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Neuropsychological Performance in Advanced Age- Influences of Demographic Factors and Apolipoprotein E: Findings from the Cache County Memory Study

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Abstract

The Cache County Study of Memory in Aging (CCMS) is an epidemiological study of Alzheimer's disease (AD), mild cognitive disorders, and aging in a population of exceptionally long-lived individuals (7th to 11th decade). Observation of population members without dementia provides an opportunity for establishing the range of normal neurocognitive performance in a representative sample of the very old. We examined neurocognitive performance of the normal participants undergoing full clinical evaluations (n=507) and we tested the potential modifying effects of *APOE* genotype, a known genetic risk factor for the later development of AD. The results indicate that advanced age and low education are related to lower test scores across nearly all of the neurocognitive measures. Gender and *APOE* ε4 both had negligible and inconsistent influences, affecting only isolated measures of memory and expressive speech (in case of gender). The gender and *APOE* effects disappeared once age and education were controlled. The study of this exceptionally long-lived population provides useful normative information regarding the broad range of "normal" cognition seen in advanced age. Among elderly without dementia or other cognitive impairment, *APOE* does not appear to exert any major effects on cognition once other demographic influences are controlled.

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INTRODUCTION

Decline across a spectrum of neurocognitive functions is common with age (Ebly et al., 1994; Mitrushina et al., 1999; Howeisson et al., 2003). Aging is associated with selective losses in functions related to psychomotor speed, sensorimotor function, and efficiency of information processing (Hertzog et al., 2003; Salthouse, 1996), some of which may be genetically mediated (Finkel et al., 2000). Other cognitive functions affected by age are memory retrieval, attentional capacity, and executive skills. As a consequence, processes such as divergent thinking, working memory and multitasking are particularly vulnerable. Changes in memory and executive functions are also reported in the early stages of Alzheimer's disease (AD; Welsh et al., 1991; 1992), mild cognitive impairment (MCI; Petersen et al., 1999), and other degenerative conditions of aging (Becker 1988; Hayden et al., 2005).

Making firm clinical distinctions between normal aging, mild cognitive impairment, and early AD requires the use of normative standards and preferably repeated observations. Although most commonly used psychometric instruments have norms for elderly populations, the samples used to derive these norms are often paid volunteers. Furthermore, it is unusual to have a broad range of tests that are co-normed within the same normative samples. Because the samples used across normative studies vary in important dimensions affecting test performance (e.g. age, geographic region, education, socioeconomic status, gender), it can be problematic to draw clinical inferences about relative performance outcomes across the various measures. The Mayo Older Adult Normative Project (MOANS) provides the most comprehensive information to date on many neuropsychological tests used in clinical practice (Ivnik et al., 1992a,b,c; 1996; Steinberg et al., 2005). Although originally representing primarily Caucasian elderly in Rochester Minnesota, some normative data from minority populations have recently been tabulated (e.g. Rilling et al., 2005). Additionally, there is new normative information on the MOANS data which provides correction for general intellectual ability (Steinberg et al., 2005 a,b), an approach which is similar to educational correction, but may be preferred among those with low intelligence (Dodrill 1997). The MOANS sample, while not population based, is more representative than typical convenience samples.

To assure generalizability, cross validation of findings in other similarly aged and well-characterized groups is important (Fastenau, 1998; Heaton et al., 1999). The population-based study in Cache County Utah, the "Cache County Study of Memory, Health and Aging" (hereafter referred to as the Cache County Memory Study or CCMS), offers an opportunity to explore normal neurocognitive performance across the entire age spectrum over age 65. The epidemiological investigation, begun in 1995, was primarily designed to prospectively determine the prevalence and incidence of dementia in an exceptionally long-lived population. With a study population enjoying average life expectancies exceeding national norms by more than 10 years in men and 8 years in women (Tschanz et al., 2005; Manton et al., 1991), the CCMS is in an ideal position to explore conditions of healthy aging and disease, such as early Alzheimer's disease, expressed in the 7^{th} through 10^{th} decades of life and beyond.

An advantage of the CCMS is that observations come from a population setting, minimizing some sources of bias often observed in normative studies. Additionally, because the study design calls for full clinical evaluation of members with suspected dementia along with age, gender, and APOE genotyped matched controls, contamination of the sample with undiagnosed

cases of early dementia is minimized. In this way, the normative standards derived from the population can be confidently used as the range of cognitively normal function most likely to be encountered within general community practices. Additionally, with dementia and other cognitive impairment excluded, the normative standards developed are more likely to reflect the range of true performance on the neuropsychological measures, facilitating the detection of mild forms of cognitive disorder in clinic applications (Sliwinski et al., 1996, 2003; Marcopolous et al, 1999; Manly et al., 2005). It is also possible to explore the influences of demographic factors (age, education, and gender) on normal cognition in aging, unconfounded by pre-dementia cases, and to determine whether genes, such as the apolipoprotein E (*APOE*) polymorphism, have effects on normal cognition beyond the well known effects on AD risk (Saunders et al., 1993).

Whether *APOE* exerts independent effects on the expression of normal cognitive abilities beyond its well-documented association with AD risk (Small et al., 2004), is a topic of some controversy. Some studies have shown lower cognitive function in non-demented individuals carrying one or more *APOE* ε4 alleles (e.g. Reed et al., 1994; Plassman et al., 1997; Caselli et al., 2004); whereas, others have suggested that group differences are related to the early AD phenotype and are not a function of normal cognitive aging (Smith et al., 1998). Data from the Cache County Study suggest that *APOE* genotype may play a role in the "timing" of AD onset (e.g. Breitner et al., 1999) while others have suggested that the ε4 allele may lead to a precipitous decline in episodic memory functions a year or two prior to fully manifest AD symptoms (Bondi et al., 1999; Baxter et al., 2003). Both sets of findings again underscore the possibility that *APOE* is related to disease transition and not normal aging, but the issue remains unresolved.

To help clarify some of these issues, we report here the neurocognitive performance of 507 normal individuals from the CCMS population study, many of whom were older than 85 at the initiation of the study. The analysis permits a full appreciation of the range of neurocognitive performance observed in healthy normal aging and allows an examination of the effects of *APOE* on neuropsychological function. We present normative data (means, standard deviation (SD), percentiles) by age group and education level. We also provide multivariable regression equations for predicting "normal" performance on common neurocognitive measures used in the clinic, based on available demographic information and with consideration to *APOE* status. In this study we examine the modifying role of age and education on neurocognitive performance. We also test the prediction that the ε4 polymorphism at *APOE* will not be related to normal neurocognitive function when care is taken to exclude diagnosable dementia and other cognitive impairments.

