

Multiscale organization of amyloid-associated vulnerability across the hippocampal memory system

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ABSTRACT

Alzheimer's disease (AD) selectively affects interconnected components of the hippocampal memory system, yet most MRI biomarkers characterize neurodegeneration using whole-hippocampal or isolated regional measurements. We tested whether amyloid-associated structural vulnerability is selectively concentrated in the cornu ammonis 1 (CA1) and the dentate gyrus (DG), reproducible across independent 1Florida ADRC and ADNI cohorts, and spatially localized within these subfields. We integrated hippocampal subfield volumetry, covariate-adjusted amyloid-associated vulnerability scores, 10,000-resample bootstrap rank-stability analysis, complementary cross-sectional clinical-stage comparisons, exploratory diffusion MRI, and within-subfield occupancy mapping.

The cornu ammonis 1 (CA1) region and the dentate gyrus (DG) retained the two highest covariate-adjusted amyloid-associated point rankings in both cohorts. In ADRC, the adjusted scores were 5.06% for CA1 and 4.38% for DG, with bootstrap Top-2 frequencies of 59.02% and 41.44%, respectively; in ADNI, the adjusted scores were 9.10% for CA1 and 9.37% for DG, with Top-2 frequencies of 73.60% and 76.40%, respectively. Bootstrap resampling quantified uncertainty in regional scores and rank positions and supported recurrent top two placement of CA1 and DG, while also demonstrating overlap in uncertainty among several ROIs. Complementary cross-sectional comparisons described CA1 and DG volume differences across clinical stages in ADRC and ADNI. Exploratory diffusion MRI identified effect-size differences in hippocampal-associated pathways, but none of the 20 region-metric comparisons survived Benjamini-Hochberg false-discovery-rate correction.

Collectively, these findings support a reproducible cross-sectional pattern of amyloid-associated vulnerability within the hippocampal memory system, centered on CA1 and DG and accompanied by spatially heterogeneous within-subfield structural loss. The diffusion MRI findings are exploratory and provide anatomical context rather than evidence of temporal ordering. Longitudinal studies are required to determine the sequence in which these abnormalities emerge.

1. Introduction

Alzheimer's disease is increasingly understood to involve selective degeneration across interconnected brain networks rather than uniform cortical atrophy. Yet most MRI biomarkers remain confined to isolated

anatomical scales, preventing an integrated understanding of how degeneration propagates across interconnected components of the hippocampal memory system.

The hippocampus and surrounding medial temporal lobe (MTL) structures are among the earliest and most clinically informative brain

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regions affected in AD (Braak and Braak, 1991; Jack et al., 2018). Whole-hippocampal volume has therefore become a widely used MRI biomarker of neurodegeneration (Frisoni et al., 2010; Jack et al., 2024). Recent studies further demonstrate that hippocampal subfield volumes vary substantially across the healthy lifespan and are influenced by MRI acquisition protocols, emphasizing the importance of anatomically precise subfield measurements (Bussy et al., 2021). However, whole-hippocampal measurements collapse anatomically distinct subfields and adjacent MTL cortices into a single scalar value, potentially obscuring selective vulnerability patterns that are central to AD pathophysiology (de Flores et al., 2015; Wisse et al., 2021; Eichenbaum, 2017).

The hippocampal formation is not a homogeneous structure (Duvernoy et al., 2013). Advances in atlas-based hippocampal segmentation have enabled increasingly reliable delineation of individual hippocampal subfields and surrounding medial temporal structures from MRI (Pipitone et al., 2014), facilitating investigations of region-specific neurodegeneration. CA1, CA2, CA3, dentate gyrus (DG), subiculum (SUB), entorhinal cortex (ERC), BA35, BA36, PHC, and the collateral sulcus participate in partially distinct anatomical and functional memory processing (Ranganath and Ritchey, 2012; Berron et al., 2017; Small et al., 2011; Yassa and Stark, 2011). Neuropathological and imaging studies suggest that AD-related degeneration is not uniformly distributed across these regions (Braak and Braak, 1991; Mueller et al., 2010; de Flores et al., 2015). Recent evidence further demonstrates that hippocampal subfields exhibit distinct sex-specific structural and hemodynamic aging trajectories, reinforcing the biological heterogeneity of hippocampal subfields even during normal aging (Wen et al., 2025). Nevertheless, most MRI studies characterize neurodegeneration at either the whole-hippocampal or individual regional level, while relatively few investigate how vulnerability is organized across the broader hippocampal memory system and its distributed anatomical network (Seeley et al., 2009; Crossley et al., 2014). Consistent with this rationale, prior work has shown that hippocampal subfield measures can provide information beyond whole-hippocampal measurements for characterizing Alzheimer's disease (Kannappan et al., 2022), further motivating anatomically resolved analysis of CA1, DG, and related medial temporal structures.

Beyond anatomical heterogeneity across hippocampal subfields and MTL regions, biological heterogeneity within clinically defined cognitive impairment presents an additional challenge (Hansson, 2021). Individuals with similar clinical conditions may differ substantially in underlying amyloid and tau pathology (Scheltens et al., 2021). Amyloid-informed participant stratification allows structural differences to be examined in relation to amyloid status rather than clinical diagnosis alone (Jack et al., 2018). This issue is particularly important for hippocampal subfield analyses, where subtle anatomical differences can be obscured by heterogeneity in disease mechanism.

Taken together, these considerations suggest that understanding AD-related vulnerability requires both biological specificity and anatomical context. However, most existing MRI studies examine these complementary levels separately. Whole-hippocampal and subfield volumetric studies provide valuable information about regional atrophy, whereas diffusion MRI studies characterize white matter pathways associated with hippocampal and medial temporal lobe circuitry (Acosta-Cabronero et al., 2012; Mito et al., 2018). These approaches are typically investigated independently, and relatively few studies integrate them with spatially resolved within-subfield analyses into a unified framework. As a result, evidence from network-level pathways, hippocampal subfields, and localized within-subfield regions is often considered separately when characterizing AD-related neurodegeneration.

Using the 1Florida ADRC as a discovery cohort and ADNI as an independent validation cohort, we tested the specific hypothesis that amyloid-associated structural vulnerability would be concentrated in CA1 and DG, reproducible across cohorts, and spatially localized within

these subfields. Cross-cohort consistency was evaluated by preservation of the CA1/DG top-two pair, agreement in regional ordering, and bootstrap rank stability. Hippocampal-associated diffusion MRI and clinical-stage analyses were treated as complementary, exploratory or descriptive analyses rather than as evidence of temporal progression.

2. Materials and methods

2.1. Study cohorts

The discovery cohort was drawn from the 1Florida Alzheimer's Disease Research Center (ADRC). Participants spanned five clinical stages, including cognitively normal, subjective cognitive decline (SCD), Early MCI, Late MCI, and Dementia. Demographic characteristics of the ADRC cohort are summarized in Table 1.

An independent external validation cohort was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) (Mueller et al., 2005), including Normal, MCI, and Dementia participants. Demographic characteristics of the ADNI cohort are summarized in Table 2. The ADRC cohort was used for discovery of amyloid-associated regional vulnerability patterns, whereas the ADNI cohort was used for external validation of ROI-level ranking reproducibility.

For both cohorts, a clinically normal reference group was constructed by selecting cognitively normal participants and excluding individuals with known amyloid positivity or tau positivity. Participants without available biomarker records were not excluded solely on the basis of missingness. This strategy was used to preserve a clinically normal reference group while reducing the influence of known AD pathology. In ADRC, this yielded a normal reference group of 15 participants. In ADNI, the corresponding clinically normal reference group included 31 participants.

In Tables 1 and 2, the A+/A− column reports the numbers of participants with positive and negative amyloid status, respectively. The Clinical AD/non-AD column reports the numbers of participants with clinician-assigned AD-related and non-AD etiologies, respectively. For the Normal row, the entry in the Clinical AD/non-AD column indicates the number of participants in the shared normal reference group.

2.2. MRI segmentation and ROI definition

High-resolution hippocampal and medial temporal lobe measurements were generated using Automated Segmentation of Hippocampal Subfields (ASHS) (Yushkevich et al., 2015). Recent deep learning approaches have substantially improved automated hippocampal segmentation (Sackl et al., 2024); however, ASHS remains one of the most extensively validated methods for anatomically detailed hippocampal subfield delineation and cross-cohort studies. For each participant, the left and right regional volumes were extracted for ten anatomically defined ROIs: CA1, CA2, CA3, DG, SUB, ERC, BA35, BA36, PHC, and collateral sulcus. The left and right volumes were combined to obtain bilateral ROI volumes, which were normalized by intracranial volume (ICV). The ICV-normalized bilateral ROI volumes served as the primary structural MRI measurements. All image data underwent quality control prior to analysis. Participants with failed image acquisition, missing

Table 1
Demographic characteristics of the ADRC discovery cohort.

