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Neuropsychological deficits associated with Alzheimer's disease in the very-old: Discrepancies in raw *vs*. standardized scores

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Abstract

The profiles of neuropsychological deficits associated with Alzheimer's disease (AD) in Young-Old (*M* age < 70) and Very-Old (*M* age > 80) patients were compared, along with possible modifying effects of apolipoprotein E (APOE) genotype on these profiles. A comprehensive battery of neuropsychological tests was administered to the two AD patient groups (Young-Old: *n* = 33; Very-Old: *n* = 48) and their respective age-matched normal control (NC) groups who remained free of dementia on follow-up examinations over a 1 to 10 year period (Young-Old: *n* = 43; Very-Old: *n* = 36). AD and NC groups did not differ in education levels or gender distributions. Young-Old AD and Very-Old AD groups were comparable in education, gender, dementia severity, and disease duration. Results showed that both AD groups achieved comparable raw scores on all the neuropsychological measures. However, when scores were standardized on the basis of performance of their respective NC groups (i.e., age-corrected *z* scores), Very-Old AD patients significantly outperformed Young-Old AD patients on tests of executive functions, visuospatial skills, and delayed memory. Furthermore, the relationship between age and memory and executive function deficits in AD was modified by APOE genotype. These data suggest that the profile of neuropsychological deficits associated with AD in the Very-Old lacks the disproportionate saliency of episodic memory and executive function deficits typical of the Young-Old.

Keywords

Aging; Alzheimer's disease; Neuropsychology; Apolipoprotein E; Very-old

INTRODUCTION

Community (population) studies in many different countries have confirmed that the prevalence of AD rises in an approximately exponential fashion between the ages of 65 and 85 (see Kawas & Katzman, 1999, for review). The prevalence of AD in the population over the age of 85 is less clear, but emerging epidemiologic evidence suggests that prevalence rates may continue to rise in this advanced age group (Evans et al., 1989; Fichter et al., 1996; McDowell et al., 1998; Rocca et al., 1998). It is now estimated that between 25% and 50% of individuals 85 years old and older will develop AD. Because individuals over the age of 80 represent the fastest growing segment of our population (U.S. Bureau of the Census, 1992),

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the development of AD in the so-called “Very-Old” (i.e., age 80 and above) is a public health problem of increasing magnitude.

The clinical detection of AD in the Very-Old poses a number of unique challenges. The boundaries between normal age-related cognitive changes and the very earliest signs ofAD may be particularly difficult to delineate in the Very-Old, primarily because many of the early structural and functional changes of AD overlap with changes observed either in normal aging or in the context of other disease processes. A number of studies have shown that normal aging is associated with mild brain atrophy on structural magnetic resonance (MR) imaging (Jack et al., 1998a, 1999; Jernigan et al., 2001; Pfefferbaum et al., 1994), decreased hemodynamic response on functional MR imaging (D'Esposito et al., 1999), reduced synaptic density (Masliah et al., 1993), increased white matter abnormalities (Guttman et al., 1998; Jernigan et al., 2001; Salat et al., 1999), and a subclinical accumulation of neuritic plaques and neurofibrillary tangles in medial temporal lobe brain regions (Green et al., 2000; Hulette et al., 1998). These brain changes are accompanied by age-related declines in information processing speed, executive functions, and efficiency of learning and recall (Corey-Bloom et al., 1996; Desgranges et al., 1998; Grady et al., 1995; Gunning-Dixon & Raz, 2000; Hulette et al., 1998; Mittenberg et al., 1989; Schacter et al., 1996; Ylikoski et al., 1993). The structural and functional decline that occurs in the Very-Old has led some investigators to suggest that less AD pathology may be needed to produce pathologic cognitive decline in the Very-Old compared to the Young-Old (see Terry et al., 1999). However, dementia may be more difficult to detect against the background of lower and more variable cognitive test scores in the appropriate age-matched normal reference group.

An additional challenge for detecting dementia in the Very-Old is that the typical profile of neuropsychological deficits associated with AD in the Young-Old may be less salient in the Very-Old patient. Numerous studies over the last two decades have shown that the dementia syndrome of AD is initially characterized by a prominent amnesia with rapid forgetting of information over time, marked executive dysfunction most evident as a deficit in shifting cognitive set, and additional deficits in certain aspects of language, visuospatial abilities, and attention (for review, see Salmon & Bondi, 1999). Because many of these abilities are those that are also detrimentally affected by normal aging (e.g., executive functions, memory processes), the prominence of specific deficits related to AD may be much less evident in the Very-Old than in the Young-Old, especially after performance is standardized to the age-appropriate normal cohort. This would result in a less distinct and somewhat atypical cognitive deficit profile associated with AD in the Very-Old compared to that of the Young-Old.

Another factor that could alter the cognitive deficit profile of AD in the Very-Old is a possible age-related change in the influence of the ε4 allele variant of the apolipoprotein E (APOE) gene. The APOE ε4 allele has been identified as a major risk factor for late-onset AD (Corder et al., 1993; Saunders et al., 1993; Strittmatter et al., 1993, 1994), but there is evidence that the associated risk wanes with advancing age (Corder et al., 1994, 1995, 1996; Rebeck et al., 1994; but see Gebner et al., 1997; Payami et al., 1997). This change in risk suggests that the phenotypic expression of the APOE ε4 allele may be age dependent. If this is the case, previously observed differences in the clinical and neuropsychological presentation of Young-Old AD patients with or without the ε4 allele (Lange et al., 2002; Smith et al., 1998) may be absent or changed in Very-Old AD patients. Several studies that have compared cognitive deficits in predominantly Young-Old AD patients with or without the ε4 allele suggest that those with the ε4 allele may have generally more severe memory impairment (Smith et al., 1998) or less ability to use strategic processes or semantic abilities in support of memory (Lange et al., 2002) than those without the ε4 allele, even when duration of illness and severity of global dementia is comparable. A decrease in the influence of the APOE ε4 allele on the

manifestation of AD in the Very-Old may attenuate these differences and modify the profile of cognitive deficits that characterizes the disease.