METHODS

Subjects

The group of 507 cognitively normal individuals in these analyses was derived from the nested case-control study within the population-based study of risk factors for dementia, the Cache County Memory Study. The procedures used to sample cognitively impaired cases and appropriately matched controls from the population are described in detail elsewhere (Breitner et al., 1999; Miech et al., 2002; Tschanz et al., 2002). Briefly, all members of the population over age 65 residing in Cache County Utah in 1994 (n=5677) were contacted to participate in the study. The individuals who agreed to participate in this population survey (n=5092) first underwent cognitive screening using either the adapted version of the modified Mini-Mental State Examination (3MS-R; see Tschanz et al., 2002) or a proxy interview (Informant Questionnaire for Cognitive Decline *IQCODE*; Jorm et al., 1989). Buccal DNA was obtained and subsequently genotyped for apolipoprotein E (*APOE*) using PCR amplification of the coding region followed by restriction isotyping (see Saunders et al., 1993). Because clinical

examination of all 5092 population members would be prohibitively expensive, only the very old individuals (90+) and those scoring below a pre-determined cutpoint on the education- and sensory-adjusted screener (<87 3MS-R or > 3.27 on IQCODE) were selected for further evaluation for possible dementia with full clinical assessments (see Khatchaturian et al., 2000). Additionally, for case-control comparisons, a large subset of individuals were randomly selected from the population and clinically assessed. Sampling fractions were designed to meet a 2:1 ratio (2 controls for each identified case of AD). Individuals were matched by gender, 5-year age group, and number of *APOE* ε4 alleles (i.e. homozygous ε4; heterozygous ε4; non ε4), except in non *APOE* ε4 carriers within the two youngest age strata (ages 65–74 years) which were sampled for a ratio of 4:1.

The clinical assessment, administered within the participant's place of residence (including nursing homes) by a nurse and psychometrist, consisted of standardized blood pressure measurement, physical and neurological exam, neuropsychological testing, a review of cognitive symptoms, along with relevant medical history and medication inventory. Individuals with suspected dementia or its prodrome were examined by a board-certified geropsychiatrist, and standard laboratory studies were obtained including neuroimaging (MRI scan or in some instances CT) whenever possible. Final dementia diagnoses were determined at expert consensus diagnostic conferences attended by board certified neurologists, geriatric psychiatrists, neuropsychologists, and behavioral neuroscientists. A full description of the diagnostic methods are presented elsewhere (Breitner et al., 1999; Miech et al., 2002).

At the completion of the iterative diagnostic process there were 993 individuals who had been fully clinically evaluated. Of these, 333 individuals had dementia, 153 had other forms of cognitive impairment (due to a host of medical factors), and 507 were clinically normal subjects. The latter group of fully evaluated normal subjects (i.e. mild cognitive disorders excluded) served as the normative sample for this paper.

Neuropsychological measures

The neuropsychological battery used in the study has been described in previous work from our group (Breitner et al., 1995) and has been adopted by a growing number of cohort and case-control studies of aging and dementia (Steffens et al., 2004; Langa et al., 2005; van der Walt et al., 2005; Plassman et al., 2006; Tschanz et al., 2000, 2002; Tschanz et al., 2006). A brief description of the measures and the order of test administration follow:

Animal Fluency (Morris et al., 1989) (AnFlu)—This test from the CERAD battery ("Consortium to Establish a Registry for Alzheimer's Disease") assesses expressive language and requires generation of exemplars to the category 'animal' within a 60 second time interval. The total score was used in the normative analyses.

Boston Naming (Kaplan et al., 1983)—The Boston Naming test is a metric of visual naming. In Wave 1 of the CCMS study, we used the 15-item CERAD version (**BNT-15**; Welsh et al., 1994). In Wave 2 of study, we switched to the more sensitive split half version of the original test (**BNT-30**), administering every other test item from the 60 item stimuli (Saxton et al., 2000; Mack et al., 1992). Scores range from 0–15 on CERAD version and 0–30 on split half version.

Mini-Mental State Examination (Folstein et al., 1975)—To determine orientation to time and place and to provide a uniform metric of cognitive function we administered the CERAD version of the Mini-Mental State examination (**MMSE**; see Eaton & Kessler, 1985). This measure retains all the standard items of the original MMSE but does not include serial

subtractions. Rather, participants are asked to spell WORLD backwards. Scores range from 0–30.

Word List Learning Test (Morris et al., 1989)—The CERAD word list learning test is a measure of verbal learning and immediate memory. Derived from the Alzheimer's Disease Assessment Scale (ADAS, Rosen et al., 1984), the test consists of a three trial list learning procedure. The maximum score on any trial is 10 (**WLM t1, WLM t2, WLM t3**). The cumulative total over all three learning trials is therefore 30 points (**WLM Tot**).

Constructional Praxis (CPrx)—Also employed in the ADAS (Rosen et al., 1984), the CERAD test of constructional praxis assesses visuospatial and motor integrative functions. Participants are presented with four individual geometric figures of increasing complexity (circle, parallelogram, overlapping rectangles, and a cube) and are required to copy the figure. In total there are 11 points on the task.

Word Recall and Recognition—This test assesses free recall for the 10-item word list after a 5 minute delay (**WLM Del**). The maximum score for this item is 10. Savings scores are also computed (% retained= Delay/Trial 3 × 100). Recognition memory for the target items is assessed through the presentation of the 10 words from the word list memory test (**WLM-Yes**) interspersed among 10 distracter items (**WLM-No**). The maximum score for each recognition task (target hits, and detection of foils) is 10.

Delayed Praxis Recall and Recognition—This is an adjunctive visual memory measure added to the CERAD battery since its original development (Yusbeh et al. 1998). The procedure is an un-cued delayed free recall of the constructional praxis figures (**DelPrx**). Total score is 11 points and savings scores are computed (total free recall/copy score × 100).

Trail Making Test – Parts A & B (Reitan & Wolfson, 1993)—Originally a subtest of the Army Core Battery, the Trail Making test is included in the battery as a measure of executive function. The test consists of two procedures, which require visual attention and scanning, motor integration, working memory and set shifting. For Part A the participant is required to connect in sequential order numbered circles scattered across a page. Time to complete the task is recorded (**TRAILS A**). Trails B is similar to Trails A but requires connecting numbers and letters scattered on a page by alternating between the two categories in sequential order (1-A, 2-B, 3-C and so on) and time to completion is recorded (**TRAILS B**).

Logical Memory I and II – Wechsler Memory Scale-Revised (Wechsler, 1983)—The logical memory subtests from the Wechsler Memory Scale-Revised assess immediate verbal recall (Logical Memory I) and delayed verbal memory after a 30 minute interval (Logical Memory II) for two narrative passages read aloud to the participant (Immediate recall: **Log Ia, Log Ib**; Delayed recall: **Log IIa, Log IIb**). Total score for each narrative is 25 points, giving a total of 50 points for immediate (**Log-I tot**) and delayed recall (**Log-II total**).

Benton Visual Retention Test (Benton, 1992)—The Benton Visual Retention Test (**Benton VRT**) is a test of visual memory for geometric figures presented on stimulus cards. Each card is presented for 10 seconds, at the end of which the participant is required to reproduce the item from memory. Total score correct is 10 (**BVRTCorr**). Error scores can go as high as 30 points (**BVRTErr**).

Controlled Oral Word Association (COWA) test from the Multilingual Aphasia Examination (Form A; Benton et al 1994)—This is a test of expressive language, which requires word generation to a given letter for sixty seconds for each of three letters. There is

no ceiling score. In general scores of 30 or higher are typical values in the published norms for normal older adults.