Clinical group	N	Age (mean ± SD)	Female/Male	Education (years)	A+ / A−	Clinical AD / non-AD
Normal	17	67.7 ± 6.7	12 / 5	15.7 ± 3.0	1 / 2	15
SCD	37	66.4 ± 8.0	20 / 17	13.9 ± 2.8	4 / 6	7 / 30
Early MCI	65	68.4 ± 7.8	37 / 28	15.3 ± 4.2	17 / 17	26 / 39
Late MCI	23	70.2 ± 7.4	8 / 15	13.8 ± 4.2	6 / 9	8 / 15
Dementia	16	70.4 ± 9.0	9 / 7	14.1 ± 2.7	8 / 3	10 / 6

Table 2

Demographic characteristics of the ADNI external validation cohort.

Clinical group	N	Age (mean $\pm$ SD)	Female/Male	Education (years)	A+ / A-	Clinical AD / non-AD
Normal	45	83.8 $\pm$ 4.7	22 / 23	16.0 $\pm$ 2.9	12 / 18	31
MCI	387	74.7 $\pm$ 8.2	194 / 193	16.3 $\pm$ 2.5	134 / 117	309 / 78
Dementia	179	76.2 $\pm$ 8.1	90 / 89	15.9 $\pm$ 2.7	105 / 13	164 / 15

segmentation, substantial anatomical artifact, or unreliable ROI measurements were excluded. The same ROI definitions and volume normalization strategy were applied across ADRC and ADNI to support cross-cohort comparison. The reproducibility of automated hippocampal subfield volumetry across scanners and imaging vendors has previously been demonstrated, supporting the reliability of regional measurements used in multicenter studies (Quattrini et al., 2020).

2.3. Multiscale imaging framework

To integrate structural MRI and diffusion MRI findings within a unified biological framework, analyses were organized across three anatomical scales of the hippocampal memory system. First, network-level vulnerability was evaluated using diffusion tensor imaging metrics extracted from hippocampal-associated white matter pathways, including the cingulum and fornix, in cognitively normal amyloid-positive and amyloid-negative participants. This analysis was considered exploratory because of the limited DTI sample size. Second, subfield-level amyloid-associated vulnerability was quantified across ten bilateral hippocampal subfield and MTL ROIs using an amyloid-informed relative loss score. Third, within-subfield spatial vulnerability was evaluated in CA1 and DG using occupancy-based analyses to determine whether volume loss within the most reproducible subfields reflected uniform shrinkage or spatially localized occupancy reduction. This framework was used to characterize amyloid-associated vulnerability across multiple anatomical scales. It was not intended to establish a temporal causal sequence between white matter alterations, subfield structural loss, and within-subfield spatial loss.

2.4. Amyloid-associated vulnerability score

For each ROI, percent volume loss relative to the shared normal reference group was calculated for amyloid-positive and amyloid-negative participants. For group g and region r , relative loss is defined as:

$$Loss_g(r) = 100 \frac{M_{normal}(r) - M_g(r)}{M_{normal}(r)} \quad (1)$$

where $M_{normal}(r)$ is the mean ICV-normalized volume in the clinically normal reference group and $M_g(r)$ is the mean volume in the comparison group. The unadjusted amyloid-associated score was quantified as:

$$Amyloid - associatedScore(r) = Loss_{A+(r)} - Loss_{A-(r)} \quad (2)$$

Covariate-adjusted scores were obtained by ordinary least squares regression of ICV-normalized ROI volume on amyloid status, age, sex, education, and clinical stage, with sex and stage entered categorically. For each ROI, the adjusted score was -100 times the A+ regression coefficient divided by the shared Normal mean. Both analyses used the same complete cases. For each cohort, 10,000 participant-level bootstrap resamples were drawn separately within A+, A-, and Normal groups, using the same sampled participants across all ROIs; each adjusted model and Normal mean was re-estimated. For each ROI,

bootstrap frequencies were calculated for each adjusted rank from 1 to 10 and for inclusion in the top two. Pointwise 95% percentile confidence intervals were calculated for both unadjusted and covariate-adjusted scores. These scores describe amyloid-associated volume differences and do not establish AD-specific neurodegeneration.

Higher positive values indicate greater additional volume reduction associated with amyloid positivity beyond that observed in amyloid-negative participants. Because amyloid-negative older adults may nevertheless harbor non-AD neurodegenerative, vascular, or mixed pathology, this measure is interpreted as an amyloid-associated vulnerability score rather than an AD-specific vulnerability score. ROIs were ranked according to their unadjusted and covariate-adjusted amyloid-associated scores. A tau-adjusted sensitivity analysis was not performed because sufficiently complete and harmonized tau biomarker data were not available across the analytic cohorts. The probability that two independent rankings of 10 ROIs would identify the same unordered top-two pair by chance was calculated as:

$$P = \frac{1}{\binom{10}{2}} = 0.022 \quad (3)$$

2.5. Visualization of volume patterns across clinical stages

Volume patterns across clinical stages were visualized in the two highest-ranked ADRC regions identified by the amyloid-associated vulnerability ranking analysis: CA1, DG. Two grouping strategies were used: clinician-assigned etiology (AD-related versus non-AD) and amyloid biomarker status (A+ versus A-). In each cohort, the same shared normal reference group was used for both grouping strategies. For the ADRC three-stage plots, SCD and Early MCI were combined into an Early Stage group, and Late MCI and Dementia were combined into a Late Stage group. The corresponding ADNI plots showed Normal, MCI, and Dementia groups (Fig. 3). Five-stage ADRC plots were used descriptively to visualize patterns across Normal, SCD, Early MCI, Late MCI, and Dementia (Fig. 4). Because several biomarker-defined stage-specific subgroups were small, the plots were interpreted descriptively rather than as formal stage-wise statistical tests.

2.6. Exploratory diffusion tensor imaging analysis

Exploratory diffusion MRI analyses were performed in cognitively normal ADNI participants to evaluate whether amyloid positivity was associated with microstructural differences in hippocampal-associated white matter pathways. The DTI subset included cognitively normal amyloid-negative participants ($n = 8$) and cognitively normal amyloid-positive participants ($n = 10$).

Tensor fitting was performed to derive fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) maps, which were subsequently registered to MNI space.

JHU white matter atlas labels (Hua et al., 2008) were used to extract tract-level diffusion metrics. Five atlas-defined regions were selected based on their anatomical relevance to the extended hippocampal memory network: the fornix column and body, bilateral hippocampal cingulum, and bilateral cingulate-gyrus cingulum. The fornix provides major connections between the hippocampal formation and subcortical structures, while the cingulum supports connections between cingulate and parahippocampal regions (Christiansen et al., 2016; Bubb et al., 2018). Group differences were summarized using mean $\pm$ SD and Cohen's d , calculated as the A+ minus A- mean difference divided by the pooled within-group SD. Two-sided Welch's t -tests were used, and Benjamini-Hochberg false discovery rate (BH-FDR) correction was applied jointly across all 20 region-metric comparisons (five regions $\times$ four metrics), with an adjusted $p < 0.05$ threshold. Given the limited sample size, DTI findings were interpreted as exploratory.

2.7. Spatial occupancy analysis of CA1 and DG

CA1 and DG were selected for within-subfield spatial analysis because they were the most reproducible top-ranked hippocampal subfields across ADRC and ADNI. For each subject, ROI masks were normalized along the hippocampal long axis after removing leading and trailing slices that did not contain ROI voxels. Because CA1 and DG differed in their typical long-axis extent, separate normalization resolutions were used for each subfield. CA1 masks were normalized into 20 equally spaced bins, whereas DG masks were normalized into 17 equally spaced bins, corresponding to the average number of occupied slices observed in each subfield. Mean occupancy profiles were computed for each clinical stage. Relative occupancy reduction was calculated with respect to the normal reference profile as

$$\text{OccupancyLoss}_g(b) = \frac{\text{Occ}_{\text{normal}}(b) - \text{Occ}_g(b)}{\text{Occ}_{\text{normal}}(b)} \quad (4)$$

where b denotes the spatial bin. Voxel-wise occupancy-loss maps were generated by comparing stage-specific occupancy probabilities with the normal reference group. These maps and corresponding 3-D surfaces were used to visualize whether structural loss within CA1 and DG was spatially localized or uniformly distributed.

ChatGPT was used to assist with code development; all AI-assisted code was reviewed, executed, and validated by the authors.

3. Results

3.1. Multiscale study framework and anatomical ROIs

Fig. 1 summarizes the multiscale imaging framework and representative anatomical regions examined in this study. As illustrated in Fig. 1A, the analytical framework was organized across three complementary spatial scales of the hippocampal memory system. At the network level, exploratory diffusion tensor imaging (DTI) analyses evaluated hippocampal-associated white matter pathways, including the cingulum and fornix. At the subfield level, amyloid-associated vulnerability was quantified across ten hippocampal and medial temporal lobe (MTL) regions using amyloid-informed structural MRI measures, followed by cross-cohort reproducibility assessment in ADRC and ADNI. At the within-subfield level, spatial occupancy analyses were performed to characterize localized patterns of structural loss within the most reproducibly vulnerable subfields.

Fig. 1B shows the anatomical locations of four representative

hippocampal/MTL regions: CA1, dentate gyrus (DG), subiculum (SUB), and parahippocampal cortex (PHC). These regions represent anatomically distinct components of the hippocampal memory system and were identified among the highest-ranked regions in the amyloid-associated vulnerability analysis. Subsequent clinical-stage volume comparisons and within-subfield spatial analyses focused on CA1 and DG.

