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Neuropsychological Markers of Cognitive Decline in Persons With Alzheimer Disease Neuropathology

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Abstract

To evaluate cognitive performance among persons who did and did not develop clinical Alzheimer disease (AD) but had AD neuropathology at autopsy, we examined neuropsychological performance in cognitively normal (Clinical Dementia Rating [CDR] = 0) participants who returned for at least one follow-up and died within 2 years of their last assessment. Non-progressors remained at CDR = 0 until death; progressors developed symptomatic AD during life (CDR > 0). Cognitive performance at baseline was compared between progressors and non-progressors on a global cognitive composite and 4 domain-specific composites (episodic memory, language, attention/working memory, and executive function). Models adjusted for age, education, sex, and non-AD neuropathology. Progressors (n = 173) had worse performance than non-progressors (n = 141) in nearly all cognitive domains. Progressors scored lower on composites of global cognition ($p < 0.001$), executive function ($p = 0.0006$), language ($p < 0.0001$), and episodic memory ($p = 0.0006$), but not on attention/working memory ($p = 0.91$). These data indicate that individuals with underlying AD neuropathology who are clinically normal but who later develop symptomatic AD have worse performance in a wide range of domains vs. individuals with underlying AD neuropathology who are clinically normal but do not become symptomatic during life. Therefore, subtle cognitive decline at baseline may indicate an increased risk of progression to symptomatic AD.

Keywords

Alzheimer disease; Braak staging; Consortium to Establish a Registry for Alzheimer's Disease (CERAD) plaque; Clinical diagnosis; Memory; Mild cognitive impairment; Neuropathology

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INTRODUCTION

The pathological hallmarks of Alzheimer disease (AD) are known to be present well before the onset of symptoms sufficient to trigger a clinical diagnosis of mild cognitive impairment (MCI), or dementia. β-Amyloidosis may begin as early as 2 decades prior to diagnosis, followed by tau proliferation resulting in neuronal injury (1–3). The final stage of "preclinical" AD may be characterized by subtle cognitive decline, although this has yet to be fully defined (3). Studies that have modeled cognitive trajectories in the preclinical stage of AD have shown cognitive declines beginning within approximately 7 years of clinical diagnosis (4, 5), with a pronounced acceleration 3 to 5 years prior to diagnosis (6, 7). However, most of these studies rely on clinical and biomarker evidence of AD in living participants, and the correspondence between clinical diagnosis, in vivo biomarkers and the "gold standard" of neuropathological diagnosis of AD remains unclear (8, 9). Thus, without autopsy confirmation, the time course and cognitive domains that characterize early cognitive decline in preclinical AD may be biased by diagnostic inaccuracies.

Until recently, a diagnosis of AD required autopsy evidence of AD-related neuropathologic change in addition to the presence of symptoms (10). The most recent standards for neuropathologic diagnosis of AD are the NIA-Alzheimer's Association (AA) guidelines, which require only the presence of AD-related neuropathologic change, and do not require evidence of clinical symptoms during life (11). This change effectively acknowledges the presence of a preclinical stage of AD in which subtle cognitive changes may be present that are insufficient to warrant a clinical diagnosis. Using autopsy-confirmed AD as a standard, we previously examined longitudinal cognitive performance in participants with neuropathologic AD who were clinically asymptomatic during life and found subtle declines in attention over time (12). This suggested that the very earliest changes in the AD continuum may be in areas other than episodic memory. In the current study, we extend these findings by examining whether there are baseline differences in cognitive performance between participants with autopsy-confirmed AD who did and who did not develop symptomatic AD, as defined by a clinical diagnosis of MCI or dementia during life.

MATERIALS AND METHODS

Study Sample

Data for this study were obtained from the National Alzheimer's Coordinating Center Uniform Data Set (UDS) (13), and Neuropathology Data Set (NPDS). Data were collected between September 2005 and December 2014 at 34 current and past National Institute on Aging Alzheimer's Disease Centers (NIA ADCs). Written informed consent was obtained from all participants. Research using the NACC database was approved by the University of Washington Institutional Review Board.

As described previously, UDS forms are used to obtain information on subject demographics, health history, and current clinical characteristics. Subjects with cognitive impairment, as well as cognitively normal subjects, are enrolled in the UDS (14). Data, including a neuropsychological test battery, are collected approximately annually.

Neuropathologic data are available for UDS subjects who consent to autopsy and die. These data are recorded in the NPDS and can be linked to UDS data.

