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Amyloid burden, cortical thickness, and cognitive function in the Wisconsin Registry for Alzheimer's Prevention

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Abstract There is a growing interest in understanding how amyloid β (Aβ) accumulation in preclinical Alzheimer's disease relates to brain morphometric measures and cognition. Existing investigations in this area have been primarily conducted in older cognitively normal (CN) individuals. Therefore, not much is known about the associations between Aβ burden, cortical thickness, and cognition in midlife. We examined this question in 109, CN, late to middle-aged adults (mean age = 60.72 ± 5.65 years) from the Wisconsin Registry for Alzheimer's Prevention. They underwent Pittsburgh Compound B (PiB) and anatomical magnetic resonance (MR) imaging, and a comprehensive cognitive examination. Blinded visual rating of the PiB scans was used to classify the participants as Aβ+ or Aβ−. Cortical thickness measurements were derived from the MR images. The Aβ+ group exhibited significant thinning of the entorhinal cortex and accelerated age-associated thinning of the parahippocampal gyrus compared with the Aβ− group. The Aβ+ group also had numerically lower, but nonsignificant, test scores on all cognitive measures, and significantly faster age-associated cognitive decline on measures of Speed & Flexibility, Verbal Ability, and Visuospatial Ability. Our findings suggest that early Aβ aggregation is associated with deleterious changes in brain structure and cognitive function, even in midlife, and that the temporal lag between Aβ deposition and the inception of neurodegenerative/cognitive changes might be narrower than currently thought.

Keywords: Preclinical AD; Amyloid; Cortical thickness; Cognition

1. Introduction

Recent research has indicated the existence of a preclinical stage of Alzheimer's disease (AD) during which pathological changes gradually accumulated in the absence of detectable cognitive symptoms [1]. Converging evidence suggests that one of the earliest brain changes seen during this preclinical stage is an increase in brain amyloid β (Aβ) deposition [1–3]. This Aβ deposition begins several years before the onset of symptoms and continues to increase as the disease progresses before it approaches a

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plateau approximately at the inception of clinical symptoms [1,4–6].

Another observable feature of the preclinical stage of AD is an alteration in brain structure that, among other neurodegenerative effects, leads to reduced cortical thickness [7]. Automated measurement of cortical thickness from anatomical magnetic resonance imaging (MRI) scans is possible with the use of computer-aided techniques [8,9]. Recently, studies have explored the connection between Aβ deposition and cortical thickness in preclinical AD using positron emission tomography (PET) tracers for Aβ, such as Pittsburgh Compound B (PiB). For example, in a study of older cognitively normal (CN) individuals, Becker and colleagues [10] found that Aβ deposition is associated with regional cortical thinning especially in posteromedial and lateral parietal structures. Similarly, Doré and colleagues [11] found that an increase in Aβ accumulation was associated with decreased cortical thickness in the posterior cingulate, precuneus, and hippocampus among CN individuals. Other studies using cerebrospinal fluid (CSF) biomarkers for Aβ have found similar associations between Aβ aggregation and structural brain changes in AD-susceptible regions [12]. Relatedly, although AD is characterized by a decline in cognition [1], the extent to which Aβ accumulation correlates with cognition among CN individuals is yet to be fully elucidated. Some investigations into the effect of Aβ on cognition among CN individuals find no associations [13–15], whereas others do reveal associations, largely in the domain of episodic memory [16,17].

Most of the research on Aβ-related cortical thinning and cognitive dysfunction has focused on older CN individuals. Therefore, the manner and extent to which Aβ deposition affects brain structure and cognition in midlife remains relatively unexplored. This is an important knowledge gap because midlife is arguably when AD-related markers of Aβ, brain structure, and cognition are starting to be dynamic.

Table 1
Characteristics of study participants*

Variable	Aβ−, n = 74	Aβ+, n = 35	*P* value
FH positive, %	70.3	82.9	.160
APOE ε4 positive, %	35.1	54.3	.058
Non-Hispanic white, %	95.8	94.3	.722
Female, %	55.4	77.1	.029
Age	59.51 (5.82)	63.27 (4.35)	<.001
Education	15.89 (2.37)	16.57 (2.34)	.164
MMSE	29.15 (1.05)	29.17 (1.34)	.945
IQCODE	46.59 (6.28)	47.66 (5.86)	.405
Interval between brain scan and cognitive assessment, months	6.58 (6.03)	6.64 (5.92)	.961

Abbreviations: Aβ, amyloid β; FH, family history of Alzheimer's disease; *APOE* ε4, the ε4 allele of the apolipoprotein E gene; MMSE, Mini-Mental State Examination; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly.

*All values are mean (standard deviation) except where otherwise indicated.