3.2. Covariate-adjusted rankings highlight CA1 and DG across independent cohorts

Table 3 summarizes the unadjusted and covariate-adjusted amyloid-associated scores, with rows ordered by the adjusted ADRC point ranking. Among the ten hippocampal and medial temporal lobe ROIs, CA1 and DG had the highest unadjusted scores in both ADRC (9.46% and 8.18%, respectively) and ADNI (16.62% and 16.43%). After adjustment for age, sex, education, and clinical stage, CA1 remained first in ADRC with a score of 5.06%, followed by DG at 4.38%. In ADNI, DG ranked first at 9.37%, closely followed by CA1 at 9.10%. Thus, both cohorts identified CA1 and DG as the two highest-ranked regions after covariate adjustment (Fig. 2a, Table 3).

The Bootstrap Top-2 percentages in Table 3 represent the frequency with which each ROI ranked among the top two based on covariate-adjusted scores across 10,000 bootstrap resamples per cohort. These frequencies were 59.02% for CA1 and 41.44% for DG in ADRC, and 73.60% for CA1 and 76.40% for DG in ADNI (Fig. 2b, Table 3). Fig. 2b shows the bootstrap frequencies for all ten rank positions, and Fig. 2c presents the score estimates with pointwise 95% bootstrap confidence intervals.

3.3. Group differences across clinical stages in top-ranked ROIs

Cross-sectional volume comparisons were performed for CA1 and DG to complement the amyloid-associated ranking analysis (Figs. 3 and 4). Fig. 3 presents three-stage plots for ADRC and ADNI under clinician-assigned etiology (AD-related versus non-AD) and amyloid status (A+ versus A-). ADRC groups were Normal, Early Stage (SCD and Early MCI), and Late Stage (Late MCI and Dementia); ADNI groups were Normal, MCI, and Dementia. In both cohorts, mean CA1 and DG volumes were lower in A+ than A- participants within symptomatic groups, with greater separation in the latter group.

Fig. 4 provides finer clinical-stage stratification in ADRC using five-stage plots (Normal, SCD, Early MCI, Late MCI, and Dementia). CA1 and DG showed volume differences across symptomatic clinical-stage groups, particularly between amyloid-positive and amyloid-negative

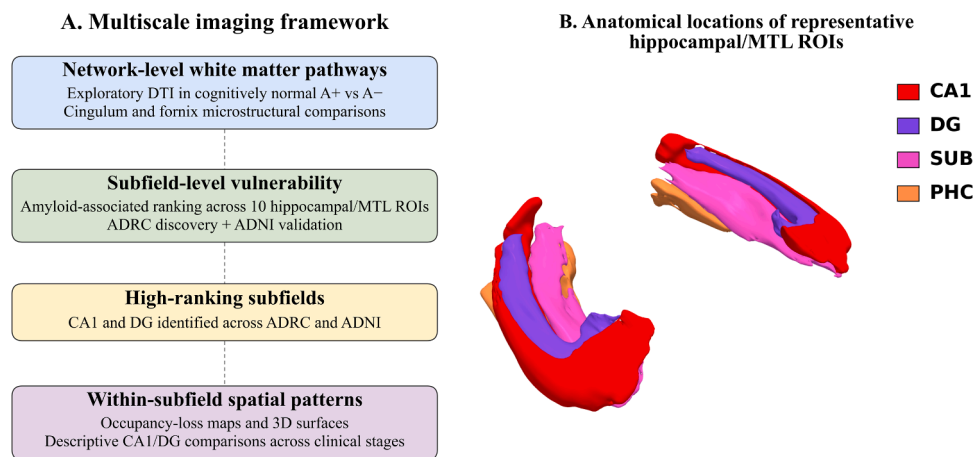


Fig. 1. Multiscale imaging framework and anatomical locations of representative hippocampal/MTL ROIs. Panel A illustrates the multiscale organization of amyloid-associated vulnerability examined in this study, spanning exploratory network-level DTI differences, subfield-level amyloid-associated vulnerability ranking, reproducible CA1/DG vulnerability across cohorts, and localized within-subfield structural loss. Panel B shows the anatomical locations of CA1, DG, SUB, and PHC generated from ASHS segmentations.

Table 3
Unadjusted and covariate-adjusted amyloid-associated ROI scores and bootstrap ranking frequencies in ADRC and ADNI.

ROI	ADRC			ADNI		
	Amyloid-associated score % (rank)	Covariate-adjusted score % (rank)	Bootstrap Top-2%	Amyloid-associated score % (rank)	Covariate-adjusted score % (rank)	Bootstrap Top-2%
CA1	9.46 (1)	5.06 (1)	59.02	16.62 (1)	9.10 (2)	73.60
DG	8.18 (2)	4.38 (2)	41.44	16.43 (2)	9.37 (1)	76.40
SUB	6.35 (4)	4.16 (3)	36.38	8.90 (7)	3.77 (6)	0.03
PHC	6.92 (3)	2.83 (4)	22.14	6.49 (8)	0.57 (9)	0.00
CA2	3.55 (5)	0.26 (5)	7.34	9.10 (6)	5.03 (5)	4.51
ERC	2.84 (7)	−0.38 (6)	3.26	13.65 (3)	8.30 (3)	39.27
BA36	2.72 (8)	−1.42 (7)	6.25	9.67 (5)	3.23 (7)	0.43
CA3	−6.61 (9)	−2.26 (8)	22.94	−0.46 (9)	3.21 (8)	2.72
BA35	3.40 (6)	−3.36 (9)	0.18	11.25 (4)	5.67 (4)	3.02
Sulcus	−20.94 (10)	−18.58 (10)	1.05	−9.24 (10)	−4.64 (10)	0.02

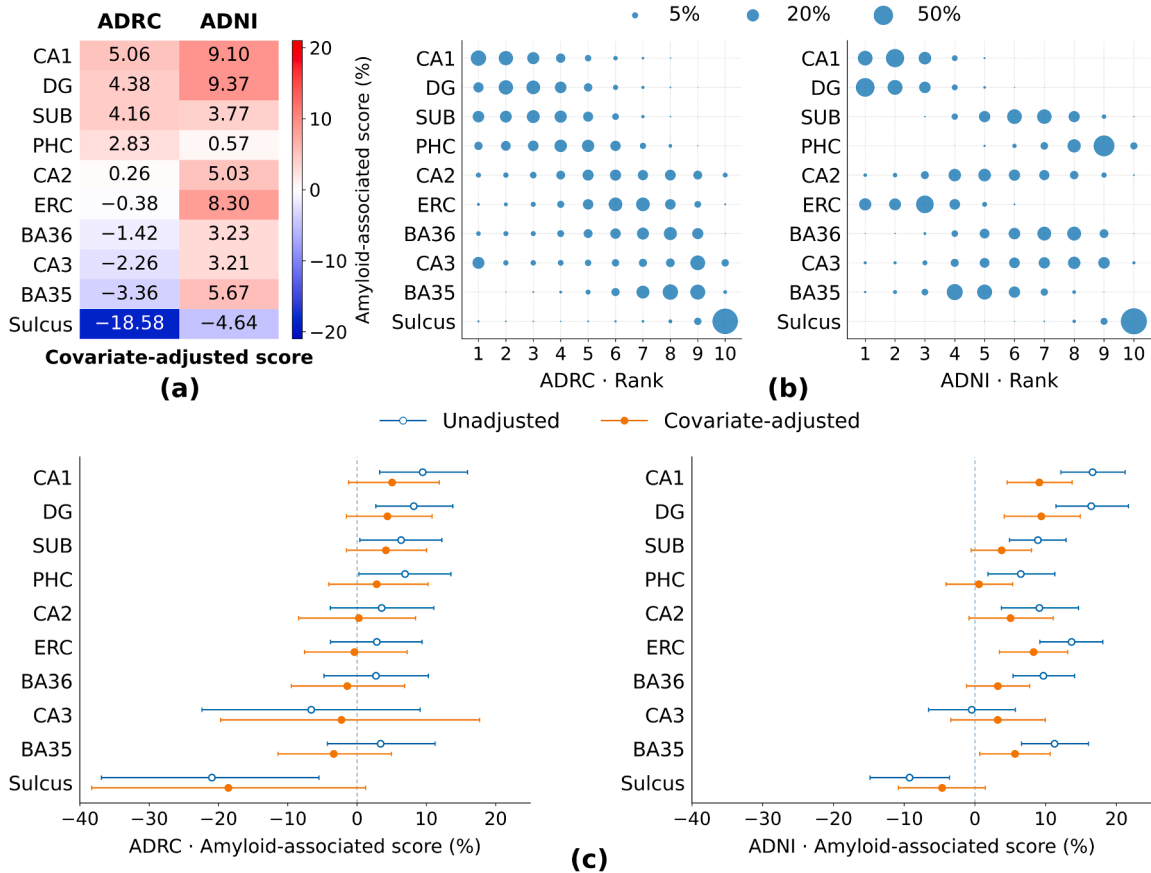


Fig. 2. Amyloid-associated ROI scores and bootstrap ranking uncertainty. (a) Covariate-adjusted scores. (b) Covariate-adjusted rank frequencies from 10,000 bootstrap resamples per cohort; bubble area represents frequency. (c) Unadjusted and covariate-adjusted scores with pointwise 95% bootstrap confidence intervals. Adjusted models included age, sex, education, and clinical stage. ROI order follows the adjusted ADRC ranking.

participants. Together, Figs. 3 and 4 provide complementary evidence describing clinical-stage volume patterns in these two selected ROIs.

