

Do Neuropsychological Tests Detect Preclinical Alzheimer's Disease: Individual-Test Versus Cognitive-Discrepancy Score Analyses

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Attempts to identify cognitive markers of a preclinical phase of Alzheimer's disease (AD) have yielded inconsistent findings. The problem may stem in part from methodologies that are insensitive to potential subgroups within the at-risk, preclinical AD population (PCAD). The present study investigated the utility of asymmetric cognitive profiles in identifying individuals at risk for AD. Twenty elderly adults who were later diagnosed with AD (PCAD) and 20 matched control participants were compared on measures of cognitive asymmetry derived from difference scores on tests of verbal and visuospatial ability. Although both groups performed similarly on the individual tests, comparisons using difference scores revealed significantly larger discrepancies between naming and visuoconstruction skills in the PCAD group. The PCAD group also had a higher frequency of asymmetric cognitive profiles relative to a normative group.

Subtle cognitive changes can precede the onset of Alzheimer's disease (AD) by as many as 7 to 10 years (Elias et al., 2000; Linn, Wolf, Bachman, & Knoefel, 1995). Findings of a long prodromal period have fostered new research into preclinical cognitive changes in normal-functioning elderly individuals at risk for AD. Early diagnosis of AD has far-reaching implications for treatment planning and potential pharmacological therapies. There is evidence that early administration of cholinesterase inhibitors may maximize therapeutic effects (Giacobini, 2000). The development of a potential vaccine against amyloid deposition (Schenk et al., 1999) also underscores the fact that neuroprotective therapies will be most effective if applied at the earliest possible phase of AD before significant neuronal damage occurs (Thal, 1999). Although risk factors like the apolipoprotein $\epsilon 4$ allele (ApoE $\epsilon 4$) can improve the accuracy of predicting who may develop AD (Mayeux et al.,

1998), genotyping may be less useful in determining when the disease process begins. To this end, neuropsychologists continue to pursue markers that would shorten the time frame within which AD can be first detected to better understand the increasingly important preclinical phase of AD.

There appears to be considerable variability in the type and extent of cognitive changes found in groups at risk for AD. Elderly individuals who later develop AD show lower scores on measures of verbal retention and abstract reasoning (Elias et al., 2000); deficits in verbal memory ability, abstract reasoning, and naming (Jacobs et al., 1995); shorter immediate auditory attention span (Linn et al., 1995); and other more generalized deficits such as a "cognitive control factor" (Fabrigoule et al., 1998) and lower Verbal and Performance IQ (Fox et al., 1996) compared with normal elderly who remain free of disease. Verbal memory deficits, however, appear to be the most frequent finding (Bondi et al., 1995; Bondi, Salmon, Galasko, Thomas, & Thal, 1999; Collie & Maruff, 2000). The question arises as to why cognitive changes have not been consistently observed in at-risk groups, even in those cases in which neuroimaging abnormalities were found (Bookheimer et al., 2000; Smith et al., 1998; Soininen et al., 1994, 1995). One possible explanation could be subgroups within the preclinical AD population with subtle asymmetric cognitive changes (Becker, Huff, Nebes, & Holland, 1988; Martin, 1990). These subgroups would be difficult to identify if comparisons were made using a single test. The present study examined whether contrasting performance in two non-memory domains could identify a preclinical AD group.

Prior research documents subgroups of AD patients with lateralized cognitive deficits in language and visuospatial skills (Albert, Duffy, & McAnulty, 1990; Haxby et al., 1986, 1990; Kanne, Balota, Storandt, McKeel, & Morris, 1998; Martin, 1990; Martin et al., 1986; Strite, Massman,

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Cooke, & Doody, 1997) and lateralized onset with asymmetric neuroanatomical changes (Franceschi et al., 1995; Giannakopoulos, Hof, & Bouras, 1994; Grady et al., 1988; Martin et al., 1986; Thompson et al., 1998). There is also preliminary neuroimaging data suggesting that asymmetric structural and metabolic anomalies can be detected in nondemented elderly at risk for AD (Celsis et al., 1997; Grady et al., 1990; Reiman et al., 1996; Small et al., 1995; Soininen et al., 1994, 1995). Given the strong evidence for asymmetry in early AD (Bugiani, Constantinidis, Ghetti, Bouras, & Tagliavini, 1991; Haxby & Rapoport, 1986; Koss, Friedland, Ober, & Jagust, 1985), it is possible that subtle changes in verbal relative to visuospatial skills (or vice versa) could occur in a preclinical phase.

