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Functional Connectivity Alterations in Early-Stage Cognitive Decline: An MRI-Based Study

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Abstract

Resting-state functional MRI has become one of the most actively studied candidate tools for detecting brain changes in Alzheimer's disease before the structural atrophy visible on conventional imaging emerges. This article synthesizes the literature on functional connectivity alterations in early-stage cognitive decline, from healthy older adults at biomarker-defined risk through mild cognitive impairment (MCI). We trace the field from the methodological foundations of intrinsic connectivity networks and graph-theoretic analysis, through the now well-replicated finding that default mode network (DMN) connectivity is reduced in at-risk and MCI populations, to whole-brain graph-theoretic evidence that this disruption preferentially targets hub regions such as the hippocampus and degrades global network efficiency rather than remaining confined to a single pathway. We review how successive diagnostic frameworks, from Petersen's original MCI criteria through the NIA-AA biomarker-based Research Framework, have progressively refined the populations these studies examine, and how multi-site cohort infrastructure such as ADNI has supported more generalizable findings. Read together, the evidence supports default mode network hypoconnectivity as a genuine, reproducible early functional signature of the Alzheimer's disease continuum, while leaving longitudinal validation of its predictive value, biomarker-based stratification of study populations, and the diagnostic utility of dynamic (non-stationary) connectivity measures as an active research agenda rather than a settled question.

Keywords: functional connectivity; resting-state fMRI; mild cognitive impairment; default mode network; Alzheimer's disease biomarkers

1. Introduction

Alzheimer's disease and the broader spectrum of age-related cognitive decline are, in their earliest stages, remarkably quiet on conventional structural imaging. Hippocampal volume loss, cortical thinning, and the frank atrophy that radiologists learn to recognize typically become apparent only after a disease process has been active for years, sometimes decades. Functional magnetic resonance imaging (fMRI), and in particular resting-state fMRI, offers a different vantage point: rather than waiting for tissue to be lost, it measures how the brain's regions are still talking to one another, moment to moment, while a person simply lies still and lets their mind wander. That capacity to detect a functional signature of disease before an obvious structural one has made functional connectivity one of the most actively pursued candidate biomarkers for early-stage cognitive decline, and it is the literature behind that pursuit that this article synthesizes.

The conceptual foundation is intrinsic connectivity: even in the absence of any explicit task, spatially distributed brain regions show temporally correlated low-frequency fluctuations in the blood-oxygen-level-dependent (BOLD) signal, organizing into reproducible large-scale networks [1]. Chief among these, for the purposes of dementia research, is the default mode network (DMN), a set of midline and lateral parietal regions — posterior cingulate cortex, precuneus, medial prefrontal cortex, and lateral parietal cortex — that is more active during rest and self-referential thought than during externally directed tasks [2]. The DMN is not simply one network among many for this literature: it overlaps substantially, anatomically, with the regions that accumulate amyloid-beta pathology earliest and most heavily in Alzheimer's disease, which is part of why its functional integrity has drawn such sustained attention as a candidate early marker [3].

This article traces that attention from its origins to its current state. We are synthesizing, not reporting new data: our aim is to pull together what the resting-state functional connectivity literature has actually found in individuals at the earliest, mildest stages of cognitive decline — healthy older adults at genetic or biomarker-defined risk, and patients meeting criteria for mild cognitive impairment (MCI) — and to be explicit about where the evidence is strong, where it is more

provisional, and where open methodological problems remain. We organize the discussion around five themes: the methodological foundations of resting-state functional connectivity and network analysis; the default mode network specifically as an early biomarker; graph-theoretic and whole-brain network approaches that look beyond any single network; the clinical and diagnostic frameworks that define the populations these studies actually study; and the methodological frontiers, and persistent gaps, that shape where the field can credibly go next.

It is worth being explicit, at the outset, about scope and candor. Much of the foundational work reviewed here comes from single-center studies with modest sample sizes, heterogeneous preprocessing pipelines, and cross-sectional designs that cannot, on their own, establish that an observed connectivity difference precedes or predicts subsequent decline rather than simply co-occurring with it. Multi-site initiatives and later methodological work have begun to address some of these limitations, but a fully validated, clinically deployed functional-connectivity biomarker for early cognitive decline does not yet exist. What does exist is a large, increasingly convergent body of evidence that functional connectivity within and between specific large-scale networks — most consistently the default mode network, but also salience, executive-control, and hippocampal-centered networks — is measurably altered before the stage of clinically obvious dementia, and that this alteration follows a recognizable topological pattern rather than a diffuse, undifferentiated one.