Subjects included in this study were required to have 1) neuropathology data available, 2) died within 2 years of their last clinical assessment, 3) 2 or more UDS visits, and 4) normal cognition at the first UDS visit. Normal cognition was defined as a global score of zero on the Clinical Dementia Rating (CDR), an instrument that summarizes an individual's cognitive and functional abilities (15). Subjects who had a CDR score of zero at every follow-up visit were considered 'non-progressors' since they did not develop clinical AD during follow-up, while subjects who had a CDR score of 0.5 or higher (clinical characteristics consistent with symptomatic dementia) from at least 1 follow-up visit were considered 'progressors.' Subjects who received a CDR score >0 but who reverted back to CDR = 0 on or before their last visit were considered non-progressors.

AD Neuropathology

The definition of AD neuropathologic change (AD-NP) was based on a modification of the NIA-AA criteria for neuropathologic AD "ABC score" (11, 16), as previously described. Briefly, Braak stage (B score) for neurofibrillary tangles (18) and Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuritic plaque frequency (19) (C score) were recorded in the NPDS. At the time of data analysis, however, a Thal phase for amyloidβ (Aβ) plaques (20) (A score) was not recorded in the NPDS. To capture the most frequent plaque type, we included "diffuse plaque," which is most likely an early form of Aβ plaque formation and is defined as plaques with no apparent dystrophic neurites, as detected by silver impregnation methods, ubiquitin, or tau immunohistochemistry. All types of Aβ plaques, including diffuse plaques, are also readily identified using Aβ immunohistochemistry.

Subjects with sparse, moderate, or frequent diffuse plaques were considered to have a Thal Aβ plaque phase of 1 or higher and thus met AD-NP inclusion criteria for this study. Likewise, subjects with sparse, moderate, or frequent neuritic plaques had a neuritic plaque C score of 1 or higher and also met study inclusion criteria. Limiting the sample to subjects with diffuse and/or neuritic plaques is similar to including all subjects meeting NIA-AA criteria for low to high AD neuropathologic change. The resulting study sample included only those subjects with Aβ plaques, excluding those without, regardless of Braak stage.

Non-AD Neuropathologic Features

Neuropathology unrelated to AD was defined with variables from the NPDS that were coded to indicate the presence or absence of each condition. Lacunes and infarcts included data on the presence or absence of large cerebral artery infarcts, lacunes (small artery infarcts and/or hemorrhages), and gross infarcts. Data on hemorrhages and microbleeds were indicated with one variable that included the presence or absence of microbleeds and both old and acute hemorrhages. Hippocampal and medial temporal lobe sclerosis was identified with one summary variable indicating presence or absence of unilateral or bilateral sclerosis. Mild, moderate, or severe cerebral amyloid angiopathy was coded as present or absent. Similarly, mild, moderate, or severe arteriosclerosis was coded as present or absent. Lewy body

pathology in the brainstem, limbic regions, neocortex, or any brain region was coded as present or absent. Data regarding other non-AD pathologies, including frontotemporal lobar degeneration and other tauopathies, were not available in the majority of cases and, therefore, were not included in analyses.

Measures of Decline

Neuropsychological test performance was assessed using the UDS neuropsychological battery (21). The tests were grouped into cognitive domains based on a previous factor analysis of the UDS battery (22). The episodic memory domain was measured by the two Logical Memory Tests, the language domain by the Boston Naming Test and the object naming tests, attention/working memory by the Digit Span tests, and executive function domain by the Trail Making tests and Digit Symbol test. At each visit, an individual test score was converted to a z-score by subtracting the mean and dividing by the standard deviation of all UDS initial-visit scores among cognitively normal subjects defined as having a CDR global score of 0. The z-scores for the tests within each domain were then averaged to obtain a standardized domain-specific composite score. Averaging all of the domain-specific scores created a global cognitive composite score. Domains missing data on at least one test were considered missing for that subject.

Statistical Analysis

Mean cognitive performance at the initial visit was estimated using linear regression with generalized estimating equations (GEE), which allowed us to account for clustering of subjects within an ADC. Each of the four cognitive domains, as well as the global composite, was an outcome measure (dependent variable) in a separate regression model, resulting in five separate models. The average score for progressors was compared to the average for non-progressors using a Wald test. Two adjusted models were run for each outcome measure. The first model was adjusted for age at initial visit, education, and sex. We were unable to adjust for race in the model due to the infrequency of non-white race in both groups. The second model was adjusted for the same characteristics as the first as well as the non-AD neuropathologic features. Adding non-AD neuropathologic features did not change results or conclusions. Several sensitivity analyses were run using different methods of adjustment for time of follow up. All regression models were fit with an independent correlation structure and robust standard errors in R 2.14.2 using the “geeglm” package.