If subtle asymmetric differences exist, however, examining a single cognitive domain may not be sufficient to detect such differences. There is evidence that "averaging individual test scores across disparate subtypes can obscure subtle group differences if those groups include homogeneous subtypes" (Mitrushina, Uchiyama, & Satz, 1995, p. 374). Use of difference scores to emphasize left-right asymmetry (see Haxby, Duara, Grady, Cutler, & Rapoport, 1985; Haxby et al., 1990; Massman & Doody, 1996; Small et al., 1995) may be necessary to identify subgroups of preclinical AD patients with subtle, asymmetric cognitive changes. The present study explored whether contrasting performance in two different cognitive domains might distinguish a preclinical AD group (PCAD) from matched elderly controls. Our hypotheses were as follows:

1. The PCAD group would have a significantly greater discrepancy between their naming and visuoconstruction ability compared with matched elderly controls when the groups are compared using a cognitive-discrepancy analysis. In contrast, we did not expect significant differences in the individual cognitive domains.

2. The PCAD group also would have a significantly higher than expected proportion of "asymmetric profiles" (i.e., differences of one standard deviation or more between verbal and visuospatial tests) compared with a larger normative group. We expected no significant difference between the elderly controls and the normative group in this respect.

Method

Participants

The 40 participants in this study were selected from a larger participant pool at the Alzheimer's Disease Research Center (ADRC) at the University of California, San Diego; the PCAD group was selected on the basis of an initial baseline classification of "normal control" with a subsequent diagnosis (approximately 1 year later) of "at risk" or "possible AD." The individuals in the PCAD group had participated as control participants for an average of 4.6 years prior to any change in diagnosis. To maintain consistency and to ensure that the PCAD group was likely to be in a preclinical phase, we used data from the testing session just prior to their change in status from control participant to "at-risk" and "possible AD" diagnosis, typically a span of 12 to 16 months. Thus, the measures of asymmetry were calculated when participants in the PCAD group were still considered control participants.

Although the PCAD group did not meet National Institute of Neurological and Communicable Disease and Stroke—Alzheimer's Disease and Related Disorders (McKhann et al., 1984) criteria for probable AD in the subsequent year, examinations revealed either mild subjective memory complaints without functional impairment ($n = 9$) or an abnormality in the participant's neurological examination. All diagnoses were based on independent, annual examinations from two ADRC senior staff neurologists. To avoid circularity, they assigned preliminary diagnoses without access to neuropsychological test data other than Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) scores.

Initially, a total of 22 PCAD individuals was included in the analysis. All but 2 individuals performed above a cutoff for impairment of 130 points (Monsch, Bondi, Salmon, & Butters, 1995) on the Mattis (1973) Dementia Rating Scale (DRS), our exclusion criterion for significant cognitive impairment. The PCAD DRS total mean was 136.1 ($SD = 3.7$). Individuals with a history of alcohol or drug abuse, learning disability, significant head injury, psychiatric illness, or other neurological disorder were excluded from the study, resulting in a sample size of 20. All participants had received medical and laboratory tests to rule out any metabolic, endocrine, or nutritional deficiencies. They had no history of stroke or significant cerebrovascular disease based on a review of their medical history. Nine of the 20 PCAD participants had been genotyped for the Apoe allele using a polymerase chain reaction. The allele distribution included two $\epsilon 2/\epsilon 4$, one $\epsilon 3/\epsilon 3$, four $\epsilon 3/\epsilon 4$, and two $\epsilon 4/\epsilon 4$ genotype.

