# Memory impairment, executive dysfunction, and intellectual decline in preclinical Alzheimer's disease

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## Abstract

In the Baltimore Longitudinal Study of Aging (BLSA), we examined the temporal unfolding of declining performance on tests of episodic memory (Free Recall on the Free and Cued Selective Reminding Test), executive function (Category Fluency, Letter Fluency, and Trails), and Verbal Intelligence (Nelson, 1982; American Version of the Nelson Adult Reading Test [AMNART]) before the diagnosis of dementia in 92 subjects with incident Alzheimer's disease (AD) followed for up to 15 years before diagnosis. To examine the preclinical onset of cognitive decline, we aligned subjects at the time of initial AD diagnosis and examined the cognitive course preceding diagnosis. We found that declines in performance on tests of episodic memory accelerated 7 years before diagnosis. Declining performance on tests of executive function accelerated 2–3 years before diagnosis, and verbal intelligence declined in close proximity to diagnosis. This cognitive profile is compatible with pathologic data suggesting that structures which mediate memory are affected earlier than frontal structures during the preclinical onset of AD. It also supports the view that VIQ as estimated by the AMNART does not decline during the preclinical onset of AD. (*JINS*, 2008, *14*, 266–278.)

**Keywords:** Alzheimer's disease, Prospective studies, Preclinical dementia, Cognition disorders, Memory disorders, Verbal learning

## INTRODUCTION

Numerous studies have demonstrated that patients who develop Alzheimer's disease (AD) experience elevated rates of cognitive decline for many years before diagnosis. Although memory decline has been a focus (Elias et al., 2000; Grober et al., 2000; Kawas et al., 2003; Linn et al., 1995; Rubin et al., 1998), other domains of cognition also show rapid decline in comparison to those who do not develop AD (Backman et al., 2004). Defining the nature and timing of cognitive changes in AD is important for several reasons. Understanding this natural history will help define prediction models and identify candidates for preventive intervention. Clarity about natural history may improve the measurement of cognitive changes in the context of prevention trials. Understanding the sequential unfolding of cognitive deficits will help inform the optimal combination of neuropsychological and radiographic measures to predict onset and will improve the correlation with AD pathology, which unfolds in a relatively orderly manner in the brain (Braak & Braak, 1991).

The usual approach to predicting AD involves enrolling a cohort of individuals without diagnosable dementia and following them over time. Factors that predict dementia onset within specific time periods are used to identify high risk groups. The most widely used approach is to identify individuals with memory impairment who do not meet criteria for dementia (Albert et al., 2001; Larrieu et al., 2002;

Petersen, 2004; Ritchie et al., 2001). A subgroup of these individuals meeting criteria for amnestic Mild Cognitive Impairment (aMCI) develop AD at elevated rates and have become the targets of secondary prevention trials (Petersen et al., 2005). The definition of MCI has been broadened to include clinical subgroups that have other cognitive deficits including impaired attention or executive dysfunction, (Albert et al., 2001; Masur et al., 1994; Saxton et al., 2004; Tierney et al., 2005), language (Jacobs et al., 1995), or visual spatial impairment (Small et al., 1997). Conversion rates to dementia vary because of differences in cohorts, MCI criteria, and the methods used to implement them. Approximately 12% of the Amnestic MCI patients in the Mayo Clinic cohort progressed to dementia each year, similar to the rates reported in other incidence studies (Petersen, 2004).

In most longitudinal studies, memory measures are better predictors of subsequent AD than executive function tests (Devanand et al., 1997; Elias et al., 2000; Linn et al., 1995; Masur et al., 1994; Rubin et al., 1998) though this point is somewhat controversial (Chen et al., 2001; Fabrigoule et al., 1998; Rapp & Reischies, 2005; Royall et al., 2004). In these prospective studies, cognitive scores at the time of a baseline assessment are used to predict the onset of dementia at future times. Because the time of baseline assessment relative to the time of onset of diagnosable dementia is highly variable, the predictive value of one test over another may depend on where in the preclinical course the individual is and on the natural history of decline in the specific domains being tested. When patients present with cognitive complaints before the onset of dementia they are at various points in the unfolding of illness.

If the goal is to examine the timing of changes before the development of dementia an alternative approach is to align subjects at the time of dementia diagnosis and look backward in time at the time course of cognitive decline in the preclinical period. These models require large numbers of incident AD patients and long follow-up times before diagnosis. Applying this approach, Hall and colleagues (2000, 2001, 2003, 2007), examined the preclinical course of cognitive decline in Bronx Aging Study (BAS) participants who went on to develop AD or AD/VaD. This work suggests that more than 8 years before diagnosis, the rate of memory decline is similar in persons who eventually develop AD and in a sample that remains dementia free after long follow-up. In persons who ultimately develop AD, memory decline accelerates approximately 7 years before diagnosis. We demonstrated this by modeling performance in the years preceding the diagnosis of dementia to estimate rates and identify discontinuities in rates of memory decline. We have referred to these discontinuities as change points and the statistical approaches that identify them as change point models (Hall et al., 2000, 2001, 2003). Using the sum of free recall on the Selective Reminding Test (Buschke, 1973), memory decline accelerates approximately 7 years before the diagnosis of AD (Hall et al., 2001). Decline in Performance IQ scores based on the Block Design, Object Assembly and Digit Symbol Subtests of the WAIS (Wechsler, 1955) accelerates approximately 2 years before diagnosis (Hall et al., 2001). This finding is likely to reflect visuo/spatial deficits in preclinical and early AD in addition to executive function deficits (Herlitz et al., 1995; Small et al., 1997).