2. Functional MRI and the Architecture of Intrinsic Connectivity Networks

Resting-state functional connectivity analysis rests on an observation that took some time to be taken seriously: the brain's BOLD signal, even with no task and no explicit stimulus, is not noise. Regions that are anatomically connected and functionally related show correlated spontaneous fluctuations, and mapping those correlations reveals a small number of consistently reproducible large-scale networks — sensorimotor, visual, auditory, dorsal attention, frontoparietal, salience, and the default mode network among them [1]. The default mode network itself was identified initially through the observation that a specific set of regions consistently deactivates during externally oriented,

attention-demanding tasks relative to passive rest, which raised the question of what, functionally, those regions were doing during the baseline state itself; subsequent work established that this "default" activity is itself organized, task-modulated, and behaviorally relevant rather than simply reflecting an absence of activity [2].

Two methodological approaches dominate how these networks are actually measured. Seed-based correlation analysis selects an a priori region of interest — the posterior cingulate cortex, for instance, as a DMN seed — and computes its correlation with every other voxel or region in the brain, producing a connectivity map anchored to that seed's chosen network. Independent component analysis (ICA), by contrast, decomposes the entire 4-dimensional fMRI dataset into a set of spatially independent components without specifying a seed region in advance, and has become a standard tool for extracting resting-state networks in a comparatively data-driven and reproducible way, including at the group level where multiple subjects' data are decomposed jointly [4]. Each approach has tradeoffs: seed-based analysis is intuitive and interpretable but depends on a defensible a priori choice of seed, while ICA avoids that dependency but requires additional steps to identify which of many extracted components correspond to a network of interest and to make components comparable across subjects and studies.

Once a network, or a set of pairwise regional correlations, has been extracted, a second methodological tradition treats the resulting connectivity matrix as a graph — a set of nodes (typically brain regions) connected by edges (functional correlations) — and applies the tools of graph theory to characterize its topology. Metrics such as clustering coefficient (how interconnected a node's neighbors are with each other), characteristic path length (the average shortest connectivity-weighted distance between any two nodes), and measures of modularity and hub structure allow a whole-brain network to be summarized by a handful of numbers that are, in principle, comparable across individuals, conditions, and studies [5]. Graph-theoretic analysis of both structural and functional brain networks converges on a picture of the healthy brain as organized for "small-world" efficiency: densely interconnected local clusters bridged by a comparatively small number of long-range connections

and hub regions, a topology that supports both specialized local processing and efficient global integration at a relatively low wiring cost [6]. This small-world, hub-based organization becomes the reference point against which network disruption in early cognitive decline is subsequently measured, and it is a central reason the literature reviewed in the following sections asks not just "is connectivity higher or lower" but "has the topology of the network itself changed."

3. The Default Mode Network as an Early Biomarker of Cognitive Decline

The single most influential empirical result motivating this entire literature is Greicius and colleagues' 2004 demonstration that default-mode network activity, measured with resting-state fMRI, reliably distinguishes patients with Alzheimer's disease from healthy older adults, with the posterior cingulate cortex and hippocampus showing the most pronounced reductions in DMN connectivity in the patient group [7]. What made this result durable, rather than a one-off finding, was that it connected two previously separate observations — that DMN regions deactivate during tasks in healthy individuals, and that those same regions are where amyloid pathology and hypometabolism are most prominent in Alzheimer's disease — into a single, testable functional claim: if the disease process targets the DMN, DMN connectivity itself should be measurably disrupted, and disrupted early.

The empirical follow-through on that claim, specifically at the earliest, pre-dementia stages, came within a few years. Sorg and colleagues studied individuals at risk for Alzheimer's disease — amnesic mild cognitive impairment patients, a population defined clinically as showing measurable memory impairment without meeting criteria for dementia — and found selective changes in resting-state network connectivity relative to matched healthy controls, with the affected networks overlapping substantially with the DMN and with regions known to show early amyloid deposition, arguing that functional network disruption is detectable at this pre-dementia, at-risk stage rather than only after a diagnosis of dementia has been made [8]. Rombouts and colleagues, working with a partially overlapping population that included both MCI and mild Alzheimer's disease patients, reported a similarly patterned result: resting-state networks, and the DMN

specifically, showed altered connectivity in MCI, with the pattern in mild Alzheimer's disease appearing as a more pronounced version of a similar disruption, consistent with a graded, continuous process rather than a sharp discontinuity between "MCI" and "dementia" as functional-connectivity phenotypes [9]. Wang and colleagues, focusing specifically on early Alzheimer's disease relative to healthy aging, likewise reported altered functional connectivity within the DMN and its component regions, reinforcing the same basic pattern from an independent cohort and analysis pipeline [10].

