

Use of IQ-Adjusted Norms to Predict Progressive Cognitive Decline in Highly Intelligent Older Individuals

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Identifying high-functioning older individuals in preclinical phases of Alzheimer's disease (AD) may require more sensitive methods than the standard approach. The authors explored the utility of adjusting for premorbid intelligence to predict progressive cognitive decline or Mild Cognitive Impairment (MCI) in 42 highly intelligent older individuals. When scores were adjusted for baseline IQ, 9 participants had executive impairments, 11 had memory impairments, and 22 scored in the normal range. None were impaired according to standard age norms. Three and a half years later, 9 participants with IQ-adjusted memory impairment declined in naming, visuospatial functioning, and memory; 6 converted to MCI. Three participants with normal memory declined. Implications for using IQ-adjusted norms to predict preclinical AD are discussed.

Traditionally, changes in memory were thought to be a consequence of normal aging (M. Albert et al., 1995; Craik & Salthouse, 1992; Petersen, Smith, Kokmen, Ivnik, & Tangelos, 1992), but recent evidence indicates that some memory declines may represent early Alzheimer's disease (AD) with the existence of a long preclinical phase between normal aging and conversion to probable AD (Goldman & Morris, 2001; Morris et al., 2001). As a result, identifying individuals in preclinical stages before the onset of clinical dementia has been a topic of intense investigation over the past decade. In part, these efforts have been inspired by the clinical availability of palliative treatments (Doody et al., 2001) as well as the promise of disease-modifying agents (Schenk, Seubert, Lieberburg, & Wallace, 2000) that could potentially have a profound impact on functional status and rate of decline if individuals were identified and treated early in the disease course. Although initiatives to develop biological (Diaz-Arrastia & Baskin, 2001) and neuroimaging markers of preclinical AD are under way (Fox et al., 1996; Fox, Warrington, Seiffer, & Rossor, 1998; Jack et al., 1999; Johnson et al., 1998; Killiany et al., 2000, 2002; Reiman et al., 2001; G. W. Small et al., 2000), performance on cognitive tests remains the most widely used method in clinical and research

settings for predicting which individuals are likely to progress to a dementia state (M. S. Albert, Moss, Tanzi, & Jones, 2001; Backman, Small, & Fratiglioni, 2001; Chen et al., 2000; Fabrigoule et al., 1998; Fox et al., 1998; Jacobs et al., 1995; Jacobson, Delis, Bondi, & Salmon, 2002; Rentz & Weintraub, 1999; B. J. Small, Fratiglioni, Almkvist, Herlitz, & Backman, 1997; Tierney et al., 1996).

Numerous retrospective and prospective studies have identified declines in episodic memory as the predominant and earliest cognitive marker of later conversion to a diagnosis of AD (M. S. Albert et al., 2001; Backman et al., 2001; Bondi et al., 1994; Fox et al., 1998; Fuld, Masur, Blau, Crystal, & Aronson, 1990; B. J. Small et al., 1997; B. Small, Fratiglioni, Viitanen, Winblad, & Backman, 2000). Over the last few years, executive dysfunction has been implicated as an early cognitive marker as well (M. S. Albert et al., 2001; Bozoki, Giordani, Heidebrink, Berent, & Foster, 2001; Chen et al., 2000, 2001) on the basis of current imaging studies that suggest involvement of the anterior cingulate gyrus early in the disease course (Johnson et al., 1998, 2001; Killiany et al., 2000). Nevertheless, episodic memory is still considered among the earliest changes associated with preclinical phases, which coincide with the neuropathological changes of AD that initially encompass the entorhinal cortex and hippocampus involved in memory processing (Gomez-Isla et al., 1996; Hyman, Van Hoesen, Damasio, & Barnes, 1984).

However, attempts at establishing objective and clinically useful criteria for defining the transition between normal memory changes for age (Blackford & LaRue, 1989; Crook et al., 1986; Hanninen et al., 1996; Levy, 1994) and memory impairment that represents evidence of preclinical AD have had varying degrees of predictive success when cognitive test norms were used (Bozoki et al., 2001; Eby, Hogan, & Parhad, 1995; Hanninen et al., 1996; Petersen et al., 1999; Ritchie, Artero, & Touchon, 2001; Ritchie & Touchon, 2000). In part, the difficulty may be related to the normative data against which individuals are compared. For example, decline or clinical change is generally measured by using cutoff scores on neuropsychological tests that are 1 to 2 standard

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deviations below the established mean for either young adults (Crook et al., 1986) or age (Blackford & LaRue, 1989; Petersen et al., 1999) depending on the criteria used. When individuals vary from the normative group, using standardized cutoff scores based on age may not be sensitive enough for detecting the subtle cognitive changes characteristic of preclinical AD. For instance, individuals with higher levels of ability are thought to have a greater "cognitive reserve," which means that these individuals have the capability of using neural networks more efficiently or the facility of calling upon alternate networks and strategies in response to neuropsychological task demands, thus allowing them to perform well (Stern, 2002). It could be assumed that individuals with higher levels of intelligence might score 1 to 2 standard deviations above the mean on cognitive tests (Katzman et al., 1989; Stern, 2002). As a result, scores in the average range on standardized tests of memory may represent a decline in some high-functioning individuals (Naugle, Cullum, & Bigler, 1990). To correct for this measurement error, recent normative data (Ivnik, Malec, Smith, Tangalos, & Petersen, 1996) as well as criteria to define Age Associated Cognitive Decline (AACD; Levy, 1994) and Mild Cognitive Impairment (MCI; Petersen et al., 2001) have included education adjustments under the assumption that level of education might provide a suitable proxy for cognitive reserve. This supposition was supported by two pivotal functional imaging studies (Stern, Alexander, Prohovnik, & Mayeux, 1992; Stern et al., 1995) in which higher levels of premorbid education and occupational attainment were associated with greater parietotemporal hypoperfusion in a group of patients with AD matched on overall dementia severity. These studies provided the initial physiological support that individuals with higher levels of education may have a greater cognitive reserve and that the neuropathological effects of AD must be more severe before the clinical symptoms of the disease are manifested. In another study, participants with higher levels of education and occupational attainment demonstrated more rapid memory decline and faster disease progression (Stern, Albert, Tang, & Tsai, 1999), providing further evidence that cognitive reserve may modulate the clinical expression of AD. Some studies have confirmed that higher levels of education influence rate of cognitive decline (Christensen et al., 1997), but others have not (Filley, Brownell, & Albert, 1985; Mortimer, Ebbitt, Jun, & Finch, 1992; Mortimer & Graves, 1993). Also, an autopsy-verified study of the effect of education on degenerative dementia showed that individuals at all levels of education had a similar duration of illness until time of death, implying higher levels of education did not retard the manifestation of cognitive symptoms and shorten disease duration (Del Ser, Hachinski, Mersey, & Munoz, 1999).

