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Asymmetry in Auditory and Spatial Attention Span in Normal Elderly Genetically At Risk for Alzheimer's Disease

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Abstract

Some studies of elderly individuals with the ApoE-e4 genotype noted subtle deficits on tests of attention such as the WAIS-R Digit Span subtest, but these findings have not been consistently reported. One possible explanation for the inconsistent results could be the presence of subgroups of e4+ individuals with asymmetric cognitive profiles (i.e., significant discrepancies between verbal and visuospatial skills). Comparing genotype groups with individual, modality-specific tests might obscure subtle differences between verbal and visuospatial attention in these asymmetric subgroups. In this study, we administered the WAIS-R Digit Span and WMS-R Visual Memory Span subtests to 21 nondemented elderly e4+ individuals and 21 elderly e4- individuals matched on age, education, and overall cognitive ability. We hypothesized that a) the e4+ group would show a higher incidence of asymmetric cognitive profiles when comparing Digit Span/ Visual Memory Span performance relative to the e4- group; and (b) an analysis of individual test performance would fail to reveal differences between the two subject groups. Although the groups' performances were comparable on the individual attention span tests, the e4+ group showed a significantly larger discrepancy between digit span and spatial span scores compared to the e4- group. These findings suggest that contrast measures of modality-specific attentional skills may be more sensitive to subtle group differences in at-risk groups, even when the groups do not differ on individual comparisons of standardized test means. The increased discrepancy between verbal and visuospatial attention may reflect the presence of "subgroups" within the ApoE-e4 group that are qualitatively similar to asymmetric subgroups commonly associated with the earliest stages of AD.

Introduction

In recent years, neuropsychologists have striven to find the earliest possible cognitive markers of a preclinical phase of Alzheimer's disease (AD) in normal-functioning elderly individuals who are at genetic risk to acquire the disorder because of the apolipoprotein E e4

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allele (ApoE-e4) (Corder, Saunders, Pericak-Vance, & Roses, 1995). Such research may, in the future, serve as a significant clinical asset if advances in the development of pharmacological agents with neuroprotective properties continue to be made (Miguel-Hidalgo, Alvarez, Cacabelos, & Quack, 2002; Vajda, 2002). One area of cognition that has shown promise as a preclinical marker of AD in elderly individuals with the ApoE-e4 allele is attention and working memory. Specifically, some studies have found that nondemented elderly with the e4 genotype show subtle deficits on neuropsychological tests that have strong attentional demands, such as the Digit Span subtest (Albert, Moss, Tanzi, & Jones, 2001; Caselli et al., 1999; Caselli et al., 2001; Linn et al., 1995; Wilson et al., 2002); WMS-R Mental Control subtest (Tierney et al., 1996), Operation Span Test (Rosen, Bergeson, Putnam, Harwell, & Sunderland, 2002), Digit Symbol subtest (Masur, Sliwinski, Lipton, Blau, et al., 1994; Yaffe, Cauley, Sands, & Browner, 1997), attentional switching and disengagement (Greenwood, Sunderland, Friz, & Parasuraman, 2000; Parasuraman, Greenwood, & Sunderland, 2002), and supra-span ability and divided attention (Rosen et al., 2002). However, several other studies have failed to replicate findings of attentional deficits in nondemented e4 elderly groups (Baeckman, Small, & Fratiglioni, 2001; Elias et al., 2000; Flory, Manuck, Ferrell, Ryan, & Muldoon, 2000; Smith et al., 1998).