Symbol Digit Modalities Test (SDMT; Smith 1973)—The SDMT is a test of rapid symbol decoding that is considered a measure of executive function. The task is for the subject to rapidly decode symbols and to write the corresponding numbers quickly below them (**SDMT Corr**). Timed for 90 seconds, the total number of completed items is scored.

Shipley Vocabulary Test (Shipley 1967)—The Shipley (**Ship**) is a test of vocabulary and word comprehension, which is used as an index of premorbid function (Kareken, 1998). Subjects are asked to read a word and pick the closest synonym from four written alternatives. Total score is 40 points and the test is prorated in instances of discontinuation.

Procedures

Included in the normative analyses were all the cognitively normal individuals who had been selected from the population for the full diagnostic evaluation as part of our case-control design (n= 507). Although some participants were age 65 at the time of screening, all individuals were at least 66 years of age at the time of the clinical examination and neuropsychological assessment. The population participating in the CCMS tends to be highly educated. The number of years of education range from no formal schooling to 20 years, with the average being high school education or beyond. Mean schooling for men (14.17, SD 3.28) is somewhat higher than that of women (12.86, SD 22.8) as would be expected in this age cohort (Tschanz et al., 2002). For this reason, the sample was subdivided into two broad educational strata: 1) “low education” is comprised of all individuals with less than 12 years of education (n=87), and 2) “high education” includes all those with a high school education or above (n= 420). To assess the effects of age on neurocognitive performance we further subdivided the sample. In the high education group there were three age strata (66–75, 76–85; 86+). Because of low numbers in the “low” education group, we subdivided it two age strata (66–85 and 86+).

Statistical analysis

Descriptive statistics (means, medians, percentiles and standard deviations [SD]) were calculated for each of the neurocognitive measures in the gender, age and education stratified subgroups. Tables containing these measures and the values obtained at various pre-selected percentiles reflecting highest to lowest performance (95^{th}, 90^{th}, 75^{th}, 50^{th}, 25^{th}, 10^{th}, and 5^{th}) were constructed to facilitate the applied use of the normative standards. Comparisons of performance on each of the measures across the different age, education and gender strata were made using either the Wilcoxon Rank Sums test or the Kruskal-Wallis test.

In separate analyses, we examined the influence of the known modifiers of test performance (age, education, gender) on each of the cognitive measures using multiple regression analysis. Prior to developing the final predictive models, models containing age, gender and gender by age interaction variables were developed separately for those with less than 12 years of education and for those with 12+ years of education. For ease of application, interaction terms were removed and final “predictive” models containing age, gender and education were created. Additionally, predictive models containing age, gender, education and an indicator for the presence of one or more *APOE* ε4 alleles were developed. These models allowed us to specifically test whether having a high-risk *APOE* genotype contributes any unique and substantial information to normal neurocognitive performance across the age continuum. The resulting prediction equations allow application of the normative information from the CCMS population to other groups, in order to determine an individual’s “expected” performance using the normative values based on age, education, gender and *APOE* status.

RESULTS

Demographic data for the different age strata are presented in Table 1. The results illustrate the advanced age and the educated nature of the sample; the majority of participants have completed 12 formal years of schooling. As a result of the matched sampling, there were a large number of individuals of advanced age in the analysis including 112 individuals in the oldest age group (85+).

The neurocognitive test battery percentile scores for healthy older adults stratified by education and age are presented in Tables 2a–c. After correction for multiple comparisons, there were few gender differences of any practical significance on the neuropsychological measures. Differences were seen on tests of verbal fluency (animal fluency) and delayed verbal recall (p's<0.03). In each instance women outperformed men on these measures and the differences were more evident in the high education strata ($p<0.001$). Because there were so few differences, the tables are not stratified by gender groups to increase the robustness of the estimates and to simplify presentation. The fifth percentile scores, suggesting the lowest possible scores in the normal population, are reported to facilitate the clinical interpretation of an individual patient's level of performance. (An explanation of the abbreviations used in the normative tables can be found in the Appendix).

Education had a significant effect on performance on nearly all variables, with individuals having higher education (>12 years) outperforming those with less education, thereby justifying the stratification by education. The effect of education was particularly evident on measures of verbal learning and memory (e.g. WLM Tot, WLM-DEL, Logical Memory), language expression (e.g. An Flu, COWA) and executive control (e.g. TRAILS A, B). On the other hand, no appreciable education effects emerged on recognition memory measures, likely due in part to scaling issues of these measures (ceiling effects).

Substantial age effects were also appreciated on the majority of neurocognitive measures. The effect was most evident in the group with higher education, likely due to the larger sample size of this group when compared to the low education group. Regardless of education strata, the older groups, particularly those older than 85, performed less well on tests of mental status (MMSE; p's <0.001), aspects of expressive language (An Flu p's ≤ 0.03; BNT-30, $p \leq 0.001$), and on tests of executive function involving visuomotor demands (TRAILS A p's ≤ 0.03; TRAILS B, p's ≤ 0.001; SDMT p's ≤ 0.005). There were interesting education-by-age effects on memory measures, with only the highly educated group showing age effects on immediate and delayed verbal memory (Word List, Logical Memory, p's ≤ 0.001). Although the group with less than 12 years education did not show age differences on delayed recall, both education strata (low and high education) showed age effects on delayed visual memory (i.e. CPrx, $p \leq 0.006$). No age effects were seen on either the lexical fluency measure (COWA) or on some measures of recognition (discriminating foils). Additionally, there were no age differences on the Shipley Vocabulary Test, a test that is often used as a proxy for premorbid verbal intelligence and is highly related to education.

APOE had no significant effect on cognitive performance in the low education group. In the group with 12 years or more education, some isolated differences emerged on the selected aspects of memory, including one delayed measure of verbal recall (WLM-DELAY= $p<0.03$), and on one measure of immediate visual memory (BVRT, $p<0.04$). No differences were seen on any other measures of memory or cognitive function, including the MMSE and tests of expressive language (An Flu, COWA), executive control (TRAILS A & B, SDMT), or memory (Log I, Log II; CPrx; CPrx Delay).

Regression Based Equations

Parameter estimates and root mean square errors (RMSEs) resulting from regression models regressing many of the neurocognitive measures on age, gender and education are listed in Table 3. An analysis of the residuals revealed four neurocognitive measures (BNT-30, CPrx, TRAILS A & B) with skewed distributions. Although variable transformations were considered to better meet the general linear model assumptions, parameter estimates based on the original untransformed variables were considered to be most useful for application to clinical settings.

As can be seen from these models, the demographic variables considered together account for 10% to 41% of the variance in test score. The SDMT appeared to be the most heavily influenced by the demographic modifiers (40%), followed by tests of naming (24–29%), rapid visuomotor processing (TRAILS A & B, 23–27%), and vocabulary (23%). CPrx was least influenced by the combined demographic factors with only 10% of the test variance attributable to demographic factors, due likely to scaling issues noted previously on this test in this sample.

