PROGRESSION AND STABILITY OF COGNITIVE ASYMMETRY IN A LARGE SAMPLE OF ALZHEIMER'S DISEASE PATIENTS

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A Thesis

Presented To

The Faculty of the Department

Of Psychology

University of Houston

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In Partial Fulfillment

Of the Requirements for the Degree of

Master of Arts

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By

William Alexander Alverson

December, 2014

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ABSTRACT

Previous research has suggested that a significant minority of patients with Alzheimer's Disease (AD) exhibit asymmetric cognitive profiles (greater verbal than visuospatial impairment or vice versa) and that these patient subgroups may differ in demographic and other characteristics. Prior studies have been relatively small, and this investigation sought to examine correlates of asymmetry in a large patient sample (N=924) and to determine if cognitive asymmetry is stable over time (in smaller subsets of patients). Participants were classified into the following cognitive profile groups: Low Verbal, Symmetric, and Low Visuospatial. Consistent with past research, 27.7% of patients were classified as having asymmetric cognitive profiles, with more patients in the Low Visuospatial subgroup. Low Visuospatial patients were younger than patients in the other subgroups, and Low Verbal patients performed worse on a measure estimating premorbid verbal intelligence. Carrying two copies of the ApoE ε4 allele was associated with having an asymmetric cognitive profile, as expected based on previous literature. Regression analyses consistently found age and the number of ε4 alleles to be significantly predictive of asymmetry. The degree of asymmetry and asymmetry classifications were relatively stable across time, based on correlations and kappa statistics across evaluations, respectively. No patients in either of the asymmetric subgroups changed classification to the opposite asymmetric subgroup over time. Repeated measures ANCOVA (with Asymmetry Index as the dependent variable) yielded significant interactions between baseline asymmetry classification and time. This indicated that the degree of asymmetry in the asymmetric subgroups became smaller (more symmetric) over time, supporting the hypothesis that asymmetry

decreases as the disease progresses. These results, considered together, provide evidence for sufficient systematic differences in asymmetry classifications to merit consideration as distinct subgroups of the disease.

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Introduction

It is a well-documented observation that patients with Alzheimer's Disease (AD) are characterized by variable clinical presentations, due to heterogeneous patterns of degeneration. Memory dysfunction is typically (though not always) prominent early in the disease, but other cognitive impairments are more variable. Further, the ability to predict the progression of their dementia is limited by this heterogeneity. One substantial source of variability established by the literature is hemispheric asymmetry, in which cognitive functions lateralized primarily to one hemisphere or the other may decline in distinct patterns (Derflinger et al., 2011; Grady et al., 1990; Martin, 1990; Strite, Massman, Cooke, & Doody, 1997).

Physiological Indications of Heterogeneity of Hemispheric Asymmetry

Neuropathological findings.

AD is known to cause global neurodegeneration, and many studies have established the deficits that can occur as a result of specific neuropathology (Zec, 1993). Fewer studies have explored the relationship between asymmetry of degeneration and cognitive abilities. Wettstein and Lang (1990) reported a clear relationship between asymmetrical hemispheric degeneration and performance on neuropsychological tests. Specifically, the authors found significant relationships between plaques and tangles in regions of each hemisphere at autopsy (parietal, temporal, frontal, and hippocampal), and impaired performances on neuropsychological measures thought to be more strongly lateralized to that same hemisphere within 10 months prior to death. Summarizing the most relevant findings, the authors reported significant negative correlations (higher plaque and tangle counts associated with lower scores) between the following measures: right parietal with cube copy; right hippocampus with delayed recall of visually presented information; right hemisphere with spatial orientation, recall, calculation,

finger position imitation, cube copying, and alternating hand movements; and left hemisphere with temporal orientation. All correlations were significant ($p < 0.05$) but varied in strength (from r = -0.37 to r = -0.66). While helpful in reinforcing lateralization of degeneration, this study lacked longitudinal data that could reveal the progression of asymmetric pathology, and had data from a limited number of subjects (N = 56).

Another study that included some data from autopsy was Rasmusson and Brandt (1995), who examined 19 patients with probable AD (18 confirmed AD at autopsy). Of the 18 with confirmed AD, 3 of the 4 patients categorized as asymmetric (1 low-verbal and 2 low-spatial) had additional pathology in the form of arterial occlusion, Parkinson's Disease, or multiple infarctions. Two of the 15 globally impaired subjects showed pathology in addition to AD. Thus, the authors concluded that cognitive asymmetry is more likely to occur when additional pathology is present. This finding can help inform the present study, although it is quite limited in the number of subjects (study N = 59; autopsy N = 19), making these findings difficult to generalize.

Structural imaging.

Anatomical data is not limited to that available from autopsy, however. Postmortem studies are complemented with structural imaging studies such as that conducted by Kumar et. al. (1994). These investigators used magnetic resonance imaging (MRI) to calculate volumes of cerebrospinal fluid (CSF) in 34 patients with probable AD and 28 age-matched controls. This measure of CSF volume was used as a proxy for cortical degeneration. It was found that the patients with AD had significantly higher CSF volumes, and significantly greater right-left volumetric asymmetry compared to the normal controls. Hemispheric asymmetry indices were calculated as the absolute value of whole brain and sulcal CSF volume in the following way:

(Right - Left)/(Right + Left). Kumar et. al (1994) also presented neuropsychological data that correlated with the asymmetric CSF volumes, which will be explored in depth later.

Similar results were obtained more recently by Derflinger et. al (2011), who utilized MRI to measure gray-matter volumes in 35 patients with AD, 24 patients with amnestic mild cognitive impairment (aMCI), and 30 age-matched controls. Derflinger et al. applied voxel-based morphometry to calculate a difference index (transformed to z-scores) for gray-matter volume by hemisphere and region, using the usual formula: (Right-Left)/(.5[Right + Left]) for each voxel. On four global measures of asymmetry (temporal, parietal, and occipital lobes; and total hemisphere), increasing asymmetry was found proceeding from the controls to those with aMCI to those with AD. These findings offer some valuable further insight into measures of asymmetry, and in fact these authors also correlated gray-matter volumes with neuropsychological test performances, which will be examined later. This study is limited by the absence of longitudinal data, however, so change in asymmetry over time could not be examined.

Functional imaging.

We expect that structural asymmetry may be accompanied by functional asymmetry, and indeed we know that there are significant changes in neural activity in AD. Positron emission tomography (PET), using glucose uptake as a measure of neural activity, have found this in patients with AD (Grady, Haxby, Schlageter, Berg, & Rapoport, 1986), as well as healthy elderly (Berardi, Haxby, Grady, & Rapoport, 1991). Grady and colleagues studied 16 patients with AD and found frontal, parietal, and temporal left/right asymmetry in nine, six, and five of the subjects, respectively, at the time of the first PET scan. Asymmetry was calculated in a manner similar to that noted above: 2(Right-Left)/(Right+Left).The authors found no significant changes

in metabolic asymmetry after a mean 15-month (range, 9 to 25 months) follow-up period, suggesting that metabolic asymmetry remains stable. Additionally, the same pattern and stability of asymmetry was found when rank ordering performance on the Syntax Comprehension Test (verbal performance) and Extended Range Drawing Test (visuospatial performance). Finally, the difference in patients' performances on these tests was correlated with metabolic indices of asymmetry for frontal and parietal regions at both time points, and with temporal metabolism at the second time point.

Additional supporting evidence was found by Haxby et. al. (1990) in a study of 32 mildly, moderately, or severely demented patients with AD and 31 healthy controls (from whom PET data was collected). A metabolic rate asymmetry index was calculated for various cortical regions, and a weighted mean was calculated for hemispheric metabolic rate using the formula: 2(Right-Left)/(Right+Left). The authors found that patients with AD had significantly greater asymmetry than controls in association cortices of the frontal, temporal, and parietal lobes. Longitudinal PET data from the *mildly impaired* AD group suggested directionally stable asymmetry over time (mean duration from initial to final follow-up evaluations was 26 months), with an *increase* in the magnitude of metabolic asymmetry. However, the authors found a different pattern of results in the *moderately impaired* AD group. In this sample, over the duration of follow-up (mean 18 months), three of five patients (with at least three PET scans) exhibited an overall decrease in asymmetry, indicating a trend toward global deterioration in the later stages of dementia. Haxby et. al. showed some significant and expected relationships between metabolic asymmetry and impairment on verbal versus visuospatial neuropsychological measures, which will be explained below.

Neuropsychological Asymmetry and Associations with Physiological Asymmetry

Many more studies have examined the neuropsychological correlates of hemispheric asymmetry and some of these studies have larger sample sizes than the physiological studies reviewed above. It should be noted here that operational definitions of 'cognitive asymmetry' vary across the literature, and will be specified in context.

