI measures. Similarly, increases in cortical mean diffusivity (cMD) were more sensitive to detecting structural brain alterations than cortical thickness or GM volume in ADNI CI participants, regardless of Aβ PET status.[116] In A+ CI individuals, increases in cMD were driven by cortical tau aggregation and partially explained Aβ-related cognitive decline. In contrast, in CI individuals with suspected non-Alzheimer's pathophysiology (A− [TN+]; SNAP), cMD increases were driven by age and WMHs and completely explained the association between age and cognitive decline. Early Aβ deposition and tau phosphorylation may

therefore initially result in cortical GM microstructural damage that precedes macrostructural changes such as cortical thinning and eventually results in cognitive decline. In SNAP, age and CSVD result in microstructural damage, leading to cognitive impairment.

4.8.4 | Changes to functional connectivity

AD can be considered a disconnection syndrome characterized by progressive degradation of brain networks. Progressive changes to functional connectivity, detected using rs-fMRI, reflect damage to the underlying neuronal networks. An initial compensatory improvement in rs-fMRI metrics may precede disruptions in functional connectivity early in disease progression. Compared to CU and MCI ADNI participants, participants with objectively defined subtle cognitive decline had higher eigenvector centrality (reflecting a node's importance within large-scale brain networks) in the left superior temporal gyrus associated with higher Auditory Verbal Learning Test scores and a higher degree of centrality in the left precuneus associated with higher Mini-Mental State Examination (MMSE) and animal fluency scores.[117] Enhancement of functional networks coinciding with preserved cognition may therefore be a feature of early disease progression, preceding more rapid network degradation and cognitive decline. In ADNI non-demented participants, locus coeruleus–hippocampus functional connectivity was associated with memory performance and moderated by education, whereas locus coeruleus–dorsolateral prefrontal cortex functional connectivity was associated with EF moderated by IQ.[118] These results suggest that preservation of functional networks may contribute to the protective effects of higher education and IQ on cognitive performance in the pre-dementia stages of AD.

Functional networks that incorporated WM regions were also altered in preclinical AD, reflecting WM damage such as myelin loss and axonal damage.[119] The observed reduction in functional connectivity and network segregation in the control, dorsal attention, and somatic motor networks was associated with Aβ deposition (Figure S12). Broader reductions in WM–GM functional connectivity were observed in AD participants and were strongly linked to cognitive impairment.[119] These results suggest that Aβ deposition may affect both GM and WM regions.

4.8.5 | Atrophy

Atrophy becomes measurable following microstructural changes to WM and GM, with MTL atrophy being a hallmark of AD. Monotonic increases in MTL atrophy were observed across worsening CSF biomarker-defined ATN stages (A−T−N− < A+T−N− < A+T+N− < A+T+N+) in both the DELCODE and ADNI cohorts.[120] Other cortical regions had non-monotonic progressions across these ATN stages, consistent with the impact of mixed pathologies that result in different sequences of biomarker abnormality (Section 7.4).

In ADNI A+ CU participants, atrophy of the cortical, central, medial, and accessory basal amygdala subnuclei was associated with temporal tau deposition.[121] Hippocampal subregions were differentially linked to changes in networks of glucose metabolism and deficits in different cognitive domains.[122] Hippocampal subregions divided along the anterior–posterior axis were found to have differences in glucose metabolism and changes in metabolic network connectivity in disease progression. The anterior subiculum was integrated into brain networks involved in object identification and language, whereas the posterior subiculum was associated with networks involved in working memory and memory retrieval. The metabolic imbalance between the anterior and posterior subiculum was most pronounced in late MCI and reflected in pronounced episodic memory deficits. This metabolic imbalance correlated with the spatial expression of genes involved in processes such as mitochondrial function, cellular metabolism, and calcium-mediated signaling, suggesting cellular dysfunction in the subregions (Figure S13). Genes involved in myeloid leukocyte and neutrophil activation may also influence hippocampal microstructure, reflected by radiomic metrics. A hippocampal radiomics model that distinguished accurately between CU and AD participants was associated with the expression of genes involved in peripheral immunity.[123] Later in disease progression, structural alterations to the thalamus related to tau accumulation in the thalamic nuclei correlate with clinical symptoms.[124] ADNI AD participants as well as MCI participants who converted to AD had a generalized atrophy of thalamic nuclei, and MCI converters had significant atrophy of the nucleus reuniens compared to stable MCI participants. This atrophy of the nucleus reuniens significantly predicted conversion from MCI to AD. The nucleus reuniens is a central hub within the thalamic Papez circuit, relaying glutamatergic inputs from the medial prefrontal cortex to the hippocampus and pre-subiculum.

4.8.6 | Genetic contributions to neurodegeneration

AD-specific patterns of neurodegeneration were identified in CU, MCI, and AD participants from the Alzheimer's and Families (ALFA) and ADNI cohorts stratified by Aβ status.[125] Further stratification using an AD PRS excluding the *APOE ε4* allele revealed that not all regions associated with AD-specific neurodegeneration were linked to high genetic risk. However, a higher probability of being in a high-genetic-risk CU A+ group was associated with neurodegeneration in regions including the MTL and temporal and frontal poles. Regions associated with high genetic risk in MCI A+ and AD A+ included the entorhinal and thalamus, and the amygdala and parahippocampal regions, respectively.

4.8.7 | Summary of neurodegeneration studies

Disease progression was characterized by a distinct pattern of glucose hypometabolism, reflecting mitochondrial dysfunction, which was

increased by *APOE ε4* carriage and associated with functional cognitive decline. WM microstructural changes were associated with amyloid and tau deposition, CVSD, and established AD risk alleles. Microstructural changes were reported in both deep and superficial WM fiber tracts and may be related to transsynaptic tau spread. WM microstructural changes may result in macrostructural changes such as WMH. Cortical GM microstructural damage was regionally associated with Aβ and tau and preceded macrostructural damage. Functional networks were progressively degraded after the initial compensatory improvement in response to Aβ deposition, and their preservation may be a resilience mechanism. The transition from N− to N+ was associated with increased Aβ processing, suggesting a feedback loop that augments the amyloid cascade. Finally, GM atrophy was associated with Aβ and tau pathology in the MTL, but wider atrophy may reflect the impact of different pathologies or sequences of abnormality.