Accordingly, in this study we sought to determine how Aβ accumulation relates to cognitive function and structural changes in AD-relevant brain regions among late to middle-aged adults at risk for AD. We investigated both the main effect of Aβ burden and its potential acceleration of normal age-associated alterations in our brain and cognitive outcome measures.

2. Materials and methods

2.1. Participants

Participants were recruited from the Wisconsin Registry for Alzheimer's Prevention (WRAP) cohort into this neuroimaging study. The WRAP is a longitudinal registry of approximately 1500 late to middle-aged adults who were cognitively healthy and between the ages 40 and 65 years at study entry [18]. One hundred and nine consecutive participants were selected based on Aβ− or Aβ+ rating in their PiB-PET scan (see section 2.2.2) and also having a usable MRI scan. They constitute a subset of the individuals described in an earlier report from our group [19]. Mean age of the sample at time of brain scan was 60.72 ± 5.65 and 62.4% were female. The sample was enriched with persons with a parental family history (FH) of AD (74.3%) and those positive for the apolipoprotein E ε4 allele (*APOE* ε4) (41.3%). The method for determining FH of AD has been described previously [18]. Study exclusion criteria included MRI contraindications, major neurological disorder (e.g., head trauma with loss of consciousness, neoplasms, and seizure disorders), current major psychiatric disease (e.g., schizophrenia), and abnormal MRI findings (e.g., ventriculomegaly). Table 1 summarizes participants' background characteristics. The University of Wisconsin Institutional Review board approved all study procedures and each subject provided signed informed consent before participation.

2.2. Neuroimaging protocol

2.2.1. PET-PiB protocol

PiB data were acquired with a 70-minute dynamic acquisition followed by reconstruction using a filtered back-projection algorithm. Data were corrected for random events, attenuation of annihilation radiation, dead time, scanner normalization, and scatter radiation, then realigned and coregistered using SPM 8 (www.fil.ion.ucl.ac.uk/spm). Finally, the images were transformed into voxel-wise distribution volume ratio (DVR) maps of PiB binding using the time activity curve of cerebellar gray matter (GM) as the reference region. More detailed descriptions of PiB radiochemical synthesis, PiB-PET scanning, and DVR map generation may be found in a previous publication [19].

2.2.2. Qualitative PiB rating

To enhance the potential clinical applicability and allow for the possibility of regional heterogeneity in Aβ deposition

within this age range when Aβ burden may only be emerging, a qualitative approach was adopted for ascertaining cerebral amyloidosis. Specifically, after achieving high inter- and intrareliability between two raters on a subset of PiB images (blinded to all pertinent subject characteristics such as age, sex, FH, *APOE* ε4 status, and cognitive function), a similarly blinded single rater visually rated all DVR maps on the intensity and pattern of cortical amyloid binding as described previously [19]. Of the 109 subjects who provided data for our analyses, 74 were classified as amyloid negative (Aβ−) and 35 were classified as amyloid positive (Aβ+). An Aβ− rating was given when the scan demonstrates no cortical amyloid burden or only nonsignificant patchy/diffuse cortical GM binding not resembling an AD pattern. In contrast, an Aβ+ classification indicated that there was unambiguous GM amyloid binding in at least three cortical lobes resembling an AD disease pattern.

For descriptive purposes (and to perhaps provide some basis for comparison with studies that use quantitative cutpoints for Aβ positivity) we fitted a receiver operating characteristic (ROC) curve with DVR data sampled bilaterally from the precuneus—a known inception site for Aβ aggregation [1,20]—as the predictor and Aβ rating as the outcome. This analysis revealed an area under the ROC curve (95% confidence interval) of 0.993 (0.979, 1.00) for discriminating Aβ− and Aβ+ participants. A DVR cutpoint of 1.10 yielded a sensitivity of 0.971 and a specificity of 0.973 for distinguishing both groups.

2.2.3. MRI protocol

The MRI scans were acquired in the axial plane on a GE × 750 3.0 T scanner with an eight channel phased array head coil (General Electric, Waukesha, WI). Three-dimensional T1-weighted inversion recovery-prepared SPGR (spoiled gradient) scans were collected using the following parameters: inversion time/echo time/repetition time = 450 ms/3.2 ms/8.2 ms, flip angle = 12°, slice thickness = 1 mm no gap, field of view = 256, matrix size = 256 × 256 × 156.