In the previously reviewed study by Wettstein and Lang (1990), these investigators found strong relationships between neuropsychological test performances and regional or hemispheric degeneration (see above for details). These early findings were important in reinforcing the lateralization of function that is also seen in a normal population and how those functions can diminish as a result of cortical atrophy. However, this article's approach to asymmetry was different from many others, in that patients were not assigned to asymmetric subgroups for analysis. In the Haxby et. al. (1990) investigation, divergent patterns of metabolic and neuropsychological asymmetry were found among mildly and moderately impaired patients with AD (N=11 and 13, respectively). The authors calculated four neuropsychological asymmetry indices to examine discrepancies between right hemisphere (visuospatial) and left hemisphere (verbal) function: Extended Range Drawing versus Syntax Comprehension; WAIS Perceptual Reasoning versus WAIS Verbal Comprehension; WAIS Perceptual Reasoning versus WAIS Memory and Freedom from Distractibility; and WMS immediate story recall versus WMS immediate visual reproduction. The authors examined the relationships between these neuropsychological discrepancies and the calculated regional (prefrontal, premotor, parietal, lateral temporal) cerebral metabolic asymmetry indices. Among moderately impaired patients, all neuropsychological discrepancies were correlated in the expected direction with regional cerebral metabolism. In mildly impaired patients, the only significant correlations were found when the sample was confined to patients who were also considered mildly impaired at final

evaluation. These significant correlations were found for the WAIS Perceptual Reasoning versus Verbal Comprehension indices, and the WMS verbal recall versus visual recall measures. This study is one of few that examined the longitudinal relationship between physiological (metabolic) asymmetry and neuropsychological asymmetry, and established that at some levels of impairment, this relationship is strong. Unfortunately, this study was also limited by a small sample size.

As mentioned previously, Kumar et al. (1994) found significantly greater cortical and ventricular CSF volume (a correlate of AD pathology), and a significantly greater degree of hemispheric asymmetry in patients with AD (N=34) than in healthy controls (N=28). Neuropsychological asymmetry was assessed by comparing performances on tests of verbal abilities (WMS Logical Memory Subtest, the California Verbal Learning Test, and the Boston Naming Test) with performances on tests of visuospatial/ visuoconstructive abilities (WMS Visual Reproduction and WAIS Block Design). For analysis of neuropsychological tests, the authors did not use an asymmetry index, but instead correlated regional CSF absolute values with test performance. They found significant inverse correlations between Block Design performance and right hemisphere and right ventricular CSF volumes, as well as between verbal learning performance and left ventricle CSF volume, as expected. Again, the authors here were interested in the relationship between asymmetry and neuropsychological test performance rather than assigning individuals to an asymmetric (or symmetric) subgroup.

Derflinger et. al. (2011) examined the relationship between gray-matter loss and neuropsychological test performances in patients with AD (n = 35), or amnestic MCI (n = 24). The authors found that performances on verbal tests (including Boston Naming and verbal fluency) were related to left hemisphere gray-matter volumes in both patients with aMCI and

AD. Unfortunately the authors did not utilize a test battery with visuospatial/visuoconstructive measures, and so could not examine relationships between performances on those types of measures with right hemisphere gray matter volumes.

As previously discussed, Rasmusson and Brandt (1995) examined autopsy data which suggested that physiological asymmetry was most likely the result of neuropathology in addition to AD or chance variation in individuals. Cognitive asymmetry profiles reflected the same. Asymmetry was calculated by two different but similar methods. The first involved converting raw test scores to z-scores and creating two composite (average) scores for verbal and spatial performance. If one composite score was below its group median and the other above its group median, the profile was considered asymmetric. The second method compared composite z-scores. A difference in scores with an absolute value of 1 or greater indicated asymmetry. Both methods found very few patients (out of a sample size of 59) asymmetric at all three time points (12-15% by method).

Features of neuropsychological asymmetry.

A number of studies which did not include costly imaging or autopsy data utilized cognitive neuropsychological indices to demonstrate asymmetry among patients with AD. Some of these studies have examined predictive factors (Finton et al., 2003; Jacobson, Delis, Bondi, & Salmon, 2005; Jacobson, Delis, Lansing, et al., 2005; Massman & Doody, 1996) and identified correlated asymmetric features (Massman & Doody, 1996) in attempts to help explain the nature and etiology of asymmetry. Massman and Doody studied 104 patients with probable AD and demonstrated that asymmetric performance on the Halstead-Reitan Finger Tapping Test (greater than expected right hand advantage; left hemisphere advantage) was associated with years of education, as well as with cognitive asymmetries (Verbal IQ vs Performance IQ, naming vs.

figure copying). Discrepancies were calculated by subtracting verbal and performance IQ scores or (verbal and visuospatial) subtest scaled scores. These findings suggest that greater education enhances verbal abilities and left-hemisphere resilience to the effects of AD, providing valuable insight to possible predictors of asymmetry.

It has been established that that the Apolipoprotein E (ApoE) ε4 allele is a risk factor for development of AD (Corder et al., 1993), and interestingly, this genetic risk factor is also associated with cognitive asymmetry in patients with probable AD (Finton et al., 2003; Jacobson, Delis, Bondi, et al., 2005) and even normal elderly controls (Jacobson, Delis, Lansing, et al., 2005). Finton and colleagues studied 200 patients with probable AD and found that patients homozygous for the ε4 allele performed worse on measures of nonverbal versus verbal abilities relative to patients heterozygous for the ε4 allele or with no ε4 alleles. Measures of verbal abilities were the Boston Naming Test, Controlled Oral Word Association, Token Test, and WAIS-R Vocabulary and Information subtests. Measures of visuospatial abilities were WAIS-R Picture Completion, Picture Arrangement, and Block Design subtests; and WMS-R Visual Reproduction I. Verbal and visuospatial composites were computed using the same method as the Rasmusson and Brandt (1995) approach outlined above. Studies with smaller sample sizes have implicated ApoE ε4 in cognitive asymmetry by demonstrating larger verbal versus visuospatial and local versus global processing discrepancies in clinical and normal populations (Jacobson, Delis, Bondi, et al., 2005; Jacobson, Delis, Lansing, et al., 2005).

The study that most closely approximates the methods of the current study is Strite, Massman, Cooke and Doody (1997), who found not only that 27.5% of 153 patients with probable AD have asymmetric cognitive profiles (10% low verbal, 17% low visuospatial), but also that asymmetric profiles are present at mild, moderate, and severe stages of dementia (as

categorized by Mini-Mental Status Exam [MMSE] scores). Strite and colleagues used previously published normative data to compute z-scores for the tests used in asymmetry analysis. Verbal or left-lateralized tests were the Boston Naming Test, and WAIS-R Comprehension, Vocabulary, and Similarities subtests. Visuospatial or right-lateralized tests were WAIS-R Block Design and Object Assembly; and WMS-R Immediate Visual Reproduction. Discrepancy scores were calculated by subtracting individual visuospatial factor scores from the verbal factor scores. Discrepancy scores of ±1 indicated an asymmetric cognitive profile. These authors established the presence of cognitive asymmetry across all stages of dementia severity using only cross-sectional data, and we now aim to establish that patterns of asymmetry persist within individuals throughout stages of dementia severity through utilizing longitudinal data obtained from a large sample of patients with AD.

In this review of the literature, some conflicting results were noted regarding the prevalence and course of asymmetry. One study suggested that asymmetry is the result of neuropathology in addition to AD (Rasmusson & Brandt, 1995), but others indicated that asymmetric profiles represent distinct subgroups of AD (Martin, 1990; Massman & Doody, 1996). Most studies with larger samples seem to suggest asymmetric profiles are indeed more prevalent than chance, and further, that these profiles remain stable through the course of the disease (Grady et al., 1986).

This review also brought to light a methodological issue present in the literature. That is, there seems to be no widely accepted method for operationalizing cognitive asymmetry. Across the studies reviewed here, there is substantial variation. Not all studies have examined asymmetry by using verbal and visuospatial composite scores, but even among those that have, they have differed in the number of measures included in each composite, as well as whether or

not either composite included a memory measure. The composites used in the present study include tests which were selected for their sensitivity to AD pathology. Composites are generated with and without memory measures (Memory-Included and Memory-Excluded) and were analyzed separately.

Purpose of the Present Study

A large body of research has established that the neuropathology of AD may differentially affect the hemispheres of the brain in a significant minority of patients, resulting in asymmetric patterns of cognitive deficits. However, there is disagreement within the literature on whether or not these asymmetric cognitive profiles are representative of distinct subgroups of AD or should be considered random variation. Much of the literature suggests that biomarker and demographic factors may contribute to the presence of these profiles, suggesting they may be more than random variation. An advantage of the current study is having access to a much larger sample than previous studies, allowing greater representativeness of the AD population. Another advantage is that data are available across several time points, representing a period of cognitive decline that is important for investigation. The present study will examine cognitive asymmetry in a large sample, over time, in order to provide evidence to clarify the discrepancies which have been found in other studies, and support the idea that these asymmetric cognitive profiles may represent distinct and clinically relevant subgroups of Alzheimer's Disease.