From the regression models, the expected “normal” test performance and the associated prediction interval [PI] can be estimated based on a few demographic characteristics. A given individual’s demographic characteristics can be weighted by the parameter estimates supplied and then summed to provide the expected score that an individual of that age, gender, and education would make. By comparing actual score to predicted score, it is possible to determine whether the actual score is within expected normal limits. As an example, the expected performance on animal fluency for a 70 year-old woman with 13 years of completed education would be calculated as follows:

$$\begin{aligned} Animal\,fluency\,(X) &= 27.71+(-0.17)\,(age)+(-0.88)(female)+0.29(education)\\ (x) &= 27.71+(-0.17)(70)+(-0.88)(1)+0.29(13)=18.7\\ 95\%PI &= x+/-1.96\,RMSE\\ 95\%PI &= 18.7+/-1.96(4.21)=10.45\ to\ 26.95. \end{aligned}$$

For any given individual, the prediction interval for the predicted score depends on their particular set of covariates and will differ from individual to individual. Individuals with extreme values in their covariates will have larger prediction intervals. Proper specification of the prediction intervals would require publication of separate variance-covariance matrices for each outcome and use of matrix algebra by the clinician using the particular set of covariate values for each individual. Consequently the RMSE, while not ideal, can be substituted as a reasonable approximation of the estimate of the desired interval but should be viewed with caution, particularly with outcome measures with skewed residuals.

To determine the influence of *APOE* genotype, separate regression models were developed incorporating *APOE* ε4 status, a potential predictor of cognitive outcome. Models containing age, gender, education and the presence of an ε4 allele as predictors are shown in Table 4. Parameter estimates for the demographic variables remained relatively unchanged indicating limited confounding caused by *APOE* ε4 in this normal group. The prediction equation for the person listed above, assuming the presence of an *APOE* ε4 allele, would be adjusted only slightly as follows:

$$\begin{aligned} Animal\,fluency\,(x) &= 28.32+(-.35)\varepsilon 4+(-0.18)\,age+(-0.86)gender+(.29)education\\ (x) &= 28.32+(-0.35)(1)+(-0.18)(70)+(-0.86)(1)+(.29)(13)=18.28\\ 95\%\mathrm{PI} &= 10.00\ \mathrm{to}\ 26.55 \end{aligned}$$

DISCUSSION

The current study provides normative values for elderly individuals without cognitive impairment on a battery of common neuropsychological measures used in both community-based studies and in clinical practice for the purpose of screening for mild cognitive disorders and dementia. The strength of this study lies in the fact that the information gathered is derived from a large, carefully examined population-based sample of normal community-dwelling older adults ranging in age from 66 to 102. Because all the individuals included in these analyses underwent full clinical evaluations that were subsequently reviewed by a panel of geriatric specialists, cases of mild early dementia have been methodically excluded from the analysis. As such, this community-based sample reduces volunteer bias and includes a range of individuals whose general health may vary from poor to excellent. The presence of medical comorbidities is common with advanced aging (Østbye et al., 2006), and hence normative samples derived in populations that reflect these medical complexities are likely to be of most merit when evaluating similar patients with cognitive complaints. This normative sample includes individuals with these typical health conditions. Over one third of the participants had hypertension that was medically treated (37.9%, 192 individuals). A smaller proportion had other cardiovascular risk conditions, such as treated hyperlipidemia (n=78, 15.5%), a history of myocardial infarction (n=69, 13.7%), or diabetes (n=62, 12.3%). A small number had coronary artery bypass graft surgery (n=40, 7.9%) or previous stroke leading to no cognitive sequelae (n=11, 2.2%). Consequently, the normative sample is representative of normal cognitive aging and not extreme robust health. This feature and the exceptional longevity in the cohort (Breitner, et al., 1999; Tschanz et al., 2006) are advantages, reflecting the breadth of normal neuropsychological function into very advanced age (i.e. beyond age 85).

The results suggest that not all neurocognitive measures in the administered neuropsychological battery are affected to the same extent by age, education, and gender, the usual factors considered in interpreting performance. Advanced age and low education were related to poorer cognitive performance across nearly all measures. Age affected performance, in particular, on tests of semantic fluency, executive function, and visuomotor integration. Memory, while sensitive to age, was inconsistently affected across education strata; verbal memory was related to age in the higher education strata but showed no such relationship in the lower education group. By contrast, performance on nonverbal memory measures (e.g. delayed constructional praxis, Benton Visual Retention test) was inversely related to age regardless of education strata. Education had particularly strong effects on tests of verbal memory, executive function, and expressive language. In this sample, gender did not appear to affect neurocognitive performance to any extent. This finding is consistent with a number of other reports that do not show gender differences on most neuropsychological measures (e.g. Fillenbaum et al., 2002), but contrasts with some other normative studies that show differences, perhaps reflecting sampling issues (Welsh et al., 1994; Collie et al., 1999).

Interestingly, the *APOE* ε4 allele, a gene polymorphism associated with AD risk (Strittmatter et al., 1993) exerted very little independent effect on normal neurocognitive performance. Although some memory measures were related to *APOE* ε4 genotype in some analyses, the findings were not robust. Other memory measures were not related to *APOE* genotype and in the regression equations APOE had a very negligible effect. These observations are important since previous work, including our own, has suggested that *APOE* may affect normal neurocognitive performance in aging in addition to being a risk factor for AD (e.g. Plassman et al., 1997; Reed et al., 1994). The current findings suggest that differences on memory measures may reflect very early, undetected disease rather than “normal” cognitive variability related to the different *APOE* polymorphisms (Smith et al., 1998; Bondi et al., 1999). Regardless of the explanation, the effects of *APOE* appear complex and additional work is needed to fully determine its influence in normal neurocognitive expression. Based on the

current work, we would recommend consideration of age, education, and gender but not of *APOE* genotype when determining the expected values for normal neurocognitive performance of individual cases.

The Cache County population has some unique characteristics that may limit generalizability. The sample is nearly entirely Caucasian and tends to be educated (Tschanz et al., 2005). Lifestyle is characterized by high physical activity in mid-life and generally there is very little use of either alcohol or tobacco, factors that likely contribute to sustained good health and longevity in the population. Although the sample size is very large, it is not as large in the lower education groups and the robustness of some estimates may be limited by missing data secondary to sensory confounding. Visual acuity difficulties may prohibit administration of some visual measures and hence the sample size is lower on these measures. This issue is inherent in all normative studies of the elderly. It should be noted that the neurocognitive measures on which we report were part of and not independent from the diagnostic evaluation of cases and controls. Although this may appear somewhat tautological, we note that the diagnosis rested on much more than the neurocognitive tests reported here. The full evaluation included an independent mental status examination (modified Mini Mental status examination), full neurological evaluation, interview of a knowledgeable informant to establish functional status, neuropsychiatric symptoms, medical history, and the individual's ability to perform higher order activities of independent living from a knowledgeable informant. After completion of full evaluation and laboratory studies (if needed) final diagnoses were adjudicated by a panel of dementia experts. Any individuals diagnosed as having a mild cognitive disorder were removed from the normative sample. Individuals who either report very mild memory changes with age or demonstrate an isolated weakness on testing but otherwise have no objective findings, either by clinician examination or by informant report, are included in the sample.

