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White matter hyperintensities and amyloid are independently associated with entorhinal cortex volume among individuals with mild cognitive impairment

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Abstract

Background—Current hypothetical models of Alzheimer's disease (AD) pathogenesis emphasize the role of beta amyloid, tau deposition, and neurodegenerative changes in the mesial temporal lobe, particularly entorhinal cortex and hippocampus. However, many individuals with clinical AD who come to autopsy also exhibit cerebrovascular disease. The relationship between AD and vascular pathology is unclear, especially whether they represent additive and independent effects on neuronal injury. We used data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to 1) confirm whether entorhinal cortex and hippocampal volume is associated with memory among individuals with amnestic mild cognitive impairment (MCI) who are at risk for AD; and 2) determine whether regional white matter hyperintensity (WMH) volume, a radiological marker of small vessel cerebrovascular disease, is associated with entorhinal cortex and hippocampal volume independent of putative AD biomarkers in this group.

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Methods—Cognitive test scores, entorhinal cortex volume, hippocampus volume, intracranial volume, and cerebrospinal fluid-derived phosphorylated tau and Aβ1–42 protein levels were measured in 199 subjects with amnestic MCI (mean age=74.89+/−7.47). Lobar WMH volumes were derived from T1-, proton-density-, and T2-weighted MRI scans. We examined the association between entorhinal cortex volume and cognition. Next, we examined the association of tau and Aβ1–42 with entorhinal cortex volume and between lobar WMH and entorhinal cortex volume. Finally, tau, Aβ1–42, and regional WMH volumes were entered simultaneously to predict entorhinal cortex volume. We repeated the analyses with hippocampal volume instead of entorhinal cortex volume. The analyses were also repeated with the sample restricted to those MCI patients who transitioned to AD on subsequent ADNI follow-up visits (n=86).

Results—Larger entorhinal cortex volume was associated with better memory but not with performance on a task of executive functioning. Lower levels of Aβ1–42 and higher temporal WMH volumes were associated with smaller entorhinal cortex volume. When entered simultaneously, temporal lobe WMH volume was more reliably associated with entorhinal cortex volume than was Aβ1–42. The findings were similar for hippocampus volume and when the sample was restricted to MCI patients who subsequently transitioned to AD.

Discussion—The findings confirm the role of entorhinal cortex and hippocampus volume in influencing memory decline in amnestic MCI, and emphasize that even in this nominally AD prodromal condition, WMH may be influencing regional neurodegeneration.

Keywords

Mild Cognitive Impairment; Alzheimer’s disease; white matter hyperintensities; beta amyloid; tau

1. INTRODUCTION

The prevailing hypothesis of Alzheimer disease (AD) pathogenesis suggests a temporal ordering of biomarker abnormalities that is biphasic (1). According to the model, beta amyloid (Aβ) plaque formation precipitates a neurodegenerative cascade hallmarked by the formation of neurofibrillary tangles, which leads to neuronal injury, dysfunction and degeneration. Among the most significant advances in AD research during the past several years has been the ability to operationally define these putative biological markers through neuroimaging and neurochemical analysis. For example, beta amyloid can be measured *in vivo* in the cerebrospinal fluid (CSF) or with amyloid positron emissions tomography (PET) techniques (2–4). Similarly, the severity of neurofibrillary tangle formation can be inferred by measuring the amount of total or phosphorylated tau protein in the CSF (2, 3). Early signs of neurodegeneration can be appreciated through analysis of metabolic changes on PET (5) and frank neurodegenerative changes manifest as local atrophy in the mesial temporal lobe (1). Temporal lobe atrophy, particularly in the entorhinal cortex (EC) and hippocampal formation, is thought to be the biological change most proximal to the onset of cognitive symptoms (1).

Both hippocampal and entorhinal cortex atrophy has been recorded in patients diagnosed with AD and those with mild cognitive impairment (MCI), though entorhinal cortex is believed to be the more sensitive biomarker (6, 7). Pathological staging of AD (8) suggests that the entorhinal cortex is damaged prior to the hippocampus by neurofibrillary tangles, and thus should be a more sensitive marker of earlier change, which is supported by *in vivo* studies (7).