Hypotheses

*Hypothesis 1: Presence of asymmetry at baseline***.**

After creating composite z-scores for verbal and visuospatial neuropsychological tests, an asymmetry index (AI) was calculated for each patient enrolled. Based on earlier work,

approximately 30% of patients were expected to show an asymmetric cognitive profile (AI > ±1), with more of those patients asymmetric in the direction of low-visuospatial.

Hypothesis 2: Factors associated with asymmetry at baseline.

As many studies previously reviewed have shown, patients homozygous for the ApoE ε4 allele are significantly more likely to show both physiological and cognitive asymmetry than those who are heterozygous or who lack the ε4 allele altogether. The same result was expected here. We predicted also that higher education would be predictive of cognitive asymmetry, as previous work has shown that education enhances left hemisphere resilience to the effects of AD neuropathology. Specific predictions regarding other demographic variables were not made, as no previous literature has provided evidence of other predictors.

Hypothesis 3: Stability of asymmetry over time.

Given the large sample and extended time period available for analysis in the present study, we expected to replicate findings of various studies using a single data set, in order to clarify prior research and resolve some conflicting evidence. Specifically, we anticipated finding asymmetry to be directionally stable over time; that the *direction* of asymmetry does not change across time points. We predicted that asymmetry would decrease over time, as dementia severity increases, indicative of expanding AD neuropathology. Taken together with the prevalence of asymmetric cognitive profiles and other associated factors, this longitudinal stability was expected to provide evidence for asymmetric cognitive profiles as distinct AD subgroups with unique predictors and progression.

Methods

Participants

Participants were patients with probable AD enrolled in the Baylor Alzheimer's Disease and Memory Disorder Center (ADMDC) longitudinal cohort study. Use of this archival database was approved by the Baylor Institutional Review Board, and the study has also received approval from the University of Houston Committee for the Protection of Human Subjects (UH CPHS). Patients included in the study must have met criteria for a diagnosis of probable AD (McKhann et al., 1984) at every time point, including baseline, and have no comorbid neurological diagnoses. Participants were administered an extensive battery of neuropsychological tests (see below) at every evaluation. Evaluations were approximately annual, and ApoE ε4 status was obtained at baseline. It is noted here that the term *baseline* is used throughout this writing to refer to the first evaluation for which data were collected as a research participant in the ADMC longitudinal cohort study. It does not imply first ever evaluation for memory complaints, or premorbid evaluation.

Before the application of additional exclusion criteria, the dataset contained 953 participants. Age at baseline was restricted to exclude participants younger than 50 (n = 7), and older than 89 (n = 11). Eleven participants with baseline MMSE scores below 11 (considered "severe") were excluded. The test scores from these remaining 924 participants were used to calculate mean neuropsychological test performance. In order to calculate composites for asymmetry analysis, participants with insufficient test data [defined as missing either memory measure (for analyses in which the composites including memory measures were utilized), or having fewer than two non-memory measures per composite; n = 300] were excluded. Ultimately, 445 participants had enough data to generate both verbal and visuospatial Memory-Excluded composites, and 438 participants had enough data to generate verbal and visuospatial Memory-Included composites.

To enhance statistical validity of repeated measures, an acceptable range of time between evaluations was set (0.75 – 1.25 years [9-15 months]). A large number of the original 924 participants (n = 301) fell outside this range and were excluded from the longitudinal analyses. After *time between evaluations* and *sufficient data* criteria were applied, Memory-Excluded composites included data from 323 participants at baseline, and Memory-Included composites included data from 318 participants. For repeated measures analyses over two time points, these same criteria were applied to all successive time points. Ultimately, Memory-Excluded analysis across two time points contained data from 234 participants, and Memory-Included analysis contained data from 232 participants. Across three time points, 111 participants made up Memory-Excluded analysis, and 109 were analyzed with Memory-Included measures.

Measures

Data from selected portions of a standardized testing battery were used. Patients were administered the same tests at initial evaluation and all subsequent annual follow-ups.

Cognitive Status and Premorbid Abilities.

Mini Mental Status Exam (MMSE). The MMSE (Folstein, Folstein, & McHugh, 1975) is a brief 30-point measure designed to screen for dementia. It samples orientation, language, memory, calculation, and visuoconstruction. It is used here as an estimate of dementia severity.

American National Adult Reading Test (AMNART). The AMNART (Grober & Sliwinski, 1991) is a test of premorbid intellectual functioning, which involves the examinee reading aloud 45 irregularly spelled words (so the participant must be familiar with the word to pronounce it correctly). Resulting scores include an error score and an estimated premorbid verbal IQ score. Only AMNART errors were analyzed, since estimated premorbid verbal IQ also considers years of education.

Verbal Measures.

WAIS-R/III Similarities. The Similarities subtest of the WAIS-R/III (Wechsler, 1981, 1997) is a test of abstract verbal reasoning in which examinees are required to identify relationships between words. Each item is scored zero to two points with a total possible score of 38 points.

Boston Naming Test (BNT). The BNT (Kaplan, Goodglass, & Weintraub, 1983) contains 60 items in order of increasing difficulty which require the patient to name objects represented by line drawings. The test contains both high frequency, easy items, and low frequency, difficult items. The BNT measures word-retrieval difficulties common in a variety of neurological conditions. Raw scores were standardized using an established normative sample (Tombaugh & Hubiey, 1997).

Category Fluency (Animals). This test (Spreen & Benton, 1977) is designed to measure an individual's ability to spontaneously generate items belonging to a semantic category, in this case animals. Examinees are asked to generate as many items as possible in sixty seconds. When generating items from semantic categories, activity is lateralized to the left temporal lobe (Baldo, Schwartz, Wilkins, & Dronkers, 2006). Normative data for this measure are adapted from Tombaugh, Kozak, & Rees (1999).

WMS-R Logical Memory I (LM-I). The LM-I subtest of the WMS-R (Wechsler, 1987) consists of two short passages read aloud to participants by the examiner. Following this reading, the examinee must recall the story as close to verbatim as possible. The score of each story is a maximum of 25, and the two are summed together for a total 50 possible points on this subtest.

Visuospatial Measures.

WAIS-R/III Block Design. The Block Design subtest of the WAIS-R/III (Wechsler, 1981, 1997) tests spatial perception, problem solving, and abstract visual processing. Examinees must replicate an abstract figure using colored blocks. The subtest is scored on accuracy and time, with a maximum score of 64 points. For both Block Design and Similarities, data from the standardization sample were used in determining age-adjusted scaled scores.

Rey-Osterrieth Complex Figure (ROCF). The ROCF (Osterrieth, 1944) requires patients to copy and then reproduce from memory a complicated line drawing. A variety of cognitive faculties are engaged, but for the purposes of this study, the ROCF copy score was a test of visuospatial abilities. Eighteen design elements are scored for accuracy and location, so there are 36 possible points. Normative scores were derived from Meyers and Meyers (1996).

WMS-R Visual Reproduction I (VR-I). The VR-I subtest of the WMS-R (Wechsler, 1987) is a test of visual memory which involves presenting the examinee with four cards with figures on them. The first three cards contain one figure, while the fourth contains two figures. After each card is presented for ten seconds, the examinee must draw the figure or figures they saw on that card. A total of 41 points are possible, with differential point values on each card. For both WMS-R subtests, standardized scores were derived using the normative sample of Ivnik et al. (1992).

Standardization of test scores

Raw scores for all subtests were converted to z-scores using relevant published norms (see above). Due to the presence of some extreme standardized scores (which could exert inordinate weight on the composite scores), data for all tests underwent 95% Winsorization (Hastings Jr, Mosteller, Tukey, & Winsor, 1947) prior to analysis. Composite scores were intended to be calculated by averaging within-domain test z-scores. However, inspection of Winsorized test

means revealed problematic differences in mean and standard deviation values between tests, due to vagaries of the normative data (particularly for the RCFT, with its high mean scores and small SDs in the normative sample, which can yield very low z-scores and high sample SDs of these z-scores). To address this issue, composite scores were generated instead by calculating deviation scores for each test by subtracting overall test mean Z-score from age-normed Z-score and dividing by the standard deviation across all tests in the composite. The following example shows how a participant's BNT score was calculated using actual study data.

$$Deviation\ Score_{BNT} = \frac{Age\ normed\ Z\ score_{BNT} - Mean\ Z_{BNT}}{SD_{Tests\ within\ verbal\ composite}} = \frac{-1.373 - (-1.199)}{1.268}$$

$$= -0.137$$

$$Composite = \frac{\sum Deviation\ Scores}{[\#\ of\ tests\ in\ composite]}$$

Composites were calculated with and without memory measures included. The *verbal (memory-excluded)* composite is the mean of available scores from WAIS-R/III Similarities, Boston Naming Test, and Category Fluency z-scores. The *verbal (memory-included)* composite also includes WMS-R Logical Memory I, and is calculated by the same method. The *visuospatial (memory-excluded)* composite is the mean of z-scores from WAIS-R/III Block Design, and Rey-Osterrieth Complex Figure copy. The *visuospatial (memory-included)* composite includes WMS-R Visual Reproduction I.

