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RESEARCH ARTICLE

Global brain activity and its coupling with cerebrospinal fluid flow is related to tau pathology

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Abstract

INTRODUCTION: Factors responsible for the deposition of pathological tau in the brain are incompletely understood. This study links macroscale tau deposition in the human brain to cerebrospinal fluid (CSF) flow dynamics using resting-state functional magnetic resonance imaging (rsfMRI).

METHODS: Low-frequency (< 0.1 Hz) resting-state global brain activity is coupled with CSF flow and potentially reflects CSF dynamics-related clearance. We examined the correlation between rsfMRI measures of CSF inflow and global activity (gBOLD–CSF coupling) as a predictor, interacting with amyloid beta (Aβ), of tau and cortical thickness (dependent variables) across Alzheimer's Disease Neuroimaging Initiative (ADNI) participants from cognitively unimpaired through mild cognitive impairment (MCI) and Alzheimer's disease (AD).

RESULTS: Tau deposition in Aβ+ participants, accompanied by cortical thinning and cognitive decline, is associated with decreased gBOLD–CSF coupling. Tau mediates the relationship between coupling and thickness.

DISCUSSION: Findings suggest that resting-state global brain activity and CSF movements comodulate Alzheimer's tau deposition, presumably related to CSF clearance.

KEYWORDS
Alzheimer's disease pathology, brain atrophy, cerebrospinal fluid (CSF) flow, CSF dynamics-related clearance, global resting-state fMRI signal, tau deposition

Highlights

- A non-invasive functional magnetic resonance imaging (fMRI) assessment of a CSF clearance-related process is carried out.
- Global brain activity is coupled with CSF inflow in human fMRI during resting state.

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- Global fMRI–CSF coupling is correlated with tau in Alzheimer's disease (AD).
- This coupling measure is also associated with cortical thickness, mediated by tau.

1 | BACKGROUND

Alzheimer's disease (AD) is pathologically characterized by the extracellular accumulation of amyloid beta (Aβ) plaques and the intracellular accumulation of hyperphosphorylated tau in the form of neurofibrillary tangles.[1] Converging evidence has shown that Aβ accelerates tau phosphorylation and promotes tau aggregation and oligomerization.[2] Tau plays an especially critical role in cognitive decline,[3,4] brain atrophy, particularly cortical thinning,[5,6] and neuronal and synaptic loss.[3,7] The deposition of tau aggregates in AD follows a stereotypical pattern, beginning in the entorhinal cortex and hippocampus and then propagating to areas that have been characterized in *post mortem* and imaging studies as Braak stages.[8,9] The neural mechanism underlying such a stereotyped pattern of tau accumulation remains elusive. Current hypotheses have attributed tau spreading to altered neural activity[10,11] and a "prion-like" mechanism manifested as abnormal tau seeds transferring through anatomically connected brain regions demonstrated in both cell and animal models[12] and via functionally connected cortical regions in humans.[13–15]

Beyond its aggregation patterns, tau clearance has received increasing attention.[16] For example, recent animal studies have identified the critical role of glymphatic function in clearing brain wastes, including Aβ and tau, via a pathway involving cerebrospinal fluid (CSF) flow and the exchange between CSF and interstitial fluid (ISF).[16–18] In mice, the sleep–wake cycle regulates ISF tau, and sleep deprivation can significantly increase ISF and CSF tau as well as tau spreading,[19] presumably due to inadequate sleep-dependent CSF dynamics-related clearance.[17] While progress has been made in assessing CSF movement-related clearance,[18,20–24] a real-time non-invasive imaging method is still needed to evaluate relationships between CSF dynamics and clearance in humans. However, CSF clearance is linked to spontaneous low-frequency (<0.1 Hz) resting-state global brain activity assessed with the global blood-oxygen-level-dependent (gBOLD) signal in functional magnetic resonance imaging (fMRI)[25–27]; observation of this phenomenon during light sleep or low arousal states supports the importance of this process in clearing brain waste[28–30] due to the strong sleep-dependent effect of CSF clearance.[17] CSF movement, a key determinant of CSF clearance,[16–18] is coupled with gBOLD during both sleep[31] and wakefulness.[25] This global brain activity and CSF movement (gBOLD–CSF) coupling has recently been proposed to reflect CSF dynamics potentially related to clearance and is also correlated with cortical Aβ in AD,[25,27] cognitive decline in AD and Parkinson's disease,[25,26] and age.[32]

Although early resting-state fMRI (rsfMRI) studies assumed the gBOLD signal was noise,[30] an increasing number of studies have suggested that gBOLD reflects slow global neural activity.[28,33–35] Specifically, concurrent fMRI-electrophysiology studies in primates have shown correlations between the gamma-band power of local field potentials in the visual cortex and rsfMRI across widespread brain regions, suggesting a significant portion of gBOLD is directly linked to neural activity.[28] Moreover, converging evidence also has demonstrated that gBOLD fluctuation indicates a brain state related to vigilance, and its amplitude increase during light sleep or low arousal states[28–30,34] implies a potential link with sleep-dependent CSF clearance.[17,19] In addition, cortical co-activations at prominent gBOLD peaks display larger signal increases in the sensory-motor network, accompanied by deactivations in the nucleus basalis, a critical component of the cholinergic system.[34] Furthermore, gBOLD correlates with strong sympathetic changes, including pupil size,[33,36] respiratory and cardiac pulsation,[37–41] and heart rate variability.[42] These sympathetic activities may constrict pial arteries and facilitate CSF movements or indirectly affect the slow (<0.1 Hz) modulation of cardiac and respiratory pulsations, accepted as the driving forces of CSF flow.[43,44] Thus, despite the lack of direct evidence, gBOLD–CSF coupling is a plausible surrogate measure of the global brain and CSF dynamics related to clearance.

Therefore, a key question arises: Does coupling between global brain activity and CSF movement (gBOLD–CSF coupling) as a measure of CSF clearance explain the amount of cortical tau deposition across participants? To address the hypothetical question, we examined multimodal data from the Alzheimer's Disease Neuroimaging Initiative-3 (ADNI3; see the full ADNI investigators list at the Appendix 1) to investigate the relationship between gBOLD–CSF coupling, tau deposition measured with PET, cortical thickness, and cognitive function.

