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Cognitive decline and brain volume loss are signatures of cerebral A β deposition identified with PIB

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Abstract

Objective—To examine the relation of amyloid-beta (A β) levels in cerebral cortex with structural brain integrity and cognitive performance in older people with a Clinical Dementia Rating (CDR) of 0 (cognitively normal).

Methods—The relations between mean cortical [¹¹C] PIB binding potential values, proportional to the density of fibrillar A β binding sites in the brain, concurrent regional brain volumes as assessed by magnetic resonance imaging, and both concurrent and longitudinal (up to 19 years) cognitive performance in multiple domains were examined in 135 CDR 0 individuals aged 65 to 88 years.

Results—Elevated cerebral A β levels, in some cases comparable to that seen in individuals with Alzheimer's disease, were observed in 29 CDR 0 individuals. Significantly smaller regional volumes in the hippocampus, temporal neocortex, anterior cingulate, and posterior cingulate were observed in these CDR 0 individuals with elevated A β levels. Concurrent cognitive performance was unrelated to A β levels but was related to regional brain volumes with the exception of caudate. Longitudinal cognitive decline was associated with elevated A β levels and decreased hippocampal volume. Decline was not limited to episodic memory but included working memory and visuospatial abilities as well.

Interpretation—[¹¹C] PIB, an *in vivo* measure of cerebral amyloidosis, is associated with regionally specific brain atrophy cross-sectionally and a pattern of longitudinal cognitive decline in multiple cognitive domains that occurs prior to the clinical diagnosis of Alzheimer's disease. These findings contribute to the understanding of the cognitive and structural consequences of A β levels in CDR 0 older adults.

Keywords

Cognitive decline; cerebral A β ; PIB; brain volumetry; preclinical Alzheimer's disease

Amyloid imaging with positron emission tomography (PET) and the [¹¹C] benzothiazole tracer, Pittsburgh Compound-B (PIB), is a noninvasive method to assess cerebral amyloid-beta (A β) levels in the brains of living people¹ and provides an important new tool in the study of Alzheimer's disease (AD). PIB binds to senile plaques and to amyloid angiopathy in human postmortem specimens,² and PIB uptake corresponds to post-mortem assessment of

parenchymal A β plaques.^{3,4} Previous reports indicate that some unimpaired older adults at death have brain amyloid plaque levels, one of the hallmarks of AD, comparable to those measured in individuals with AD.⁵⁻⁷ Similarly, some unimpaired older people have elevated A β levels as assessed *in vivo* with [¹¹C]PIB.^{8,9}

Although abnormal amyloid plaque levels can occur in nondemented people, the extent to which their presence is associated with behavioral deficit or brain atrophy is unclear. Four studies addressed the relation between brain A β levels and concurrent objective cognitive performance in clinically unimpaired people; their results conflict. One study (N = 32)¹⁰ reported that higher plaque levels were correlated (-.38) with poorer episodic memory but not other types of cognitive ability. This might be expected if, as is usually thought, the earliest detectable deficit in AD is in episodic memory. Individuals with very early symptomatic AD may not satisfy the current criteria for clinical diagnosis of AD, which require another cognitive deficit and interference with function. Three other studies of 20¹¹ and 43,¹² and 37¹³ cognitively normal individuals failed to find any consistent relation between [¹¹C]PIB level and any cognitive domain. In terms of brain atrophy, one of these studies observed correlations between [¹¹C]PIB levels and hippocampal volume in clinically normal individuals.¹³ Differences between clinically normal individuals with or without elevated [¹¹C]PIB levels have been observed in the temporal pole but not other cortical regions or the hippocampus.^{11,14}

In this report we evaluated the relation between brain A β levels and concurrent cognitive performance as well as structural brain integrity in 135 people without clinically detectable cognitive impairment. Longitudinal cognitive performance was also examined to determine if the course varied with plaque burden or regional brain volume.