The conflicting results of the above studies suggest that education adjustments may not be the best proxy of cognitive reserve and could underestimate native ability (S. M. Albert & Teresi, 1999; Naugle et al., 1990; Satz, 1993; Schmand, Smit, Geerlings, & Lindeboom, 1997). In an effort to determine the best estimate of cognitive reserve, another functional imaging study used three measures of premorbid ability including demographic estimations, levels of education, and word reading estimates of premorbid IQ (Alexander et al., 1997). They found that although all three measures of premorbid ability were associated with hypoperfusion in frontal and parietal association regions consistent with AD, a word

reading estimate of premorbid IQ was more sensitive to the neurophysiological effects of AD than were the other variables (Alexander et al., 1997).

This study explored whether accounting for an individual's estimated premorbid IQ could potentially resolve some of the inherent problems in differentiating individuals at risk for progressive decline from those with normal memory changes for age, particularly when individuals have abilities that vary from those of the normative group. We examined one segment of older individuals who fit these criteria, namely, those with high intelligence.

Using a method for adjusting standardized test norms based on IQ (Rentz et al., 2000), the present study predicted subsequent cognitive decline in a sample of highly intelligent older individuals, who at baseline, 3 1/2 years earlier, had scored in the normal range on standardized tests for age and gender where available. Participants were assigned to groups based on IQ-adjusted impairments in memory or executive functions to determine which cognitive domain declines first in highly intelligent older individuals. We chose these subgroups based on previous reports in the literature that individuals in preclinical phases of AD have early changes in memory (i.e., total learning or delayed recall) and executive function (i.e., mental flexibility and set shifting on Trails B; Reitan, 1979; see also M. S. Albert et al., 2001; Chen et al., 2000, 2001). We explored two questions: (a) Compared with standardized methods of stratification by age and education, do IQ-adjusted norms provide a better estimate of future cognitive decline in a sample of individuals whose baseline level of ability varies from that of the normative group, and (b) which cognitive realms based on IQ-adjusted impairments were the most sensitive predictors?

Method

Participants

Participants were drawn from a cohort of 221 community-dwelling older individuals participating in a prospective longitudinal study of aging and AD at Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts. The Institutional Review Board, Human Research Committee, at Brigham and Women's Hospital annually approved this study, and participants gave informed consent. At entry, all participants were living independently in the community. They underwent a comprehensive medical and psychiatric interview, as well as a neurological evaluation to rule out any major neurological disorders that might contribute to cognitive dysfunction. None of the participants had a history of alcoholism; drug abuse; or current serious neurologic, medical, or psychiatric illness. They were characterized by demographic information and on the Blessed Dementia Rating Scale (Blessed, Tomlinson, & Roth, 1968), the American version of the National Adult Reading Test (AMNART; Ryan & Paolo, 1992), and the Geriatric Depression Scale (Yesavage et al., 1983).

Fifty-eight participants from the total cohort of 221 community-dwelling older individuals were initially selected for this study because, at baseline, they performed in the normal range across all cognitive tests on the basis of published test norms for Controlled Oral Word Association using FAS (the letters *F*, *A*, and *S*; Benton, Varney, deS. Hamsher, & Spreen, 1983), Buschke Selective Reminding Test (SRT; Masur, Fuld, Blau, Crystal, & Aronson, 1990), Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983), and Visual Form Discrimination Test (VFDT; Benton et al., 1983). None of the participants had a Blessed Dementia Rating Scale score of greater than 1 or a Geriatric Depression Scale score in the depressed

range (score > 11). Of those 58 participants, 42 participants with estimated AMNART IQs in the superior range (120 or greater) were included in this study.

Cognitive Measures

All participants underwent an experimental battery of neuropsychological tests measuring cognitive domains that included the following: executive functions (word generation to the letters *F*, *A*, and *S* and categories of animals, fruits and vegetables; CAT; Monsch et al., 1992), memory (SRT), language (BNT), and visuospatial processing (VFDT).

Procedures for Adjusting for Higher Levels of Ability

Although there are several established methods for estimating premorbid ability, including education and socioeconomic status, intellectual ability was chosen because intelligence has been proposed to be a better estimate of baseline functioning (Satz, 1993; Schmand et al., 1997) and may control for higher levels of native ability when participants have not had the advantages of education. However, to determine if the IQ-adjusted method is a better estimate of premorbid ability than is educational status, participants were reclassified using years of education as well.

IQ-Adjusted Method

Premorbid IQ was estimated at entry into the study using the AMNART. The AMNART is a reading list of 50 irregular words that are scored correct if pronounced accurately. IQ is determined based on an error score. Numerous studies have demonstrated pronunciation accuracy to correlate highly with measured intelligence on Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981) Verbal IQ (VIQ; $r = .80$ to $.95$; Friedman, Ferguson, Robinson, & Sunderland, 1992; Nelson & O'Connell, 1978; Ryan & Paolo, 1992; Wiens, Bryan, & Crossen, 1993), and it has shown adequate reliability and stability in healthy older individuals and questionable-mild dementia when used in a longitudinal epidemiological study (Schmand, Geerlings, Jonker, & Lindeboom, 1998). However, we recognize that use of the AMNART is not a perfect measure of premorbid IQ for all older individuals, for all disease conditions, or even in the earliest detectable stages of AD (O'Carroll, 1995; Storandt, Stone, & LaBarge, 1995). Also, using an estimate of premorbid ability as a baseline from which to measure subsequent decline presumes that individuals perform at a consistent level across all cognitive domains. Although this is a standard theoretical assumption in neuropsychology (Filskov & Leli, 1981), a reading test is an inaccurate measure of premorbid IQ for those individuals with reading difficulties or non-English-speaking participants. Thus, all participants in this study were English speaking, scoring in superior ranges of ability, and had no history of learning disabilities or diagnosis of dementia, even in the earliest stages.