RESULTS

Neuropathologic data were available for 3345 UDS subjects. Restricting the sample to those who received a diagnosis of low to high AD neuropathologic change and who died within 2 years of their last available assessment reduced the sample to 2381 subjects. The data were further limited to subjects who enrolled with a CDR global score of 0 and had at least 2 UDS visits. Of the resulting analytic sample of 314 subjects, 173 (55%) had progressed to symptomatic AD and 141 (45%) remained with CDR 0 through their final clinical assessment.

Demographic characteristics and neuropathology findings are described in Tables 1 and 2. As shown in Table 1, subjects completed 2 to 7 annual visits, with the majority of subjects completing more than 2 visits (82%). Progressors and non-progressors were similar in terms of age at first UDS visit, education, race, and sex distribution but a higher percent of progressors had 1 or 2 APOE ε4 alleles. Progressors more often made 3 or more visits and had a longer period of time between first visit and last visit, (mean of 1515 days vs. 1243 days for non-progressors). Correspondence between clinical diagnoses and CDR global score at the last available visit was high. Of the non-progressors, only 9/141 (6%) were given a clinical diagnosis of MCI or dementia. Alternatively, only 15/173 (9%) of progressors were given a clinical diagnosis of normal cognition. Progressors had slightly more ischemic lesions (infarcts and lacunes) and hemorrhagic pathology (hemorrhages or microbleeds) as well as more arteriosclerosis and cerebral amyloid angiopathy. Progressors also had more pronounced AD neuropathologic change (neuritic plaques, diffuse plaques, and Braak stage I or higher). The presence of Lewy body pathology was similar between progressors and non-progressors.

Differences in mean scores (β) between progressors and non-progressors are presented, adjusted for age, education, and sex in Table 3. The average progressor performed 0.33 SDs worse than the average non-progressor on the Global Composite. Progressors also performed significantly worse than non-progressors in several cognitive domains including Episodic Memory, Executive Functioning, and Language; however, there were no group differences on the Attention composite score. Table 4 describes an additional model that further adjusted for non-AD neuropathologic variables including the presence of infarcts or lacunes, the presence of hemorrhages or microbleeds, and the presence of cerebral amyloid angiopathy. Hippocampal and medial temporal lobe sclerosis were absent in the vast majority of cases (91% – 98%), and were, therefore, not included in models. Overall results from these more comprehensive models were nearly identical to models that did not include non-AD neuropathologic variables, suggesting that group differences in cognitive functioning were not associated with non-AD neuropathology.

Given the differences in length of follow up for the two groups, several sensitivity analyses were carried out in which the above models were repeated: 1) with additional adjustment for length of time between first and last visit, 2) restricting the analysis to only persons who had 4 or fewer years between first and last visit, and 3) both methods combined. Each of these 3 methods was performed with and without adjustment for non-AD neuropathology (Supplementary Tables 1a–c and 2a–c). All statistically significant associations remained significant at the $\alpha = 0.05$ level, except for episodic memory; in analyses limited to subjects with only 4 years of follow-up the association of episodic memory and progressor status was just above our prescribed α-level ($p = 0.05–0.07$). These models involved excluding observations, which decreased the total number of subjects and hence the statistical power was also decreased.

DISCUSSION

The aim of this study was to describe baseline cognitive performance among individuals who were cognitively normal at study entry but died with AD neuropathology. We had a

particular interest in determining whether those who progressed to MCI or dementia were different at baseline from those who remained cognitively normal till death. Our analyses revealed that progressors had statistically significantly poorer cognitive functioning at baseline in global cognitive functioning and in every domain of cognition except attention. The largest effects were observed on tests of executive functioning where progressors scored, on average, 0.60 SDs worse than non-progressors. Progressors also scored statistically significantly worse on tests of language and episodic memory.