Our goals here were to assess the time course of cognitive decline before AD diagnosis in an independent cohort using distinct neuropsychological procedures covering a broader range of cognitive domains. This approach to studying the preclinical course requires long-term follow-up because memory decline accelerates 7 years before diagnosis. The Baltimore Longitudinal Study of Aging (BLSA) is ideal because of the long-term neuropsychological and clinical follow-up, careful clinical diagnoses, and the large number of incident cases of AD. In this study, memory was assessed with the Free and Cued Selective Reminding Test (FCSRT: Grober & Buschke, 1987). FCSR differs from Selective Reminding, used in the BAS, in that category cues are used both in the study and test phases, controlling attention and cognitive processing. This test has excellent discriminative validity for dementia at cross-section and excellent predictive validity for incident dementia (Grober et al., 1988, 2000, 2008). We used learning as our measure of memory instead of delayed recall or retention because of prior data suggesting that learning defined as the sum of free recall across three test trials was sensitive to preclinical disease, whereas retention tested 30 min later was not (Grober & Kawas, 1997).

Measures of executive function included Category Fluency (animals, fruits, vegetables; Rosen, 1980), Letter Fluency (FAS; Spreen & Strauss, 1998), and Part B of Trailmaking (Reitan, 1958), tests that are sensitive to prevalent and incident dementia. We recognize that "executive function" is not a unitary entity and that the term encompasses a broad range of cognitive processes (Stuss & Alexander, 2007). Verbal IQ was estimated by the American Version of the Nelson Adult Reading Test (AMNART), which involves reading words that cannot be pronounced by sounding them out (e.g., depot, naïve; Grober & Sliwinski, 1991). The reading of irregular words is a valid and reliable method for estimating current VIQ in normal elderly individuals (Blair & Spreen, 1989; Grober & Sliwinski, 1991) and is fairly insensitive to decline in early dementia (Grober & Sliwinski, 1991; Nelson & McKenna, 1975).

The onset and rate of decline in memory, executive function, and VIQ during the preclinical period was estimated by aligning incident AD cases at the time of diagnosis and analyzing the trajectory of decline for each test. We predicted that memory decline would precede decline in executive function based on the temporal unfolding of memory impairment followed by Performance IQ decline in the BAS and based on other studies indicating that in persons with the amnestic form of Mild Cognitive Impairment (MCI), executive function deficits predict the subsequent development of AD (Albert et al., 2001; Bozoki et al., 2001; Chen et al., 2001; Fabrigoule et al., 1998; Rapp & Reischies, 2005). We also predicted that verbal IQ would decline close

to the time of diagnosis when social and occupational functioning is finally impaired, heralding imminent conversion to dementia. Finally, we provide information on the cognitive trajectories on the tests in individuals who did not develop dementia. Because dementia has a long preclinical trajectory, some individuals who do not develop full-blown dementia during follow-up are likely to experience cognitive decline which would become diagnosable after the end of follow-up. Inclusion of these individuals in a normal aging group leads to overestimates of age-associated decline (Sliwinski et al., 1996). Therefore, we analyzed this group of study participants to estimate age-associated decline uncontaminated by AD-related cognitive decline.

## METHODS

### Subjects

The BLSA is a volunteer cohort followed by the National Institute on Aging since 1958 to study prospectively the effects of normal aging (Shock et al., 1984). These community-dwelling volunteers are predominately white, of upper middle socioeconomic status, and with an above-average educational level. This report uses data collected on BLSA participants who had follow-up between January 1985 and October, 2000 (Kawas et al., 2000). There were 1006 active participants who had neuropsychological testing that included the measures used here and neurologic examinations in addition to the usual BLSA protocols.

They returned every 2 years for 2.5 days of these multi-disciplinary evaluations. Work-up of incident dementia cases included appropriate laboratory (thyroid function tests, serum B12 level, complete blood count, electrolytes, and chemistry panel) and imaging studies (CT or MRI scan of the brain) as well as informant and medical record information. The National Institute on Aging Intramural Research Program and the Johns Hopkins School of Medicine Institutional Review Board approved this study and all participants gave written informed consent.

Diagnosis of dementia in this study was established by the neurological examiner at each biennial visit by applying DSM III-R criteria (American Psychiatric Association, 1987) for dementia. To make a diagnosis, the examiner conducted a structured mental status examination and had access to the Blessed Information Memory-Concentration test (BIMC), but was blinded to all other neuropsychological testing, including the tests being examined here to avoid circularity. When available, the examiner also used informant information. BSLA participants with a diagnosis of dementia were further classified by diagnostic category using NINCDS-ADRDC criteria for probable and possible AD (McKhann et al., 1984).

The subjects for this analysis included a sample with incident AD as well as a longitudinally followed sample that never developed dementia. Overall, 155 incident cases of dementia were identified among BLSA participants during follow-up (Kawas et al., 2000). Of these, 92 had AD

and underwent longitudinal neuropsychological testing for an average of 4.6 years before diagnosis. Sixty-eight percent of these participants had at least two testing waves of testing and 51% had at least three waves with an average of 2.4 years between waves. We also assessed 822 study participants who were not diagnosed with dementia over the course of the follow-up period. Their performance permits the identification of age-associated changes on the tests of interest.

### FCSRT

FCSRT measures memory under conditions that control attention and cognitive processing. It is used in five major longitudinal aging studies besides the BLSA: (1) Einstein Aging Study (EAS; Grober et al., 1988); (2) Mayo Older Adults Normative Study (Petersen et al., 1995); (3) Berlin Aging Study (Lindenberger & Reischies, 1999); (4) Canadian Study of Health and Aging (Tuokko et al., 1995); and (5) Personnes Agees QUID (Sarazin et al., 2007). FCSR is also used in the Alzheimer's Disease Cooperative Study Instrumentation Protocol to identify persons with prevalent dementia and trigger clinical evaluations for incident dementia (Ferris et al., 2006). Performance has been highly associated with early dementia and preclinical dementia in several cohorts (Grober et al., 1988, 2000, 2008; Grober & Kawas, 1997; Lindenberger & Reischies, 1999; Petersen et al., 1994, 1995; Tounsi et al., 1999; Tuokko & Crockett, 1989) and is not associated with education (Ivnik et al., 1997) or race (Grober et al., 1998, 2008). The test takes 10 to 15 min to administer, depending upon the mental status of the patient. Scoring is quick, easy, and unambiguous and test–retest reliability is high (.93; Lindenberger & Reischies, 1999). FCSR is well tolerated by patients and provides clinicians with useful diagnostic information (Tuokko et al., 1995).

