Influence of amyloid and APOE on cognitive performance in a late middle-aged cohort

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Abstract

INTRODUCTION—Few studies have examined the effects of amyloid and APOE genotype on cognition among middle-aged individuals.

METHODS—We included 464 cognitively normal, test-naïve, participants with PiB-PET amyloid imaging, mean age of 62.7 (range 51–71 years), enrolled in the Mayo Clinic Study of Aging.

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Participants completed multiple cognitive assessments, including a standard neuropsychological battery and the CogState computerized battery, over 30 months of follow-up. Linear mixed models were used to examine the effects of amyloid and APOE genotype on baseline cognition and cognitive decline.

RESULTS—Elevated amyloid was not associated with tests of episodic memory, but did predict declines on tests of executive function. APOE genotype was not associated with cognition. Among APOE ε4 non-carriers, higher amyloid was predictive of decline on tests of executive function and on one episodic memory test.

DISCUSSION—Elevated amyloidosis and APOE genotype does not appear to exert a dramatic influence on cognition in middle-age.

Keywords

Amyloid; *APOE*; Alzheimer's disease; Cognitive aging; Cohort studies; PET

1. Introduction

The pathophysiological brain changes associated with Alzheimer's disease (AD) are thought to begin decades before clinical symptoms based on autopsy and clinical studies [1–3]. Therefore, the earliest identification of at-risk individuals will provide the greatest window of opportunity to prevent or delay disease symptoms. AD secondary prevention trials of at risk cognitively normal individuals, defined as significant amyloid- beta accumulation or the presence of at least one apolipoprotein E (APOE) ε4 allele, are in the planning stages or ongoing. Most studies examining the effects of amyloid and APOE genotype on cognition have utilized cohorts aged 65 and older, with mean ages of the cohorts typically in the mid- to late 70's [4–12]. It is important to also determine the effects of amyloid and APOE genotype on cognition in younger cohorts. This information may help better discern at what age population screening for amyloid and APOE genotype is most predictive of cognitive decline if potential secondary preventive treatments are found to be effective.

A challenge in assessing the impact of an anti-Alzheimer therapy in middle-age is that, in general, there is little cognitive change but notable practice effects [13]. As a result, it is difficult to quantify the effects of risk and biological factors, such as amyloid and APOE genotype, on cognitive decline and to estimate potential treatment effects. Several studies are now focused on identifying neuropsychological tests that are more sensitive to subtle cognitive changes among cognitively normal individuals. One area of interest is computerized testing.

A computerized battery may have advantage over standard neuropsychological tests or other cognitive screening measures by being more sensitive and efficient, removing ceiling and floor effects, providing real-time data entry and precise recording of accuracy and speed, and minimizing practice effects [14,15]. Few studies have examined the performance of computerized cognitive batteries in a large middle-aged cohort. Characterization of the longitudinal trajectories of cognitively normal individuals in middle-age on standard neuropsychological and computerized cognitive tests for practice effects and sensitivity to

change is critical. We recently described the feasibility of the CogState computerized battery, and factors that affect performance among 1,660 non-demented individuals enrolled in the Mayo Clinic Study of Aging [16]. In the present study, we first assessed cognitive changes over 30 months across standard neuropsychological measures and the CogState computerized battery in a cohort of 464 cognitively normal individuals, mean [SD] age of 62.7 [5.4] years, enrolled in the Mayo Clinic Study of Aging. We then examined the influence of amyloid and APOE genotype on baseline cognition and cognitive trajectories.

2. Methods

2.1. Participants

The Mayo Clinic Study of Aging (MCSA) is a population-based study of cognitive aging among Olmsted County, MN residents that initially began in October 2004, enrolling individuals aged 70 to 89 years, as previously described [17]. Given the importance of understanding risk factors and the development and progression of AD pathophysiology in late middle-age, we expanded the study to also enroll a population-based sample of individuals aged 50–69 using the same stratified random sampling methodology as in the original cohort. The Olmsted County population, aged 50–69 (n = 31,502), was sampled by 5-year age groups and sex beginning on November 1, 2011. The present study included 464 individuals, aged 50–69, who were cognitively normal and test naïve at baseline, and had amyloid imaging and APOE genotype.

2.2. Standard protocol approvals, registrations, and patient consents

The study protocols were approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. All participants provided written informed consent.

2.3. Participant assessment

MCSA full study visits occurred every 15 months and included a physician examination, an interview by a study coordinator, and neuropsychological testing [17]. The physician examination included a medical history review, complete neurological examination, and administration of the Short Test of Mental Status [18]. The study coordinator interview included demographic information, medical history and questions about memory to both the participant and an informant using the Clinical Dementia Rating scale [19]. During the time with the study coordinator, the participants also completed the CogState computerized battery.

The neuropsychological battery was administered by a psychometrist and included nine tests covering four domains: 1) **memory** (Auditory Verbal Learning Test Delayed Recall Trial [20]; Wechsler Memory Scale-Revised Logical Memory II & Visual Reproduction II) [21]; 2) **language** (Boston Naming Test [22] and Category Fluency [23]; 3) **executive function** (Trail Making Test B [24] and WAIS-R Digit Symbol subtest [25]; and 4) **visuospatial skills** (WAIS-R Picture Completion and Block Design subtests) [25]. Trail Making Test A [24] was also administered. Blood was collected and APOE genotype was determined.