Despite these several factors that could alter the clinical presentation of AD in the Very-Old, there are few detailed neuropsychological studies comparing the profile of early cognitive deficits associated with AD in Very-Old and Young-Old cohorts. Furthermore, there are no studies that compare the impact of APOE genotype on the early neuropsychological manifestation ofAD in these two age groups. To address these issues, the present study compared the performances of mildly demented AD patients whose mean age was over 80 (i.e., Very-Old) and under 70 (i.e., Young-Old) on a battery of neuropsychological tests known to be sensitive to the cognitive deficits that typify AD. Cognitive test performances of the Very-Old and Young-Old AD patients were normalized to their respective age-matched healthy control participants' performance prior to the comparison in order to reduce the impact of normal aging on their deficit profile. APOE genotype was determined so that a possible interaction between age and ε4 allele status on the cognitive deficit profile engendered by AD could be examined.

Thus, the present study was designed to (1) identify the most salient cognitive markers of early AD in the Very-Old, (2) compare the profiles of cognitive deficits in Young-Old and Very-Old patients with AD on both raw and standardized scores, and (3) determine whether APOE genotype differentially affects neuropsychological deficit patterns in these two cohorts. Specifically, we predicted that Very-Old AD patients would exhibit apparently less severe cognitive impairment than Young-Old patients with a similar estimated disease duration, primarily because their performance would be referenced to lower and more variable test scores in their age-matched normal control group. We further predicted that the profile of cognitive deficits that characterizes early AD in the Young-Old would be less salient in the Very-Old, since many of the most prominent deficits are those that are also affected in normal aging. Finally, given the rather specific effect of APOE ε4 genotype on memory and executive functions (Albert et al., 2001; Bondi et al., 1999; see also Collie and Maruff, 2000, for review), we expected that any interactive effect of age and APOE genotype on cognitive performance would be limited to those abilities.

METHODS

Research Participants

One-hundred sixty individuals participated in this study: 43 Young-Old NC participants, 33 Young-Old AD patients, 36 Very-Old NC participants, and 48 Very-Old AD patients. All participants were part of larger cohorts participating in either the University of California, San Diego (UCSD) Alzheimer's Disease Research Center, or a UCSD/San Diego VA Healthcare longitudinal study of normal aging. Participants were selected without regard to ethnicity or race. Written informed consent was obtained from all participants (or their conservators) after the protocol of the study had been fully explained. The diagnosis of AD was made by two senior staff neurologists according to the criteria developed by the NINCDS-ADRDA (McKhann et al., 1984). Historically, diagnostic accuracy rates (i.e., histopathologic confirmation at autopsy of individuals clinically diagnosed with probable or possible AD) at our center have been 90% or higher (Galasko et al., 1994). The NC participants were either spouses of the patients or were volunteers obtained through newspaper advertisements or community lectures. Volunteers with a history of alcoholism, drug abuse, learning disability, neurologic or severe psychiatric illness were excluded.

Subjects were divided into two groups on the basis of their age at testing: (1) a Young-Old group that was comprised of individuals aged 70 years or younger (range: ages 56–70), and (2) a Very-Old group that was comprised of individuals aged 75 years or greater (range: ages

75–90). In addition, following this initial step, we selected all those who had finished a complete neuropsychological evaluation that included the *California Verbal Learning Test* (CVLT; Delis et al., 1987). This method of selection and group assignment, with a five year age gap (i.e., subjects were not enrolled if they fell between the ages of 71 and 75), resulted in an approximately 15 year age difference between the Young-Old and Very-Old groups (see Table 1).

Age, education, gender—Consistent with the design of the study, a one-way ANOVA confirmed a highly significant difference in age among the four groups [$F(3,156) = 267.53$, $p < .001$]; however, *posthoc* comparisons using Tukey's HSD statistic revealed that neither the Young-Old NC and Young-Old AD groups ($p = .12$), nor the Very-Old NC and Very-Old AD groups ($p = .25$) differed from one another in age. All other age comparisons between Young-Old and Very-Old groups (e.g., Young-Old AD *vs*. Very-Old AD; Young-Old AD *vs*. Very-Old NC, etc.) were significant (all Tukey HSDs: $p < .001$; see Table 1). The four groups did not differ in years of education completed [one-way ANOVA: $F(3,156) = 0.29$, $p = .83$] or in gender distribution [χ^2 (3, $N = 160$) = 0.74, $p = .86$].

APOE genotype—The distribution of APOE genotype polymorphisms differed significantly across the four groups [χ^2 (3, $N = 160$)= 9.08, $p = .03$; see Table 1], but did not differ significantly within each diagnostic group [Young-Old *vs*. Very-Old NC: $\chi 2(1, N = 79) = 2.27$, $p = .13$; Young-Old *vs*. Very-Old AD: $\chi^2(1, N = 81) = 1.95$, $p = .16$]. The Very-Old NC participants had the lowest ε4 allelic frequency (28%), followed by the Young-Old NC (44%), Very-Old AD (48%), and Young-Old AD (64%) groups.

