Cerebrospinal Fluid β-Amyloid and Phospho-Tau Biomarker Interactions Affecting Brain Structure in Preclinical Alzheimer Disease

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Objective: To assess the relationships between core cerebrospinal fluid (CSF) biomarkers and cortical thickness (CTh) in preclinical Alzheimer disease (AD).
Methods: In this cross-sectional study, normal controls (n = 145) from the Alzheimer's Disease Neuroimaging Initiative underwent structural 3T magnetic resonance imaging (MRI) and lumbar puncture. CSF β-amyloid$_{1–42}$ (Aβ) and phospho-tau$_{181p}$ (p-tau) levels were measured by Luminex assays. Samples were dichotomized using published cutoffs (Aβ$^+$/Aβ$^-$ and p-tau$^+$/ptau$^-$). CTh was measured by Freesurfer. CTh difference maps were derived from interaction and correlation analyses. Clusters from the interaction analysis were isolated to analyze the directionality of the interaction by analysis of covariance.
Results: We found a significant biomarker interaction between CSF Aβ and CSF p-tau levels affecting brain structure. Cortical atrophy only occurs in subjects with both Aβ$^+$ and p-tau$^+$. The stratified correlation analyses showed that the relationship between p-tau and CTh is modified by Aβ status and the relationship between Aβ and CTh is modified by p-tau status. p-Tau–dependent thinning was found in different cortical regions in Aβ$^+$ subjects but not in Aβ$^-$ subjects. Cortical thickening was related to decreasing CSF Aβ values in the absence of abnormal p-tau, but no correlations were found in p-tau$^+$ subjects.
Interpretation: Our data suggest that interactions between biomarkers in AD result in a 2-phase phenomenon of pathological cortical thickening associated with low CSF Aβ, followed by atrophy once CSF p-tau becomes abnormal. These interactions should be considered in clinical trials in preclinical AD, both when selecting patients and when using MRI as a surrogate marker of efficacy.

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The pathophysiological processes of Alzheimer disease (AD) begin many years before the diagnosis of AD dementia. β-Amyloid$_{1–42}$ (Aβ) deposition is thought to be an early event, and the biomarkers related to brain amyloidosis are the first to become abnormal.[1,2] The long preclinical phase in AD is divided into 3 stages based on operational research criteria[1]: asymptomatic cerebral amyloidosis (stage 1), stage 1 plus evidence of early neurodegeneration (stage 2), and stage 2 plus subtle cognitive decline (stage 3). Nonetheless, a subset of

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cognitively normal individuals show evidence of early neurodegeneration in the absence of Aβ deposition (suspected non-Alzheimer pathophysiology [SNAP]).[3] The possibility of Aβ-independent neurodegenerative processes in AD does not fit current biomarker models.[4]

The relationship between the amyloidosis and brain structure is controversial. Several cross-sectional studies have reported cortical thinning[5–9] or hippocampal atrophy,[10] whereas other studies found no relationship[11] or even increased gray matter in relation to Aβ deposition.[12,13] There are several possible explanations for these discrepancies. First, the age range sampled varies across studies, and not all brain changes in aging reflect incipient AD.[14] Second, the relationship between cerebrospinal fluid (CSF) Aβ and cortical thickness (CTh) in preclinical stages may not be linear.[15] Third, possible interactions between CSF biomarkers in preclinical AD might confound this relationship. For example, longitudinal volume loss or cognitive decline in preclinical AD only occurred in those subjects who, in addition to brain amyloidosis, had abnormal CSF levels of phospho-tau$_{181p}$ (p-tau).[16,17] These data suggest that abnormally elevated p-tau is a critical link between Aβ deposition and accelerated volume loss in AD-vulnerable regions.[16]

It is essential to determine the interactions between core CSF biomarkers and CTh to establish the sequence of events in preclinical AD. These interactions could impact on the design and interpretation of prevention trials in preclinical AD. The objective of this study was to disentangle the interactions between CSF Aβ and p-tau levels affecting CTh, based on the following hypotheses: (1) atrophy occurs in the presence of both Aβ and p-tau in preclinical AD, and (2) CSF Aβ in the absence of elevated CSF p-tau might be associated with increased CTh.