The elderly control group also consisted of nondemented elderly individuals who served as control participants at the ADRC. We selected from individuals who had at least 3 consecutive years of "normal control" status, without any evidence of cognitive decline, in order to decrease the likelihood that any participants in the control group were in a preclinical stage of AD. Data were used from the participants' testing approximately 18 to 24 months prior to their latest "normal control" diagnosis. The control group met the same exclusion criteria (head injury, alcoholism, cerebrovascular disease, etc.) as the experimental group. The normal elderly control group ($n = 20$) was matched one-to-one with the PCAD group on age, years of education, and total DRS score (see Table 1). No other neuropsychological test scores were used in this selection process. Twelve of the 20 elderly controls had been genotyped for the Apoe allele with the following results: two $\epsilon 2/\epsilon 3$, one $\epsilon 2/\epsilon 4$, eight $\epsilon 3/\epsilon 3$, and one $\epsilon 3/\epsilon 4$ genotype. All participants in both groups were right-handed and were selected without regard to gender, ethnicity, or race.

Table 1
Demographic Characteristics of Groups

Variable	Mean		Standard deviation	
	PCAD	Control	PCAD	Control
Age (years)	74.5	75.9	5.9	7.5
Education (years)	14.8	14.0	3.0	3.2
Percentage female	45.0	50.0		
Years as normal control	4.6	3.0	2.7 ^a	0.0 ^b

Note. There were 20 participants in the preclinical Alzheimer's disease (PCAD) group and 20 in the control group.

^a PCAD group participated as controls prior to change in diagnosis. ^b Elderly control group was selected after 3 years of normal control status.

Measures and Procedures

The neuropsychological measures were administered as part of the participants' annual neuropsychological examination at the ADRC. A trained psychometrist under the supervision of a neuropsychologist administered all tests. Examiners were unaware of the group status of the participants. The examination used a short (30-item) form of the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983). Our BNT total score included the number of spontaneously correct and semantically cued responses within the prescribed time limit. The examination also included the Block Design subtest (BD) of the Wechsler Intelligence Scale for Children—Revised (WISC–R; Wechsler, 1974). The WISC–R was originally selected over the Wechsler Adult Intelligence Scale—Revised (WAIS–R; Wechsler, 1981) to minimize floor effects in AD patients. Our WISC–R total score was the total number of points received for correct completion of the design within the time limits, as well as time bonus points when applicable (Items 4 to 11).

The BNT and BD were selected as measures of naming and visuoconstruction for several reasons. Past studies have documented that these tests are sensitive to asymmetric cognitive changes in early AD patients (Delis et al., 1992; Fujimori et al., 1998; Jacobs et al., 1995; Massman et al., 1993). The BNT and BD also have been used to predict rate of cognitive decline in AD (Carswell, 1999; Rasmusson, Carson, Brookmeyer, Kawas, & Brandt, 1996), to identify AD subgroups (Johnson, Head, Kim, Starr, & Cotman, 1999) and to distinguish among dementia subtypes (Boone et al., 1999). Most important, we selected the BNT and BD because of their sensitivity to left and right temporoparietal dysfunction, respectively (Ford-Booker, 1996; Hu et al., 2000; Langfitt & Rausch, 1996; Sawrie et al., 2000; Warrington, James, & Maciejewski, 1986). These regions undergo some of the earliest neurodegenerative changes in AD.

Statistical Analyses

Our first hypothesis comparing the discrepancy between the BNT and BD (asymmetry scores) was tested using a yoked design (Wilcoxon signed-ranks test for matched pairs) because participants were closely matched on a one-to-one basis on three variables. Nonparametric techniques were necessary because of a negatively skewed distribution on the BNT and a nonnormal, positively skewed distribution on the asymmetry scores. Data transformations did not approach a normal distribution. We calculated asymmetry scores by converting the raw test scores on the BNT and BD to standardized scores (z scores) based on the larger, University of California, San Diego ADRC normal elderly control group ($n = 108$). This normative cohort did not include the 40 study participants. We calculated the asymmetry score as the absolute value of the difference between BNT and BD standard scores. The absolute value was used because only the magnitude of the difference score was of interest in this analysis. In accordance with Cohen's power analysis (Cohen, 1992), a recommended sample size of 26 in each group would be necessary to detect group differences given a large effect size ($d = .8$) with $p = .05$ (two-tailed). Given our directional hypotheses, our sample size of 40 was likely to be sufficient to detect a "minimal meaningful difference" (Tabachnik & Fidell, 1996, p. 37) with an alpha level of .05 for statistical analyses.