Our findings revealed that there were substantial baseline differences between individuals who developed clinical manifestations of AD during life and those who did not. However, the differences were not as expected in that they were not limited to minor changes in one area of cognition but rather manifested across nearly all domains of cognition. The most pronounced effects were seen on tests of executive functioning followed by language and episodic memory. These results suggest that evidence of subtle cognitive decline at baseline may be an indicator of risk of disease progression rather than an indicator of the presence of AD pathology. In addition, neuropathology unrelated to AD, including the presence of infarcts or lacunes, hemorrhages or microbleeds, hippocampal and medial temporal lobe sclerosis, and cerebral amyloid angiopathy, had no impact on the results. This is in contrast to studies that have found associations between vascular neuropathology and cognitive dysfunction during life (23–25).

Other studies on the topic of cognitive changes in preclinical AD have tended to show changes in only 1 or 2 domains and have most recently identified attention/working memory as the most common domain in which changes occur (26–29). Methodologically, the majority of these studies used neuroimaging to determine AD status or were based only on clinical symptoms (29), whereas our study defined AD using neuropathologic features, the “gold standard.”

More recently, several studies have used autopsy-verified AD to evaluate neuropsychological changes in the preclinical phase of AD. One study compared asymptomatic persons with and without AD NP and found no differences in trends over time (30). A second study compared asymptomatic persons with and without AD-NP and found no cross-sectional differences at baseline or final evaluation but found differences in slope of decline for several tests (i.e. word list delayed recall, verbal fluency, constructional praxis) (31). Another study found that those who progressed to autopsy-confirmed AD had a sharp inflection point approximately 1 to 3 years prior to the clinical diagnosis on tests of visuospatial ability and episodic memory (7). Two other studies looked at the correlation of degree of pathology with neuropsychological test scores in asymptomatic people, finding more advanced pathology associated with worse performance on episodic and working memory in one study (32), and for multiple domains (episodic memory, semantic knowledge, visuospatial ability, and executive functioning) in the other study (33). Thus, very few studies have found lower test scores across multiple domains in asymptomatic persons with AD-NP.

Identification of individuals at greatest risk of developing symptomatic AD is critical for secondary prevention trial participant selection. Enrichment strategies for prevention studies

typically rely on medical history and demographic variables and are increasingly using methods that are costly (e.g. amyloid imaging) and often invasive (e.g. cerebrospinal fluid biomarkers) to detect the presence of AD pathology in cognitively normal individuals (34). The current results indicate that subtle but widespread cognitive impairment at baseline assessment may be useful as a noninvasive and inexpensive strategy for participant selection.

The current results show lower cross-sectional scores across multiple domains at baseline for people with AD-NP who eventually did convert to MCI or dementia. Except for studies by Johnson et al (7), and Price et al (33), which showed changes in multiple domains, all other known autopsy-confirmed studies showed either no changes, or only changes in 1 or 2 domains, or more subtle changes detected only by following trends over time (vs. cross-sectional changes). Most of the prior autopsy studies looked at persons who were asymptomatic at the time of death, in comparison to the current study that looked at baseline changes in people who did eventually develop symptoms. Thus, it can be postulated that these persons were further along in the course of their cognitive decline and that changes in multiple domains likely occur later in the preclinical course.

Our results also stand out in comparison to a prior study with NACC UDS data that compared changes in cognitive trajectories for asymptomatic people with and without AD-NP (12). Similar to studies described above, that study showed changes in only attention/working memory. Of note, the group of people with AD-NP in that prior study constitutes some of the non-progressor group in the current study; however, that prior study compared cognitive performance in persons with and without AD-NP, all of whom remained asymptomatic until death. Thus, the fact that no changes in attention/working memory were noted in the current study may signify that such changes occur early and have already occurred by the time the more widespread changes in other domains appear. Putting the 2 studies together, it can be postulated that attention/working memory might be the earliest subtle neuropsychological domain to be affected in the preclinical phase of AD, followed by more widespread changes in other domains later on, closer to the time a person develops noticeable symptoms.