A parallel line of evidence came from linking functional connectivity directly to amyloid pathology rather than to clinical diagnosis alone. Sperling and colleagues studied cognitively normal older adults using Pittsburgh Compound-B PET imaging to quantify amyloid burden alongside task-based and resting measures of DMN function, and found that greater amyloid deposition was associated with impaired default network function even in the absence of clinical symptoms, directly supporting the idea that DMN functional disruption is not merely a correlate of clinical decline but can be detected at a genuinely preclinical, biomarker-defined stage that precedes measurable cognitive impairment [3]. This finding matters a great deal for how the field frames "early": it pushes the earliest detectable functional signature back past the boundary of MCI into a stage where standard cognitive testing may be entirely normal, which is precisely the window in which a biomarker would be most useful for identifying candidates for early intervention or closer monitoring.

Not every functional change in this population is a straightforward reduction, however, and later work has been careful to note that the DMN disruption seen in Alzheimer's disease is not simply a generic loss of connectivity affecting the whole brain uniformly. Zhou and colleagues compared behavioral variant frontotemporal dementia and Alzheimer's disease directly and showed that the two disorders produce dissociable, network-specific patterns of connectivity change — frontotemporal dementia preferentially disrupting a frontal salience-related network and Alzheimer's disease preferentially disrupting the DMN — a result that is important less for the frontotemporal dementia comparison itself than for what it establishes methodologically: that connectivity disruption in

neurodegenerative disease is topologically selective and can be used, in principle, to distinguish between different degenerative processes rather than only to detect "abnormality" in general [11]. Damoiseaux and colleagues extended the DMN story longitudinally, following patients over time and showing that functional connectivity changes track clinical deterioration in Alzheimer's disease, which is a meaningfully different and stronger claim than a single cross-sectional group difference: it suggests connectivity is not just a static marker of disease presence but a dynamic one that moves together with clinical trajectory, which is closer to what would be needed for a marker used to monitor progression or treatment response [12].

4. Network Topology and Graph-Theoretic Signatures of Early Decline

Taken together, the DMN-focused literature makes a strong and now well-replicated case that one specific large-scale network shows early, reproducible functional disruption. Reducing the story to a single network, however, risks understating what graph-theoretic, whole-brain analyses have added: that the disruption in Alzheimer's disease and its prodromal stages is not confined to the DMN's internal connectivity but is visible in the global topological organization of the brain's functional network as a whole. Supekar and colleagues applied graph-theoretic analysis to resting-state functional connectivity in Alzheimer's disease and found a loss of small-world network properties relative to healthy controls, alongside a specific reduction in the connectivity of hippocampal regions to the rest of the network — a result that connects the whole-brain topology literature directly back to the region most classically implicated in memory and in Alzheimer's disease pathology, and that demonstrates the disruption is measurable both at the level of a single region's connections and at the level of the graph's overall organizational efficiency [13].

This convergence between "which regions lose connectivity" and "how does the graph's global structure change" is a genuinely useful methodological pairing, because each approach compensates for a limitation in the other. A purely seed-based or single-network approach can show that a specific pathway is disrupted but says little about whether that disruption is an isolated event or part of a broader reorganization of brain-wide communication; a purely graph-theoretic,

whole-brain summary metric can characterize that broader reorganization but, on its own, can be agnostic about which specific regions or networks are driving the change. Used together, as in the hippocampal-connectivity and small-world results from Supekar and colleagues, they support a more specific claim than either could alone: that early Alzheimer's disease-related decline involves a targeted loss of connectivity in disease-relevant hub regions (the hippocampus prominently among them) that is severe enough to measurably degrade the efficiency of the whole-brain network's topology, rather than a diffuse, uniform weakening of connections everywhere [13,6].