2 | METHODS

2.1 | Participants and data

We included 95 participants from ADNI3 who had available tau positron emission tomography (tau-PET) (^{18}F-Flortaucipir [FTP]), Aβ-PET (either [^{18}F]florbetaben [FBB] or [^{18}F]florbetapir [FBP]), rsfMRI (TR = 0.607 s only), and structural MRI (cortical thickness) data. Participants included four different clinical diagnosis (http://adni.loni.usc.edu/study-design/): six AD patients, 22 with mild cognitive impairment (MCI), five participants with subjective memory concern (SMC), and 62 healthy controls. We further categorized the participants into cognitively impaired (AD and MCI) and unimpaired (SMC and control) groups. Cognitive performance was measured with the Montreal Cognitive Assessment (MoCA). Our cohort thus includes 46 Aβ− and 49 Aβ+ participants, including 21 unimpaired Aβ+ and 28 impaired Aβ+ individuals. All participants provided written informed consent.

Ethical approval from the individual Institutional Review Board (IRB; http://adni.loni.usc.edu/wp-content/uploads/2013/09/DOD-ADNI-IRB-Approved-Final-protocol-08072012.pdf) was granted to the investigators at each ADNI participating site. All the ADNI data were collected per the principles of the Declaration of Helsinki.

Aβ-PET status, tau-PET regional standardized uptake value ratios (SUVRs), rsfMRI scans, cortical thickness, and MoCA were obtained from the same study visit (the time interval between pairwise modalities was no more than 183 days[45]). The file "UC Berkeley—AV1451 PVC 8 mm Res Analysis [ADNI2,3] (version: 2023-02-17)" was used to provide the tau-PET SUVR.[46,47] Both "UC Berkeley—AV45 8 mm Res Analysis [ADNIGO,2,3] (version: 2023-02-17)" and "UC Berkeley—FBB 8 mm Res Analysis [ADNI3] (version: 2023-02-17)" were used to provide the Aβ-PET status (thresholds for Aβ+ were AV45–Aβ > 1.11 SUVR or FBB–Aβ > 1.08 SUVR using the whole cerebellum as reference region).[48] Cortical thickness was downloaded from ADNI as "UCSF—Cross-Sectional FreeSurfer (6.0) [ADNI3] (Version: 2022-08-17)." MoCA score was also directly acquired from ADNI as "Montreal Cognitive Assessment (MoCA) [ADNIGO,2,3]." All these data, as well as the rsfMRI and cortical thickness, are publicly accessible on the ADNI website (http://adni.loni.usc.edu/). It is worth noting that the cognitively impaired group included only individuals who were Aβ+, while the cognitively unimpaired group included Aβ+ and Aβ− individuals.

RESEARCH IN CONTEXT

1. **Systematic review**: A systematic literature search was carried out using traditional (eg, PubMed) sources to identify articles studying tau deposition and clearance in Alzheimer's disease (AD). Despite the different approaches that have been used to investigate cerebrospinal fluid (CSF) flow clearance of tau, human studies on tau clearance with non-invasive fMRI have never been formally conducted.
2. **Interpretation**: Our findings suggest the decreased coupling between CSF flow and global brain activity could play a critical role in promoting tau pathology, presumably through reduced CSF clearance. Tau mediates the link between CSF clearance and brain atrophy.
3. **Future directions**: Future studies may investigate a causal association between impaired CSF flow and tau accumulation through a longitudinal study. Moreover, direct evidence is needed to link CSF inflow fMRI signal and CSF dynamics-related clearance. Prospective studies should also examine whether global brain activity and associated physiological processes, including cardiac and respiratory functions, co-modulate CSF dynamics-related clearance.

2.2 | Image acquisition and preprocessing

All rsfMRI scans were acquired using 3 Tesla MR scanners from multiple ADNI participating sites following a unified protocol (http://adni.loni.usc.edu/methods/documents/mri-protocols/). The MRI data used in the current study were collected on Siemens MRI scanners (Siemens Medical Solutions, Siemens, Erlangen, Germany). Each MRI session began with a T1-weighted (T1w) MPRAGE sequence (flip angle = 9°, spatial resolution = 1 × 1 × 1 mm^3, echo time [TE] = 3.0 ms, repetition time [TR] = 2300 ms), which was used for cortical thickness, anatomical segmentation, and registration.[49] During rsfMRI acquisition, 976 fMRI volumes were collected with an echo-planar image (EPI) sequence with TR/TE = 607/32 ms (flip angle = 50°, spatial resolution = 2.5 × 2.5 × 2.5 mm^3, slice thickness = 2.5 mm; see details at: http://adni.loni.usc.edu/methods/documents/).

PET imaging was acquired according to standardized protocols at each ADNI site. FTP-PET data were acquired from 75 to 105 min after injection of 10 mCi tracer. FBP-PET and FBB-PET data were acquired from the 50 to 70 min after injection of 10 mCi tracer and the 90 to 110 min after injection of 8.1 mCi tracer,[48,50] respectively (https://adni.loni.usc.edu/wp-content/uploads/2012/10/ADNI3-Procedures-Manual_v3.0_20170627.pdf).

We preprocessed structural MRI using FreeSurfer version 7.1 (https://surfer.nmr.mgh.harvard.edu/fswiki/DownloadAndInstall5.3)[51] to derive FreeSurfer regions of interest (ROIs), that is, DKT-68 parcel,[52] in participants' native space and extract the parcel-based cortical thickness. Following a previous study,[25] we preprocessed the rsfMRI data using FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki)[53] and AFNI (https://afni.nimh.nih.gov/)[54] with a modification of excluding rsfMRI sessions with excessive head motion (session-mean frame-wise displacement [FD] larger than 0.6 mm or the maximal FD larger than 3 mm).[55] The general procedures for rsfMRI preprocessing include motion correction, skull stripping, spatial smoothing (full width at half maximum [FWHM] = 4 mm), and temporal filtering (bandpass filter, 0.01 to 0.1 Hz). As in previous studies,[25,40] we also removed the first 20 and last 20 volumes for each rsfMRI session to reduce the edge effect from the temporal filtering and to ensure a steady magnetization.