Methods

Participants

The 135 participants were recruited from the community and enrolled as controls in longitudinal studies at the Washington University Alzheimer Disease Research Center beginning in 1985. All were clinically evaluated to be cognitively healthy (Clinical Dementia Rating¹⁵ [CDR] = 0) at entry and remained CDR 0 through amyloid and structural imaging beginning in April, 2004. The CDR 0 designation excludes even minimal cognitive deficit, including mild cognitive impairment. See Table 1 for sample characteristics. All procedures were approved by the university's human subjects committee; written informed consent was obtained from participants and their collateral sources. Data from many of these participants have appeared in previous reports from the center.

Clinical assessment

At entry and annual follow-up experienced clinicians determined if the person was impaired (CDR > 0) or not (CDR = 0) based solely on semistructured interviews with participants and their knowledgeable collateral sources (usually spouse or adult child) followed by a neurological examination of the participant. The clinician determined if any cognitive problems represented decline from former level of function for that individual and interfered to some degree with the person's ability to carry out accustomed activities. The assessment included a health history, medication inventory, assessment of depression and aphasia, and the MiniMental State Examination (MMSE).¹⁶ Clinicians varied from year to year; they were unaware of the results of previous clinical evaluations and of previous and current psychometric test results. The CDR staging and diagnostic protocol is sensitive to clinical progression and highly predictive (93%) of autopsy-confirmed AD.^{17,18}

Psychometric assessment

A few weeks after the annual clinical assessment a 1.5-hour psychometric battery¹⁹ was administered. Examination of the factor structure of the battery revealed a stable four-factor structure of one global and three specific factors (all at the same level) in samples with autopsy-confirmed AD and no dementia.¹⁹ Four measures formed each of three specific factors; all 12 measures contributed to the global factor. The Verbal Memory factor included Wechsler Memory Scale (WMS)²⁰ Logical Memory (immediate recall) and Associate Learning, Wechsler Adult Intelligence Scale (WAIS)²¹ Information, and the Boston Naming Test.²² The Visuospatial factor included Benton Visual Retention Test: Form D-Copy,²³ WAIS Digit Symbol and Block Design, and Trailmaking A.²⁴ The Working Memory factor included Letter Fluency (S, P),²⁵ and WMS Mental Control and Digit Span (forward and backward). The Benton measure was dropped after 2003. Therefore, unweighted mean *z* scores on the remaining tests for each factor were averaged to form the four composites analyzed here. The reference group for the *z* scores was 310 participants (initial assessment) from the center's data archives who remained CDR 0 as long as they were followed, including many people from the current sample.

PIB imaging

Median time between PET imaging and concurrent clinical assessment was 3.9 months (range = same day to 1.4 years); median time to concurrent psychometric assessment was 4.1 months (range = same day to 1.5 years). Initial cognitive assessment occurred up to 19 years prior to imaging. Detailed information on the imaging procedures was reported previously.⁸ Imaging was conducted using a Siemens 961 HRECAT PET scanner (CTI, Knoxville, KY) or a Siemens 962 HR+ ECAT PET scanner (CTI) in a darkened, quiet room. A thermoplastic mask minimized head motion, and participants kept their eyes closed during the scan. Radiochemical synthesis of [¹¹C]PIB was conducted according to published literature.²⁶ After a transmission scan to measure attenuation, [¹¹C]PIB (5.3 to 20.1 mCi, mean = 12.1 mCi) was administered intravenously simultaneous with initiation of a 60-minute dynamic PET scan in three dimensional mode (septa retracted; 24 × 5 seconds frames; 9 × 20 seconds frames; 10 × 1 minute frames; and 9 × 5 minute frames). The measured attenuation factors and a ramp filter were used to reconstruct the dynamic PET images. A fully three-dimensional single scatter simulation algorithm was used to correct scatter.²⁷ Participants also underwent anatomic magnetic resonance imaging (MRI) using medium resolution (1mm × 1mm × 1.25 mm) MPRAGE T1- weighted volume acquisitions. A high-resolution, low noise anatomic image data set for region-of-interest determination was created for each participant by aligning and averaging two 133 MPRAGE sequences.^{8,28} Each participant's structural MRI was registered to a standard atlas target²⁹ that minimizes bias due to atrophy. Alignment of PET and MRI within a participant was accomplished with an in-house cross-modal registration algorithm.⁸ ANALYZE (Mayo Clinic, Rochester, MN) was then used to create three-dimensional regions of interest for each participant based on the individual's MRI. Detailed information on the boundaries of specific regions is available.⁸ Regions of interest were then applied to unblurred images of the PET dynamic data, yielding high-resolution regional time-activity curves. Each time-activity curve was analyzed for PIB-specific binding using the Logan graphical analysis,³⁰ with cerebellum data as a reference tissue input function.³¹ The cerebellum served as the reference because there is little specific binding of PIB in postmortem samples of cerebellar cortex even among those with AD at autopsy.²⁶ The “slope” produced by Logan graphical analysis is equal to the tracer distribution volume (DV) in the tissue of interest when compared with the input function. A binding potential (BP)³² for each region of interest was calculated using the equation $BP = DV - 1$ to express the regional binding values in a manner proportional to the number of binding sites. BP values from the prefrontal cortex, gyrus rectus, lateral temporal, and precuneus regions of interest were averaged to calculate a mean cortical binding potential (MCBP) value based on brain regions known to have high PIB uptake among