The amount of variance in score accounted for by the demographic characteristics was in some instances quite limited (as low as 9–10% for naming and constructional praxis). Speeded measures, such as the Trail Making Tests and the SDMT, as well as some measures of new verbal learning (WLM total) and vocabulary (Ship) were the most influenced by the combined factors of age, education, and gender. Overall, the findings we report are actually in keeping with those of other studies in more diverse populations (e.g. Fillenbaum et al., 2002). Factors that may account for some of the variability across test measures include differences in instrument psychometrics (e.g. reliability, skew) and influences of homogeneity in population characteristics, which may act to restrict the range of score values. It is also likely that other factors not measured here, such as native intelligence and genetics, play larger roles on neuropsychological performance across the lifespan. Studies in twin samples suggest that heritability accounts for 30% or more of the variability in late life neurocognitive performance (Brandt et al., 1993). The findings from this fully evaluated clinical sample are likely to represent the broad spectrum of normal aging, unconfounded by clinically diagnosable early dementia states or MCI. A comparison of older normative values obtained in very healthy volunteer cohorts (e.g. CERAD battery, Welsh et al, 1994) indicates that the cut-points for impairment are higher with these older normative values (see Figure 1). The result is that more individuals, particularly those with low education, will screen as impaired using the older normative values. The community normative values presented here are likely more representative of true population normative tendencies. The percentiles presented using these new population norms and the predictor equations derived from the data should assist researchers and clinicians in estimating the bounds of expected performance for similarly aged individuals observed in other settings and provide a basis for decisions regarding the need for further diagnostic evaluation.

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Dr. Welsh-Bohmer and Dr. Breitner designed the neuropsychological and clinical assessment procedures for this study. Dr. Tschanz provided training and oversight of all field staff and reviewed all individual neuropsychological test results to render professional diagnoses. The board-certified or board-eligible geriatric psychiatrists or neurologists who examined the study members included in these analyses of our Wave 1 and Wave 2 data include Drs Steinberg, Breitner, Steffens, Lyketsos, and Green. Dr. Williams also examined several subjects and provided expert neurologic consultation. Autopsy examinations were conducted by Dr. Townsend. Ms. Leslie coordinated the autopsy enrollment program. Diagnosticians at the expert consensus conferences included Drs Breitner, Burke, Lyketsos, Plassman, Steffens, Steinberg, Toohill, Tschanz, and Welsh-Bohmer.

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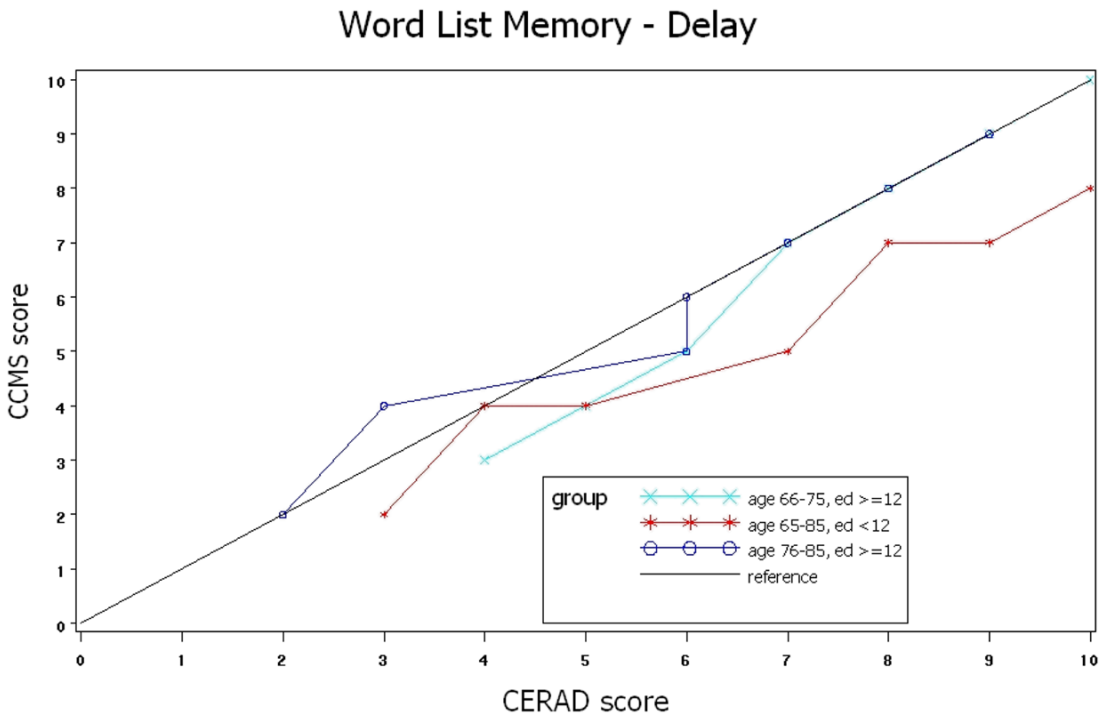

Figure 1.
Normative values for the CERAD Word List Memory Delayed Recall from the Cache County Population Norms are plotted against the normative standards published using the CERAD normative sample. In general there is good agreement in values with the two norm sets, however, for those with low education (<12 years) the CERAD norms tend to have a higher central tendency than the Cache County norms, which will lead to higher cut-points for impairment in this subgroup.

Table 1

Demographic Summary

	66–75 years		76–85 years		86+ years		Total Sample	
	Men n=84	**Women n=93**	**Men N=104**	**Women n=114**	**Men n=39**	**Women n=73**	**Men n=227**	**Women n=280**
Age (yrs)								
Mean (sd)	71.9 (2.8)	71.7 (2.6)	81.0 (2.7)	80.5 (2.9)	90.5 (3.3)	90.5 (3.4)	79.3 (7.2)	80.2 (7.8)
Min	66.3	66.0	76.0	76.0	86.3	86.1	66.3	66.0
Max	76.0	75.9	85.7	85.9	97.5	102.5	97.5	102.5
Education (yrs)								
Mean (sd)	14.5 (3.3)	13.3 (2.2)	13.9 (3.5)	13.2 (2.4)	12.3 (3.7)	12.4 (2.2)	13.9 (3.5)	13.0 (2.3)
Min	9.0	8.0	7.0	8.0	7.0	8.0	7.0	8.0
Max	20.0	19.0	20.0	20.0	20.0	18.0	20.0	20.0
***APOE* ε4 Number (%)**	47 (55.9)	57 (61.3)	52 (50.5)	67 (58.8)	10 (25.6)	18 (24.7)	109 (48.2)	142 (50.7)

Table 2

Table 2a. Normative Information for Subjects (< 12 Years of Education)