All participants (N = 95) had Aβ-PET (N = 32 FBP; N = 63 FBB) and tau-PET data. To generate the PET data in DKT-68 parcels, several preprocessing steps were performed, including image averaging, spatial smoothing, and registration to the (structural) MRI space to extract the tau or Aβ intensity in gray matter and each DKT-68 parcel.[52] We then normalized parcel-wise tau with the inferior cerebellar reference region to derive the tau SUVR and further applied partial volume correction (PVC) to reduce the influence of low image resolution and limited tissue sampling.[47] Regarding the Aβ SUVR, we normalized the FBP or FBB intensity in target gray matter using the whole cerebellum reference region.

2.3 | Extraction of gBOLD and CSF inflow signals

We derived the gBOLD signal by averaging the rsfMRI (Z-normalized) time series across all voxels in the gray matter region (see a

representative example in Figure S1B, upper, green, corresponding to the signal in Figure S1A, green).[25] We used the Harvard-Oxford cortical and subcortical structural atlases (https://neurovault.org/collections/262/) to define the gray matter mask, which was then transformed into the native fMRI space of each participant referring to previous studies.[25,27] Thus, the subject-specific gray matter mask was generated for each subject. The rsfMRI in individual original space went through the above preprocessing procedures (not including nuisance regression; to avoid the CSF signal regression attenuating the CSF inflow signal and to avoid the motion parameter regression weakening the gBOLD signal; refer to the detailed explanation and preprocessing steps in previous studies[25,26,40]). The preprocessed rsfMRI signal was averaged across each individual's gray matter mask to derive the gBOLD signal for each participant.

To derive the CSF inflow signal, the preprocessed fMRI in the original individual space was averaged across the CSF voxels at the bottom slice of fMRI acquisition to maximize sensitivity to the CSF inflow effect following previous studies.[25,27] Because fresh spins in the bottom slice that did not experience any radiofrequency pulse flow into the imaging volume, their signals are higher than those of local spins that have reached the steady state. All participants have individual CSF masks (Figure S1B, lower, corresponding to the signal in Figure S1A, purple) with similar voxel numbers (~14).

2.4 | Coupling between gBOLD and CSF inflow signals

We also calculated the cross-correlation functions between the gBOLD signal and the CSF inflow signal (by assessing Pearson's correlation) at the negative peak of the mean cross-correlation, a lag of +4.856 s (arrow in Figure S1C), to evaluate the gBOLD–CSF coupling for each participant, as was done previously.[25]

2.5 | Correlating gBOLD–CSF coupling with cortical Aβ, tau, thickness, and MoCA

We first compared gBOLD–CSF coupling (adjusted for age and sex) between Aβ– and Aβ+ groups (two-sample *t* test). For each of these subgroups (ie, the Aβ–, Aβ+, unimpaired Aβ+, and impaired Aβ+) and the entire cohort, we correlated the gBOLD–CSF coupling (age- and sex-adjusted) with cortical tau SUVR in each DKT-68 parcel and then mapped this to the brain surface (using WorkBench software [version 1.5.0; https://www.humanconnectome.org/software/workbench-command]) to see the spatial distribution of correlation coefficients. We further tested the coupling-tau correlation in four ROIs, including Braak V–VI ROI, Braak III–IV ROI,[8,9] temporal meta-ROI,[56] and entorhinal cortex across participants within each subgroup. We quantified the regional tau burden by (volume-weighted) averaging FTP SUVR (PVC-ed; normalized to the inferior cerebellar gray matter region) in these DKT-68 parcels belonging to Braak V–VI and III–IV ROIs, as well as the temporal meta-ROI (referring to: https://adni.bitbucket.io/reference/docs/UCBERKELEYAV1451/UCBERKELEY_AV1451_Methods_2021-01-14.pdf).

Similarly, we calculated the regional thickness by averaging the thickness in these DKT-68 parcels belonging to Braak V–VI and III–IV ROIs, as well as the temporal meta-ROI.

2.6 | Determining the mediating role of tau in the coupling–thickness association

After examining the aforementioned relationships, we investigated whether tau mediated the effect of gBOLD–CSF coupling on cortical thickness. We first averaged tau SUVR and cortical thickness across all participants and compared their distribution patterns by correlating them across DKT-68 parcels. Similarly, the tau difference between Aβ+ and Aβ– groups (reflecting the tau spreading with AD progression) was spatially compared with that difference in thickness. We further evaluated the inter-participant similarity between tau and thickness in each of the above four ROIs across participants within each of these different subgroups, including the Aβ–, Aβ+, unimpaired Aβ+, and impaired Aβ+ ones. We then examined the hypothesis that tau mediated the association between gBOLD–CSF coupling and cortical thickness using a mediation analysis[57] in the Braak V–VI ROI, Braak III–IV ROI, or temporal meta-ROI among the groups of the whole cohort, Aβ+, and impaired Aβ+, among which the coupling–tau and coupling–thickness associations were significant in Figures 1 and 2. The possibility that coupling mediated the relationship between tau and thickness was also tested in these ROIs.

2.7 | Statistical analysis

A two-sample *t* test was performed for group comparisons on continuous measures. We used Fisher's exact test[58] to compare categorical measures (ie, sex) between subgroups characterized for Aβ pathology progression. Pearson's correlation was used to quantify the linear correlation between different variables. Single-level mediation analysis[57] was performed to test the hypothesis of tau mediating the coupling–thickness link. We also applied this mediation analysis to test the other possibility that coupling could mediate the tau–thickness relationship. An interaction effect test was also applied for the Aβ (or the diagnostic information) and coupling measure on the tau deposition. A *p*-value of no more than 0.05 was considered statistically significant. We applied a multiple comparison correction with the false discovery rate (FDR) method for our major results.