participants with AD.⁸ Two measures were used in analyses: the quantitative MCBP and MCBP dichotomized at 0.20³³ so that annual rates of cognitive change could be estimated for those with (positive) and without (negative) substantial brain amyloid plaque burden.

Regional volumetry

The interval between structural imaging ranged from 0 days to 1.6 years (median = 3.4 months) for PET, 0 days to 1.25 years (median = 3.1 months) for clinical assessment, and 0 days to 1.5 years (median = 2.9 months) for psychometrics. One to four T1-weighted images were acquired in one scanning session in 118 participants on either a Sonata 1.5T ($n = 4$), Vision 1.5T ($n = 34$), or Trio 3.0T scanner ($n = 80$). There was no difference in proportion of individuals with $\text{MCBP} \leq 0.20$ across scanners. Image processing steps are described in detail in previous publications^{28,34,35} and include motion correction, averaging across scans, atlas transformation, and inhomogeneity correction. Processing resulted in registered structural data resampled to 1 mm³ voxels in the atlas space of Talairach and Tournoux.²⁹ Regional volume estimates were obtained using the Freesurfer image analysis suite, which implements an automated probabilistic labeling procedure.^{35,36} Each voxel in an image is assigned a neuroanatomical label based on probabilistic information from a manually labeled training set that included healthy adults and AD patients. This technique generates volumes with a high correspondence to manually generated volumes.³⁶ Regions of interest (ROI) included the caudate nucleus, prefrontal cortex (combined superior, middle and inferior frontal gyri), orbital frontal, lateral parietal (combined inferior parietal, superior parietal, and supramarginal regions), temporal neocortical (combined superior, middle, and inferior temporal gyri), anterior cingulate, posterior cingulate, precuneus, hippocampal, and parahippocampal regions (including entorhinal cortex) regions. Intracranial volume (ICV) was used to adjust ROIs for head size variation based on a covariance approach: Adjusted volume in cubic millimeters = raw volume - $b \times (\text{ICV} - \text{mean ICV})$, where b is the slope of the regression of a region-of-interest volume on ICV and mean ICV. Although there are concerns regarding biases in across scanner and field strength aggregation, there is also evidence of reliability of some Freesurfer-derived quantitative estimates.^{37,38} A comparison across the Vision 1.5T and Trio 3T scanners of Freesurfer-derived volumes for regions examined here yielded an average intraclass correlation of .81 ($n = 13$).

Statistical analyses

Variables were assessed for normality with one-sample Kolmogorov-Smirnov tests. Pearson correlations were computed for quantitative variables; ϕ was used for two dichotomous variables; t and chi-square tests were used for cross-sectional group comparisons. Statistical significance was defined by $P < .05$.