For the second hypothesis, we operationally defined *asymmetric profile* as a z -score difference (BNT minus BD) greater than 1 SD in accordance with past studies (Delis et al., 1992; Jacobson et al., 1998; Massman et al., 1993; Strite et al., 1997). We examined the frequency of this qualitative profile using the nonparametric pro-

cedure chi-square (at $p < .05$). The expected frequency of scores used in the chi-square analysis was based on three factors: (a) assumptions of a normal distribution of z scores, (b) confirmation of an approximate normal distribution in the larger ADRC database of community control participants ($n = 108$; 31% with difference scores greater than 1 SD and $-1 SD$), and (c) previous research on cognitive asymmetry in elderly and AD participants (Demadura, Delis, Jacobson, & Salmon, 2001; Massman & Doody, 1996; Strite et al., 1997).

Post hoc analyses were used to examine the sensitivity and specificity of asymmetric profiles and to compare their predictive utility with recall ability and genotype, as partial data were available from a smaller subgroup of the 40 participants. Because of the small, unequal group sizes and allele combinations, the genotyped participants were dichotomized for analysis into at-risk genotype (including $\epsilon 3/\epsilon 4$ and $\epsilon 4/\epsilon 4$ participants; $n = 7$) and not at-risk genotype (including $\epsilon 2/\epsilon 3$, $\epsilon 2/\epsilon 4$, and $\epsilon 3/\epsilon 3$ participants; $n = 14$) according to recent estimates of relative risk for developing AD (Corder et al., 1995; Higgins, Large, Rupniak, & Barnes, 1997). Twenty-six participants had received memory testing with the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1983) and we examined the long-delay free recall variable because of its sensitivity to preclinical AD memory changes (Bondi et al., 1999). Because of unequal sample sizes and non-normal distributions, the group data were dichotomized into a memory deficit group (1–4 standard deviations below the mean; $n = 9$) and a normal memory group (1 standard deviation below the mean to 3 standard deviations above the mean; $n = 17$) according to the age-scaled mean from the CVLT normative data.

Results

Descriptive Statistics

The PCAD and the elderly control groups were not significantly different with respect to the demographic and cognitive variables on which they were matched (age, $p = .54$; educational level, $p = .53$; total DRS score, $p = .43$; see Table 1). In addition, the groups did not differ on WAIS–R Vocabulary subtest scores ($p = .28$), which were used as an estimate of overall intellectual functioning. The gender composition of the groups also was equivalent, $\chi^2(1, N = 20) = 0.20, p = .65$. In the PCAD group, 10 participants had a BNT z score that exceeded their BD z score, and vice versa. In the elderly control group, 11 of 20 participants had BNT z scores greater than BD z scores.

Analysis 1

Asymmetry scores were compared using a Wilcoxon signed-ranks test for matched pairs. The group means were significantly different on the asymmetry measure, with the average discrepancy for the PCAD group ($M = 1.42, SD = 1.11$) more than twice as large as that of the elderly control group ($M = 0.64, SD = 0.57$), yielding an effect size of .94 (Cohen's d). A comparison of the groups' distributions of asymmetry scores also indicated significant differences (Kruskal–Wallis $H = 8.54, p = .003$), with the PCAD group's scores more positively skewed with a larger range of scores (see Figure 1). The groups showed comparable performance on the BNT and BD individually. A

comparison of individual test means did not yield significant group differences on the BNT ($p = .26$) or on the BD ($p = .21$; see Table 2).

Analysis 2

We compared the frequency of asymmetric cognitive profiles (i.e., greater than 1 standard deviation discrepancy between the BNT and BD test) in the two groups using an expected frequency of 31% for asymmetric profiles. This was based on the larger cohort of normal control participants ($n = 108$) in the ADRC database. Ten of the 20 PCAD participants had an asymmetric profile, $\chi^2(1, N = 20) = 4.80$, p (one-tailed) = .04. In contrast, 25% (5 of 20) individuals in the control group had an asymmetric cognitive profile, $\chi^2(1, N = 20) = .09$; p (one-tailed) = .26, a frequency not significantly different from expected levels (see Table 3).