To test the effect of head motion on our coupling metrics and tau, we evaluated the participant-wise head motion with mean FD[59] and correlated this with tau in the four aforementioned ROIs and gBOLD–CSF coupling across participants from both the entire cohort and each subgroup. The coupling–tau association was retested after regressing out the participant-wise head motion measure, the mean FD, from gBOLD–CSF coupling, and then correlating the coupling with tau in the Braak

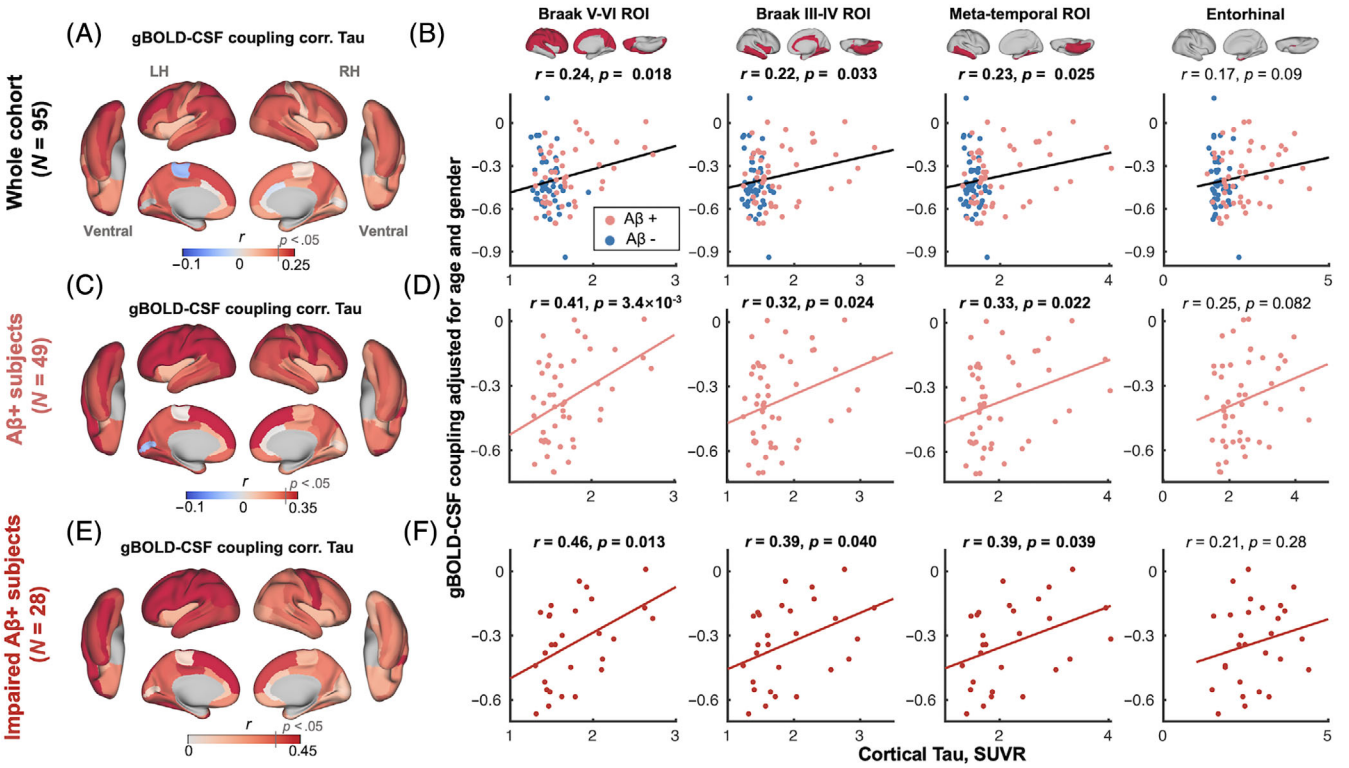

FIGURE 1 gBOLD–CSF coupling is correlated with cortical tau across whole cohort and Aβ+ participants. (A) gBOLD–CSF coupling was positively correlated with tau in most cortical regions across all participants, that is, participants with weaker (less negative) coupling had more tau deposition. (B) gBOLD–CSF coupling (strength) significantly decreased with more tau deposition in Braak V–VI, Braak III–IV, and temporal meta-ROI across the whole cohort (all $r > 0.22$, all $p < 0.033$; $N = 95$). This association was marginally significant ($r = 0.17$, $p = 0.09$) for tau in entorhinal cortex. The FDR was used for the multiple comparison correction ($p_{corrected}$ values were 0.044, 0.044, 0.044, and 0.09 for the first column to the fourth column). (C–F) These associations between gBOLD–CSF coupling and regional tau were also evident among Aβ+ and/or specifically impaired Aβ+ participants (all $r > 0.32$, all $p < 0.040$; in Braak V–VI, Braak III–IV, and temporal meta-ROI), but not for the Aβ− and unimpaired Aβ+ participants (Figure S2). In Figure 1D, the $p_{corrected}$ values were 0.014, 0.032, 0.032, and 0.082. In Figure 1F, the $p_{corrected}$ values were .052, .053, .053, and .28. Aβ+: cortical AV45–Aβ > 1.11 SUVR or cortical FBB–Aβ > 1.08 SUVR. Impaired group: AD and MCI participants. Each point represents one participant. The linear regression line was estimated based on the linear least-squares fitting (the same hereinafter unless noted otherwise). Aβ, amyloid beta; AD, Alzheimer's disease; FBB, [^{18}F]florbetaben; FDR, false discovery ratio; gBOLD–CSF, global brain activity and CSF movement; MCI, mild cognitive impairment; ROI, region of interest; SUVR, standardized uptake value ratio.

V–VI ROI, Braak III–IV ROI, and temporal meta-ROI among the whole cohort, Aβ+, or impaired Aβ+ participants.

Similar to the foregoing analyses on the coupling–tau association, we also correlated the gBOLD–CSF coupling with cortical thickness in the same sets of ROIs or MoCA scores across the same groups of participants.

3 | RESULTS

3.1 | Cohort demographics

Participant characteristics are shown in Table 1. Aβ+ and Aβ− participants were different ($p < 0.001$) in age and MoCA but had a similar sex ratio. The Aβ− participants were also relatively younger than both the unimpaired and impaired Aβ+ individuals (both $p < 3.7\times10^{-3}$). The impaired Aβ+ participants had a higher proportion of males than Aβ− and unimpaired Aβ+ participants ($p = 0.042$).