The question arises as to why there have been inconsistent findings of attentional deficits in normal elderly at risk for AD. Several factors likely contribute to these discrepant findings, including across-study differences in sample size, power, and mean age of the subject groups. Clues to another possible reason for the inconsistent findings may be derived from neuroimaging studies of elderly subjects at risk for AD. Specifically, neuroimaging results suggest a higher incidence of asymmetric structural and metabolic changes in at-risk individuals (Bigler et al., 2002; Celsis et al., 1997; Geroldi et al., 2000; Small et al., 1995; Soininen, et al., 1994). Such findings would be expected, given that asymmetric neurodegeneration and lateralized cognitive deficits are frequent findings in early AD (Albert, Duffy, & McAnulty, 1990; Demadura, Delis, Jacobson, & Salmon, 2001; Martin, 1990; Massman & Doody, 1996; Strite, Massman, Cooke, & Doody, 1997), with greater verbal/visuospatial asymmetries in the e4 genotype in AD (Finton et al., 2003). If subtle cognitive asymmetries also occur in preclinical AD, then an analysis of individual test scores of modality-specific tests may fail to detect these changes. That is, averaging individual test scores across distinct patient subtypes may fail to identify subtle lateralized cognitive profiles (Mitrushina, Uchiyama, & Satz, 1995).

Consistent with this possibility, a recent study by Jacobson, Delis, Bondi, & Salmon (2002) found support for the importance of analyzing scores that characterize cognitive asymmetry rather than comparing individual test scores in elderly subjects at risk for AD. In this investigation, a nondemented elderly group who later converted to AD did not differ from a matched control group when scores on the Boston Naming Test and Block Design subtest were compared individually. However, a standard-score discrepancy analysis between these two tests revealed a significantly higher frequency of asymmetric cognitive profiles in the at-risk group compared to the elderly controls who did not develop AD (50% vs. 25%, respectively). These findings are promising, because the presence of cognitive asymmetry was found to improve the prediction of normal elderly who later converted to AD (relative risk ratio of 2.50).

In the present study, we investigated whether or not a cognitive-discrepancy analysis would be more sensitive than an individual-test analysis in detecting a potential preclinical stage of AD using tests that assess another domain of cognition: attention span. Given that impairment in attention frequently accompanies early-stage deficits in AD (Parasuraman & Martin, 1994; Perry, Watson, & Hodges, 2000), subtle changes in lateralized attention skills may prove to be a useful preclinical marker for conversion to AD. Specifically, we analyzed

the performance of cognitively intact e4+ and matched e4- elderly groups on the Digit Span and Spatial Span subtests. We hypothesized that relative to the e4- group, a) the e4+ group would show a higher incidence of asymmetric cognitive profiles when comparing Digit Span/Spatial Span performances; and (b) an analysis of individual-test performance would fail to reveal differences between the two subject groups.

Method

Participants

The participants in this study were originally recruited to serve as control subjects for a large, longitudinal study on neurocognition and health changes in elderly at risk for AD at the University of California San Diego Alzheimer's Disease Research Center (UCSD ADRC). Some of the participants were recruited through advertisements and others were family members and spouses of AD patients who were being followed at the ADRC. We conducted a retrospective analysis of all individuals who had completed both the Digit Span and Visual Memory Span subtests as part of their full neuropsychological examination (see Salmon & Butters, 1992). There were 23 eligible participants with at least one ApoE-e4 allele (e4+ group), but two individuals (both ε3/ε4 genotype) were excluded because they performed below a cut-off for cognitive impairment of 130 points based on the Mattis Dementia Rating Scale (DRS) (Monsch, Bondi, Salmon, Butters, et al., 1995). The genotype distribution for the remaining 21 e4+ positive individuals was 17 ε3/ε4, two ε2/ε4, and two ε4/ε4 genotypes. The comparison group of 21 participants without the e4 allele (e4- group) were randomly selected from a larger group of elderly control subjects and matched on a one-to-one basis using three criteria: age, total years of education and total DRS score. The genotype distribution for the e4- group was six ε2/ε3, and fifteen ε3/ε3 homozygous individuals. Neuropsychological test results were used only from the baseline examination, or from the first administration of the span tests to reduce the possibility of practice effects. All participants had been genotyped for the apolipoprotein E allele according to the methods described by Saunders and colleagues (1993), but they were unaware of the genotype results at the time of the neuropsychological testing. All participants were examined by a staff neurologist and received medical and laboratory tests to rule out any metabolic, endocrine, or nutritional deficiencies. None of the participants had a history of alcohol or drug abuse, learning disability, head injury with loss of consciousness, stroke, significant cerebrovascular disease or other neurologic disorder. None were currently taking medications that would significantly impair cognition such as neuroleptics, opiates, benzodiazepines, or major tranquilizers. The Diagnostic Interview Schedule II (Robins, Helzer, Croughan, & Ratcliff, 1981) was administered and none of the participants met criteria for major depression, dysthymia, or other significant psychiatric illness. Written informed consent was obtained from all participants. All participants were right-handed and were selected without regard to gender, ethnicity or race.