2.4. Diagnostic determination

For each participant, performance in a cognitive domain was compared with the age-adjusted scores of cognitively normal individuals previously obtained using Mayo's Older American Normative Studies [26]. This approach relies on prior normative work and extensive experience with the measurement of cognitive abilities in an independent sample of subjects from the same population. Subjects with scores of 1.5 SD below the age-specific mean in the general population were considered for possible cognitive impairment. A final decision to diagnose mild cognitive impairment (MCI) was based on a consensus agreement between the study coordinator, examining physician, and neuropsychologist, after taking into account education, prior occupation, visual or hearing deficits, and reviewing all other participant information [17,27]. Individuals who performed in the normal range and did not meet criteria for MCI or dementia were deemed cognitively normal. Performance on the CogState computerized cognitive battery was not used to determine a diagnosis.

2.5. CogState computerized battery administration

Participants completed the CogState battery every 7.5 months (at the full in-clinic study visit every 15 months, and also at a CogState-only visit at the midpoint between the full study visits). Administration of the CogState battery included four card tasks and the Groton Maze Learning Test (GMLT), as previously described [16,28]. Given the previous literature showing an initial practice/learning effect between the first and second administration [29], at the baseline visit we administered a short practice battery, followed by a two-minute rest period, then the complete battery. Subsequent visits included a brief introduction to the test (i.e., the participant completed a few practice attempts), followed immediately by the complete battery. The computerized battery included measures of psychomotor function (Detection; DET), attention (Identification; IDN), visual episodic memory (One Card Learning; OCL), and visual working memory (One Back; ONB). The GMLT measures spatial working memory, learning efficiency, and error monitoring (outcomes included moves per second and total number of errors).

The CogState battery provides a large number of equivalent alternative forms for serial assessments. This is achieved by having a large stimulus set from which exemplars are randomly chosen, resulting in a different set of exemplars that are used each time an individual takes the test. The paradigm remains constant but the items are randomly chosen. Furthermore, the correct response (either yes or no) is randomly chosen for each trial of the task, and the inter-stimulus interval has a random interval that varies for each trial of the task. For the GMLT there are 20 possible hidden pathways, matched for number of tiles and turns, that are presented in a random, non-recurring order.

2.6. Amyloid PET methods

PET images were acquired using a PET/CT scanner (DRX or DRXT, GE Healthcare). A CT image was obtained for attenuation correction. The ^{11}C PiB-PET scan, consisting of four 5-minute dynamic frames, was acquired from 40–60 minutes after injection. Image analysis was done using our in-house fully automated image processing pipeline [30]. An amyloid PET standardized uptake value ratio (SUVR) was determined by calculating the median uptake over voxels in the prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and

posterior cingulate/precuneus regions of interest (ROIs) for each subject and dividing this meta ROI by the median uptake over voxels in the cerebellar gray matter ROI of the atlas. The data were partial volume corrected using a 2-compartment approach (brain and non-brain). The median value of PET voxels corresponding to grey matter was calculated for each ROI. We primarily analyzed amyloid as a continuous variable. We also utilized cut-offs for elevated amyloid of SUVR ≥ 1.4 [30].

2.7 Statistical methods

Raw scores of all individual computerized and neuropsychological tests were converted to z-scores using baseline results. Select z-scores were inverted so that higher z-scores meant better performance for all cognitive tests. The trajectories of each computerized test, individual neuropsychological test and domain-specific z-scores over the 30-month follow-up were examined using linear mixed models with maximum likelihood estimation and an unstructured covariance matrix. This approach permitted assessment of the average rate of change per year in all cognitive tests while accounting for the dependence of within-subject repeated measures over time. Multivariable models were adjusted for age, sex, and education.

We also used linear mixed models to separately examine the effect of baseline amyloid (as a continuous variable) and the presence of an APOE ε4 allele on baseline cognition and longitudinal average rate of change per year for all cognitive tests. Models included terms for baseline amyloid or presence of an APOE ε4 allele (indicating the relationship between amyloid or APOE ε4 and baseline cognitive z-score), time (indicating annual change in the cognitive z-score over the follow-up), and the interaction between either amyloid or presence of an APOE ε4 allele and time (indicating whether baseline amyloid or APOE ε4 predicted change in cognition). To examine the interaction between amyloid and presence of an APOE ε4 allele on baseline and longitudinal cognition, we utilized the linear mixed models for amyloid (as described above) and stratified by the presence of an APOE ε4 allele. We did examine interactions between amyloid and sex in predicting cognitive change, including stratifying by the presence of APOE ε4 allele. However, none of the interactions were significant so these results are not presented.

Permutation testing was performed for the mixed models to address the large number of statistical tests. Between-subject effects were permuted as to maintain within-subject correlations. A random subset of 10,000 combinations from all possible permutations were selected and used for analysis. After permutation testing, $P < .05$ was considered statistically significant. All statistical analyses were performed using SAS (SAS Institute, Cary, NC).

3. Results

The baseline characteristics of the 464 cognitively normal participants are shown in Table 1. The mean [SD] age of the sample was 62.7 [5.4] years and 52% were men. The mean PiB-PET SUVR [SD] was 1.3 [1.2] and 81 (17.5%) had elevated brain amyloid based on the cutpoint of SUVR ≥ 1.4. The age of the youngest individual with elevated amyloid was 59 years. Compared to individuals with amyloid SUVR<1.4, those with SUVR ≥ 1.4 were significantly older, had less education, more frequently had an APOE ε4 allele and

performed worse on some CogState and neuropsychological tests in unadjusted analyses (Table 1). Individuals with an APOE ε4 allele, versus those without, had higher amyloid levels, and performed worse on some standard neuropsychological tests in the executive and language domains in unadjusted analyses.