Dementia severity, functional status, and disease duration—As expected, AD patients scored significantly lower than NC participants on the Mattis Dementia Rating Scale (Mattis, 1988; DRS) [one-way ANOVA $F(3,156)= 136.72$, $p < .001$]; however, the DRS scores did not differ significantly between the two AD groups [Tukey HSD: $p = .88$] or the two NC groups [Tukey HSD: $p = .90$]. The two AD groups did not differ from one another in the estimated years of disease duration [$t(79) = 1.27$, $p = .21$]. Furthermore, a subset of participants with Pfeffer Outpatient Disability ratings (Young-Old NC: $n = 23$; Young-Old AD: $n = 25$; Very-Old NC: $n = 25$; Very-Old AD: $n = 44$) demonstrated that AD patients scored significantly worse on ratings of functional status [one-way ANOVA $F(3,113) = 79.35$, $p < .001$]; however, Pfeffer scores did not differ significantly between the twoAD groups [Tukey HSD: $p = .54$] or the two NC groups [Tukey HSD: $p = .93$].

Follow-up intervals—In order to minimize the possibility that the NC groups were contaminated by individuals with preclinical AD, all but 4 of the 43 Young-Old NC participants and 3 of the 36 Very-Old NC participants had 1 to 11 years of annually-administered follow-up testing to ensure that their non-demented status was maintained beyond the time of their initial assessment (i.e., the data used in the present study). The NC groups averaged more than three years of follow-up testing and did not differ significantly in this regard [$t(77) = 0.43$, $p = .67$; see Table 1]. Participants were not included in the NC groups if any of the follow-up evaluations resulted in a change in diagnostic status from normal to demented, “preclinical” dementia,Mild Cognitive Impairment (MCI), or other classification indicative of significant cognitive decline.

Materials and Procedure

All participants were administered a comprehensive battery of neuropsychological tests that included measures of confrontation naming, letter and category fluency, vocabulary, visuospatial ability, psychomotor speed, visuomotor sequencing, set-shifting skills, novel problem solving, and learning and memory. The specific tests used in the present study (see

Table 2) have been described previously (Salmon & Butters, 1992). Each participant was tested individually by a trained psychometrist in a quiet, well-lit room.

RESULTS

Profile Analysis

Mean (and *SD*) raw scores from each of the four groups are presented in Table 2. Before inspecting individual neuropsychological test performances, each of the test scores of the two AD groups were z-transformed relative to their respective NC group and submitted to a profile analysis using multivariate analysis of variance (MANOVA). Prior to analysis, *z* scores were modified to ensure that negative scores represented poorer performance and then averaged into the following neuropsychological domains based largely on prior factor analytic groupings demonstrated by Bondi et al. (2002): (1) *Language*: Boston Naming Test, Letter and Category Fluency, and WAIS–R Vocabulary; (2) *Executive Functions*: modified WCST Categories and Perseverative Errors, Trailmaking Test Part B; (3) *Visuoconstructive and Psychomotor Skills*: WISC–R Block Design, WAIS–R Digit Symbol, Trailmaking Test Part A; (4) *Immediate Recall*: CVLT Trials 1–5 Total Recall, WMS–R Logical Memory Immediate Recall; (5) *Delayed Recall*: CVLT Long-Delay Freeand Cued-Recall, WMS–R Logical Memory Delayed Recall, and (6) *Recall Savings*: CVLT Percent Long-Delay Savings, WMS–R Percent Delayed Recall Savings. The resulting mean levels of performance in each of the six neuropsychological domains for the Young-Old and Very-Old AD groups are shown in Figure 1.

The six neuropsychological domain composites, representing a within-subjects factor, were then submitted along with two between-subjects factors [age group (Young-Old AD *vs*. Very-Old AD) and APOE genotype (ε4 *vs*. non-ε4)] to a mixed-model MANOVA. Results of the MANOVA revealed a significant main effect of age group [$F(1,72) = 21.07$, $p < .001$, $\eta^2 = .23$] but not APOE genotype [$F(1,72) = 0.32$, $p = .57$, $\eta^2 = .01$], a significant within-subjects domain effect [Multivariate $F(5,68) = 21.42$, $p < .001$, $\eta^2 = .61$], a significant age group by domain interaction [Multivariate $F(5,68) = 11.41$, $p < .001$, $\eta^2 = .46$] but not APOE × Domain interaction [Multivariate $F(5,68) = 1.68$, $p = .15$, $\eta^2 = .11$], and a significant three-way interaction of Age Group × APOE Genotype × Neuropsychological Domain [Multivariate $F(5,68) = 3.90$, $p = .004$, $\eta^2 = .22$].

As shown in Figure 1, pairwise comparisons (with a Bonferroni-corrected significance level: .05/6 = .008) revealed that the age group by domain interaction was the result of significantly worse *z* scores for the Young-Old AD group than for the Very-Old AD group on tests of executive functions [$t(77) = 5.02$, $p < .001$, $\eta^2 = .25$], visuoconstructive and psychomotor skills [$t(76) = 2.85$, $p = .006$, $\eta^2 = .10$], and delayed recall savings [$t(79) = 2.78$, $p = .007$, $\eta^2 = .09$]. A borderline non-significant difference was observed for immediate recall [$t(79) = 2.73$, $p = .008$, $\eta^2 = .09$], and no significant group differences were noted for language skills [$t(79) = 1.74$, $p = .09$, $\eta^2 = .04$] or delayed recall [$t(79) = 0.75$, $p = .46$, $\eta^2 = .01$].