At entry, test scores were evaluated by two methods: (a) use of the standard published norms to determine abnormal performance and (b) use of adjusted norms in which the "mean" value of the standardized published norms was raised to match the individual's IQ level in a method previously described (Rentz et al., 2000). Adjustments were based on the WAIS-R IQ standardization sample in which the mean IQ of the population is 100 and the standard deviation is 15. IQ scores that were between 120 and 129 are approximately 1.7 standard deviations above the population mean of 100. IQ scores that were greater than 130 are approximately 2 standard deviations above the mean. If the estimated AMNART IQ was ≥ 120 but ≤ 129 , the normative mean was adjusted upward by 1.7 standard deviations and a new adjusted mean was established for this IQ range. If the estimated AMNART IQ was ≥ 130 , the normative mean was adjusted upward by 2 standard deviations and a new adjusted mean was established for this IQ range. Abnormal test scores were initially set at 2 standard deviations below the new adjusted mean, consistent with other diagnostic

criteria distinguishing normal age-related change from late-life forgetfulness (Blackford & LaRue, 1989). We reclassified participants' performance as abnormal based on cutoff scores at 1.5 standard deviations, consistent with criteria for MCI (Petersen et al., 1999). Table 1 shows the cutoff scores for the IQ-adjusted norms used in this study.

All participants scored in the normal range using standardized norms for age and gender where available. On the basis of normal or abnormal test performances adjusted for IQ, participants were placed into three groups. Group 1 consisted of cognitively stable controls: those participants who scored in the normal range for IQ across all tests. Group 2 consisted of participants with executive impairment: those participants who scored below cutoffs for IQ on tests of either letter or category fluency but had IQ-adjusted performances in the normal range on tests of memory, language, and visuospatial functioning. Because our participants did not have a measure of performance on Trails B at baseline, we chose impairment on word fluency as a measure of executive dysfunction because various reports have shown that verbal fluency for letters and categories involves frontal neural networks that allow for the strategic activation and retrieval of knowledge, as well as processes for inhibition and switching between mental sets (Baldo & Shimamura, 1998; Rende, Ramsberger, & Miyake, 2002), similar to some of the cognitive processes needed for Trails B. Group 3 consisted of participants with memory impairment: those participants who scored in the abnormal range for IQ on at least one subset of the SRT but scored normally for their ability on tests of executive function (i.e., word fluency), language, and visuospatial functioning. No participant had impairments in both memory and executive functions.

Procedures for Adjusting for Education

IQ-adjusted norms were also contrasted with the more commonly used estimation of cognitive reserve, years of education. These stratifications were logically derived because the norms for the tests used in this study did not have education adjustments. Therefore, if participants attained 12 to 16 years of education, they were considered to function in the average to high-average range of ability, or equivalently to someone with an IQ between 100 and 119; participants with 17 to 19 years of education were considered to function in the high-average to superior range of ability, or equivalently to someone with an IQ between 120 and 129; and participants with greater than 19 years of education were considered to function in the very superior range, or equivalently to someone with an IQ greater than 130. The cutoff scores found in Table 1 were used to classify participants into three groups as having normal performance, executive impairment, and memory impairment based on their years of education.

Longitudinal Assessment

Participants were reevaluated approximately 3 1/2 years later with the same tests as mentioned above. A reliable informant, who knew the participant well, was also administered a structured interview to complete the Clinical Dementia Rating Scale (CDR; Morris, 1993).

Outcome Measures

The primary outcome measure was a decline of 1.5 standard deviations from the mean on experimental cognitive tests from baseline. Secondary outcome measures were conversion to a diagnosis of MCI or AD. MCI was defined based on Petersen criteria (Petersen et al., 1999) as (a) memory complaints corroborated by an informant; (b) CDR score of 0.5, with impairments in at least the domain of memory; (c) memory test performance ≥ 1.5 standard deviations from the mean for age on the SRT; and (e) *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; DSM-IV; American Psychiatric Association, 1994) criteria for dementia not met. AD was defined based on DSM-IV criteria, and diagnosis was made based on a standard clinical exam by a clinical neurologist.

Table 1
Cutoff Scores Derived for Highly Intelligent Older Individuals and Stratified by Years of Education

Test	1.5 SD			2 SD		
	EQ 110-119 Education 12-16	EQ 120-129 Education 17-19	EQ ≥ 130 Education 20+	EQ 110-119 Education 12-16	EQ 120-129 Education 17-19	EQ ≥ 130 Education 20+
FAS/Category generation						
FAS total score	<31	<44	<47	<32	<37	<41
Category generation	<38	<50	<53	<40	<45	<48
Selective Reminding Test						
Total recall	<30	<47	<50	<33	<43	<46
LTS	<16	<42	<46	<22	<36	<40
LTR	<12	<37	<41	<18	<32	<35
Delayed recall	<1	<7	<8	<3	<6	<7
MC	<11	<11	<11	<11	<11	<11
Boston Naming Test (60 items)						
Age						
60-64	<51	<57	<58	<52	<54	<55
65-69	<47	<56	<57	<49	<51	<53
70-74	<44	<55	<57	<46	<50	<51
75-79	<39	<53	<54	<42	<48	<49
80+	<38	<55	<56	<41	<46	<49
Visual Form Discrimination						
Test						
Men (age 55-75+)	<25	<29	<30	<26	<28	<28
Women (age 55-75+)	<26	<30	<31	<27	<28	<28

Note. EQ = estimated IQ; FAS = 60-s word generation to the letters F, A, and S; Selective Reminding Test scores: LTS = long-term store, LTR = long-term retrieval, MC = multiple choice.