3.4. Network-level DTI differences in cognitively normal amyloid-positive participants

To determine whether the structural vulnerability identified within hippocampal subfields extended to the broader memory network, exploratory diffusion tensor imaging (DTI) analyses were performed in cognitively normal amyloid-negative (A−) and amyloid-positive (A+) participants (Figs. 5 and 6, Table 4). Tract-level diffusion metrics, including fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD), were evaluated across

hippocampal-associated white matter pathways. Within these five regions, the largest absolute Cohen's d values occurred in the cingulum, with moderate effects in the fornix. These pathways are anatomically linked to the hippocampal memory system and therefore provide complementary network-level context for the structural MRI findings.

Table 4 reports group means $\pm$ SD, Cohen's d, unadjusted p values, and BH-adjusted p values for all 20 comparisons across the five regions and four diffusion metrics (FA, MD, RD, and AD). Fig. 6 shows the anatomical locations of these regions and the corresponding effect-size patterns.

The largest diffusion differences were observed within the cingulum. Specifically, the left cingulum (cingulate gyrus) demonstrated lower RD and MD values in amyloid-positive participants compared with amyloid-

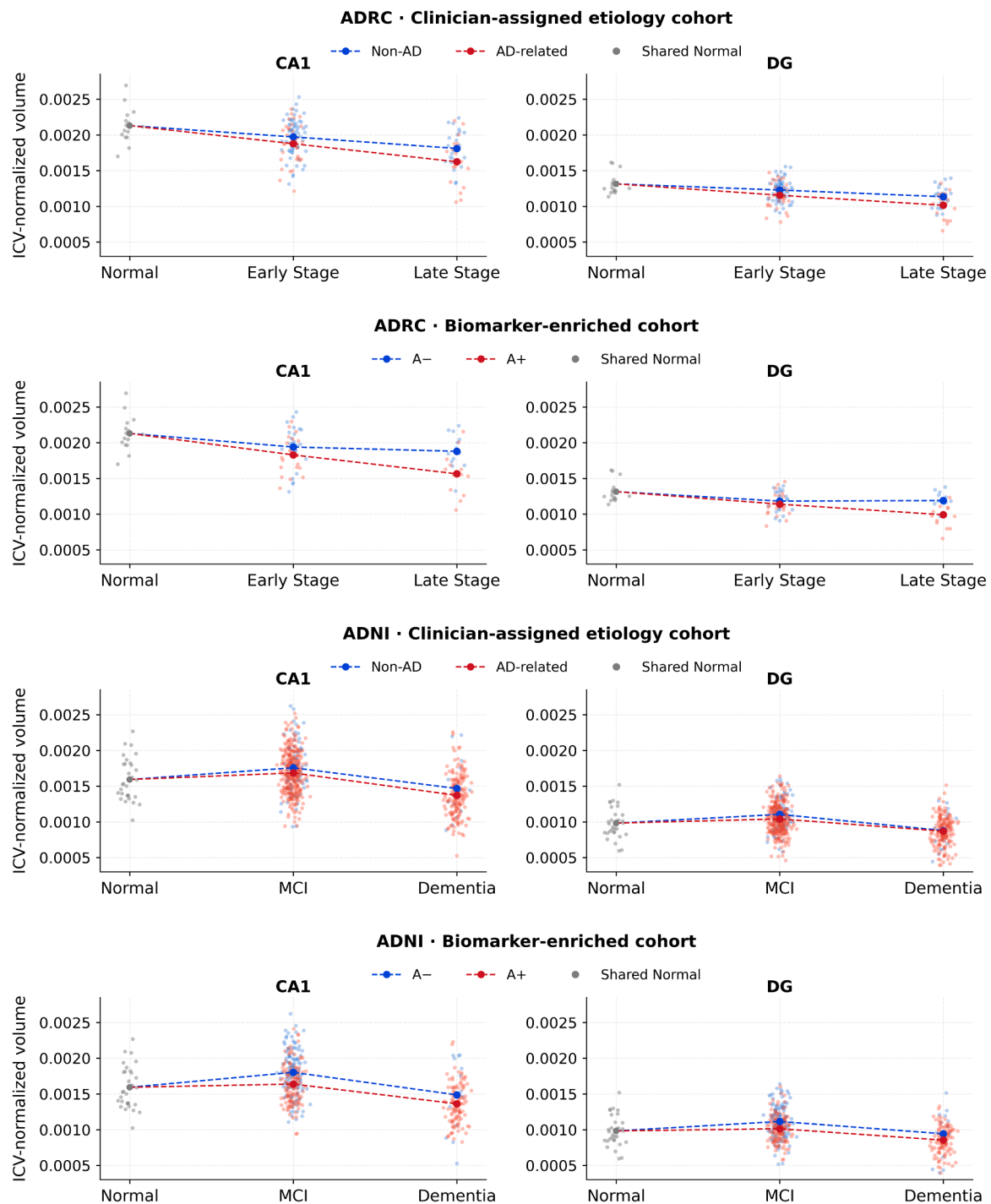


Fig. 3. Three-stage CA1 and DG volume patterns in ADRC and ADNI. Rows show, from top to bottom, ADRC clinical AD-related versus non-AD, ADRC A+ versus A−, ADNI clinical AD-related versus non-AD, and ADNI A+ versus A− comparisons. ADRC Early Stage combines SCD and Early MCI, and Late Stage combines Late MCI and Dementia; ADNI groups are Normal, MCI, and Dementia. Small points represent individual ICV-normalized bilateral volumes; dashed lines connect group means. Each cohort uses its own shared Normal reference group.

negative participants (RD: $d = -1.13$, $p = 0.043$; MD: $d = -1.01$, $p = 0.079$), while the right cingulum exhibited similar but smaller effects. Additional moderate differences were identified within the fornix, including higher FA ($d = 0.47$) and lower MD ($d = -0.48$) values in the amyloid-positive group. Representative tract-level FA and MD distributions are shown in Fig. 5, and effect sizes across all five regions and four diffusion metrics are summarized in Fig. 6b.

Although the participants were cognitively normal, MD and RD differed descriptively according to amyloid status in selected

hippocampal-associated pathways. These cross-sectional observations do not establish that white-matter alterations occur early or precede hippocampal structural changes. They are reported as exploratory network-level observations that provide anatomical context for the structural MRI findings.

Because the diffusion MRI cohort was modest in size (Normal A−, $n = 8$; Normal A+, $n = 10$), and none of the 20 region–metric comparisons reached statistical significance after Benjamini–Hochberg false discovery rate (BH-FDR) correction, these analyses should be considered