			66–85 Yrs.							>86 Yrs.								
	N	Mean (s.d.)	95%	90%	75%	50%	25%	10%	5%	N	Mean (s.d.)	95%	90%	75%	50%	25%	10%	5%
An Flu	51	16.4 (3.9)	23.0	22.0	19.0	17.0	14.0	11.0	10.0	36	14.5 (4.3)	22.0	20.0	17.0	14.0	12.0	9.0	6.0
BNT-15	43	13.7 (1.2)	15.0	15.0	15.0	14.0	13.0	12.0	11.0	32	12.1 (2.9)	15.0	15.0	14.0	13.0	11.0	10.0	7.0
BNT-30	*									*								
MMSE	51	27.1 (2.3)	30.0	30.0	29.0	27.0	26.0	24.0	23.0	36	25.1 (2.4)	30.0	28.0	27.0	25.5	23.0	21.0	21.0
WLM t1	51	3.9 (1.5)	7.0	6.0	5.0	4.0	3.0	2.0	1.0	36	3.4 (1.2)	6.0	5.0	4.0	3.0	3.0	2.0	2.0
WLM t2	51	5.8 (1.8)	8.0	8.0	7.0	6.0	5.0	3.0	3.0	36	5.3 (1.5)	8.0	7.0	6.0	5.0	4.5	4.0	2.0
WLM t3	51	6.8 (2.0)	10.0	9.0	8.0	7.0	6.0	4.0	3.0	36	6.5 (1.4)	9.0	8.0	8.0	6.0	6.0	4.0	4.0
WLM Tot	51	16.5 (4.5)	25.0	23.0	19.0	17.0	13.0	10.0	9.0	36	15.3 (3.3)	21.0	20.0	18.0	15.0	13.0	11.0	10.0
WLM Del	51	5.3 (1.7)	8.0	7.0	7.0	5.0	4.0	4.0	2.0	36	4.9 (1.7)	8.0	7.0	6.0	5.0	4.0	3.0	2.0
WLM%Ret	51	86.4 (62.9)	133.3	100.0	88.9	80.0	62.0	55.6	50.0	36	75.9 (26.2)	125.0	100.0	83.0	75.0	62.5	50.0	40.0
WLM Yes	51	9.1 (1.4)	10.0	10.0	10.0	10.0	8.0	7.0	6.0	36	9.0 (1.1)	10.0	10.0	10.0	9.0	8.0	8.0	7.0
WLM No	51	9.8 (0.5)	10.0	10.0	10.0	10.0	10.0	10.0	9.0	36	9.5 (1.3)	10.0	10.0	10.0	10.0	9.5	9.0	5.0
CPrx	50	9.7 (1.2)	11.0	11.0	11.0	10.0	9.0	8.0	8.0	31	9.4 (1.1)	11.0	11.0	10.0	9.0	9.0	8.0	7.0
DelPrx	50	7.4 (2.3)	10.0	10.0	9.0	8.0	6.0	4.5	2.0	31	5.5 (3.0)	9.0	9.0	8.0	6.0	3.0	2.0	0.0
TRAILS A	50	54.3 (16.0)	33.0	36.0	41.0	53.5	62.0	75.0	84.0	27	71.1 (34.1)	39.0	39.0	49.0	58.0	91.0	106.0	125.0
TRAILS B	49	159.2 (67.2)	76.0	79.0	106.0	141.0	191.0	277.0	305.0	24	232.8 (103.9)	128.0	132.0	156.0	208.0	290.0	345.0	417.0
LOG – Ia	50	9.3 (2.9)	14.0	13.5	11.0	9.0	8.0	5.5	4.0	36	9.0 (3.7)	15.0	14.0	12.5	8.0	6.5	5.0	5.0
LOG – Ib	50	10.3 (3.5)	17.0	15.0	12.0	10.0	8.0	5.5	5.0	35	9.0 (3.3)	15.0	13.0	12.0	9.0	6.0	5.0	4.0
LOG-I tot	50	19.7 (5.5)	29.0	27.5	23.0	19.0	16.0	12.5	11.0	36	17.7 (6.3)	28.0	27.0	23.0	17.0	13.5	10.0	10.0
LOG-IIa	50	6.3 (3.3)	11.0	11.0	9.0	6.0	4.0	2.0	2.0	35	6.4 (3.5)	14.0	11.0	8.0	5.0	4.0	3.0	0.0
LOG-IIb	50	7.9 (4.2)	15.0	14.0	11.0	7.0	4.0	3.0	2.0	35	6.6 (3.6)	14.0	13.0	9.0	6.0	4.0	3.0	2.0
LOG-II-tot	50	14.2 (6.7)	24.0	22.5	21.0	13.5	9.0	6.0	4.0	35	13.0 (6.2)	24.0	22.0	17.0	11.0	8.0	7.0	4.0
BVRTCorr	49	4.7 (2.2)	8.0	8.0	6.0	5.0	3.0	2.0	1.0	28	4.2 (1.8)	6.0	6.0	5.5	4.5	3.0	2.0	1.0
BVRTErr	49	9.8 (4.6)	3.0	4.0	6.0	11.0	12.0	17.0	18.0	28	10.8 (3.9)	6.0	6.0	9.0	10.0	13.0	15.0	15.0
COWA	50	26.7 (8.3)	40.0	38.5	32.0	26.0	21.0	17.5	13.0	34	25.2 (9.9)	44.0	38.0	34.0	24.0	16.0	12.0	10.0
SDMTCorr	48	25.9 (7.4)	37.0	37.0	31.0	25.5	21.0	15.0	14.0	26	20.9 (5.8)	30.0	30.0	25.0	20.5	17.0	13.0	12.0
Ship	50	27.1 (4.7)	34.0	32.1	30.8	27.4	25.8	20.3	16.8	33	26.3 (5.4)	35.0	34.0	29.5	26.8	22.0	21.5	15.8