Data Analysis

All statistical analyses were performed using statistical software (SPSS, Version 10.0). All tests were two-tailed, with statistical significance (alpha) set at .05. For descriptive statistics, we calculated differences between groups using independent-samples *t* tests for continuous variables. We also used chi-square analyses to determine whether there would be differences in the gender composition between groups according to both the IQ-adjusted and education-adjusted methods. For the cognitive measures, we performed several calculations to determine change.

One set of analyses involved a straightforward analysis of variance (ANOVA) to determine differences between raw mean scores on baseline and retest scores for each group. This analysis was performed to assess the general trend of the data without considering the effects of practice, age, education, gender, and regression to the mean.

A second set of analyses that would account for the above effects and more stringently assess meaningful change was then performed. Raw scores were transformed into uniform meaningful change scores that adjusted for age, sex, education, practice effects, and regression to the mean in the following steps. A meaningful change score was calculated for all neuropsychological measures by converting the difference between baseline and retest scores into *z* scores. The method to determine this *z* score is described as a *regression predicted deviation score*: $z \text{ score} = (Y_o - Y_p)/SE$, where Y_o = observed score and Y_p = predicted retest score. The predicted retest score (Y_p) and standard error are the variables that are susceptible to variance other than change due to meaningful cognitive decline. Therefore, we included into these variables the degree of change that may be due to additional random effects such as regression to the mean and practice as well as variations in cognitive performance with age or education by performing a regression analysis using scores from 30 older individuals of similar age and estimated IQ. The test scores of these participants were not the same as those used in the experimental design. They were chosen to represent the normative sample (NS) because they scored in the normal range over a 3-year period, indicating cognitive stability. Baseline and retest scores of the NS were entered into a linear regression equation to calculate the residual coefficient and the standard error of the estimate. $Y_p = (\text{NS residual coefficient} \times \text{baseline score}) + \text{NS standard error of estimate}$, where the residual coefficient and the standard error of estimate were acquired from the equation conducted with data from the NS.

Using standardized norms to indicate change by regressing baseline scores of control participants against their own retest scores has been established as a statistically reliable approach for test-retest conditions (McSweeney, Naugle, Chelune, & Luders, 1993). Dividing the difference between an individual's observed and predicted retest scores by the standard error of the regression line—that is, $(\text{observed} - \text{predicted})/SE_{\text{reg}}$ —one obtains a standardized *z* score that reflects the degree of departure from the expected retest score in standard deviation units. This method accounts for the degree of variance from errors due to regression to the mean, practice effects, and random environmental effects (Chelune, Naugle, Luders, Sedlak, & Awad, 1993).

All 42 participants in the study were then compared with the NS using baseline and retest scores in the equation to acquire a change

score (z_{chg}) for all participants on each of the cognitive measures: $z_{\text{chg}} = (Y_o - Y_p)/SE$, where Y_o = observed sample retest score; $Y_p = (\text{NS residual coefficient} \times \text{observed sample baseline}) + \text{NS } SE_{\text{estimate}}$; SE = NS standard error. For each z_{chg} score a very high *z* score (2.0) would indicate that a score remained stable or improved, with a low *z* score (−1.0) indicating decline.

To calculate inferential statistics, we performed several steps. Independent samples *t* tests were used to determine the amount of difference in *z* scores between the control group, executive impairment group, and memory impairment group for all cognitive measures. Each individual was then categorized as predicted to decline or as not predicted to decline on each measure. Cognitive decline was defined across all tests as a decline of greater than 1.5 standard deviations from the mean decline in controls on the retest score from the baseline test score. A chi-square analysis was then performed to test for the significance of differences in proportions between individuals demonstrating impairments in memory and control participants. A two-tailed probability value of $\leq .05$ was considered statistically significant. Each individual was subsequently categorized to determine those who went on to meet criteria for MCI or AD and those who did not develop MCI or AD based on their scores on retest.

We were interested in examining whether IQ-adjusted memory impairments could predict conversion to MCI or dementia. Therefore, an odds ratio was calculated to determine the likelihood that those with memory impairments who were predicted to decline in fact declined, in comparison with those without memory impairments who declined (Pagano & Gauvreau, 1993). The odds ratio was calculated in the following manner. The number of participants with memory impairments who converted to MCI (Mem_a) was divided by the number of participants with memory impairment who did not convert (Mem_b), giving the following equation: Mem_a/Mem_b . In the second step, the number of participants in the control group who demonstrated conversion to MCI (C_a) was divided by the number of participants in the control group who did not convert (C_b): C_a/C_b . In the final step, the quotient from the first equation was divided by the quotient from the second equation to give the following equation: $(Mem_a/Mem_b)/(C_a/C_b)$. The quotient from this final equation provided the odds ratio with a 95% confidence interval.

Results

Participant Characteristics

All 42 participants returned for follow-up testing. The mean time to follow-up was 41.5 ($SD = 10$) months since entry into the study. When IQ-adjusted norms were used to identify groups, the same participants were classified into the same groups at both the 1.5- and 2-standard-deviation cutoff ranges. Twenty-two participants were classified as cognitively stable controls, 9 as having executive impairment, and 11 as having memory impairment. There were no participants with both memory and executive impairments.

Participants with memory impairment ($M = 72.8$, $SD = 4.7$) were significantly older than those with executive impairment ($M = 64.2$, $SD = 11.9$), $t(18) = 2.21$, $p < .05$, but not compared with stable controls ($M = 69.5$, $SD = 7.3$). Participants with executive impairment ($M = 128.0$, $SD = 3.2$) had a significantly higher estimated IQ than cognitively stable participants ($M =$

124.6, $SD = 3.8$), $t(29) = -2.33$, $p < .05$, but they were not different from participants with memory impairment ($M = 125.82$, $SD = 3.34$). No significant differences in age, education, or estimated IQ existed between the cognitively stable controls and the participants with memory impairment. Table 2 summarizes the characteristics of each participant group.