Measures and Procedures

The neuropsychological measures were administered by a trained psychometrist under the supervision of a neuropsychologist as part of an annual neuropsychological examination. Included in the test battery were the Digit Span (DS) subtest from the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981), the Visual Memory Span (SS) subtest of the Wechsler Memory Scale-Revised (Wechsler, 1987), and the Mattis Dementia Rating Scale (DRS). The DS subtest consists of forward and backward conditions in which the examiner reads aloud a series of numbers of increasing length and the participant is asked to repeat them in the same order. In the backward condition, the examiner again reads a series of numbers of increasing length, but the participant must repeat the numbers in reverse order. The SS subtest is the visuospatial analogue of DS and also consists of forward and backward

conditions. The examiner touches a series of colored squares in a specific sequence and the participant must reproduce that sequence. In both DS and SS, the sequences are increased in length by one unit on each subsequent trial until the participant fails two trials in a row. The forward sequences are presented prior to the backward series. These tests have also been used to document cognitive asymmetry in AD (Almkvist, 1996; Cherry, Buckwalter, & Henderson, 1996) and lateralized cognitive changes in other populations (Carlesimo, Fadda, Lorusso, & Caltagirone, 1994; Rapport, Webster, & Dutra, 1994). Both the total DS and SS scores and individual forward and backward sequences were included in the analyses. To contrast asymmetry scores with more traditional cognitive measures, we also compared age-scaled percentile scores on DS and SS, and the long-delay free recall trial of the California Verbal Learning Test (CVLT) (Delis, Kramer, Kaplan, Ober, 1987). The CVLT is a learning and memory test consisting of 16 words from four semantic categories. There are five learning trials followed by presentation of an interference list, short and long-delay (20 min.) free and semantically cued recall as well as recognition memory indices.

Statistical Analyses

Scores on the DS & SS subtests were analyzed individually and in terms of an asymmetry score that measured the size of the DS/SS discrepancy. The asymmetry score was calculated by first converting the raw test scores on the DS and SS subtests to standardized scores (*z*-scores) based on the larger, UCSD ADRC elderly, normal control group (n = 108). This normative group did not include the 42 study participants. We then calculated an asymmetry score using the absolute value of the difference between DS and SS standard scores. The absolute value was used because the magnitude of the difference score was of primary interest in this analysis irrespective of its direction. As expected, this distribution of scores was significantly negatively skewed, and a square root transformation was used to approximate a normal distribution for parametric analyses. We then compared raw and standard scores for the DS and VS forward, backward, and total scores, as well as the calculated asymmetry score for group differences using a one-way analysis of variance (ANOVA). In accordance with Cohen's power analysis (Cohen, 1992), a recommended sample size of $n = 20$ in each group would be necessary to detect group difference given a large effect size ($d = .8$) with $p = .05$ (two-tailed). Our sample size of $N = 42$ was likely to be sufficient to detect a “minimal meaningful difference” with an alpha level of .05 given our directional hypotheses (Tabachnik & Fidell, 1996). We also examined the frequency and predictive value of an asymmetric profile in the two groups. In accordance with past studies (Demadura et al., 2001; Finton et al., 2003; Jacobson et al., 2002), this asymmetric profile was operationally defined as a z-score difference (DS – SS) greater than 1 SD. The relative frequency of these profiles was examined using Chi-Square analyses and odds ratio estimates. Additional post-hoc analyses were conducted to illustrate the predictive utility of the asymmetry score. In separate comparisons, raw scores from DS and SS were converted to age-scaled percentile scores and groups were compared with 2-tailed t-tests. In addition, groups were compared on the total number of words recalled on the CVLT long-delay free recall (LDFR), and on age and gender adjusted standard scores (Paolo, Troester, & Ryan, 1997) for LDFR.