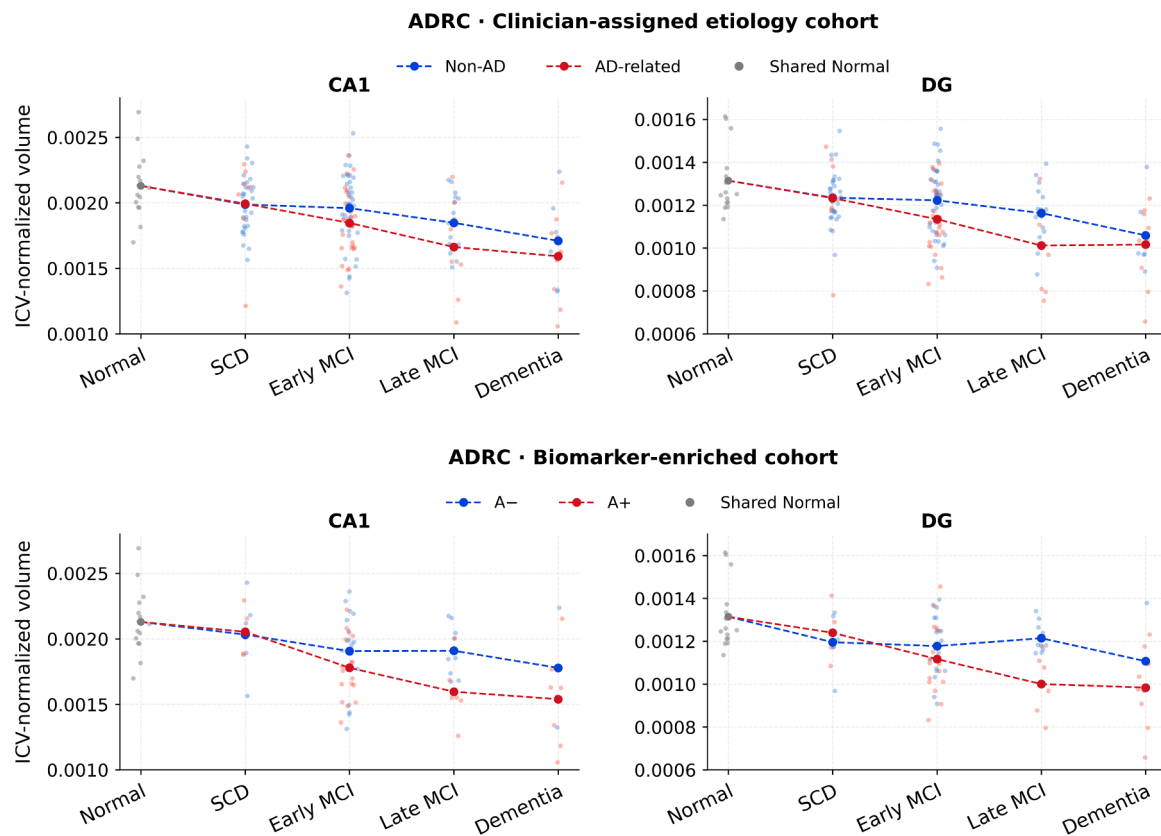


Fig. 4. Five-stage CA1 and DG volume patterns in ADRC. The upper row compares clinical AD-related and non-AD groups, and the lower row compares A+ and A− groups across Normal, SCD, Early MCI, Late MCI, and Dementia. Small points represent individual ICV-normalized bilateral volumes; dashed lines connect group means. Both comparisons use the same shared Normal reference group.

exploratory and interpreted cautiously. The observed diffusion differences should not be viewed as definitive evidence of preclinical white matter degeneration but rather as preliminary network-level observations that complement the structural MRI findings and motivate validation in larger longitudinal cohorts.

3.5. CA1 and DG show spatially localized within-subfield occupancy loss

Because CA1 and DG consistently emerged as the two highest-ranked hippocampal subfields across ADRC and ADNI, these regions were further examined using spatial occupancy analyses. In both regions, occupancy loss was not uniformly distributed across the structure. Instead, localized regions of elevated occupancy loss were observed across clinical stages, indicating spatially heterogeneous patterns of structural change. Importantly, these spatial occupancy maps provide anatomical information that cannot be recovered from regional volume measurements alone. By preserving the spatial distribution of structural change, occupancy analysis reveals localized patterns that are obscured when structural change is summarized by a single volumetric value. Representative occupancy-loss maps are shown in Fig. 7. Both CA1 and DG demonstrated localized occupancy reduction rather than uniform loss throughout the entire subfield. The observed patterns suggest that volume reduction within these regions is spatially organized, with structural differences concentrated within specific anatomical locations rather than distributed evenly across the subfields. Fig. 8 provides a three-dimensional visualization of the occupancy-loss maps shown in Fig. 7 by projecting the same relative occupancy-loss values onto the corresponding three-dimensional subfield surfaces. Consistent with the two-dimensional maps, occupancy loss remained spatially heterogeneous within both CA1 and DG rather than uniformly distributed throughout the subfields. The two-dimensional and three-dimensional

visualizations demonstrate that structural loss within vulnerable hippocampal subfields is spatially organized rather than reflecting homogeneous shrinkage across the entire region.

Whereas conventional volumetric measurements quantify the magnitude of tissue loss, occupancy mapping characterizes where structural loss occurs within each hippocampal subfield. This additional spatial dimension provides complementary anatomical information that may distinguish different spatial patterns of structural loss even when overall regional volumes are similar.

3.6. Summary of multiscale vulnerability patterns

Table 5 synthesizes the principal findings across the four complementary analyses examined in this study and places structural MRI findings and exploratory DTI observations within a common anatomical framework. The four analytical levels provide distinct but integrated information regarding the anatomical organization of regional structural vulnerability.

At the network level, exploratory diffusion MRI described effect-size differences within the cingulum and fornix, but none remained significant after BH-FDR correction. These observations provide hypotheses for future studies of hippocampal-associated white matter pathways.

At the regional level, CA1 and DG retained the two highest covariate-adjusted amyloid-associated point rankings in ADRC and ADNI, providing a focus for further cross-cohort assessment (Marek et al., 2022). Complementary cross-sectional comparisons characterized CA1 and DG volume differences across clinical stages in ADRC and ADNI under both grouping strategies.

At the within-subfield level, occupancy analyses show that structural loss within CA1 and DG is spatially heterogeneous instead of uniformly distributed. Differences in the spatial extent of localized occupancy loss

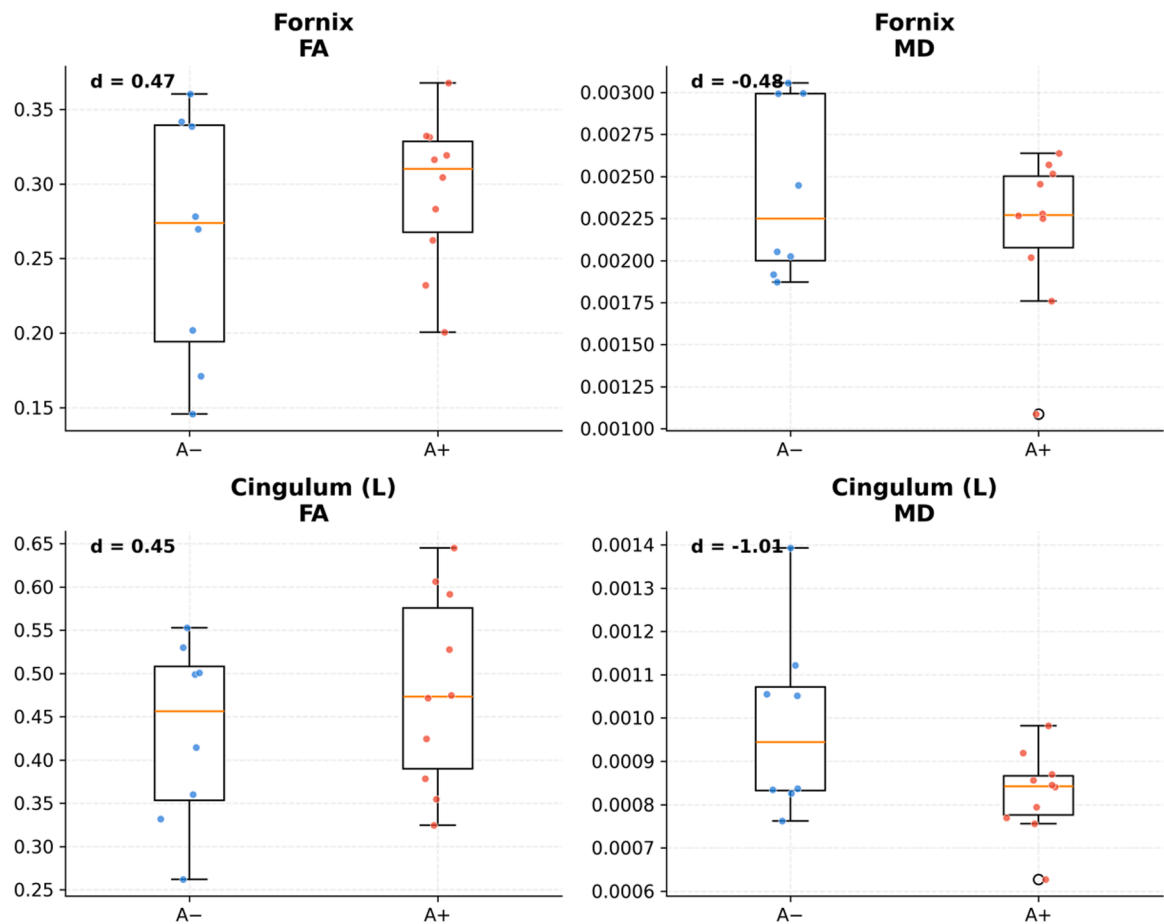


Fig. 5. Representative exploratory DTI differences between cognitively normal amyloid-negative (A-) and amyloid-positive (A+) participants. Boxplots with individual data points show selected tract-metric combinations from the exploratory DTI analysis, including FA and MD measures from the fornix and left cingulum (cingulate gyrus). Cohen's d values are shown within each panel. These examples were selected to illustrate representative diffusion patterns observed in hippocampal-associated white matter pathways. FA and MD summary statistics are provided in Table 4, and effect sizes for all four metrics are shown in Fig. 6b.