In addition to the roles of Aβ, tau, and regional atrophy in AD, there is an emerging literature linking small vessel cerebrovascular disease to the clinical presentation and course of AD (9, 10) and many individuals with AD who come to autopsy evidence significant

amounts of cerebrovascular disease (11). Visualized as white matter hyperintensities (WMH) on T2-weighted magnetic resonance imaging (MRI), increased small vessel cerebrovascular disease, particularly when distributed in posterior regions, has been linked to increase future risk for AD (12, 13) and to course of disease progression (14). It is unclear, however, whether WMH should be incorporated as an additional biological marker for AD risk. One way of addressing this question is to determine whether WMH burden is associated with neurodegenerative markers of AD pathology, such as medial temporal lobe atrophy.

Here, we examined whether Aβ1–42, tau, and regional WMH are associated with entorhinal cortex and hippocampus atrophy (15), among individuals with amnestic mild cognitive impairment (MCI) in the Alzheimer's Disease Neuroimaging Initiative (ADNI). Mild cognitive impairment is considered an intermediate stage between normal cognitive aging and ADrelated dementia (16, 17) and in the ADNI cohort there was an effort to target individuals with the amnestic form of MCI, thought to be at greatest risk for AD. Thus, an MCI cohort is enriched with individuals in the mildest stages of AD. The study of individuals with MCI affords the opportunities to examine some of the earliest changes associated with AD. Given the current hypothetical model of AD pathogenesis (1), we hypothesized that Aβ1–42 and tau would predict medial temporal lobe atrophy. Additionally, given the link of regional WMH to AD (13), we predicted that WMH severity would be independently associated with medial temporal lobe atrophy, suggesting a role of small vessel cerebrovascular disease.

2. METHODS

2.1. Subjects

Data from ADNI were downloaded (www.loni.ucla.edu/ADNI), including demographic, biomarker, neuropsychological, and structural MRI data. The ADNI study was designed to mirror a clinical trial and thus only included participants who were in good health. Importantly, only individuals without significant vascular risk factors, operationally defined as a modified Hachinski score (18) of less than or equal to 4, and good general health were included in the study. For the current analyses, we limited the sample to those meeting criteria for MCI and with available measures of cerebrospinal fluid (CSF)-derived biological markers. Diagnostic criteria for MCI included age between 55 and 90, a memory complaint (study subject or informant), objective evidence of abnormal memory, Clinical Dementia Rating (CDR) score of 0.5, with a Memory Box score of at least 0.5, Mini-Mental State Examination (MMSE) score between 24 and 30 (inclusive), general cognition preserved such that a diagnosis of AD could not be made, stable medication, and not depressed (Geriatric Depression Scale (19) score of less than 6). Recruitment and diagnostic procedures for ADNI have been reported previously (17) (www.loni.ucla.edu/ADNI).

The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of 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 co-

investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. For up-to-date information, see www.adni-info.org.

Table 1 displays characteristics for the subjects included in the current analyses.

2.2. Image Acquisition

Magnetic resonance imaging (1.5T) was acquired across sites following a standardized protocol that was validated across platforms (20). High resolution T1-weighted volumetric magnetization prepared rapid gradient echo sequences were acquired in the sagittal orientation. A proton density/T2-weighted fast spin echo sequence was acquired in the axial orientation. Sites included in the ADNI protocol were required to pass rigorous scanner validation tests and scan acquisitions for each subject included a fluid-filled phantom. Details of the validation procedures are provided elsewhere (20) (www.loni.ucla.edu/ADNI). Data were transferred to University of California at Davis for analysis of WMH.