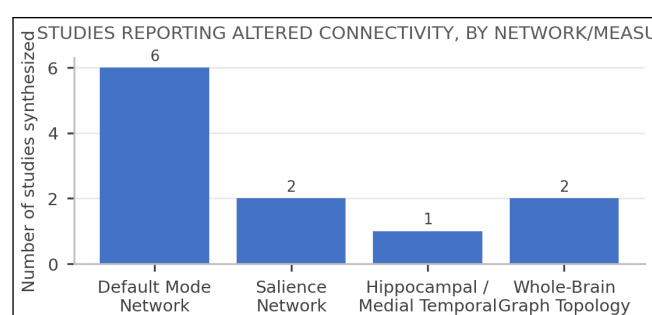


Figure 1: Number of foundational studies synthesized in this review reporting altered resting-state functional connectivity within each large-scale network or graph-theoretic measure, across the early Alzheimer's disease risk spectrum (at-risk, MCI, and early AD populations) [7,8,9,10,3,12,14,11,13,6].

It is also in this graph-theoretic and multi-network context that the salience network becomes relevant to the early-decline literature, even though it was not originally characterized in a dementia population. Seeley and colleagues established the salience network — anchored in anterior insula and dorsal anterior cingulate cortex — as a dissociable intrinsic connectivity network distinct from the DMN, involved in detecting behaviorally relevant stimuli and coordinating the switch between internally oriented (default mode) and externally oriented (executive/attention) processing [14]. The relevance for early cognitive decline is that this DMN-to-executive switching function depends on functional connectivity between networks, not just within them, and later work reviewing resting-state connectivity findings across neuropsychiatric and neurodegenerative disorders has noted that altered connectivity is rarely confined to a single isolated network, but often involves a shift in the balance and coupling between the DMN and networks like the salience and frontoparietal executive networks that normally regulate it [15]. This inter-network perspective is a useful corrective to any oversimplified "the DMN is

where the disease is" framing: what the literature actually supports is closer to a claim about disrupted coordination between specific networks, with the DMN as the most consistently and severely affected node in that broader system.

5. Diagnostic Frameworks, Cohorts, and Clinical Criteria

None of the functional connectivity findings above can be interpreted without knowing, precisely, what population is being studied, and this is a point on which the field has had to do substantial independent work, separate from the imaging methodology itself. "Mild cognitive impairment" is not a single, self-evident category; Petersen's foundational clinical formulation defined MCI as an intermediate state between normal age-related cognitive change and dementia, characterized by measurable memory or other cognitive impairment that is nonetheless insufficient to meet criteria for a dementia diagnosis, and explicitly framed MCI as a clinically and etiologically heterogeneous entity rather than a single disease with a single expected outcome [16]. That heterogeneity matters directly for functional connectivity research, because a study's "MCI" sample can, depending on inclusion criteria, be enriched for individuals who will progress to Alzheimer's disease, individuals whose impairment has another or no identifiable cause, or a mixture of both, and the resulting connectivity findings will reflect whatever mixture happened to be recruited.

Table 1: Successive clinical and biomarker-based frameworks used to define early-stage cognitive decline populations in the functional connectivity literature, and the basis each uses for classification.

Framework / Resource	Introduced	Population Defined	Basis for Classification
Petersen MCI criteria	2004 [16]	Amnesic and non-amnesic mild cognitive impairment	Clinical history and cognitive testing showing measurable impairment insufficient for a dementia diagnosis; no biomarker requirement
NIA-AA "MCI due to AD" recommendations	2011 [17]	MCI attributable specifically to underlying Alzheimer's pathophysiology	Clinical MCI criteria combined with optional supporting biomarker evidence (CSF, structural or molecular imaging)
NIA-AA Research Framework (AT[N])	2018 [18]	Biological Alzheimer's disease across the full symptom spectrum, including cognitively unimpaired	Amyloid, tau, and neurodegeneration biomarker status, defined independently of clinical symptom stage

Framework / Resource	Introduced	Population Defined	Basis for Classification
ADNI multi-site cohort	2010 (ongoing) [19]	Cognitively normal, MCI, and mild Alzheimer's disease arms studied longitudinally	Harmonized multi-site MRI, PET, cognitive, and biofluid biomarker protocol across diagnostic groups