3.1. Cognitive trajectories

The longitudinal performance on the CogState tests, over 5 visits (30 months), are shown in Fig. 1 and Supplementary Table 1. Essentially all CogState tests showed better performance over time in linear mixed models adjusting for age, sex, and education. Most of the computerized tests primarily showed a practice effect at the second and third visits. However, mean levels of OCL accuracy (Fig. 1, One Card Accuracy) showed continued practice effects for each subsequent visit up to 5 visits. The longitudinal performance on the standard neuropsychological tests and domain-specific z-scores are shown in Figs. 2A and 2B and Supplementary Table 2. All domain-specific and many individual test z-scores also demonstrated better performance over time, adjusting for age, sex, and education, with the exception of Category Fluency, WAIS-R Block Design, and Language z-score. The longitudinal trajectories of most domain-specific and individual neuropsychological test z-scores were similar to most computerized tests, with an initial practice effect followed by a leveling off or slight increase (see Fig. 2).

3.2. Effects of amyloid, APOE ε4 allele, and their interaction for predicting cognitive decline

Overall, there were few associations between baseline amyloid and either baseline cognition or cognitive change, including tests of episodic memory. At baseline, increasing amyloid SUVR was associated with poorer performance on computerized tests of psychomotor speed (DET; b = −0.92, P = .002), visual working memory (ONB; b = −0.62, P = .014), and spatial working memory (GMLT Total Errors; b = −0.71, P = .013), but did not predict cognitive decline on these tests (Table 2). Higher baseline amyloid was predictive of cognitive decline on the WAIS-R Digit Symbol (b = −0.24, P = .011) and the Executive domain (b = −0.22, P = .011). APOE genotype alone was not cross-sectionally associated with any cognitive test and also did not longitudinally predict change on any test.

The relationship between baseline amyloid and baseline and longitudinal performance on some of the cognitive tests differed by the presence of an APOE ε4 allele (Table 3). Among APOE ε4 carriers, higher baseline amyloid was associated with poorer performance on baseline psychomotor speed (DET; b = −1.26, P = .002) and spatial working memory (GMLT Total Errors; b = −1.01, P = .017). There was also a trend for poorer baseline performance on the Wechsler Memory Scale-Revised Logical Memory II delayed recall (b = −0.069, P = .053). However, among APOE ε4 carriers, amyloid did not predict change on any cognitive test.

Interestingly, and in contrast to the above results, among APOE ε4 non-carriers higher baseline amyloid was associated with better baseline performance on the Wechsler Memory Scale-Revised Logical Memory II delayed recall (b = 1.30, P = .005; Table 3). Further, higher baseline amyloid predicted cognitive decline on the Wechsler Memory Scale-Revised

Logical Memory II delayed recall (b = −0.038, *P* = .047), WAIS-R Digit Symbol (b = −0.24, *P* = .011) and the Executive domain (b = −0.22, *P* = .011).

3.3. Sensitivity analyses

In additional analyses we utilized an amyloid PiB-PET cutoff of SUVR 1.4. Participants with SUVR 1.4 did not perform worse on any cognitive test at baseline or longitudinally. In other analyses, we restricted the sample to the 121 individuals with data at all visits but the results did not differ. We also reran the analyses excluding the 5 individuals with incident MCI but the results remained. Lastly, we determined the effect of the APOE genotype and amyloid level on censoring, but neither was predictive of missing data or loss-to-follow-up.

4. Discussion

In this study of late middle-aged cognitively normal individuals enrolled in the population-based Mayo Clinic Study of Aging, we found few associations between brain amyloid levels, as measured by PiB PET, and cross-sectional and longitudinal measures of cognition over 30 months, including tests of episodic memory. APOE genotype alone was not cross-sectionally or longitudinally associated with cognition. However, some of the associations between amyloid and cognition varied by APOE genotype.

Observational studies examining the effect of amyloid and APOE genotype on cognition in cognitively normal individuals, who are substantially older than in the current study, have been inconsistent [4–12,31–34]. A meta-analysis focused on cognitively normal older individuals reported that amyloid was associated with worse episodic memory and there were trends for associations with executive function and global cognition [35]. However, while the associations were statistically significant, the effect sizes were small. Notably, most studies examining the effect of amyloid and APOE ε4 genotype on cognition in older individuals are of individuals aged 70 and older. The age of the study population is important because the appearance of abnormal amyloidosis increases with age beginning in the late 50s [36]. Declines in memory become more rapid after the seventh decade, corresponding to the period in which the symptoms of sporadic AD begin to increase in prevalence [37,38].