Subjects and Methods

Study Participants and Clinical Classification

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations, as a $60-million, 5-year public–private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The principal investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California, San Francisco. ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations, and subjects have been recruited from >50 sites across the United States and Canada. The initial goal of ADNI was to recruit 800 subjects, but ADNI has been followed by ADNI-GO and ADNI-2. To date, these 3 protocols have recruited >1,500 adults, aged 55 to 90 years, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow-up duration of each group is specified in the protocols for ADNI-1, ADNI-2, and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see www.adni-info.org. We restricted the study to those normal controls with 3T MRI and available CSF results (177 subjects were selected for analysis).

CSF Analyses

ADNI PROCEDURE. Methods for CSF acquisition and biomarker measurement using the ADNI cohort have been reported previously.[18] Aβ and p-tau were measured using the multiplex xMAP Luminex platform (Luminex Corporation, Austin, TX) with INNO-BIA AlzBio3 (Innogenetics, Ghent, Belgium) immunoassay kit–based reagents. Using proposed CSF cutoffs,[18] we divided the sample into Aβ-positive ($\leq$192pg/ml), Aβ-negative (>192pg/ml), p-tau–positive ($\geq$23pg/ml), and p-tau–negative (<23pg/ml) subjects.

MRI Acquisition

ADNI PROCEDURE. The details of acquisition are available elsewhere (http://www.adni-info.org).

CTH PROCEDURE. Cortical reconstruction of the structural images was performed with the FreeSurfer software package (v5.1; http://surfer.nmr.mgh.harvard.edu). The procedures have been fully described elsewhere.[19] Estimated surfaces were inspected to detect errors in the automatic segmentation procedure. Of the 177 N3-processed MRIs analyzed, 32 were excluded because of segmentation errors, and 145 were included in the analyses.

Statistical Methods

Group analyses were made using SPSS (SPSS Inc, Chicago, IL). Comparisons between groups were performed using 2-tailed Student t test for continuous variables and with a chi-square test for categorical variables. CTh analyses were performed using linear modeling of the thickness maps as implemented in FreeSurfer with age and gender as covariates. A Gaussian kernel of 15mm full-width at half maximum was applied. To avoid false positives, we tested Monte Carlo simulation with 10,000 repeats in Qdec (family-wise error [FWE], $p < 0.05$). Only regions that survived FWE are presented in the figures.

The main objective of our work was to demonstrate a statistical interaction between CSF p-tau and CSF Aβ status

TABLE. Demographic and Cerebrospinal Fluid Data

Characteristic	ADNI Value
No.	145
Age, mean yr (SD)	73.4 (6.2)
Female sex, %	51.0
Aβ, mean pg/ml (SD)	227.6 (65.1)
Aβ positive, %	26.9
p-tau, mean pg/ml (SD)	25.2 (13.2)
p-tau positive, %	43.4
MMSE, mean (SD)	29.1 (1.1)

Aβ = β-amyloid$_{1–42}$; ADNI = Alzheimer's Disease Neuroimaging Initiative; MMSE = Mini-Mental State Examination; p-tau = phospho-tau$_{181p}$; SD = standard deviation.

affecting CTh. To answer this question, 2 approaches were used: interaction and stratified correlation analysis. We first performed a vertexwise interaction analysis across the whole cortical mantle, showing voxels with an amyloid (positive or negative) by p-tau (positive or negative) interaction. We focused on regions that survived the interaction and then analyzed the directionality of the interaction and the main and interactive effects of each variable in an analysis of covariance (ANCOVA), covarying for the effects of age and sex. Specifically, we used the following model:

$$\text{CTh} = \beta_0 + \beta_1 \cdot \text{p-tau} + \beta_2 \cdot \text{A}\beta + \beta_3 \cdot (\text{p-tau} \cdot \text{A}\beta) + \text{covariates} + \varepsilon$$

To ensure that our results were not due to a categorical treatment of variables, we also conducted an interaction analysis to assess whether the relationships between CTh and one CSF biomarker (treated as a continuous variable) were affected by the status of the other dichotomized CSF biomarker. We then analyzed the directionality of this interaction in scatterplots at the maximum significant vertex. Finally, we performed stratified correlation analyses to further study the relationships between CTh and CSF biomarkers.

Results

The Table summarizes the demographic, clinical, and CSF data. Applying the published cutoffs,[18] the proportion of CSF Aβ-positive subjects (26.9%) was lower than the proportion of p-tau–positive subjects (43.4%). The group of Aβ-positive subjects had a higher proportion of p-tau–positive subjects (79.5%) than the group of Aβ-negative subjects (30.2%; $p < 0.001$).