Before drawing conclusions from the data, however, some limitations must be addressed. First, retrospectively fitting UDS neuropathology data to the NIA-AA criteria has shortcomings. Persons earlier in the study period might have undergone less sensitive autopsy techniques that would have missed the presence of Aβ deposits, which might lead to an underassessment of cases that would have met NIA-AA criteria if they had been fully assessed. However, this would apply to both progressors and non-progressors and would likely not bias the results of the study. Second, more highly educated, wealthier and white persons are more likely to volunteer as asymptomatic controls and to consent to autopsy. Thus, the generalizability of the findings is limited. Third, some ADCs use neuropsychological results in their diagnoses of MCI and dementia. This would lead to a possible ascertainment bias that would tend to bias the results towards false positive assessment of clinical symptoms in later visits. However, the differences in test scores that were detected in this study were at the baseline visit, when all subjects were classified as asymptomatic. This suggests that this possible limitation would not have biased the findings

detected at baseline, which are the main finding of the study. Furthermore, diagnoses were based on the CDR global score, not the clinical diagnosis. Fourth, our adjustments for non-AD neuropathology were not comprehensive and did not include data on frontotemporal lobar degeneration with TDP-43 pathology (FTLD-TDP) or FTLD with tauopathy (FTLD-Tau). Fifth, clinical diagnosis and the CDR global score did not align in some participants, which may represent a misclassification of symptomatic status. We anticipate, however, that this did not bias the study results because there were only a few people in each group who had a different diagnosis than the diagnosis that would have been expected based on CDR alone. Finally, there is a potential for survival bias in that subjects living longer had more opportunity to progress than those who died closer to their initial visit. We explored this possibility in post-hoc sensitivity analyses. Adjustment for potential survival bias produced results that remained statistically significant for executive function, language and the global composite score; and were significant or very nearly significant for episodic memory.

Despite these limitations, this study has major strengths. It provides data on standardized neuropsychological tests for multiple visits in people who had autopsy confirmed AD neuropathologic changes. Also, it is one of the first studies with autopsy confirmed AD to assess neuropsychological test scores in people who were asymptomatic at first assessment and who then eventually developed cognitive impairment. Thus, these data allow us to draw reasonable conclusions about neuropsychological changes that people with underlying AD-NP manifest while they are still otherwise asymptomatic and especially shortly before they do develop symptoms. This study has shown that individuals with underlying AD neuropathology who are clinically normal but who later develop a clinical diagnosis of MCI or dementia have subtle evidence of lower performance in a wide range of domains compared with individuals with underlying AD neuropathology who are clinically normal but who do not later develop a clinical diagnosis of MCI or dementia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Frequency of Clinical and Demographic Characteristics

Characteristic	Non-progressor (n = 141)		Progressors (n = 173)	
Number of visits made				
2	37	(26%)	18	(10%)
3	24	(17%)	29	(17%)
4	28	(20%)	34	(19%)
5	19	(14%)	43	(25%)
6	17	(12%)	28	(16%)
7	13	(9%)	15	(9%)
8	3	(2%)	5	(3%)
9	0	(0%)	1	(1%)
Age at first UDS visit				
<60	0	(0%)	3	(2%)
60–69	4	(3%)	4	(2%)
70–79	25	(18%)	11	(6%)
80–89	61	(43%)	60	(35%)
90–94	35	(25%)	44	(25%)
95+	16	(11%)	51	(30%)
Education[a]				
No college	32	(23%)	39	(23%)
1 – 4 years of college	66	(47%)	83	(49%)
At least some graduate school	43	(30%)	48	(28%)
Race[b]				
White	136	(97%)	166	(97%)
Black	2	(1%)	3	(2%)
Multiracial	3	(2%)	2	(1%)
Sex				
Female	88	(62%)	108	(62%)
Male	53	(38%)	65	(38%)
APOE ε4[c]				
Non-carrier	107	(82%)	112	(70%)
Heterozygous	22	(17%)	46	(29%)
Homozygous	1	(1%)	1	(1%)

[a] 3 progressors were missing data on education

[b] 2 progressors were missing data on race; defined using NACC derived variable “naccnihr”

[c] 11 non-progressors and 14 progressors were missing data on APOE ε4 allele frequency

NACC, National Alzheimer’s Coordinating Center; UDS, Uniform Data Set.

