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Word-list Intrusion Errors Predict Progression to Mild Cognitive Impairment

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Abstract

Objective—Preclinical Alzheimer's disease (AD) defined by a positive AD biomarker in the presence of normal cognition is presumed to precede mild cognitive impairment (MCI). Subtle cognitive deficits and cognitive inefficiencies in preclinical AD may be detected through process and error scores on neuropsychological tests in those at risk for progression to MCI.

Methods—Cognitively normal participants (n=525) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) were followed for up to five years and classified as either "stable normal" (n=305) or "progressed-to-MCI" (n=220). Cox regressions were used to determine if baseline process scores on the Rey Auditory Verbal Learning Test (AVLT) (intrusion errors, learning slope, proactive interference, retroactive interference) predicted progression to MCI and a CDR score of 1 after considering demographic characteristics, APOE ε4 status, cerebrospinal fluid AD biomarkers, ischemia risk, mood, functional difficulty, and standard neuropsychological total test scores for the model.

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Results—Baseline AVLT intrusion errors predicted progression to MCI (HR: 1.04, 95% CI: 1.01–1.07, p=.008) and improved model fit after the other valuable predictors were already in the model, χ^2(df=1)=6.330, p=.012. AVLT intrusion errors also predicted progression to CDR = 1 (HR: 1.10, 95% CI: 1.02–1.18, p=.016) and again improved model fit, χ^2(df=1)=4.682, p=.030.

Conclusions—Intrusion errors on the AVLT contribute unique value for predicting progression from normal cognition to MCI and normal cognition to mild dementia (CDR=1). Intrusion errors appear to reflect subtle change and inefficiencies in cognition that precede impairment detected by neuropsychological total scores.

Keywords

Process scores; Intrusion errors; preclinical AD; MCI; subtle cognitive decline

Introduction

According to NIA-AA guidelines (Sperling et al., 2011), objective changes in cognition during preclinical Alzheimer's disease (AD) do not occur until Stage 3 and invariably follow amyloidosis (Stage 1) and neurodegeneration (Stage 2). However, recent evidence suggests that this proposed temporal sequence is not invariant. Cognitively normal elderly participants who progressed to mild cognitive impairment (MCI) in the Alzheimer's Disease Neuroimaging Initiative (ADNI) study were more likely to have neurodegeneration than amyloidosis as their first indication of preclinical AD. Furthermore, they were just as likely to have operationally-defined subtle cognitive decline as amyloidosis as their first indication (Edmonds et al., 2015a). These findings indicate that measures of subtle cognitive change can be as important as other markers of preclinical AD and suggest that additional research is needed to identify the most sensitive and specific cognitive measures that can be used with other AD biomarkers (e.g., β-amyloid, tau/hyperphosporylated-tau) to detect preclinical disease.

It is well established that memory impairment characterized by rapid forgetting over a delay interval is one of the most sensitive indicators of early AD (e.g. Delis et al., 1991, Welsh et al., 1991). However, there is evidence that additional process features of performance on tests of learning and memory may provide useful information about early cognitive changes related to AD (e.g., Libon et al., 2011; Loewenstein et al., 2004).

Analysis of these *process scores* (i.e., behavior that speak to the errors and process by which a test score is achieved), largely advanced by Kaplan (1988) and her colleagues (e.g., Delis, Kramer, Kaplan, E., & Ober., 2000; Lamar et al, 2010; Price et al., 2009), emphasize the importance of understanding the underlying nature of the brain-behavior interaction that leads to a specific outcome or achievement such as the total score on a neuropsychological measure. Process analysis of serial word-list learning and memory has been applied to AD (e.g., Cahn et al., 1997; Davis et al., 2002; Delis et al., 1991; Libon et al., 1996; Loewenstein et al., 2004), subcortical dementias (e.g., Massman, Delis, Butters, Levin & Salmon, 1990), and MCI (e.g., Libon et al., 2011). In addition, early AD is associated with abnormally slow learning across trials of a word-list memory task (i.e., a flattened learning slope), increased susceptibility to interference, and a greater frequency of extra-list intrusion errors (Cahn et

al., 1997; Delis et a., 1991; Price et al., 2011; Loewenstein et al., 2004; Salmon & Bondi, 2009). Similar process features have been observed in the word-list memory test performance of patients with amnestic MCI, including rapid forgetting, increased production of intrusion errors, and an increased tendency to endorse foils on a recognition measure (Libon et al., 2011).

Only a few studies have examined process scores on word-list memory test performance and error profiles in cognitively normal older adults or those with preclinical AD. Bondi and colleagues (Bondi et al., 1994) found that non-demented older adults with a family history of AD had worse recall across learning trials and, after a delay interval, exhibited a greater "recency" effect (i.e., a tendency to recall words from the end of a list), and made more intrusion errors than those without a family history. Another study showed that delayed free recall and cued-recall intrusion errors from a word-list learning test, and apolipoprotein E (APOE) ε4 genotype, all significantly and independently predicted progression to AD in cognitively normal older adults (Bondi et al., 1999). Mistridis and colleagues (Mistridis, Krumm, Monsch, Berres, & Taylor, 2015) found more rapid forgetting (i.e. worse savings scores), poorer recognition discriminability, and more intrusion errors on a word-list memory task in cognitively normal older adults who later developed MCI compared to those who remained normal. In their study, faster forgetting emerged 8 years prior to the diagnosis of MCI, while poorer recognition discriminability and more intrusion errors became apparent 2 years prior to the MCI diagnosis.

The results of these studies suggest that process and error scores from word-list memory measures may be useful for identifying cognitive difficulty or inefficiency in preclinical AD prior to the emergence of frank impairment on neuropsychological total scores. To examine this possibility, the present study determined the added value of word-list memory test process scores to standard neuropsychological total scores, cerebrospinal fluid (CSF) AD biomarkers (β-amyloid, tau, hyperphosporylated-tau), and genetic susceptibility for predicting progression from cognitively normal to MCI over a 5-year period. The inclusion of CSF biomarkers is particularly innovative since these biomarkers are the basis for the working definition of preclinical AD (Sperling et al., 2011), and to our knowledge, this is the first study to examine neuropsychological process scores as predictors of progression to MCI after controlling for these CSF markers. Reliable identification of persons at risk for AD will allow greater opportunity to intervene earlier to prevent or delay future decline.