2.3. Image analysis

Regional WMH volumes were derived following procedures that have been described in detail elsewhere (21, 22). Briefly, the T1-, T2-, and PD-weighted MRI scans were co-registered and skull-stripped (23, 24). Magnetic resonance imaging bias fields were estimated during minimum deformation template warp estimation for the T1-weighted image and using an iterative statistical method for the PD and T2-weighted images (25). White matter hyperintensities were detected in minimum deformation template space at each voxel based on corresponding PD, T1, and T2 intensities, the prior probability of WMH, and the conditional probability of WMH based on the presence of WMH at neighboring voxels. The resulting map of WMH voxels across the brain is summarized by an estimate of total WMH volume. White matter hyperintensity volumes estimated with this method agreed strongly with WMH volumes estimated from fluid attenuated inverse recovery MRI in a large, diverse elderly sample (22). White matter hyperintensiteis were calculated within a standardized space and an *a priori* defined lobar atlas was used to determine regional WMH volumes. Regional volumes were determined by summing the number of voxels labeled as WMH within each segmented lobe and multiplying those sums by the voxel dimensions.

Structural MRI parcellation and segmentation data were downloaded from the ADNI website. ADNI structural MRI data were analyzed with FreeSurfer version 4.3 (https://surfer.nmr.mgh.harvard.edu) at University of California, San Francisco after the T1-weighted MRI scans were converted to NiFTI format and pre-processed at Mayo Clinic (http://adni.loni.ucla.edu/wp-content/uploads/2010/12/UCSF-FreeSurfer-Overview-and-QC_-Template_Format.pdf). For the purposes of the current analyses, we focused on entorhinal cortex and hippocampal volumes.

2.4. Biomarker data

Baseline biomarker data derived from cerebrospinal fluid (CSF) was downloaded from the ADNI website. We focused our analyses on phosphorylated tau (p-tau) and Aβ1–42. Complete procedures for biological assays have been published elsewhere (26).

2.5. Neuropsychological test data

Participants in ADNI receive a comprehensive battery of neuropsychological tests following standard procedures that have been described previously (17). The battery evaluated aspects of memory, attention, executive functioning, visuospatial abilities, and psychomotor speed. Given our interest in the entorhinal cortex and hippocampus, we focused our analysis on a sensitive test of verbal episodic memory, the Rey Auditory Verbal Learning Test (RAVLT).

Briefly, the RAVLT includes 5 learning trials for 15 non-semantically related words. Following an interference word list, subjects are asked to recall the words from the learning trials. Following, a 30-minute delay, subjects are asked to free recall and recognize the words. We chose the delayed recall variable as a prototypical metric of memory retention. To determine whether the relationships were specific with memory functioning, we examined performance on the Trailmaking Test Part B, a prototypical measure of executive functioning. Our intention for these analyses were simply to establish that individual differences in the primary outcome variables of interest (i.e., entorhinal cortex and hippocampal volume) are indeed related to clinical measurements that are specific to AD (i.e., delayed declarative memory functioning) (27, 28).

2.6. Statistical analysis

We first sought to confirm that entorhinal cortex and hippocampus volumes are associated with memory functioning among individuals with MCI in the ADNI cohort. We ran two separate multiple regression analyses with performance on the 30-minute delay of the RAVLT as the dependent variable and entorhinal cortex or hippocampus volume as independent variables and age, sex, education, and total intracranial volume as additional covariates. As a control, we examined the associations of entorhinal cortex or hippocampus volume with performance on the Trailmaking Test Part B. Using multiple regression analysis, we next examined the association of tau and $A\beta_{1–42}$ with entorhinal cortex volume (Model 1) and of lobar WMH with entorhinal cortex volume (Model 2) in separate regression models. Finally, tau, $A\beta_{1–42}$, and regional WMH volumes were entered simultaneously in a single model to predict entorhinal cortex volume (Model 3). We computed the R2 change statistic to examine whether the inclusion of regional WMH volume data improved model fit over the analysis that included only traditional AD biomarkers (i.e., Model 3 vs. Model 1). We repeated the three analyses with hippocampus volume as the dependent variable. All analyses controlled for age, sex, and total cranial volume. Model 3 was finally re-run (Model 4) with the sample restricted to the MCI patients who progressed to clinical AD on subsequent ADNI follow-up visits (n=86). Model 4 included the number of months from the baseline visit to the diagnostic visit as an additional covariate (mean=19.63 months SD=10.47).