Recent studies of younger individuals have not found a relationship between amyloid and episodic memory. A cross-sectional study of 137 individuals, mean age of 60 (range 30–89 years), found a significant dose-response effect of mean cortical amyloid on processing speed and fluid reasoning, but not on working memory, episodic memory, or crystallized intelligence [12]. Another study of 201 individuals with a mean age of 64 (range 46–73 years) also did not find an association between amyloid burden and cognition [39]. Our observations are unique in the literature due to the larger sample size of 464 late middle-aged participants with a mean age of 62.6 (range 51–71 years). Overall, we found few associations between amyloid and cognition. Further, amyloid was more strongly associated with measures of attention and executive function than with measures of episodic memory. Among individuals with an APOE ε4 allele, we did observe cross-sectional associations between amyloid and visual working memory, and a trend for an association between higher amyloid and delayed episodic memory on the Logical Memory test. However, amyloid was

not predictive of cognitive decline in APOE ε4 carriers. Only among APOE ε4 non-carriers did we find that higher amyloid was predictive of decline on one episodic memory test and on tests of executive function. It is possible that, when stratifying by APOE ε4 carrier status, our sample size among APOE ε4 carriers did not allow for enough power to detect an association. However, there were no trends and our sample was still twice the size of previous studies of middle-aged individuals. We conducted several sensitivity analyses to assure there was not a methodological reason for this observation, but we did not identify one. There are multiple possible explanations for these findings. First, some studies suggest that changes in executive function may precede declines in memory among individuals who later develop AD [40–42]. Our results would support these deductions. Second, it is possible that APOE ε4 carriers had cognitive decline prior to enrolling in the study, and therefore did not have substantial additional cognitive decline over the next 30 months. Thus, we only saw an association between amyloid and cognition among non APOE ε4 carriers. Lastly, a large number of statistical tests were performed. While we did utilize permutation testing, it is still possible that some of the observed associations may be due to type 1 error. Longitudinal studies with longer follow-up in young- and middle-aged adults with serial imaging and cognition are needed to further elucidate our results.

Much research has focused on identifying the best compilation of neuropsychological test items aimed at detecting the smallest amount of cognitive change in the shortest period of time in cognitively normal individuals e.g., [43,44]. A computerized battery may have an advantage over standard neuropsychological tests or other cognitive screening measures by being more sensitive and efficient, removing ceiling and floor effects, providing real-time data entry, suitability for off-site or long-distance use and longitudinally screening for and assessing cognition at the population-level [14–16]. However, few studies have examined the longitudinal performance of computerized cognitive batteries in middle-aged individuals. In the present study, we assessed cognition with both the CogState computerized battery and standard neuropsychological tests. With the exception of the CogState OCL accuracy measure, practice effects on the CogState computerized tests and standard neuropsychological tests were similar in this group of middle-aged individuals. Because computerized testing may be more suitable to longitudinal screening, and screening large populations, these results suggest that computerized tests may offer a means for longitudinally assessing cognition in this age group. Indeed, we have previously demonstrated the acceptability and feasibility of computerized testing, in the clinic and at home, among non-demented individuals aged 50 and older enrolled in the Mayo Clinic Study on Aging [28]. We did not, however, expect the sustained practice effects observed for the OCL accuracy measure in this age group. Previous studies have not observed such large practice effects on the OCL, including when administered 4 times in one day [29]. Reasons for our observation are not fully understood but are important for discerning the use of this test as a cognitive outcome measure in both clinical trials and longitudinal epidemiological studies. Implicit memory may play a role in this phenomenon wherein the participant derives some benefit from having completed the procedure previously despite unpredictability in the interstimulus intervals and the response required for successful completion of each item.

Strengths of our study include the large number of late middle-aged individuals, the population-based prospective cohort design, and the comprehensive evaluation of

participants. One limitation is that we only assessed the effect of amyloid on cognition in this analysis. Neurodegenerative markers are altered closer in time to the development of cognitive symptoms [1–3,45]. Future analyses will need to assess the effects of neurodegeneration, including cortical thickness and tau pathology in this age group. Further longitudinal exploration of computerized tests in this age group is also warranted to better understand the observed practice effects and how they might affect estimates of treatment effects in clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations

AD	Alzheimer's disease
APOE	apolipoprotein E
AVLT	Auditory Verbal Learning Task
DET	detection
GMLT	Groton Maze Learning Test
IDN	identification
MCI	mild cognitive impairment
MCSA	Mayo Clinic Study of Aging
OCL	One Card Learning
ONB	One Back
PiB PET	Pittsburgh compound B positron emission tomography
ROIs	regions of interest
SUVR	standardized uptake value ratio
TMT-A	Trail Making Test, Part A
TMT-B	Trail Making Test, Part B
WAIS-R	Wechsler Memory Scale-Revised Logical Memory II

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Research in context

1. Systematic review

We reviewed the literature in PubMed that focused on detecting early cognitive changes and the effects of amyloid and APOE genotype on cognition. Several studies are now focused on identifying neuropsychological tests that are more sensitive to subtle cognitive changes. However, few studies have examined the performance of computerized cognitive batteries in a large population-based middle-aged cohort. Studies examining the effects of amyloid and APOE genotype on cognition have primarily utilized cohorts aged 65 an older.

2. Interpretation

With the exception of the CogState One Card Learning (OCL) accuracy measure, practice effects on the CogState computerized tests and standard neuropsychological tests were similar in this group of middle-aged individuals aged 51–71. However, a sustained practice effect was observed for the OCL accuracy measure in this age group. Elevated amyloidosis and APOE genotype did not appear to exert a dramatic influence on cognition in middle-age. If anything, amyloid was more strongly associated with measures of attention and executive function than with measures of episodic memory.