Interaction Analyses: Synergistic Interactions between CSF Biomarkers Affecting Brain Structure

Figure 1 presents the vertexwise interaction analysis across the whole cortical mantle, showing voxels with an amyloid by p-tau interaction. Extensive clusters emerged, one mainly in the lateral occipital, middle temporal, and inferior parietal regions and cortical areas around superior temporal sulcus (bankssts) and another in fusiform and occipital regions in the right hemisphere. We then isolated the clusters, averaged the CTh, and plotted it in box and whisker plots for each cluster (see Fig 1B, C). As hypothesized, amyloid abnormalities in the absence of tau abnormalities were associated with increased CTh in both clusters. In the presence of p-tau, however, the directionality changed toward cortical thinning in subjects who were both Aβ^+ and p-tau$^+$.

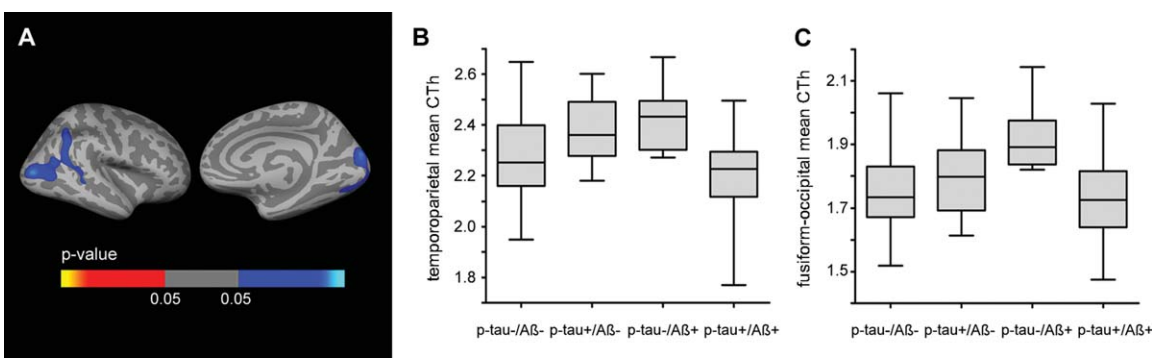

FIGURE 1: Interaction analyses in Alzheimer's Disease Neuroimaging Initiative: familywise corrected ($p < 0.05$) clusters with a β-amyloid$_{1–42}$ (Aβ^+ or Aβ^-) by phospho-tau$_{181p}$ (P$_T^+$ or P$_T^-$) interaction. (A) Areas in which there is an interaction between the dichotomized (Aβ and P$_T$) biomarkers covaried for age and gender displayed across the lateral and medial hemispheres of the cerebral cortex. (B, C) Box and whisker plots for all normal controls, illustrating the individual cortical thickness (CTh) values in the temporoparietal (B) and fusiform–occipital (C) clusters, based on cerebrospinal fluid (CSF) Aβ and CSF P$_T$ status for all participants. The central black lines show the median value, regions above and below the black lines show the upper and lower quartiles, respectively, and the whiskers extend to the minimum and maximum values. As illustrated, the Aβ^+/P$_T^-$ individuals demonstrated increased CTh values, and the Aβ^+/P$_T^+$ showed decreased CTh values.