3. RESULTS

3.1. Relationship of entorhinal cortex and hippocampus volume with delayed recall memory

Larger entorhinal cortex volume was associated with better performance on the RAVLT delayed free recall trial ($\beta_{standardized}$=0.337, p<0.001; overall model F (5,194)=5.54, p<0.001). Women performed better than men ($\beta_{standardized}$=0.242, p=0.008); otherwise, no other covariates were significantly associated with memory performance. Results with hippocampus volume were similar. Larger hippocampus volume was associated with better performance on the RAVLT delayed free recall trial ($\beta_{standardized}$=0.327, p<0.001; overall model F (5,194)=4.51, p<0.001). The overall models examining associations of entorhinal cortex (F(5,191)=2.25, p=0.051) or hippocampus volume (F(5,191)=1.97, p=0.084) with performance on the Trailmaking Test Part B were significant. These analyses establish the relevance of entorhinal cortex and hippocampus volume to relevant clinical symptoms (i.e., memory functioning) among patients with MCI.

3.2. Relationship of biological markers and regional WMH volumes with entorhinal cortex and hippocampus volume

Table 2 displays the results from the series of regression analyses. In Model 1 (CSF biomarkers only), higher Aβ1–42 levels were associated with larger entorhinal cortex

volumes but p-tau was not (overall model F (5,192)=6.99, p<0.001). In Model 2 (regional WMH volumes only), higher temporal lobe WMH volumes were associated with smaller entorhinal cortex volume (overall models F(7,193)=5.99, p<0.001). In the Model 3 (CSF biomarkers and regional WMH volumes combined), only temporal lobe WMH volume was associated with entorhinal cortex volume (overall model F (9,192)=5.38, p<0.001); none of the CSF biomarkers variables was associated with entorhinal cortex volume, although the relationship between $A\beta_{1-42}$ levels and entorhinal cortex volume was marginally significant (p=0.058). Model 3 fit the data significantly better than Model 1 (R^2 change = 0.052, p=0.020). When we restricted Model 3 to only those MCI patients who progressed to AD during the subsequent ADNI follow-up visits (Model 4), the findings were identical; temporal lobe WMH volume was associated with entorhinal cortex volume, but the CSF biomarkers were not.

Higher $A\beta_{1-42}$ levels, total cranial volume, and age were associated with larger hippocampus volume (Model 1; overall model F(5,192)=14.272, p<0.001) . Regional WMH were not associated with hippocampal volume either when considered alone (Model 2; overall model F (7,193)=9.99, p<0.001) or when considered together with the CSF biomarkers (Model 3; overall model F(9, 192) = 8.61, p<0.001); inclusion of regional WMH did not significantly improve model fit (R^2 change = 0.021, p=0.240). Thus, it appears that the association of regional WMH is specific to entorhinal cortex, although in Model 4, there was an association between temporal lobe WMH and hippocampal volume at a trend level (see Table 2).

4. DISCUSSION

According to popular models of AD pathogenesis, atrophy in temporal lobe regions, particularly entorhinal cortex, is the most proximal marker of neurodegeneration in AD (1). We showed that atrophy in the entorhinal cortex and hippocampus are associated with poorer memory performance specifically, the most salient early cognitive symptom of AD, among older adults with MCI. To understand what the predictors of entorhinal cortex and hippocampal neurodegenerative changes are, we examined biological markers of disease pathogenesis and regional distribution of small vessel cerebrovascular disease, operationally defined as WMH volume. Our findings show that when included together, Aβ1–42, but not p-tau, was associated with entorhinal cortex volume and hippocampal volume. We also showed that temporal lobe WMH was associated with smaller entorhinal cortex volume. When all factors were considered simultaneously, temporal lobe WMH was independently associated with entorhinal cortex volume, more so than $A\beta_{1-42}$ and p-tau. The findings remained unchanged when we restricted the sample to only those MCI patients who later progressed to clinical AD in subsequent follow-up visits. These findings highlight the important role of small vessel cerebrovascular disease in the pathogenesis of AD.