2.2.4. Automated MRI image analysis

Thickness of cortical structures and volume of subcortical structures were obtained for select regions of interest (ROIs) using the FreeSurfer image analysis suite version 5.1.0 (http://surfer.nmr.mgh.harvard.edu/) [8,9]. Briefly, the T1 MRI images were skull stripped and transformed into Talairach space. Then, using a standard atlas, the images are segmented, and volumes of subcortical regions, e.g., the hippocampus and amygdala, were obtained via this segmentation. Next, cortical surface meshes were created, defined as the gray/white matter boundary (the white matter surface) and the gray/CSF boundary (the pial surface). After topology correction and deformation of the surface meshes, the surfaces were parcellated based on a template atlas. Cortical thickness measurements were obtained by calculating the distance along a normal vector from each vertex in the white matter surface to the pial surface. The thickness values at each vertex within an ROI were averaged to obtain the ROI measurements. We focused on eight medial temporal and posteromedial cortex ROIs in this study. These ROIs were chosen because of their involvement in the AD cascade. Cortical thickness measurements were obtained from the entorhinal cortex, parahippocampal gyrus, fusiform gyrus, cingulate isthmus, posterior cingulate, and the precuneus, whereas volumetric measurements were obtained from the hippocampus and amygdala. Measurements were averaged across hemispheres to obtain a single value for each ROI.

Although the FreeSurfer automated procedure is 100% reproducible, user inspection and iterative control point editing are often required for maximal performance accuracy, and thus was implemented in this study to ensure proper cortical reconstruction. In our hands, intra- and interrater reliability is excellent (intraclass correlation coefficient > 0.99), based on a training sample of 10 brains of varying age and scan quality, rated by three technicians twice in blind fashion.

2.3. Neuropsychological assessment

All 109 participants completed a comprehensive neuropsychological battery [18] that included the Mini-Mental State Examination and other psychometric measures that span traditional cognitive domains of memory, attention, executive function, language, and visuospatial ability. Earlier factor analytic studies of the psychometric measures within the larger WRAP cohort [21,22] showed that these tests map onto six cognitive factors: Immediate Memory, Verbal Learning & Memory, Working Memory, Speed & Flexibility, Visuospatial Ability, and Verbal Ability. The individual tests which loaded onto these factors were as follows: Immediate Memory: Rey auditory verbal learning test (RAVLT) Trials 1 and 2 [23]; Verbal Learning & Memory: RAVLT Trials 3 to 5 and Delayed Recall Trial [23]; Working Memory: Digit Span and Letter-Numbering Sequencing subtests from the Wechsler Adult Intelligence Scale—3rd edition [24]; Speed & Flexibility: Stroop Test interference trial [25], and Trail Making Test A and B [26]; Visuospatial Ability: Block Design and Matrix Reasoning subtests from the Wechsler Abbreviated Scale of Intelligence (WASI) [27] and Benton Judgment of Line Orientation [28]; Verbal Ability: Vocabulary and Similarities subtests from the WASI [27], Boston Naming Test [29], and Reading subtest from the Wide-Range Achievement Test, 3rd edition [30]. These factor scores were used in our evaluation of the association between Aβ retention and cognition in this study. The mean interval between brain scan and neuropsychological assessment was 6.60 ± 5.97 months.

2.4. Statistical analyses

Group differences on background characteristics were analyzed using either t-tests or chi-square tests as

appropriate. We used age- and sex-adjusted analyses of covariance (ANCOVAs) to investigate the main effect of amyloid burden (Aβ+ vs. Aβ−) on ROI measures of brain structure. For the hippocampus and amygdala, an additional adjustment was made for intracranial volume. To investigate whether Aβ induces an acceleration of age-associated structural brain changes, we fitted a series of multiple regression models that controlled for age and sex, while testing for interactions between age and Aβ rating. Where significant, these interactions would indicate a differential effect of aging on brain structure among Aβ+ subjects compared with Aβ− subjects.

Analyses of the relationship between amyloid burden and cognitive function were conducted in the same manner as those for brain structure. That is, age-, sex-, and education-adjusted ANCOVAs were used to investigate the main effect of amyloid burden (i.e., Aβ+ vs. Aβ−) on the cognitive factors, whereas age-, sex-, and education-adjusted multiple regression models, that included age*Aβ rating interactions, were used to investigate whether age-related cognitive decline is more pronounced among Aβ+ individuals. All analyses were performed using SPSS 21.0 (IBM Corp., Armonk, NY), and only findings that met an alpha threshold of 0.05 (two-tailed) were deemed significant.

3. Results

3.1. Subject characteristics

The Aβ− and Aβ+ groups differed in age and sex, and these variables were included as covariates in our analyses. As expected, there was a tendency for *APOE* ε4+ persons to be disproportionally represented within the Aβ+ group, although this was nonsignificant. The groups did not differ in any other background characteristics, including the time interval between brain and cognitive assessment. These findings are shown in Table 1.

3.2. Aβ and brain structure

Table 2 summarizes our analyses of the main effect of Aβ burden on brain structure. The Aβ+ group exhibited significant cortical thinning in the entorhinal cortex compared with the Aβ− group. There were no group differences in any other ROIs examined.