4.9 | Cognitive decline

The ultimate result of the chain of pathological events described thus far is cognitive and functional decline. Early changes can be clinically detected by objective or subjective cognitive tests in preclinical individuals. Subjective cognitive decline (SCD) is the perception by either the participant or an informant that their cognitive abilities are worsening compared to a prior level of performance, in the absence of objective cognitive impairment.

Informant-reported SCD has been shown to increase with worsening clinical stage, whereas self-reported SCD has been shown to decrease, reflecting a growing lack of self-awareness of cognitive deficits.[20] Subjective memory complaints, a subset of SCD, were less associated with cognitive decline than overall cognitive performance in CU participants.[126] However, SCD may also predict the presence of AD pathology. The construct SCD-*plus* incorporates several features (subjective memory concerns and worries about this, recent onset of SCD, onset older than 60 years, study partner confirmation, feeling of worse performance than peers) of which subjective memory decline and concerns about this were individually associated with abnormal Aβ in a multicohort study of CU participants.[127] The endorsement of multiple features predicted not only Aβ positivity but also the presence of abnormal tau. SCD-*plus* may therefore be a behavioral marker of preclinical AD.

Conversely, maintenance of episodic memory performance in ADNI CU participants (measured by ADNI-Mem) was associated with lower baseline global Aβ and tau binding and larger hippocampal volumes than in participants who declined in cognition, despite the two groups having the same baseline episodic memory score.[128] Maintenance of EF and global cognition (measured by ADNI-EF and PACC, respectively) in the same participants was associated with a lower baseline global Aβ and greater hippocampal volumes. The rate of change of these AD biomarkers did not differ between cognitive maintainers and cognitive decliners. The study suggests that the maintenance of cognitive performance in "successful agers" can be attributed to initial levels of AD pathology (Figure S14).

In MCI participants, decline in informant-reported subjective memory was strongly cross-sectionally associated with greater cortical Aβ binding in the IMAP+ (International Mind, Activities and Urban Places) cohort, with replication in ADNI.[129] Furthermore, in ADNI MCI participants, informant-reported subjective memory decline was associated with neuroimaging hallmarks of AD such as lower MTL GM volumes, worse glucose metabolism in the precuneus, posterior cingulate cortex, and angular gyrus, and worse memory. Screening for informant-reported SCD in MCI may therefore help identify participants with an increased likelihood of AD at earlier stages.

Irregular word reading can reflect cognitive and semantic decline in AD, especially in the early stages of the disease.[130] In ADNI participants, errors in irregular word reading were significantly correlated with cognitive impairment and dementia severity, with errors increasing across early MCI, late MCI, and AD patient groups compared to CU participants. Hippocampal and anterior temporal lobe (ATL) atrophy was associated with poorer irregular word reading performance, suggesting that this measure may be more effective at detecting semantic deficits in AD.

Harmonization of cognitive scores across cohorts has enabled large-scale GWASs with the power to detect genetic associations with memory performance. ADNI data have been included in studies that have identified novel genetic contributions to cognitive decline and have also allowed exploration of racial/ethnic and sex differences. The genetic architecture of memory decline overlapped with that of AD, having genes such as *APOE*, *BIN1*, *CR1*, *ECHDC3*, and *CD2AP* in common, and that of function overlapped with the genetic architecture of other neuropsychiatric and immune disorders.[131] A PRS for attention deficit/hyperactivity disorder (ADHD) was associated with cognition and AD biomarkers.[132,133] CU participants with a higher ADHD-PRS had a greater cognitive decline in both EF and memory, and this was associated with Aβ deposition, increased CSF p-tau181, and frontoparietal atrophy.[132] A higher ADHD-PRS in CI participants was associated with higher CSF p-tau181, but not Aβ42, and with frontoparietal glucose hypometabolism.[133] These studies suggest that ADHD exacerbates AD pathology and cognitive impairment beyond the expected EF impairment. Awareness of the heightened risk of cognitive decline in patients with these backgrounds may guide clinical interventions.

A novel cross-ancestry locus and three loci specific to non-Latinx blacks were associated with memory performance, mapping to the novel genes *SLC25A44*, *BSX*, and *DPP8*, which are involved in CSVD and hypertension, circadian rhythm, and T-cell activation and cell death, respectively.[131] Women have been shown to have an early episodic and verbal memory advantage that is lost in AD dementia. Another large-scale study leveraging harmonized memory scores reported no significant differences in the heritability of memory performance between sexes or different ancestries (NHW versus non-Hispanic Black).[134] The study identified an X chromosome locus associated with memory performance in non-Hispanic Black women, mapping to *EGL6* (Figure S15), and two additional sex-specific loci, *CBLN2* and *SCHIP1/IQCJ-SCHIP*. Subsequent gene set analysis implicated the heparan sulfate signaling pathway involved in female sex biology. An X-chromosome-wide asso-

ciation study in ADNI using FAQ scores as an endophenotype identified a genome-wide significant SNP in *ZFP92*, which encodes a zinc finger protein.[135]

Harmonized longitudinal measures of memory, language, and EF across multiple cohorts were used as endophenotypes in a large-scale pleiotropy GWAS that reported associations between established AD risk loci and individual cognitive domains.[136] SNPs in the *APOE* region were associated with performance across all cognitive domains, whereas variants in *CR1* and *MS4A6A* were associated specifically with memory, and *BIN1* was associated with both language and memory. These findings suggest that the genetic architecture underlying AD risk overlaps with that of cognition, particularly memory. Eight novel loci were identified with differential associations to cognitive domains. Synaptogenesis signaling was the top pathway identified by pathway analysis, corroborating the critical role of synaptic function in cognitive decline. Finally, rare variants may also contribute to cognition. Two rare loss-of-function variants in *RBKS*, encoding ribokinase, were associated with worse performance on MMSE, implicating decreased D-ribose catalysis in lower cognitive performance.[137]

These studies position cognitive tests as potential non-invasive indicators of AD pathology and progression, with subjective memory concerns associated with amyloid positivity in non-demented participants and with neurodegeneration in MCI participants and irregular word reading associated with cognitive impairment. Successful agers who maintain episodic memory performance may do so due to lower levels of initial AD pathology. The genetic underpinnings of cognitive performance have been investigated using harmonized cognitive scores in large-scale GWASs.