FCSR begins with a study phase in which subjects are asked to search a card containing four pictures (e.g., grapes) for an item that goes with a unique category cue (e.g., fruit). After all four items are identified, immediate recall of just those four items is tested. The search is performed again for items not retrieved by cued recall. The search procedure is continued until all 16 items are identified and retrieved in immediate recall. The study procedure is followed by three trials of recall each consisting of free recall followed by cued recall for items not retrieved by free recall. The sum of free and cued recall on each trial is called total recall. Items not retrieved by cued recall are re-presented. There is 20 seconds of interference between trials. The FCSR procedure is described in greater detail elsewhere (Grober & Buschke, 1987; Grober et al., 2008). The measure of learning used here was the sum of free recall over the 3 test trials.

### Executive function tests.

In the Letter Fluency task, subjects generate words that begin with the letters F, A, and S for 1 min each (Spreen & Benton, 1969). The dependent measure is the total number

of words generated. In the Category Fluency test, subjects have 1 min each to generate exemplars of animals, fruits, and vegetables (Rosen, 1980). The dependent measure is the total number of exemplars generated. Part B of the Trailmaking test involves connecting dots containing numbers and letters arrayed randomly on a page in alternating sequence (Reitan, 1958). The dependent measure we used here is the reciprocal of the time it takes for the subject to complete the task expressed in seconds. This speed measure permitted easier comparisons with the other executive function tests.

## Verbal IQ

The AMNART was used to estimate verbal IQ. It consists of 50 words that cannot be pronounced by sounding them out (e.g., depot, naïve). Estimated verbal IQ was computed using number of errors on the AMNART and years of education according to the following formula: $118.56 - [.88 * \text{(number of errors)}] + (.56 * \text{years of education})$.

## Statistical Methods

Linear Mixed Models for longitudinal data (Diggle et al., 1994; Laird & Ware, 1982) were used to model free recall, Category Fluency, Letter Fluency, Trailmaking speed, and estimated Verbal IQ over time for each subject who developed incident AD. The principal model examined was one in which the scores decline at a constant rate up to some point in time, and then at a more rapid rate subsequently. The time at which the rate of decline changes is called the change point. The change point was estimated from the data using the profile likelihood method as described in Hall et al. (2003). Briefly, the method is to fit linear mixed models using maximum likelihood for a wide range of possible change points; in this study we used intervals of 0.1 years as the spacing. The models are compared using the likelihood as a goodness of fit measure. The change point for which the likelihood is the greatest is the maximum likelihood estimate, and the estimates of the rates of decline given that best change point are the maximum likelihood estimates for those parameters as well. A confidence interval for the change point is computed by including all the possible change point values for which the likelihood of the model given the change point is sufficiently close to that of the maximized likelihood. For the 95% confidence intervals reported in this study the critical value is 0.1466 times the value of the maximized likelihood. The change point itself was deemed to be statistically significant when the estimates of the rate of decline before and after the change point were significantly different from each other; only significant change points are reported.

Because age is a significant risk factor for dementia and is associated with decline in some cognitive domains even in healthy elderly, it was evaluated as a possible confounder by inclusion as a covariate in the models. The effect of age did not achieve statistical significance as a predictor of any of the measures examined in this report, and none of the change points changed by more than 0.2 years when age was removed from the model. Similar results have previously reported for memory (Hall et al., 2000).

Alternative models, which used a quadratic polynomial to describe a smooth decline over the entire natural history, were also examined; these models were also compared using the likelihood as the goodness of fit measure. In all models, random effects were used to take into account the heterogeneity of the subjects and the repeated observations on each subject. Trailmaking times were highly skewed, and we analyzed the data on the inverse scale, which has the interpretation of speed. Subjects who did not complete the task within 5 min had their observations set to speed zero. For all models, model comparisons showed that there was significant heterogeneity in the slopes both before and after the change points.

To estimate the degree to which the accelerated decline characteristic of preclinical AD differs from the decline characteristic of normal aging, we estimated the rates of age-associated decline in the 822 study participants who were not diagnosed with dementia over the course of the follow-up period. The models for the cases and noncases can be directly compared because the change point models used for the cases were adjusted for age. However, because there must be substantial decline in cognitive function before dementia can be diagnosed, it is very likely that some of the 822 study participants were already experiencing the accelerated cognitive decline characteristic of preclinical AD before follow-up ended. Including these participants in the normal aging group would result in biased estimates of age-associated cognitive decline (Sliwinski et al., 1996). Therefore, we additionally analyzed the tests of interest in these 822 participants excluding one, two, three, or four observations proximal to the end of follow-up.

## RESULTS

Table 1 shows demographic information and average baseline scores on the neuropsychological battery for the 92 incident AD cases. Figure 1 shows the "spaghetti plot" of the sum of free recall across the three learning trials as a function of time before the clinical diagnosis for the 92 study participants who developed AD during the follow-up period. Negative values on the *x*-axis indicate years before diagnosis. There is clearly a downward trend over time. Superimposed on this plot is a bold line showing the best fitting change point model of free recall as a function of time before diagnosis. The profile likelihood function for this model is shown graphically in Figure 2. The horizontal line defines the 95% confidence interval for the change point estimate. The flattening out of the profile likelihood to the left make it impossible to estimate the lower 95% confidence limit. However, the upper limit is 5.0 years before diagnosis. Memory decline accelerates 7.1 years before diagnosis. The model indicated no significant decline in recall before this point which is shown by the flat line in Figure 1.