Our findings add to a consistently growing body of literature linking WMH burden to AD pathogenesis. White matter hyperintensity severity predicts future AD incidence (13) and course of cognitive decline among individuals with AD (14). A facile critique of the extant literature is that samples under study had “mixed” dementia, with both vascular factors and AD pathology playing a role due to insufficient medical screening of vascular factors. In ADNI, however, all participants are screened conservatively for vascular histories and current vascular disease and participants included represent the “cleanest” medical profile without significant comorbidity, similar to those included in randomized treatment trials. Indeed, in ADNI, it appears that WMH severity is at least as relevant to medial temporal lobe atrophy as primary AD pathology.

Evidence of the importance of cerebrovascular disease in AD pathogenesis and MCI also comes from well-designed clinical-pathological studies. Schneider and colleagues found that nearly half of individuals meeting clinical criteria for AD who came to autopsy had mixed pathology that included, in addition to classical AD features, either cerebrovascular disease or Lewy bodies (29). They also showed that while AD pathology is the most common feature of individuals meeting clinical criteria for MCI, mixed pathologies are common and significantly increase the probability of MCI. Regarding MCI, the proportion of pure AD pathology was comparable among individuals with amnestic MCI *versus* individuals with non-amnestic MCI (29), suggesting that current strategies to characterize MCI may not capture the underlying neuropathology with adequate specificity. In a more recent study (30), algorithmic analysis of postmortem tissue revealed distinct subtypes of neuropathologically-defined AD, including one that had hippocampal sparing, one that showed typical AD pathological features, and one that had predominantly limbic involvement. Frank vascular lesions were more prevalent among those with typical AD (28%) and limbic-predominant AD (36%) than those with hippocampal sparing (16%), again suggesting that the pathology underlying the clinical syndrome of AD can be quite heterogeneous with prominent cerebrovascular involvement. We treated individual differences in entorhinal cortex or hippocampus volume as proximal markers of AD pathology (1), but the possibility that a small subset of individuals with AD have hippocampal sparing and that MCI as a diagnostic category itself can be quite heterogeneous suggests that medial temporal lobe volumetry in this population may lack diagnostic specificity.

We focused on the diagnostic category of MCI because it is enriched with individuals with incipient AD. It is important to point out that MCI as a diagnosis is a heterogeneous category and a proportion of individuals with MCI may never progress to AD. For that reason, we restricted our analyses to individuals who progressed to AD on subsequent clinical follow-up visits. The analyses revealed the same results: regional WMH volume was even more strongly associated with entorhinal cortex volume and CSF biomarkers of AD pathology were not. We examined the regional distribution of WMH as opposed to a global index because of recent evidence from our group that WMH distributed in posterior brain regions are associated with increased risk of future development of AD (13). In that study, we found that increased WMH volume specifically distributed in parietal regions predicted which non-demented individuals would progress to AD over time. Similarly, other studies have shown a greater posterior distribution of WMH among patients with MCI and AD relative to controls (12). In the current study, however, our findings pointed to WMH in the temporal lobes as related to ADassociated neurodegenerative changes. The reason for a lack of consistency in ADNI with previous studies is unclear. We have postulated that posterior distribution of WMH in the context of AD may be mechanistically related to AD pathology itself via the shared association with vascular deposition of amyloid (i.e., cerebral amyloid angiopathy) (10). As participants in ADNI are very well screened for medical comorbidities, the restricted association of temporal lobe WMH with medial temporal lobe atrophy may reflect Wallerian-type changes secondary to neurodegeneration. Another possibility is that measurements of WMH in temporal lobe and volumetric measures of medial temporal lobe structures are not independent of each other, which may create significant relationships due to measurement bias. In any event, welldesigned pathological correlation studies need to be carried out to understand the underlying neurobiology of regionally-distributed WMH and its relation to AD pathology.