Table 2
Main effect of Aβ on brain structure*,†

Region	Aβ−, n = 74	Aβ+, n = 35	*P* value
Entorhinal	3.47 (0.03)	3.32 (0.05)	.017
Parahippocampal	2.65 (0.03)	2.71 (0.04)	.266
Fusiform	2.62 (0.02)	2.62 (0.02)	.988
Cingulate isthmus	2.49 (0.02)	2.51 (0.03)	.615
Posterior cingulate	2.63 (0.02)	2.58 (0.03)	.175
Precuneus	2.41 (0.01)	2.37 (0.02)	.128
Hippocampus	3955.33 (44.74)	3871.82 (66.03)	.315
Amygdala	1649.71 (25.20)	1596.95 (37.19)	.260

Abbreviation: Aβ, amyloid β.
*All values are estimated mean (standard error), adjusted for age and sex.
†All values are thicknesses (in mm) except for hippocampus and amygdala, which are volumes in mm^3.

As a secondary analysis, we examined whether local amyloid burden is correlated with colocalized measures of brain structure using Pearson correlations. For this, FreeSurfer was used to extract mean PiB retention values within each of the eight ROIs by coregistering each participant's DVR image to their FreeSurfer-rendered T1 volume, and then using FreeSurfer's automatic cortical parcellation (APARC) + automatic segmentation (ASEG) template as a mask for extracting mean PiB values in the ROIs. Correlations were conducted using bilateral measures obtained by averaging ROI values across hemispheres. Consistent with the group analyses shown in Table 2, we found that higher entorhinal cortex Aβ accumulation was correlated with decreased entorhinal cortical thickness ($r(107) = -0.22$, $P = .020$). We also found a significant association between increased amygdala Aβ burden and decreased amygdala volume ($r(107) = -0.23$, $P = .016$). Although the remaining correlations were all in the expected negative direction (i.e., higher Aβ being associated with reduced thickness/volume), they failed to meet our threshold for statistical significance (*P*s >.1). These results are plotted in Fig. 1.

Our analyses of the impact of Aβ burden on age-related structural changes revealed a trend for the Aβ+ group to have more pronounced age-associated thinning of the parahippocampal gyrus compared with the Aβ− group (age*Aβ rating $P = .059$). Although none of the other ROIs were significant (age*Aβ rating *P*s >.1), the beta coefficient for the age*Aβ rating term was negative in virtually all analyses, indicating a similar acceleration of age-associated thinning within the Aβ+ group. These findings are plotted in Fig. 2.

3.3. Aβ and cognition

Results of the main effect of Aβ on cognition are summarized in Table 3. The Aβ+ group exhibited numerically lower scores on all six cognitive factors relative to the Aβ− group. However, these differences did not meet our criterion for statistical significance (*P*s >.1). With respect to the Aβ-induced acceleration of age-related cognitive decline, we found that Aβ+ participants demonstrated significantly greater age-associated cognitive decline on Speed & Flexibility (age*Aβ rating $P = .034$), and also showed trends for a faster rate of age-associated cognitive decline on Verbal Ability and Visuospatial Ability (age*Aβ rating *P*s =.058 and .089, respectively). These results are shown in Fig. 3.

4. Discussion

In this study, we examined the relationship between Aβ burden, structural brain changes, and cognitive function among CN, late to middle-aged adults at risk for AD. We found that global Aβ burden was associated with cortical