When we identified the three groups based on education-adjusted cutoff scores, 29 participants were classified as cognitively stable controls, 7 participants as having executive impairment, and 6 participants as having memory impairment. According to the education-adjusted method, the group with memory impairment ($M = 72.6$, $SD = 4.6$) was significantly older than the group with executive impairment ($M = 64.2$, $SD = 11.9$), $t(18) = -2.17$, $p < .05$. Stable control participants ($M = 14.83$, $SD = 2.39$) had significantly fewer years of education than participants with executive impairment ($M = 17.57$, $SD = 2.37$), $t(34) = -2.73$, $p < .05$, and participants with memory impairment ($M = 18.17$, $SD = 0.98$), $t(34) = -3.33$, $p < .05$. Participants with executive impairment ($M = 128.29$, $SD = 3.50$) had significantly higher scores on a measure of estimated IQ than did stable control participants ($M = 125.24$, $SD = 3.02$), $t(34) = -2.33$, $p < .05$.

The 30 older adults who composed the NS in the statistical analysis included 6 men and 24 women with a mean age of 69.1 ($SD = 6.1$), mean estimated IQ of 125.9 ($SD = 3.6$), mean education of 16.1 ($SD = 2.6$), and a mean Geriatric Depression Scale score of 3.6 ($SD = 2.7$). No statistical differences existed in age, years of education, Geriatric Depression Scale scores, and estimated IQ between these stable controls and the group of 42 participants in the study.

With respect to gender, overall the men ($n = 11$, $M = 18.2$) attained significantly more years of education than the women

($n = 31$, $M = 14.9$), $t(40) = 4.23$, $p < .01$. Using the IQ-adjusted method, there were no significant differences in gender composition between the cognitively stable control group ($n = 22$; 3 men and 19 women), the group with memory impairment ($n = 11$; 4 men and 7 women), and the group with executive impairment ($n = 9$; 4 men and 5 women), $\chi^2(2, N = 42) = 3.93$, $p > .05$, but in the education-adjusted method there were significant differences in the gender composition between the cognitively stable control group ($n = 29$; 4 men and 25 women), the group with memory impairment ($n = 6$; 3 men and 3 women), and the group with executive impairment ($n = 7$; 4 men and 3 women), $\chi^2(2, N = 42) = 7.53$, $p = .02$. There were no significant differences in gender composition between the NS ($n = 30$; 6 men and 24 women) and the groups with impairment from the experimental sample ($n = 20$; 8 men and 12 women), $\chi^2(1, N = 50) = 2.38$, $p > .05$, using the IQ-adjusted method. However, after reclassification using the education-adjusted method, gender composition was significantly different between the NS ($n = 30$; 6 men and 24 women) and the groups with impairment from the experimental sample ($n = 13$; 7 men and 6 women), $\chi^2(1, N = 43) = 4.93$, $p = .03$.

Analysis of Mean Raw Scores

Results of the ANOVA demonstrated significant differences between cognitively stable controls and participants with memory impairment in category fluency for baseline scores, $F(2, 39) = 14.46$, $p < .01$; SRT for total recall for baseline, $F(2, 39) = 7.63$, $p < .01$, and retest, $F(2, 39) = 4.89$, $p = .01$; long-term storage for baseline, $F(2, 39) = 20.6$, $p < .01$, and retest, $F(2, 39) = 6.99$, $p < .01$; long-term retrieval for baseline, $F(2, 39) = 19.48$, $p < .01$, and retest, $F(2, 39) = 5.81$, $p < .01$;

Table 2
Demographic Information

Demographic	Overall ($n = 42$)	Stable control		Executive impairment		Memory impairment	
		IQ adjusted ($n = 22$)	Education adjusted ($n = 29$)	IQ adjusted ($n = 9$)	Education adjusted ($n = 7$)	IQ adjusted ($n = 11$)	Education adjusted ($n = 6$)
Gender							
Female	31	19	25	5	3	7	3
Male	11	3	4	4	4	4	3
Age							
<i>M</i>	69.24	69.50	68.45 ^a	64.22 ^b	65.86	72.82 ^b	75.33 ^a
<i>SD</i>	8.33	7.31	7.28	11.88	9.08	4.73	7.76
Education (years)							
<i>M</i>	15.88	15.64	14.83 ^{c,d}	16.78	17.57 ^{c,d}	15.64	18.17 ^c
<i>SD</i>	2.64	2.48	2.39	2.99	2.37	2.77	0.98
Estimated IQ							
<i>M</i>	125.67	124.64 ^b	125.24 ^e	128.00 ^b	128.29 ^e	125.82	125.67
<i>SD</i>	3.73	3.81	3.02	3.20	3.50	3.34	3.20
Geriatric Depression Scale							
<i>M</i>	3.36	3.68	4.24 ^f	3.44	1.57 ^f	2.64	0.83 ^f
<i>SD</i>	3.39	2.98	3.35	5.34	1.27	2.20	0.75

^a Education adjusted: Participants with memory impairment were significantly older than stable control participants ($p < .05$). ^b IQ adjusted: Participants with memory impairment were significantly older than participants with executive impairment ($p < .05$). No other significant age differences were found. Participants with executive impairment had a significantly higher estimated IQ than stable control participants ($p < .05$). No other significant IQ differences were found. ^c Education adjusted: Participants with memory impairment had significantly more years of education than participants with executive impairment ($p < .05$) and stable control participants ($p < .05$). ^d Education adjusted: Participants with executive impairment had significantly more years of education than stable control participants ($p < .05$). ^e Education adjusted: Participants with executive impairment had significantly higher estimated IQ scores than stable control participants ($p < .05$). ^f Education adjusted: Stable control participants had significantly higher scores on the Geriatric Depression Scale than participants with executive impairment ($p < .05$) and participants with memory impairment ($p < .05$).

delayed recall for baseline, $F(2, 39) = 10.33, p < .01$, and retest, $F(2, 39) = 7.00, p < .01$; 30-min delayed recall for baseline, $F(2, 39) = 9.07, p < .01$, and retest, $F(2, 39) = 9.61, p < .01$; and on multiple-choice retest only, $F(2, 39) = 3.53, p < .05$ (see Table 3).