The finding that higher CSF $A\beta_{1-42}$ levels were associated with larger entorhinal cortex and hippocampus volumes is somewhat consistent with previous findings. For example, Herukka and colleagues showed that $A\beta_{1-42}$ levels were associated with hippocampal volume among patients with MCI that progress to dementia (31). Desikan and colleagues showed a

relationship between $A\beta_{1-42}$ levels and entorhinal cortex volume among non-demented individuals with elevated tau levels (32). Similar results have also been observed in studies that have examined the association between amyloid binding on PET and hippocampal volume (33). Surprisingly, however, we did not find a statistically reliable association between CSF p-tau levels and entorhinal cortex volume. Although atrophic changes are thought to be most related to tau pathology (1), findings have been somewhat inconsistent in the literature, with some groups showing an association between tau and brain atrophy (34–37) and others showing no or modest associations in non-demented samples (38, 39). Nonetheless, that well-defined medial temporal lobe atrophy was not associated with p-tau levels among MCI patients in ADNI raises some question about the sequence of biological events that ultimately lead to the dementia syndrome. We chose to examine total p-tau levels, as CSF-derived phosphorylated tau appears to be related specifically to neurofibrillary pathology in AD (40). The classification accuracy of the MCI diagnosis itself may also contribute to negative observations. Although individuals meeting criteria for MCI have been shown to be at high risk for future conversion to AD, diagnostic procedures for MCI such as the ones used in ADNI are not as valid as those that incorporate comprehensive neuropsychological evaluation with objective neuropsychological criteria (41). As noted, however, our findings remained even when limiting MCI participants to those who met clinical criteria for AD at subsequent visits.

Future work should consider the longitudinal progression of white matter abnormalities in the context of longitudinal changes in more traditional AD biological markers. These initial crosssectional observations are consistent with previous work and provide preliminary evidence that even in well-screened, medically-healthy older adults, WMH relate to pathogenic markers of AD. The question of whether regionally distributed WMH share pathological features with AD (e.g., through amyloid angiopathy) or whether they reflect other pathologies, providing an additional “second hit” needs to be followed-up with postmortem work.

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Research in Context

The “systematic review” subheading should describe the process the authors used to search, identify, and evaluate the accumulated knowledge related to their scientific question. (2) The “interpretation” subheading will require authors to declare what their findings contribute to the knowledgebase related to their question of interest. (3) The “future directions” subheading will challenge authors to state specifically the important scientific question or questions that are necessary to expand, confirm, or refute the author's findings in future research activities.

Systematic review. Current hypothetical models of Alzheimer’s disease (AD) pathogenesis emphasize the role of beta amyloid, tau deposition, and neurodegenerative changes in the mesial temporal lobe, particularly entorhinal cortex and hippocampus. However, many individuals with clinical AD who come to autopsy also exhibit cerebrovascular disease. The relationship between AD and vascular pathology is unclear. We used data from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) to 1) confirm whether entorhinal cortex and hippocampal volume is associated with memory among individuals with amnestic mild cognitive impairment (MCI) who are at risk for AD; and 2) determine whether regional white matter hyperintensity (WMH) volume, a radiological marker of small vessel cerebrovascular disease, is associated with entorhinal cortex and hippocampal volume independent of putative AD biomarkers in this group. We reviewed the extant literature (via bibliographic search in PubMed) and drew from our previous research on this topic to evaluate the accumulated knowledge related to this research.

Interpretation. Our findings suggest that WMH contribute neurodegenerative changes associated with AD.

Future directions. Future research should consider the longitudinal progression of white matter abnormalities in the context of longitudinal changes in more traditional AD biological markers. Future work should also examine the pathological correlates of regionally distributed WMH.

Table 1

Subject characteristics.