Results

The e4+ and e4- groups were not significantly different ($p > .10$) with respect to age, educational level, gender distribution, or total Mattis DRS score (see Table 1). Neither group was significantly different from the larger ADRC normal control comparison group on DS total score (normative group mean = 14.59; SD = 4.53) or on SS total score (mean = 14.56; SD = 2.58).

Individual and Asymmetry Score Analysis

The groups were compared using a one-way analysis of variance (ANOVA) with the Statistical Package for the Social Sciences software program. When the groups were compared on the individual tests, there were no significant differences ($p > .10$) on DS total or SS total. Similarly, there were no significant group differences on the individual forward or backward span measures for DS or SS. The groups were significantly different ($p = .008$) however, when compared using the asymmetry score measuring the difference between DS and SS scores, with the e4+ group having a larger mean asymmetry score as well as significantly different variances (see Table 2 and Figure 1).

Qualitative Analyses of Asymmetry Profiles

We analyzed the frequency and predictive value of an asymmetric profile in the two subject groups, which was defined as a greater than 1 SD difference between DS and SS scores. A chi-square analysis indicated that there was a significant relationship between genotype and an asymmetric profile ($p = .011$) (see Table 3). Fifty-two percent of the e4+ group had a discrepancy greater than 1 SD, while only 19% of the e4- group had this large a discrepancy (see Figure 2).

The odds ratio indicated that the likelihood of obtaining this large a DS/SS discrepancy was more than 5 times greater in the e4+ group. Dichotomizing the groups into asymmetric versus non-asymmetric profiles resulted in a specificity of 80.9 and a positive predictive value of 75.0 compared to a sensitivity value of 57.1 and negative predictive value of 65.4 (see Table 4).

Contrast Measures

Raw scores for DS and SS were converted to age-scaled percentiles scores (Wechsler, 1987). Both groups performed within normal limits for their age groups, with scores ranging from the 56th percentile to the 73rd percentile. There were no significant differences between e4+ and e4- groups on either forward or backward DS or SS using age-adjusted norms. See Table 5 for percentile scores and statistical comparisons.

CVLT data for the year in which the span tests were administered was available for 39 of the 41 participants. On the long-delay free recall variable, the e4- group recalled slightly more words compared to the e4+ group (10.1 vs. 8.1). The raw scores were also converted to standard scores with age and gender corrected norms (Paolo et al., 1997). Again, both e4+ and e4- groups performed within normal limits (e4+ z-score = -.25; e4- z-score = .21) compared to same age peers. The groups were not significantly different using age and gender corrected z-scores (see Table 5). Asymmetry scores were not significantly correlated with LDFR scores (Pearson $r = .07$; $p = .65$).

Discussion

We investigated whether normal elderly with the ApoE-e4 allele would show a larger discrepancy between verbal and spatial span tasks relative to a matched elderly group without the e4 allele. Using individual-test analyses, the groups were not significantly different on the individual Digit Span and Spatial Span totals, nor did the total scores differ when compared on forward and backward components of these tests. However, when the groups were compared in terms of asymmetric profiles, the e4+ group had a significantly larger discrepancy between Digit Span and Spatial Span *z*-scores relative to the e4- group. Subsequent analyses revealed a significant association between genotype and a Digit Span/Spatial Span asymmetry. The likelihood of attaining a greater than 1 SD or greater difference between Digit Span and Spatial Span *z*-scores was five times higher for the e4+

than for the e4- group. These findings of cognitive asymmetry are consistent with a previous study of nondemented elderly individuals who were evaluated one to two years prior to conversion to a possible AD diagnosis (Jacobson et al., 2002). As with the current study, Jacobson and colleagues found no significant between-group differences using individual-test analyses of the Boston Naming Test and Block Design subtest of the WAIS-R, but a contrast measure showed a higher frequency of asymmetric cognitive profiles in the preclinical AD group. Taken together, these studies suggest that a contrast or discrepancy score might be more sensitive to the detection of subtle cognitive differences in at-risk elderly than an analysis of the mean scores of individual tests.