Analysis of Transformed z Scores

IQ-adjusted method. The results of t tests for independent samples revealed significant differences in change scores between cognitively stable controls and participants with memory impairment in naming on the BNT, $t(31) = 2.11, p = .04$; visuospatial functioning on the VFDT, $t(31) = 2.01, p = .05$; and in episodic memory on the SRT for total recall, $t(31) = 2.28, p = .03$; delayed recall, $t(31) = 2.14, p = .04$; and 30-min delayed recall, $t(31) = 2.20, p = .04$. The results of t tests for independent samples revealed no significant differences on any of the cognitive tests between stable controls and participants with executive impairment (see Figure 1).

Table 3
Scores for All Groups at Baseline and Follow-Up

Test	Stable control ($n = 22$)		Executive impairment ($n = 9$)		Memory impairment ($n = 11$)	
	M	SD	M	SD	M	SD
FAS						
Time 1	50.27	10.10	46.33	14.53	46.55	11.33
Time 2	53.23	10.33	52.56	13.88	56.00	11.84
CAT						
Time 1	55.45	5.81	43.44*	7.18	48.82*	7.18
Time 2	51.73	8.61	47.78	6.00	49.45	10.04
BNT						
Time 1	57.68	1.67	56.44	2.60	55.82*	2.44
Time 2	58.23	1.90	57.22	3.42	55.82*	3.49
VFDT						
Time 1	31.09	1.38	30.56	1.74	30.82	1.47
Time 2	30.45	2.02	31.00	1.66	29.00	2.53
SRT-TR						
Time 1	51.36	4.81	52.33	4.00	45.36*	4.70
Time 2	51.14	8.00	51.89	8.31	43.18*	5.29
SRT-LTS						
Time 1	44.05	7.22	48.56	7.94	29.55*	6.67
Time 2	42.23	11.78	47.11	14.82	28.73*	8.91
SRT-LTR						
Time 1	41.64	7.00	44.56	6.95	27.55*	6.73
Time 2	40.09	12.21	42.22	15.27	26.45*	8.02
SRT-SD						
Time 1	8.14	2.05	8.11	1.62	5.18*	1.54
Time 2	8.09	2.22	7.89	3.02	4.82*	2.40
SRT-LD						
Time 1	9.05	1.76	9.56	1.33	6.64*	1.96
Time 2	9.32	2.03	8.44	2.94	5.36*	2.94
SRT-MC						
Time 1	11.91	0.29	11.89	0.11	11.64	0.67
Time 2	11.95	0.21	11.67	0.71	11.55*	0.52

Note. FAS = 60-s word generation to the letters *F, A, and S*; CAT = 60-s category generation to animals, fruits, and vegetables; BNT = Boston Naming Test; VFDT = Visual Form Discrimination Test; SRT = Selective Reminding Test; TR = total recall; LTS = long-term store; LTR = long-term retrieval; SD = short delay (10 min); LD = long delay (30 min); MC = multiple choice.

* $p < .05$ when compared with stable control group.

Education-adjusted method. The results of t tests for independent samples revealed a significant decline in change scores only on the VFDT between cognitively stable controls and participants with memory impairment, $t(33) = 3.5, p = .00$, and a significant improvement in change scores between the cognitively stable controls and participants with executive impairment, $t(33) = -2.3, p = .03$. There were no significant differences on measures of memory, executive functions, or naming.

Chi-Square Analysis

IQ-adjusted method. Of the 11 older individuals with initial IQ-adjusted impairments in memory, 9 (82%) exhibited significant decline and 6 (55%) went on to meet MCI criteria. No participant, by retest, received a diagnosis of AD. Only 3 (10%) of the 31 older individuals with normal IQ-adjusted memory performances went on to meet MCI criteria. None of the participants with IQ-adjusted decrements in executive functions converted to MCI, but 1 participant showed a significant decline of more than 1 standard deviation but less than 1.5 standard deviations from the mean on tests of memory. The chi-square analysis revealed that baseline IQ-adjusted memory impairments significantly predicted subsequent decline to MCI criteria, $\chi^2(2, N = 42) = 9.7, p = .01$.

Education-adjusted method. In comparison to the IQ-adjusted method, only 2 of the 6 participants (33.3%) who demonstrated initial memory impairments went on to meet MCI criteria. A closer examination of the 36 participants who had normal memory for education revealed that 7 participants showed significant declines in memory (19.4%) and 4 participants met MCI criteria (11.1%). Two of the 7 participants (28.6%) who had decrements in executive functions converted to MCI. The chi-square analysis demonstrated that baseline education-adjusted criteria did not significantly predict conversion to MCI, $\chi^2(2, N = 42) = 1.0, p = .12$.

Odds-Ratio Analysis

IQ-adjusted method. Highly intelligent older individuals with baseline IQ-adjusted declines in memory were 11.2 times more likely to develop MCI than those with normal memory for their ability (odds ratio = 11.2; 95% confidence interval = 2.0–60.1).

Education-adjusted method. According to the education-adjusted method, highly intelligent older individuals with baseline declines in memory were only 2.4 times more likely to develop MCI than those with normal memory for their ability. The probability of detecting MCI using the education-adjusted method (odds ratio = 2.4) was 8.8 times less sensitive than the IQ-adjusted method (odds ratio = 11.2).