3. Future Directions

Neurodegenerative markers may be more predictive of cognitive symptoms. Future analyses will need to assess the effects of neurodegeneration, including cortical thickness and tau pathology, on cognition in middle-aged individuals. In addition, longitudinal exploration of computerized tests in this age group is critical to better understand the observed practice effects and how they might affect estimates of treatment effects in clinical trials.
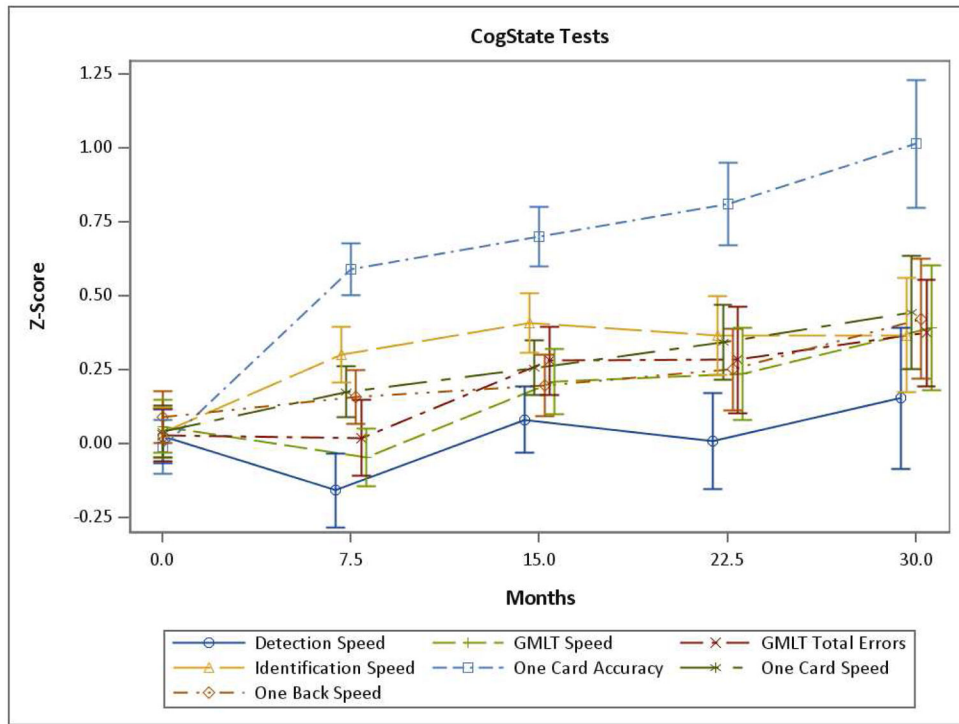
Fig. 1. The longitudinal performance on all CogState computerized tests over 5 visits (30 months)
GMLT, Groton Maze Learning Test.
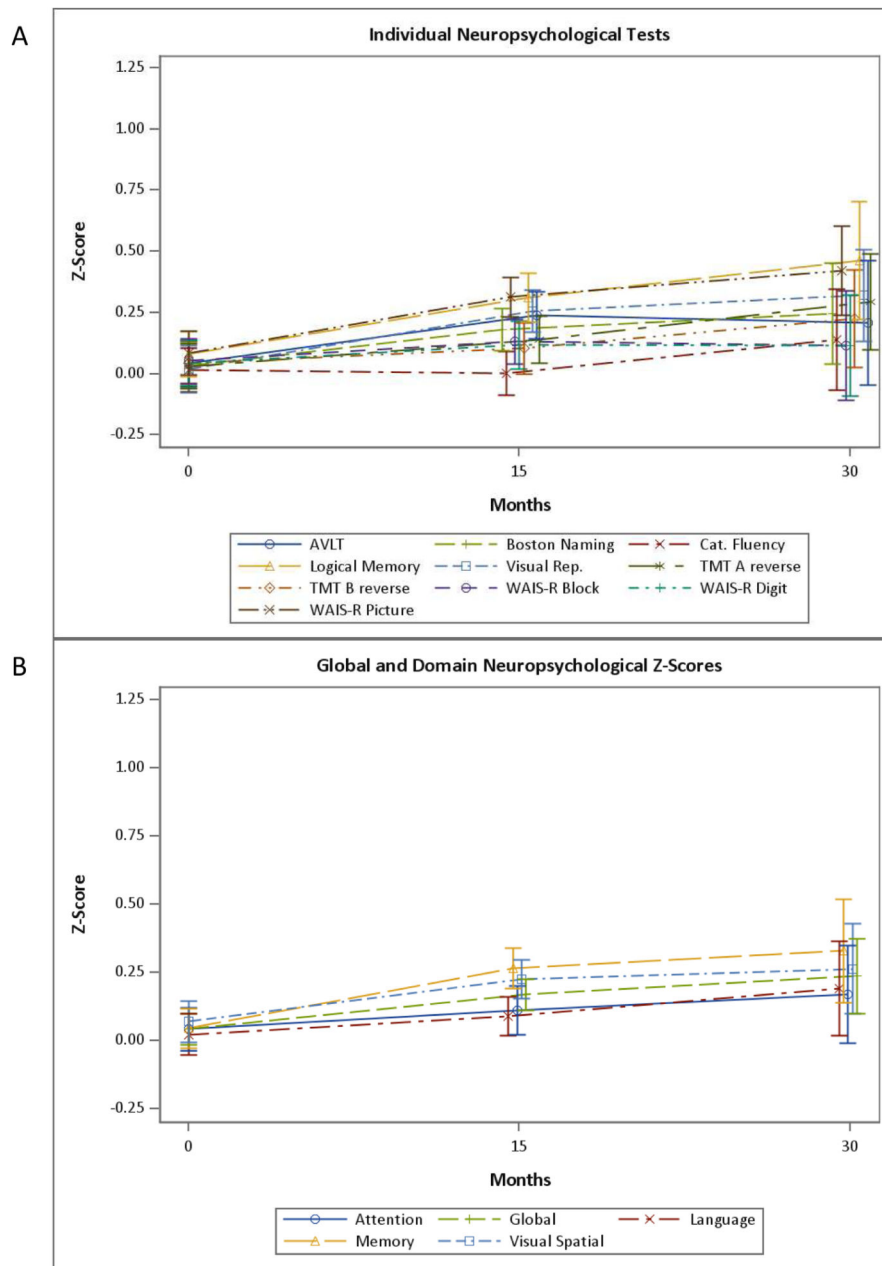
Fig. 2. The longitudinal performance of: A) the individual standard neuropsychological tests, and B) domain-specific z-scores over 3 visits (30 months)
AVLT, Auditory Verbal Learning Test; TMT-A, Trail Making Test, Part A; TMT-B, Trail Making Test, Part B; WAIS-R, Wechsler Memory Scale-Revised Logical Memory II.

