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Short Reports

Amyloid imaging and cognitive decline in nondemented oldest-old: The 90+ Study

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Abstract

Background: The goal of this study was to examine cross-sectional and longitudinal associations between cognitive performance and beta amyloid (Aβ) load determined by florbetapir F18 positron emission tomography (PET) in nondemented oldest-old.

Methods: Thirteen nondemented (normal or cognitively impaired nondemented) participants (median age, 94.2 years) from The 90+ Study underwent florbetapir-PET scanning within 3 months of baseline neuropsychological testing. Amyloid load was measured with a semi-automated quantitative analysis of average cortical-to-cerebellar standardized uptake value ratio (SUVr) and a visual interpretation (Aβ– or Aβ+). Neuropsychological testing was repeated every 6 months.

Results: At baseline, SUVr correlated significantly with tests of global cognition and memory. During follow-up (median, 1.5 years), the Aβ+ group had steeper declines on most cognitive tests, particularly global cognitive measures.

Conclusion: This preliminary study suggests that greater amyloid load is associated with poorer cognition and faster cognitive decline in nondemented oldest-old. Amyloid load may identify individuals at increased risk of developing Alzheimer's disease.

Keywords: Oldest-old; PET amyloid imaging; Cognitive aging; Cognitive decline; Florbetapir

1. Introduction

The ability to image cerebral beta amyloid (Aβ) deposition during life with positron emission tomography (PET) scanning [1,2] is a major advance in neuroscience and a powerful research tool for the investigation of Alzheimer's disease (AD) and cognition in aging. Previously, studies of amyloid deposits and cognition were dependent on clinical pathological investigations, with a single amyloid measurement performed at the end of life. Recent studies have demonstrated that PET scanning with amyloid-binding ligands correlates with the presence and density of Aβ at autopsy [2]. It has been hypothesized that amyloid deposition is an early event in the pathogenesis of AD, increasing rapidly and reaching a plateau before the appearance of clinical symptoms [3]. In this scenario, normal individuals with amyloid deposition may be at higher risk of developing AD and may be experiencing subtle cognitive decline [3,4].

The oldest-old are the fastest growing segment of the population and have high rates of dementia [5] and cognitive decline. A high proportion of nondemented individuals older than age 90 have significant amyloid deposition on autopsy [6,7]. It is unknown whether these individuals are at higher risk of developing dementia, are experiencing cognitive decline, or perhaps are even protected from the development of clinical AD. We examined the cross-sectional and longitudinal relationship between cognitive performance and amyloid load (florbetapir PET uptake) in 13 nondemented oldest-old individuals.

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2. Methods

Participants were part of The 90+ Study, a longitudinal, population-based investigation of dementia and aging in the oldest-old. Individuals were invited to participate in this imaging study as part of an investigation to examine the relationship between measurements of brain amyloid using florbetapir PET scanning and levels of amyloid burden as measured by postmortem histopathological assessment [2].

To meet inclusion criteria for our study, individuals had to be nondemented: normal or cognitively impaired nondemented (CIND) and agree to postmortem examination. Participants were followed every 6 months with procedures that include the Mini-Mental State Exam (MMSE), Modified MMSE (3MS), Animal Fluency, Boston Naming Test (BNT), and the California Verbal Learning Test (CVLT) short form [8]. At each visit, a trained neurological examiner determined cognitive status (normal, CIND, or dementia). Dementia was diagnosed using the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (DSM-IV) criteria [9]. Participants with either cognitive or functional impairment resulting from cognition not severe enough to meet DSM-IV diagnostic criteria for dementia were classified as CIND [9]. The neurological examiner had access to the 3MS and MMSE, but was blinded to the remainder of the neuropsychological testing.

Each participant underwent a 10-minute PET scan at approximately 50 minutes after injection of 370 MBq of florbetapir F18. A semi-automated quantitative analysis was performed to calculate the standardized uptake value ratio (SUVr) using the mean of six predefined anatomically relevant cortical regions (frontal, temporal, parietal, anterior cingulate, posterior cingulate, and precuneus), relative to entire cerebellum. These SUVr values were used as our primary amyloid load variable for our cross-sectional analyses. Florbetapir-PET images were also assessed visually by three trained nuclear medicine physicians using a semiquantitative score ranging from 0 point (no amyloid) to 4 points (high levels of cortical amyloid). The median of the three visual scores was used to dichotomize participants into Aβ– (score, 0–1 point) and Aβ+ (score, 2–4 points) groups for our longitudinal analyses. All procedures were approved by the University of California at Irvine institutional review board.

2.1. Statistical methods

The visit closest to the PET scan was considered the baseline visit. For our cross-sectional analysis, Pearson correlation coefficients were calculated to assess the correlation between SUVr and neuropsychological scores at baseline. To analyze change in cognitive performance over time in Aβ– and Aβ+ participants, we took two different approaches. First, because of the small number of participants, we took a simple approach and estimated a slope for each participant, with a linear regression of neuropsychological test scores as a function of years from baseline. The average slope was then compared between Aβ– and Aβ+ participants using *t*-tests and Wilcoxon's rank tests. As a second approach, we

Table 1
Characteristics of participants by amyloid load status at baseline: The 90+ Study

	All participants (N = 13)	Aβ– (n = 9)	Aβ+ (n = 4)
Characteristic	Median (range)		
Age at baseline, y	94.1 (90–99)	94.1 (90–99)	94.4 (93–96)
Days between baseline visit and PET scan	42 (8–87)	46 (11–87)	25 (8–66)
Follow-up, y	1.5 (0–1.6)	1.5 (0–1.6)	1.4 (1.1–1.6)
No. of visits	4 (1–4)	4 (1–4)	3.5 (3–4)
Average cortical SUVr	1.1 (0.9–2.1)	1.0 (0.9–1.2)	1.6 (1.3–2.1)
Median visual score of amyloid load	1.0 (0–4)	1.0 (0–1)	3.5 (2–4)
3MS score at baseline	93 (80–99)	94 (90–97)	85 (80–99)
MMSE score at baseline	28 (24–30)	28 (25–30)	26.5 (24–29)
CVLT 10-min delay score at baseline	7 (0–9)	7.5 (5–9)	3.5 (0–8)
Animal fluency at baseline	12 (9–19)	12 (9–19)	12 (9–18)
BNT score at baseline	14 (13–15)	14 (13–15)	14 (13–14)
Gender, n (%)			
Women	9 (69)	7 (78)	2 (50)
Men	4 (31)	2 (22)	2 (50)
Education, n (%)			
≤High school	6 (46)	4 (44)	2 (50)
>High school	7 (54)	5 (56)	2 (50)
Cognitive diagnosis at baseline, n (%)			
Normal	8 (62)	7 (78)	1 (25)
CIND	5 (38)	2 (22)	3 (75)
Demented during follow-up, n (%)	3 (23)	1 (11)	2 (50)

Abbreviations: 3MS, Modified Mini-Mental State Exam; Aβ–, low amyloid load according to median visual score (0–1 point); Aβ+, high amyloid load according to median visual score (2–4 points); BNT, Boston Naming Test; CIND, cognitive impairment no dementia; CVLT, California Verbal Learning Test; MMSE, Mini-Mental State Exam; SUVr, standardized uptake value ratio.