The longitudinally measured cognitive composites while individuals were CDR 0 were examined using PROC MIXED (SAS 9.1; SAS Institute, Inc, Cary, NC). In the analysis examining amyloid burden, the model included the fixed effect quantitative MCBP and the random variable time from date of imaging (negative values before imaging, positive values after). A significant interaction between MCBP and time indicated that rate of longitudinal change varied with level of brain A β . Analogous analyses were conducted using regional brain volume instead of MCBP. To reduce capitalization on chance only three regions (hippocampus, posterior cingulate, precuneus) known to be affected early in the course of AD³⁹ or to have high A β deposition^{1,8} were examined. The longitudinal analyses were repeated using MCBP dichotomized at 0.20³³ and hippocampal volume dichotomized at the 25th percentile to estimate rates of annual cognitive change (i.e., slopes in z score units) for those with high versus low amyloid burden or volume loss.

Results

The cognitive composites and all measures of regional volume were normally distributed, but MCBP was skewed. As shown in Table 1, 29 people with CDR 0 at time of imaging had values ≥ 0.20 . MCBP was uncorrelated with age, education, gender, or MMSE ($r_s \leq .14$), but 65% of the PIB positive group had one or two APOE $\epsilon 4$ alleles compared with 24% in PIB negative group ($\phi = .29$). MCBP was also uncorrelated with any of the cognitive composites (global, $-.05$; verbal memory, $-.09$; spatial, $.02$; working memory, $.03$) or individual cognitive measures (r_s ranged from $-.14$ to $.06$) assessed concurrently with PET imaging. As depicted in Figure 1, significant differences in volumes between the PIB positive ($n = 26$) and negative ($n = 92$) groups were observed in hippocampus, temporal neocortex, anterior cingulate, and posterior cingulate with trends in precuneus ($P = .08$) and parahippocampal regions ($P = .07$). There were no differences in the remaining regions. Controlling for APOE status did not change the results. Similar results were obtained with the data from the scanner with the largest sample (Trio 3T; 63 PIB negative, 17 PIB positive).

There was a significant interaction between time and MCBP in the longitudinal analyses for two specific composites: visuospatial and working memory. As shown in Table 2 slopes for the PIB negative group were not significantly different from 0, whereas slopes for the positive group were significantly different from 0 and downward for the visuospatial and working memory composites. Figure 2 illustrates the actual longitudinal course on the visuospatial composite of participants from the PIB positive group who had at least four cognitive assessments; those with fewer assessments were not included in the figure to reduce overlap.

The nonsignificant group by time interaction for verbal memory was surprising given the common expectation that very early AD affects memory. Because the verbal memory factor included both episodic and semantic memory measures, the four individual tests were examined separately. The interaction was significant for Associate Learning, a standard test of episodic memory. The slope for the PIB negative group was upward (0.03), whereas it was downward (-0.05) for the PIB positive group. The interaction was not significant for any of the other verbal memory measures. The lack of significance on Logical Memory may be related to substantial missing data on this measure near the time of PET imaging; the funding agency required substitution of a different version on September 1, 2005.

In terms of the relation between regional volume and cognition measured concurrently, the global composite was moderately correlated with all regions except caudate ($r_s = .19$ to $.41$). The strongest regional correlations were seen with the spatial composite ($r_s = .29$ to $.54$). The verbal composite was modestly correlated with volume in all regions ($r_s = .21$ to $.28$) except caudate and parahippocampus. Working memory was correlated only with volume in lateral temporal ($r = .27$) and anterior cingulate ($r = .19$) regions. In longitudinal analyses relating regional volume to cognitive course, there was a significant interaction of hippocampus volume and time for the global, verbal, and spatial composites and a trend for working memory. Dichotomizing hippocampal volume at the 25th percentile produced the slopes shown in Table 2. Those with less volume had negative slopes. The interaction between time and volume in either the posterior cingulate or the precuneus was not significant for any of the composites.