3.2 | fMRI-based CSF clearance measure is related to tau across Aβ+ participants

CSF inflow rsfMRI signal was negatively correlated with gBOLD signal with a +4.856-s time lag (Figure S1C; with a representative example in Figure S1, A and B), similar to the previous finding.[25] The gBOLD–CSF coupling appeared to be stronger in the Aβ− group than in the Aβ+ group, showing a trend similar to that in the previous study,[25] although not significant (Figure S1D). Importantly, the coupling was positively correlated with tau in most cortical regions across all participants, that is, participants with more cortical tau deposition had weaker (less negative) coupling (Figure 1A). This association was significant for regional tau deposition in the Braak V–VI ROI (isocortical regions), Braak III–IV ROI (limbic area; see Ref. 9 for detailed cortical regions), and temporal meta-ROI[56] across the whole cohort (all $r > 0.22$, all $p < 0.033$; $N = 95$; $p_{corrected}$ were 0.044, 0.044, 0.044, and 0.09 for the first column to the fourth column; Figure 1B). A marginally significant correlation was found between the coupling measure and tau in the entorhinal

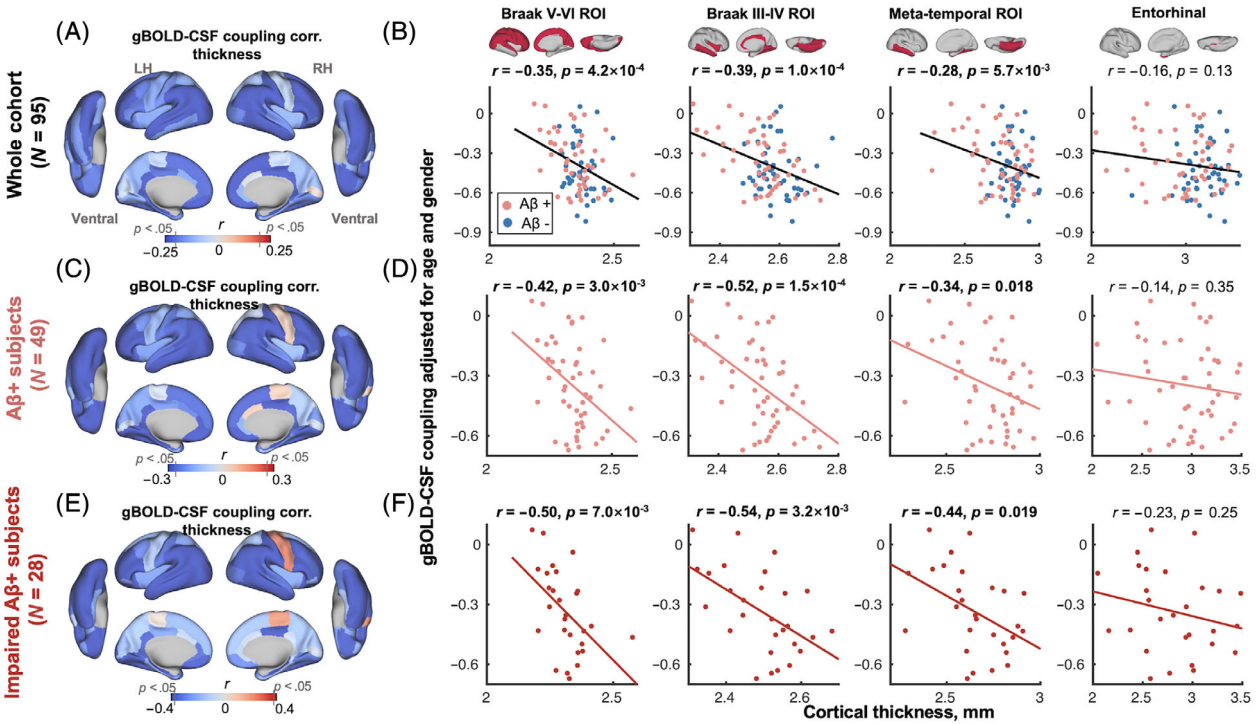

FIGURE 2 gBOLD–CSF coupling is correlated with cortical thickness across whole cohort and Aβ+ participants. (A) Participants with weaker (less negative) gBOLD–CSF coupling had thinner cortices in the majority of brain regions, especially in the frontal, parietal, and temporal lobes, including DMN and FPN. (B) The gBOLD–CSF coupling strength significantly decreased with thinner cortices in Braak V–VI, Braak III–IV, and temporal meta-ROIs across the whole cohort (all $r < -0.28$, all $p < 5.7\times10^{-3}$; $N = 95$). Although not significant, the coupling–thickness association in the entorhinal region showed a trend similar to those in other ROIs noted above ($r = -0.16$, $p = 0.13$). The FDR was used for the multiple comparison correction ($p_{corrected}$ values were 8.0×10^{-4}, 4.0×10^{-4}, 7.6×10^{-3}, and 0.13 for the first to fourth columns). (C–F) Among Aβ+ participants, particularly impaired Aβ+ ones, the coupling–thickness association remained striking (all $r < -0.34$, all $p < 0.019$ in Braak V–VI, Braak III–IV, and temporal meta-ROI in D and F), while this was not the case in the Aβ− and unimpaired Aβ+ participants (Figure S5). In Figure 2D, the $p_{corrected}$ values were 6.0×10^{-3}, 6.0×10^{-4}, .024, and .35. In Figure 2F, the $p_{corrected}$ values were .014, .013, .025, and .25. Each point represents one participant. Aβ, amyloid beta; DMN, default mode network; FPN, frontoparietal network; gBOLD–CSF, global brain activity and CSF movement; ROI, region of interest.

TABLE 1 Participant characteristics.

N = 95	Aβ− (N = 46)	Aβ+ (N = 49)	p-value
Age	69.4 (7.8)	75.8 (6.9)	$\mathbf{6.5\times10^{-5}}$
Sex (M/F)	17/29	23/26	0.4
Diagnosis (AD:MCI:SMC:Control)	0:0:1:45	6:22:4:17	–
MoCA	25.1 (2.8) (2 N/A)	22.3 (4.8) (1 N/A)	$\mathbf{1.0\times10^{-3}}$

Note: Data represent the mean (SD) unless otherwise indicated. A two-sample *t* test was applied to compare the continuous measures, while a Fisher's exact test between groups was used for the sex ratio. Aβ+: cortical AV45–Aβ > 1.11 SUVR or cortical FBB–Aβ > 1.08 SUVR.
Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease group; M/F, male/female; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment; SMC, subjective memory concern; SUVR, standardized uptake value ratio, referring to whole cerebellum reference region.