Table 1

Participant characteristics (N = 464)

Characteristics	ALL Mean (SD)/N(%)	Aβ≥1.4 (N=81) Mean (SD)/N(%)	Aβ<1.4 (N=383) Mean (SD)/N(%)	APOE E4+ (N=130) Mean (SD)/N(%)	APOE E4− (N=334) Mean (SD)/N(%)
Age	62.7 (5.4)	66.6 (2.8)	61.9 (5.5) ***	63.2 (5.2)	62.5 (5.5)
Men	240 (51.7%)	35 (43.2%)	205 (53.5%)	66 (50.8%)	174 (52.1%)
Education	15.3 (2.3)	14.7 (2.5)	15.4 (2.3) **	15.0 (2.3)	15.4 (2.3)
Amyloid SUVR	1.3 (0.2)	1.6 (0.3)	1.3 (0.1)	1.4 (0.3)	1.3 (0.1) **
Aβ≥1.4 SUVR	81 (17.5%)			37 (28.5%)	44 (13.2%) ***
Any APOE E4 allele	130 (28.0%)	37 (45.7%)	93 (24.3%) ***		
CogState Tests					
Detection (DET)	2.6 (0.1)	2.6 (0.1)	2.6 (0.1)	2.6 (0.1)	2.6 (0.1)
Identification (IDN)	2.7 (0.1)	2.8 (0.1)	2.7 (0.1) **	2.7 (0.1)	2.7 (0.1)
One Card Learning (OCL)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1) *	1.0 (0.1)	1.0 (0.1)
One Back (ONB)	2.9 (0.1)	2.9 (0.1)	2.9 (0.1) **	2.9 (0.1)	2.9 (0.1)
GMLT Total Errors	50.7 (18.1)	56.1 (17.6)	49.4 (18.0) **	50.4 (17.9)	50.8 (18.2)
GMLT Speed	0.6 (0.1)	0.5 (0.1)	0.6 (0.1) ***	0.6 (0.1)	0.6 (0.1)
Neuropsychological Tests (Raw Scores)					
Logical Memory delayed recall	21.9 (7.5)	21.5 (7.3)	21.9 (7.6)	21.4 (8.3)	22.0 (7.2)
AVLT delayed recall	9.3 (3.3)	8.8 (3.1)	9.5 (3.3)	9.1 (3.2)	9.4 (3.3)
Visual Reproduction delayed recall	27.4 (6.9)	25.3 (6.6)	27.8 (6.9) ***	27.2 (7.1)	27.4 (6.9)
WAIS-R Digit Symbol	53.1 (10.7)	49.5 (9.5)	53.9 (10.8) **	51.3 (10.9)	53.8 (10.6) *
TMT-A	149.0 (9.2)	146.1 (10.1)	149.7 (8.9) **	147.8 (10.3)	149.5 (8.7)
TMT-B	230.0 (24.4)	222.9 (24.2)	231.5 (24.2) ***	225.9 (25.4)	231.6 (23.9) *
WAIS-R Picture Completion	14.8 (2.4)	14.2 (2.6)	14.9 (2.4) *	14.6 (2.5)	14.9 (2.4)
WAIS-R Block Design	29.8 (8.9)	26.2 (8.0)	30.5 (8.9) ***	29.0 (8.5)	30.0 (9.0)
Boston Naming Test	56.5 (3.3)	56.4 (3.3)	56.6 (3.3)	55.8 (3.2)	56.8 (3.3) ***
Category Fluency	49.7 (10.1)	49.1 (9.9)	49.8 (10.1)	48.4 (10.0)	50.2 (10.1)

Characteristics	ALL Mean (SD)/N(%)	Aβ 1.4 (N=81) Mean (SD)/N(%)	Aβ<1.4 (N=383) Mean (SD)/N(%)	APOE E4+ (N=130) Mean (SD)/N(%)	APOE E4− (N=334) Mean (SD)/N(%)
Global and Domain-specific Scores					
Global z-score	0.0 (0.6)	−0.2 (0.6)	0.1 (0.6) ***	−0.1 (0.7)	0.1 (0.6) *
Memory z-score	0.0 (0.8)	−0.1 (0.8)	0.1 (0.8) *	0.0 (0.9)	0.1 (0.8)
Language z-score	0.0 (0.8)	0.0 (0.8)	0.0 (0.8)	−0.2 (0.8)	0.1 (0.8) **
Executive function z-score	0.0 (0.9)	−0.3 (0.8)	0.1 (0.9) ***	−0.1 (0.9)	0.1 (0.8) *
Visual spatial z-score	0.1 (0.8)	−0.3 (0.8)	0.1 (0.8) ***	0.0 (0.8)	0.1 (0.8)
Incident MCI	5 (1.1%)	1 (1.2%)	4 (1.0%)	2 (1.5%)	3 (0.9%)
Number of CogState exams	3.5 (1.0)	3.5 (1.0)	3.5 (1.0)	3.5 (1.0)	3.5 (1.0)
Number of Neuropsychological exams	2.1 (0.6)	2.2 (0.6)	2.1 (0.6)	2.1 (0.6)	2.1 (0.6)

