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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