Methods

Procedure

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information on ADNI, see www.adni-info.org. This study was approved by the Institutional Review Boards at each of

the participating institutions, and written informed consent was obtained from all participants or authorized representatives at each site.

Participants

ADNI participants were between ages 55 and 90 years old, were on stable permitted medications, completed at least 6 years of education or work history equivalent, were fluent in English or Spanish, had a reliable study partner, had a Geriatric Depression Scale < 6, a Hachinski Ischemic Score ≤ 4, adequate visual/auditory acuity, and good general health. Participants were excluded at enrollment if they had a history of significant head trauma or neurologic disease.

All non-demented ADNI participants were reclassified as "normal" or MCI based on application of Jak and Bondi's actuarial neuropsychological criteria (Bondi et al., 2014; Jak et al., 2009) to their baseline data.[1] Participants were classified as MCI if (1) they had an impaired score, defined as >1 standard deviation (SD) below the age/education/gender-corrected normative mean on two measures within at least one cognitive domain [memory (Rey Auditory Verbal Learning Test delayed recall and recognition), language (category fluency and 30-item Boston naming Test), or processing speed/executive function (Trail Making Test Parts A and B]; or (2) they had one impaired score, defined as >1 SD below the age/education/gender-corrected normative mean, across all three cognitive domains sampled; or (3) they were rated by an informant to have a Functional Activities Questionnaire score of ≥ 6. If none of these criteria were met, the participant was diagnosed as cognitively normal.

This procedure identified 754 cognitively normal participants (at baseline) who were considered for inclusion in the current study. Of these participants, 201 were excluded because of missing CSF biomarkers, genetic testing or other baseline variables, and 28 were excluded for no follow-up data, and, therefore, no opportunity to assess for progression to MCI. A final analytic sample of 525 cognitively normal participants was used in the primary analyses. The Jak and Bondi actuarial neuropsychological MCI criteria were then applied to data collected at the 6-, 12-, 24-, 36-, 48-, and 60-month follow-up visits to determine which of these 525 participants progressed to MCI within 5 years of baseline. Based on this determination, participants were classified as *"Stable normal"* (n=305) or "*progressed to MCI"* (n=220). Table 1 presents baseline demographic and clinical characteristics for the entire sample and separately for the *stable normal* and *progressed-to-MCI* groups. The 229 excluded participants were older [$t(751)=3.65$, $p<.001$, $d=.29$], slower on the Trail Making Test, Part A [$t(751)=2.39$, $p=.017$, $d=.19$], and had a flatter Rey Auditory Verbal Learning Test learning slope [$t(751)=-2.44$, $p=.015$, $d=.19$] than the 525 included participants, but did not differ on any other demographic, clinical, biomarker, or cognitive variables. Because the majority of excluded participants were excluded due to missing CSF data (n=191), a follow up analysis was run that included all participants with baseline neuropsychological data and

[1]The Jak and Bondi actuarial neuropsychological MCI criteria were applied because they more accurately diagnose MCI than the original ADNI criteria (Bondi et al., 2014). The original ADNI criteria are susceptible to false-positive (i.e., participants diagnosed as MCI but had normal cognitive and biomarker profiles, normal cortical thickness maps, normal amyloid imaging levels, and lower rates of decline; Bangen et al., 2016; Bondi et al., 2014, Edmonds et al., 2015b, 2016a) and false-negative (i.e., participants diagnosed as normal but had impaired cognitive scores, abnormal biomarkers, and rates of progression consistent with MCI; Edmonds et al., 2016b) diagnostic errors.

with at least one follow up visit (n=716) to determine whether the inclusion of these participants changed the pattern of process score effects.

Of the 525 participants included in the primary analysis, all participants had a baseline CDR score of 0 or 0.5; within 5 years, 22 progressed to a Clinical Dementia Rating (CDR) = 1, which is consistent with a mild dementia classification (Burke et al., 1988; Morris, 1993). A secondary analysis examining time to progression to CDR = 1 was used to support the primary findings related to progression to MCI.

Measures

Depression and Functional Impairment—The Geriatric Depression Scale (GDS; Sheikh & Yesavage, 1986) was used to assess depressive symptomatology. Higher scores indicate more depressive symptoms. The informant-rated Functional Activities Questionnaire (FAQ; Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982) was used to measure difficulty with daily activities (e.g., paying bills, remembering appointments, shopping). Higher scores indicate more functional difficulty. The CDR (Morris, 1993) is based on informant and participant interviews that assess cognitively-driven functional change. Scores are independent of neuropsychological measures and a CDR score of 1 correspond a classification of mild dementia. The CDR was not used in participant diagnostic classification, but was used as an independent validation of the primary analysis results.

Biological Markers of AD—CSF concentrations of β-amyloid ($A\beta_{1–42}$), total tau (t-tau), and hyperphosporylated-tau ($p\text{-}tau_{181p}$) were used to assess AD pathology. Lower CSF levels of $A\beta_{1–42}$ and higher levels of $p\text{-}tau_{181p}$ and t-tau are indicative of greater AD pathology in the brain. APOE ε4 status was included as a dichotomous variable of genetic AD susceptibility. APOE ε4 positivity is related to a higher rate of development of AD (e.g., Bondi et al., 1995). A modified Hachinski score (Rosen, Terry, Fuld, Katzman, & Peck, 1980) was used to quantify ischemia risk.

Neuropsychological Total Scores—Total scores from standard neuropsychological tests included: (1) free recall across Trials 1–5 on the Rey Auditory Verbal Learning Test (AVLT; Rey, 1964); (2) 30-minute delayed free recall on the Rey AVLT; (3) correct responses on the Animal Fluency test; (4) correct responses (spontaneous and with semantic cues) on the 30-item Boston Naming Test (BNT); (5) time (seconds) to complete the Trail Making Test (TMT) Part A; and (6) time (seconds) to complete the TMT Part B.