4.10 | Neuropsychiatric symptoms

In addition to cognitive impairment, AD patients frequently suffer from a range of neuropsychiatric symptoms (NPSs), which can be highly distressing, reduce quality of life for both patients and caregivers, and result in early institutionalization. These are commonly measured using the Neuropsychiatric Inventory (NPI) and divided into the subsyndromes of hyperactivity (aggressiveness, disinhibition, irritability, aberrant motor behavior, euphoria), psychosis (delusions, hallucinations, nighttime behavior), affective disorders (depression, anxiety), and apathy. NPSs may manifest early in disease progression, even before the onset of significant cognitive impairment[138] and may be distinct from psychiatric disorders not associated with AD. As existing antipsychotics and antidepressant medications are less effective in AD patients and can be associated with increased morbidity and mortality, an understanding of NPS neurobiology may help identify pharmacological and non-pharmacological treatment strategies. Recent ADNI studies support a range of NPSs in AD as sequelae of AD progression.

Mild behavioral impairment (MBI), analogous to MCI, was recently defined based on the easily measurable NPSs and found to be associated with CSF AD biomarkers, a greater rate of incident dementia, and a decline in memory and EF,[138] suggesting diagnostic and prognostic utility.

A study of the interrelationships among NPS trajectories, Aβ accumulation, and cognitive decline in ADNI non-demented participants found that Aβ deposition was not associated with NPSs cross-sectionally or longitudinally, although baseline NPSs were moderately related to declines in specific cognitive domains, particularly memory.[139] However, individual NPS domains may have differential associations with AD pathology and disease progression. Three latent classes of NPSs were identified in ADNI MCI and AD participants.[140] Around half of the participants had minimal NPS symptoms, around 40% suffered predominantly from apathy, anxiety, and depression and were characterized by faster declines in memory and EF, and the remainder were characterized by multiple NPS domains and the greatest rate of MCI to AD progression. MBI with apathy was associated with higher CSF p-tau181 and p-tau181/Aβ42, whereas no associations were observed in MBI with non-apathy subsyndromes.[141] Similarly, CSF levels of t-tau/Aβ42 were associated with apathy in ADNI MCI and AD participants, whereas affective disorders were associated with CSF Aβ42 only.[142] Baseline tau binding in temporal (EC) and parietal (supramarginal gyrus) regions associated with AD predicted increasing apathy over time.[143] Cortical Aβ binding in AD-typical regions also predicted apathy trajectory and, in combination with regional tau, predicted higher levels of apathy.[143]

CSVD may also affect NPSs. CMBs interacted with CSF t-tau/Aβ42 to worsen apathy and were associated with the hyperactivity NPS subsyndrome.[142] WMH burden within specific WM tracts was associated with hyperactivity and apathy,[144] suggesting CVSD may also exert an influence on specific NPS subsyndromes.[142,144] Finally, laterality of tau binding was associated with NPSs such that predominantly right temporal tau was associated with worse anxiety and hallucinations in both AD and frontotemporal dementia than symmetric tau binding.[145]

Neuroinflammation, disruption of brain networks, and *APOE* are other potential neurobiological mechanisms that may contribute to NPSs. Microglial activation may be a common causal factor in both AD and depression.[146] In non-demented ADNI participants with minimal depressive symptoms (preceding subclinical depressive symptoms), levels of the microglial biomarker CSF sTREM2 were lower, with higher levels considered protective (Section 4.4).[146] In this group, minimal depressive symptoms were associated with Aβ pathology but not tau pathology, as well as cognition and hippocampal volume. The association between minimal depressive symptoms and Aβ pathology was partially mediated by CSF sTREM2, whereas the association with cognition was partially mediated by Aβ pathology.[146]

Similarly, higher baseline levels of CSF sTREM2 were longitudinally associated with lower Geriatric Depression Scale (GDS) scores in MCI *APOE ε4* non-carriers.[147] This association was dependent on CSF Aβ42, but not tau.[147]

Astrocytic dysfunction has also been implicated in NPSs. Three clusters of CSF biomarkers of astrocytic function, GFAP, chitinase-3-like protein 1 (YKL-40), and aquaporin-4, were identified in ADNI participants: (1) a cluster with high levels of all three biomarkers, (2) a cluster with elevated YKL-40 only, and (3) a cluster with elevated GFAP and YKL-40.[148] The first cluster was associated with the highest levels of p-tau181 and NPS severity, whereas the second cluster showed the

lowest association with NPS subdomains. These findings suggest that astrocytic activity may contribute to NPS severity and subdomains.

Disinhibition was related to changes in large-scale intrinsic brain networks in ADNI AD participants and participants with behavioral variant frontotemporal dementia from the Frontotemporal Lobar Degeneration Neuroimaging Initiative.[149] In both types of dementia, disinhibition was associated with reduced global efficiency of the cognitive control network (also known as executive control network), involved in higher-level cognitive processes such as EF. In AD, disinhibition was also associated with changes in characteristics of the salience network.[149] Therefore, the disruption of intrinsic brain networks in AD progression may result not only in cognitive impairment but also in the development of NPSs.

A GWAS of nine NPS domains in MCI and AD participants from an Alzheimer's Disease Research Center discovery cohort, with findings replicated in ADNI,[150] identified SNPs within the *APOE ε4* allele that were associated with anxiety and delusions, and a SNP in *ADAMTSL1* that was associated with agitation. Measures of global cognition and clinical status only partially mediated these associations (27% to 39%), suggesting that additional mechanisms independent of cognitive impairment may contribute to these symptoms.

Finally, delusions are commonly experienced by AD patients and have been proposed to be part of the continuum with false memories, which are nearly ubiquitous in AD patients. In the ADNI AD participants, delusions were not associated with false memories, or with regional atrophy implicated in false memories (MTL and ventral visual stream), suggesting that delusions do not arise from misremembering.[151]

These recent ADNI studies support NPSs in AD as (1) distinct from neuropsychiatric syndromes outside of dementia; (2) arising in early stages of disease progression; (3) related to hallmarks of disease progression such as Aβ and tau deposition, microglial activation, or perturbation of neural networks; and (4) increasing risk for future progression and cognitive decline. NPSs appear to be intertwined with many aspects of disease progression, and therefore, the contribution of ADNI studies to better understanding the neurobiology underlying NPSs has broad implications in AD research and treatment.

5 | THE EFFECT OF DIET AND THE GUT MICROBIOME

Diet and, more recently, the gut microbiome have been linked to AD risk. The Mediterranean diet has been associated with reduced AD risk by limiting saturated fat intake and supporting a healthy gut microbiome. A dysfunctional gut microbiome may exacerbate inflammation and produce metabolites able to cross the BBB and affect brain health or result in abnormal neural signaling to the brain via the vagus nerve.