Defining asymmetry

The visuospatial composite (mean) z-score was subtracted from the verbal composite (mean) z-score, yielding an asymmetry index (AI; shown below), from which we determined if an appreciable difference exists, and in what direction.

$$Asymmetry\ Index\ (AI) = Composite_{Verbal} - Composite_{Visuospatial}$$

Using this equation, an AI of ±1 or greater indicated a difference of at least one standard deviation between composites. A positive AI indicated a relatively higher verbal composite score (Low Visuospatial subgroup), whereas a negative AI described a relatively higher visuospatial composite score (Low Verbal subgroup). These categorizations were used in later analyses.

Results

Analysis of Larger Baseline Sample

Demographics.

Of the 924 participants with baseline data, 67.3% were female, and 94.4% were non-Hispanic Caucasians. The mean age of participants was 74.12 (*SD* = 8.06). Participants had a mean estimated symptom duration of 3.58 years (*SD* = 2.01). Education was analyzed categorically, with participants grouped by having fewer than 12, 12, and greater than 12 years of education. The groups contained 112 participants (12.2%), 267 participants (29.0%), and 542 participants (58.8%), respectively. ApoE ε4 status was obtained from 833 participants. Of these, 13.6% (*n* = 113) were homozygous for the allele, 49.2% (*n* = 410) were heterozygous for the allele, and 37.2% (*n* = 310) lacked the allele altogether.

Test performance.

Performance on neuropsychological tests was also examined in the entire baseline sample. Winsorized means were calculated prior to generation of composite scores. Winsorized and non-Winsorized test means are presented in Table 1 below. As anticipated for this sample of Alzheimer's patients, age-normed performance on neuropsychological measures was generally below expected values. The proportion of values for each test which were Winsorized varied across measures. For example, as discussed earlier, due to ceiling effects of Rey-Osterrieth Complex Figure copy scores in the normative sample, performance of many participants yielded

extremely low z-scores, leading to Winsorization of a larger proportion of those values. Performance on Similarities and Block Design subtests are reported separately for WAIS-R and WAIS-III.

Table 1.

Mean Baseline Performance on Neuropsychological Tests, Whole Sample

	Unadjusted		95% Winsorized		% values adjusted
Test	Mean	SD	Mean	SD	
MMSE[a] (n = 942)	20.41	4.93			
Similarities (overall; n = 888)	-0.670	1.017	-0.693	0.971	8.7%
WAIS-R Similarities[b] (n = 533)	-0.664	0.993			
WAIS-III Similarities[b] (n = 355)	-0.680	1.053			
BNT (n = 913)	-1.672	1.901	-1.604	1.721	7.1%
Animals (n = 861)	-1.945	1.098	-1.957	1.034	0.9%
LM I (n = 942)	-2.044	0.714	-1.984	0.824	0.1%
RCFT copy (n = 463)	-3.032	4.136	-2.157	2.074	21.6%
Block Design (overall; n = 864)	-1.014	1.019	-1.022	0.999	3.6%
WAIS-R Block Design[b] (n = 511)	-1.053	1.014			
WAIS-III Block Design[b] (n = 353)	-0.958	1.025			
VR I (n = 942)	-1.863	0.973	-1.792	1.049	1.0%

Note. [a]Mean raw score is presented. [b]Winsorized z-scores are not reported for these subtests separately, as they are not handled separately in the analysis.

Discrepancies between unadjusted z-scores on Similarities and Block Design were calculated and analyzed using independent samples *t*-tests to determine if there were significant differences between the WAIS-R versus WAIS-III versions. This analysis only included participants who were included in asymmetry analysis (had sufficient data to merit inclusion in analysis). While significant differences existed in performance on the subtests themselves [Similarities, $t(442) = 3.93$, $p < .001$; Block Design, $t(443) = 4.25$, $p < .001$], the differences between the subtests were not significantly different on the WAIS-R versus the WAIS-III [$t(442) = -0.31$, $p = .758$). For this reason, subtest scores from both WAIS versions were included in further analysis.

Correlations among non-Winsorized test scores at baseline are presented in table 2, and correlations among Winsorized test scores in table 3, below. All tests were significantly correlated with one another, but correlations within composites were generally higher than correlations across composites. Exceptions to this were present and are explored later.

Table 2.

Correlations Between Baseline Unadjusted Neuropsychological Test Scores, Whole Sample

	Sim	BNT	Animals	LM I	RCFT	BD
BNT	.56[a]	-				
Animals	.36[a]	.43[a]	-			
LM I	.46[a]	.41[a]	.34[a]	-		
RCFT	.29[a]	.14[a]	.15[a]	.24[a]	-	
BD	.49[a]	.33[a]	.35[a]	.35[a]	.59[a]	-
VR I	.34[a]	.26[a]	.29[a]	.40[a]	.35[a]	.51[a]

Note. [a]$p < .01$, two-tailed. Shaded values represent correlations within composites.

Table 3.

Correlations Between Baseline Winsorized Neuropsychological Test Scores, Whole Sample

	Sim	BNT	Animals	LM I	RCFT	BD
BNT	.52[a]	-				
Animals	.35[a]	.46[a]	-			
LM I	.38[a]	.38[a]	.26[a]	-		
RCFT	.36[a]	.20[a]	.19[a]	.22[a]	-	
BD	.49[a]	.27[a]	.28[a]	.27[a]	.63[a]	-
VR I	.30[a]	.23[a]	.25[a]	.29[a]	.42[a]	.47[a]

Note. [a]$p < .01$, two-tailed. Shaded values represent correlations within composites.

Asymmetry at baseline.

Hypothesis 1: Presence of asymmetry at baseline. Composite scores at baseline were calculated both with and without memory measures included. It should be noted here that a significant discrepancy existed between the number of participants with complete verbal compared to visuospatial composites (n = {924, 439}), since the RCFT was added to the battery

at a later time than the remaining measures. Mean composite and AI values were calculated by excluding participants who did not have valid data for both. In order to determine whether the inclusion of memory measures significantly altered the mean composite scores or mean AI value, paired samples t-tests were performed. The inclusion of memory measures in composites significantly decreased the verbal composite scores, $t(437) = 3.749$, $p < .001$. But adding the memory measures did not significantly alter the visuospatial composite scores or the AI values [$t(437) = .497$, $p = .62$; $t(437) = 1.648$, $p = .100$, respectively]. AI values with and without memory measures were significantly correlated with one another ($r = .96$, $p < .001$), and agreement between asymmetry classification with and without memory measures was good (Kendall's tau-b; $r_\tau = .84$, $p < .001$). However, it should be noted that the inclusion of memory measures in composite score and AI calculations did slightly alter the relative proportions of participants in each asymmetry classification, with a tendency toward an increasing proportion of patients in the Symmetric category. These results are summarized in table 4, below.

Table 4.

Composite and Asymmetry Index Descriptive Statistics

	Scale	N	Mean	SD
Memory-Excluded	Verbal Composite	445	0.187	0.700
	Visuospatial Composite		0.090	0.891
	AI		0.096	0.901
		Low Verbal	Symmetric	Low Visuospatial
	Asymmetry Classification	11.5%	72.3%	16.2%
	Scale	N	Mean	SD
Memory-Included	Verbal Composite	438	0.162	0.624
	Visuospatial Composite		0.094	0.810
	AI		0.068	0.791
		Low Verbal	Symmetric	Low Visuospatial
	Asymmetry Classification	8.4%	78.5%	13.0%

The results presented in table 3 partially support the hypothesis that predicted approximately 30% of participants would be classified as asymmetric (27.7% Memory-Excluded classification), although the proportion was less similar when memory measures were included. Furthermore, in both classifications, more of these participants were considered Low Visuospatial (16.2% versus 11.5%), which supported the hypothesis.