Abbreviations: APOE, apolipoprotein E; SUVR, Standard Uptake Value Ratio; GMLT, Groton Maze Learning Test; AVLT, Auditory Verbal Learning Test; WAIS-R, Wechsler Memory Scale-Revised Logical Memory II; TMT-A, Trail Making Test, Part A; TMT-B, Trail Making Test, Part B. MCI, Mild Cognitive Impairment.

*** *P* < .001,

** *P* < .01,

* *P* < .05.

Table 2

Multivariable linear mixed models examining the effect of amyloid on cognitive decline[*]

Cognitive z-scores	Baseline Amyloid		Time		Baseline Amyloid * time	
	b(se)	P value**	b(se)	P value**	b(se)	P value**
CogState Tests						
Detection (DET)	−0.92 (0.28)	.002	−0.17 (0.21)	.399	0.19 (0.15)	.208
Identification (IDN)	−0.43 (0.24)	.074	0.03 (0.14)	.814	0.13 (0.11)	.218
One Card Learning (OCL)	−0.13 (0.24)	.569	0.38 (0.18)	.033	0.05 (0.13)	.719
One Back (ONB)	−0.62 (0.24)	.014	0.10 (0.14)	.446	0.02 (0.10)	.817
GMLT Total Errors	−0.71 (0.27)	.013	0.13 (0.23)	.543	0.04 (0.17)	.786
GMLT Speed	−0.27 (0.24)	.272	0.32 (0.15)	.032	−0.10 (0.11)	.326
Individual Standard Neuropsychological Tests						
Logical Memory delayed recall	−0.10 (0.24)	.822	−0.15 (0.18)	.052	0.21 (0.13)	.330
AVLT delayed recall	0.04 (0.25)	.880	0.18 (0.16)	.246	−0.04 (0.12)	.704
Visual Reproduction delayed recall	−0.10 (0.24)	.690	−0.15 (0.18)	.407	0.21 (0.13)	.120
WAIS-R Digit Symbol	−0.33 (0.24)	.173	0.39 (0.12)	.004	−0.24 (0.09)	.011
TMT-A	−0.18 (0.25)	.456	0.12 (0.19)	.528	−0.02 (0.14)	.905
TMT-B	−0.09 (0.25)	.710	0.31 (0.17)	.068	−0.19 (0.12)	.114
WAIS-R Picture Completion	0.13 (0.22)	.581	0.04 (0.18)	.799	0.07 (0.13)	.608
WAIS-R Block Design	−0.17 (0.24)	.465	0.05 (0.14)	.730	−0.005 (0.10)	.966
Boston Naming Test	0.16 (0.24)	.512	−0.03 (0.13)	.837	0.07 (0.09)	.484
Category Fluency	−0.05 (0.22)	.833	0.13 (0.15)	.382	−0.10 (0.11)	.372
Global and Domain-specific Scores						
Global z-score	−0.09 (0.14)	.527	0.11 (0.06)	.057	−0.03 (0.04)	.510
Memory z-score	−0.08 (0.67)	.679	0.09 (0.10)	.364	0.03 (0.07)	.704
Language z-score	0.06 (0.19)	.770	0.05 (0.10)	.605	−0.02 (0.07)	.823
Executive function z-score	−0.21 (0.21)	.330	0.35 (0.11)	.004	−0.22 (0.08)	.011
Visual spatial z-score	−0.03 (0.19)	.862	0.03 (0.12)	.763	0.04 (0.09)	.656

Abbreviations: GMLT, Groton Maze Learning Test; AVLT, Auditory Verbal Learning Test; WAIS-R, Wechsler Memory Scale-Revised Logical Memory II; TMT-A, Trail Making Test, Part A; TMT-B, Trail Making Test, Part B.

[*]
Models adjust for baseline age, sex, and education.

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Notes: Baseline amyloid refers to the cross-sectional association between baseline amyloid (as a continuous variable) and baseline cognitive performance. Time refers to the annual change in *z*-score for the cognitive dependent variable. The baseline amyloid*time variable refers to annual rate of change in the dependent cognitive variable for each unit increase in baseline amyloid SUVR.