cortex ($r = 0.17$, $p = 0.09$). The positive coupling–tau relationship was evident for all Aβ+ and also just for the impaired Aβ+ participants (Figure 1, C–F; $p_{corrected}$ for Figure 1D: 0.014, 0.032, 0.032, 0.082; $p_{corrected}$ for Figure 1F: 0.052, 0.053, 0.053, 0.28), but not for the unimpaired Aβ+ participants alone (Figure S2B). The Aβ and gBOLD–CSF coupling showed a significant interaction effect on tau in the Braak V–VI ROI ($p = 4.3 \times 10^{-3}$), Braak III–IV ROI ($p = 0.020$), and temporal meta-ROI ($p = 0.021$), while the diagnostic group and coupling showed no significant interaction effect on tau in the ROIs (all $p > 0.099$), which was related to the limited sample size of the cognitively impaired group. Among the Aβ− participants, individuals with stronger coupling showed higher tau deposition in the Braak V–VI ROI, Braak III–IV ROI, and temporal meta-ROI, but this was marginally significant (all $p > 0.052$; Figure S2A). Of note, head motion during fMRI was not associated with either tau or gBOLD–CSF coupling (Figure S3), and tau remained strongly

correlated with the gBOLD–CSF coupling after adjusting for head motion (Figure S4).

Among the entire cohort, participants with stronger gBOLD–CSF coupling (more negative) had higher MoCA scores ($r = -0.23$, $p = 0.027$; $N = 92$). This trend was also found across Aβ+ individuals and the impaired Aβ+ ones, although not significant (both $r < -0.25$, both $p < 0.11$).

3.3 | Tau partially mediates the strong association between gBOLD–CSF coupling and cortical thickness

We next examined the coupling–thickness association, as tau is closely associated with cortical atrophy and ultimately leads to cognitive decline.[3,4,60] Similar to the coupling–tau links discussed earlier, gBOLD–CSF coupling was also significantly related to cortical thickness in widespread cortical regions, including the Braak V–VI ROI, Braak III–IV ROI, and temporal meta-ROI, across the entire group of participants, and more specifically among the impaired Aβ+ participants (Figure 2; see detailed $p_{uncorrected}$ and $p_{corrected}$ in the figure caption), but not in the Aβ– and unimpaired Aβ+ groups alone (Figure S5).

Cortical tau and thickness showed a similar spatial distribution pattern averaged across the entire cohort and when contrasting Aβ+ and Aβ– participants (both $p < 1.9\times10^{-4}$; Figure 3A and B). Cortical tau and thickness were also closely associated across participants (all $p < 0.05$; Figure S6). Given the corresponding spatial pattern and the predictive role of tau in brain atrophy,[60] we used mediation analysis to examine whether tau in Braak V–VI ROI, Braak III–IV ROI, and the temporal meta-ROI mediated the observed relationship between gBOLD–CSF coupling and cortical thickness in the same regions. We found that tau in the three ROIs played a significant role in mediating the coupling–thickness link across the whole cohort ($p < 0.021$; Figure 3C; see detailed $p_{corrected}$ in the figure caption). Among Aβ+ participants, the mediation effect was marginally significant ($p < 0.063$) for the Braak III–IV ROI and the temporal meta-ROI and significant for the Braak V–VI ($p = 0.039$; Figure 3D). The mediation was less robust in impaired Aβ+ participants (Figure 3E; only significant in the meta-temporal region, $p = 0.035$), which may be attributed to the limited sample size of this group ($N = 28$). Together, these results suggest that tau is a mediator of the association between CSF dynamics of clearance relevance, reflected by gBOLD–CSF coupling and cortical thickness.

We also examined whether coupling mediated the tau–thickness relationship (Figure S7) and found the mediation was significant for the Braak V–VI and Braak III–IV ROIs ($p < 0.042$), although it was marginally significant in the Braak III–IV among Aβ+ participants ($p = 0.055$).

4 | DISCUSSION

We show an association between resting-state global brain activity and tau pathology, including the pattern of tau deposition and relevant brain atrophy and cognitive decline. The coupling between global brain activity, quantified by gBOLD, and CSF movement was associated with tau deposition in widespread neocortical regions that approximate the later stages of tau deposition. This finding was evident in the whole cohort but more striking for the Aβ+ and impaired Aβ+ participants, as would be expected since the tau burden is likely to be greater for these groups. The Aβ and gBOLD–CSF coupling showed a significant interaction effect on tau. Weaker gBOLD–CSF coupling, which may indicate declining CSF clearance, was also associated with reduced cortical thickness in the same regions, likely related to the mediating role of tau. Together, these results suggest that resting-state global brain activity helps to determine the stereotyped pattern of tau deposition in the neocortex among individuals with elevated Aβ, presumably via its effect on CSF dynamics-related clearance.

Pathological tau aggregation has received increasing attention because of its strong relation to brain atrophy and cognitive impairment.[3,7] While a majority of recent studies have attributed the stereotyped pattern of tau accumulation over cortical regions to neural activity and anatomical and functional connectivity,[10–15,61,62] other data have repeatedly demonstrated that the brain's clearance system affects tau pathology[16] through CSF flow.[18,19] This pathway clears brain waste through CSF movement pushing the exchange between CSF and ISF and its solutes, including Aβ and tau.[18,19]

Our study investigated the association between tau deposition in several Braak stages, indicative of different stages of tau pathology[8,9] and the coupling between global brain BOLD and CSF inflow signals, as a unique evaluation of CSF dynamics-related clearance. Previous studies suggested that Aβ facilitated the spread and pathogenicity of tau.[63] Consistently, particularly among the participants with elevated Aβ, our study emphasizes that gBOLD–CSF coupling could also affect tau deposition and further affect cortical thickness, particularly in the neocortex, including Braak III–IV, V–VI, and meta-ROI regions, but not in the Braak I region, that is, entorhinal cortex, where tau deposits in normal aging without Aβ elevation.[64] This would imply the different mechanisms of tau deposition in the entorhinal cortex and other Braak staging regions and that tau deposition in the latter appears to be more complicated and related to the comodulation of Aβ and CSF clearance assessed by the gBOLD–CSF coupling. In addition, our observations suggest that the coupling-related CSF clearance of tau is more sensitive to AD stages with fast tau accumulation (ie, Aβ+ stage). In this stage, tau deposition in entorhinal cortex is elevated but could have slower accumulation that is more difficult to capture by the coupling measure. Furthermore, the spatial location of atrophy is closely associated with tau deposition, especially when Aβ is elevated.[63] This may also explain why the coupling was correlated with thickness in the regions where tau was significantly associated with the coupling metrics.