Table 2

Frequency of Neuropathologic Features

	Non-progressors (n = 141)	Progressors (n = 173)
CERAD neuritic plaque frequency[a]		
None	24 (17%)	13 (8%)
Sparse	53 (37%)	54 (31%)
Moderate	39 (28%)	63 (36%)
Frequent	25 (18%)	43 (25%)
Diffuse plaque frequency[b]		
None	6 (5%)	3 (2%)
Sparse	35 (29%)	34 (22%)
Moderate	34 (28%)	36 (24%)
Frequent	45 (38%)	78 (52%)
Braak Stage[c]		
0	6 (4%)	2 (1%)
I–II	69 (50%)	44 (25%)
III–IV	59 (42%)	74 (43%)
V–VI	6 (4%)	53 (31%)
Infarcts or lacunes[d]		
Not Present	110 (78%)	106 (61%)
Present	30 (21%)	67 (39%)
Hemorrhorages and microbleeds[e]		
Not Present	134 (95%)	163 (94%)
Present	7 (5%)	10 (6%)
Arteriosclerosis[f]		
Not Present	25 (21%)	23 (15%)
Present	96 (79%)	130 (85%)
Lewy body pathology[g]		
Not Present	115 (83%)	142 (83%)
Present	24 (17%)	30 (17%)
Cerebral amyloid angiopathy[h]		
Not Present	73 (53%)	60 (35%)
Present	66 (47%)	111 (65%)

[a] Defined using NACC derived variable “naccneur”.

[b] 21 non-progressors and 22 progressors were not assessed for diffuse plaques; defined using NACC derived variable “naccdiff”.

[c] 1 non-converter was not assessed for Braak & Braak neurofibrillary tangle stage; defined using NACC derived variable “naccbraa”.

[d] 1 non-converter was missing data on infarcts; defined using NACC derived variable “naccinf”.

[e] Defined using NACC derived variable “nacchem”.

[f] 20 non-converts and 20 progressors were missing data on arteriosclerosis; defined using NACC derived variable “naccarte”.

[g] 2 non-progressors and 1 converter were missing data on Lewy body pathology; defined using NACC derived variable “nacclewy”.

[h] 2 non-progressors and 2 progressors were missing data on cerebral amyloid angiopathy; defined using NACC derived variable “naccamy”.

CERAD, Consortium to Establish a Registry for Alzheimer’s Disease; NACC, National Alzheimer’s Coordinating Center; UDS, Uniform Data Set.

Table 3

Mean Test Score at First Assessment: Adjustment Method 1

	Non-progressors		Progressors			
Test by domain	**n**	**Mean (SD)[a]**	**n**	**Mean (SD)[a]**	**Estimate (95% CI)[b]**	**P-value[c]**
Episodic memory	128	0.18 (0.95)	152	−0.30 (0.98)	−0.34 (−0.50, −0.18)	.0001
Attention	130	−0.12 (0.85)	152	−0.17 (0.84)	−0.03(−0.23,0.18)	.80
Executive function	131	−0.38 (0.89)	141	−1.01 (1.25)	−0.58 (−0.83, −0.32)	<.0001
Language	129	−0.12 (0.61)	149	−0.55 (0.72)	−0.38 (−0.54, −0.22)	<.0001
Global composite	121	−0.10 (0.52)	130	−0.49 (0.60)	−0.33 (−0.46, −0.19)	<.0001

[a] The mean scores and standard deviations presented are raw values, not estimated from the model.

[b] The term “estimate” indicates the difference in means cores between progressors and non-progressors, adjusted for the variables in the model.

[c] p values were determined from generalized estimating equations model predicting test score by AD-NP status adjusting for age at visit (continuous), education (categorical), and sex (categorical).

AD-NP, Alzheimer disease neuropathologic change; CI, confidence interval.

Table 4

Mean Test Score at First Assessment: Adjustment Method 2

	Non-progressors		Progressors			
Test by domain	**n**	**Mean (SD)[a]**	**n**	**Mean (SD)[a]**	**Estimate (se)[b]**	**p value[c]**
Episodic memory	108	0.13 (0.91)	133	−0.33 (0.97)	−0.44 (−0.68, −0.19)	.0006
Attention	109	−0.13 (0.82)	133	−0.18 (0.86)	−0.01(−0.24,0.21)	.91
Executive function	108	−0.38 (0.93)	120	−1.01 (1.29)	−0.60 (−0. 94, −0.26)	.0006
Language	109	−0.11 (0.61)	130	−0.56 (0.74)	−0.43 (−0.61, −0.24)	<.0001
Global composite	104	−0.11 (0.50)	114	−0.50 (0.61)	−0.34 (−0.50, −0.18)	<.0001

[a] The mean scores and standard deviations presented are raw values, not estimated from the model.

[b] The term “estimate” indicates the difference in means cores between progressors and non-progressors, adjusted for the variables in the model.

[c] P-values were determined from generalized estimating equations model predicting test score by Alzheimer disease neuropathologic change status adjusting for age at visit, education, sex, presence of infarcts or lacunes, presence of hemorrhages or microbleeds, and presence of cerebral amyloid angiopathy.