Hypothesis 2: Factors associated with asymmetry at baseline. Chi-square analysis was performed to detect significant relations between asymmetry classifications (according to both Memory-Excluded and -Included composites) with demographic variables including sex, ApoE ε4 genotype (coded as the number of ε4 alleles), and education (coded as less than 12 years, 12 years, and greater than 12 years education). The relation between sex and Memory-Included asymmetry classification was significant such that females were more likely to be classified as Symmetric, χ^2 (2, N = 438) = 8.98, $p < .05$. However, this association was not significant for Memory-Excluded asymmetry classification. The relation between ApoE ε4 genotype and

Memory-Excluded asymmetry classification was significant, χ^2 (4, N = 432) = 10.83, $p < .05$. The presence of two ε4 alleles was associated with greater likelihood of asymmetric classification, and seemingly in the direction of Low Visuospatial. When examining asymmetry classification with memory measures, the relation was non-significant. Asymmetry category was also coded as a binary variable to collapse both directions of asymmetry for chi-square analysis. Across the same demographic variables, education (as a nominal variable), ApoE ε4 status, and sex, the only significant relation that emerged was between sex and binary asymmetry classification, but only for classification which included memory measures, χ^2 (1, N = 438) = 8.98, $p < .01$. In this case, females were again more likely classified Symmetric, and men more likely to be Asymmetric (Low Verbal or Low-Visuospatial).

Next, Memory-Excluded asymmetry classification group means were compared for demographics including age at baseline, years of education, estimated symptom duration, AMNART-estimated premorbid IQ, AMNART Error score, MMSE, and GDS. An analysis of variance showed that the effect of asymmetry classification was significant for age at baseline [F(2,442) = 21.75, $p < .001$], but no other demographic variables. The proportions of females in each classification (61.1% to 68.9%) were similar to the proportion in the whole sample (67.1%). Among Low Verbal performers, most (52.9%) carried no ε4 alleles while 35.3% were heterozygous. In the Symmetric classification, 48.6% were heterozygous for the allele and 36.4% did not carry the allele. For Low Visuospatial performers, most (47.1%) of the group was heterozygous, and the proportions of homozygous participants and those who are not carriers were approximately evenly split. Significant differences existed between groups for AMNART-estimated premorbid IQ [F(2,418) = 4.91, $p < .01$], number of errors on AMNART [F(2,417) = 5.24, $p < .01$], and baseline GDS [F(2, 433) = 3.26, $p < .05$].

Table 5.
Differences Between Asymmetry Group Means of Demographic and Other Baseline Variables (Memory-Excluded)

		Mean (SD)		
		Low Verbal (n = 51)	Symmetric (n = 322)	Low Visuospatial (n = 72)
Age at baseline[a]		77.15 (5.52)[2]	75.18 (7.51)[2]	69.18 (9.38)
% Female		64.7%	68.9%	61.1%
ApoE ε4 alleles	0	52.9%	36.4%	27.9%
	1	35.3%	48.6%	47.1%
	2	11.8%	15.0%	25.0%
Estimated symptom duration (years)		3.63 (2.07)	3.47 (1.95)	3.62 (1.97)
AMNART[a]		105.74 (10.00)[1,2]	110.42 (9.74)	110.53 (10.44)
AMNART Errors[a]		23.94 (10.44)[1,2]	19.04 (9.94)	18.69 (10.13)
MMSE		21.25 (4.57)	21.76 (4.23)	21.94 (4.01)
GDS[b]		7.00 (5.26)[1]	5.34 (4.34)	6.06 (4.78)
Verbal Composite		-0.515 (0.49)	0.224 (0.67)	0.516 (0.41)
Visuospatial Composite		0.938 (0.46)	0.192 (0.81)	-0.964 (0.39)
AI		-1.452 (0.36)	0.032 (0.52)	1.480 (0.29)

Note. [a]$p < .01$, [b]$p < .05$, [1]Significant difference from Symmetric, [2]Significant difference from Low Visuospatial.

Post-hoc analysis using the Tukey adjusted criterion for significance indicated that the average age of participants in the Low Visuospatial asymmetry classification was younger than that of participants in the Low Verbal and Symmetric groups. Low Verbal participants had significantly lower estimated premorbid IQ than Symmetric and Low Visuospatial participants. Low Verbal participants also had significantly higher number of errors on the AMNART compared to Symmetric and Low Visuospatial participants.

Analysis of variance was also used to compare demographics by Memory-Included asymmetry classification. Groups only differed on age at baseline evaluation, $F(2,435) = 12.06$, $p < .001$. In this case, lower proportions of the asymmetric subgroups were female, while in the Symmetric subgroup, the proportion was more similar to the whole sample. Most Low Verbal participants carried no ε4 alleles, but a large minority was heterozygous for the allele. Among Symmetric participants, 47.2% were heterozygous while 36.1% carried no alleles. In the Low Visuospatial group, 46.3% were heterozygous and 33.3% carried no alleles. The results are presented in table 6.

Table 6.

Differences Between Asymmetry Group Means of Demographic and Other Baseline Variables (Memory-Included)

		Mean (SD)		
		Low Verbal (n = 37)	Symmetric (n = 344)	Low Visuospatial (n = 57)
Age at baseline[a]		76.24 (7.42)[2]	74.95 (7.38)[2]	69.78 (9.82)
% Female		54.1%	70.6%	54.4%
ApoE ε4 alleles	0	51.4%	36.1%	33.3%
	1	40.5%	47.2%	46.3%
	2	8.1%	16.7%	20.4%
Estimated symptom duration (years)		3.51 (1.93)	3.49 (1.98)	3.69 (2.07)
AMNART		107.20 (9.61)	110.11 (9.94)	110.18 (10.62)
AMNART Errors		22.68 (10.26)	19.32 (10.13)	19.05 (10.19)
MMSE		21.92 (4.56)	21.68 (4.31)	22.05 (3.88)
GDS		6.03 (5.21)	5.49 (4.47)	6.24 (4.86)
Verbal Composite		-0.461 (0.43)	0.177 (0.62)	0.472 (0.42)
Visuospatial Composite		0.916 (0.37)	0.167 (0.75)	-0.884 (0.35)
AI		-1.377 (0.37)	0.010 (0.52)	1.355 (0.23)

Note. [a]$p < .001$, [1]Significant difference from Symmetric, [2]Significant difference from Low Visuospatial.

Post hoc comparisons were performed using Tukey adjusted significance criterion. Participants classified as Low Visuospatial were significantly younger than participants classified as Low Verbal or Symmetric.

Additional group comparisons examined differences in asymmetry *index*, as opposed to asymmetry *classification*, by sex, ApoE ε4 genotype, and education level (coded in three levels,

as before). No significant differences in AI values were found based on sex or education. Analysis of variance showed significant differences in AI between ApoE ε4 genotype groups, for both Memory-Excluded [$F(2,429) = 3.91$, $p < .05$] and Memory-Included [$F(2,423) = 4.86$, $p < .01$] AI. Post-hoc analysis using the Tukey post-hoc criterion for significance showed the mean AI values (Memory-Excluded and -Included) for ε4 homozygous participants ($M = 0.27$, $SD = 0.92$; $M = 0.25$, $SD = 0.77$) was significantly higher than that of participants who lacked the ε4 allele ($M = -0.06$, $SD = 0.94$; $M = -0.08$, $SD = 0.83$), but not significantly different from those heterozygous for the ε4 allele. The results of this analysis suggest that ε4 homozygosity (versus having no ε4 alleles) was associated with more positive AI values (relatively lower visuospatial composites). To fully appreciate the relationship between ε4 genotype and AI, the latter was also recoded into an absolute value index so that asymmetry would be collapsed across directions. Analysis of variance showed no significant difference between ApoE groups in these absolute AI values. Correlations were computed between absolute value of AI and MMSE at baseline. With memory measures excluded or included, the correlations were weak and non-significant. Thus, cross-sectionally, greater dementia severity was not associated with more symmetric cognitive profiles.

Linear regression was performed to examine the prediction of AI values from demographic variables, MMSE scores, AMNART errors, and number of ApoE ε4 alleles. Regression analyses were performed using Memory-Excluded and Memory-Included AI values as the dependent variables. Beginning with the Memory-Excluded analysis, demographic predictors (age at baseline, sex, and categorical education) were entered first. In this model, age was the only significant predictor, such that older age predicted lower AI [$\beta = -0.258$, $t(405) = -5.38$, $p < .001$]. Overall variance in AI predicted by the model was R^2 (adjusted) = .064, $F(1,405)$