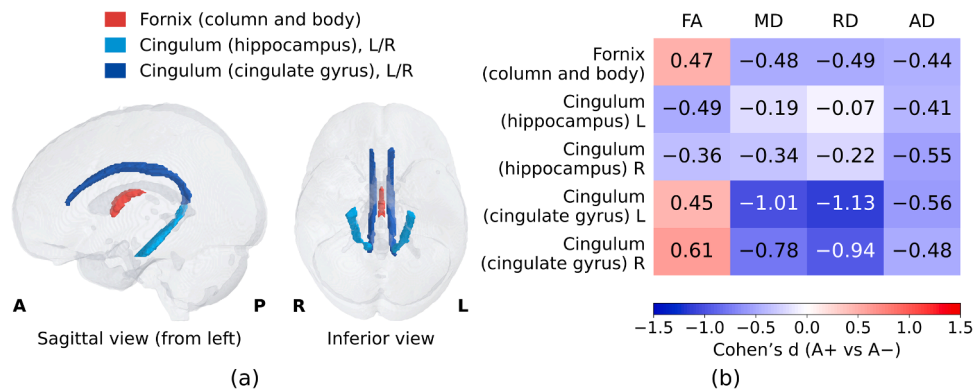


Fig. 6. Exploratory DTI comparisons in cognitively normal ADNI participants (A-, $n = 8$; A+, $n = 10$). (a) Anatomical locations of the five JHU atlas-defined regions. (b) Cohen's d for FA, MD, RD, and AD; positive values indicate higher values in A+ than A- participants; negative values indicate lower values. A/P, anterior/posterior; L/R, left/right.

across clinical-stage groups indicate that structural loss is anatomically organized within vulnerable hippocampal subfields, providing spatial information beyond conventional volumetric measures.

Table 5 highlights that each analytical scale addresses a distinct biological question. Exploratory diffusion MRI describes between-group differences within hippocampal-associated pathways, vulnerability ranking identifies the selectively affected hippocampal subfields, cross-sectional comparisons characterize differences in these abnormalities

across clinical stages, and occupancy mapping localizes structural loss within those vulnerable structures. These approaches address complementary anatomical questions; the DTI observations remain exploratory.

4. Discussion

This study supports a selective, multiscale, and spatially organized cross-sectional pattern of amyloid-associated structural vulnerability

Table 4

Tract-level diffusion tensor imaging metrics in cognitively normal amyloid-negative and amyloid-positive participants.

Region	Metric	Normal A–Mean $\pm$ SD ($n = 8$)	Normal A+Mean $\pm$ SD ($n = 10$)	Cohen's d	p-value	BH-adjusted p
Fornix (column and body of fornix)	FA	0.2635 $\pm$ 0.0825	0.2950 $\pm$ 0.0508	0.47	0.364	0.534
	MD	0.00242 $\pm$ 0.00052	0.00218 $\pm$ 0.00047	–0.48	0.335	0.534
	RD	0.00214 $\pm$ 0.00055	0.00189 $\pm$ 0.00045	–0.49	0.329	0.534
	AD	0.00299 $\pm$ 0.00047	0.00277 $\pm$ 0.00051	–0.44	0.361	0.534
Cingulum (hippocampus) L	FA	0.3434 $\pm$ 0.0568	0.3143 $\pm$ 0.0604	–0.49	0.309	0.534
	MD	0.00103 $\pm$ 0.00022	0.00100 $\pm$ 0.00017	–0.19	0.710	0.747
	RD	0.00085 $\pm$ 0.00023	0.00084 $\pm$ 0.00017	–0.07	0.889	0.889
	AD	0.00139 $\pm$ 0.00020	0.00131 $\pm$ 0.00019	–0.41	0.401	0.534
Cingulum (hippocampus) R	FA	0.3509 $\pm$ 0.0584	0.3342 $\pm$ 0.0345	–0.36	0.491	0.585
	MD	0.00097 $\pm$ 0.00013	0.00093 $\pm$ 0.00012	–0.34	0.497	0.585
	RD	0.00080 $\pm$ 0.00015	0.00077 $\pm$ 0.00012	–0.22	0.661	0.735
	AD	0.00132 $\pm$ 0.00011	0.00125 $\pm$ 0.00014	–0.55	0.253	0.534
Cingulum (cingulate gyrus) L	FA	0.4313 $\pm$ 0.1054	0.4799 $\pm$ 0.1112	0.45	0.357	0.534
	MD	0.00099 $\pm$ 0.00021	0.00083 $\pm$ 0.00010	–1.01	0.079	0.534
	RD	0.00075 $\pm$ 0.00018	0.00058 $\pm$ 0.00012	–1.13	0.043	0.534
	AD	0.00146 $\pm$ 0.00034	0.00131 $\pm$ 0.00018	–0.56	0.292	0.534
Cingulum (cingulate gyrus) R	FA	0.4135 $\pm$ 0.0769	0.4639 $\pm$ 0.0868	0.61	0.211	0.534
	MD	0.00099 $\pm$ 0.00032	0.00082 $\pm$ 0.00010	–0.78	0.176	0.534
	RD	0.00077 $\pm$ 0.00027	0.00059 $\pm$ 0.00010	–0.94	0.107	0.534
	AD	0.00144 $\pm$ 0.00043	0.00128 $\pm$ 0.00017	–0.48	0.375	0.534

within the hippocampal memory system rather than uniform hippocampal atrophy (Seeley et al., 2009; Crossley et al., 2014). By integrating high-resolution hippocampal subfield morphometry and localized within-subfield spatial analyses, with exploratory hippocampal-associated diffusion MRI as complementary context, we identified a reproducible anatomical pattern across two independent cohorts. The results characterize cross-sectional organization and should not be interpreted as establishing a temporal sequence of degeneration. Thus, this framework combines structural MRI findings with exploratory diffusion MRI observations to examine the anatomical organization of hippocampal vulnerability (Braak and Braak, 1991; Ranganath and Ritchey, 2012; de Flores et al., 2015; Wisse et al., 2021).

Across the ADRC and ADNI cohorts, CA1 and the dentate gyrus (DG) had the two highest amyloid-associated point rankings after adjustment for demographic factors and clinical stage.

Structural MRI analyses provided complementary evidence of selective hippocampal vulnerability. Cross-sectional comparisons across clinical stages described group volume differences in CA1 and DG in both cohorts, while localized occupancy analyses showed that structural loss within these subfields was spatially heterogeneous rather than homogeneous. Exploratory diffusion MRI identified effect-size differences in hippocampal-associated white matter pathways, particularly the cingulum and fornix, but none survived BH-FDR correction; these observations therefore provide anatomical context rather than confirmatory evidence of network-level structural loss.

4.1. Amyloid-associated vulnerability as a multiscale hippocampal memory-system pattern

The principal contribution of this study is evidence that amyloid-associated structural vulnerability can be characterized across complementary anatomical scales and is not fully captured by a single imaging measure. Whole-hippocampal volumetry, hippocampal subfield analysis, exploratory diffusion MRI, and within-subfield occupancy mapping provide complementary measurements spanning global structural loss, selective regional vulnerability, pathway-level differences, and localized structural change.

Although whole-hippocampal volume remains one of the most widely used structural MRI biomarkers of AD (Frisoni et al., 2010; Jack et al., 2024), reducing the hippocampal formation to a single volumetric measure can obscure the distinct anatomical and functional roles of its constituent regions. The present findings show that structural change is concentrated within selectively vulnerable subfields, particularly CA1 and DG, and not uniformly distributed throughout the hippocampal

formation (Braak and Braak, 1991; Small et al., 2011). This selective pattern is consistent with an organized pattern of hippocampal structural vulnerability rather than diffuse tissue loss.

The multiscale framework extends this interpretation beyond gray-matter volumetry while preserving the distinction between confirmatory and exploratory evidence. At the network level, diffusion MRI provides exploratory characterization of hippocampal-associated pathways, particularly the cingulum and fornix, which support communication between medial temporal, limbic, and cortical memory regions (Acosta-Cabronero et al., 2012; Mito et al., 2018; Bubb et al., 2018; Christiansen et al., 2016). At the regional level, amyloid-informed structural MRI identifies hippocampal subfields with the largest amyloid-associated volume differences. At the within-subfield level, occupancy mapping shows that structural loss is spatially localized rather than uniformly distributed, thereby preserving anatomical information that conventional ROI volumetry cannot capture. These analyses are complementary and do not, in this cross-sectional design, establish a temporal hierarchy.

This interpretation is consistent with evidence that neurodegenerative disorders affect distributed functional and structural networks rather than isolated regions independently (Seeley et al., 2009; Crossley et al., 2014). In the present study, however, the cingulum and fornix findings are exploratory and should not be interpreted as demonstrating that pathway alterations precede or cause CA1/DG structural changes. The perforant pathway is mechanistically relevant because it provides a principal entorhinal input to DG and CA circuitry; recent high-field MRI and histopathological work demonstrated perforant-path fiber loss in preclinical and early AD (Uchida et al., 2025b). Direct perforant-path analysis was not available in the present dataset and should be evaluated in future studies using dedicated acquisitions and tractography methods.

Recent advances in atlas-based segmentation (Pipitone et al., 2014), reliability-focused validation (Quattrini et al., 2020), longitudinal subfield measurement (Shaw et al., 2020), and deep learning-based segmentation (Sackl et al., 2024) have substantially improved the precision of hippocampal morphometry. The present study complements these methodological developments by focusing not on segmentation performance itself, but on the biological organization revealed when anatomically precise measurements are integrated across spatial scales. This multiscale perspective therefore extends conventional hippocampal volumetry toward a more biologically interpretable representation of structural change across the hippocampal memory system.