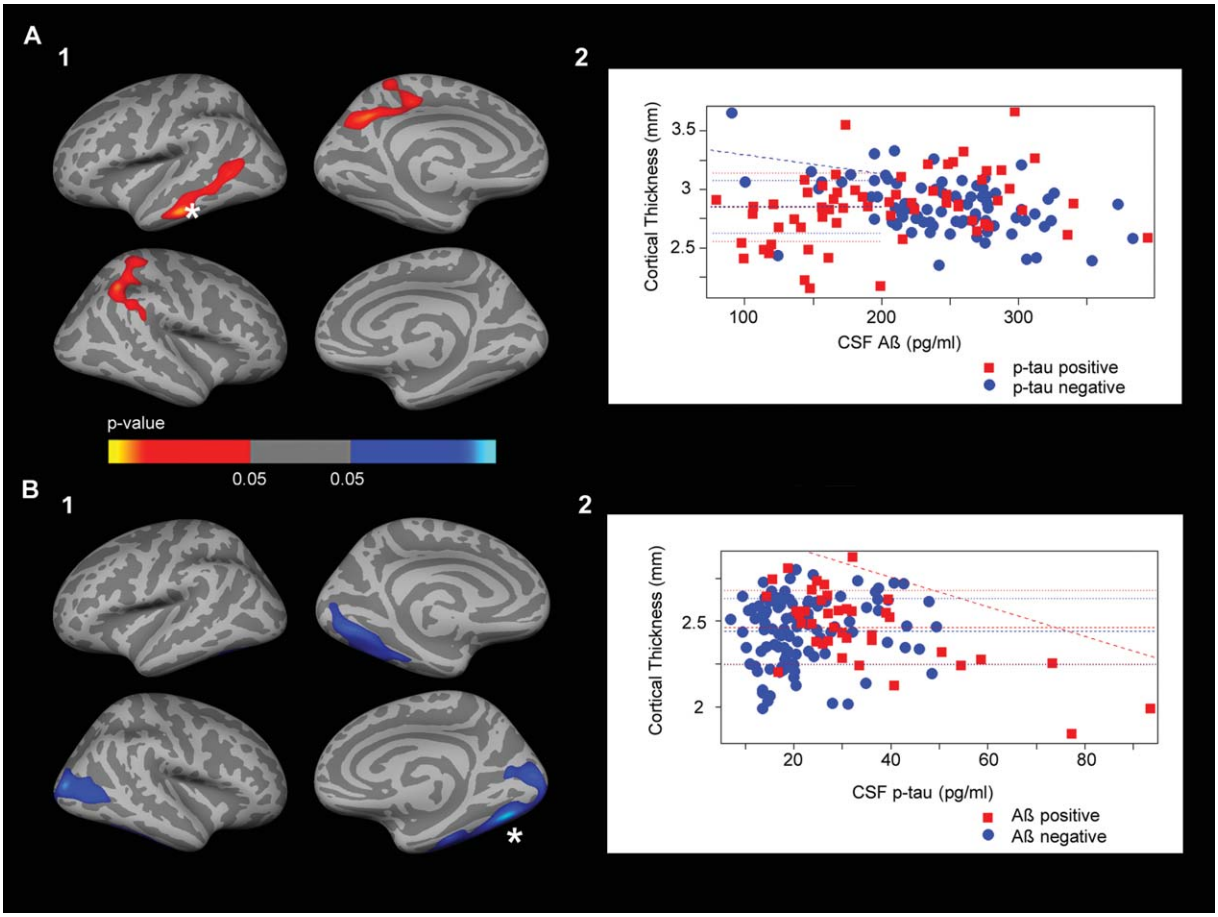

FIGURE 2: Interaction analyses in Alzheimer's Disease Neuroimaging Initiative: familywise corrected ($p < 0.05$) clusters in which the correlation between cortical thickness (CTh) and 1 biomarker is modified by the status of the other dichotomized biomarker. (A1) Areas in which the β-amyloid$_{1-42}$ (Aß)–CTh correlation is modified by phospho-tau$_{181p}$ (p-tau) status. (A2) Scatterplot showing CTh and Aß values at the maximum significant vertex in the laterotemporal cluster. P-tau–positive subjects are shown in red, and p-tau–negative subjects are shown in blue. (B1) Areas in which the p-tau–CTh correlation is modified by Aß status. (B2) Scatterplot showing CTh and p-tau values at the maximum significant vertex (asterisks) in the fusiform cluster. Aß–positive subjects are shown in red, and Aß–negative subjects are shown in blue. Red–yellow indicates a positive correlation, and blue indicates a negative correlation. CSF = cerebrospinal fluid.

We also examined the main and interactive effects of CSF p-tau and CSF Aβ on CTh with ANCOVA analyses in the FWE corrected clusters, controlling for age and sex. Both the main and interactive effects were significant in the model in both clusters (interaction term between CSF p-tau and CSF Aβ status: β-coefficient = -0.246, standard error [SE] = 0.053, $p < 0.001$ for the fusiform–occipital cluster, and β-coefficient = -0.306, SE = 0.064, $p < 0.001$ for the temporoparietal cluster; main effect of CSF p-tau: β-coefficient = 0.186, SE = 0.047, $p < 0.001$ for the fusiform–occipital cluster, and β-coefficient = 0.206, SE = 0.056, $p < 0.001$ for the temporoparietal cluster; main effect of CSF Aβ: β-coefficient = 0.068, SE = 0.031, $p < 0.028$ for the fusiform–occipital cluster, and β-coefficient = 0.150, SE = 0.037, $p < 0.001$ for the temporoparietal cluster).