Table 2b. Normative Information for Subjects Aged 66–85 (>= 12 Years of Education)																		
			66–75 Yrs.							76–85 Yrs.								
	N	Mean (s.d.)	95%	90%	75%	50%	25%	10%	5%	N	Mean (s.d.)	95%	90%	75%	50%	25%	10%	5%
An Flu	158	18.7 (4.4)	26.0	24.0	22.0	18.0	16.0	14.0	12.0	186	17.5 (4.5)	25.0	24.0	20.0	17.0	14.0	12.0	11.0
BNT-15	145	14.3 (0.8)	15.0	15.0	15.0	14.0	14.0	13.0	13.0	166	14.1 (1.0)	15.0	15.0	15.0	14.0	14.0	13.0	13.0
BNT-30	12	25.3 (2.1)	28.0	28.0	26.5	25.5	24.0	22.0	22.0	20	26.0 (2.2)	30.0	29.0	27.5	26.0	24.5	23.0	22.5
MMSE	158	28.7 (1.5)	30.0	30.0	30.0	29.0	28.0	27.0	26.0	186	27.9 (1.8)	30.0	30.0	29.0	28.0	27.0	25.0	24.0
WLM t1	158	4.7 (1.5)	7.0	7.0	6.0	5.0	4.0	3.0	2.0	186	4.3 (1.6)	7.0	6.0	5.0	4.0	3.0	2.0	2.0
WLM t2	158	7.1 (1.4)	9.0	9.0	8.0	7.0	6.0	5.0	5.0	186	6.5 (1.5)	9.0	8.0	8.0	7.0	6.0	4.0	4.0
WLM t3	158	8.1 (1.4)	10.0	10.0	9.0	8.0	7.0	6.0	6.0	185	7.6 (1.4)	10.0	9.0	8.0	8.0	7.0	6.0	5.0
WLM Tot	158	19.9 (3.6)	25.0	25.0	22.0	20.0	17.0	15.0	14.0	186	18.4 (3.8)	24.0	23.0	20.0	19.0	16.0	14.0	11.0
WLM Del	158	6.8 (1.9)	10.0	9.0	8.0	7.0	5.0	4.0	3.0	186	6.0 (1.9)	9.0	8.0	7.0	6.0	5.0	4.0	2.0
WLM%Ret	158	84.4 (27.8)	112.5	100.0	100.0	84.5	75.0	60.0	50.0	185	79.4 (21.0)	112.5	100.0	90.0	80.0	67.0	55.6	40.0
WLM Yes	158	9.7 (0.7)	10.0	10.0	10.0	10.0	10.0	8.0	8.0	186	9.3 (1.0)	10.0	10.0	10.0	10.0	9.0	8.0	7.0
WLM No	158	9.9 (0.3)	10.0	10.0	10.0	10.0	10.0	10.0	9.0	186	9.9 (0.3)	10.0	10.0	10.0	10.0	10.0	10.0	10.0
CPrx	158	10.1 (0.9)	11.0	11.0	11.0	10.0	9.0	9.0	8.0	183	10.0 (1.0)	11.0	11.0	11.0	10.0	9.0	9.0	8.0
DelPrx	158	8.7 (1.9)	11.0	11.0	10.0	9.0	8.0	6.0	5.0	183	8.0 (2.3)	11.0	11.0	10.0	8.0	7.0	5.0	4.0
TRAILS A	157	39.9 (12.7)	25.0	27.0	32.0	38.0	45.0	56.0	65.0	183	50.3 (20.5)	29.0	32.0	37.0	44.0	59.0	76.0	91.0
TRAILS B	155	108.1 (48.1)	55.0	63.0	75.0	99.0	127.0	164.0	202.0	176	137.1 (59.3)	64.0	73.0	102.5	125.0	159.0	222.0	282.0
LOG – Ia	155	11.6 (3.7)	17.0	16.0	14.0	12.0	9.0	7.0	5.0	182	10.9 (3.7)	17.0	16.0	13.0	11.0	8.0	6.0	4.0
LOG – Ib	155	12.2 (3.8)	18.0	17.0	14.0	12.0	9.0	7.0	6.0	179	11.2 (3.6)	17.0	16.0	13.0	11.0	9.0	6.0	5.0
LOG-I tot	155	23.8 (6.5)	34.0	32.0	29.0	24.0	19.0	16.0	13.0	182	21.9 (6.8)	32.0	30.0	26.0	22.0	18.0	14.0	10.0
LOG-IIa	154	9.2 (3.8)	15.0	14.0	12.0	9.0	6.0	5.0	3.0	177	8.2 (3.9)	15.0	13.0	10.0	8.0	6.0	3.0	2.0
LOG-IIb	154	10.6 (3.9)	17.0	15.0	13.0	11.0	8.0	5.0	4.0	177	9.0 (3.6)	16.0	13.0	11.0	9.0	7.0	4.0	4.0
LOG-II-tot	154	19.9 (6.9)	31.0	28.0	25.0	20.0	15.0	11.0	8.0	177	17.2 (6.6)	28.0	26.0	21.0	17.0	13.0	9.0	6.0
BVRTCorr	158	6.0 (1.6)	9.0	8.0	7.0	6.0	5.0	4.0	3.0	180	5.1 (1.8)	8.0	7.0	6.0	5.0	4.0	3.0	2.0
BVRTErr	158	6.9 (3.5)	2.0	3.0	4.0	7.0	9.0	11.0	13.0	180	8.8 (3.6)	3.0	4.0	6.0	9.0	11.0	13.5	15.0
COWA	157	34.2 (11.0)	50.0	49.0	42.0	35.0	26.0	19.0	17.0	184	34.0 (10.2)	51.0	48.0	41.0	34.0	26.5	21.0	19.0
SDMTCorr	157	37.8 (7.3)	50.0	47.0	44.0	39.0	33.0	28.0	26.0	175	31.9 (7.9)	46.0	43.0	37.0	31.0	26.0	21.0	19.0
Ship	158	31.4 (4.4)	39.0	37.0	34.3	31.1	28.8	26.0	25.0	183	31.1 (4.8)	38.0	37.0	34.0	31.8	28.0	24.5	21.8

Table 2c. Normative Information for Subjects Aged 86+ (>= 12 Years of Education)

			86+ Yrs.						
	N	**Mean (s.d.)**	**95%**	**90%**	**75%**	**50%**	**25%**	**10%**	**5%**
An Flu	76	15.2 (4.3)	25.0	21.0	17.5	15.0	13.0	10.0	9.0
BNT-15	71	12.4 (2.4)	15.0	14.0	14.0	13.0	12.0	10.0	9.0
BNT-30	*	10.0 (14.1)	*	*	*	*	*	*	*
MMSE	76	26.5 (2.9)	30.0	29.0	29.0	27.0	25.0	22.0	20.0
WLM t1	75	3.9 (1.6)	7.0	6.0	5.0	4.0	3.0	2.0	1.0
WLM t2	75	5.9 (1.7)	8.0	8.0	7.0	6.0	5.0	4.0	3.0
WLM t3	74	7.0 (1.8)	10.0	9.0	8.0	7.0	6.0	5.0	4.0
WLM Tot	75	16.7 (4.5)	24.0	22.0	19.0	17.0	14.0	12.0	10.0
WLM Del	74	5.1 (2.0)	9.0	8.0	7.0	5.0	4.0	3.0	1.0
WLM%Ret	73	74.5 (24.7)	116.7	100.0	87.5	75.0	62.5	42.9	22.2
WLM Yes	74	9.0 (1.5)	10.0	10.0	10.0	10.0	9.0	7.0	6.0
WLM No	74	10.0 (0.2)	10.0	10.0	10.0	10.0	10.0	10.0	9.0
CPrx	64	9.6 (1.2)	11.0	11.0	11.0	10.0	9.0	8.0	7.0
DelPrx	62	7.1 (2.5)	11.0	10.0	9.0	7.0	5.0	4.0	3.0
TRAILS A	59	65.8 (30.1)	38.0	39.0	47.0	56.0	75.0	109.0	135.0
TRAILS B	50	166.3 (64.2)	83.0	102.5	116.0	145.5	222.0	261.0	298.0
LOG – Ia	71	9.6 (3.6)	16.0	14.0	12.0	10.0	7.0	5.0	4.0
LOG – Ib	70	9.0 (3.4)	14.0	13.0	11.0	9.0	6.0	5.0	4.0
LOG-I tot	71	18.5 (6.4)	27.0	26.0	24.0	19.0	15.0	11.0	7.0
LOG-IIa	70	6.8 (3.8)	13.0	11.0	10.0	7.0	4.0	2.0	1.0
LOG-IIb	70	6.9 (3.8)	12.0	11.5	9.0	7.0	4.0	2.5	2.0
LOG-II-tot	70	13.7 (7.0)	23.0	22.0	17.0	14.0	9.0	4.5	3.0
BVRTCorr	57	4.3 (1.8)	8.0	7.0	5.0	4.0	3.0	2.0	1.0
BVRTErr	57	10.1 (3.5)	5.0	6.0	8.0	10.0	13.0	15.0	17.0
COWA	75	31.0 (8.5)	45.0	43.0	36.0	32.0	25.0	20.0	15.0
SDMTCorr	54	26.9 (7.3)	38.0	36.0	33.0	26.0	21.0	18.0	15.0
Ship	72	30.4 (5.0)	38.3	37.3	34.0	30.5	27.5	23.5	22.3

*Sample size (n<10) was insufficient for reasonable comparisons.