AVLT Process Scores—The Rey AVLT is a 15-item word-list learning and memory test that includes 5 learning trials with auditory presentation of the 15 words and immediate recall on each trial (List A Trials 1–5), an interference trial with a different list of words (List B), a short-delay free recall trial for List A words immediately after List B (Trial 6), a long delay free recall trial for List A words after 30-minutes of unrelated testing (Trial 7), and delayed recognition of List A words presented among an equal number of new distractor words. Four process scores from the Rey AVLT were used in the present analyses. An *intrusion errors* score was calculated as the total number of intrusion errors across all immediate (List A Trials 1–5, List B) and delayed free recall (short- and long-delay) trials.

An intrusion was defined as the production of any word that was not on the list that was being recalled (i.e., extra-list). A *learning score* was calculated as (List A Trial 5 – List A Trial 1)/5. This measure provides an estimate of the learning slope across trials. A larger score indicates faster learning. A *proactive interference* score was calculated as List B/Mean of List A Trials 1–5 (Loewenstein et al., 2004). A lower score indicates greater susceptibility to proactive interference (i.e., previous learning inhibits new learning). A *retroactive interference* score was calculated as List A Trial 6/List A Trial 5 (Loewenstein et al., 2004). A lower score indicates greater susceptibility to retroactive interference (i.e., new learning inhibits recall of previously learned information).

Statistical Analyses

Baseline demographic and clinical characteristics for each group (i.e., stable normal or progressed-to-MCI) were examined using independent samples *t*-tests for normally distributed variables, Mann-Whitney *U* tests for non-normally distributed variables, or chi-squared tests for categorical variables.

Progression to MCI—The primary analyses used Cox proportional hazards models to examine the predictors of time to MCI diagnosis. Specifically, the four models were run to examine the added predictive value of the individual process score variables (Model 1: intrusion errors, Model 2: learning slope, Model 3: proactive interference, Model 4: retroactive interference) after other relevant variables were already included in the model. Because raw data were used for the analyses, demographic variables (age, education, sex) were entered in Block 1. Then, GDS, FAQ, Hachinski score, APOE ε4 status, p-tau, t-tau, β-amyloid, category fluency, BNT, Trails A, Trails B, AVLT immediate recall, and AVLT delayed recall were considered for Block 2 and a forward stepwise procedure was used to determine which of these variables were included in the model so that only predictors that add value were included. Block 3 included the individual process score to determine whether the model fit was improved with the addition of this variable. Model fit was evaluated with the change in log-likelihood (i.e., −2LL) using a chi-square test to compare the change in fit with the addition of the third block that included the process score.

In these analyses, time-to-MCI was the number of months from the initial neuropsychological assessment to the neuropsychological assessment when they first met criteria for MCI. Participants who did not progress to MCI during their follow-up period were censored at their last occasion. Multicollinearity of the independent variables was assessed and all variance inflation factor (VIF) values were less than 3. The model was also run with all variables entered in the model (rather than using a stepwise approach for Block 2) and the pattern of process score results did not differ, so the more parsimonious stepwise approach was reported.

Follow-up analyses were then conducted to determine whether the effect of the process scores was different when the CSF variables (p-tau, t-tau, β-amyloid) were excluded from the model, allowing for a larger sample size. The 4 models described above were replicated without the CSF variables.

Progression to CDR=1—Secondary Cox models were used to examine the predictors of time to CDR = 1. The same approach as described above for the time-to-MCI analyses were completed, including the forward stepwise approach for block 2, which lead to slightly different predictors in the model.

For process scores that added significant predictive value for progression, Kaplan-Meier curves were used to obtain a graphical display. The continuous process score variables were re-coded into categorical variables for the Kaplan-Meier curves such that −1 SD and below the mean was coded as 0, −1 to +1 SD was coded as 1, and +1 SD and above was coded as 2. The ±1 SD criteria were used to be largely consistent with the 1 SD cutoffs that are used in the MCI criteria. A Log Rank test was used to determine if there were significant differences between the categorical process score variables.

Results

Results of the baseline comparisons between participants who remained cognitively normal versus those who progressed to MCI within 5 years are shown in Table 1. Compared to those who remained cognitively normal, participants who progressed to MCI were more likely to be older, male, had more depressive symptoms, had more functional difficulty, were more likely to be an APOE ε4 carrier, had higher CSF t-tau levels, lower CSF β-amyloid levels, poorer performance on all neuropsychological total scores (AVLT immediate and delayed recall, category fluency, BNT, TMT Part A and Part B), more AVLT intrusion errors, a shallower learning slope on AVLT Trials 1–5, and greater AVLT retroactive interference (i.e., less recall after AVLT List B as a proportion of Trial 5 recall).

Progression to MCI

The results of the Cox models examining the predictors of time to MCI are shown in Table 2. Blocks 1 and 2 (Block 1: demographics; Block 2: stepwise predictors) were the same across the four models. For Block 2, the forward stepwise procedure included the following variables: FAQ, category fluency, BNT, AVLT delayed recall, APOE ε4 status, and t-tau. Blocks 1 and 2 showed significant incremental improvement in model fit: Block 1 $\chi^2(3)=9.23$, $p<.026$ and Block 2 $\chi^2(6)=153.37$, $p<.001$.

With the addition of intrusion errors (Block 3), there was a significant incremental improvement in model fit, $\chi^2(1) =6.33$, $p=.012$. With all variables in the model, AVLT intrusion errors significantly predicted time-to-MCI (HR: 1.04, 95% CI: 1.01–1.07, p=.008) along with more education (HR: 1.07, 95% CI: 1.01–1.13, p= 0.015), more functional difficulty (HR: 1.24, 95% CI: 1.23–1.36, p<.001), APOE ε4 carrier status (HR: 1.38, 95% CI: 1.03–1.85, p=.032), higher CSF t-tau levels (HR: 1.00, 95% CI: 1.00–1.01, p=.019), lower AVLT delayed recall (HR: 0.87, 95% CI: 0.84–0.91, p<.001), lower category fluency (HR: 0.93, 95% CI: 0.90–0.96, p<.001), and lower BNT (HR: 0.86, 95% CI: 0.81–0.91, p<.001).

The three additional models examining learning slope, proactive interference, and retroactive interference in Block 3 showed that these process scores did not predict progression to MCI above and beyond the other variables included in Blocks 1 and 2 (all ps>.05). The Kaplan-

Meier curves of intrusion errors predicting progression to MCI is shown in Figure 1. The overall Log Rank comparison for the categorical intrusion errors was significant, $\chi^2(2)=11.43$, $p=.003$.