Discussion

In our sample of highly intelligent participants, IQ-adjusted memory impairments at baseline predicted that 11 individuals were at risk for future decline when standardized norms indicated that they were performing in the normal range for age. Three and a half years later, 9 of the 11 participants declined (82%) and 6 (55%) went on to meet MCI criteria. Although education-adjusted memory impairment demonstrated predictive value, it identified only 6 individuals as being at risk for cognitive decline, and 3 1/2 years later 2 declined (33%) and both went on to meet MCI (33%)

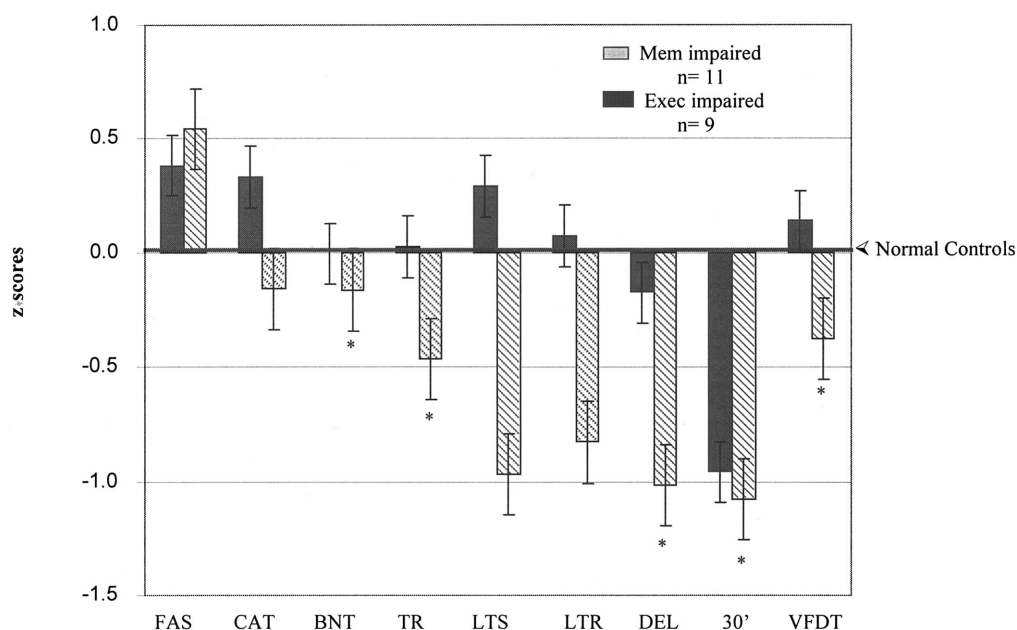


Figure 1. Mean linear regression change scores ($\pm SE$) for 60-s word generation to the letters *F*, *A*, and *S* (FAS), categories (CAT), Boston Naming Test (BNT), Visual Form Discrimination Test (VFDT), and Buschke Selective Reminding Test: total recall (TR), long-term store (LTS), long-term retrieval (LTR), delayed recall (DEL), and 30-min delayed recall (30'). Older individuals with memory (mem) impairment demonstrated statistically significant changes in naming, visuospatial functioning, and episodic memory from cognitively stable controls. The 9 older individuals with initial executive (exec) deficits showed no significant changes from controls. * $p < .05$.

criteria. Standardized norms for age did not identify any of the participants in the sample as being at risk for progressive decline.

There are several explanations as to why IQ-adjusted norms may provide a better estimate of decline than do norms for age and education. First, theories in the literature suggest that higher levels of intelligence or education may provide a functional reserve that delays the onset of cognitive symptoms associated with dementia (Katzman, 1993; Schmand et al., 1997; Stern, 2002; Stern et al., 1994, 1999). Because IQ-adjusted impairments are measured from estimates of an individual's premorbid intelligence, rather than a normative average, IQ-adjusted cutoff scores have the potential of identifying very early changes in cognition that would be normalized by standardized test norms, particularly in highly intelligent individuals at older age ranges. Also, IQ-adjusted norms avoid the pitfalls of educational and occupational bias as a measure of native ability, particularly for individuals in this aged cohort who were unable to advance their education because of life events (i.e., world war, financial depression) or bearing in mind that earlier generations of women traditionally chose marriage and family over educational attainment. In our sample, the majority of participants with significantly fewer years of education were women. When the IQ-adjusted method was used, no significant differences in gender composition were found between stable controls and groups with impairment. However, education adjustments placed more women into the stable control group who were considered to be at risk based on the IQ-adjusted method. These findings support the supposition that the IQ-adjusted method may provide a better gauge of native ability than education adjustments when individuals are highly intelligent.

Second, the use of IQ-adjusted norms also has the potential of controlling for some of the inaccuracies that may be inherent in the normative data (Sliwinski, Lipton, Buschke, & Stewart, 1996). For example, there is no guarantee that normative databases of older participants are free of preclinical AD, despite every effort to ensure that participants included in NSs are dementia free. Without a definitive antemortem biological marker for determining the presence of AD pathology, normative scores at lower ranges on cognitive tests have been implicated as possible evidence of early pathological change (Katzman, 1993; Katzman et al., 1988; Morris et al., 1996; Price & Morris, 1999; Sliwinski & Buschke, 1997; Sliwinski et al., 1996) and subsequent conversion to a diagnosis of AD (Sliwinski et al., 1996). Although those publishing norms in the last several years have attempted to control for measurement error by including demographics for age, education, and level of intelligence (Ivnik et al., 1992, 1996; Kittner et al., 1986; Richardson & Marottoli, 1999; Tuokko & Woodward, 1996), there is only one known normative study of older individuals that excluded participants if signs of a clinical dementia were present 2 years after baseline normative data were obtained (Bolla, Gray, Resnick, Galante, & Kawas, 1998). Although it will take many years to establish new normative databases based on longitudinal samples, use of an IQ-adjusted method may provide a temporary solution for clinicians and research investigators evaluating older highly intelligent individuals.