Neuropsychological Tests- Abbreviations: ***An Flu:*** Animal Fluency Test; ***BNT-15,*** Boston Naming Test 15 items; ***BNT-30***,Boston Naming Test 30 items; ***MMSE***, Mini-Mental Status Examination; ***WLM t1***, Word List Memory Task Trial 1 learning; ***WLM t2***, Word List Memory Task Trial 2 learning; ***WLM t3***, Word List Memory Task Trial 3 learning; **WLM Tot**, Word List Memory Task Total Learning; ***WLM Del***, Word List Memory Delayed Recall; ***WLM%Ret***, Word List Memory Savings Delay & Trial 3; ***WLM Yes***, Word List Recognition of Targets; ***WLM No***, Word List Recognition Foils; ***CPrx***, Constructional Praxis; ***DelPrx***, Delayed Recall of Constructional Praxis; ***TRAILS A***, Trail Making Test Part A; ***TRAILS B,*** Trail Making Test Part B; ***LOG Ia***, Wechsler Memory Scale R- Log Memory Paragraph A immediate recall; ***LOG Ib,*** Wechsler Memory Scale R- Log Memory Paragraph B immediate recall; ***LOG-I tot***, Wechsler Memory Scale R- Log Memory I A & B total immediate recall***; Log- IIa,*** Wechsler Memory Scale R- Log Memory Paragraph A, delayed recall; ***LOG-IIb,*** Wechsler Memory Scale R- Log Memory Paragraph B delayed recall; ***LOG-II-tot***, Wechsler Memory Scale R II Total delayed recall; ***BVRTCorr***, Benton Visual Retention Test correct score; ***BVRTErr***, Benton Visual Retention Test total error score; ***COWA***, Controlled Oral Word Association Test; ***SDMTCorr***, Symbol Digit Modality Test correct score; ***Ship***, Shipley Vocabulary Test.

Table 3

Multiple Regression Parameter Estimates After Regressing Neurocognitive Measures on Age, Gender and Education

Dependent Variable	n	Intercept	Age in Years	Gender (female=1 male=0)	Education (years)	RMSE	R^2
An Flu	507	**27.71**	**−0.17** §	**−0.88** *	**0.29** §	**4.21**	0.16
BNT-15	457	**20.96**	**−0.10** §	**−0.23**	**0.05** *	**1.45**	0.24
BNT-30	43	**48.00**	**−0.38** †	**−0.25**	**0.46** *	**4.01**	0.29
WLM Tot	506	**26.17**	**−0.17** §	**1.45** §	**0.35** §	**3.70**	0.20
WLM Del	505	**10.44**	**−0.08** §	**0.82** §	**0.13** §	**1.80**	0.18
CPrx	486	**11.86**	**−0.04** §	**0.04**	**0.06** §	**1.00**	0.10
TRAILS A	476	**−51.64**	**1.43** §	**−2.59**	**−0.72** *	**19.83**	0.23
TRAILS B	469	**−121.96**	**4.18** §	**−3.90**	**−4.80** §	**57.98**	0.27
LOG-I tot	494	**37.64**	**−0.27** §	**0.35**	**0.36** ‡	**6.37**	0.13
LOG-II tot	486	**34.54**	**−0.30** §	**0.04**	**0.44** §	**6.62**	0.15
BVRTCorr	472	**10.24**	**−0.09** §	**0.10**	**0.14** §	**1.70**	0.18
BVRTErr	472	**−0.34**	**0.18** §	**−0.77** *	**−0.35** §	**3.49**	0.21
COWA	500	**26.59**	**−0.16** †	**3.41** §	**1.23** §	**9.61**	0.16
SDMTCorr	457	**68.34**	**−0.64** §	**1.55** *	**0.97** §	**7.03**	0.41
Ship	496	**23.33**	**−0.05**	**0.44**	**0.80** §	**4.38**	0.23

Pvalue symbols:

* <.05

† <.01

‡ <.001

§ <.0001

Table 4

Multiple Regression Parameter Estimates After Regressing Neurocognitive Measures on *APOE* ε4, Age, Gender and Education

Dependent Variable	n	Intercept	APOE ε4 Present	Age in Years	Gender (f=1; m=0)	Education(years)	RMSE	R^2
An Flu	506	**28.32**	**−0.35**	**−0.18** §	**−0.86** *	**0.29** §	**4.22**	0.16
BNT-15	456	**20.73**	**0.13**	**−0.10** §	**−0.23**	**0.05** *	**1.45**	0.24
BNT-30	43	**49.29**	**−0.53**	**−0.39** †	**−0.31**	**0.45** *	**4.06**	0.29
WLM Tot	505	**26.77**	**−0.35**	**−0.17** §	**1.47** §	**0.35** §	**3.70**	0.20
WLM Del	504	**10.42**	**0.02**	**−0.08** §	**0.81** §	**0.13** §	**1.81**	0.18
CPrx	485	**11.79**	**0.05**	**−0.03** §	**0.04**	**0.06** §	**1.01**	0.10
TRAILS A	475	**−52.52**	**0.63**	**1.44** §	**−2.66**	**−0.72** *	**19.86**	0.23
TRAILS B	468	**−120.99**	**−0.51**	**4.18** §	**−3.97**	**−4.81** §	**58.09**	0.27
LOG-I tot	493	**38.43**	**−0.41**	**−0.27** §	**0.33**	**0.36** ‡	**6.38**	0.13
LOG-II tot	485	**35.48**	**−0.50**	**−0.30** §	**0.01**	**0.44** §	**6.61**	0.15
BVRTCorr	471	**11.11**	**−0.57** ‡	**−0.10** §	**0.13**	**0.14** §	**1.68**	0.21
BVRTErr	471	**−2.43**	**1.38** §	**0.19** §	**−0.84** †	**−0.34** §	**3.43**	0.24
COWA	500	**25.37**	**0.71**	**−0.15** *	**3.38** §	**1.23** §	**9.61**	0.16
SDMTCorr	460	**69.81**	**−1.01**	**−0.65** §	**1.58** *	**0.97** §	**7.02**	0.41
Ship	495	**22.88**	**0.26**	**−0.05**	**0.43**	**0.80** §	**4.39**	0.23

Pvalue symbols:

* <.05

† <.01

‡ <.001

§ <.0001

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