To ensure that our results were not due to a categorical treatment of variables, we also conducted an interaction analysis to assess whether the relationship between CTh and 1 CSF biomarker (treated as a continuous variable) was affected by the status of the other dichotomized CSF biomarker. We found an interaction between CSF Aβ and p-tau levels affecting brain structure. As hypothesized, cortical thinning occurred in subjects who were both Aβ^+ and p-tau$^+$. Figure 2A1 shows the Aβ–CTh correlation by p-tau status analysis (areas in which the relationship between Aβ levels and CTh was modified by p-tau status). Extensive clusters emerged mainly in middle and inferior temporal, bankssts, inferior parietal, and precuneus regions in the left hemisphere and superior and inferior parietal and supramarginal regions in the right hemisphere. Figure 2A2 shows the CTh values for each Aβ value (p-tau positive and p-tau

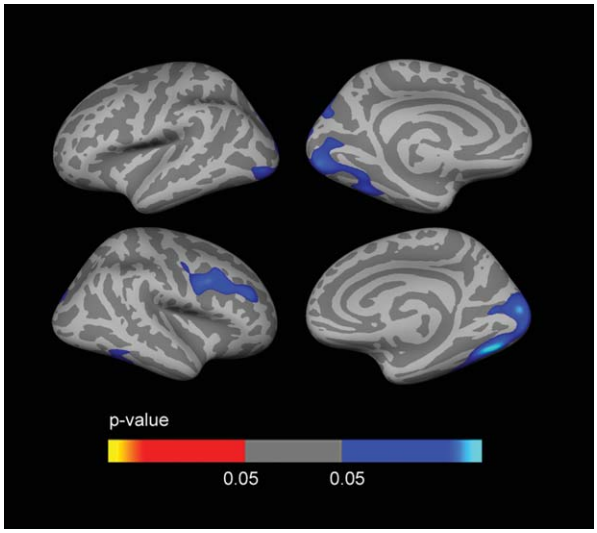

FIGURE 3: Cerebrospinal fluid phospho-tau$_{181p}$ (p-tau)–cortical thickness (CTh) correlation in β-amyloid–positive subjects. Only regions that survived familywise error (FWE) correction for multiple comparisons ($p<0.05$) are shown. Red–yellow indicates a positive correlation, and blue indicates a negative correlation. In β-amyloid$_{1–42}$–negative subjects, no significant clusters (FWE corrected) of correlations were found between p-tau and CTh.

negative were analyzed separately) at the maximum significant vertex in the laterotemporal cluster. Similar results were found in all FWE corrected clusters (results not shown).

Figure 2B1 shows the p-tau–CTh correlation by Aβ status analysis. Extensive clusters emerged in fusiform and lingual areas in the left hemisphere and in fusiform, inferior temporal, and lateral occipital areas in the right hemisphere. Figure 2B2 shows the CTh values for each p-tau value (Aβ positive and Aβ negative were analyzed separately) at the maximum significant vertex in the fusiform and inferior temporal areas. Similar results were found in all FWE corrected clusters (results not shown).

We performed stratified correlation analyses to further assess whether the relationship between p-tau and CTh is modified by Aβ status and whether the relationship between Aβ and CTh is modified by p-tau status.

Relationship between CSF p-Tau and CTh Is Modified by Aβ

Figure 3 shows the p-tau–CTh correlation analyses in Aβ-positive and Aβ-negative subjects. In Aβ-positive subjects, extensive clusters (FWE corrected) of decreasing CTh in relation to increasing CSF p-tau values emerged in fusiform, lingual, lateral occipital, and superior parietal areas in the left hemisphere and rostral middle frontal, caudal middle frontal, precentral, inferior temporal, fusiform, and occipital regions in the right hemisphere. In Aβ-negative subjects, no significant clusters (FWE corrected) of correlations were found between p-tau and CTh.

Correlation Analyses: Relationships between CSF Aβ and CTh Are Modified by p-Tau

Figure 4 shows the Aβ–CTh correlation analyses in p-tau–negative and p-tau–positive subjects, respectively. In p-tau–negative subjects, extensive clusters (FWE corrected) of increasing CTh in relation to decreasing CSF Aβ values emerged in middle temporal, inferior parietal, bankssts, and lateral occipital areas in the left hemisphere and inferior parietal, superior parietal, and precuneus areas in the right hemisphere. In p-tau–positive subjects, no significant clusters (FWE corrected) of correlations were seen between Aβ and CTh.