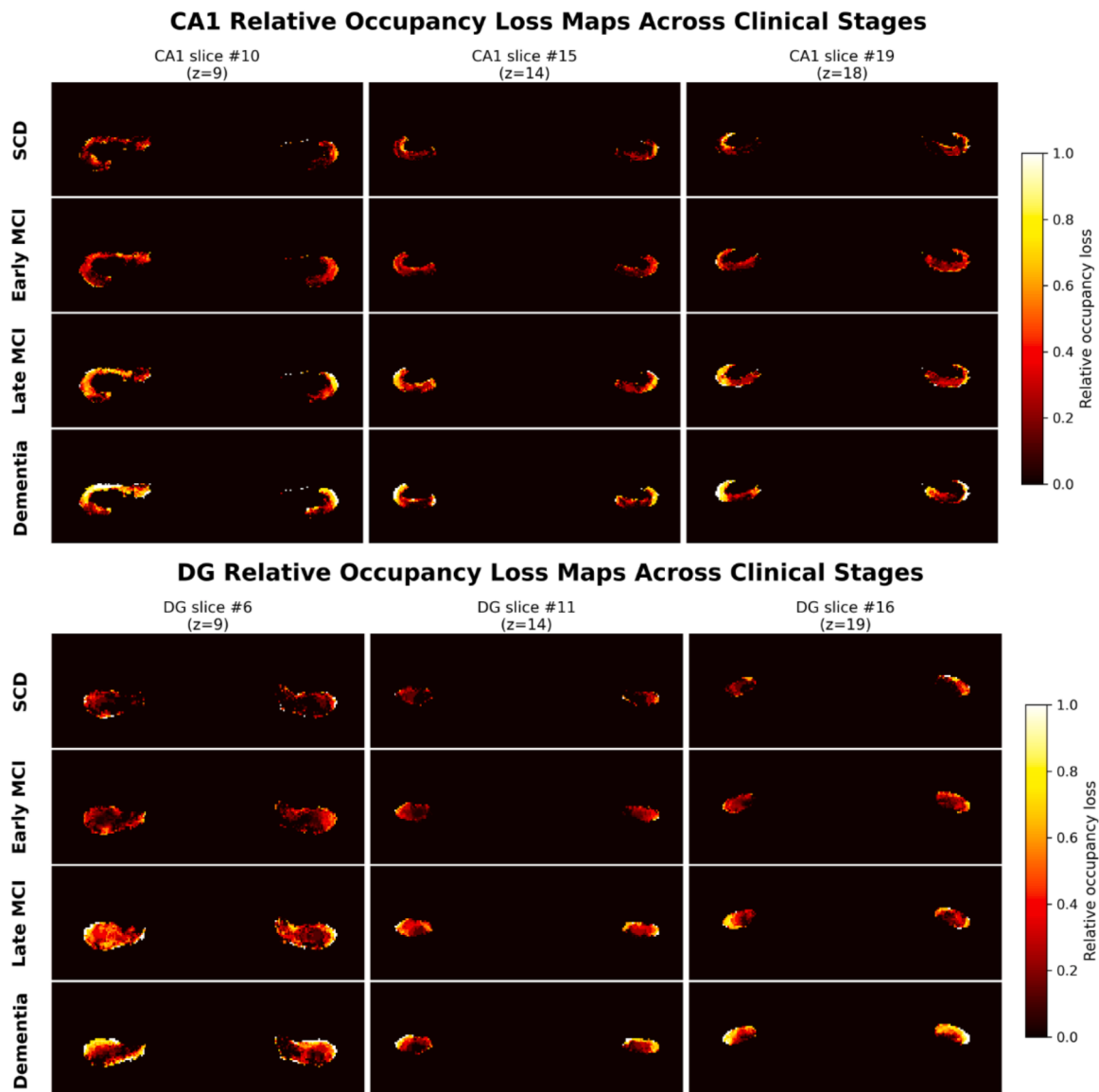


Fig. 7. CA1 and DG relative occupancy loss maps across clinical stages. Representative slices are shown for each subfield. Relative occupancy loss was calculated with respect to the normal reference group. Warmer colors indicate greater occupancy loss. Both CA1 and DG demonstrate spatially localized patterns of occupancy reduction rather than uniform loss across the entire subfield.

4.2. Reproducible CA1 and DG vulnerability across independent cohorts

A principal finding is that CA1 and DG retained the two highest covariate-adjusted amyloid-associated point rankings across independent cohorts. Despite differences between ADRC and ADNI in recruitment strategy, participant demographics, biomarker availability, disease-stage composition, and imaging characteristics, both cohorts independently converged on the same dominant anatomical signature. This level of reproducibility is particularly important for MRI biomarker development, where many imaging findings fail to generalize across independent populations (Marek et al., 2022).

Bootstrap rank frequencies and score confidence intervals quantified sampling uncertainty around the point rankings, with variation in exact rank positions and overlapping intervals among several ROIs (Fig. 2b,c). The results support recurrent top-two placement of CA1 and DG across cohorts, while variation in exact rank positions and overlapping confidence intervals among several ROIs caution against interpreting the point rankings as a rigid or fully separable hierarchy. Recent longitudinal segmentation frameworks such as LASHIS have further improved

the consistency of hippocampal subfield measurements over time (Shaw et al., 2020), underscoring the importance of robust segmentation strategies for identifying reproducible anatomical biomarkers across independent cohorts.

The joint emergence of CA1 and DG is biologically compelling because these structures occupy complementary positions within the hippocampal circuit (Eichenbaum, 2017; Small et al., 2011). DG performs sparse encoding and pattern separation of incoming cortical information, whereas CA1 integrates processed hippocampal output before transmitting information to widespread neocortical regions (Yassa and Stark, 2011; Eichenbaum, 2017; Small et al., 2011). Their joint identification as highly ranked vulnerable subfields therefore suggests disruption of both memory encoding and memory integration, extending conventional descriptions of hippocampal atrophy toward a systems-level interpretation of hippocampal dysfunction. This interpretation is consistent with neuropathological observations demonstrating selective hippocampal vulnerability during the earliest stages of AD (Braak and Braak, 1991; de Flores et al., 2015; Wisse et al., 2021).

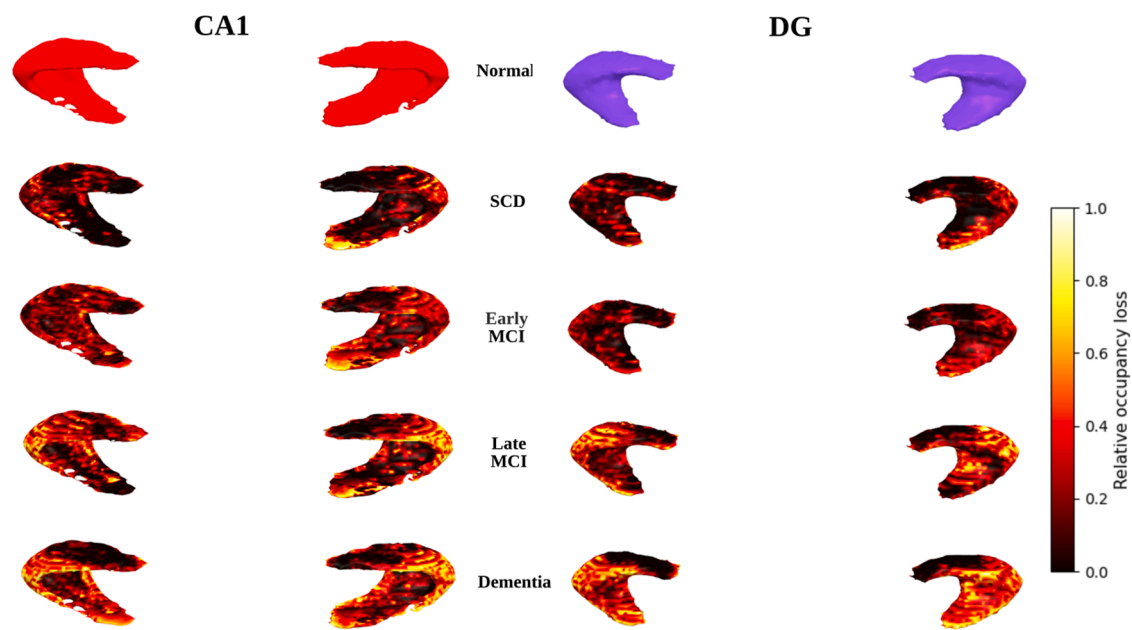


Fig. 8. Three-dimensional visualization of the relative occupancy-loss maps shown in Fig. 7. Relative occupancy-loss values were projected onto three-dimensional surfaces of the CA1 and DG subfields to provide an anatomically intuitive visualization of the spatial distribution of localized occupancy loss. Both CA1 and DG demonstrate spatially localized patterns of occupancy reduction rather than uniform loss across the entire subfield.

Table 5
Summary of multiscale imaging findings.