**Table 1.** Demographic information and average baseline scores on the neuropsychological for 92 incident AD cases

| Group | AD | |
|---|---|---|
| *N* | 92 | |
| | Mean | SD |
| Age at baseline | 79.8 | 6.9 |
| Gender | 48% M | |
| Education in years | 16.5 | 3.0 |
| BIMC | 3.7 | 3.3 |
| MMSE | 26.8 | 2.9 |
| Free recall from FCSR | 27.7 | 8.4 |
| Letter Fluency (FAS) | 39.0 | 13.3 |
| Category Fluency (FAV) | 38.0 | 12.9 |
| Trailmaking, Part A (sec) | 54.4 | 24.0 |
| Trailmaking, Part B (sec) | 164.8 | 139.8 |
| Estimated VIQ | 118.9 | 8.2 |

*Note*. AD = Alzheimer's disease; BIMC = Blessed Information Memory-Concentration test; MMSE = Mini-Mental State Examination; VIQ = verbal IQ.

After the first change point, recall declines 1.48 points per year [approximate 95% confidence interval (CI): 0.97, 1.98] until a second change point occurs closer to the time of diagnosis (2.6 years), after which recall declines 2.90 points per year (approximate 95% CI: 2.42, 3.38). The 4.5-year difference was significant (95% CI: 1.5, 7.2).

## Executive Function

Change point models were developed for Category Fluency, Letter Fluency, and Trailmaking Speed. Figures 3, 4, and 5 show the spaghetti plots and the best fitting change point model for each test. Performance on each test declines during the long preclinical period. At approximately 3 years before diagnosis, an acceleration of decline is observed on each test. The results are summarized in Table 2. Category Fluency begins to decline more rapidly 3.0 years before diagnosis, Letter Fluency begins to decline more rapidly 2.5 years before diagnosis and Trailmaking Speed also begins to decline more rapidly 2.9 years before diagnosis. These change points did not differ. For all tests, the yearly decline before the change point was significantly less than the yearly decline after the change point.

## Estimated VIQ

Figure 6 shows the spaghetti plot of estimated verbal IQ as a function of time before the clinical diagnosis for the 92 incident AD cases. Superimposed on this plot is a bold line indicating the expected score as a function of time before diagnosis determined by the best fitting change point model for verbal IQ. Estimated verbal IQ is unchanged until 0.4 years before diagnosis (95% CI: 1.1 years before, 0.1 years after), when it begins to decline more rapidly. The model results indicated further that the rate of decline before the change point is 0.28 verbal IQ points per year (95% CI: 0.009 increase, 0.58 decrease) or 1 point every 6 years and that the rate of decline after the change point is 1.58 points per year (95% CI: 0.61, 2.55) or almost 8 points every 5 years.

Table 3 shows rates of decline with respect to age in the 822 study participants who did not develop dementia during follow-up. For each measure, up to four observations at the end of each person's follow-up were excluded from analysis, with the complete data analysis indicated by "none"
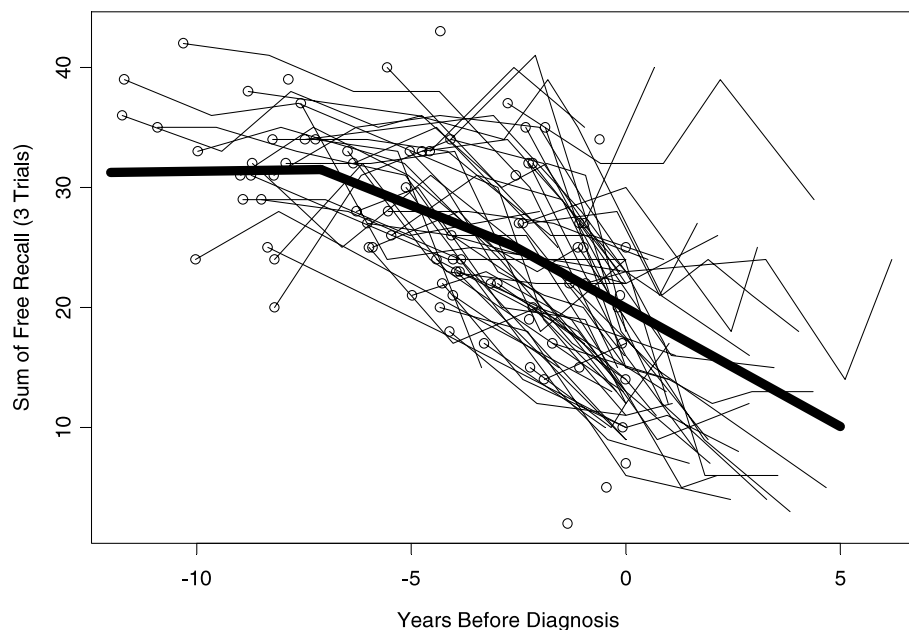