Bile acids, synthesized from cholesterol by gut microbiota, are involved in lipid metabolism, and some have been associated with AD features such as Aβ load, t-tau, glucose hypometabolism, hippocampal atrophy, and cortical atrophy.[152] Higher levels of conjugated primary bile acids in serum were reported in ADNI female MCI converters than non-converters.[153] Thirteen gut microbiota metabolites (six bile acids, four branched-chain amino acids, and three excitatory neurotransmitters) were associated with AD clinical stage in participants from a Chinese cohort.[154] These were also significantly altered in AD versus CU ADNI participants and in seven further cohorts[154] and were associated with elevated blood ammonia levels, suggesting that ammonia abnormality linked to these metabolites may be associated with AD. Finally, vascular burden may influence the effect of bile acids. A secondary conjugated bile acid, glycodeoxycholic acid, was associated with worse cognition in ADNI participants with low WMH burden only.[152]

Dietary factors may directly influence AD risk. Long-term supplementation with omega-3 fatty acids was associated with a 64% reduced risk of AD in ADNI participants; a meta-analysis of previous studies found a lower risk of cognitive decline.[155] Saturated long-chain fatty acids, found in red and processed meats and other sources and known to promote systemic inflammation, were associated with a 1.3- to 2.2-fold increased risk of conversion from MCI to AD but had no influence on earlier diagnostic conversion.[156] However, the cause-and-effect nature of these associations is unclear because dietary habits are also associated with socioeconomic status, genetics, education, and access to health care.

6 | LBD IN AD

Evidence of co-pathologies is seen in a high proportion of individuals with AD neuropathological change. Neuropathological examination of ADNI *post mortem* cases revealed LBD to be the second most common co-pathology, present in around half of individuals with evidence of intermediate to high AD neuropathological change.[157] The presence of α-Syn seeds increased across clinical groups,[158] and α-Syn positivity was associated with faster cognitive decline,[159,160] a greater risk of clinical conversion,[160] and earlier symptom onset.[161] α-Syn positivity was associated with LBD-like features such as posterior cortical hypometabolism,[162–164] increased risk of hallucinations,[164] and impairments in EF and visuospatial domains.[164] Posterior cortical hypometabolism mediated the association between the presence of α-Syn seeds and clinical disease severity,[163] consistent with the role misfolded α-Syn plays in synaptic dysfunction.[158]

However, in combination with AD pathology, α-Syn positivity exacerbated AD-typical cognitive decline. ADNI non-demented participants with evidence of both Aβ and LBD pathology had the greatest subjective cognitive decline (both self-report and study partner).[165] In ADNI CI participants grouped by CSF AD (p-tau181/Aβ42) and LBD (α-Syn) biomarker positivity, the AD+/LB+ group had the worst baseline and the fastest decline in PACC and MMSE (Figure S16)[162,164] and the worst memory impairments of all groups.[164] The effect of α-Syn on this cognitive decline may be mediated by temporoparietal hypometabolism.[164]

This exacerbation of the effects of AD pathology on disease progression by α-Syn may be evidence of synergistic crosstalk between pathological proteins previously reported in neurodegenerative diseases.[159]

Interactions between α-Syn, Aβ, and tau pathologies appear to be complex. α-Syn may interact with Aβ. In ADNI participants across the AD spectrum, α-Syn positivity was cross-sectionally associated with higher levels of Aβ but not tau pathology[166] (Figure S17), and conversion from α-Syn− to α-Syn+ was associated with CSF Aβ42 positivity.[159] However, other studies reported that α-Syn positivity was more strongly correlated with CSF p-tau181 and t-tau than with Aβ42.[158,160] The finding that α-Syn positivity was associated with greater Aβ-related CSF p-tau181, and accumulation of fibrillar tau in AD-typical regions[167] (Figure 7) may explain this discrepancy by suggesting that α-Syn co-pathology accelerates Aβ-induced tau deposition and is therefore associated with both pathologies. All three pathologies (Aβ, p-tau181, and α-Syn) predict clinical conversion, with Aβ positivity being the greatest indicator of risk.[159] Inflammatory cytokines TNFR1 and ICAM1 mediated the association between CSF α-Syn and CSF p-tau181 and t-tau.[160] One possible interpretation of these varied results is that α-Syn interacts with Aβ pathology synergistically or additively to exacerbate tau pathology via inflammatory mechanisms; however, future studies are required to determine the exact molecular mechanisms. One final consideration of the effects of α-Syn co-pathology in AD is the different aggregation states of the molecule, which may have differential effects on the rate of progression and risk of clinical conversion.[158]

7 | AD HETEROGENEITY

Clinical trials are complicated by the difficulty of selecting individuals who are likely to progress during the trial period, and treatment strategies using a personalized medicine approach must consider the underlying factors that contribute to disease heterogeneity. Recent ADNI studies have explored the issue of heterogeneity by identifying and characterizing biological subtypes and their relationship to cognitively defined subgroups, further characterizing MCI heterogeneity, elucidating different pathways of disease progression, and investigating the contribution of comorbidities.

7.1 | Biological subtypes of AD

Orthogonal axes of severity and typicality were developed from structural MRI studies,[168] providing a conceptual framework for heterogeneity. Two subtypes, hippocampal-sparing (also known as cortical dominant) and limbic predominant (aka subcortical dominant), represented extremes of the continuous typicality dimension, encompassing the degree of abnormal neurodegeneration. Two further subtypes, typical AD, and minimal atrophy represented extremes of an orthogonal continuous severity dimension, encompassing the overall degree of atrophy (see Veitch et al.[20] for more details). Recent ADNI studies have characterized AD subtypes based on Aβ deposition,[169] hypometabolism,[170] functional connectivity, tau,[171] imaging genetics, and multiple modalities.[169,170,172,173]