The primary time-to-MCI analyses were then replicated in a follow-up series of models that did not include the CSF variables (p-tau, t-tau, β-amyloid), which allowed for a larger sample size (n=716). For Block 2, the forward stepwise procedure included the following variables: FAQ, APOE ε4 status, AVLT delayed recall, category fluency, BNT, and TMT Part B. For these analyses, the addition of intrusion errors again improved model fit, $\chi^2(1)=10.31$, $p=.001$. With all variables in the model, AVLT intrusion errors significantly predicted time-to-MCI (HR: 1.04, 95% CI: 1.02–1.06, $p=.001$). Again, learning slope, proactive interference, and retroactive interference in Block 3 showed that these process scores did not predict progression to MCI above and beyond the other variables included in Blocks 1 and 2 (all ps>.05).

Progression to CDR=1

Of the 525 participants included in this analysis, 22 participants progressed to a CDR score = 1, consistent with mild dementia, within 5 years. The results of the Cox models examining the predictors of time to CDR=1 are shown in Table 3. Blocks 1 and 2 (Block 1: demographics; Block 2: stepwise predictors) were the same across the four models. For Block 2, the forward stepwise procedure included the following variables: GDS, FAQ, TMT Part B, AVLT delayed recall, and t-tau. Blocks 1 (demographics) did not show a significant improvement in model fit, $\chi^2(3)=7.73$, $p=.052$, but Block 2 showed significant incremental improvement in model fit, $\chi^2(5)=48.26$, $p<.001$.

With the addition of intrusion errors (Block 3), there was again a significant incremental improvement in model fit, $\chi^2(1)=4.68$, $p=.030$. With all variables in the model, AVLT intrusion errors significantly predicted time-to-CDR=1 (HR: 1.10, 95% CI: 1.02–1.18, $p=.016$), along with more depressive symptoms (HR: 1.41, 95% CI: 1.05–1.89, $p=.021$), more functional difficulty (HR: 1.61, 95% CI: 1.22–2.14, $p=.001$), higher CSF t-tau levels (HR: 1.01, 95% CI: 1.01–1.02, p=.002), lower AVLT delayed recall (HR: 0.80, 95% CI: 0.68–0.94, $p=.008$), and slower TMT Part B (HR: 1.02, 95% CI: 1.01–1.02, $p<.001$). The models with learning slope, proactive interference, and retroactive interference in Block 3 showed that these process scores did not predict progression to CDR=1 above and beyond the other variables included in Blocks 1 and 2 (all ps>.05). The Kaplan-Meier curves of intrusion errors predicting progression to CDR=1 is shown in Figure 2. The overall Log Rank comparison for the categorical intrusion errors was significant, $\chi^2(2)=9.95$, $p=.007$.

Discussion

Our results suggest that intrusion errors on the AVLT contribute unique value in predicting progression from cognitively normal to MCI as well as to mild dementia (CDR=1) within 5 years. These results are significant after considering other variables shown to be important predictors of these outcomes for the model, including demographic characteristics (e.g., Chen et al., 2016; Solfrizzi et al., 2004), depressive symptoms (e.g., Palmer et al., 2007; Teng, Lu, & Cummings, 2007), daily functioning (Lau, Parikh, Harvey, Huang, & Farias,

2015; Nowrangi, Rosenberg, & Leoutsakos, 2016), vascular risk (Pase et al., 2016; Solfrizzi et al., 2004), genetic susceptibility (e.g., Bondi et al., 1995, 1999; Fleisher et al., 2007), CSF AD biomarkers (e.g., Hansson et al., 2006; Shaw et al., 2009; Sperling et al., 2011; Vemuri et al., 2009), and neuropsychological total scores (e.g., Blacker et al., 2007; Bondi et al., 1999; Chen et al., 2016; DeCarli et al., 2004; Fleisher et al., 2007). After considering these variables for the model and inclusion of the variables that had predictive value, intrusion errors significantly improved the fit of the model and were a significant predictor of progression to MCI and progression to mild dementia. This result was also consistent when CSF variables were not considered in the analysis, which allowed for a larger sample size.

Evidence that intrusion errors predict clinical progression is consistent with previous work highlighting elevated intrusion errors in MCI (e.g., Libon et al., 2011) or non-demented individuals at risk for AD (due to APOE ε4 positivity or family history of AD; Bondi et al., 1994, 1999) relative to normal control participants. It is notable that much of this prior work has centered on intrusion errors produced from cued-recall trials of a word list memory tests such as the California Verbal Learning Test (CVLT/CVLT-II) or the Philadelphia (repeatable) Verbal Learning Test (PrVLT; e.g., Bondi et al., 1999; Delis, Kramer, Kaplan, & Ober, 2000; Libon et al., 2011; Price et al., 2009); however, our findings with the AVLT suggest that even under free-recall conditions normal older adults produce intrusion errors and that these errors may be clinically meaningful. The higher frequency of intrusion errors made by normal participants who progressed to MCI within 5 years appears to capture subtle cognitive changes or inefficiencies that are not apparent in standard total neuropsychological test scores.

The underlying mechanism for the increased frequency of intrusion errors made by cognitively normal elderly who progress to MCI and/or a CDR of 1 is unclear. Previous investigators have speculated that elevated intrusion errors in patients with AD may be related to deficits in semantic memory that occur in the context of a largely intact ability to search through associative pathways. This search results in activation of a large number of irrelevant, semantically-related words that AD patients find hard to discriminate from the target words, and this leads to an elevation in the rate of intrusions (e.g., Fuld, 1982; Kramer et al., 1988). Alternatively, inefficient search and self-monitoring strategies related to frontal lobe deficits may be contributing to elevated intrusion errors.

Consistent with previous studies (Crocco, Curiel, Acevedo, Czaja, & Lowenstein, 2014; Loewenstein et al., 2004; Woodard, Dunlosky, & Salthouse, 1999), we found significant differences in learning slope and retroactive interference scores at baseline between stable normal participants and those who progressed to MCI; however, these measures did not significantly predict progression to MCI or mild dementia once other predictors were included in the models. This may be because variance was already subsumed by the large number of other predictors and the association between these variables and change is relatively weak. It is possible that changes in retroactive interference and learning slope may develop a stronger association with cognitive decline later in the disease process rather than in this early preclinical stage (up to 5 years prior to progression to MCI).