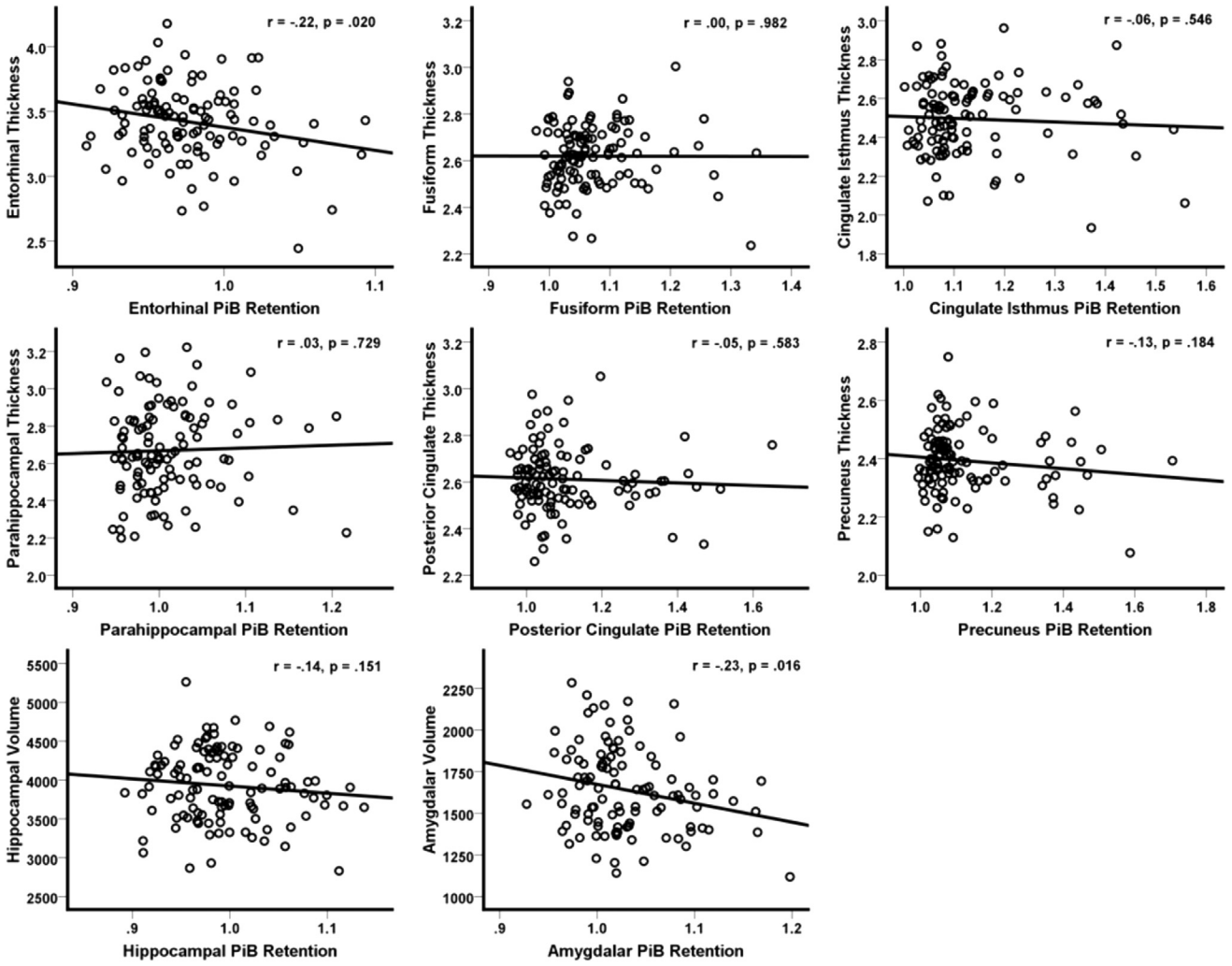

Fig. 1. Correlations between amyloid beta (Aβ) burden and colocalized magnetic resonance imaging (MRI) measures. The plots depict correlations between regional cortical thickness and Pittsburgh Compound B (PiB) binding extracted from the same brain region.

thinning in the entorhinal cortex. Thickness of the entorhinal cortex was also negatively correlated with colocalized PiB retention, further strengthening the evidence for the impact of Aβ burden on the structural integrity of the entorhinal cortex. In addition to this main effect of Aβ accumulation on brain structure, we also observed an Aβ-induced acceleration of age-related structural change, especially within the parahippocampal gyrus. Although Aβ accumulation did not exert a similar main effect on cognition as it did on brain structure within this overall CN cohort, we found evidence that it was associated with faster age-related decline in cognitive performance, particularly in the domain of Speed & Flexibility.

The observed Aβ-induced alteration in the entorhinal cortex—detected in both global Aβ analyses and colocalized PiB/MRI analyses—is consistent with other studies revealing the loss of cortical mass in the entorhinal region, as a result of amyloid aggregation in the elderly [11,31]. The entorhinal cortex, which is a key afferent to the hippocampus, has been evidenced as a crucial center of AD pathology and one of the earliest areas to demonstrate degeneration [32]. Furthermore, volume of the entorhinal cortex is a reliable indicator of future decline from mild cognitive impairment to AD [33,34] and, when tested in CN samples, is able to better predict future cognitive decline than structural changes in other medial temporal regions, including the hippocampus [34,35].