**
Adjusted *P* value obtained through permutation testing.

Table 3

Multivariate linear mixed models examining the effect of amyloid and APOE E4 genotype on baseline cognition and cognitive decline

| | No APOE E4 allele (N=337) | | | | | | 1 APOE E4 allele (N=131) | | | | | |
| | Baseline Amyloid | | Time | | Baseline Amyloid * time | | Baseline Amyloid | | Time | | Baseline Amyloid * time | |
Cognitive z-scores	b(se)	P value**	b(se)	P value**	b(se)	P value**	b(se)	P value**	b(se)	P value**	b(se)	P value**
CogState Tests												
Detection (DET)	0.20 (0.48)	.683	0.02 (0.30)	.939	0.04 (0.23)	.861	−1.26 (0.40)	.002	−0.29 (0.34)	.379	0.27 (0.24)	.236
Identification (IDN)	0.50 (0.43)	.254	0.05 (0.22)	.831	0.12 (0.17)	.446	−0.28 (0.34)	.410	−0.01 (0.22)	.967	0.15 (0.15)	.314
One Card Learning (OCL)	−0.27 (0.45)	.553	−0.11 (0.22)	.605	0.19 (0.16)	.228	−0.51 (0.31)	.099	0.23 (0.19)	.219	−0.09 (0.13)	.519
One Back (ONB)	0.01 (0.43)	.981	0.52 (0.28)	.068	−0.04 (0.21)	.839	−0.36 (0.31)	.250	0.20 (0.25)	.417	0.15 (0.17)	.387
GMLT Total Errors	−0.16 (0.74)	.720	0.06 (0.35)	.847	0.08 (0.26)	.732	−1.01 (0.37)	.017	0.26 (0.36)	.414	−0.04 (0.25)	.859
GMLT Speed	0.36 (0.43)	.410	0.33 (0.22)	.135	−0.13 (0.17)	.429	−0.53 (0.34)	.124	0.46 (0.22)	.040	−0.16 (0.15)	.287
Individual Standard Neuropsychological Tests												
Logical Memory delayed recall	1.30 (0.46)	.005	0.66 (0.25)	.010	−0.38 (0.19)	.047	−0.69 (0.35)	.053	0.10 (0.23)	.650	0.03 (0.16)	.840
AVLT delayed recall recall	0.28 (0.47)	.553	0.37 (0.25)	.136	−0.19 (0.19)	.294	−0.03 (0.30)	.930	0.06 (0.21)	.780	0.05 (0.15)	.756
Visual Reproduction delayed recall	0.52 (0.45)	.241	−0.02 (0.29)	.954	0.11 (0.22)	.608	−0.48 (0.30)	.109	−0.27 (0.25)	.266	0.28 (0.17)	.107
WAIS-R Digit Symbol	−0.01 (0.46)	.994	0.69 (0.20)	.003	−0.48 (0.15)	.004	−0.40 (0.30)	.181	0.28 (0.14)	.069	−0.14 (0.10)	.186
TMT-A	0.55 (0.43)	.198	0.42 (0.29)	.141	−0.23 (0.22)	.278	−0.45 (0.37)	.216	−0.21 (0.30)	.467	0.17 (0.21)	.381
TMT-B	0.29 (0.45)	.497	0.41 (0.23)	.077	−0.26 (0.17)	.120	−0.05 (0.36)	.876	0.25 (0.32)	.393	−0.15 (0.22)	.454
WAIS-R Picture Completion	0.55 (0.42)	.196	0.21 (0.27)	.436	−0.07 (0.20)	.724	−0.04 (0.29)	.881	0.07 (0.26)	.791	0.09 (0.18)	.633
WAIS-R Block Design	0.35 (0.45)	.447	−0.01 (0.21)	.960	0.02 (0.16)	.879	0.44 (0.29)	.123	0.22 (0.21)	.291	−0.09 (0.15)	.531
Boston Naming Test	0.68 (0.15)	.147	−0.06 (0.20)	.762	0.07 (0.15)	.614	0.05 (0.29)	.862	0.16 (0.19)	.389	−0.02 (0.13)	.859
Category Fluency	0.43 (0.41)	.296	0.10 (0.24)	.662	−0.08 (0.18)	.675	−0.19 (0.29)	.545	0.14 (0.20)	.472	−0.11 (0.14)	.408
Global and Domain-specific Scores												
Global	0.45 (0.25)	.077	0.23 (0.09)	.010	−0.13 (0.07)	.063	−0.28 (0.19)	.145	0.08 (0.08)	.345	0.01 (0.06)	.918
Memory	0.69 (0.36)	.052	0.32 (0.16)	.049	−0.14 (0.13)	.246	−0.46 (0.25)	.071	−0.07 (0.14)	.632	0.14 (0.10)	.155
Language	0.55 (0.35)	.123	0.01 (0.16)	.929	0.01 (0.12)	.974	−0.07 (0.25)	.786	0.15 (0.14)	.283	−0.07 (0.10)	.482
Executive function	0.14 (0.39)	.706	0.54 (0.16)	.002	−0.37 (0.12)	.004	−0.23 (0.27)	.401	0.25 (0.18)	.150	−0.14 (0.12)	.251
Visual spatial	0.44 (0.25)	.224	0.10 (0.18)	.581	−0.03 (0.13)	.847	−0.26 (0.25)	.287	0.13 (0.18)	.456	0.01 (0.12)	.938

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Abbreviations: APOE, apolipoprotein E; GMLT, Groton Maze Learning Test; AVLT, Auditory Verbal Learning Test; WAIS-R, Wechsler Memory Scale-Revised Logical Memory II; TMT-A, Trail Making Test, Part A; TMT-B, Trail Making Test, Part B.

*
Models adjust for baseline age, sex, and education.

**
Adjusted *P* value obtained through permutation testing

Notes: Baseline amyloid refers to the cross-sectional association between baseline amyloid (as a continuous variable) and baseline cognitive performance. Time refers to the annual change in *z*-score for the cognitive dependent variable. The baseline amyloid*time variable refers to annual rate of change in the dependent cognitive variable for each unit increase in baseline amyloid SUVR.