The correlation analyses in the whole cohort, if not stratified, found no significant clusters (FWE corrected) of association between CTh and Aβ or p-tau (results not shown).

Discussion

This study shows that interactions between markers in preclinical AD result in a two-phase phenomenon of pathological cortical thickening in relation to decreasing CSF Aβ, followed by atrophy when CSF p-tau becomes abnormally elevated. We show that CSF p-tau modifies the effects of Aβ on CTh in different cortical regions and vice versa. CTh increased with amyloid deposition (measured by CSF Aβ) in the absence of abnormal p-tau

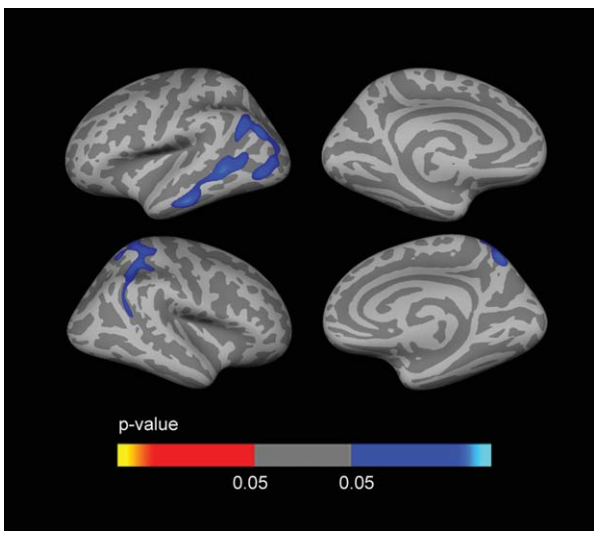

FIGURE 4: Cerebrospinal fluid β-amyloid$_{1–42}$ (Aβ)–cortical thickness (CTh) correlation in phospho-tau$_{181p}$ (p-tau)-negative subjects. Only regions that survived familywise error correction (FWE) for multiple comparisons ($p<0.05$) are shown. Red–yellow indicates a positive correlation, and blue indicates a negative correlation. In p-tau–positive subjects, no significant clusters (FWE corrected) of correlations were found between Aβ and CTh.

levels. Conversely, amyloid deposition increased the deleterious effect of p-tau on brain structure.

The relationship between Aβ and brain structure in preclinical AD remains highly controversial, with variable results across studies.[5–13] Our present findings could help explain these discrepancies by incorporating the effects of the interaction between biomarkers into the model. Our interaction and stratified analyses clearly suggest that biomarkers interact in preclinical AD. CSF p-tau modified the effects of Aβ on CTh and vice versa. CTh increases were found in relation to decreasing CSF Aβ values in the absence of elevated p-tau, whereas no relationship was observed between Aβ and CTh in p-tau–positive individuals. Conversely, amyloid deposition, assessed by CSF Aβ levels, dramatically increased the deleterious effect of p-tau on brain structure. We found cortical thinning in relation to increasing CSF p-tau levels in CSF Aβ-positive subjects, but no relationships in Aβ-negative individuals. Our findings confirm and extend the interaction between CSF Aβ and p-tau affecting brain structure recently described by Desikan et al.[16,17] Conversely, the finding of cortical thickening in *PSEN1* asymptomatic mutation carriers,[20] sporadic preclinical AD,[12,13,15] and APOEε4 carriers[21,22] suggests an inverted U-shape relationship between CSF Aβ levels and CTh.[15] Our present results help to integrate these 2 observations. Brain atrophy has been described in subjects with very low CSF Aβ values.[9,15] Subjects with very low CSF Aβ values, in turn, are more likely to show abnormally elevated CSF p-tau levels in ADNI (see Fig 2B2). We hypothesize that the inverted U-shape relationship between CSF Aβ levels is due to a 2-phase phenomenon of pathological cortical thickening in relation to Aβ that is followed by atrophy once the synergistic effect with p-tau predominates.[16]