We compared the groups on several age-adjusted measures, to determine if the e4+ group would be identified using more traditional summary measures. The age-scaled percentile scores for DS and SS did not significantly distinguish between the groups, and both groups were performing within the average to above-average range for same-age individuals. We also contrasted our asymmetry measure with delayed verbal recall, another frequently used indicator of incipient AD. The e4+ group recalled fewer words on the CVLT LDFR compared to the e4- group, and this trend may represent a change in memory ability suggesting preclinical AD. But the e4+ age-adjusted scores for the CVLT long-delay free recall were not significantly different from those of the e4- group. With a few exceptions, the e4+ participants would not be characterized as having significant memory deficits according to age and gender adjusted norms. In a discriminant function analysis, the DS-SS asymmetry score correctly classified slightly more cases compared to the raw scores for CVLT LDFR (71.4% vs. 64.3%). Interestingly, there was little association between delayed recall scores and asymmetry scores suggesting that a verbal/spatial asymmetry might contribute unique information about the e4+ group AD. The predictive utility for either measure, or a cognitive profile will require a longitudinal study following some individuals to an AD diagnosis.

The present results suggest that the inconsistencies of past studies of attentional deficits in e4+ groups might be the result of asymmetrically impaired subgroups. When a given e4+ sample contains roughly equivalent numbers of “low verbal” and “low spatial” individuals, a comparison of means on a single test would likely not yield group differences. Theoretically, however, a single “low verbal” or “low spatial” subgroup could predominate in any given sample. This was the case in a recent study of cognitive asymmetries in early AD patients with the e4 allele, which showed a predominance of “higher verbal” relative to nonverbal ability (Finton et al., 2003) that was identified using difference scores. In the present study, eight of those e4+ individuals who had a greater than 1 SD Digit Span/Spatial Span difference were in the “high verbal” ability subgroup, with only 3 participants in the “high spatial” subgroup. The presence of subgroups within the larger e4+ group may contribute to the lack of consistent findings in attention span performance, especially in studies of smaller sample sizes.

Although premorbid abilities may contribute to the current results, another explanation for these findings may be a greater incidence of lateralized decline in either verbal or visuospatial abilities in e4+ groups. Alzheimer's disease frequently presents with initially heterogeneous neurodegeneration (Mitrushina et al., 1995); and numerous studies have documented lateralized cognitive profiles that corresponded to greater right or left hemisphere involvement (Haxby, Duara, Grady, Cutler, & Rapoport, 1985; Haxby et al., 1990). Using digit and spatial span tests, Cherry and colleagues (Cherry et al., 1996) proposed that the subsidiary systems underlying digit and spatial span (phonological loop and visuospatial scratchpad) could be independently affected in AD in addition to a central executive deficit (Collette, Van der Linden, Bechet, & Salmon, 1999). Similar findings of selective impairment in verbal or spatial span (Collette, Salmon, Van der Linden, Degueldre,

& Franck, 1997; Grossi, Becker, & Trojano, 1994; Trojano, Chiacchio, De Luca, & Grossi, 1994) have been documented in AD subgroups, confirming the heterogeneity of attention deficits in early AD. It follows that the subtle differences in verbal relative to spatial span in e4+ participants might reflect the earliest stage of these asymmetric changes. Future longitudinal designs will be required to determine the prognostic value of cognitive asymmetries. In the current study, a large Digit Span/Spatial Span discrepancy occurred in slightly more 50% of the e4+ group compared to 19% of the e4- group, resulting in better specificity than sensitivity. However, only a subset of e4+ individuals will go on to develop AD and a modest positive predictive value would be expected given this model.