It is important to note that our baseline IQ-adjusted predictions of decline were not flawless when individuals were assessed over an average of 3.5 years. Eighty-two percent of participants in our sample with IQ-adjusted memory impairments declined, and only

55% met MCI criteria. None of the participants in our sample converted to a diagnosis of AD. Although IQ-adjusted norms provided a better estimate of decline for participants with memory impairment (82%) than did education (33%), there may be several reasons why IQ-adjusted memory impairments failed to predict conversion to MCI. First, there is no consensus as to which neuropsychological tests should be used to define MCI (Ritchie & Touchon, 2000). Second, fluctuations in performance are common in participants with memory impairments who come from the general population as our participants did (M. S. Albert et al., 2001; Ritchie et al., 2001). Third, recent studies have shown that individuals with initial memory impairments can remain stable for 3 to 6 years prior to receiving a diagnosis of AD and then exhibit an accelerated decline (Goldman & Morris, 2001; B. Small et al., 2000). Fourth, in our study, 3 1/2 years may have been an insufficient period to assess conversion to MCI or AD, particularly in our sample, in which individuals were younger as a group, with a mean age of 72, and were highly intelligent. Finally, several studies suggest that not all individuals with episodic memory impairments decline to a diagnosis of dementia. Rather, some memory declines may be the result of another process and not preclinical AD (Bowen, Teri, & Kukull, 1997; Bozoki et al., 2001; Ebly et al., 1995; Hanninen et al., 1996; Malec, Smith, Ivnik, Petersen, & Tangalos, 1996).

In addition to predicting decline, IQ-adjusted norms were capable of predicting 19 of 22 older individuals (86%) who remained cognitively stable over 3.5 years. Education-adjusted norms were slightly less accurate, with 24 of 29 older individuals (83%) remaining cognitively stable over the same time frame. Standardized norms for age predicted that all 42 individuals would remain normal, but based on the findings of this study, only 30 of 42 participants remained stable (71%), suggesting a high false-positive rate of prediction. In situations in which clinicians or research investigators need to make decisions about normalcy, IQ-adjusted norms provide a slightly more accurate estimation of which older individuals would remain stable over 3.5 years than do education-adjusted norms. However, the differences were minimal, suggesting that either method is advantageous over standardized norms for age when determining which individuals would remain stable over time.

The second question we addressed was which IQ-adjusted impairments were most predictive of subsequent cognitive decline. The cognitive task that was most predictive of decline in our sample of highly intelligent older individuals was impaired memory retrieval, particularly after a 30-min delay. Delayed-recall measures have been predictive of conversion to AD in several longitudinal studies (Collie et al., 2001; Petersen, Smith, Ivnik, Kokmen, & Tangalos, 1994; B. Small et al., 2000; Tierney et al., 1996). We also found significant differences in total learning scores on the SRT (see Figure 1), consistent with other reports in the literature (M. S. Albert et al., 2001; Stern et al., 1999). More recently, there have been two reports indicating that declines in paired associative memory may be an early cognitive marker of preclinical AD (De Jager, Milwain, & Budge, 2002; Fowler, Saling, Conway, Semple, & Louis, 2002).

Changes in executive functions were predictive of subsequent decline in 1 participant in our sample but not of conversion to MCI. This finding was surprising because category generation is diminished throughout the course of AD (Monsch et al., 1992) and

declines in letter fluency have been associated with a shorter duration of illness (Coen et al., 1996). Other investigators have found that deficits in both memory and executive functions were the most useful predictor of conversion to AD (M. S. Albert et al., 2001; Bozoki et al., 2001; Chen et al., 2000). Our failure to find conversion to MCI in this domain may have been due to small sample size and the fact that these older individuals had normal memory rather than initial memory impairments together with executive dysfunction. Also, we defined executive compromise as impairments in either FAS or category generation for their IQ. At retest, participants with executive impairment as a group improved on both FAS and categories, demonstrating no significant declines (see Table 3). It is possible that if we initially defined participants with executive impairment as having impairments in both FAS and categories, we might have found a decline in executive performance—or, the executive components (i.e., activation retrieval and set shifting) involved in word fluency tasks may not be the same features that produced executive compromise using Trails B (M. S. Albert et al., 2001; Chen et al., 2001).

Initial changes in language and processing speed have also been associated with a future dementia (Jacobs et al., 1995; Masur, Sliwinski, Lipton, Blau, & Crystal, 1994; Sliwinski & Buschke, 1997; Tierney et al., 1996). Our highly intelligent older individuals predicted to decline were normal at baseline on tasks of language and visuospatial processing, but those who did convert to MCI showed declines in naming and visuospatial tasks approximately 3 1/2 years later.

A number of longitudinal studies have defined normal age-related changes (Collie et al., 2001; Flicker, Ferris, & Reisberg, 1993; Masur et al., 1994; Petersen et al., 1992; S. A. Small, Stern, Tang, & Mayeux, 1999), but to our knowledge, there have been no studies examining normal age-related changes in highly intelligent older individuals. In our sample, stable controls showed no significant declines in acquisition, learning, or delayed recall on the SRT from Time 1 to Time 2 (see Table 3). Also, no significant changes were noted in language and visuospatial ability. Two studies demonstrated a similar longitudinal performance in healthy aged individuals (Sliwinski & Buschke, 1997; S. A. Small et al., 1999), but others have indicated that there are normal declines in memory acquisition and learning with increasing age (Petersen et al., 1992; S. A. Small et al., 1999). When one is evaluating healthy older individuals who are highly intelligent, our study suggests that stability of performance across all cognitive domains, including delayed-recall measures, may be the most distinguishing feature, whereas declines on tests of delayed recall over 30 min may be the most predictive sign of those highly intelligent older individuals who are likely to decline.

The strength of this study is its longitudinal follow-up, but several major limitations are apparent. The sample size is small, and no one to date has converted to meet criteria for clinical AD. However, the older individuals who converted to MCI had significant changes in several cognitive domains including memory, naming, and visuospatial functioning, which is consistent with what is known about the clinical course of AD (Rentz & Weintraub, 1999), and we intend to follow these participants over time.

This study is a promising start for using a simple and easy alternative method for predicting early cognitive changes when older individuals do not match the normative group. Because discoveries in the field of AD and other related dementias rely on

accurate knowledge of cognitive status, the development of measurement tools that are sensitive to all older individuals of various backgrounds, education, and abilities would be an important contribution.

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