The National Institute on Aging–Alzheimer's Association workgroups, convened specifically to update diagnostic criteria in light of advancing biomarker science, refined this picture considerably. Albert and colleagues' 2011 recommendations for the diagnosis of MCI due to Alzheimer's disease specifically incorporated biomarker evidence — including, potentially, imaging and cerebrospinal fluid markers of the underlying Alzheimer's pathophysiological process — into the diagnostic framework, moving the field toward defining MCI subtypes not just by clinical presentation but by the likelihood that Alzheimer's disease pathology specifically, as opposed to some other cause, underlies the observed impairment [17]. This shift culminated in the 2018 NIA-AA Research Framework, which proposed defining Alzheimer's disease research biologically, along the amyloid/tau/neurodegeneration ("AT[N]") axis, explicitly independent of clinical symptom stage — meaning that, under this framework, a cognitively unimpaired older adult with positive amyloid and tau biomarkers is classified as having biological Alzheimer's disease, distinct from but related to the clinical MCI or dementia stage that may or may not yet be present [18]. For functional connectivity research targeting "early-stage cognitive decline," this framework is consequential: it offers a principled way to define a study population by underlying biology (amyloid- and tau-positive, cognitively normal or mildly impaired) rather than by clinical symptoms alone, which is precisely the kind of population in which a functional connectivity signature — if it exists — would be expected to appear earliest, as the Sperling and colleagues result linking amyloid burden directly to DMN function already illustrated [3,18].

Cohort infrastructure has mattered as much as diagnostic criteria in making this literature possible at meaningful scale. The Alzheimer's Disease Neuroimaging Initiative (ADNI), described in its foundational clinical and methods publications, was designed explicitly as a longitudinal, multi-site study combining serial MRI, PET, cognitive and clinical assessment, and biofluid biomarkers across cognitively

normal, MCI, and Alzheimer's disease participants, with the goal of developing and validating exactly the kind of biomarker — including, though not originally centered on, resting-state functional connectivity — that this article's literature is built around [19]. ADNI and comparable multi-site initiatives matter for functional connectivity research specifically because single-center studies, however well-conducted, are vulnerable to scanner-specific and site-specific artifacts that can masquerade as, or obscure, genuine disease-related connectivity differences; a multi-site design with harmonized acquisition and standardized diagnostic criteria is one of the more credible paths toward functional connectivity findings that generalize beyond the sample and scanner in which they were first observed.

6. Methodological Frontiers: Dynamic Connectivity and Synthesis Across Studies

Every study discussed so far treats functional connectivity as, in effect, a static property computed over an entire resting-state scan: a single correlation value, or a single graph, summarizing several minutes of data. A more recent methodological development treats this as an oversimplification. Hutchison and colleagues' influential review of dynamic functional connectivity lays out the evidence that connectivity between regions is not stationary even within a single resting-state scan, but fluctuates over the course of minutes in ways that carry information beyond what a single time-averaged correlation captures, while also cataloguing the substantial methodological and interpretive challenges — including the difficulty of distinguishing genuine neural non-stationarity from sampling variability, physiological noise, or head motion artifact — that any claim of "dynamic" connectivity change must contend with [20]. For early-stage cognitive decline research specifically, this raises an open and only partially answered question: if DMN connectivity is disrupted in at-risk or MCI populations, is that disruption better characterized as a stable reduction in average connectivity, or as an altered pattern of switching between different momentary connectivity states over the scan — and do these two characterizations carry different diagnostic or mechanistic information? The dynamic connectivity literature raises this question more clearly than it currently answers it for the dementia-risk population specifically, and it represents one of the more promising unresolved extensions of the

static-connectivity findings reviewed above.

Synthesizing across the growing number of individual studies is itself a methodological challenge that the field has had to confront directly, because the DMN, salience-network, and graph-theoretic findings summarized above come from studies that differ in scanner field strength, preprocessing pipeline, motion-correction approach, seed or parcellation choice, and precise clinical inclusion criteria — any of which can shift an individual study's specific numerical result even when the qualitative direction of the finding is consistent. Dennis and Thompson's review of functional brain connectivity using fMRI in aging and Alzheimer's disease performs exactly this synthesizing function, drawing together findings across the DMN, other resting-state networks, and graph-theoretic whole-brain measures into a single account of what is and is not consistently replicated across the literature, and is candid that while DMN hypoconnectivity in Alzheimer's disease and at-risk populations is among the most consistently replicated findings in the field, the picture for other networks, and for the earliest preclinical stages specifically, is less uniform and more dependent on methodological choices than the DMN result [21]. That kind of explicit synthesis work is, in our view, as important a contribution to this literature as any individual empirical study, precisely because it is the mechanism by which a set of individually modest-sized, methodologically heterogeneous studies becomes a body of evidence that a reader — or a clinician, or a biomarker developer — can actually weigh.