**Fig. 1.** Spaghetti plot for the sum of free recall as a function of time before diagnosis for the 92 incident Alzheimer's disease cases.
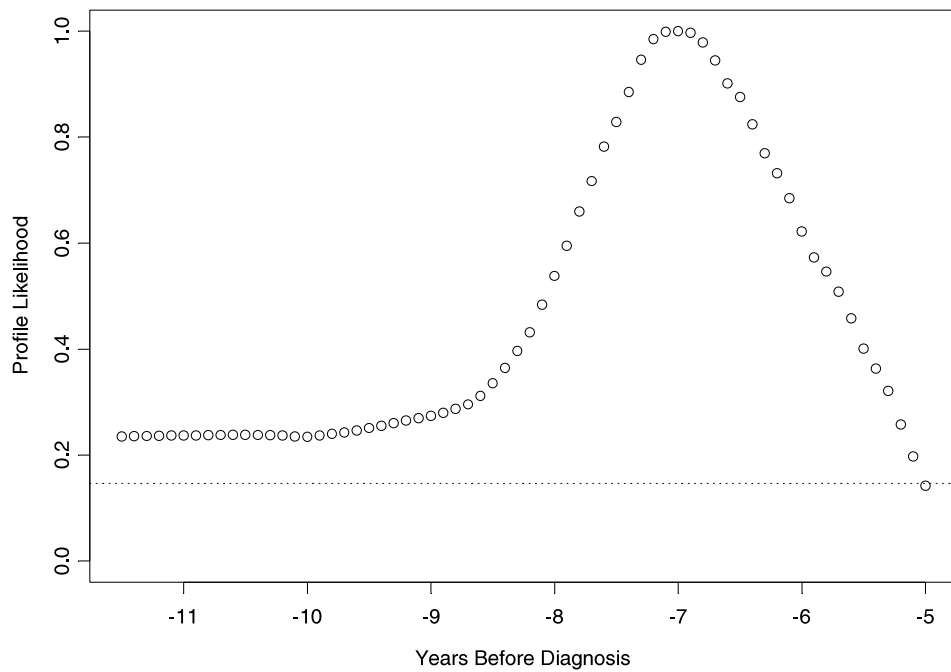
**Fig. 2.** Profile likelihood values for the first change point in free recall. The maximum value of the graph occurs at 7.1 years before diagnosis and is the value for the first change point best supported by the data.

in the "Waves Dropped" column. Rates of decline diminished notably for all measures except Trailmaking when the last observation was dropped. While there was no difference in the rates of decline observed in the executive function measures whether one or two observations at the end of the follow-up were dropped, excluding the second, third, or fourth free recall measure resulted in progressively less steep rates of decline in among the noncases.
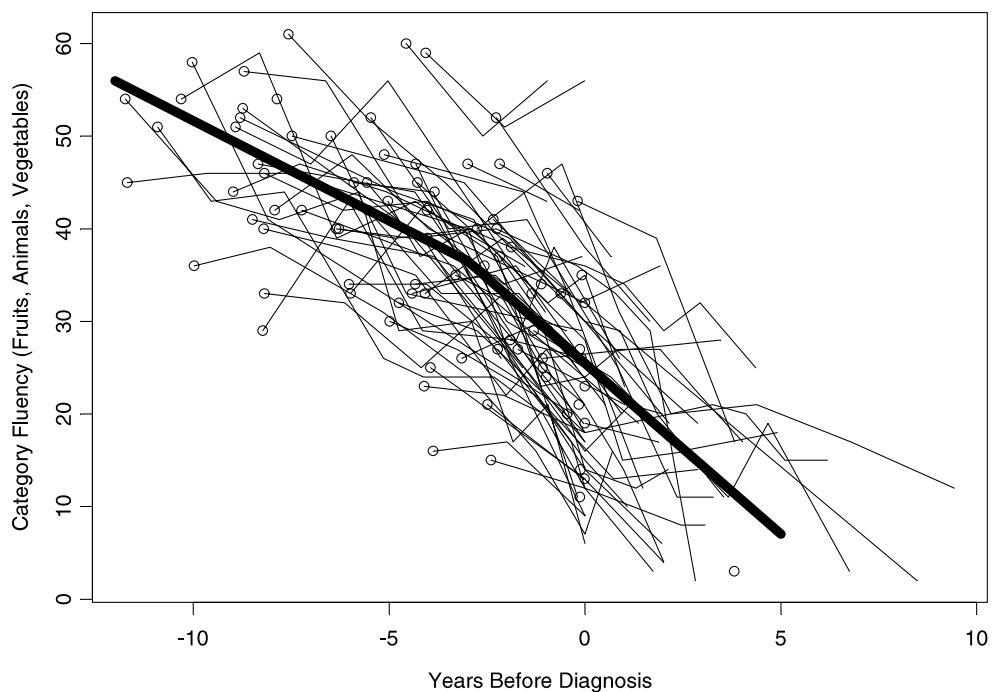


**Fig. 3.** Spaghetti plot for category fluency (sum of the number of fruits, animals, and vegetables named in 60 s for each of the three categories) as a function of time before diagnosis.
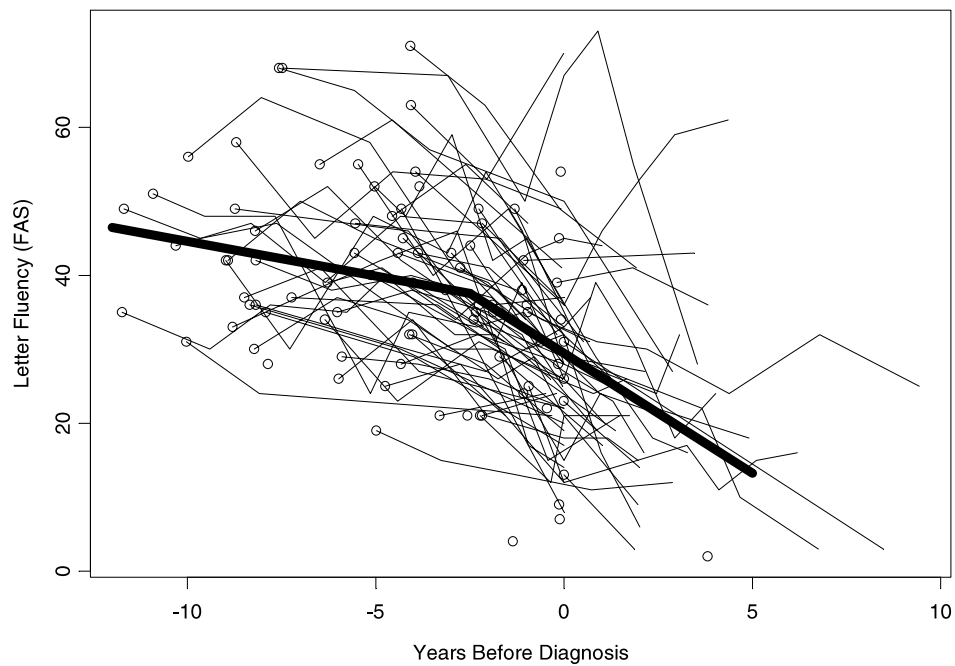
**Fig. 4.** Spaghetti plot for letter fluency (sum of the number of words beginning with "f," "a," and "s" named in 60 s for each of the three categories) as a function of time before diagnosis.