= 28.906, $p < .001$. The second model added baseline MMSE, AMNART errors, and number of ApoE ε4 alleles as predictive variables. AMNART errors [β = -0.129, $t(402) = -2.54$, $p < .05$] and MMSE scores [β = -0.118, $t(402) = -2.30$, $p < .05$] predicted lower AI, and ApoE ε4 genotype [number of ε4 alleles; β = .094, $t(402) = 1.97$, $p < .05$] was predictive of AI in the positive direction (greater number of ε4 alleles predicted high AI. The adjusted variance predicted was R^2 =.087, $F(4,402) = 10.63$, $p < .001$. The additional variables in the second model significantly improved the predictive ability of the model, $F(3,402) = 4.30$, $p < .01$. Next, AI with memory measures was analyzed. The same regression models were compared. In the first model, age at baseline as well as education were significant predictors of AI, such that older age predicted more negative asymmetry, β = -0.210, $t(402) = -4.31$, $p < .001$, as did greater education, β = -0.106, $t(402) = -2.18$, $p < .05$. Overall variance predicted by this model was R^2 = 0.048, $F(2,402) = 11.23$, $p < .001$. The next model, including additional predictors, yielded effects for MMSE [β = -0.125, $t(399) = -2.42$, $p < .05$], AMNART errors [β = -0.166, $t(399) = -3.13$, $p < .01$], and number of ε4 alleles (β = 0.118, $t(399) = 2.47$, $p < .05$). The addition of these variables to the model significantly improved predictive capacity of the model [$F(3,399) = 6.16$, $p < .001$). Variance predicted by this model was $R^2 = 0.083$, $F(5,399) = 4.83$, $p < .001$. In both Memory-Excluded and –Included analyses, age at baseline, baseline MMSE, AMNART errors, and ApoE genotype were significant predictors of the AI. Interestingly, education was predictive of Memory-Included AI when added into the model. While no hypotheses were made about how demographic variables such as age or sex would be related to degree and direction of asymmetry, it was hypothesized that ApoE ε4 genotype and education, would be significantly predictive of greater asymmetry, with greater education contributing to higher overall verbal performance. Indeed ApoE genotype was significantly predictive of asymmetry, although the findings

regarding education are equivocal, to the extent that education was, in this case, predictive of lower relative verbal performance, but only when memory measures were included.

Analysis of Longitudinal Sample

Longitudinal sample compared to excluded participants.

The participants in the longitudinal sample were compared, on demographic and other factors, to the participants who were in the baseline sample but excluded from longitudinal analysis, for failing to meet criteria for inclusion. Independent samples t-tests as well as chi-square analysis were performed, and participants did not differ on age, baseline MMSE, or AMNART errors at baseline. There was no significant association between assignment to either sample and sex, number of ε4 alleles, or education. However, independent sample t-tests did reveal significant differences in asymmetry index, both excluding and including memory measures [$t(436) = 2.57$, $p = .011$ and $t(443) = 2.18$, $p = .03$, respectively]. Mean Memory-Excluded AI for participants in the longitudinal sample was -0.003 ($SD = 0.926$) and 0.211 ($SD = 0.926$) for participants not in longitudinal analysis. Mean Memory-Included AI for participants included and not included in longitudinal analysis was -0.007 ($SD = 0.652$) and 0.186 ($SD = 0.818$), respectively.

Demographics.

After exclusion criteria were applied, 323 participants remained for longitudinal analysis across baseline and at least one follow up. Of these, 66.9% were female, and 95.4% were non-Hispanic Caucasian. The mean age of participants was 74.49 ($SD = 7.45$). Participants' mean estimated symptom duration was 3.55 years ($SD = 1.99$). 31 participants (9.6%) attained fewer than 12 years of education, 88 (27.3%) completed 12 years, and 203 (63.0%) completed more than 12 years of education. ApoE status was obtained from 317 of these participants. 17.7% (n =

56) were homozygous for the ε4 allele, 47.0% were heterozygous, and 35.3% of the sample lacked the allele altogether.

Test Performance.

Performance on neuropsychological tests at baseline was analyzed. As above, Winsorized means were calculated, and both Winsorized and non-Winsorized test means are presented in table 7, below.

Table 7.
Mean Baseline Performance on Neuropsychological Tests, Longitudinal Sample

	Unadjusted		Winsorized		% values adjusted
Test	Mean	SD	Mean	SD	
MMSE[a]	21.76	4.16			
Similarities	-0.471	0.979	-0.495	0.930	4.0%
BNT	-1.212	1.681	-1.199	1.636	1.9%
Animals	-1.822	1.153	-1.850	1.000	1.6%
LM I	-1.955	0.734	-1.955	0.734	0.0%
RCFT copy	-2.967	4.149	-2.250	2.339	16.7%
Block Design	-0.708	0.981	-0.723	0.945	2.2%
VR I	-1.674	1.036	-1.686	0.999	1.9%

Note. [a]Mean raw score is presented.

Correlations among non-Winsorized test scores are presented in table 8, and correlations among Winsorized test scores in table 9, below. Test scores were all significantly correlated with one another ($p < .01$). However, correlations were *generally* higher within (0.31 to 0.64) than across composites (0.16 to 0.51).

Table 8.

Correlations Between Baseline Unadjusted Neuropsychological Test Scores, Longitudinal Sample

	Sim	BNT	Animals	LM I	RCFT	BD
BNT	.49[a]	-				
Animals	.34[a]	.41[a]	-			
LM I	.45[a]	.36[a]	.31[a]	-		
RCFT	.32[a]	.16[a]	.19[a]	.28[a]	-	
BD	.51[a]	.26[a]	.26[a]	.35[a]	.59[a]	-
VR I	.32[a]	.21[a]	.24[a]	.32[a]	.36[a]	.47[a]

Note. *$p < .01$, two-tailed. Shaded values represent correlations within composites.

Table 9.

Correlations Between Baseline Winsorized Neuropsychological Test Scores, Longitudinal Sample

	Sim	BNT	Animals	LM I	RCFT	BD
BNT	.50[a]	-				
Animals	.37[a]	.45[a]	-			
LM I	.45[a]	.37[a]	.33[a]	-		
RCFT	.39[a]	.22[a]	.24[a]	.30[a]	-	
BD	.51[a]	.25[a]	.28[a]	.34[a]	.64[a]	-
VR I	.32[a]	.21[a]	.28[a]	.31[a]	.43[a]	.47[a]

Note. [a]$p < .01$, two-tailed. Shaded values represent correlations within composites.

Asymmetry at baseline.

As above, composite scores at baseline were calculated both with and without memory measures included. Paired samples *t*-tests were performed to detect differences between AIs that

exclude or include memory measures. In this smaller sample, including memory measures in composites did not significantly alter either verbal or visuospatial composite scores, or the degree of asymmetry [$t(317) = -.144$, $p = .886$; $t(317) = .216$, $p = .829$; $t(317) = -.278$, $p = .781$, respectively]. AI values with and without memory measures were significantly correlated with one another ($r = .96$, $p < .001$). Asymmetry classification with and without memory measures showed moderately good agreement (Kendall's tau-b; $r_\tau = .64$, $p < .001$). In this smaller sample, the inclusion of memory measures in composite scores seemed to have a more pronounced impact on the relative proportions of participants in each asymmetry classification, again with increased classification as Symmetric. These results are summarized in Table 10, below.

Table 10.
Composite and Asymmetry Index Descriptive Statistics

	Scale	N	Mean	SD
Memory-Excluded	Verbal Composite	323	-0.003	0.753
	Visuospatial Composite		0.000	0.898
	AI		-0.004	0.926
		Low Verbal	Symmetric	Low Visuospatial
	Asymmetry Classification	14.2%	71.8%	13.9%
	Scale	N	Mean	SD
Memory-Included	Verbal Composite	318	0.001	0.609
	Visuospatial Composite		0.008	0.620
	AI		-0.007	0.652
		Low Verbal	Symmetric	Low Visuospatial
	Asymmetry Classification	6.3%	87.7%	6.0%

Hypothesis 3: Stability of asymmetry over time.

Asymmetry classification across time. A variety of methods were used to assess the degree to which asymmetric profiles remain stable over time. Given that sample sizes changed

over time due to attrition, additional exclusion criteria were applied across time points. For example, when analyzing data across three evaluations, participants were excluded if the time elapsed between their second and third evaluations (or between their first and second, as applied earlier) was outside the acceptable range, or if insufficient data was available at any time point. Separate analyses were conducted for participants with only one follow-up evaluation (two time points total) and two follow-up evaluations. As in previous samples, asymmetry classifications which exclude or include memory measures are presented separately.

Across successive time points, the proportions of participants who were classified in one of the asymmetric groups decreased (i.e., Symmetric classification increased). Examining classifications without memory measures, participants classified as Symmetric at baseline were 71.8% of the sample. At second evaluation, 73.1% were Symmetric and at third evaluation, 81.4% were Symmetric. The same directional trend was also evident when memory measures were included in the composites. At baseline, 87.7% of participants were Symmetric. This proportion remained similar at first follow up (87.6%), but then increased to 92.4% at the second follow-up. When data are restricted by exclusion criteria, the proportions are different. Table 11 provides an overview of this information. Qualitatively, there was a distinct difference in relative proportions of asymmetry classifications based on whether or not memory measures are taken into account. The inclusion of memory measures resulted in a greater proportion of the sample being classified as Symmetric, or considered to be more globally impaired. While it appears there are not large differences in asymmetry classifications between baseline and first follow up evaluations (approximately one year apart), a greater proportion of the sample was classified as Symmetric at second follow up (approximately two years after baseline evaluation). It was predicted that the proportion of participants that would be classified as *asymmetric* (in either

direction) would be approximately 30%, Baseline classifications that do not incorporate memory measures were found to be relatively close to this predicted percentage, and within the range of proportions of asymmetric cognitive profiles elsewhere in the literature (see Introduction).