Proactive interference scores were not significantly different in those who remained cognitively normal and those who progressed to MCI. This differs from previous studies that found increased susceptibility to proactive interference in MCI compared to normal control participants on a proactive semantic interference score (Crocco et al., 2014; Ebert & Anderson, 2009; Loewenstein et al., 2004, 2007). The difference may arise because previous studies, unlike the current study, used target word lists or items that were semantically related, used an interference list that included words/items from the same semantic categories as the primary list, and included cued recall conditions that might elicit intrusion errors (e.g., Crocco et al., 2014).

A strength of the present study is that the large sample size and wide range of variables made it possible to examine the added utility of memory test process scores in predicting progression to MCI and mild dementia after considering other known predictors of MCI and dementia, including genetic information and CSF biomarkers that have been used to stage preclinical AD (Edmonds et al., 2015a; Sperling et al., 2011). Our study is in a unique position to show the added value of neuropsychology, including neuropsychological process scores, in prediction progression from cognitively normal to MCI and mild dementia. The examination of neuropsychological process scores in the context of a cognitively normal sample that had CSF markers of AD is particularly innovative.

The three CSF biomarkers considered for inclusion in the model are those specified by Jack and colleagues (2016) in the Amyloid/Tau/Neurodegeneration (A/T/N) model. An incidental finding from the present study is that baseline CSF levels of total tau, a marker of neurodegeneration, emerged as the only unique CSF predictor of progression to MCI and mild dementia using the stepwise method. This is consistent with our previous finding from the ADNI sample that neurodegeneration was more likely than β-amyloid to be the first pathologic marker of AD in normal participants who progressed to MCI (Edmonds et al., 2015a). It is also consistent with neuropathological evidence that abnormal tau begins to accumulate in the brain decades before β-amyloid in AD (Braak et al., 2011; 2013), and highlights the importance of adopting a definition of preclinical AD that does not require β-amyloid to be the first stage or pathologic marker to emerge (Edmonds et al., 2015a; Jack et al., 2016; cf. Sperling et al., 2011).

A second incidental finding was that higher education was predictive of progression to MCI (though not for progression to CDR=1) when all of the variables were included in the model, even though there was no significant difference between the stable normal and progressed-to-MCI groups in years of education at baseline. This finding was unanticipated and would need to be replicated in other samples. One possible explanation given the lack of relationship between education and progression to MCI in the initial, unadjusted analyses is that there is a suppressor effect when other predictors are added to the model, resulting in education predicting progression. Alternatively, this finding may reflect exhausted cognitive reserve in highly educated participants. The mean education within ADNI is high (16.35 years) and further examination of the data suggested that in the context of the adjusted Cox model this effect may be particularly driven by individuals with graduate school education. Indeed, higher education may confer greater cognitive reserve (Stern et al., 1994) that allows an individual to accumulate more AD pathology for a given level of neuropsychological

performance relative to those with lower education with the same level of neuropsychological performance; therefore, those with higher cognitive reserve would be expected to progress faster (Roe, Xiong, Miller, & Morris, 2007; Stern, 2012). Thus, the most highly educated individuals may have entered the current study with greater pathologic burden than those with lower education and were no longer able to compensate for the accumulated pathology over the 5-year period. Further study, however, is needed to examine this possible education effect more comprehensively.

A potential limitation of the current study is that some of the measures used as baseline predictors of time to transition to MCI were also used to diagnose MCI later in the study. This was unavoidable given the restricted number of neuropsychological measures available in ADNI. This duplication presents as circularity or criterion contamination if our primary question was related to the predictive value of the standard neuropsychological total scores. However, our question was focused on the predictive value added by AVLT process scores that were not considered in the diagnosis of MCI. Furthermore, these MCI findings were replicated when a follow-up model was conducted that examined predictors of time to a CDR score = 1. The CDR is an independent measure that was not considered in the MCI diagnosis based on the neuropsychological criteria.

It is important to consider that, in general, there were a small number of intrusion errors made by cognitively normal participants, and similar to other variables often used to identify preclinical AD (e.g., $A\beta_{1–42}$), the overall effect size for number of intrusion errors when comparing stable normal participants to progressed-to-MCI on baseline intrusion errors was relatively small. This finding is not surprising given the participants in this study are cognitively normal older adults; however, this finding may make the clinical application of using intrusion errors to identify preclinical AD somewhat difficult. Future work is needed to determine whether these intrusion errors in combination with other process scores may create a robust method of identifying those cognitively normal older adults at elevated risk for decline.

The results of the present study suggest that clinically relevant errors and subtle cognitive inefficiencies on word list learning and memory tests occur in older adults who are cognitively normal according to standard neuropsychological total test scores. These subtle changes may contribute to the ability to predict the subsequent development of MCI and AD in older adults. Importantly, intrusion errors predicted progression to MCI and mild dementia even after considering AD CSF biomarkers that make up the working definition of preclinical AD (Sperling et al., 2011) as well as other known risk factors, thus highlighting the importance of neuropsychological assessment that considers more that neuropsychological total scores. Future work should continue to examine the role of process scores on memory and other cognitive tests as tools to improve diagnostic and predictive accuracy for preclinical AD.

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Public Significance Statement

The results of this study show the added value of memory word-list intrusion errors in predicting cognitively normal older adults' progression to mild cognitive impairment after accounting for a large number of other factors known to predict progression to Alzheimer's disease. Using neuropsychological process/error scores may allow for earlier detection of subtle cognitive changes or cognitive inefficiencies that have not yet emerged as clinical impairments on neuropsychological testing. Reliable identification of persons at risk for cognitive decline would allow for greater opportunity to intervene earlier to prevent or delay future decline.