Our correlational analyses of colocalized Aβ accumulation and brain structure also elicited an association between increased amyloid and decreased amygdala volume, which was not evident in our group analyses. The amygdala is a mesial temporal structure observed to decrease in mass early in disease progression, and further exhibits a prominent volumetric decrease during the latter stages of AD [36]. Amygdala volume is a viable predictor of both future decline and the severity of decline in early and mild AD, and may be a better predictor than volume of the hippocampus [36–41]. In studies of AD individuals, the amygdala has been found to correlate with performance in the domains of memory, orientation, and recall [38,39]. Similar results have been

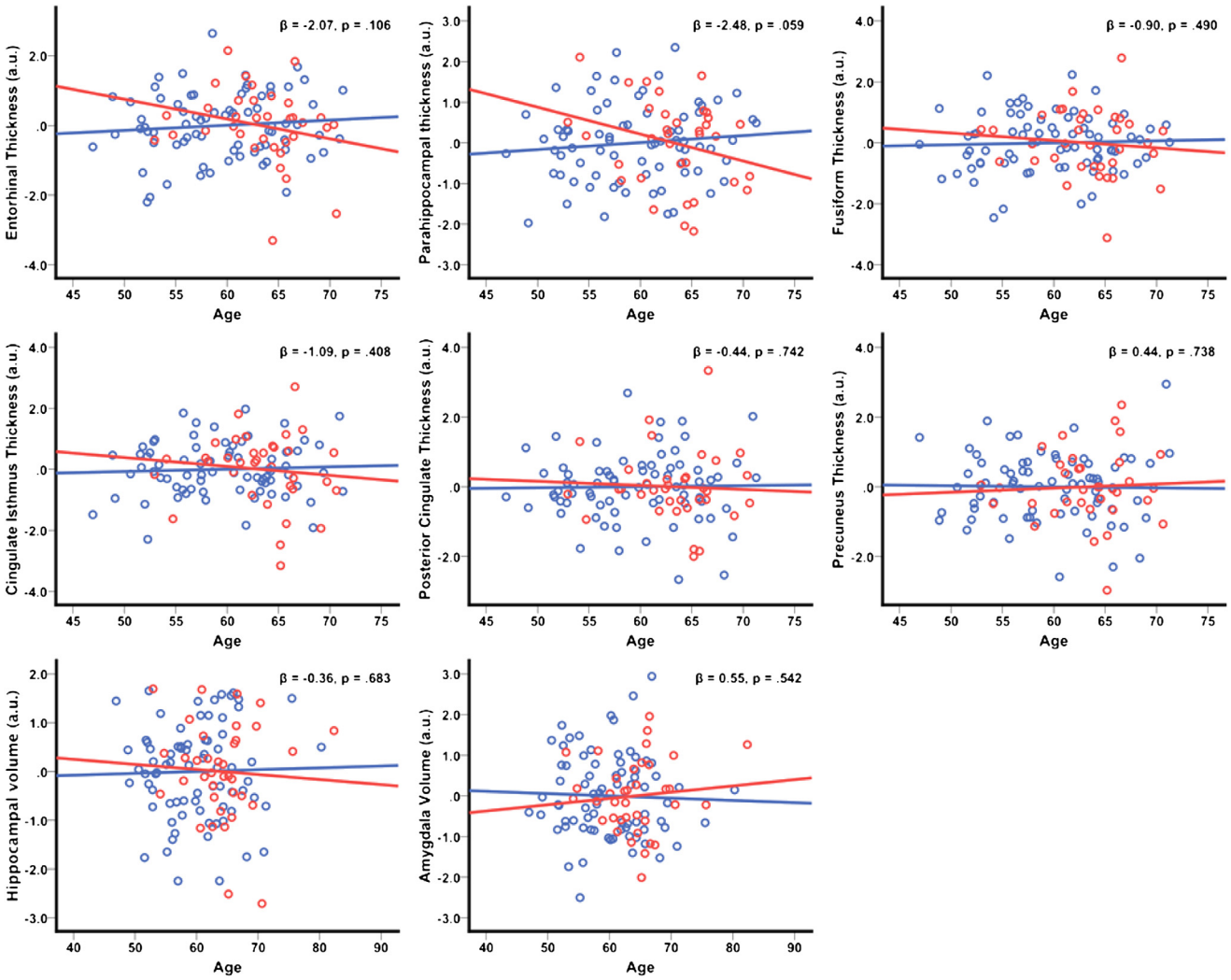

Fig. 2. Amyloid beta (Aβ) burden accelerates age-related brain structural changes. The plots depict predicted values derived from the regression equation (circles), with the line of best linear fit overlaid. Red circles/line = Aβ+ group, blue circles/line = Aβ− group.

found in studies of CN individuals [42], with decreased amygdala volume consistently associated with more advanced cognitive decline. It is noteworthy that, although statistical significance in tests of the effect of colocalized Aβ on brain structure was only reached for the entorhinal cortex and amygdala, a general trend for increased Aβ to track with decreased brain structural integrity was observable across all the ROIs examined. This suggests a rather pervasive effect of Aβ burden on brain morphometry, although this interpretation needs to be made with caution given the rather modest magnitude of the observed correlations.