7. Open Challenges

Several limitations recur across this literature and deserve to be named directly rather than left implicit. First, sample size and single-site design remain a real constraint for a meaningful fraction of the foundational studies reviewed here, including several of the earliest and most influential DMN-in-MCI results; replication in larger, multi-site, harmonized cohorts of the kind ADNI was built to enable is necessary before any specific connectivity metric should be treated as a validated biomarker rather than a promising research finding [8,9,19]. Second, cross-sectional design dominates this literature; while Damoiseaux and colleagues' longitudinal tracking of connectivity alongside clinical deterioration is an important exception, most of the DMN and graph-theoretic findings summarized here

compare groups at a single timepoint, which cannot on its own distinguish a connectivity signature that predicts future decline from one that simply co-occurs with a given clinical stage without carrying independent predictive information [12].

Third, the field has not fully resolved how to handle the clinical and biological heterogeneity within "MCI" as a study population, even with the NIA-AA biomarker-informed criteria available; a connectivity study that does not stratify its MCI sample by amyloid or tau status risks averaging together individuals on genuinely different underlying trajectories, which can dilute or distort an otherwise real effect [16,17,18]. Fourth, dynamic connectivity analysis, while conceptually promising for capturing information a static correlation cannot, has not yet been applied to early-stage cognitive decline populations with the same volume and consistency of evidence that supports the static DMN findings, and the methodological challenges the dynamic connectivity literature has identified in distinguishing genuine neural state-switching from artifact apply with particular force in older, at-risk populations who tend to move more in the scanner and whose vascular physiology differs from that of the young, healthy volunteers dynamic-connectivity methods were often first validated on [20]. Fifth, and more general: preprocessing and analytic pipeline choices — parcellation scheme, motion-correction and scrubbing thresholds, global signal regression or its omission, seed selection for seed-based analyses — vary enough across the studies synthesized here that direct quantitative comparison of effect sizes across studies is often not meaningful, and the field would benefit from more consistent adoption of a shared analytic standard, of the kind large consortia have begun to promote, before cross-study meta-analysis of specific connectivity values becomes fully reliable.

None of these limitations, in our reading, undermine the core qualitative claim this literature supports — that functional connectivity, and DMN connectivity specifically, is measurably altered before the stage of clinically obvious dementia. What they do argue for is caution about overstating how close that finding currently is to being a validated, individually diagnostic clinical tool, as opposed to a well-replicated group-level research finding that motivates continued, larger-scale, longitudinal, and methodologically harmonized

investigation.

8. Conclusion

The literature synthesized here supports a specific and, by now, well-replicated claim: resting-state functional connectivity within the default mode network is measurably reduced in individuals with mild cognitive impairment and in cognitively normal older adults at biomarker-defined risk for Alzheimer's disease, and this reduction is neither confined to a single isolated pathway nor uniform across the whole brain, but follows a recognizable pattern targeting disease-relevant hub regions such as the hippocampus and degrading the broader efficiency of whole-brain network topology [7,8,13]. That functional signature appears to be detectable earlier than the stage of frank dementia, plausibly as early as the presence of amyloid pathology in still cognitively normal individuals, and appears in at least some studies to track ongoing clinical deterioration rather than remaining static [3,12].

Realizing the clinical promise implicit in that pattern depends on treating the remaining gaps as a research agenda rather than a reason for skepticism about the pattern itself: larger and more consistently harmonized multi-site cohorts building on the infrastructure ADNI established, longitudinal designs capable of testing connectivity's predictive rather than merely concurrent value, biomarker-informed stratification of clinically defined populations along the lines the NIA-AA frameworks now enable, and continued methodological development — particularly around dynamic, non-stationary connectivity measures — to determine whether they add diagnostically useful information beyond what static, time-averaged connectivity already provides [17,18,20]. The consistency with which independent research groups, using different cohorts, scanners, and analytic approaches, have converged on default mode network disruption as an early feature of the Alzheimer's disease continuum is, in our assessment, the strongest available argument that this is a genuine biological signal rather than an artifact of any single study's methodology — and it is precisely that convergence that justifies the continued, deployment-oriented investment the open challenges identified above call for.

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Conflict of Interest

The authors declare that they have no competing interests relevant to the content of this article.

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Ethical Approval

Not applicable. As a literature synthesis, this article did not involve the recruitment of human participants, animal subjects, or the collection of any primary data.

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