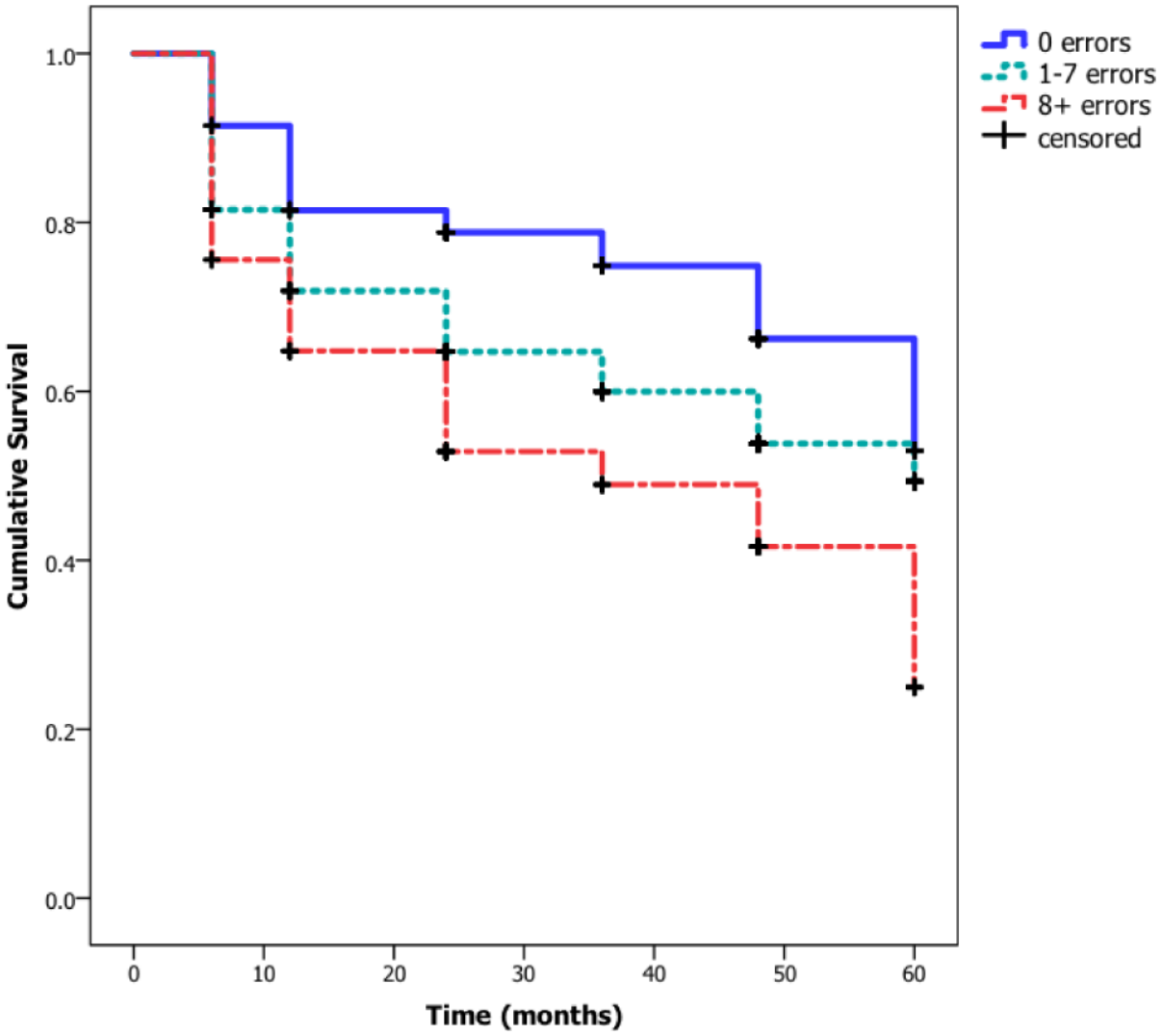

Figure 1.

Kaplan-Meier estimates of the rate of progression from cognitively normal to MCI (220 participants out of 525 progressed within 5 years) by number of baseline intrusion errors. Intrusion error categories were based on >1 SD below the mean (0 errors), −1 to +1 SD (1–7 errors) and >1 SD above the mean (8+ errors) of the error score distribution.