Discussion

The longitudinal cognitive decline in PIB-positive older adults and volumetric reductions in multiple brain regions suggest that cerebral amyloidosis in nondemented aging is not a benign process. Over a fifth (22%) of individuals with a CDR of 0 had substantial cerebral amyloidosis. The reported prevalence of symptomatic AD at age 75 years in population studies.^{40,41} is consistent with this frequency of PIB positive, cognitively normal individuals and provides

inferential support for the notion of preclinical AD. Estimates of preclinical AD based on neuropathological studies⁵⁻⁷ are somewhat higher (30-40%), but those samples were older than this sample examined *in vivo* (e.g., 85 vs. 75 years). Because AD is age-associated, a higher prevalence rate is expected in older samples. Elevated [¹¹C]PIB in CDR 0 individuals was accompanied by smaller hippocampal and temporal neocortical volumes, brain regions known to be affected early in the course of the disease.³⁹ As the hippocampus has only mild levels of A β binding,⁸ these volumetric reductions may indicate pathological processes (e.g., neurofibrillary pathology) in addition to amyloid deposition. In either case, the existence of atrophy further substantiates the concept of preclinical AD. Structural imaging work has focused on the medial temporal lobe, but atrophy was also observed in cingulate cortex, which is consistent with the topographical distribution of gray matter loss observed in voxel-wise analyses in AD.⁴² Smaller hippocampal volume¹³ and thinning of the temporal pole¹⁴ has been observed in nondemented individuals with amyloid deposition. Reduced cerebrospinal fluid levels of A β ₄₂, another marker of cerebral amyloidosis in preclinical AD, also is associated with whole brain atrophy in cognitively normal individuals.⁴³

The longitudinal cognitive course for people with low levels of A β in the brain and greater volume in the hippocampus indicates that most older adults maintained an essentially flat cognitive trajectory in contrast with the slightly downward cognitive course for those with either elevated A β levels or reduced hippocampal volume. Annual estimated slopes for the PIB-positive group were not large, but they included the entire course while CDR 0. More dramatic decline in performance would be expected if it were possible to identify when a person changes from a flat course to a downward one and if more sensitive measures were available, especially of memory. Because PIB and volume values were available from only one time it is unknown if the cognitive decline began before, concurrently with, or after increased cerebral A β burden or hippocampal atrophy. Clearly, however, amyloidosis, atrophy, and deterioration in cognitive test performance occur prior to clinical diagnosis of dementia, even at a center that successfully diagnoses dementia much earlier than is typical.¹⁸

The factors examined here are not process-pure measures, but decline occurred in visuospatial ability and working memory as well as a measure of episodic memory. This widespread effect on cognition is consistent with the widespread distribution of cerebral amyloid burden observed here and reported previously.^{8,9,11} Continued focus solely on episodic memory in diagnosing dementia means that other types of cognitive deficits that may even precede memory difficulties are not evaluated, making it difficult to assess their influence. Additionally, dependence on cognitive test performance at a single point in time is ineffectual for detection of dementia in its earliest stage. Although correlated with regional brain volume, concurrent cognitive measures were unrelated to A β ; time between cognitive and amyloid assessment was occasionally lengthy, but 85% were within 6 months. It appears that individual differences in cognitive ability, including memory, are too large to allow effective assessment of very early symptomatic AD through comparison with normative values.¹⁸ The individual's current performance must be compared with previous levels either by serial testing or by informant-based clinical assessment that compares current functioning with previously attained levels.