Cognitive tests are only indirect measures of underlying neural structures and functions, and caution is warranted when inferring anatomical bases of these tests. However, findings of asymmetric cognitive profiles are intriguing given preliminary neuroimaging findings. These studies have shown atypical asymmetries in mesial temporal and parietal regions in individuals at risk for AD (Reiman, Caselli, Yun, Chen, et al., 1996; Small et al., 1995; Soininen et al., 1994). Findings of lateralized cognitive profiles 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; Demadura et al., 2001). The lateralized cognitive deficits noted in these studies presumably reflect lateralized onset in AD with asymmetric changes likely to present in temporoparietal regions (Franceschi et al., 1995; Grady et al., 1990; Haxby et al., 1990). There are a number of potential mechanisms that could explain attentional-process dissimilarities in subgroups at increased risk for AD. For example, Lawrence and Sahakian (1995) hypothesize that attention and working memory dysfunction in a preclinical phase of AD may be linked to degeneration of cholinergic system in the basal forebrain supporting frontoparietal cortical connections (DeKosky et al., 2002; Levy, Parasuraman, Greenwood, Dukoff, & Sunderland, 2000). In addition, there is hypometabolism in posterior cingulate, parietal and prefrontal regions that are critical to attentional ability (Reiman et al., 1996), Further, PET studies have confirmed that association cortices of the parietal and frontal lobes often show uneven, or asymmetric hypometabolism early in the disease course (Buck, Black, Behrmann, Caldwell, & Bronskill, 1997; Haxby et al., 1990). Consequently, future studies with functional neuroimaging techniques may assist in identifying the neural basis of attentional asymmetries as identified in this study.

Limitations of the present study include many of those inherent in a retrospective analysis. First, differences in the level of task difficulty between Digit Span and Spatial Span is a potential limitation. Although a subgroup of the participants (28%) had greater spatial than verbal span, the overall group means indicate that spatial span ability was the more difficult task for the majority of participants. In this context, a larger discrepancy could represent a differential effect of task difficulty. This is a frequent limitation in studies characterizing lateralized group differences, as many visuospatial tasks generally are considered to be more cognitively demanding than their verbal counterparts (Cherry et al., 1996; Orsini, Trojano, Chiacchio, & Grossi, 1988). Although a larger DS/SS discrepancy was present in the e4+ group in both the forward and the more difficult backward conditions, a possible disparity in verbal/spatial task difficulty represents a potential confound. Only psychometrically matched tests constructed from items matched on difficulty level and reliability would produce truly equivalent verbal and spatial measures (see Miller, Fujioka, Chapman, & Chapman, 1995). An additional limitation is that our sample excluded any individuals whose DRS scores suggested significant cognitive impairment. Although the intent was to exclude any participant with undiagnosed mild cognitive impairment or early-stage AD from the sample, selecting this cohort may have changed or limited the distribution of Digit Span or Spatial Span scores. In addition, we could not assess an ApoE-e4 gene-dose effect on attentional asymmetries because our sample included a limited number of individuals who

were homozygous for the apolipoprotein E e4/4 allele. Finally, because we restricted our investigation to tests of attention, the possibility remains that the asymmetries noted here may exist in other domains, and on other tasks, such as motor dexterity tests.

The present findings have a number of implications for investigations of normal, elderly individuals who are at risk for AD. Markers of preclinical AD are difficult to identify because of the heterogeneity of the neuropsychological dysfunction associated with the disease process (Visser, Verhey, Ponds, & Jolles, 2002). It is likely that more sensitive measurement methods will be needed to supplement standardized neuropsychological tests in building a profile with improved utility for predicting conversion to AD. Consistent with Jacobson et al. (2002) and Rosen et al. (2002), the results of the current study suggest that the use of contrast measures may be more sensitive than analyses of single-test means for detecting subtle cognitive changes characteristic of a preclinical stage of AD.