## DISCUSSION

We examined the temporal unfolding of declining memory performance, executive function, and verbal IQ during the preclinical course of AD by aligning subjects on time of AD diagnosis and then examining cognition over the preceding years. Taking this approach, an orderly pattern of decline emerged, in accordance with our predictions. The principal model examined was one in which the scores decline at a constant rate until some point in time, and then rate of decline accelerates after that point. The points of accelerating cognitive decline (change points) were estimated from the data using the profile likelihood method (Hall et al., 2000, 2001, 2003, 2007). We found that declines in mem-
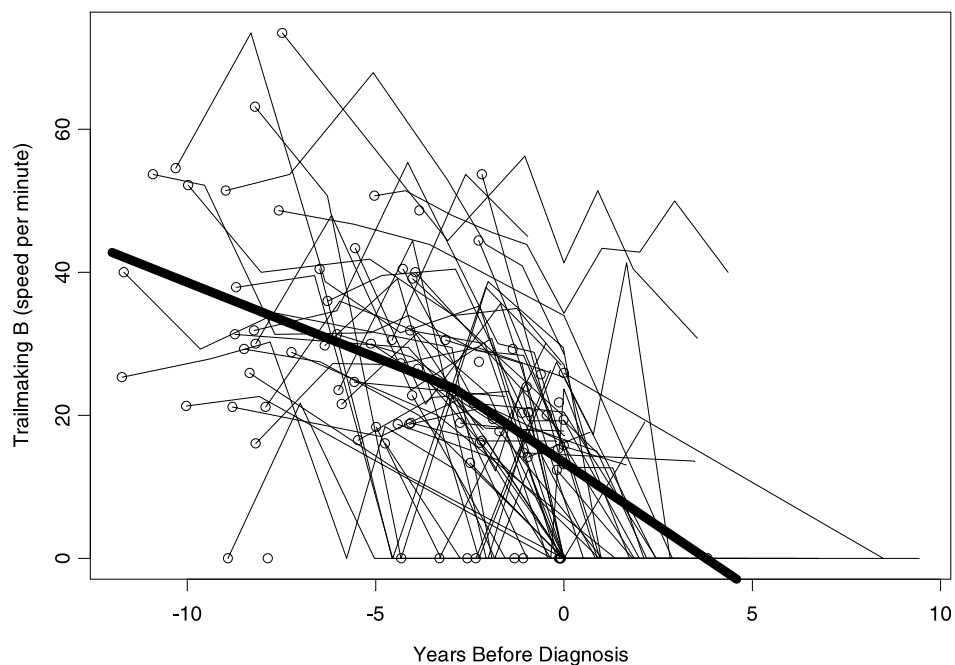


**Fig. 5.** Spaghetti plot for Trailmaking B speed, the reciprocal of elapsed time, as a function of time before diagnosis.

**Table 2.** Change points and rates of decline on executive function tests during the preclinical course of dementia

| Test | Time of accelerated decline (change point) | Pre-change point rate of decline | Post-change point rate of decline |
| --- | --- | --- | --- |
| Category Fluency | 3.0 years (95% CI: 1.7,5.0) | 1.97 points/year (95% CI: 1.50, 2.45) | 3.50 points/year (95% CI: 2.91, −4.09) |
| Letter Fluency | 2.5 years (95% CI: 1.5, 4.9) | 0.91 points/year (95% CI: .23, 1.33) | 3.21 points/year (95% CI: 2.25, 3.91) |
| Trailmaking Speed | 2.9 years (95% CI: 1.1, 8.3) | 1.90 per minute per year (95% CI: 1.07, 2.73) | 3.36 per minute per year (95% CI: 2.48, 4.24) |

*Note.* CI = confidence interval.

ory, executive function, and verbal IQ were best described using change point methods. Memory decline in preclinical AD, as measured by free recall from FCSR, is best described using a two-change point model, reflecting two different points of accelerated memory decline. Approximately 7 years before diagnosis, subjects show acceleration in the rate of memory decline. There was no significant decline in recall before this point. A second acceleration in the rate of memory decline was observed 2 to 3 years before diagnosis, the same time that decline on three distinct measures of executive function accelerates. Finally, close to the time of diagnosis, there is an accelerated decline in estimated verbal IQ.

Despite differences in sample characteristics and cognitive measures, these results are consistent with previous observations in the BAS cohort (Hall et al., 2001). In both samples, using different memory tests, decline accelerated 7 years before diagnosis. There are important methodological differences between FCSR and SR that produce significantly different levels of recall in the same subjects (Grober et al., 1997). Nonetheless, the change point in memory decline as measured by these two different tests occurred at the same time point relative to diagnosis. However, there was an important potential difference in the change point models. In the BAS, memory decline occurred at a constant rate until diagnosis (Hall et al., 2001), while there was a second change point for recall in the BLSA, coinciding with the change point for executive function. This difference may reflect the larger sample in the BLSA; the BAS may not have had sufficient power to detect a second change point. Alternatively, differences in sample characteristics or procedural differences in the tests may account for the discrepancy.