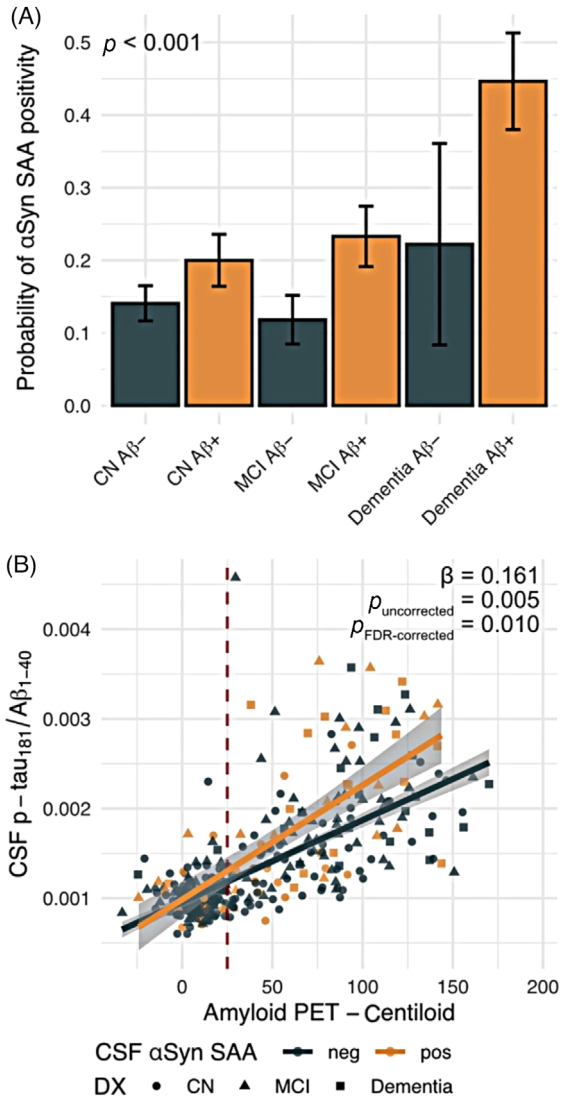

FIGURE 7 Bar plot illustrating probability of αSyn SAA positivity stratified by amyloid status and clinical syndrome severity. Statistical significance was determined via logistic regression controlling for age. (A) Scatterplot illustrating interaction effect between amyloid-PET and αSyn SAA status on cross-sectional levels of CSF p-tau$_{181}$/Aβ$_{1\text{-}40}$ as an indicator of earliest tau pathophysiology. Diagnostic groups are indicated by shape, the cut point of amyloid-PET positivity is indicated by the dashed red line at 25 CL. The beta value indicates the strength of the amyloid-PET × CSF αSyn SAA interaction effect as determined by linear regression, controlling for age, sex, and study site. FDR correction for multiple comparisons ($p < 0.05$) was applied for the main analyses (B) adjusting for five statistical tests. Reproduced under open access from Franzmeier et al.[167]

Two subtypes with distinct spatiotemporal patterns of Aβ deposition were reported in ADNI MCI and CU participants using the Subtype and Stage INference (SuStaIN) algorithm.[169] A subcortex-priority subtype, characterized by initial Aβ deposition in subcortical regions followed by cingulate, insula, and cortical regions, was less severe, with better CSF biomarkers and cognition and lower progression to AD. A cortex-priority subtype, characterized by initial abnormality in

the cingulate followed by the cortical, insula, and subcortical regions, was more severe, with worse CSF biomarkers, cognition, and conversion to AD. This more severe subtype appeared to encapsulate two of the three subtypes reported by a previous study.[174] Validation in an external cohort is needed to resolve these differences.

Tau staging from tau PET imaging has largely relied on the use of ROIs derived from neuropathological Braak staging. This has drawbacks in that Braak staging represents a moment in time rather than an in vivo process. Two studies used data-driven approaches to analyze cross-sectional and longitudinal tau abnormality patterns.[86,87] In A+ ADNI participants across the AD spectrum, a novel index summarizing abnormal tau deposition across 70 brain regions, the Spatial Extent Index,[86] largely recapitulated Braak staging, with more than 80% of participants having patterns of abnormal tau deposition that followed this linear pattern. However, heterogeneity in regional cortical tau deposition was particularly apparent in MCI participants who had the highest rates of tau accumulation but the least overlap (<50%) of regions of abnormal tau deposition. The degree of overlap was greater in AD participants, indicating that multiple pathways of cortical tau deposition converge later in disease progression.

A tau pathology staging model developed in ADNI and replicated in the OASIS cohort identified eight patterns of tau covariance, divided into four stages.[87] It begins with MTL tau binding (stage 1), then sequentially adds the temporal and parietal lobes (stage 2), occipital and lateral frontal lobes (stage 3), and remaining orbitofrontal, insula, and sensory motor regions (stage 4) of tau binding. Higher stages were correlated with increased severity of CDR, higher regional Aβ binding, *APOE ε4* allele carriage, and an increased risk and speed of clinical progression (Figure S18). This staging system outperformed Braak-based ROIs in dementia classification, suggesting it captures additional biologically relevant tau binding.

Not all participants on the AD spectrum follow the stereotypical spread of tau outlined above. Considerable heterogeneity was reported and may contribute to different AD subtypes or reflect other disease trajectories. Around 10% of ADNI participants did not fit into a data-driven staging method.[87] These participants were characterized either by MTL-sparing tau deposition, consistent with previously described MTL-sparing or hippocampal-sparing subtypes[20] or by a pronounced lateralization in tau binding.[87] Finally, tau binding in the MTL in the absence of Aβ positivity has been termed primary age-related taupathy (PART). These participants from three cohorts, including ADNI (Harvard Aging Brain Study, AVID-A05), had no abnormal Aβ accumulation but a moderated rate of tau accumulation in the EC with concomitant increases in CSF p-tau181 and colocalized atrophy and slower cognitive decline than A+ participants with MTL tau.[175] Similarly, in A− CU participants from four studies, including ADNI, MTL tau was associated with more moderate neurodegeneration and cognitive impairments than in A+ participants.[85] These studies suggest that A− participants with MTL tau accumulation are on a slower and more moderate non-AD trajectory.

Three hypometabolism subtypes were identified in MCI participants in ADNI and the Italian INTERCEPTOR cohort.[170] The first was characterized by cortical and hippocampal hypometabolism and likely represents typical AD. The second was characterized by predominantly MTL hypometabolism, severe hippocampal atrophy, the oldest age, and the lowest conversion to AD, and the authors suggest that it may have contributions from different pathological substrates, such as PART or limbic-predominant age-related TDP-43 encephalopathy. The third was characterized by predominantly cortical hypometabolism, younger age, the greatest conversion to AD, and increased MTL metabolism that may represent an early compensatory resilience mechanism. Twelve percent of ADNI MCI and AD participants with predominantly cortical hypometabolism have a pattern of posterior occipital hypometabolism suggestive of LBD pathology.[176] This pattern was associated with lower regional Aβ and tau burden in MCI participants, EF rather than memory deficits, and a higher risk of developing hallucinations. The authors conclude that these patients may have LBD co-pathologies that contribute to the clinical phenotype, although autopsy confirmation is required.