Analysis	Modality	Contrast	Measure	Main finding	Interpretation
Network-level pathways	DTI	Cognitively normal A+ vs A–	FA, MD, RD, AD; Cohen’s d	Effect-size differences in cingulum and fornix	Exploratory white matter findings in cognitively normal participants
Subfield-level regions	ASHS volume	A+ vs A– within ADRC and ADNI	Unadjusted and covariate-adjusted amyloid-associated scores	CA1 and DG had the two highest adjusted point ranks in both cohorts	Agreement in leading point ranks, with bootstrap uncertainty
Clinical-stage volume patterns	ASHS volume	AD-related vs non-AD and A+ vs A– across clinical stages	ICV-normalized volume	CA1 and DG showed group volume differences across clinical stages	Descriptive cross-sectional clinical-stage patterns
Within-subfield spatial patterns	Occupancy analysis	Clinical-stage groups relative to shared Normal	Relative occupancy loss maps and 3D surfaces	Spatially localized occupancy reduction in CA1 and DG	Descriptive within-subfield spatial heterogeneity

4.3. Biological specificity and network-level organization

A major methodological contribution of this study is an amyloid-informed framework that emphasizes structural differences associated with amyloid positivity while avoiding the stronger claim of AD specificity. Clinical diagnostic groups frequently encompass substantial biological heterogeneity, particularly during MCI, where amyloid, tau, vascular pathology, and mixed neurodegenerative processes often coexist (Jack et al., 2018; Hansson, 2021; Scheltens et al., 2021; Vogel et al., 2021). Amyloid stratification therefore provides biological enrichment, but amyloid-negative participants should not be regarded as a disease-free reference population.

The proposed amyloid-associated vulnerability score quantifies regional volume differences associated with amyloid status and is complemented by regression adjustment for age, sex, education, intracranial volume normalization, and clinical stage. This approach is consistent with the broader transition toward biologically informed disease models (Jack et al., 2018, 2024), while recognizing that amyloid status alone does not capture tau burden, vascular injury, or other co-pathologies. Cross-sectional clinical-stage comparisons provide complementary descriptive evidence rather than independent validation of the ranking analysis.

Exploratory diffusion MRI described group effect sizes within the cingulum and fornix, key pathways supporting the hippocampal memory system (Acosta-Cabronero et al., 2012; Mito et al., 2018; Bubb et al.,

2018). Because none of the 20 DTI comparisons survived BH-FDR correction, these observations should not be interpreted as evidence that AD disrupts these pathways or as confirmation of a network-level disease model. Rather, they identify anatomically relevant candidate pathways for future adequately powered longitudinal and multimodal studies designed to test whether white-matter abnormalities covary with CA1/DG vulnerability.

4.4. Spatial organization and implications for MRI biomarkers

Perhaps the most novel observation of this work is that structural loss within the most vulnerable hippocampal subfields is spatially heterogeneous rather than uniformly distributed. Conventional ROI volumetry cannot distinguish diffuse from localized structural loss.

Occupancy analysis shows that structural loss within CA1 and DG is concentrated within localized anatomical regions, with differences in spatial extent across clinical-stage groups. Consequently, identical regional volumes may conceal fundamentally different spatial patterns of tissue loss, revealing an additional anatomical dimension beyond conventional volumetric biomarkers. For example, two participants with comparable CA1 volume reduction may exhibit markedly different spatial distributions of structural loss, with tissue loss concentrated in different portions of the subfield. Conventional ROI volumetry treats these individuals as anatomically equivalent because both produce similar total volume estimates. In contrast, occupancy analysis preserves

the spatial organization of tissue loss, thereby distinguishing localized patterns of structural change that are unseen to global volumetric measurements. This localized organization is consistent with neuropathological observations that AD affects anatomically selective neuronal populations (Braak and Braak, 1991; de Flores et al., 2015; Wisse et al., 2021).

Methodologically, occupancy analysis complements conventional ROI volumetry by preserving anatomical localization while avoiding voxel-wise statistical inference (Iglesias et al., 2015). It does not, however, directly quantify tissue-intensity heterogeneity within preserved anatomy. Radiomic and texture-based approaches may provide complementary information beyond volume and occupancy by characterizing subregional signal heterogeneity; recent hippocampal-substructure work supports this direction (Uchida et al., 2026). Future studies should determine whether combining occupancy with radiomic features improves biological characterization or prediction. Rather than replacing whole-hippocampal volume, the proposed multiscale framework complements existing biomarkers by integrating global volumetry, selectively vulnerable hippocampal subfields, localized occupancy patterns, and exploratory hippocampal-associated white-matter measures.

4.5. Limitations and future directions

Several limitations should be considered when interpreting these findings. First, the cross-sectional design precludes determination of temporal relationships among hippocampal-associated white-matter differences, selective subfield structural loss, and localized occupancy loss. Longitudinal multimodal studies are needed to establish within-individual change and temporal ordering. A 30-year longitudinal cohort demonstrated regionally heterogeneous biomarker and MRI change points, underscoring the need to distinguish cross-sectional stage differences from within-individual temporal progression (Uchida et al., 2025a).

Second, several biomarker-defined subgroups, particularly those included in the diffusion MRI analyses, were modest in size. The diffusion MRI findings should be regarded as exploratory and require validation in larger cohorts with harmonized imaging protocols. No DTI comparison survived BH-FDR correction, limiting the strength of network-level inferences.

Third, complete biomarker characterization was not available for every participant. In particular, sufficiently complete and harmonized tau data were not available for a tau-adjusted sensitivity analysis. Future studies incorporating amyloid, tau, vascular measures, plasma biomarkers, and longitudinal cognitive assessments will be important for determining the extent to which the observed structural pattern is specific to AD biology versus mixed or co-occurring pathology.

Fourth, although ADRC and ADNI differed in participant characteristics, recruitment strategies, and disease-stage composition, CA1 and DG retained the top two covariate-adjusted point rankings in both cohorts, although their bootstrap top-two frequencies differed between cohorts. Validation in larger international cohorts will further establish the generalizability of this cross-cohort pattern.

Finally, the present analyses combined bilateral hippocampal measurements to maximize robustness. Future investigations should examine hemispheric asymmetry, longitudinal occupancy dynamics, regional connectivity, and multimodal integration to determine whether additional biologically meaningful imaging signatures can be identified.

Despite these limitations, the proposed framework provides a biologically interpretable foundation for future neuroimaging studies integrating structural MRI, diffusion MRI, molecular biomarkers, functional connectivity, and artificial intelligence-based analyses. Such multimodal approaches may improve early disease detection, longitudinal monitoring, and therapeutic evaluation while providing a more comprehensive understanding of selective hippocampal vulnerability in AD.

5. Conclusion

This study supports a reproducible cross-sectional pattern of amyloid-associated structural vulnerability across complementary components of the hippocampal memory system. Covariate-adjusted analyses in independent ADRC and ADNI cohorts identified the cornu ammonis 1 (CA1) and the dentate gyrus (DG) as the two highest amyloid-associated point-ranked subfields, with bootstrap analyses quantifying the uncertainty and stability of these rankings.

Beyond identifying selectively vulnerable regions, occupancy mapping showed spatially heterogeneous structural loss within CA1 and DG. Complementary clinical-stage analyses described cross-sectional volume differences, whereas the DTI findings remain exploratory and did not survive correction for multiple comparisons. These analyses therefore support anatomical organization but do not establish temporal progression.

Rather than competing with existing MRI biomarkers, the proposed framework integrates conventional volumetry, amyloid-associated subfield vulnerability, localized occupancy mapping, and exploratory hippocampal-associated diffusion measures into a biologically interpretable framework. Longitudinal and multimodal validation, including tau, perforant-path, and radiomic/texture analyses, will be required to determine temporal sequence, disease specificity, and incremental predictive value.

Ethics statement

The studies involving human subjects were approved by the 1Florida Alzheimer's Disease Research Center under IRB-202000316-IAA (approval date: March 12, 2026; renewal date: February 19, 2027). The studies were conducted in accordance with applicable local legislation and institutional requirements, and participants provided written informed consent. ADNI data were obtained and used in accordance with ADNI's institutional ethics, informed-consent, and data-use requirements.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the authors used ChatGPT to assist with language refinement. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

CRediT authorship contribution statement

Xueting Cui: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Thony Yan Liang:** Data curation, Conceptualization. **Micheal Adeyosoye:** Data curation, Conceptualization. **Mina Ezzati:** Writing – review & editing. **Bipul Simkhada:** Writing – review & editing. **Mercedes Cabrerizo:** Writing – review & editing. **Rosie Curiel Cid:** Writing – review & editing, Resources. **Monica Rosselli:** Writing – review & editing. **Armando Barreto:** Writing – review & editing. **Naphtali D. Rishe:** Writing – review & editing. **David A. Loewenstein:** Writing – review & editing, Resources. **Malek Adjouadi:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data and code availability statement

The data used in this study were obtained from the 1Florida Alzheimer's Disease Research Center (1Florida ADRC) and the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. The 1Florida ADRC data analyzed in this study are not publicly available due to participant privacy and data governance requirements. Access requires completion of human-subjects research training (CITI certification) and an approved data use agreement, and the data are available from the 1Florida ADRC on reasonable request, subject to those conditions. ADNI data are available through the ADNI database (<https://adni.loni.usc.edu>) upon registration and approval. The analysis code used in this study is available from the corresponding author upon reasonable request.

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