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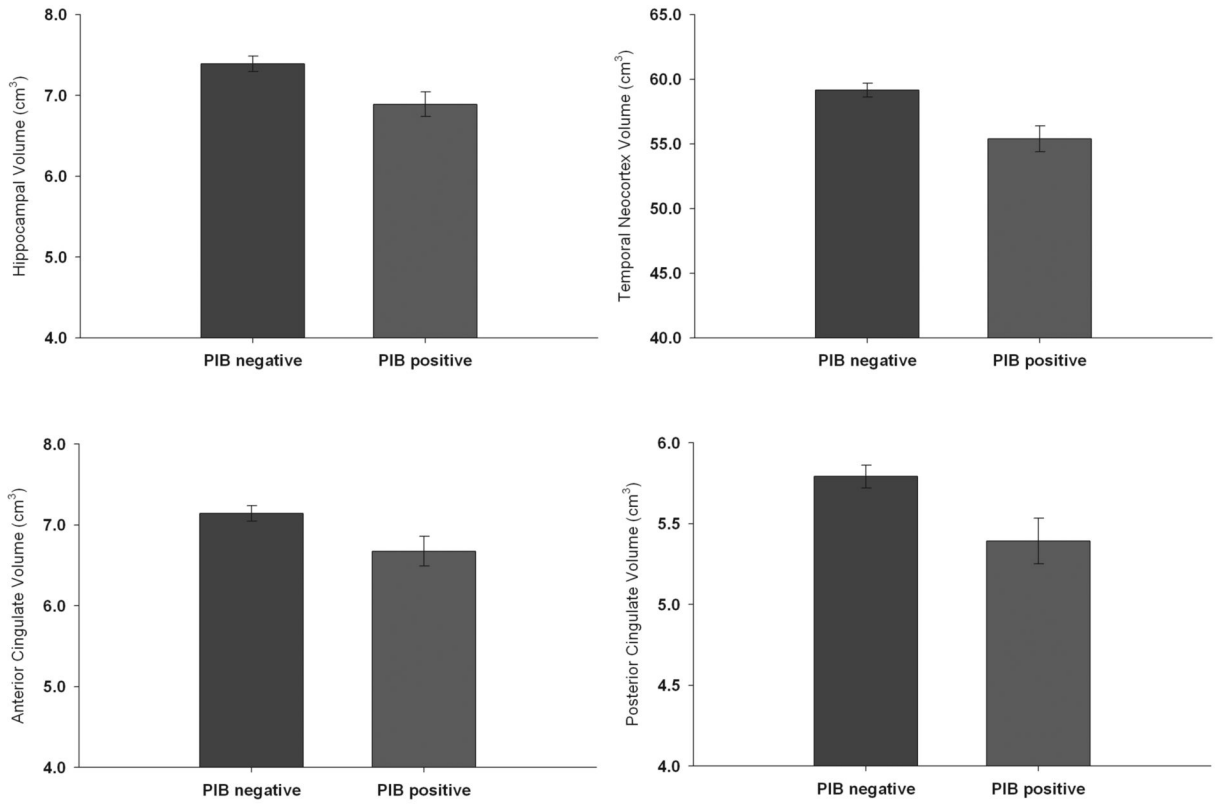


Figure 1. Bar graphs depicting mean regional volumes in the amyloid positive and negative groups. Error bars are SEM.