Application of SuSTaIN to ADNI multimodal data, including CSF biomarkers and cognitive tests in addition to imaging (Aβ, tau, and FDG PET, and structural MRI) data, identified five distinct subtypes.[172] These subtypes, named for the initial abnormality in the sequence of events, were reported in A+ participants and partially overlapped with imaging-defined subtypes (Figure S19). The typical AD early tau and typical AD late tau subtypes likely represented the archetypal disease progression of the typical AD atrophy subtype. The late tau subtype differed in the appearance of abnormal tau and p-tau181 only after changes in MRI markers and had greater EF impairment and higher WMH burden than the early tau subtype. A cortical subtype characterized by younger age, the lowest proportion of *APOE ε4* carriers, A+ and AD participants, and the slowest MCI to AD progression, clearly overlapped with the atrophy-defined cortical subtype. The least common subtype had initial subcortical atrophy, low proportions of *APOE ε4* carriers and A+ participants, and high WMH burden, and was mostly male. This subtype is congruent with imaging-defined limbic predominant subtype but was not replicated in a subset of only A+ participants, suggesting this is not a true AD subtype. Finally, a cognitive subtype had a severe phenotype despite low WMH burden but had no clear parallels to atrophy-defined subtypes.

These studies of imaging- and multimodal-derived subtypes did not consider the effects of underlying genetic variants. A deep learning method that linked imaging phenotypes to genetic variants was applied to multiple cohorts, including ADNI in the iSTAGING study.[177] Four imaging genetic subtypes were identified, with significant differences in five SNPs in *HLA-DRA*, *HLA-DQA1*, *ECHDC3*, *MRC1*, and *APOE* that differed in proteomic biomarker profiles, atrophy, and cognition (Figure 8). The A1 subtype had a benign phenotype and the lowest frequency of identified risk alleles, and may represent a resilience subtype with protective alleles. The A2 subtype had predominant MTL atrophy consistent with the limbic-predominant atrophy subtype and the highest frequencies of variants in *APOE* and the *HLA* region, implying the involvement of inflammatory mechanisms. The A3 subtype was consistent with the typical AD atrophy subtype and had widespread brain atrophy and the worst CSF biomarkers, cognition, and vascular pathology, with higher levels of variants in the *HLA* region. This may represent