Our results showed a close association between the global BOLD and CSF inflow fMRI signal at rest. Several lines of evidence support a link between resting-state global brain activity and CSF dynamics-related clearance. First, global brain activity, measured by gBOLD fMRI signal and whole-brain electrophysiology signals,[30,34] is coupled with CSF movement,[25–27,31,32] a key determinant of CSF clearance.[16–18] This coupling is particularly striking during sleep,[31] when glymphatic

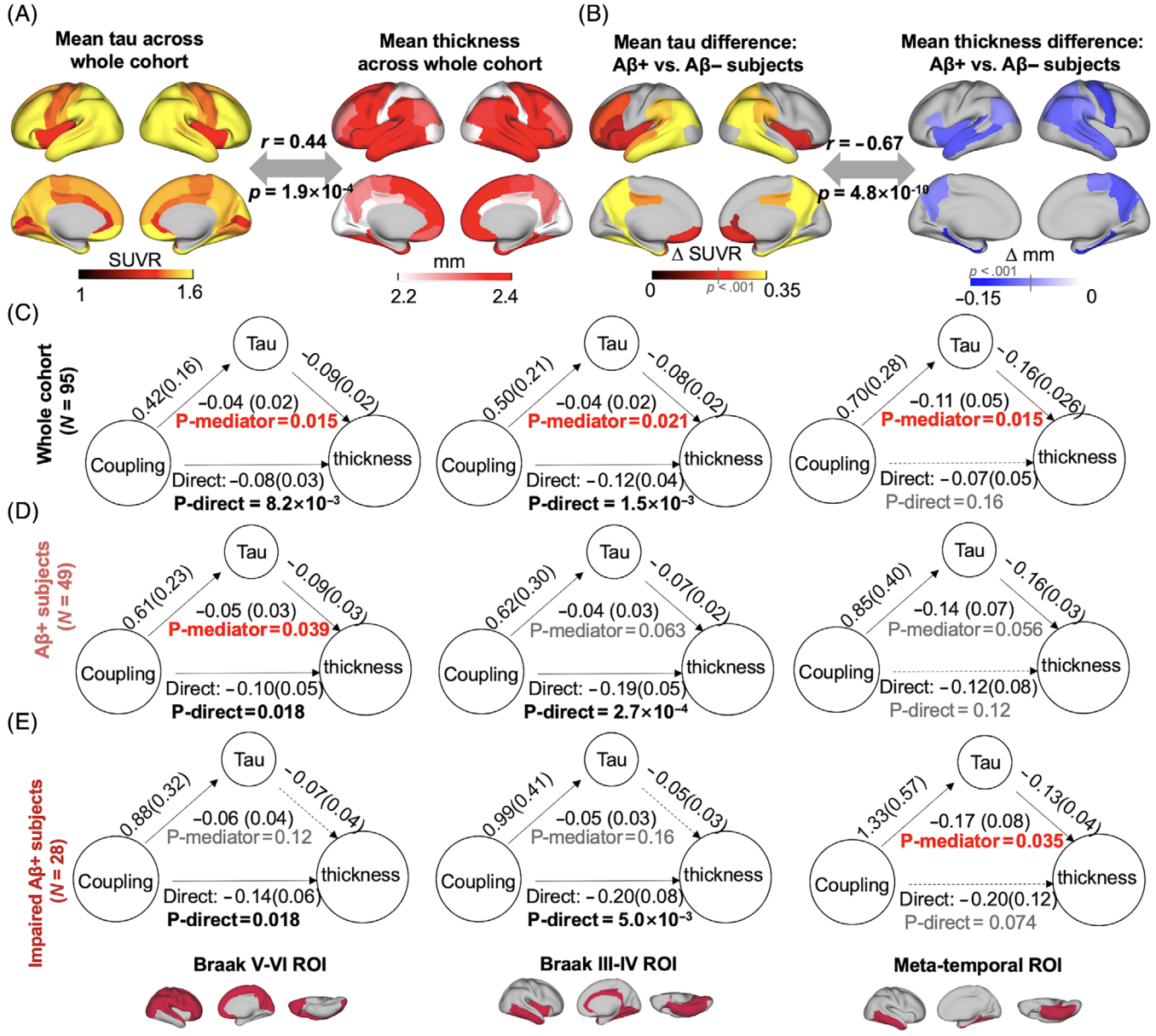

FIGURE 3 The association between coupling metrics and thickness is mediated by tau. (A and B) Averaged map of cortical tau and thickness across all participants ($r = 0.44$, $p = 1.9\times10^{-4}$), as well as the difference between Aβ– and Aβ+ participants ($r = -0.67$, $p = 4.8\times10^{-10}$), indicative of tau and atrophy distributions were similar. This close association between tau pathology and atrophy is also consistent with their significant correlation across participants (Figure S6). (C–E) Across entire cohort and Aβ+ participants, tau mediated the significant association in Figure 2 between gBOLD–CSF coupling and thickness throughout cortex, including Braak V–VI, Braak III–IV, and meta-temporal area ($p < 0.039$, except for the marginally significant relationship [$p < 0.063$] in Braak III–IV and meta-temporal among Aβ+ participants), whereas the mediation effect was weaker for impaired Aβ+ ones, which might be attributed to the limited sample size. In Figure 3C, the $p_{corrected}$ values were 0.021, 0.021, and 0.021. In Figure 3D, the $p_{corrected}$ values were .063, .063, and .063. In Figure 3E, the $p_{corrected}$ values were 0.16, 0.16, and 0.11. Significant direct and mediation effects were highlighted with black and red bold formatting, respectively. gBOLD–CSF, global brain activity and CSF movement.