As shown in Figure 2, pairwise comparisons (with a Bonferroni-corrected significance level: .05/12 = .004) revealed that the three-way interaction appeared to be due to a more deleterious effect of the APOE ε4 allele for the Very-Old AD group on recall savings [Young-Old AD *vs*. Very-Old AD with the ε4 allele: $t(42) = 0.34$, $p = .74$, $\eta^2 = .003$; see Figure 2a] compared to its non-ε4 counterparts who significantly outperformed its Young-Old AD group on recall savings [Young-Old AD *vs*. Very-Old AD without a copy of the ε4 allele: $t(35) = 4.02$, $p < .001$, $\eta^2 = .32$; see Figure 2b]. An opposite pattern of greater deficits on tests of visuospatial functions for the Young-Old AD group with an ε4 allele compared to its Very-Old AD counterparts was demonstrated [Young-Old AD *vs*. Very-Old AD with the ε4 allele: $t(41) = 4.29$, $p < .001$, $\eta^2 = .31$; see Figure 2a], whereas the two non-ε4 AD age groups were comparably impaired on visuospatial functions [Young-Old AD *vs*. Very-Old AD without a copy of the

ε4 allele: $t(33) = 0.18$, $p = .86$, $\eta^2 = .001$; see Figure 2b]. On tests of executive functions, the Young-Old AD group performed significantly worse than the Very-Old AD group, whether or not they were ε4 carriers [ε4: $t(41) = 4.65$, $p < .001$, $\eta^2 = .35$; non-ε4: $t(34) = 3.48$, $p = .001$, $\eta^2 = .26$].

Univariate Analyses

Raw score comparisons of individual test performances—As shown in Table 2, the Very-Old NC group produced lower mean raw scores than the Young-Old NC group on most of the 20 neuropsychological test measures (*ps* < .05 on 15 of the 20 independent samples *t*-test comparisons), although variability in scores for the two age groups were comparable on the majority of measures (*ps* > .05 associated with Levene's test for equality of variances on 14 of the 20 measures). In contrast, independent samples *t*-tests revealed that the Young-Old and Very-Old AD groups scored comparably on all of the raw neuropsychological test score comparisons (all *p*-values > .05; also, *ps* > .05 associated with Levene's test for equality of variances on 17 of the 20 measures). It should also be highlighted that the results were equivalent, whether or not equal variance assumptions were met.

Standardized score comparisons of individual test performances—This pattern of discrepant raw score results between the NC andAD groups would be expected to result in Very-Old AD patients appearing less cognitively impaired than the Young-Old AD patients once their performances are viewed against the backdrop of normal age-related cognitive decline. To directly examine this notion, and as discussed above, scores achieved by the Young-Old and Very-Old AD patients on each test measure were converted to *z* scores based upon the means and standard deviations of their respective NC groups (see Table 3).Aseries of 2 (Young-Old AD *vs*. Very-Old AD) × 2 (APOE ε4 *vs*. non-ε4) ANOVAs using *z*-transformed test scores were performed to examine the effects of age and APOE genotype on the degree of impairment in AD groups on each of the individual test measures.

Age effects: Main effects for age (with a Bonferroni-corrected significance level: .05/20 = .002) using the age-normalized *z* scores revealed significantly poorer performance in the Young-Old AD group compared to the Very-Old AD group on tests of executive functions [modified WCST perseverative errors: $F(1,75) = 14.65$, $p < .001$, $\eta^2 = .16$; modified WCST categories: $F(1,77) = 64.96$, $p < .001$, $\eta^2 = .46$], psychomotor skills [WAIS–R Digit Symbol: $F(1,75) = 12.66$, $p = .001$, $\eta^2 = .14$], and learning and memory [WMS–R Logical Memory Immediate Recall: $F(1,77) = 22.12$, $p < .001$, $\eta^2 = .22$; Delayed Recall: $F(1,77) = 99.30$, $p < .001$, $\eta^2 = .56$; Delayed Recall Savings: $F(1,77) = 44.52$, $p < .001$, $\eta^2 = .37$]. The Young-Old AD group performed significantly better than the Very-Old AD group on only one test measure [CVLT Long-Delay Free Recall: $F(1,77) = 78.17$, $p < .001$, $\eta^2 = .50$], although this latter score had a pronounced floor effect (i.e., both AD groups' means averaged less than one item). Thus, in all but one case (CVLT Long-Delay Free Recall), Very-Old AD patients demonstrated better scores than Young-Old AD patients.

APOE genotype polymorphism effects: There was only one significant main effect of APOE genotype, with APOE ε4 non-carriers [mean $z = -7.05$] performing below that of ε4 carriers [mean $z = -2.86$] in terms of perseverative errors on the modified WCST [$F(1,75) = 11.48$, $p = .001$, $\eta^2 = .13$].

Age × APOE Genotype interactions: Significant Age × APOE Genotype interaction effects were obtained for five of the neuropsychological test measures. The presence of an APOE ε4 allele had a more deleterious effect on performance in the Very-Old AD group than in the Young-Old AD group on two measures of story recall [WMS–R Logical Memory Delayed Recall: $F(1,77) = 8.38$, $p = .005$, $\eta^2 = .10$; WMS–R Logical Memory Delayed Recall Savings:

$F(1,77) = 8.34$, $p = .005$, $\eta^2 = .10$]. In contrast, the APOE ε4 allele had a more deleterious effect on performance in the Young-Old AD group than in the Very-Old AD group on measures of visuomotor sequencing [Trails A: $F(1,77) = 10.86$, $p < .001$, $\eta^2 = .12$; Trails B: $F(1,77) = 5.35$, $p = .02$, $\eta^2 = .07$] and in terms of perseverative errors on the modified WCST [$F(1,75) = 7.35$, $p = .008$, $\eta^2 = .09$; see Table 3].

DISCUSSION

The results of the present study suggest that, when AD patients are compared to their age-appropriate control groups, the profile *and* severity of neuropsychological dysfunction typified in the Young-Old is no longer observed in the Very-Old. That is, the profile of neuropsychological deficits associated with AD in the Very-Old is less severe from that in the Young-Old when patients are compared using standardized scores. Despite being matched on education, gender, frequency of the APOE ε4 allele, disease duration, global dementia severity (as measured by the Mattis DRS), and degree of functional impairment, Very-Old AD patients exhibited a more mild degree of deficit on age-corrected *z* scores than did their Young-Old AD counterparts. This was evident in the significant group effect in the profile analysis (see Figure 1) which confirmed that the composite *z* score collapsed across the six cognitive domains showed less overall impairment for the Very-Old AD group (overall mean $z = -2.51$) than for the Young-Old AD group (overall mean $z = -3.35$). Furthermore, cognitive domains most affected following age-corrections in the Very-Old AD patients included those that are usually the most severely affected early in the disease in the Young-Old patients, namely, retention of episodic memories (i.e., savings scores) and executive functions. Because of these age-related differences, the profile of cognitive deficits associated with AD in the Very-Old lacks the disproportionate saliency of episodic memory and executive function deficits typical of the disease in the Young-Old. Thus, clinicians may be likely to commit false negative diagnostic errors in the Very-Old if they expect the level of severity and pattern of impairment (relative to age-appropriate normative data) to be the same as in the Young-Old patient.

Our results also demonstrate dramatic differences in the rawscore versus standardized score profiles of neuropsychological impairment between Young-Old and Very-Old AD patients. When inspecting raw scores, both AD groups showed comparable impairments across *all* of the neuropsychological variables examined. Given that the rawscoreswere comparable between AD groups, the distinct profiles of cognitive impairment associated withAD in the Very-Old and Young-Old arose primarily from differences in performance exhibited by the respective age-matched normative reference cohorts. The Very-Old control participants performed significantly worse than the Young-Old control participants on nearly all of the cognitive tests, with the largest differences apparent on tests of memory, executive functions, and category fluency. These findings are consistent with previous reports of the adverse effects of normal aging on these cognitive abilities (Corey-Bloom et al., 1996; Gunning-Dixon & Raz, 2000; Hulette et al., 1998; Mittenberg et al., 1989). It is important to note that this decline in cognitive ability was evident in the Very-Old NC group despite largely excluding individuals who may have been in a preclinical stage of AD. In addition, although the mean scores of the Very-Old NC group tended to be significantly lower than those of the Young-Old NC group, the variance associated with the different measures was similar for the two groups. In fact, the standard deviations were nominally larger in the Young-Old than in the Very-Old NC group for 11 of the 20 cognitive measures (see Table 2). This similarity in the degree of test score variability between the two groups makes it unlikely that the “better” *z* scores of the Very-Old AD patients compared to the Young-Old AD patients is an artifact of increased variability with aging in the control group; rather, the current results suggest that it is the result of lower mean scores in the Very-Old normal control group.

As such, the present results underscore the importance of a normative reference group that is as free as possible of individuals who may be in a preclinical stage of AD. Numerous studies have now shown that subtle cognitive changes can precede the diagnosis of AD by a few years or more (Bäckman et al., 2001; Bondi et al., 1994, 1995, 1999; Chen et al., 2001; Lange et al., 2002; Linn et al., 1995; Masur et al., 1994; Rubin et al., 1998; Small et al., 1998, 2000; Smith et al., 1998). As Sliwinski and colleagues (1996) have shown, the inclusion of such individuals with preclinical AD in a normative sample leads to an underestimate of the mean, an overestimate of the variance, and an overestimate of the effect of age on a given cognitive measure, all of which reduces the sensitivity of the measure for detecting mild impairment. Thus, future studies of the effects of normal aging on cognition might consider risk factors for the development of dementia in their samples and longitudinally follow individuals to document that no obvious signs of dementia develop in the years soon after the collection of normative data (La Rue et al., 1992; but see Bäckman et al., 2002).

Our results also suggest that using highly screened samples of normal older adults helped to limit variability in test performances among the Very-Old more than it helped to buttress mean scores. However, national standardization samples from which many standardized scores are derived tend to demonstrate both lower mean values *and* greater variability in test performances with advancing age (Heaton et al., 1990, 1996). Less stringent inclusion and exclusion criteria, greater percentages of racial and ethnic subgroups, socioeconomic substrata, lower education levels, and greater numbers of sites and examiners involved in data collection, would presumably increase the variance associated with test scores. In all likelihood, the net effect would result in even less sensitive standardized measures to detect normal from deficient test performances in the Very-Old than was demonstrated in the current study with our highly screened NC samples.

One might argue that an approach using highly screened samples of older adults might be setting standards too high and that the normative reference groups would be comprised of only those “optimally” aging individuals and, thus, would not be representative of “normal” aging. However, the inclusion of NC participants with a variety of medical and systemic conditions in this—and other—studies is contrary to this notion, as long as those conditions are not thought to adversely affect cognition. Indeed, the strategy used by the Mayo clinic's older American normative studies (Ivnik et al., 1992; Malec et al., 1992) have included in their samples individuals with chronic illnesses such as hypertension and diabetes, but whose cognitive capacity and daily functioning were not considered to be adversely affected by their illness.

Our findings also imply that similar decrements in sensitivity for AD may be observed both in the classification of Mild Cognitive Impairment (MCI; Petersen et al., 1995, 1999) as well as in other, non-cognitive measures such as volumetric assessments on structural MR imaging (e.g., Jack et al., 1998a, 1998b). For example, in contrast to the obvious cognitive impairment of Young-Old AD patients (i.e., scores −3 to −6 *SD*s below normal), the cognitive impairment of Very-Old AD patients was less apparent (i.e., scores −2 to −3 *SD*s below normal). Thus, the suggested use of −1.5 *SD*s or below on memory testing for the identification of MCI may need adjustment upward if it is to retain sensitivity for the detection of MCI in the Very-Old. With respect to MR imaging, there may be less volumetric integrity (and more variability) in medial temporal lobe structures in the Very-Old. Consequently, imaging approaches that measure change in these structures as a diagnostic sign of AD may also be rendered less useful in this cohort because of the greater backdrop of hippocampal atrophy and variability with age (see Jernigan et al., 2001).

Consistent with previous studies (Basun et al., 1995; Bondi et al., 1999; Corder et al., 1995; Normann et al., 1995; Dal Forno et al., 1996; DeKosky et al., 1995; Gomez-Isla et al., 1996; Growdon et al., 1996; Kurz et al., 1996; Small et al., 1998; Smith et al., 1998), there was little

overall effect of APOE genotype on the cognitive performance of the NC participants or AD patients in the Very-Old or Young-Old cohorts (e.g., no main effect of APOE genotype in the multivariate analysis and in all but one of the ANOVAs). However, there were interactions between age and the presence of the APOE ε4 allele on the severity of impairment exhibited by patients with AD on some measures of memory, visuomotor sequencing, and perseverative responding, but these interaction effects were not consistent across measures. The ε4 allele was associated with *worse* performance in AD on story recall measures in the Very-Old, but not Young-Old, whereas it was associated with *better* performance on the Trail-Making Test (Parts A and B) and perseverative responses on the Wisconsin Card Sorting Task in the Very-Old, but not Young-Old. These findings, though preliminary, are consistent with prior studies demonstrating APOE-related effects to be limited to tests of episodic memory and executive functions (see Bondi et al., 1999; Smith et al., 1998).

Finally, there appeared to be some differences with respect to the sensitivity of the two types of memory tests. It appeared that the Very-Old AD patients were better able than the Young-Old AD patients to exploit the additional semantic and contextual support provided by the story-learning format of the *WMS–R* Logical Memory test relative to the list-learning format of the *CVLT*. Also, APOE genotype appeared to further modify this relationship since the Very-Old AD patients with the APOE ε4 allele derived less benefit from this additional support than did the non-carriers. These findings must be interpreted cautiously, however, in light of their raw scores on these measures, because both groups were performing near floor levels on the memory tests. For example, both groups of AD patients were retaining only 10 to 20 of the material after a delay period.

The presence of these floor effects demonstrates that inspection of the raw scores in such cases may clarify—rather than cloud—interpretation of episodic memory performance in the Very-Old. For example, a number of studies in the literature demonstrate that healthy older adults typically produce retention rates on the *WMS–R* at or above 60% for delayed recall of the story material (Butters et al., 1988; Cullum et al., 1990; Incalzi et al., 1995; Tröster et al., 1993). Thus, any individual for whom the retention rate falls below 30 or 40% should raise the possibility of significant episodic memory disturbance. Because the raw score comparisons of the two AD groups failed to reveal *any* significant differences on the test measures, examining raw scores might help obviate some of the diminution in standard score profiles observed in the present study. At a minimum, our results demonstrate that mild decrements on standardized neuropsychological test scores in the Very-Old likely represent large and clinically significant deficits, particularly for tests of episodic memory, executive functions, and visuospatial skills.

Taken together, our results clearly argue against the simple application of our understanding of neuropsychological changes in early AD in the Young-Old to the detection of the disease in the Very-Old. Because of normal age-related changes in cognitive performance, and possible age-related changes in the influence of the APOE ε4 allele on cognition, a multi-faceted approach that integrates neuropsychological assessment, APOE genotyping, and emerging neuroimaging technologies, may be needed to characterize the early and preclinical stages of AD in this fastest growing and most vulnerable segment of our population. The development and refinement of methods for the early and accurate detection of AD in the Very-Old is an important goal of neuropsychological research given that preventative and neuroprotective agents designed to impede the progression of the disease are under development (see Thal, 1999).

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Fig. 1.
Mean levels of performance indicated in *z*-score units of young-old (dotted lines) and Very-Old (solid lines) Alzheimer's disease groups on each of six neuropsychological domains. Error bars denote standard error of the mean.

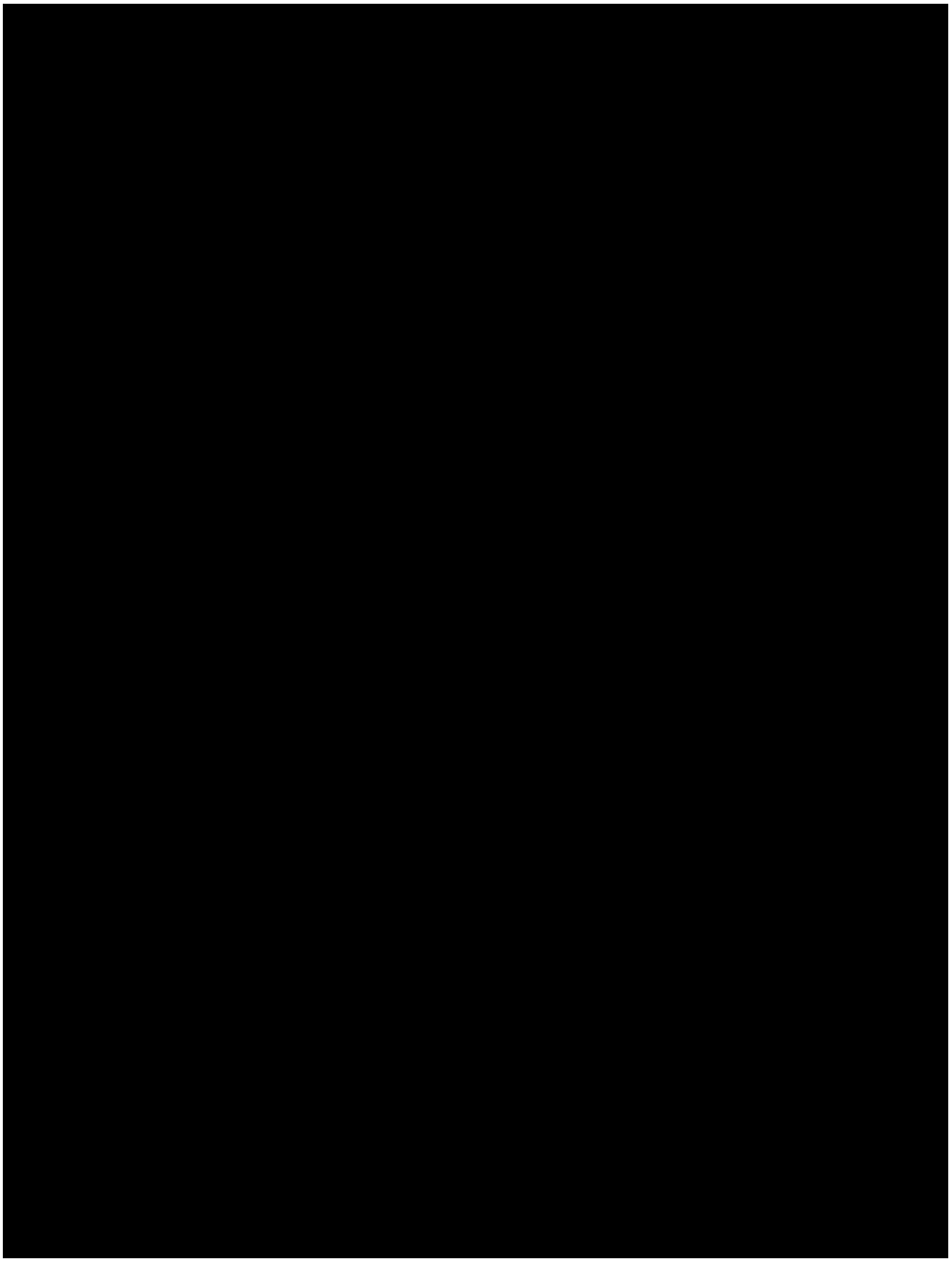

Fig. 2.
Mean levels of performance indicated in *z*-score units of young-old AD (solid lines) and Very-Old AD (dotted lines) groups either with an APOE ε4 allele (a) or without an ε4 allele (b) on each of the six neuropsychological domains. Error bars denote standard error of the mean.

Table 1

Summary of demographic variables, APOE genotypes, and global cognitive status of young-old and very-old normal control and Alzheimer disease groups

	Normal control groups				Alzheimer disease groups				
	Young-old (*n* = 43)		Very-old (*n* = 36)		Young-old (*n* = 33)		Very-old (*n* = 48)		
Variables	**M**	**SD**	**M**	**SD**	**M**	**SD**	**M**	**SD**	***p*-values[d]**
Demographics and Global Cognition									
Age	66.72	(2.85)	79.17	(2.90)	65.12	(3.97)	80.44	(2.80)	<.001[a]
Education	14.67	(2.26)	14.53	(2.43)	14.09	(2.44)	14.38	(3.65)	.83[a]
Gender (women/men)	19/24		18/18		17/16		21/28		.86[b]
Disease duration	—		—		4.21	(2.16)	3.54	(2.45)	.21[c]
Mattis Dementia Rating Scale	139.70	(3.20)	138.47	(3.24)	112.85	(11.65)	114.21	(10.07)	<.001[a]
APOE Genotypes (ε4/non-ε4)	19/24		10/26		21/12		23/25		.03[b]
Years of Follow-up Evaluations (in which NCs remained non-demented)	3.27	(2.02)	3.50	(2.63)	—		—		.67[c]

[a] *P*-value associated with 4 group (Young-Old NC; Young-Old AD; Very-Old NC; Very-Old AD) one-way ANOVA.

[b] *P*-value associated with 4 group (Young-Old NC; Young-Old AD; Very-Old NC; Very-Old AD) chi-square.

[c] *P*-value associated with an independent samples *t* test (Young-Old AD *vs*. Very-Old AD or Young-Old NC *vs*. Very-Old NC).

Table 2

Mean (and *SD*) raw scores of the neuropsychological tests for young-old and very-old normal control and Alzheimer disease groups

Variables	Normal control groups					Alzheimer disease groups				
	Young-old (*n* = 43)		Very-old (*n* = 36)			Young-old (*n* = 33)		Very-old (*n* = 48)		
	M	SD	M	SD	*p*-values[a]	M	SD	M	SD	*p*-values[b]
Language										
Boston Naming Test (30-item)	28.09	(1.39)	27.19	(2.27)	.03	21.27	(6.35)	20.58	(5.44)	.60
Letter Fluency (FAS Total)	39.05	(10.29)	39.31	(12.01)	.92	23.00	(11.38)	26.73	(12.33)	.17
Category Fluency (AFV Total)	48.49	(10.74)	42.11	(8.98)	.006	21.82	(8.09)	24.42	(9.13)	.19
WAIS–R Vocabulary	55.05	(8.33)	58.53	(6.15)	.04	43.06	(13.44)	44.73	(12.49)	.57
Visuoconstructional/ Psychomotor Skills										
WAIS–R Digit Symbol	48.07	(10.53)	40.11	(9.99)	.001	17.19	(13.20)	22.04	(12.12)	.10
WISC Block Design	43.91	(10.48)	38.72	(9.72)	.03	16.82	(12.76)	21.13	(11.99)	.13
Trail Making Test (Part A; s)	41.02	(14.99)	47.72	(14.90)	.05	97.82	(43.91)	86.54	(37.06)	.22
Sequencing/ Executive Function										
Trail Making Test (Part B; s)	88.79	(30.36)	102.81	(33.77)	.06	266.18	(60.72)	249.44	(67.00)	.26
Modified Wisconsin Card Sort										
Categories	5.63	(0.82)	4.94	(1.67)	.01	1.91	(1.71)	2.47	(1.80)	.17
Perseverative errors	0.40	(1.22)	2.08	(3.99)	.02	7.88	(9.86)	12.51	(12.37)	.08
Learning and Memory										
WMS–R Logical Memory										
Immediate Recall	25.70	(6.37)	22.94	(7.18)	.08	7.09	(4.88)	8.04	(5.44)	.42
Delayed Recall	21.19	(6.48)	16.17	(6.68)	.001	1.64	(2.18)	2.00	(3.11)	.56
Percent Delay Recall Savings	81.93	(12.23)	69.13	(18.75)	.001	20.97	(23.57)	19.98	(27.94)	.87
California Verbal Learning Test										
Total List A Immediate Recall	48.07	(10.81)	40.89	(7.72)	.001	16.91	(7.46)	18.67	(7.37)	.30
List A Trial 5 Recall	11.74	(2.80)	10.03	(2.32)	.004	4.06	(1.94)	4.33	(1.62)	.49
Short-Delay Free Recall	9.79	(3.61)	7.72	(2.69)	.006	1.39	(1.80)	1.02	(1.56)	.33
Short-Delay Cued Recall	10.79	(3.32)	9.14	(2.28)	.01	2.82	(2.07)	2.77	(2.20)	.92
Long-Delay Free Recall	9.60	(3.98)	8.31	(2.48)	.09	0.94	(1.77)	0.48	(1.24)	.17
Long-Delay Cued Recall	10.81	(3.45)	9.08	(2.80)	.02	2.55	(2.04)	2.00	(1.99)	.23
Percent Long-Delay Savings	79.57	(24.07)	84.02	(22.65)	.40	20.56	(33.90)	9.24	(22.12)	.07

[a] *P*-value associated with an independent samples *t* test comparing Young-Old NC to Very-Old NC groups.

[b] *P*-value associated with an independent samples *t* test comparing Young-Old AD to Very-Old AD groups.

Table 3

Means (and *SD*s) of age-corrected *z*-scores of the young-old (*M* age < 70) and very-old (*M* age > 80) Alzheimer disease groups

Variables	Alzheimer disease group Age-corrected *z* scores				*p*-values[a]
	Young-old (*n* = 33)		Very-old (*n* = 48)		
	M	SD	M	SD	
Language					
Boston Naming Test (30-item)	−4.89	(4.56)	−2.92	(2.40)	.013
Letter Fluency (FAS Total)	−1.56	(1.11)	−1.05	(1.03)	.035
Category Fluency (AFV Total)	−2.48	(0.75)	−1.97	(1.02)	.016
WAIS–R Vocabulary	−1.44	(1.61)	−2.24	(2.03)	.061
Visuoconstructive/Psychomotor Skills					
WAIS–R Digit Symbol	−2.93	(1.25)	−1.81	(1.21)	<.001
WISC Block Design	−2.58	(1.22)	−1.81	(1.23)	.007
Trail Making Test (Part A; sec)	3.79	(2.93)	2.61	(2.49)	.054*
Sequencing/Executive Function					
Trail Making Test (Part B; s)	5.84	(2.00)	4.34	(1.98)	.001*
Modified Wisconsin Card Sort					
Categories	−4.55	(2.09)	−1.48	(1.08)	<.001
Perseverative Errors	6.14	(8.10)	2.61	(3.10)	.008*
Learning and Memory					
WMS–R Logical Memory					
Immediate Recall	−2.92	(0.77)	−2.07	(0.76)	<.001
Delayed Recall	−3.02	(0.34)	−2.12	(0.47)	<.001*
Percent Delay Recall Savings	−4.98	(1.93)	−2.62	(1.49)	<.001*
Learning and Memory					
California Verbal Learning Test					
Total List A Immediate Recall	−2.88	(0.69)	−2.88	(0.95)	.991
List A Trial 5 Recall	−2.75	(0.69)	−2.45	(0.70)	.061
Short-Delay Free Recall	−2.33	(0.50)	−2.49	(0.58)	.188
Short-Delay Cued Recall	−2.40	(0.62)	−2.79	(0.97)	.045
Long-Delay Free Recall	−2.18	(0.44)	−3.15	(0.50)	<.001
Long-Delay Cued Recall	−2.40	(0.59)	−2.53	(0.71)	.397
Percent Long-Delay Savings	−2.45	(1.41)	−3.30	(0.98)	.002

[a] *P*-value associated with main effect for age group (young-old AD; very-old AD).

* Significant Age × APOE genotype interactions indicated by an asterisk (*) at p < .025.