Table 3
Main effect of Aβ on cognition*

Cognitive domain	Aβ−, n = 74	Aβ+, n = 35	*P* value
Verbal Ability	0.15 (0.11)	−0.05 (0.16)	.330
Visuospatial Ability	0.35 (0.11)	0.11 (0.16)	.229
Speed & Flexibility	0.07 (0.09)	−0.16 (0.14)	.193
Working Memory	0.17 (0.14)	−0.11 (0.21)	.282
Verbal Learning & Memory	−0.15 (.12)	−0.17 (0.18)	.938
Immediate Memory	−0.14 (0.12)	−0.17 (0.19)	.905

Abbreviation: Aβ, amyloid β.
*All values are estimated mean (standard error), adjusted for age, sex, and education.

Our findings also suggest that Aβ may accelerate the age-related loss of brain tissue in the parahippocampal gyrus. This is interesting because the parahippocampal gyrus encompasses the entorhinal cortex and, like the entorhinal cortex, is an early induction site for AD-related neurodegeneration [43]. Thus, our findings with respect to Aβ's main effect on cortical thickness and its acceleration of age-related cortical thinning are quite convergent, jointly corroborating prior neuropathological studies that have shown the parahippocampal-entorhinal strip to be highly susceptible to the AD degenerative cascade [32,43–46]. Similar to our colocalized PiB/MRI analyses, although only the parahippocampal gyrus neared statistical significance in

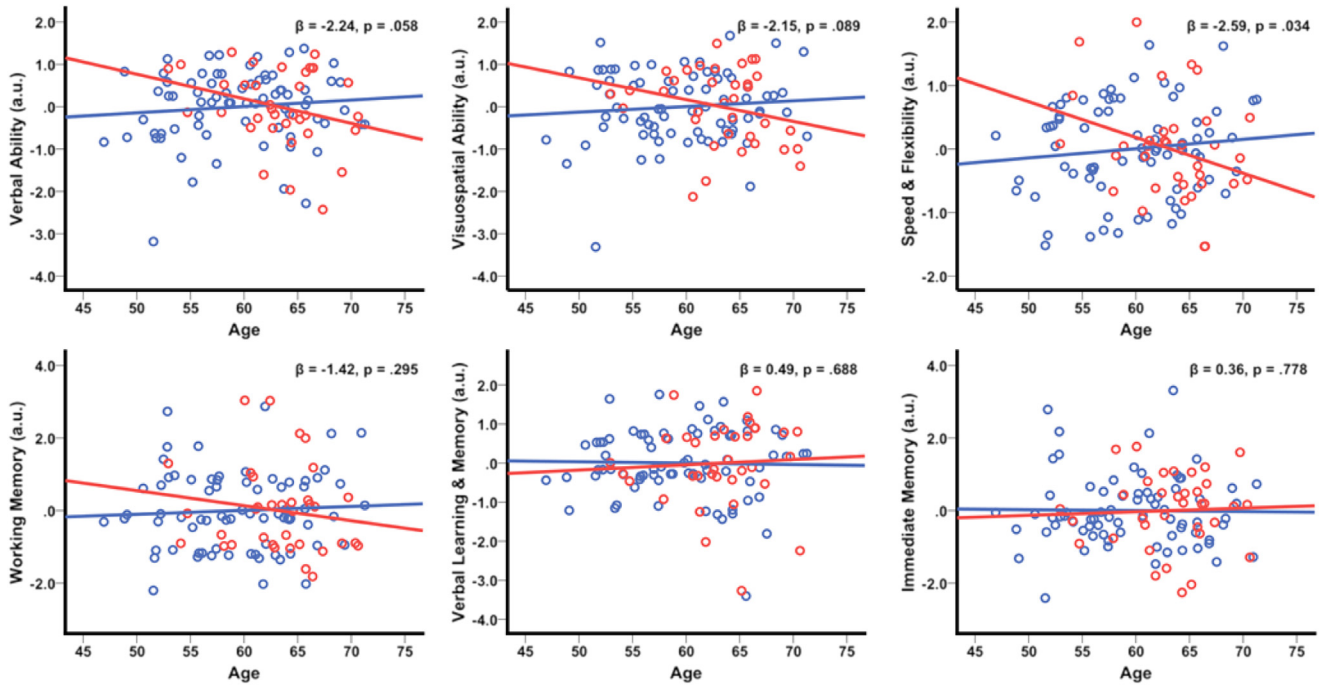

Fig. 3. Amyloid beta (Aβ) burden accelerates age-related cognitive decline. The plots depict predicted values derived from the regression equation (circles), with the line of best linear fit overlaid. Red circles/line = Aβ+ group, blue circles/line = Aβ− group.

our analysis of the potential Aβ-induced acceleration of age-related cortical thinning, there was a general tendency for increased Aβ to be associated with faster age-related cortical thinning across the other ROIs examined. This supports the notion that even ostensibly mild Aβ aggregation might not be innocuous, perhaps becoming more pernicious with the passage of time [47].