CSF clearance can be 20-fold stronger than wakefulness.[17] More recently, the coupling between gBOLD and CSF inflow rsfMRI signals is correlated with various AD risk factors, cortical Aβ deposition,[25,27] older age,[32] and cognitive decline in AD and Parkinson's disease (PD),[25,26] further supporting the relationship between global brain activity and CSF dynamics-related clearance. Second, neuronal firing cascades that underlie global spontaneous brain events[33] and gBOLD signal are often accompanied by the modulation of sympathetic outflow, including cardiac and respiratory pulsations,[37–41] heart rate variability,[42] and pupil size.[33,36] The sympathetic activity could not only facilitate peri-arterial CSF movements via arterial constriction[41,65] but also arouse slow (<0.1 Hz) modulations of cardiac and respiratory pulsations, considered as the major driving forces of glymphatic CSF movement.[43,44] Third, the intrinsic subcortical vasoactive pathways,[65] particularly the basal-cortical projections[66] relevant to the cholinergic system and astrocytes, are involved with

the modulation of global brain activity on vascular tone.[41] Importantly, while a small proportion of perivascular neurons have direct contact with the vessel wall, most abut astrocytic endfeet[65] constituting the astroglial aquaporin-4 (AQP4) channels that facilitate CSF flow.[18] A recent study suggested that intrinsic large astrocytic Ca^{2+} spikes were coupled with the negative gBOLD peaks.[67] In short, global brain activity and specific neural and physiological factors play a critical role in supporting CSF flow and thus could affect AD progression by moderating the "accumulation-removal balance" of toxic proteins, such as Aβ and tau.

In our study, we observed the strength of gBOLD–CSF coupling reflecting CSF dynamics-related clearance decreased with tau deposition. Recent studies in animal models have repeatedly demonstrated the role of CSF clearance or glymphatic function in tau aggregation.[19,68–70] Using intracortical injection of human tau into mice, a previous study tracked the tau clearance pathway and found that tau could be removed by CSF flow, especially in traumatic brain injury, a risk factor for tau aggregation.[68] Further investigations on tau and CSF clearance suggested that tau was cleared from the brain by an AQP4-dependent mechanism.[69,70] For example, a recent mouse study suggested that impaired CSF–ISF exchange and AQP4 polarization, especially using an AQP4 inhibitor, in the glymphatic system could exacerbate or even induce pathogenic accumulation of tau.[69] The same study further showed an inverse association between CSF clearance and tau deposition in the healthy mouse cortex.[69] In addition, the glymphatic CSF clearance was hypothesized to affect the cell-to-cell propagation of tau in brain,[71] since tau can be secreted and taken up by both neurons and glia,[72] and tau secretion to the extracellular space plays an important role in intracellular tau spreading.[68,73] Beyond these mouse studies, a recent human study identified the relationship between reduced whole-brain CSF clearance activity, assessed with diffusion tensor image analysis along the perivascular space (DTI-ALPS), and the deposition of tau using PET along with cognitive decline.[74] All these studies suggest the role of CSF movement clearing tau, which supports the idea that the CSF clearance-related gBOLD–CSF coupling is related to tau deposition.

It is not surprising that we observed that tau mediated the association between CSF clearance and cortical thickness. Our results showing an association between coupling and atrophy were consistent with a recent study showing that the impaired CSF clearance in TAR DNA-binding protein 43 transgenic mice, mimicking the pathology of amyotrophic lateral sclerosis, was accompanied by neocortical atrophy.[75] More importantly, middle-aged AQP4 knock-out mice showed elevated tau in both CSF and hippocampus, as well as severe brain atrophy with thinner cortices and hippocampus.[70] This brain atrophy was attributed to neuronal loss, including the reduction of dentate granule cells and pyramidal cell layer neurons in the piriform cortex, presumably modulated by tau aggregation induced by the AQP4 deficiency.[70] Of note, our results may also pose the possibility that the coupling mediates the tau–thickness association. This could result from the very strong association between tau and thickness and their significant correlations with the coupling metrics. However, it is hard to determine the causal relationship between variables, and a longitudinal study is needed.

There are a few limitations of the present study. First, we used a cross-sectional analysis that did not have information about rates of tau accumulation. In addition, it is possible that elevated tau accumulation in the cortical brain influences CSF dynamics and clearance or even global brain activity, which further leads to a decreased gBOLD–CSF coupling. A longitudinal design should be used to test the hypothesis that the tau accumulation rate is linked to fMRI-based gBOLD–CSF coupling or an alternative hypothesis that the tau deposition leads to a decrease of CSF inflow or global brain activity and the coupling measure over years. Second, direct evidence that gBOLD–CSF coupling reflects CSF dynamics-related clearance is needed to validate and extend our findings that global brain activity affects CSF flow and may further modulate CSF clearance. We also note that some of the main results were marginally significant or not significant after multiple comparison corrections, which could come from imaging noise and the imperfect methodology to quantify the coupling strength between CSF inflow and gBOLD. Third, the lack of electroencephalogram (EEG) monitoring of sleep or arousal state was also a limitation of this study. Although it is challenging to acquire EEG-fMRI data for both healthy aging and AD patients, at rest or during sleep, it would be interesting for future studies to investigate the role of sleep and arousal state in the association between tau pathology and the coupling between global brain activity and CSF inflow.

In summary, this study provides initial evidence that CSF dynamics, reflected by the coupling between global brain activity and the CSF movement signals, is closely associated with tau pathology in people with elevated Aβ, presumably because poorer CSF clearance promotes abnormal protein aggregation.

AUTHOR CONTRIBUTIONS

Feng Han and William J Jagust conceptualized and designed the study; Feng Han, JiaQie Lee, Jacob Ziontz, Tyler Ward, Susan M Landau, and William J Jagust curated the data and performed analyses; Feng Han, Xi Chen, Suzanne L Baker, and Theresa M Harrison and William J Jagust designed and performed assays; Feng Han. and William J Jagust wrote the original draft, and JiaQie Lee; Feng Han, Xi Chen, Jacob Ziontz, Tyler Ward, Susan M Landau, Suzanne L Baker, Theresa M Harrison and William J Jagust reviewed and edited the manuscript; William J Jagust supervised the project; and all authors read and approved the manuscript.

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CONFLICT OF INTEREST STATEMENT

W.J.J. has served as a consultant for Biogen, Eisai, Clario, and Lilly. The remaining authors declare no competing financial interests. Author disclosures are available in the Supporting Information.

DATA AVAILABILITY STATEMENT

The multimodal data, including subject characteristics, rsfMRI, structural MRI, Aβ-PET, tau-PET, and MoCA measures are all publicly available at the ADNI website upon the approval of the data use application (http://adni.loni.usc.edu/). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see www.adni-info.org. All the codes used in the present study are available from the corresponding author upon request.

CONSENT STATEMENT

All human subjects provided written 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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