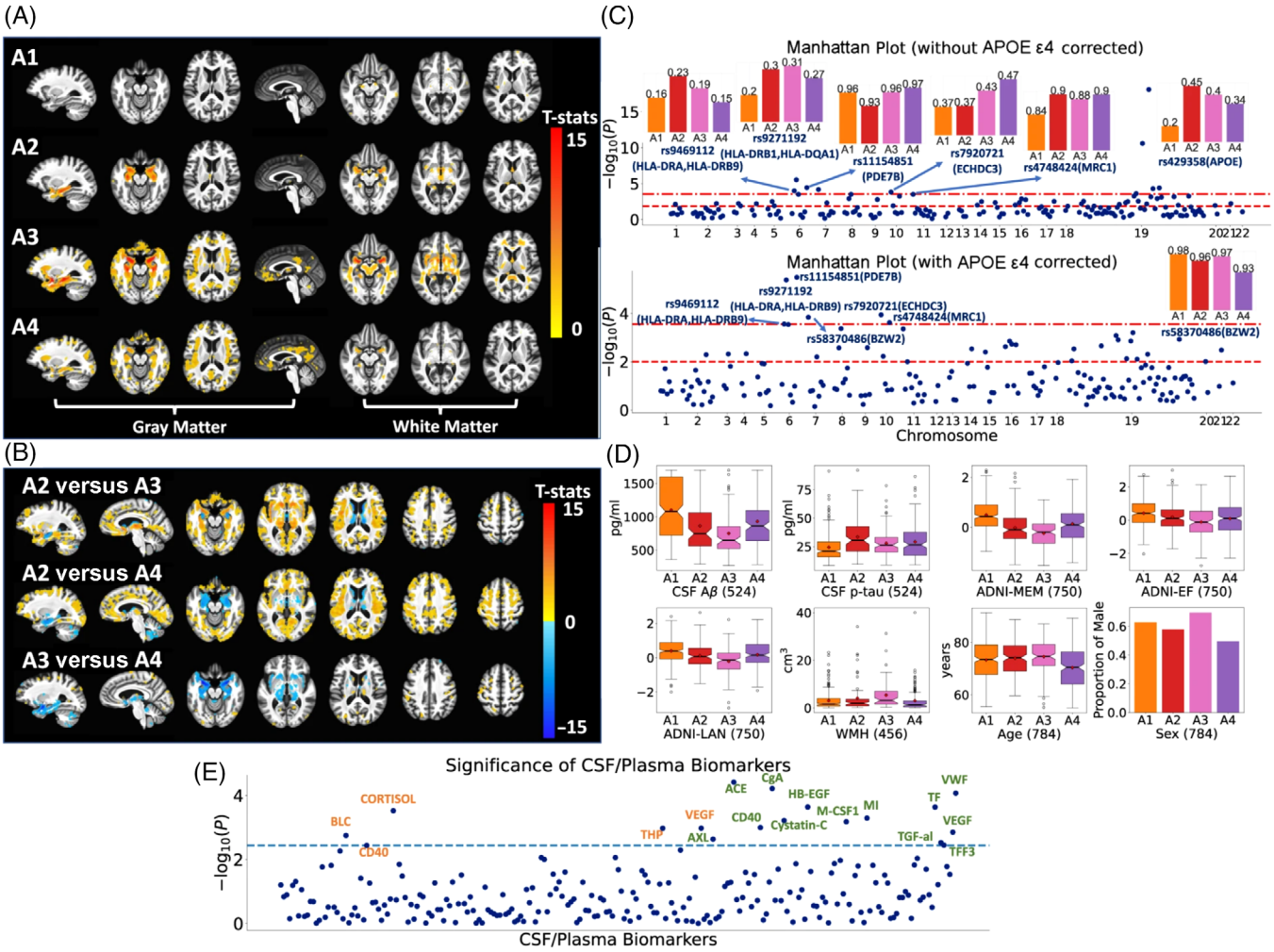

FIGURE 8 Gene-SGAN identifies four subtypes of brain changes related to AD (A1, A2, A3, and A4). (A) The four subtypes display distinct imaging patterns compared with HC. Warmer colors indicate greater brain atrophy in each subtype relative to HC. (B) The four subtypes also differ in their imaging patterns relative to one another. In each pairwise comparison (subtype i vs subtype j), warmer colors reflect regions where subtype i shows relatively larger tissue volumes, while cooler colors indicate the opposite. For both panels (A and B), voxel-wise two-sided *t*-tests were conducted between groups, and multiple comparisons were corrected using FDR corrections with a significance threshold of $p < 0.05$. (C) The four subtypes show distinct genetic underpinnings. The Manhattan plot highlights significant SNP-subtype associations across 178 AD-associated SNPs, tested using a one-tailed likelihood-ratio test within multinomial logistic regression models, with (below) and without (above) adjusting for *APOE ε4*. The two dashed lines denote the *p* value thresholds of 0.05 after adjusting for multiple comparisons via Bonferroni (top) and B-H methods (bottom), respectively. SNPs surviving Bonferroni correction are labeled with their SNP IDs and mapped genes. For each SNP, the effective allele, defined as the AD risk allele from prior literature, is shown with its EAF across subtypes; higher EAF indicates higher AD risk. (D) The four subtypes differ in their clinical, cognitive, and demographic characteristics; including CSF Aβ and p-tau (other CSF biomarkers were separately evaluated in (E). Box-and-whisker plots and bar plots reveal clinical, demographic, and cognitive variables of MCI participants by subtype. Sample sizes for each variable are presented beside their variable names. (E) The four subtypes show significant differences in CSF and plasma biomarkers. The Manhattan plots show the significance of differences (ANOVA test; one-tailed test) among four AD-related subtypes. The dashed line represents the B-H corrected significance line. Orange-colored names: plasma biomarkers; green-colored names: CSF biomarkers (centerline = median; red marker = mean; box = upper and lower quartiles; whiskers = 1.5× interquartile range; points = outliers). Reproduced under open access from Yang et al. [177]

co-occurring AD and vascular pathology in which inflammatory mechanisms are key. Finally, the A4 subtype had predominantly cortical atrophy and the highest levels of a variant in *ECHDC3* that has been associated with AD only in non-*APOE ε4* carriers. All three subtypes were associated with characteristics of typical AD, suggesting that there may be multiple genetic pathways to the archetypal phenotype. These studies suggest that atrophy-defined subtypes have distinct genetic architectures, supporting their biological and clinical relevance.

7.2 | Cognitively defined subgroups

How do subgroups identified from relative impairments across cognitive domains relate to imaging-defined subtypes and what is their biological relevance? Atrophy patterns of cognitively defined subgroups in ADNI MCI and AD participants showed a predominantly (50% to 74%) typical AD pattern with variations in the proportion of participants with limbic-predominant or hippocampal-sparing patterns,[178] and participants with EF impairment had the greatest proportion of hippocampal-sparing atrophy and no limbic-predominant atrophy, whereas those with memory impairment had the lowest proportion of hippocampal-sparing atrophy and a higher proportion of limbic-predominant atrophy. Those participants with multiple domain impairments had the lowest proportion of typical AD atrophy. Participants with visuospatial impairment had greater posterior cortical atrophy, a pattern associated with LBD, and those with language impairment had widespread left-side-dominant atrophy. Biologically relevant gene sets based on Aβ plaques and NFTs differed across cognitively defined subgroups.[179] Cognitive domain impairments were also associated with changes in functional networks in MCI participants from ADNI and a Chinese cohort.[180] Single-domain amnestic MCI was characterized by alterations in high-order cognitive networks such as the DMN and frontoparietal network. Multidomain MCI, representing a more impaired presentation, was characterized by alterations in primary sensory networks, such as the visual and motor sensory networks. These studies suggest that cognitively-defined subgroups partially reflect atrophy patterns and may be underlain by specific mechanistic pathways.

7.3 | MCI heterogeneity

MCI is a particularly heterogeneous clinical entity, perhaps marking the midpoint of disparate disease trajectories. Four groupings of cognitive trajectories in longitudinal Alzheimer's Disease Assessment Scale–Cognitive Subscale scores were reported in ADNI MCI participants.[181] Around a quarter of participants, the youngest and most educated, did not decline, and a third showed only mild decline. A further quarter of participants were characterized by moderate decline and a higher proportion of *APOE ε4* carriers, while the remaining participants were aggressive decliners with the highest proportion of *APOE ε4* carriers, worse CSF biomarkers, cognition, hypometabolism, and smaller hippocampal volume.

Inclusion of comorbidities (vascular factors, depression, hearing loss, traumatic brain injury) in multimodal subtyping of ADNI MCI participants identified four subtypes.[182] These ranged from having the best prognosis with no conversion to AD to the worst prognosis with the fastest conversion to AD. The frequency of comorbidities, particularly hypertension and hearing loss, increased with worsening prognosis. Non-demented participants with self-reported hearing loss had worse baseline and longitudinal function and cognition in multiple domains, including those not related to hearing, such as visuospatial ability.[183] However, hearing loss was not associated with a greater risk of diagnostic conversion.

7.4 | Differing pathways of disease progression

Deviations from the sequence of biomarker abnormalities outlined by Jack et al.[23] have been frequently described and may represent different pathways of disease progression. A personalized causal model based on amyloid cascade identified three clusters of endophenotypic variation, with one representing a less severe disease course.[184] Application of SuSTaIN to ADNI Aβ and tau PET data with neuropathological confirmation in ROSMAP identified pathways with both initial Aβ and initial tau deposition[185] (Figure S20). Initial widespread neocortical and MTL Aβ deposition preceding neocortical tau deposition was present in a higher proportion of *APOE ε4* carriers. This likely represents a typical AD pathway in which the interaction of age-related MTL tau with neocortical Aβ initiates tau spread beyond the MTL. Conversely, initial mild tau in MTL and cortical regions preceding Aβ deposition was observed primarily in *APOE ε4* non-carriers and may represent PART in which mild tau spread beyond the MTL in the absence of Aβ (around 4% of participants in multiple cohorts including ADNI) had a CSF A−T+ profile consistent with PART.[186] However, this group also included *APOE ε4* carriers who had an increased rate of Aβ deposition, implying they belong on the AD spectrum. These participants were less educated, and the authors suggest that a lack of resilience may contribute to this alternative pathway. It is important to note that the amyloid cascade hypothesis allows for the independent initiation of both pathologies.