Table 11.
Proportions of Asymmetry Across Evaluations

	Evaluation	N	Low Verbal (% of sample)	Symmetric (% of sample)	Low Visuospatial (% of sample)
Memory-Excluded	Baseline	234	14.1	73.5	12.4
	Follow up 1		12.0	73.1	15.0
	Baseline	111	14.4	76.6	9.0
	Follow up 1		9.9	80.2	9.9
	Follow up 2		8.1	81.1	10.8
Memory-Included	Baseline	232	6.5	87.5	6.0
	Follow up 1		6.0	87.5	6.5
	Baseline	109	4.6	89.9	5.5
	Follow up 1		3.7	89.9	6.4
	Follow up 2		3.7	92.7	3.7

Correlations between AI values across time points were calculated to examine the extent to which the index fluctuates similarly across time. Again, data were analyzed within subsets of the sample which had no invalid data in any of the time points in question. Positive, moderately strong, significant correlations (r = .63 to .75, all two-tailed $p < .01$) existed between AI values across time points.

Table 12.
Correlations of AI (Memory-Excluded) Across Evaluations

		Follow up 1	Follow up 2
Baseline + 1 eval (n = 234)	Baseline	.73[a]	
Baseline + 2 evals (n = 111)	Baseline	.65[a]	.63[a]
	Follow up 1	-	.63[a]

Note. [a]$p < .01$ two-tailed significance test.

Table 13.
Correlations of AI (Memory-Included) Across Evaluations

		Follow up 1	Follow up 2
Baseline + 1 eval (n = 232)	Baseline	.75[a]	
Baseline + 2 evals (n = 109)	Baseline	.68[a]	.64[a]
	Follow up 1	-	.69[a]

Note. [a]$p < .01$ two-tailed significance test.

Next, the stability of asymmetry classification across evaluations was assessed. Inspection of crosstabulations for each comparison provided information about participants' change in asymmetry classification from one evaluation to another. It was hypothesized that although asymmetry classification could change in some participants from asymmetric to symmetric, no participants should change from one asymmetric category to the reverse asymmetric category. This was supported by the analysis; no patients changed from the Low Verbal to the Low Visuospatial classification or vice versa. The percentage of participants that

did change classification between successive evaluations ranged from 8.4% to 26.1%. Cohen's Kappa was used as a measure of agreement between asymmetry classifications at different time points. For analysis which examined stability across more than two evaluations, Cohen's Kappa was calculated between each evaluation and the three resulting values were averaged. This average Kappa equally weights agreement between all evaluations to generate an overall measure of stability. As in previous analyses, data were analyzed separately for classifications which excluded or included memory measures, and further subdivided by the number of evaluations participants had. Tables 14 and 15 include inter-evaluation Kappa as well as average Kappa across time points, where applicable, and separately for classification excluding and including memory measures, respectively. Kappa values between 0.2 and 0.4 are considered moderate agreement, and values from 0.6 to 0.8 are considered good agreement beyond chance.

Table 14.
Cohen's Kappa Between Asymmetry Classification (Memory-Excluded) Across Evaluations

		Follow up 1	Follow up 2	Mean Kappa
Baseline + 1 eval (n = 234)	Baseline	.390[a]		
Baseline + 2 evals (n = 111)	Baseline	.305[a]	.370[a]	.313
	Follow up 1	-	.265[a]	
Note. [a]$p < .01$ that agreement is different from 0.				

Table 15.
Cohen's Kappa Between Asymmetry Classification (Memory-Included) Across Evaluations

		Follow up 1	Follow up 2	Mean Kappa
Baseline + 1 eval (n = 232)	Baseline	.467[a]		
Baseline + 2 evals (n = 109)	Baseline	.409[a]	.382[a]	.428
	Follow up 1	-	.494[a]	
Note. [a]$p < .01$ that agreement is different from 0.				

Degree of asymmetry across time. Additional investigation into the extent and stability of asymmetry over time was performed using repeated measures ANCOVA. As in previous analyses, results are presented separately for AI values which exclude or include memory measures. Table 16 includes descriptive information for the Memory-Excluded and -Included AI over time, segregated by baseline asymmetry classification.

Table 16.
Mean and SD of AI Across Time Points, by Baseline Asymmetry Classification (Memory-Excluded and Memory-Included)

		Mean (SD)		
	Time point	Low Verbal	Symmetric	Low Visuospatial
Memory-Excluded	1	-1.487 (0.407)	-0.016 (0.504)	1.529 (0.345)
	2	-1.023 (0.862)	-0.004 (0.709)	1.146 (0.724)
	1	-1.377 (0.265)	-0.038 (0.516)	1.635 (0.344)
	2	-0.667 (0.689)	-0.061 (0.628)	1.178 (0.839)
	3	-0.629 (0.668)	0.066 (0.638)	0.939 (0.827)
Memory-Included	1	-1.312 (0.306)	-0.012 (0.479)	1.292 (0.156)
	2	-1.210 (0.663)	0.029 (0.533)	0.910 (0.553)
	1	-1.170 (0.096)	-0.065 (0.472)	1.339 (0.114)
	2	-0.908 (0.749)	-0.019 (0.469)	0.919 (0.711)
	3	-0.838 (0.690)	0.028 (0.509)	0.638 (0.745)

Analysis of participants who had data at two consecutive evaluations including baseline was performed with age at baseline and AMNART error scores as covariates, and baseline asymmetry classification (based on Memory-Excluded AI) as the between-group factor. Covariates were chosen based on what predictors were significant in baseline regression analysis. The analysis revealed no main effect of time on AI. There was, however, a significant interaction between time and baseline asymmetry classification, $F(2,223) = 13.96$, $p < .001$. AI in both asymmetric groups decreased (in absolute value) while Symmetric participants remained relatively stable, close to zero. When expanded to include a third evaluation, again no main effect of time was noted. The interaction of time and baseline asymmetry classification was significant, such that AI again decreased (in absolute value) in both asymmetry classifications, and remained near zero in the Symmetric classification, $F(4,202) = 10.13$, $p < .001$.

Next, repeated measures analysis was performed for the memory-inclusive AI in the same way as above, with education added as a covariate, as it emerged as a significant predictor in the baseline regression. Again, the between-group variable was the memory-inclusive asymmetry group classification, this time based on the memory-inclusive AI. Across two time points, there was no main effect of time. The interaction of time and asymmetry classification was again significant, $F(2,219) = 5.522$, $p = .007$. Low Verbal and Symmetric participants had little change in AI between evaluations, while Low Visuospatial mean AI decreased (in absolute value) over time. Including a third evaluation in the analysis yielded similar results. There was no main effect of time, and the interaction between time and asymmetry classification was significant as before, with AI of both asymmetry classifications becoming closer to zero, and remaining close to zero for Symmetric participants, $F(4,194) = 4.58$, $p = .001$.

To address the hypothesis of diminishing asymmetry being associated with increasing severity of cognitive impairment, correlations between changes in MMSE and AI absolute values were examined. This was performed for Memory-Excluded and Memory-Included AI. Interestingly, there were no significant correlations between these difference scores. A follow-up analysis of MMSE scores at different time points revealed that mean MMSE did not differ between baseline asymmetry classifications at any time point. This result was the same for Memory-Included asymmetry classification. These data are summarized in table 17, below.

Table 17.
Mean and Standard Deviation of MMSE by Evaluation Number, Collapsed Across All Asymmetry Groups

	Time Point	Mean	SD
Memory-Excluded (n = 111)	1	23.16	3.20
	2	21.72	3.71
	3	20.34	4.49
Memory-Included (n = 109)	1	23.18	3.23
	2	21.74	3.75
	3	20.44	4.47

The above analyses suggest that while MMSE does tend to decrease over time, there are not differential effects of dementia severity on the presence or direction of baseline asymmetry.