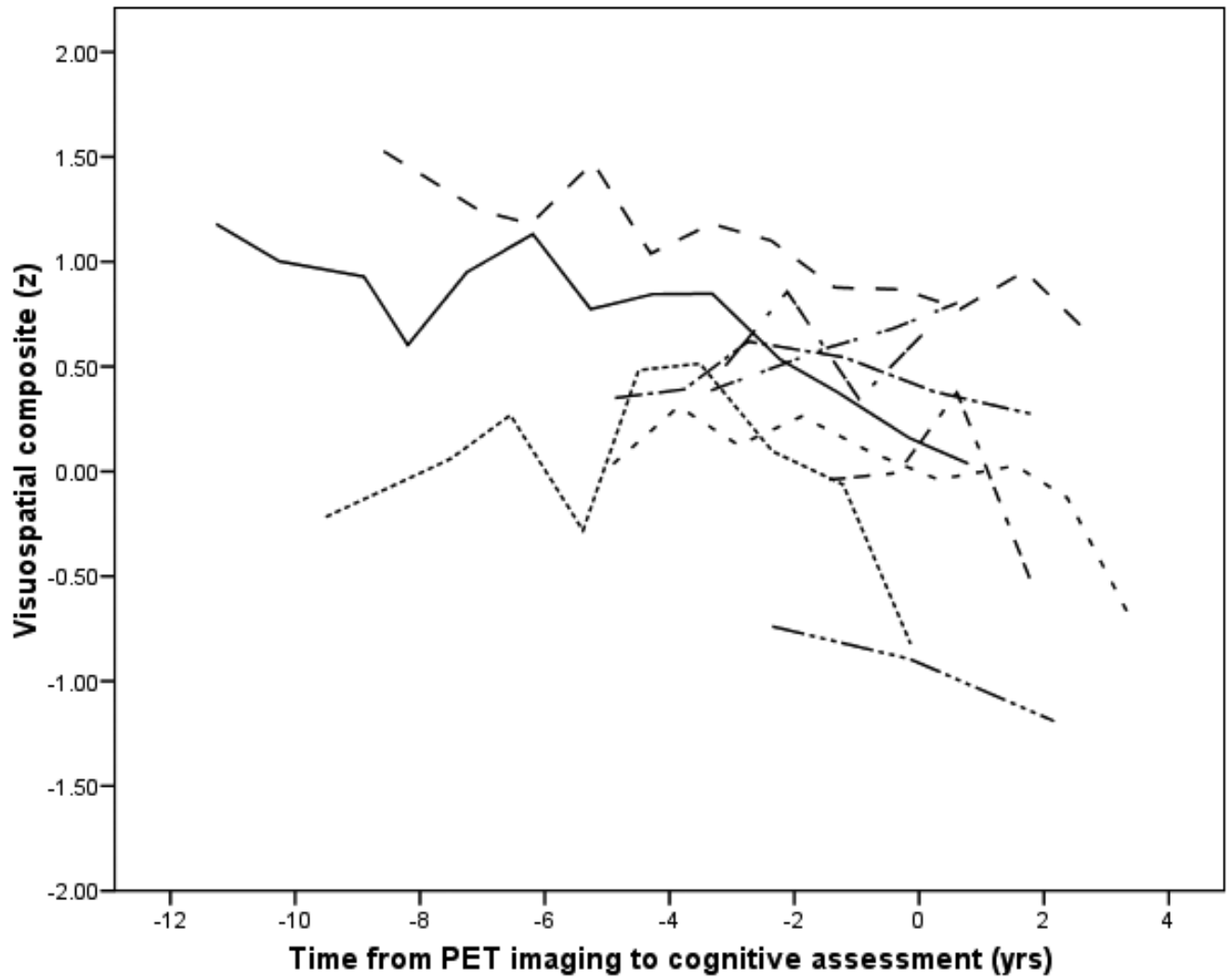


Figure 2. Longitudinal course of participants with high amyloid values (MCBP \geq .20) and at least four cognitive assessments. Zero on the time axis is time of imaging.

Table 1Sample characteristics of [¹¹C] PIB positive and negative groups*

	Negative group (n = 106)	Positive group (n = 29)	P values
Age at amyloid imaging, y	74.3 (6.2)	75.6 (6.3)	.30
Education, y	15.5 (2.6)	15.8 (3.7)	.57
MMSE at amyloid imaging	28.8 (1.2)	28.4 (1.8)	.29
Women, %	68	62	.55
APOE > 1 ε4, %	24	65	<.0001

Abbreviations: MMSE, Mini Mental Status Exam;¹⁶ APOE, apolipoprotein E.

* Values are expressed as mean (SD) unless otherwise indicated.

Table 2

Annual rate of change in [^{11}C] PIB positive and negative groups on four cognitive composites (z scores)

Composite	Negative group	Positive group	Group \times Time P values
Global, slope (SE)	-.01 (.01)	-.02 (.01)	.25
Verbal memory, slope (SE)	.01 (.01)	.00 (.02)	.65
Visuospatial, slope (SE)	-.01 (.01)	-.05 (.01)	.03
Working memory, slope (SE)	.00 (.01)	-.04 (.01)	.02

Table 3

Annual rate of change on four cognitive composites (z scores) in individuals above and below the 25th percentile of hippocampal volume

Composite	Above	Below	Volume × Time P values
Global, slope (SE)	.00 (.01)	-.03 (.01)	.01
Verbal memory, slope (SE)	.03 (.01)	-.01 (.02)	.01
Visuospatial, slope (SE)	.00 (.01)	-.05 (.01)	.01
Working memory, slope (SE)	-.01 (.01)	-.03 (.01)	.06