Understanding the linkage between Aβ and cognition is of great importance to the study of AD [48]. The evidence for an association between Aβ accumulation and cognition in CN cohorts is, however, mixed. Several cross-sectional studies in CN individuals have found no evidence of a relationship between Aβ accumulation and cognition [13–15], but some do find an association, primarily within the domain of episodic memory [16,17]. A meta-analysis of studies investigating Aβ-cognition effects in CN individuals [49] suggested that although there is a modest association between amyloid accumulation and cognition, effect sizes in areas other than episodic memory and global cognition are small. Chetelat and colleagues [47] suggested that the variations in the observed effect of Aβ on cognition may be due to differences in the underlying characteristics of the study samples, especially in age and *APOE* ε4 status. In the present study, we found that, despite the apparent Aβ-induced degeneration of the entorhinal cortex and amygdala—two structures critical to episodic memory—there were no statistically significant main effect of Aβ on memory or other cognitive functions, although the Aβ+ group consistently exhibited lower cognitive test scores than the Aβ− group. Still, the effects of Aβ on cognition were not inconsequential, as we discovered an enhancing effect of Aβ on age-related cognitive decline, particularly in Speed & Flexibility, which is a cognitive function that is highly vulnerable to aging effects [50]. Fig. 3 demonstrates that, in four of the six cognitive domains tested, Aβ+ individuals exhibit a marked decline in cognitive performance with increasing age, whereas Aβ− individuals do not exhibit such a decline. This acceleration of "normal" age-related changes might represent an important approach to the study of Aβ's effect on cognition, especially in a relatively young cohort that is only starting to accumulate Aβ.

A key limitation of this study is its cross-sectional nature. Although we used statistical tests of interactions between age and Aβ rating to approximate the longitudinal effects of Aβ burden on brain structure and cognition, a truly prospective design with serial imaging and cognitive data would have enabled us to better track the progression of structural and cognitive changes among individuals with versus without Aβ burden. As the WRAP cohort is ongoing, and additional imaging and cognitive data are being collected, we will be uniquely positioned to investigate such questions in the future. Second, we determined cerebral amyloidosis via qualitative ratings. Although this approach has potential clinical value (patients are likely to be more interested in whether their PiB scans are indicative of AD versus whether their PiB binding is 1.2) and has established precedence in the literature (for an excellent review, see Chetelat et al. [47]), there is a possibility that we might have made different observations had we used a quantitative approach such as by averaging PiB uptake in select ROIs. Similarly, although our

use of an ROI approach to investigate the effect of Aβ burden on brain structure made our enquiry focused and hypothesis driven, it may have resulted in a failure to detect findings that were outside the examined ROIs. In addition, although FreeSurfer has been shown to yield segmentations that are reliable and concordant with manual measurements [51], we cannot entirely exclude the possibility that there might have been some variation in its performance across subjects within our sample. Finally, although our analyses overall showed that Aβ has a measurable, detrimental impact on brain structure and cognitive function, many of the tests did not attain statistical significance at the set threshold (i.e., $P = .05$). This might reflect inadequate power on our part to statistically detect these changes that are, arguably, only starting to occur and thus relatively subtle in magnitude. Future studies with larger sample sizes would be helpful in further testing this study's objectives.

In summary, this study found that increased Aβ burden is associated with deleterious changes in brain morphometry and cognition in a late to middle-aged, CN cohort with risk factors for AD. These findings, and those from other groups [7,10,31,34], provide evidence that the temporal window between Aβ deposition and the inception of neurodegenerative changes might be narrower than currently thought [1–3]. Further longitudinal analyses will help us better understand the prognostic value of Aβ deposition within this relatively young and risk-enriched cohort.

RESEARCH IN CONTEXT

1. Systematic review: We searched PubMed using the terms: "amyloid," "amyloid burden," "amyloid deposition," "PiB," "cortical thickness," "brain volume," "brain morphometry," "brain structure," "cognition," "cognitive function," and "Alzheimer's disease" or "dementia."
2. Interpretation: The relationship between amyloid β (Aβ) accumulation and brain morphometric measures/cognition in preclinical Alzheimer's disease (AD) is attracting considerable scientific interest. This study adds to the current knowledge base, by showing that increased Aβ is associated with an acceleration of deleterious age-related changes in brain morphometry and cognition in a middle-aged, asymptomatic cohort at risk for AD. These findings suggest that the temporal lag between Aβ deposition and the initiation of neurodegenerative/cognitive changes might be narrower than currently thought.
3. Future directions: Continued follow-up of our cohort will help us better understand the prognostic value of Aβ deposition within this relatively young and risk-enriched cohort.

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