Discussion

Hypothesis 1

Many published studies which have examined aspects of cognitive asymmetry have not aimed to describe asymmetric cognitive profiles themselves, and as such, may not report proportions of their samples which are classified into asymmetric versus symmetric performance profiles. Of the few studies that do, estimates of the prevalence of cognitive asymmetry (in either direction) range from 12% to almost 50% (Houston et al., 2005; Massman & Doody, 1996; Massman et al., 1993; Rasmusson & Brandt, 1995; Strite et al., 1997), depending largely on the size of the sample in question and on the methods by which "asymmetry" was defined or calculated. Based on studies with the most similar sample and methodology, it was hypothesized that asymmetry would exist in approximately 30% of participants at baseline evaluation. While the actual percentages obtained in the present study ranged from 12.3% to 28.2%, it is believed that the larger baseline sample, with asymmetry classifications that exclude memory measures was most

representative of a population of patients with AD; that value is 27.6% of participants with asymmetric cognitive profiles. Including memory measures in determination of asymmetry classification yielded lower proportions of asymmetric cognitive profiles, due to an overall decrease in mean AI. In the larger baseline sample, a greater proportion of participants were classified as Low Visuospatial than were classified as Low Verbal, as expected. This was not the case in the smaller longitudinal sample, but as previously mentioned, it is believed that the baseline sample was more representative of the overall AD population.

Hypothesis 2

Previously published literature suggests a strong relationship between ApoE genotype and cognitive asymmetry and that having more ε4 alleles would be associated with an overall higher degree of asymmetry (Bigler et al., 2002; Finton et al., 2003; Geroldi et al., 2000; Jacobson, Delis, Bondi, et al., 2005). The present study sought to replicate such findings. Chi-square analysis supported the relation between ε4 status and asymmetry classification, and one-way ANOVA revealed significantly greater AI values in participants with two copies of the ε4 allele compared to participants with no copies of the ε4 allele. However, there were no significant differences between these two subgroups compared to participants with one copy of the ε4 allele. Linear regression analysis demonstrated that the number of ε4 alleles was predictive of AI. This hypothesis was therefore generally supported.

It was predicted, as in previous literature (Massman & Doody, 1996), that higher level of education would be associated with and predictive of greater asymmetry due to increased left-hemisphere cognitive reserve (Schmand et al., 1997; Stern, Alexander, Prohovnik, & Mayeux, 1992). This finding was not replicated when analyzing data without memory measures, but in fact, the opposite pattern was found when memory measures were included. The lack of

significance in the former of those findings could be the result of relatively high education and high similarity among participants in the sample. For the Memory-Included analysis, the result was surprising. A possible explanation is that performance on Logical Memory I influenced the Verbal Composite enough to lead to an overall decrease in AI, across asymmetry classifications. This would also account, in part, for the tendency toward a greater proportion of Symmetric profiles when memory measures were included. Additional consideration is warranted for the significantly lower performance (and greater number of errors) on the AMNART for Low Verbal versus Symmetric and Low Visuospatial participants (Memory-Excluded classification). Since the AMNART is a relatively resistant measure of premorbid abilities, it is possible this finding suggests that the AD cognitive profile may reflect a premorbid cognitive profile. Another interpretation could support the "education and cognitive reserve" hypothesis, that greater premorbid verbal functioning does indeed predict better verbal performance in the cognitive profile.

While other predictions were not made regarding demographic variables associated with asymmetry, a number of analyses did examine these variables. The finding that emerged repeatedly was the association between age and asymmetry. Mean age for the Low Visuospatial group was significantly younger than in the two other subgroups, and age was a significant predictor of AI in every model analyzed. Otherwise, results were equivocal and not replicated across samples, for example the significant relation between sex and asymmetry classification in chi-square analysis, which was exclusive to the Memory-Included classification. Age was the only demographic variable strongly and reliably associated with asymmetry. One possibly interesting finding was that of higher score (greater self-reported depression) on the GDS in Low Verbal performers. Davidson (2000) discusses affective style in terms of approach-withdrawal

tendencies and their relation to left versus right hemisphere activation. In this model, greater ratings of depression in Low Verbal participants may not be surprising, as more extensive neurodegeneration in the left hemisphere would not only be associated with worse verbal performance, but also with greater right pre-frontal activation, or a stronger "withdrawal" tendency. Although the difference was small, its biological basis may merit future research.

Hypothesis 3

The prediction was made that across time points, the direction of asymmetry would remain relatively stable despite expected changes in the magnitude of asymmetry. This was examined in a number of ways, including correlations, Cohen's kappa, and repeated measures ANCOVA. It is noted here that across all analyses, no participants were classified asymmetric in one direction at one evaluation and classified asymmetric in the opposite direction at another. This was consistent with previous research, and supported the hypothesis in the present study, that asymmetry is directionally stable.

Correlations of AI between time points were in the moderate range and significant, suggesting relative consistency across evaluations. Agreement in asymmetry classifications between successive time points, and across all time points, was moderate and significant for Memory-Excluded classification, but was somewhat smaller for Memory-Included classification. This discrepancy is likely due to the greater proportion of Symmetric classifications when memory measures were taken into account. These findings, together, suggested that asymmetry is generally stable, as is the classification of patients with AD into these subgroups.

Across two evaluations, there was very little change in the relative proportions of asymmetric classifications, despite some reclassification of participants across evaluations. Time as a factor did not significantly change AI, however the interaction of time and baseline

asymmetry classification did. That is to say, mean AI in asymmetric classifications significantly changed with a tendency toward zero (a decrease in the magnitude of asymmetry) over time. Across three evaluations, there was an overall decrease in the proportion of participants classified as asymmetric. That is, asymmetry tended to diminish as people became more globally, or symmetrically, impaired. This was the case when classification included or excluded memory measures.

While MMSE and AI absolute value both decreased over time, no *significant* association between the two was established. In spite of this, it can be assumed, based on the somewhat predictable pattern of AD pathology, the AI tends toward zero as the neurodegenerative process proceeds.

Limitations of the Study

The present study was limited by a number of methodological issues. The inclusion of a variety of tests introduces issues related to the standardization of test scores. Specifically, test scores in this sample were standardized using different normative samples, either from standardization samples or normative studies, and the various normative samples are not necessarily completely comparable. Future studies of asymmetry could benefit from utilizing their own normative sample with characteristics similar to their patient sample.

Another related limitation was the lack of a consistent definition or way to operationalize asymmetry within the field. As previously mentioned, studies have varied in their calculations of cognitive asymmetry, some including and others excluding memory measures, and rarely using consistent tests to assess asymmetry. The composites in this study included multiple measures validated for their lateralization, and thus should be representative of true cognitive asymmetry, when it is present. The inclusion of memory measures, while intended to improve the robustness

of the asymmetry statistics, had the effect of decreasing the overall measure of asymmetry. Thus, the operationalization of asymmetry is an important consideration in future work.

Many participants had insufficient data to be included in some analyses. This was particularly an issue due to the lack of ROCF copy scores. Scores for this test were missing for a large number of participants, and as a result, they could not be included in analysis. A greater number of tests which are shown to lateralize to one hemisphere or the other would enhance the assumed accuracy of the asymmetry measures, and help to account for participants who are missing data from multiple measures.

Some tests, due to sharing standardization samples or similar scoring criteria, were highly related, even across composites (e.g., WAIS Similarities and Block Design). Ideally, the tests contributing to each composite would be less strongly or significantly correlated across composites, in order to demonstrate dissociation between them.

The operationalization of asymmetry assumes that the measures used are relatively "pure", that is that the measures themselves are dependent only on the functions they intend to measure. However, it is well-established that this is not the case. For example, the Rey-Osterrieth Complex Figure copy, used in the present study as a visuospatial measure, is often used as a measure of executive function due to the high demands on organization and planning. Even among visuospatial (and supposedly non-verbal) memory measures, often verbal strategies are used to enhance encoding of visuospatial information.

Although some participants had data from many evaluations available, their numbers were few. In order to maintain relatively large samples throughout analysis, evaluations were limited to a maximum of three (over a period of roughly two years). A greater number of

evaluations over a longer timeframe would provide a more complete picture of cognitive asymmetry over the course of the disease.

The process of Winsorizing the test scores presented another issue. This transformation was necessary to reduce the variation within and across test scores and to ensure that a test such as the ROCF (with its more extreme scores) did not exert disproportionate influence on the composite scores. However, this process led to an additional difficulty. While most test scores were within the 95% performance interval, several tests, most notably the ROCF copy, had a large percentage of scores transformed (over 20% of scores). This was due to ceiling effects in scoring and relatively high scores in the normative sample. Asymmetry analysis would likely benefit from the use of a different visuospatial measure with psychometric properties more comparable to the other tests in the composite.

Implications

The aim of this study was to expand upon previous investigations by characterizing cognitive asymmetry in a sample of Alzheimer's Disease patients much larger than currently exists in the published literature. The present study has hopefully provided some clarification on controversial findings which have been published in smaller studies. Cognitive asymmetry was found in a sizeable subgroup of patients in the study, consistent with previous work in this area. Key additional findings were that: 1) Patients classified as Low Visuospatial performers were younger than patients with Symmetrical or Low Verbal performance profiles; 2) Patients with two ε4 alleles were more likely to show an asymmetric cognitive profile; and 3) Cognitive asymmetry was generally stable across time (at least in the 2-year time window examined), although there was some tendency for the magnitude of asymmetry to lessen over time.

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