The amyloid-first pathway may itself be heterogeneous. In ADNI A+ participants, the SuStAIN algorithm applied to multimodal data (CSF biomarkers, MRI, cognition) identified three distinct pathways. In around a quarter of participants, CSF p-tau181 became abnormal first, followed by Logical Memory and hippocampal volume in the sequence of biomarkers expected in the amyloid cascade. However, a larger group (39%) was characterized by an initial change in memory that preceded p-tau181 abnormality and hippocampal atrophy. Participants in this group were older and more cognitively impaired, and the authors suggest this trajectory may represent a mixture of AD and other copathologies. A final group had WMHs as an initial abnormal biomarker and was characterized by the highest proportion of hypertension and lacunes, likely representing participants with greater CSVD burden.

Similarly, only around half of ADNI participants were characterized by the predicted timing of biomarker abnormalities.[187] The remaining participants were characterized by metabolic changes and atrophy preceding Aβ abnormality and a lower proportion of *APOE ε4* carriers. This heterogeneity appears to increase across disease progression. Greater abnormal deviations from regional patterns of atrophy, Aβ, and tau burden were associated with greater cognitive decline.[188]

7.5 | Summary of studies of AD heterogeneity

Converging evidence from recent ADNI studies using a range of modalities supports the existence of biological subtypes along the conceptual axes of typicality and severity. These subtypes appear to involve not only AD pathologies but a range of co-pathologies, vascular burden, distinct genetic architectures, and reserve/resilience. Cognitive subgroups partially overlap with biological subtypes. Different sequences of biomarker abnormalities have been identified and may be related to co-pathologies. Subtypes at the extremes of the typicality continuum may represent different pathways, from minimal to widespread atrophy. As therapeutic options for AD increase, recognition of the positioning of the patient within this range of heterogeneity will be vital to ensure optimal success in treatment.

8 | CONCLUSIONS

The "big picture" to emerge from recent high-impact research-oriented ADNI studies is that of the intertwined contributions of multiple factors to AD progression and the recognition that they are an integral rather than separate aspect of AD, ultimately contributing to the wide range of clinical presentations. This has profound implications for clinical management and the development of AD treatment strategies.

The trajectory of disease progression proposed by the amyloid cascade hypothesis appears to be observed in only a minority of participants, with the remainder following different trajectories influenced by resilience and factors that increase susceptibility, such as genetic and epigenetic differences, and the presence of co-pathologies and comorbidities. These factors influence different steps in the sequence of events and offer potential targets for clinical intervention. An initial perturbation of the glymphatic system impedes clearance of Aβ and tau, leading to their accumulation. The *APOE ε4* allele, along with other genetic risk alleles, confers greater susceptibility to Aβ deposition. Vascular risk factors that result in hypoperfusion and ischemic injury impair glymphatic clearance and initiate a feedback loop via microglial activation, exacerbating WMH burden and further impeding Aβ clearance. These factors may also have an Aβ-independent effect on cognition and are therefore promising targets for clinical management.

Microglial and astrocytic activation in response to initial Aβ deposition is protective. However, prolonged exposure to Aβ results in neuroinflammation, which in turn impedes Aβ plaque phagocytosis and results in the release of phosphorylated tau. The neuroinflammatory effects of *APOE ε4* may be greater in women than in men. Systemic inflammation arising from certain AD risk factors can further promote neuroinflammation, "supercharging" the disease process. Microglial and astrocytic activation additionally contributes to synaptic dysfunction. Some AD genetic risk loci are associated with synaptic dysfunction, and perturbation of the neuronal E–I balance, particularly in the cholinergic system of the basal forebrain, has been documented as an early step in disease progression.

Tau PET scans of ADNI participants have associated regional Aβ deposition with regional tau accumulation, which may, in turn, drive synaptic dysfunction. Polygenic loci beyond the *APOE ε4* allele appeared to be influential in the transition to tau positivity, and the characteristic pattern of tau spread was underlain by regional expression of established AD risk alleles and DNA methylation changes. Tau propagation was affected by changes to functional and structural networks, particularly demyelination and axonal connections. Initial tau deposition in the MTL was associated with memory impairment, whereas more widespread tau deposition was associated with impairment of further cognitive domains and function.

Dysregulation of mitochondrial bioenergetic pathways contributed to AD progression, resulting in oxidative stress and hypometabolism. Specific genetic loci contributed to mitochondrial dysfunction or to improved bioenergetic age, a potential mechanism of resilience. Glucose hypometabolism patterns were associated with *APOE ε4* carriage and cognitive decline. Regional WM microstructural changes, such as axonal demyelination, preceded macrostructural changes and were linked to Aβ and tau deposition, CSVD, and AD risk alleles. Alterations to cortical GM microstructure also preceded visible atrophy. Functional network perturbations observed in preclinical AD were followed by AD-specific patterns of atrophy related to AD risk alleles.

Ultimately, cognitive, functional, and behavioral decline become measurable, initially as subjective cognitive decline and MBI in preclinical individuals, followed by further cognitive and functional impairments and the development of NPSs. Differences in the genetic architecture of memory were reported between groups of different ancestry and in women. Harmonized cognitive scores across cohorts enabled large-scale GWASs to discover further risk loci. NPSs seem to result from AD progression and are distinct from NPSs outside of dementia, being influenced by pathological proteins, CSVD, neuroinflammation, network disruption, and AD risk alleles.

Additional contributions to AD progression were elucidated, namely, the possible influence of diet and the gut microbiota. and of LBD, enabled by the recent development of the α-Syn SAA. LBD appears to interact with Aβ pathology to exacerbate neuroinflammation and the accumulation of tau pathology.

Heterogeneity in clinical presentation and disease course results from the multifactorial nature of disease progression. Spatiotemporal biological subtypes of AD, based on PET, MRI, and multimodal approaches, provide support for consistent AD subtypes of differing severity, associated with factors such as vascular risk, co-pathologies, or resilience. Subtypes based on cognitive difference partially recapitulate groups identified through imaging and genetic analyses. Deviations from the canonical sequence of biomarker abnormalities are common and may be related to co-pathologies.

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All human subjects provided informed consent.

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SUPPORTING INFORMATION

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

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