Post Hoc Analyses

Table 4 shows the sensitivity, specificity, and predictive values for the asymmetric profile using two cutpoints. The asymmetric profile (greater than 1 *SD* difference between BNT and BD standard scores) had 71.4% sensitivity and 61.5% specificity in differentiating PCAD from the elderly control group. Using a lower cutoff to define asymmetry (0.8 *SD* difference) resulted in improved specificity and positive predictive value compared with the higher 1 *SD* definition. Compared with the CVLT long-delay free recall, the asymmetric profile had better specificity but worse sensitivity. Table 4 shows the predictive values for genotype, which were superior to recall and asymmetry.

The relative risk estimates in Table 5 show the association between the presence of an asymmetric cognitive profile and a diagnosis of at-risk, possible AD. The relative risk of a possible AD diagnosis was more than four times greater for those with an asymmetric profile (odds ratio of 2.50) than for participants without significant asymmetry (less than 1 standard deviation; odds ratio = 0.625). Revising our definition of asymmetry to a 0.8 standard deviation difference increased the risk to 2.29 for asymmetric versus 0.308 for nonasymmetric individuals. The contingency coefficient

assessing the relationship between asymmetry and preclinical AD status were .300 for a 1 standard deviation asymmetry definition ($p = .04$) and .411 for a 0.8 standard deviation discrepancy definition ($p = .004$).

Associations With Other Cognitive and Demographic Variables

Significant group differences were also found with the CVLT long-delay free recall variable in the smaller subsample of participants ($Z = -2.32$, $p = .02$), yielding an effect size (d) of .91. Estimates of risk showed that this sample of participants with memory testing had a 10-fold increased risk (0.556 for the normal memory group vs. 5.0 for the memory deficit group) of being included in the PCAD group (contingency coefficient = .379, $p = .037$). We did not find a significant association between asymmetric status and memory status (Somers' $d = -.126$, $p = .61$). Genotype had the highest predictive value (contingency coefficient = .522) for PCAD status (see Table 5).

We conducted post hoc analyses to explore the relationship of asymmetry scores with current cognitive functioning. There were no significant associations between asymmetry scores and total DRS score (Spearman's $r_s = -.082$, $p = .61$) or between asymmetry score and WAIS-R Vocabulary subtest (Spearman's $r_s = -.117$, $p = .47$). Because a moderate effect size was evident when groups were compared on the Vocabulary subtest scores ($d = .51$), we performed an analysis of covariance to determine whether any significant group differences in intellectual functioning (as represented by the Vocabulary scores) influenced asymmetry scores. When we used Vocabulary scores as a covariate, $F(1, 38) = 0.185$, $p = .67$, there was still a significant group effect for asymmetry scores, $F(1, 38) = 6.67$, $p = .014$, with observed power (η^2) of .711.

Discussion

In this study, we investigated whether discrepancies between two cognitive domains could distinguish a preclinical phase of AD. Both the PCAD and the elderly control groups were matched on age, years of education, and total DRS scores. As expected, the groups did not differ on either the BNT or the BD when compared individually. Although the PCAD group scored somewhat lower on both tests, their performance was not in the deficit range and likely reflected their current level of cognitive functioning, as they were ostensibly healthy and without significant functional impairment.