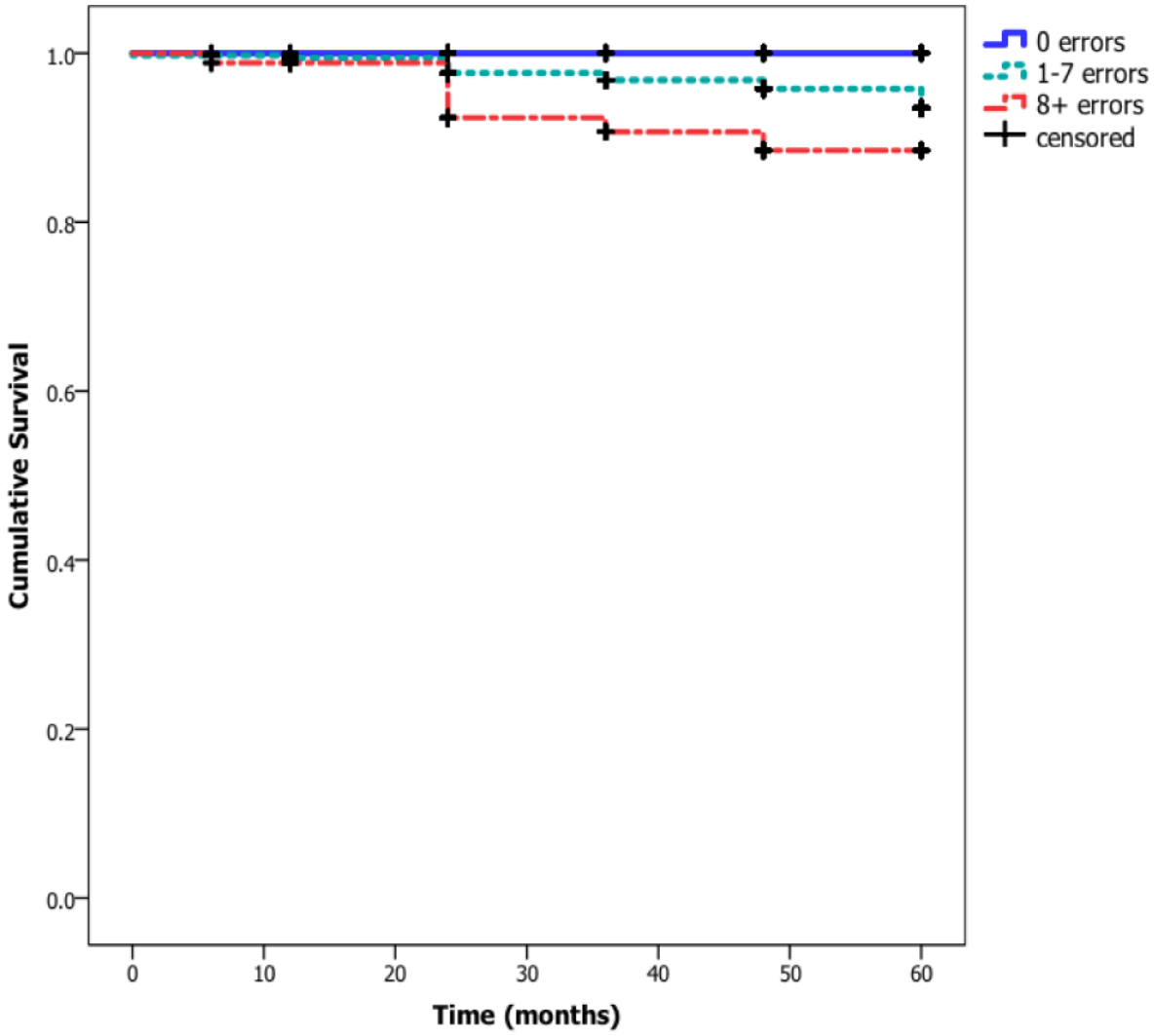

Figure 2.

Kaplan-Meier estimates of the rate of progression from cognitively normal to CDR=1 (22 participants out of 525 progressed within 5 years) by number of baseline intrusion errors. Intrusion error categories were based on >1 SD below the mean (0 errors), −1 to +1 SD (1–7 errors) and >1 SD above the mean (8+ errors) of the error score distribution.

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Table 1

Baseline demographic and clinical characteristics

	Analytic Sample N=525		Stable Normal N=305		Progressed-to-MCI N=220				
	Mean (SD)	**Range**	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**	***t*, *U*, or χ^2 statistic**	**p-value**	**Effect size d, r, or φ**
Demographics and emotional/functional inventories									
Age	72.82 (6.97)	55.21–89.74	72.32 (6.74)	56.25–88.86	73.56 (7.25)	55.21–89.74	t=−2.02	.044	d=.178
Education	16.35 (2.65)	6–20	16.45 (2.57)	6–20	16.23 (2.76)	8–20	t=0.93	.352	d=.083
Female, %	48.7%	–	53.1%	–	42.3%	–	χ^2=6.1	.014	φ=.107
GDS	1.21 (1.33)	0–6	1.11 (1.28)	0–5	1.35 (1.38)	0–6	U=30063.00	.033	r=.093
FAQ	0.57 (1.13)	0–5	0.34 (0.80)	0–5	0.89 (1.42)	0–5	U=27109.50	<.001	r=.209
CDR, 0/0.5	304/221	–	214/91	–	90/130	–	χ^2=44.88	<.001	φ=.292
Biological, genetic, and vascular markers									
APOE ε4 positive, %	32.8%	–	28.2%	–	39.1%	–	χ^2=6.89	.009	φ=.115
$A\beta_{1–42}$	197.91 (50.28)	88.00–300.00	204.31 (26.72)	88.00–293.00	189.03 (53.69)	94.40–300.00	U=27820.50	.001	r=.146
t-tau	70.38 (36.17)	17.70–288.00	63.18 (28.52)	20.90–173.00	80.37 (42.76)	17.70–288.00	U=24860.00	<.001	r=.221
$p\text{-}tau_{181p}$	32.55 (17.75)	6.90–137.00	31.19 (17.10)	6.90–137.00	34.43 (18.47)	9.40–94.00	U=30502.00	.076	r=.078
Hachinski	0.56 (1.15)	0–4	0.52 (0.63)	0–3	0.63 (0.70)	0–4	χ^2=3.91	.418	φ=.086
Neuropsychological total scores									
AVLT immediate	44.62 (10.13)	12–71	47.54 (9.73)	18–71	40.57 (9.25)	12–64	t=8.28	<.001	d=.732
AVLT delay	7.59 (3.72)	0–15	8.76 (3.56)	0–15	5.95 (3.32)	0–15	t=9.09	<.001	d=.804
Category Fluency	20.69 (5.06)	6–38	21.99 (4.98)	6–38	18.89 (4.64)	10–36	t=7.24	<.001	d=.640
BNT	28.17 (1.88)	18–30	28.61 (1.45)	22–30	27.57 (2.22)	18–30	U=23954.00	<.001	r=.250
TMT A	32.27 (9.51)	13–73	31.27 (9.04)	13–69	33.66 (9.99)	16–73	U=28855.00	.006	r=.120
TMT B	82.02 (37.26)	32–300	76.57 (34.14)	32–300	89.57 (40.06)	41–300	U=25400.50	<.001	r=.207
Process scores									
Intrusion errors	4.16 (4.27)	0–32	3.48 (3.39)	0–15	5.09 (5.12)	0–32	U=27167.50	<.001	r=.163
Learning Slope	1.21 (0.48)	−0.20–2.40	1.29 (0.44)	0.00–2.40	1.09 (0.50)	−0.20–2.20	t=4.61	<.001	d=.417
Proactive Interference	0.58 (0.20)	0.00–1.67	0.58 (0.18)	0.00–1.13	0.59 (0.22)	0.00–1.67	t=−0.57	.532	d=.050
Retroactive Interference	0.75 (0.22)	0.00–1.25	0.80 (0.20)	0.00–1.18	0.69 (0.24)	0.00–1.25	t=5.73	<.001	d=.524

Note: GDS=Geriatric Depression Scale; FAQ=Functional Activities Questionnaire; APOE ε4=apolipoprotein epsilon 4 allele status; Aβ1–42=amyloid-beta; t-tau=total tau; p-tau181p=hyperphosporylated tau; AVLT=Rey Auditory Verbal Learning Test; TMT=Trail Making Test. Hachinski full sample median=0; stable normal median=0; progressed-to-MCI median=1.