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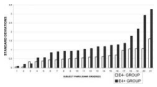

Figure 1.
Asymmetry scores: distribution of *z*-score differences (BNT – BD).

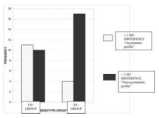

Figure 2.
Frequency of DS/SS discrepancy greater than 1 SD.

Table 1

Demographic Characteristics and Mattis Dementia Rating Scale Total Score

	e4- group		e4+ group	
Variable	**Mean**	**(SD)**	**Mean**	**(SD)**
Age (years)	73.1	(4.7)	74.8	(8.1)
Education (years)	14.4	(3.0)	15.6	(3.0)
Percent female	66.0		53.0	
Mattis DRS total score	138.7	(3.6)	137.5	(4.9)

Table 2

Group Means, t-tests for Span Tests and Asymmetry Score

	e4- group				e4+ group						
	Raw score		z-score		Raw score		z-score		Statistical comparisons		
Measure	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	**F value**	***p***	**Cohen's *d***
WAIS-R Digit Span Total	15.4	(3.2)	.12	(.70)	16.1	(4.0)	.29	(.88)	.46	.50	.21
Digits forward	8.0	(1.9)	–.01	(.83)	8.5	(2.1)	.21	(.89)	.63	.43	.24
Digits backward	7.3	(1.8)	.21	(.66)	7.6	(2.3)	.32	(.88)	.20	.65	.14
WMS-R Visual Memory											
Span Total	14.0	(2.2)	–.20	(.89)	14.0	(2.4)	–.22	(.97)	.04	.95	.02
Span forward	7.7	(1.4)	–.02	(.89)	7.5	(1.5)	–.14	(.94)	.18	.68	.13
Span backward	6.3	(1.2)	–.32	(.84)	6.5	(1.2)	–.23	(.79)	.15	.70	.12
Asymmetry score											
(DS – SS z-score difference)			.62	(.37)			1.19	(.81)	7.69	.008	.92

Table 3

Chi-Square Tests of Frequencies for Asymmetric Profile Greater then 1 SD

	Asymmetric profile (>1 SD)	Non-asymmetric profile (<1 SD)	Chi-square
e4+ group	n = 11	n = 10	
	52%	48%	
E4- group	n = 4	n = 17	6.46*
	19%	81%	

* p = .011

Table 4

Predictive Validity and Odds Ratio for 1 SD Discrepancy Profile

Asymmetric profile	*Sensitivity*[a]	*Specificity*[b]	*PPV*[c]	*NPV*[d]	Odds ratio (C.I.)
>1SD difference in DS/SS	57.1	80.9	75.0	65.4	5.67 (1.41-22.76)

[a] Sensitivity calculated as true positives/(true positives + false positives)

[b] Specificity calculated as true negatives/(true negatives + false positives)

[c] Positive predictive value: calculated as true positives/(true positives + false negatives)

[d] Negative predictive value: calculated as true negatives/(true negatives + false negatives)

Table 5

Group Means, t-tests for Age Adjusted Contrast Measures

	e4- group		e4+ group				
Measure	**Mean**	**(SD)**	**Mean**	**(SD)**	***t***	***p***	**Cohen's *d***
CVLT Long Delay Free Recall							
Standard score (age adjusted)	.21	(1.1)	–.25	(1.4)	1.2	.23	.40
Raw score	10.1	(3.2)	8.1	(3.7)	1.9	.07	.62
WMS-R Visual Memory Span (age adjusted)							
Forward (percentile)	59.8	(29.5)	56.4	(31.1)	.36	.71	.06
Backward (percentile)	62.7	(23.8)	62.1	(20.7)	.08	.93	.01
WAIS-R Digit Span (age adjusted)							
Forward (percentile)	61.4	(28.9)	63.5	(29.3)	–.22	.82	.11
Backward (percentile)	73.4	(18.0)	73.3	(24.4)	.01	.99	.03