All three executive function tests showed accelerated decline in a relatively narrow window from 2 to 3 years before diagnosis. This result is consistent with change point models developed in the BAS from the Block Design, Object Assembly and Digit Symbol Subtests of the WAIS; these models show that performance IQ accelerated 2 years before
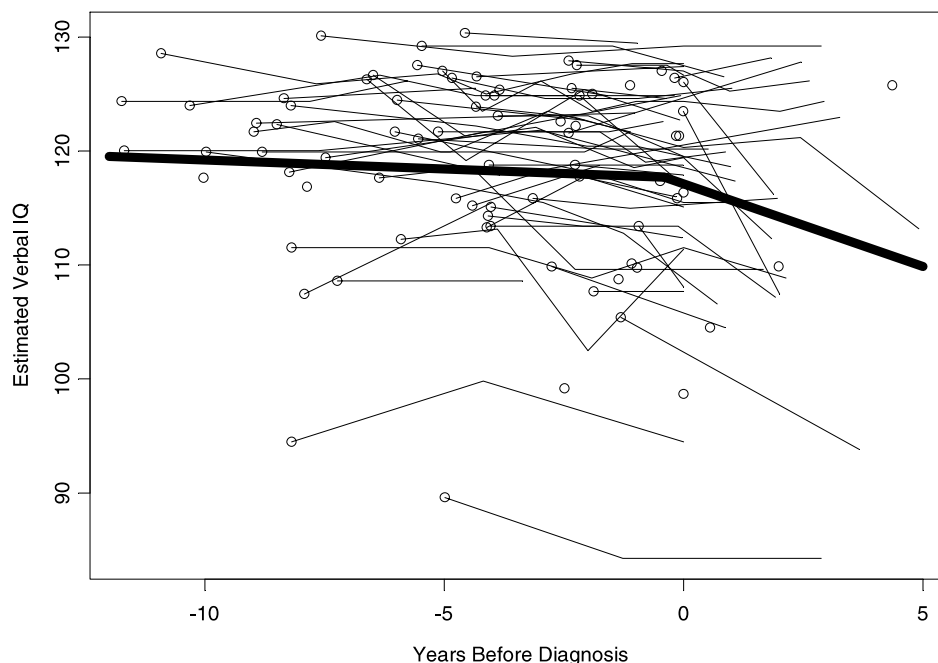


**Fig. 6.** Spaghetti plot of estimated verbal IQ as a function of time before diagnosis.

**Table 3.** Rates of age-associated decline in persons who were not diagnosed with dementia

| Test | Waves dropped | $N$ | Est. | Std. Error | 95% CI |
|------|------|------|------|------|------|
| Free Recall | None | 822 | −0.201 | 0.019 | (−0.239, −0.162) |
| | 1 | 666 | −0.154 | 0.021 | (−0.195, −0.113) |
| | 2 | 543 | −0.107 | 0.023 | (−0.152, −0.061) |
| | 3 | 446 | −0.057 | 0.026 | (−0.107, −0.006) |
| | 4 | 335 | −0.009 | 0.032 | (−0.071, 0.053) |
| Category Fluency | None | 827 | −0.521 | 0.031 | (−0.582, −0.460) |
| | 1 | 668 | −0.478 | 0.037 | (−0.550, −0.406) |
| | 2 | 545 | −0.484 | 0.042 | (−0.567, −0.401) |
| Letter Fluency | None | 826 | −0.397 | 0.036 | (−0.467, −0.326) |
| | 1 | 668 | −0.350 | 0.042 | (−0.433, −0.267) |
| | 2 | 545 | −0.354 | 0.049 | (−0.450, −0.258) |
| Trailmaking Speed | None | 802 | −0.014 | 0.001 | (−0.015, −0.012) |
| | 1 | 651 | −0.013 | 0.001 | (−0.015, −0.012) |
| | 2 | 532 | −0.013 | 0.001 | (−0.015, −0.011) |
| Estimated Verbal IQ | None | 717 | 0.020 | 0.016 | (−0.010, 0.051) |
| | 1 | 574 | 0.009 | 0.020 | (−0.031, 0.048) |
| | 2 | 474 | 0.005 | 0.023 | (−0.040, 0.049) |

*Note*. "Waves dropped" is the number of observations on each study participant at the end of that participant's follow-up period excluded from analysis. *N* is the number of study participants included in the analysis. Estimates are in units of points per year on each measure, except for Trailmaking, which is in units of speed (units per minute per year). CI = confidence interval.

diagnosis (Hall et al., 2001). The uniformity in the time of acceleration of executive decline across two cohorts and many tests suggest that before the development of diagnosable AD the processes measured by these tests show measurable acceleration at approximately the same time. This does not necessarily mean that the tests tap the same underlying cognitive processes. The time of acceleration is compatible with data from other studies showing that executive function deficits in persons with the amnestic form of MCI predict development of AD over 2 to 3 years of follow-up (Albert et al., 2001; Bozoki et al., 2001; Chen et al., 2001; Fabrigoule et al., 1998; Rapp & Reischies, 2005).

The acceleration of decline in verbal IQ as estimated by the AMNART occurred in close proximity to diagnosis as we predicted. Intelligence level is a good predictor of the amount of brain damage an individual can sustain before functional deficits become apparent (Stern, 2002). Before diagnosis, the capacity to use existing brain networks efficiently or to recruit alternative networks is sufficient to enable the individual to appear normal in their social and occupational functioning. Near the point of diagnosis, this cognitive reserve is no longer sufficient to compensate for the accumulated pathology and impaired functioning becomes apparent, heralding imminent conversion to dementia.