Table 2

Hazard ratios for the final model predictors of time to MCI by process variable.

	Intrusion Errors			Learning Slope			Proactive Interference			Retroactive Interference		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Block 0 (−*2LL*=2601.84)												
Block 1 (−*2LL*=2592.61)												
Age	.983	0.963–1.003	.930	0.986	0.966–1.006	.175	0.987	0.967–1.007	.193	0.986	0.966–1.006	.175
Education	1.071	1.013–1.132	**.015**	1.067	1.010–1.128	**.021**	1.062	1.006–1.121	**.029**	1.063	1.006–1.122	**.029**
Female	0.955	0.711–1.282	.758	0.984	0.731–1.325	.914	0.945	0.704–1.269	.707	0.973	0.724–1.308	.858
Block 2 (−*2LL*=2439.25)												
FAQ	1.238	1.123–1.364	**<.001**	1.244	1.130–1.371	**<.001**	1.268	1.149–1.399	**<.001**	1.251	1.135–1.379	**<.001**
APOE ε4 positive	1.377	1.028–1.845	**.032**	1.352	1.010–1.809	**.043**	1.358	1.015–1.816	**.039**	1.373	1.026–1.838	**.033**
Total tau	1.004	1.001–1.007	**.019**	1.004	1.001–1.007	**.015**	1.004	1.001–1.007	**.019**	1.004	1.000–1.007	**.024**
AVLT delayed recall	0.872	0.835–0.911	**<.001**	0.879	0.840–0.920	**<.001**	0.865	0.829–0.903	**<.001**	0.878	0.838–0.919	**<.001**
Category Fluency	0.931	0.901–0.961	**<.001**	0.933	0.904–0.963	**<.001**	0.931	0.902–0.961	**<.001**	0.934	0.905–0.965	**<.001**
BNT	0.857	0.805–0.913	**<.001**	0.858	0.806–0.914	**<.001**	0.862	0.810–0.918	**<.001**	0.858	0.805–0.913	**<.001**
Block 3	−*2LL*=2432.92, $\Delta\chi^2$=6.33, *p*=.012			−*2LL*=2436.87, $\Delta\chi^2$=2.38, *p*=.123			−*2LL*=2437.20, $\Delta\chi^2$=2.042, *p*=.153			−*2LL*=2437.74, $\Delta\chi^2$=1.508, *p*=.219		
Process variable	1.040	1.010–1.071	**.008**	0.782	0.573–1.068	.122	0.626	0.328–1.197	.157	0.665	0.348–1.271	.217

Note: Learning Slope=(Trial 5-Trial 1)/5; Proactive Interference=List B/(Mean of List A, Trials 1–5); Retroactive Interference=Trial 6/Trial 5; HR=hazard ratio; CI=95% Confidence interval; −2LL=−2 Log Likelihood; FAQ=Functional Activities Questionnaire; APOE ε4=apolipoprotein epsilon 4 allele status; AVLT=Rey Auditory Verbal Learning Test; BNT=Boston Naming Test. Block 2 used a forward stepwise procedure; additional variables included in Block 2, but not included in the mode were: GDS, Hachinski score, $A\beta_{1-42}$, p-tau, AVLT immediate recall, TMT Part A, and TMT Part B.

Table 3

Hazard ratios for the final model predictors of time to CDR=1 by process variable.

	Intrusion Errors			Learning Slope			Proactive Interference			Retroactive Interference		
	HR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Block 0 (−*2LL*=261.30)												
Block 1 (−*2LL*=253.57)												
Age	0.990	0.927–1.056	.754	1.006	0.944–1.073	.844	1.006	0.942–1.074	.869	1.007	0.945–1.073	.822
Education	1.049	0.870–1.266	.615	1.034	0.863–1.239	.717	1.036	0.866–1.240	.698	1.050	0.871–1.267	.606
Female	1.370	0.465–4.037	.569	1.245	0.431–3.599	.685	1.261	0.440–3.618	.666	1.371	0.472–3.980	.562
Block 2 (−*2LL*=205.32)												
GDS	1.409	1.053–1.885	**.021**	1.304	0.986–1.724	.062	1.287	0.972–1.703	.078	1.315	0.992–1.745	.057
FAQ	1.613	1.219–2.135	**.001**	1.592	1.208–2.099	**.001**	1.631	1.240–2.146	**<.001**	1.647	1.237–2.194	**.001**
Total tau	1.013	1.005–1.022	**.002**	1.011	1.003–1.020	**.006**	1.012	1.004–1.020	**.004**	1.012	1.004–1.020	**.004**
AVLT delayed recall	0.798	0.675–0.942	**.008**	0.784	0.664–0.925	**.004**	0.785	0.664–0.927	**.004**	0.828	0.696–0.985	**.033**
TMT Part B	1.016	1.009–1.024	**<.001**	1.014	1.007–1.022	**<.001**	1.015	1.007–1.022	**<.001**	1.015	1.008–1.023	**<.001**
Block 3	−*2LL*=200.64, $\Delta\chi^2$=4.68, *p*=.030			−*2LL*=204.91, $\Delta\chi^2$=0.41, *p*=.524			−*2LL*=204.71, $\Delta\chi^2$=0.61, *p*=.436			−*2LL*=203.43, $\Delta\chi^2$=1.89, *p*=.169		
Process variable	1.095	1.017–1.179	**.016**	1.400	0.491–3.994	.529	0.460	0.0633–3.339	.443	0.204	0.021–1.967	.169

Note. Learning Slope=(Trial 5-Trial 1)/5; Proactive Interference=List B/(Mean of List A, Trials 1–5); Retroactive Interference=Trial 6/Trial 5; HR=hazard ratio; CI=95% Confidence interval; −2LL=−2 Log Likelihood; GDS=Geriatric Depression Scale; FAQ=Functional Activities Questionnaire; APOE ε4=apolipoprotein epsilon 4 allele status; AVLT=Rey Auditory Verbal Learning Test; TMT=Trail Making Test. Block 2 used a forward stepwise procedure; additional variables included in Block 2, but not included in the mode were: Hachinski score, $A\beta_{1-42}$, p-tau, AVLT immediate recall, Category Fluency, and TMT Part A.