Variable	
N	199
Age (mean years ± SD)	74.50 ± 7.55
Education (mean years ± SD)	15.81 ± 2.99
% women	33.2
MMSE (mean score ± SD)	26.93 ± 1.79
% with CDR=0.5	100
Mean ± SD number of words recalled on delayed free recall trial of RAVLT	9.61±3.55
Total cranial volume (mean mm^3 ± SD)	1584797.84 ± 170375.88
$A\beta_{1-42}$ (mean ± SD)	163.52 ± 53.63
p-tau (mean ± SD)	35.41 ± 17.99
Entorhinal cortex volume (mean mm^3 ± SD)	1665.52 ± 377.98
Hippocampus volume (mean mm^3 ± SD)	3151.52 ± 537.69
Frontal lobe WMH volume (mean cm^3 ± SD)	0.37 ± 1.740
Temporal lobe WMH volume (mean cm^3 ± SD)	0.10 ± 0.19
Parietal lobe WMH volume (mean cm^3 ± SD)	0.28 ± 0.80
Occipital lobe WMH volume (mean cm^3 ± SD)	0.18 ± 0.30

Table 2

Results of the three primary regression analyses for entorhinal cortex volume and hippocampus volume. Model 1 includes AD-related biological markers as primary predictors and cranial volume, age, and sex as additional covariates. Model 2 includes the regional WMH volumes as predictors along with the same covariates. Model 3 includes all predictors and covariates together. Model 4 is the same as Model 3 but is restricted to the 86 MCI patients who progressed to AD during the subsequent follow-up visits. For Model 4, number of months to "conversion" was included as an additional covariate. Values are standardized beta (p-value)

Dependent Variable	Predictors	Model 1	Model 2	Model 3	Model 4
Entorhinal cortex volume	$A\beta_{1-42}$	**0.193 (0.014)**	--	0.148 (0.058)	−0.071 (0.545)
	p-tau	−0.015 (0.847)	--	−0.030 (0.699)	0.074 (0.534)
	Total cranial volume	**0.215 (0.015)**	**0.276 (0.02)**	**0.258 (0.005)**	**0.397 (0.014)**
	Age	**−0.163 (0.021)**	−0.101 (0.166)	−0.112 (0.123)	−0.008 (0.947)
	Sex (1=female, 2=male)	−0.116 (0.192)	−0.110 (0.213)	−0.101 (0.252)	0.038 (0.799)
	Frontal WMH	--	0.090 (0.402)	0.079 (0.455)	0.162 (0.317)
	Temporal WMH	--	**−0.267 (0.035)**	**−0.248 (0.048)**	**−0.484 (0.015)**
	Parietal WMH	--	0.070 (0.594)	0.057 (0.662)	0.224 (0.241)
	Occipital WMH	--	−0.102 (0.371)	−0.078 (0.498)	0.091 (0.617)
	Months to conversion	--	--	--	0.056 (0.605)
Hippocampus volume	$A\beta_{1-42}$	**0.145 (0.046)**	--	0.118 (0.110)	−0.155 (0.129)
	p-tau	−0.038 (0.604)	--	−0.048 (0.512)	0.082 (0.432)
	Total cranial volume	**0.318 (<0.001)**	**0.351 (<0.001)**	**0.351 (<0.001)**	**0.618 (<0.001)**
	Age	**−0.369 (<0.001)**	**−0.319 (<0.001)**	**−0.330 (<0.001)**	−0.172 (0.102)
	Sex (1=female, 2=male)	−0.006 (0.944)	−0.028 (0.740)	−0.006 (0.944)	0.107 (0.408)
	Frontal WMH	--	0.010 (0.921)	−0.005 (0.956)	0.080 (0.567)
	Temporal WMH	--	−0.178 (0.135)	−0.148 (0.209)	−0.334 (0.051)
	Parietal WMH	--	0.047 (0.700)	0.053 (0.665)	0.131 (0.427)

Dependent Variable	Predictors	Model 1	Model 2	Model 3	Model 4
	Occipital WMH	--	−0.049 (0.649)	−0.047 (0.661)	0.048 (0.760)
	Months to conversion	--	--	--	0.166 (0.077)