Significant differences were found, however, when the groups were compared in terms of asymmetric cognitive abilities, even though overall naming and visuoconstruction abilities were comparable. The PCAD had a larger discrepancy between BNT and BD z scores, with a moderate effect size (.94) obtained. We also examined the frequency of an a priori definition of asymmetry (greater than 1 standard deviation difference) compared with a larger normative group. We found that the PCAD group had a significantly higher proportion of asymmetric profiles relative to the

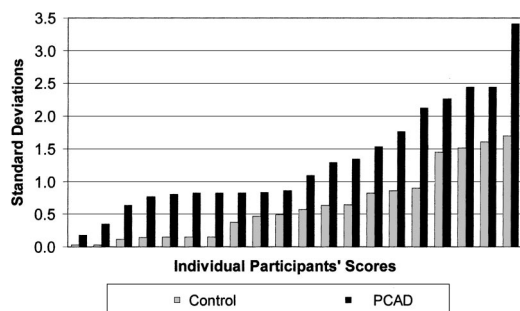


Figure 1. Asymmetry scores: distribution of z -score differences (Boston Naming Test scores minus Block Design subtest scores). PCAD = preclinical Alzheimer's disease.

Table 2
Group Means for Neuropsychological Tests and Asymmetry Scores

Measure	Mean		Standard deviation		Z ^a	Cohen's <i>d</i>
	PCAD	Control	PCAD	Control		
DRS total score	136.1	136.8	3.7	2.8	-0.84 ^b	.18
WAIS-R Vocabulary	53.6	57.9	9.1	7.6	-1.33	.51
CVLT (LDF)	5.1	9.2	5.1	3.1	-2.32 ^{*b}	.91
Boston Naming Test	26.4	27.6	2.9	1.9	-1.13	.49
WISC-R Block						
Design	37.8	41.5	8.8	8.3	-1.25	.43
Asymmetry score	1.42	0.64	1.11	0.55	-2.51 ^{**}	.94

Note. PCAD = preclinical Alzheimer's disease; DRS = Dementia Rating Scale; WAIS-R = Wechsler Adult Intelligence Scale—Revised; CVLT (LDF) = California Verbal Learning Test (long-delay free recall); WISC-R = Wechsler Intelligence Scale for Children—Revised.

^a Wilcoxon signed-ranks test for matched pairs. ^b Mann-Whitney *U*.

* $p < .05$. ** $p = .01$.

normative group that reflected a normal distribution of scores. Thus, we concluded that the PCAD group contained a subgroup of individuals with larger discrepancies between verbal and visuospatial domains relative to the control group. It is likely that averaging individual test scores across disparate subtypes in the PCAD group would have obscured subtle asymmetric differences.

Although cognitive tests are only indirect measures of underlying neural structures and functions, these findings of asymmetric cognitive profiles are intriguing given preliminary neuroimaging findings. These studies have shown atypical asymmetries in mesial temporal and parietal lobe regions in individuals at risk for AD (Reiman et al., 1996; Small et al., 1995; Soininen et al., 1994, 1995). Findings of cognitive asymmetry in at-risk individuals also are consistent with the asymmetric neuropsychological profiles identified in mildly demented patients with AD (Albert et al., 1990; Delis et al., 1992). The lateralized cognitive deficits noted in these studies presumably reflect lateralized onset with asymmetric neuroanatomical changes in temporoparietal regions (Franceschi et al., 1995; Grady et al., 1990; Haxby et al., 1990). Our results suggest that mild asymmetric differences in BNT relative to BD performances in a PCAD group could be a precursor to the prominent naming or visuoconstruction deficits characteristic of the early to middle stages of AD.

Caution is warranted when inferring anatomical or functional changes in anatomy on the basis of cognitive tests;

consequently, future studies with functional magnetic resonance imaging may assist in identifying the neural basis of cognitive asymmetry. Other study limitations include a modest sample size and smaller, unequal subgroups of participants with genotyping and memory data. It is possible that the negative findings using BNT and BD individually reflect lack of power rather than no differences in the populations. In addition, the smaller subgroups required us to dichotomize groups on several variables, thereby losing information and preventing a direct comparison of memory and asymmetry as predictors. Finally, we could not address premorbid asymmetry or issues regarding stability and change in cognitive profiles with our cross-sectional design. Consequently, an individual who suffers a decline in an area of premorbid strength may actually demonstrate symmetric cognitive performance. Future prospective, longitudinal designs should address these issues of premorbid abilities and the stability of cognitive asymmetry.