Our results are biologically plausible. In human neuropathological studies, a phase of nuclear/cellular hypertrophy before clinical onset has been described, followed by cellular atrophy.[15,23] MRI studies in double amyloid precursor protein (APP)/PS1 transgenic mouse models have shown an increase in cerebral and intracranial size.[24,25] The reciprocal influence between Aβ and tau also has strong biological support.[26] Tau inclusions appear before Aβ deposition in most people as they age,[27] but AD dementia arises only when Aβ deposition coexists.[28] Furthermore, the Aβ accumulation can enhance tau pathology in transgenic mouse models.[29,30] In this respect, a very recent and elegant work in humans and mouse models shows that APP expression acts to potentiate and accelerate tau toxicity in driving lateral entorhinal cortex dysfunction.[31] Conversely, tau is necessary for Aβ-induced neurotoxicity,[32] and reducing endogenous tau ameliorates Aβ-induced deficits in an AD mouse model.[33]

This work has potential clinical implications. First, our results support the notion that tau and Aβ pathological changes could be independent processes but have clear pathogenic synergies. In previous studies, limited to examination of the entorhinal cortex, CSF Aβ was only found to be associated with atrophy in the entorhinal cortex in the context of abnormal CSF p-tau.[16,34] Here, we extend this analysis to all brain vertex and find a similar pattern in several cortical association areas. Second, the amyloid cascade hypothesis has been challenged by recent findings, which show that neuronal injury biomarkers might be independent of Aβ.[3] Our results show that tau-related atrophy in different cortical regions in AD, at least that reflected by abnormally high CSF p-tau, is substantially enhanced in the presence of Aβ. This finding is in agreement with Vos and colleagues' work, in which the progression rate of participants in the SNAP group (CSF tau was used as a marker of neuronal injury) did not differ from that of individuals classed as normal as opposed to stages 2 and 3, in which higher progression rates were found.[35] Third, our work may help clarify some unexpected findings in antiamyloid immunotherapy trials. In the active (AN1792 trial)[36] and passive (solanezumab[37] and bapineuzumab[38]) immunization trials, the active arm showed shrinkage or no changes on MRI (http://www.alzforum.org/new/detail.asp?id=3312). As discussed in these studies, it is unlikely that brain shrinkage is due to neuronal death, because CSF tau was reduced after treatment. Our finding of cortical thickening with amyloid deposition in the absence of abnormal p-tau supports the possibility that brain shrinkage after immunotherapy is caused directly or indirectly (ie, by reducing Aβ-associated inflammation) by the reduction of amyloid deposition. Finally, our results highlight the limitations of amyloid imaging alone when selecting subjects in clinical trials in preclinical AD.

The strengths of this study are the inclusion of a relatively high number of subjects and the finding that the results survived multiple comparisons correction. The study has several limitations. The first of these is the lack of complete overlap between thickened and thinned regions in the stratified correlation analyses (see Figs 3 and 4). Nonetheless, the analysis of the directionality of the interaction and the ANCOVA analyses (see Fig 1), and the analyses treating CSF biomarkers as continuous variables support the existence, at least in some regions, of a 2-phase phenomenon in preclinical AD. Moreover, different factors can explain the absence of complete overlap between thickening and thinning. Amyloid and tau pathologies show different deposition patterns in AD,[27,28,39] with areas in which one pathology predominates over the other. In

addition, several local and general protective and compensatory mechanisms might modulate the effects of the AD pathophysiological process on brain structure in different regions.[40] Longitudinal studies will help to confirm this sequence of events. Finally, another limitation is the indirect assessment of brain amyloidosis and neurofibrillary pathology through CSF biomarkers. We cannot therefore directly correlate CTh with local amyloid deposition or neurofibrillary pathology in the brain. Thus, the results should be interpreted in relation to CSF biomarkers and not to pathophysiological processes. It is expected that novel tau imaging techniques in combination with amyloid imaging will help to determine the individual regional changes that occur during the preclinical phase of the disease.

In conclusion, the interactions between biomarkers in preclinical AD determine a 2-phase phenomenon that consists of pathological cortical thickening in relation to decreasing CSF Aβ followed by atrophy once the synergistic effect with p-tau predominates. The use of biomarkers in future clinical trials for AD should therefore be reconsidered, first because amyloid imaging alone cannot dissect these processes and second, because the use of MRI as a surrogate marker of efficacy should incorporate this 2-phase phenomenon.

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Data used in preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). As such, the investigators within ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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Authorship

J.F. and E.V. contributed equally to the article.

Potential Conflicts of Interest

Nothing to report.

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