The Influence of Handedness on the Clinical Presentation and Neuropsychology of Alzheimer Disease

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Background: Research on the influence of handedness on the clinical presentation and neuropsychology of Alzheimer disease (AD) is scarce.

Objective: To compare clinical presentation and neuropsychological test performance of right- and left-handed patients with AD.

Design: We hypothesized that left-handedness would be associated with younger onset, more rapid progression, and possibly cognitive hemispheric asymmetry. After determining handedness with the Edinburgh Inventory for Handedness for 922 patients with AD, 18 left-handed patients were compared with 18 right-handed patients matched individually on Mini-Mental State Examination scores, education, and age. We compared clinical characteristics (eg, age of onset), estimated rate of initial cognitive decline, language and visuospatial test performances, and patterns of cognitive and motor asymmetries for the 2 groups.

Setting: Alzheimer’s Disease Research Center at Baylor College of Medicine, