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Executive function asymmetry in older adults genetically at-risk for Alzheimer's disease: Verbal *versus* design fluency

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Abstract

Recent studies have reported cognitive asymmetries in patients with Alzheimer's disease (AD) and in individuals with apolipoprotein E ε4 (APOE ε4) genotype who are in the preclinical phase of AD. This increased frequency of cognitive asymmetry, typically defined as a significant discrepancy (in either direction) between verbal and spatial abilities, often occurs despite an absence of differences on traditional measures of central tendency (i.e., mean test scores). We prospectively studied the relationship between APOE genotype and two modality-specific executive-function tasks: The Verbal Fluency and Design Fluency tests of the Delis-Kaplan Executive Function System (D-KEFS) in 52 normal functioning older adult participants who were grouped according to the presence ($n = 24$) or absence ($n = 28$) of the APOE ε4 allele. Nondemented older adults with the APOE ε4 allele demonstrated a greater frequency of cognitive asymmetric profile on the new switching conditions of the Verbal and Design Fluency measures than the APOE non-ε4 individuals. This study further supports the utility of assessing cognitive asymmetry for the detection of subtle cognitive differences in individuals at-risk for AD, and suggests that dual-task executive function tests (i.e., fluency plus switching) may serve as a useful preclinical marker of AD. (*JINS*, 2005, *11*, 863–870.)

Keywords: Neuropsychology, APOE, Cognitive discrepancy, Aging, Preclinical, Normal

INTRODUCTION

Recent research has made important advances in identifying a prodromal or preclinical phase of Alzheimer's disease (AD). This research has benefited considerably from the discovery of a genetic risk factor for AD, the apolipoprotein E ε4 allele (APOE ε4; Corder et al., 1993; Saunders et al., 1993; Strittmatter et al., 1993). The APOE ε4 allele appears to promote the early appearance of beta-amyloid and neurofibrillary tangles associated with AD in older individuals (Warzok et al., 1998). Despite the clinical importance of this research, APOE ε4 genotype, when considered alone, has generally shown fair to poor predictive value for the disease. For example, estimates of the probability of development of AD in individuals with the APOE ε4 allele range from only 10 to 50 percent (Henderson et al., 1995; Myers et al., 1996). In addition, it has been found that nearly half of the individuals diagnosed with AD do *not* have the APOE ε4 genotype, and that the presence of an ε4 allele accounts for a relatively small (but significant) portion of the incidence of AD (Evans et al., 1997; Myers et al., 1996). Most important, APOE genotyping has not proven to be helpful in determining *when* an individual will develop AD (Roses, 1997). There is growing importance to identifying the initial onset of AD, because early administration of cholinesterase inhibitors may maximize therapeutic effects (Giacobini, 2000). In addition, the development of a potential vaccine against amyloid deposition has created the clinical

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need to identify AD at the earliest possible phase in order for neuroprotective therapies to be most effective (Schenk et al., 1999).

In the light of the above limitations, it has been suggested that APOE genotyping combined with neuropsychological testing may prove to be a more effective method for early detection of preclinical AD than genotyping alone. Accordingly, neuropsychologists have used knowledge of APOE genotype to explore cognitive measures that might predict development of AD in older individuals (Albert et al., 2001; Bondi et al., 1995, 1999; Caselli et al., 2001; Jacobson et al., 2002; Lange et al., 2002). These studies presume that groups of normal-functioning elderly with the APOE ε4 allele have a higher proportion of individuals with preclinical AD pathology than groups without the ε4 allele. This assumption was borne out in a retrospective study by Bondi and colleagues (1999), who found (a) significantly worse learning and memory in a group of nondemented older adults with the APOE ε4 allele than in a group without the ε4 allele; and (b) that these differences disappeared when those who subsequently developed AD were removed from the analyses. In their study, roughly 20% (6/29) of the individuals in the APOE ε4 group went on to develop probable or questionable AD, whereas only about 2% (1/64) of the non-ε4 individuals developed dementia during longitudinal follow-up. Thus, a higher percentage of individuals in the APOE ε4 group than in the non-ε4 group appeared to be in the preclinical stages of AD, and it was these individuals who drove the APOE group differences in learning and memory.

Several additional studies have reported subtle cognitive differences between asymptomatic older adults with and without the APOE ε4 genotype. For example, a number of retrospective investigations found that older individuals with at least one APOE ε4 allele had lower scores on measures of verbal memory and executive functions than those who did not have an ε4 allele, or lower verbal memory and executive function scores in older adults who later developed AD compared with those who did not subsequently develop the disease (Albert et al., 2001; Bondi et al., 1995; Caselli et al., 2001; Chey et al., 2000; Craft et al., 1998; Elias et al., 2000; Jacobs et al., 1995; Linn et al., 1995; Mayeux et al., 2001). These reports have not been consistent, however, as other investigations have failed to replicate these findings (Reiman et al., 2001; Small et al., 1998; Smith et al., 1998).

Recently, Jacobson et al. (2002), suggested several possible reasons for the inconsistent findings in past neuropsychological investigations of preclinical AD. First, a genetic model would predict that only a subgroup of individuals with the APOE ε4 allele would develop AD (Martin, 1990), and this subgroup's early subtle cognitive deficits may be masked in analyses of central tendencies that included the entire APOE ε4 group. Second, APOE ε4 individuals who are in a preclinical phase of AD might exhibit only subtle cognitive declines that remain within the average range and have not reached a level of "impairment," as traditionally defined by neuropsychologists. And third, since patients diagnosed with AD often initially exhibit asymmetrical neuropathology and corresponding lateralized cognitive deficits, it follows that APOE ε4 subjects who are in a preclinical phase of AD also may display subtle asymmetric cognitive deficits. These lateralized differences may cancel each other out when test scores are analyzed in terms of central tendency (e.g., test means) for the entire group of APOE ε4 individuals, thereby failing to identify subgroups of preclinical AD subjects with *relative* deficits in verbal or visuospatial abilities.

In line with this latter possibility, Jacobson et al. (2002) found that nondemented older adults with preclinical AD (who later developed AD) did not differ significantly from matched older control subjects on measures of naming (Boston Naming Test, BNT; Kaplan et al., 1983) or visuospatial construction (WISC-R Block Design, BD; Wechsler, 1974) when the groups' mean test scores were compared. However, an analysis of the difference in performance on the two tests did reveal a subtle cognitive decline in the preclinical AD group compared with the normal comparison group. Specifically, the magnitude of verbal-visuospatial discrepancy, defined as each subject's absolute z-score difference between the two tasks, was significantly greater in the preclinical AD group than in the normal comparison group. Furthermore, the preclinical AD group demonstrated a significantly higher frequency of asymmetric cognitive profile (i.e., greater than one standard deviation discrepancy between BNT and BD) than the comparison group. These findings suggest that an analysis of cognitive asymmetry may be a more useful method than group mean analyses of individual tests for detecting subtle cognitive declines in individuals who are at risk for AD.

The present study attempts to extend past investigations in this area through a *prospective* investigation of subtle cognitive asymmetry in normal-functioning older adults with or without the APOE ε4 allele. Previous studies of cognitive decline in normal-functioning individuals with the ε4 allele have been *retrospective* investigations that analyzed neuropsychological test results from several years before dementia developed. Such analyses are subject to methodological problems such as limited availability of results from sensitive neuropsychological tests and subject selection biases. In addition, whereas most studies have reported primarily memory deficits in this population, there is some evidence for subtle executive-function deficits in normal functioning individuals with the ε4 allele (Albert et al., 2001; Chey et al., 2000; Elias et al., 2000; Jacobs et al., 1995; Linn et al., 1995). The possibility of early executive-function deficits in those genetically at risk for AD is also supported by neuroimaging evidence of prefrontal changes (Bookheimer et al., 2000; Reiman et al., 1996, 2001). Thus, the present study also extends previous investigations by focusing on potential asymmetries in performance on verbal and visuospatial tests of executive functions. Our study used two new executive-function tasks from the Delis-Kaplan Executive Function System (D-KEFS; Delis et al.,

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2001a): the Verbal Fluency Test and the Design Fluency Test. These tasks were selected because (a) they allow an analysis of asymmetric performance between primarily verbal and nonverbal executive-function tasks; and (b) they incorporate a new switching condition that requires both fluent generation of responses *and* cognitive flexibility, thereby increasing cognitive demands and possibly the sensitivity of these tasks to subtle dysfunction. We hypothesized that normal-functioning older individuals with one copy of the APOE ε4 allele would exhibit a higher frequency of asymmetric performance on the two fluency tasks than matched control subjects without the ε4 allele, particularly when comparing performances on the new dual-task fluency tests that also require cognitive flexibility.

METHOD

Participants

Fifty-two healthy older adults participated in this study. Nineteen were recruited from the local community, and 33 were selected from a larger pool of control subjects from the Alzheimer's Disease Research Center (ADRC) at the University of California, San Diego (UCSD). Both cohorts of participants were recruited in a similar manner through newspaper advertisements and community lectures (i.e., not through clinic-based or medical referral sources) for participation in a longitudinal study of normal aging. All individuals were in good health and living independently at the time of participation in this study, and all were selected without regard to ethnicity or race. Informed consent was obtained from all individuals included in this study. All participants completed medical history questionnaires, were evaluated by a senior neurologist, and had blood drawn for APOE genotyping and additional laboratory analyses. They were considered to be normal based on medical, neurologic, laboratory, and cognitive screening measures described in detail previously (Galasko et al., 1990; Salmon & Butters, 1992). Individuals with a history of head trauma, stroke/TIA, other neurological disorder, major psychiatric disorder (including depression), learning disability, or alcoholism and/or other substance abuse were excluded. Participants from the ADRC were chosen based on demographic characteristics so that the two genotype groups were well matched. There were no significant differences between the two cohorts with regard to age [$t(50) = .10$, $p = .92$], education [$t(50) = .41$, $p = .68$], gender [$\chi^2(1, N = 52) = 2.45$; $p = .12$], DRS Total Score [$t(49) = .76$, $p = .45$], or APOE status [$\chi^2(1, N = 52) = 2.56$; $p = .11$].

Participants were grouped on the basis of their APOE genotype, with 24 individuals having inherited one copy of the APOE ε4 allele and 28 individuals without the APOE ε4 allele. The APOE allele distribution in the present sample consisted of six ε2/3, one ε2/4, 22 ε3/3, and 23 ε3/4. Study participants were genotyped for the APOE allele using a polymerase chain reaction based method discussed in Saunders et al. (1993).

Materials and Procedures

The neuropsychological measures included in this study were administered to participants at the baseline (first year) testing of a prospective, longitudinal study of preclinical AD. All tests were administered by a trained psychometrist.

The primary measures administered for this study were the Verbal Fluency Test and the Design Fluency Test of the D-KEFS (Delis et al., 2001a). The Verbal Fluency Test includes three trials or conditions: The traditional letter and category fluency trials and a new Verbal Fluency/Switching condition (see the D-KEFS Examiner's Manual for details). The D-KEFS Verbal Fluency/Switching task requires subjects to generate words while switching back and forth between two semantic categories (i.e., fruits and furniture). The D-KEFS Design Fluency Test also consists of three trials: Filled Dots, Empty Dots Only, and Switching. For the Filled Dots condition, participants are instructed to connect dots using only four straight lines to make as many unique designs as possible. The Empty Dots Only condition is similar to the Filled Dots condition except that examinees are instructed to connect only empty dots in the presence of filled-dot distracters. For the new Design Fluency/Switching condition, subjects are asked to draw different four-lined designs while switching between connecting filled and unfilled dots. Each of the Verbal and Design Fluency conditions is timed for 60 seconds and the number of correct verbal responses or designs drawn is recorded.

Statistical Analyses

Cognitive asymmetry scores were calculated by first converting subjects' raw scores on the D-KEFS Verbal Fluency and Design Fluency tests into *Z*-scores based on the D-KEFS national normative study (Delis et al., 2001b). Each subject's Design Fluency *Z*-score was then subtracted from his/her corresponding Verbal Fluency *Z*-score, yielding a standardized discrepancy score for the two measures. Participants whose absolute discrepancy *Z*-score was 1.5 standard deviations or greater were classified as "asymmetric," and participants whose absolute discrepancy *Z*-score was less than 1.5 SD were classified as "symmetric" (see Matarazzo & Herman, 1985). This use of a calculated asymmetry score was based on similar methodology used in previous studies of cognitive asymmetry (see Demadura et al., 2001; Finton et al., 2003; Jacobson et al., 2002). Differences in the frequency of asymmetric standardized scores on the fluency measures between the two subject groups were evaluated using chi-square analysis. In addition, group differences between mean raw scores on the various fluency tasks were examined with independent samples *t*-tests.

RESULTS

Demographic Characteristics and Global Cognitive Functioning

The APOE ε4 group and the non-ε4 group were not statistically different with regard to demographic characteristics

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Table 1. Demographic and cognitive characteristics of the APOE ε4 and non-ε4 groups

	Apolipoprotein E				
	ε4 (*n* = 24)		Non-ε4 (*n* = 28)		
Variables	*M*	*SD*	*M*	*SD*	*p*-values
Demographics					
Age	75.0	(8.2)	77.3	(7.0)	.29
Education	14.9	(2.3)	14.9	(2.3)	.99
Gender (women/men)	11/13		20/8		.06[a]
Global cognition					
DRS total (144 points maximum)	139.8	(3.9)	140.2	(2.6)	.58
DRS attention	36.4	(0.6)	36.3	(0.8)	.48
DRS initiation/perseveration	36.1	(1.4)	36.3	(1.4)	.64
DRS construction	5.3	(0.8)	5.6	(0.5)	.15
DRS conceptualization	37.9	(1.5)	38.0	(1.5)	.80
DRS memory	24.2	(1.3)	24.0	(1.3)	.57

Note. *P*-values associated with an independent samples *t* test. [a]*P*-value associated with the chi-square statistic.

of age, level of education, or gender distribution (see Table 1). Also shown in Table 1, the groups did not differ on the Total Score or any of the subtest scores of the Dementia Rating Scale, a measure of global cognitive functioning (DRS; Mattis, 1973). All participants scored well within the normal range and above an established cutoff for impairment of 130 points on the Total Score (Monsch et al., 1995).

Group mean analyses

Table 2 shows the mean raw scores on the various D-KEFS fluency subtests for the APOE ε4 and non-ε4 groups. When overall mean scores were compared, no statistical differences were observed between the groups on any of the traditional fluency measures or on the new fluency/switching measures.

Discrepancy analyses

As predicted, the APOE ε4 group displayed a significantly greater frequency of asymmetric pattern than the non-ε4 group when performances on the verbal and design fluency/switching tasks were compared. As shown in Table 3, approximately 38% of the APOE ε4 individuals demonstrated an asymmetric fluency/switching profile, whereas only 14% of the APOE non-ε4 participants showed such cognitive discrepancy ($\chi^2 = .27$; $p = .05$). Table 3 also illustrates that among those individuals who showed an asymmetric profile, neither genotype group was more likely to show either a "high verbal" or "high spatial" asymmetry pattern (Fisher's Exact Test; $p = .56$). That is, the frequency of the direction of the asymmetry tended to be similar for both genotype groups. However, when the frequency of asymmetric pat-

Table 2. Mean raw D-KEFS fluency scores for the APOE ε4 and non-ε4 groups

	Apolipoprotein E				
	ε4 (*n* = 24)		Non-ε4 (*n* = 28)		
D-KEFS variables	*M*	*SD*	*M*	*SD*	*p*-values
Letter fluency	41.0	(12.9)	42.0	(11.6)	.77[a]
Category fluency	36.0	(8.1)	34.5	(7.6)	.47[a]
Design fluency[b]	15.8	(4.6)	16.3	(5.2)	.72[a]
Verbal Fluency/Switching	13.2	(3.8)	13.7	(3.3)	.64[a]
Design Fluency/Switching	5.7	(2.2)	5.9	(2.2)	.76[a]

[a]*P*-value associated with an independent samples *t* test. [b]Design Fluency Filled Dots and Empty Dots Only conditions, combined.

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Table 3. Frequencies of asymmetric profiles on the D-KEFS fluency/switching tests for APOE ε4 and APOE non-ε4 subjects

Asymmetry profile	Asymmetry direction			
Genotype group	Asymmetric[a]	Non-asymmetric[a]	High verbal[b]	High spatial[b]
APOE ε4	9 (37.5%)	15 (62.5%)	4 (44.4%)	5 (55.6%)
APOE non-ε4	4 (14.3%)	24 (85.7%)	3 (75.0%)	1 (25.0%)

Asymmetry is defined as a 1.5 or greater *SD* discrepancy between fluency measures. [a]Chi-square test; $\chi^2 = .27$, $p = .05$. [b]Fisher's Exact test; $p = .56$.

tern relative to the entire sample was compared between genotype groups, there was a slight trend, though not significant, for the APOE ε4 group to have a higher rate of high spatial asymmetry (5/24 = 21%) than the APOE non-ε4 group (1/28 = 4%) [Fisher's Exact Test; $p = .08$], while the high verbal asymmetry profile occurred at about the same frequency in both APOE genotype groups (ε4: 4/24 = 17%; Non-ε4: 3/28 = 11%) [Fisher's Exact Test; $p = .69$].

In contrast, the groups did not differ significantly in the frequency of asymmetric profiles when the traditional fluency measures were compared (Letter Fluency *versus* the combined Filled Dots and Empty Dots Only conditions of Design Fluency: $\chi^2 = .05$, $p = .72$; Category Fluency *versus* the combined Filled Dots and Empty Dots Only conditions of Design Fluency: $\chi^2 = .14$, $p = .31$).

Post hoc analyses

Table 4 shows the associations between the APOE genotype and presence of an asymmetric cognitive profile for the different fluency measures. For the fluency/switching measures, the relative risk of an APOE ε4 genotype was more than three times greater for individuals with an asymmetric profile (odds ratio = 2.625) than for participants without significant asymmetry (odds ratio = .729). The relative risk of an APOE ε4 genotype was substantially lower when predicted by asymmetry in performance on the more traditional fluency tasks.

DISCUSSION

This study represents one of the first prospective investigations of cognitive asymmetry in normal-functioning older adults with or without the APOE ε4 allele. In addition, whereas most studies of cognitive deficits in nondemented elderly with the APOE ε4 allele have focused primarily on memory functioning, in the present investigation, we explored the possibility of subtle asymmetric executive-function deficits in this population. The rationale for investigating executive-functioning as a possible preclinical marker of AD derives from recent neuroimaging studies (e.g., fMRI and PET) that have demonstrated increased prefrontal brain response and hypometabolism in this at-risk group (Bookheimer et al., 2000; Reiman et al., 2001). In the present study, we used two new executive-function tests: (a) a verbal fluency task that has a new condition that simultaneously assesses category fluency and cognitive switching; and (b) a nonverbal fluency task that also has a new condition that concurrently evaluates design fluency and cognitive switching. These tasks were selected because (a) the dual nature of these executive-function switching tasks likely increases processing demands, thereby enhancing their sensitivity to subtle frontal dysfunction; and (b) the tests allow an analysis of cognitive asymmetry in the performance of primarily verbal *versus* spatial executive-function tasks. It was hypothesized that a higher frequency of asymmetric cognitive performances between verbal and design

Table 4. Odds ratios for the D-KEFS fluency tests

	Asymmetry profile		
Predictor ($N = 52$)	Odds ratio	95% Confidence interval (lower-upper)	χ^2
VF/Switching *vs.* DF/Switching			.27*
Asymmetric group	2.625	.924–7.456	
Nonasymmetric group	.729	.517–1.029	
Letter fluency *vs.* Design fluency[a]			.05
Asymmetric group	.833	.304–2.288	
Nonasymmetric group	1.056	.785–1.420	
Category fluency *vs.* Design fluency[a]			.14
Asymmetric group	1.944	.518–7.304	
Nonasymmetric group	.887	.696–1.129	

*Chi-square test; $p = .05$. [a]Design fluency filled dots and empty dots only, combined.

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fluency tasks would be found in the ε4 group compared to the non-ε4 group, especially for the dual-task tests that also require cognitive switching.

The two genotype groups were comparable with regard to age, education level, gender distribution, and global cognitive functioning, with both groups' DRS scores falling well within normal limits. As expected, we did not find significant mean differences between the two genotype groups when we analyzed performances on the Verbal Fluency and Design Fluency conditions individually. In fact, mean scores for the groups were nearly identical with no evidence of a trend toward differences in performance. In contrast, and as predicted, there was a significant group difference in the frequency of asymmetric pattern for the two fluency/switching tasks. That is, individuals possessing an APOE ε4 allele demonstrated a significantly higher frequency of asymmetric performance between the verbal *versus* spatial fluency/switching tasks compared to the non-ε4 group. We did not observe this asymmetric performance for the more traditional fluency tests that did not require cognitive flexibility. Furthermore, we found that among those who showed an asymmetric profile, both genotype groups were equally likely to demonstrate "high verbal" *versus* "high spatial" asymmetric profiles. However, when the frequency of type of asymmetric profile relative to the entire group was compared between genotypes, there was a trend for the APOE ε4 group to have a higher rate of "high spatial" asymmetry, but not "high verbal" asymmetry, than the APOE non-ε4 group. Thus, while there appears to be an increased likelihood of cognitive asymmetry in normal functioning older adults with the APOE ε4 allele, the direction of the asymmetry is less clear, but perhaps the occurrence of "high spatial" pattern may be influenced by APOE genotype.

Our findings are consistent with Jacobson et al. (2002) who also found that normal-functioning individuals with the APOE ε4 genotype demonstrated a significantly higher frequency of asymmetric performance than those without the ε4 genotype on tasks of more fundamental cognitive skills (i.e., naming *vs.* visuoconstructional ability). These findings are consonant with those from several studies that identified subgroups of AD patients with asymmetric verbal *versus* nonverbal profiles (see Delis et al., 1992; Demadura et al., 2001; Finton et al., 2003; Fisher et al., 1999; Haxby et al., 1985). Because the early occurrence of lateralized cognitive deficits is common in AD patients, it follows that asymmetric cognitive profiles may serve as a useful preclinical marker of AD in at-risk people. Furthermore, these findings are consistent with neuroimaging investigations that have documented asymmetric metabolic dysfunction in both normal older adults who are at-risk for AD and nondemented individuals who have subsequently developed AD (Hogh et al., 2001; Small et al., 1995).

Several limitations of the present study should be noted. First, the sample of APOE ε4 individuals does not include APOE ε4 homozygotes who have the greatest risk of developing AD, or APOE ε2 homozygotes who have a decreased risk of developing the disease. Inclusion of such individuals in future studies may actually amplify the APOE genotype-driven differences in asymmetry observed in the present study, and would better allow the results to be generalized to the entire population of older adults. Second, we do not know with certainty which participants will go on to develop AD dementia and which will not, making it impossible to predict future cognitive decline or conversion to AD on the basis of cognitive asymmetry. Longitudinal studies in our laboratory and others are currently underway to investigate whether or not the asymmetric cognitive profiles that we have identified in older adults with the APOE ε4 genotype enhance the ability to predict which normal older adults are likely to suffer an AD diagnosis in the future.

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