We also examined cognitive course in individuals who did not develop dementia. Using all of the data, there was decline in each test over the follow-up period. Some of this decline may reflect the inclusion of individuals with MCI or preclinical dementia. To assess the potential influence of preclinical dementia, we removed one, two, three, and four successive waves of follow-up beginning with the last. Removing later waves of follow-up reduced estimated rates of decline for all measures; this finding most likely reflects the influence of preclinical dementia in the group who did not develop dementia (Sliwinski et al., 1996). Rates of decline in the executive function tests were similar whether one or two observations at the end of the follow-up were dropped, whereas excluding the second, third, and fourth free recall observation resulted in progressively less steep rates of decline, most likely because decline in free recall begins 4 or more years earlier than decline in the executive function measures. A subject destined to have AD in 5 years might have accelerated memory decline without acceleration in executive dysfunction. Finally, the rates of decline among AD cases before the change points for all three executive function tests were significantly more rapid than the rates of decline among noncases on all three measures. This finding may reflect accelerated decline in executive function before the beginning of data collection in this study, in individuals who go on to develop AD.

The BLSA is a volunteer sample with an unusually high level of education. Nonetheless, the age-specific incidence rates for AD are comparable with other studies (Kawas et al., 2000). Women and those with low education tended to be at higher risk of AD in keeping with other published studies (Jorm & Jolley, 1998; Stern et al., 1994). Lack of power, particularly in those with low education and in the oldest age groups limited the significance of these trends (Kawas et al., 2000). Because this sample is not population-representative, change points and rates of change are likely to differ in less well educated cohorts who are presumed to

have less cognitive reserve (Stern, 2002). Higher education delays the onset of accelerated cognitive decline; once it begins it is more rapid in persons with more education (Hall et al., 2007). The conversion time from onset of incident MCI to the diagnosis of AD in the BLSA was estimated by asking informants when the first symptoms of memory loss were noticed. The median conversion time from first memory symptoms to diagnosable AD was 4.4 years with an interquartile range of 2.3 to 7.4 years (Kawas et al., 2000).

The decision to use learning as our measure of memory instead of retention may seem contrary to the prevailing view that retention is a better predictor of future dementia than initial learning (Welsh et al., 1991). Our decision was based on previous BLSA findings in which learning defined by the sum of free recall from FCSR was lower in incident AD cases than controls, while retention for both groups was perfect measured by the ratio of delayed free recall to third learning trial 30 min earlier. We have argued that the retention deficit in preclinical and early AD is best examined with memory tests like FCSR, which control attention and initial processing to obtain maximum learning, which is the basis for subsequent retention (Grober & Kawas, 1997). Measuring retention of inadequately learned material can lead to contradictory results as previous studies on forgetting in early AD have shown (e.g., Becker et al., 1987; Moss et al., 1986).

The unfolding of memory and executive dysfunction during the preclinical onset of illness may provide a way to reconcile discrepancies in the predictive value of memory and executive function tests in preclinical AD. Based on the present findings, the predictive validity of a test would be expected to vary with time during the preclinical onset of AD. Early in the course of decline, say 5 to 7 years before diagnosis, memory performance might more sensitively predict future AD than executive dysfunction. As the time of diagnosis approaches, measures of executive dysfunction may become as discriminating. This expectation was confirmed in a study in which incident AD cases were divided into those who developed dementia 1–3 years after baseline, 3–5 years, and 5–8 years (Saxton et al., 2004). Memory tests were predictive throughout the follow-up period, whereas executive function tests including Trailmaking and Category Fluency became predictive 5 years before diagnosis. The predictive validity of the tests used in the current assessment for prevalent and incident AD is beyond the scope of this study; these issues will be addressed in future studies.

The patterns of cognitive decline observed during the preclinical onset of AD reflect the simultaneous influence of functioning brain systems as well as disease- and age-related changes. The onset and rate of decline in memory and executive function is consistent with the temporal–spatial progression of AD pathology. Pathologic studies demonstrate that the entorhinal cortex first involved in preclinical AD subserves memory (Gomez-Isla & Hyman, 2003; Grober et al., 1999). The present results suggest that 7 years before the diagnosis of AD, changes in entorhinal cortex may be sufficient to produce a measurable acceleration of memory decline. Potential neural substrates for these changes might include neuronal loss, neurotic pathology, or more likely, alterations in metabolism (Gomez-Isla & Hyman, 2003). Executive function shows accelerated decline 2 to 3 years before diagnosis. A second acceleration of memory decline also occurs at this time. This finding suggests that AD related neuropathology in frontal circuits may reach a point of functional consequence 3 years before diagnosis. Close to the time of diagnosis, AD-related neural changes in the temporal lobe produce the accelerated decline in verbal IQ that was observed. This is when compensation for the accumulated pathology collapses and impaired functioning becomes apparent.

A limitation of this study is the absence of a group with nonAD dementias, for example, individuals who develop vascular dementia (VaD) on follow-up, the most common etiology for dementia after AD. Clinicians have long been interested in the possible role of cognitive profiles in distinguishing patients with AD from those who have VaD (Duff Canning et al., 2004; Graham et al., 2006; Laukka et al., 2004; Looi & Sachdev, 1999). Although the spatial–temporal progression of AD pathology corresponds with the unfolding of memory impairment followed by executive dysfunction revealed by change point methods, this profile may not be unique to AD. Cognitive impairment is present in preclinical VaD (Almkvist et al., 1999; Ingles et al., 2007; Laukka et al., 2004) and the profile is similar to preclinical AD (Laukka et al., 2004). Three years before diagnosis, the cognitive profile of persons destined to develop AD was indistinguishable from that of persons destined to develop VaD. Both groups displayed memory impairment and executive dysfunction, although these deficits were somewhat more pronounced in the incident AD group (Laukka et al., 2004). Because the time of baseline assessment relative to the time of onset of diagnosable dementia is highly variable, the cognitive profile will depend on where in the preclinical course the individual is and on the natural history of decline in the test domain. Thus, despite similar cognitive profiles, there may be differences in the onset and rate of cognitive decline in preclinical AD and VaD: executive dysfunction may begin earlier than memory decline in preclinical VaD, opposite to the pattern observed in preclinical AD. Future studies are needed to define the nature and timing of cognitive changes in preclinical VaD.

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