Although the true clinical utility of an asymmetric profile might require a longitudinal analysis, these preliminary data suggest that using cognitive asymmetry alone as an indicator of impending AD would result in a high proportion of false positives in the general population. A more stringent criterion for asymmetry (i.e., more than a 0.8 standard deviation difference), however, did increase the relative risk ratio and raised the positive predictive value to 75%. The

Table 3
Chi-Square Tests of Frequencies for Asymmetric Profile

Group	Observed <i>N</i>	Expected <i>N</i>	χ^2 (1)
Preclinical			
Asymmetric	10	5.6	4.80*
Nonasymmetric	10	14.4	
Control			
Asymmetric	5	5.6	0.09
Nonasymmetric	15	14.4	

* $p < .05$ (one-tailed).

Table 4
Predictive Validity Percentages for Asymmetry, Genotype, and Memory

Variable	Sensitivity	Specificity	PPV	NPV
Asymmetric profile				
> 1.0 <i>SD</i>	71.4	61.5	50.0	80.0
> 0.8 <i>SD</i>	71.4	73.6	75.0	70.0
CVLT (LDF)	88.8	52.9	50.0	90.0
Apoe genotype	85.7	78.6	66.6	91.6

Note. PPV = positive predictive value; NPV = negative predictive value; CVLT (LDF) = California Verbal Learning Test (long-delay free recall).

Table 5
Odds Ratios and Contingency Coefficients for Asymmetry, Genotype, and Memory

Predictor	Odds ratio	95% confidence interval (lower–upper)	Contingency coefficient
Asymmetric profile > 1.0 SD (<i>n</i> = 40)			.300*
Asymmetric group	2.500	0.938–6.661	
Nonasymmetric group	0.625	0.383–1.020	
Asymmetric profile > 0.8 SD (<i>n</i> = 40)			.411**
Asymmetric group	2.290	1.21–4.318	
Nonasymmetric group	0.308	0.121–0.783	
Recall ability (CVLT; <i>n</i> = 26)			.379*
Below average ^a	5.000	0.731–34.203	
Average ^b	0.556	0.326–0.946	
ApoE genotype (<i>n</i> = 21)			.522**
At risk ^c	8.000	1.158–55.257	
Not at risk ^d	0.364	0.142–0.930	

Note. CVLT = California Verbal Learning Test.

^a Below average memory: 1–3 standard deviations below age-scaled mean (CVLT). ^b Average memory: below 1 standard deviation through 4 standard deviations above age-scaled mean (CVLT). ^c At-risk genotype includes $\epsilon 3/4$ and $4/4$. ^d Not at-risk genotype includes $\epsilon 2/3$, $\epsilon 2/4$, and $\epsilon 3/3$.

* $p < .05$. ** $p < .01$.

subsample of participants who had data available from the CVLT suggested that long-delay free recall was only a slightly better predictor of PCAD group membership. Recall ability and asymmetry showed similar positive (50% vs. 50%) and negative (80% vs. 90%) predictor values. Although the data were limited, a qualitative analysis indicated that asymmetry and CVLT long-delay free recall did not have a significant association in the PCAD group. Of the 8 individuals with asymmetric profiles, 3 had memory performance within normal limits the year prior to their diagnosis. Although genotype was consistently a more accurate predictor relative to asymmetry and recall, genotype may be a superior predictor of disease incidence rather than disease onset.

These findings have a number of implications for investigations of elderly individuals who are in a preclinical phase of AD. Use of difference scores or contrast measures may be more sensitive than analyses of single test means in identifying subgroups of at-risk individuals with subtle, lateralized cognitive changes. Additionally, cognitive asymmetry might prove useful in populations with a relatively high base rate of preclinical AD, such as $\epsilon 4$ allele carriers or those with a strong family history of AD. Finally, use of nonmemory measures in conjunction with recall measures might improve our ability to detect preclinical AD, given our findings that cognitive asymmetry identified individuals who were still demonstrating normal memory performance shortly before a possible AD diagnosis. The ability to discriminate age-related changes in cognition from deficits pathognomonic of AD will become increasingly important if pharmacological interventions are developed that slow the progression of AD. The current study highlights the importance of considering alternative methods of defining cognitive changes by analyzing subtle cognitive discrepancies in people at risk for AD.

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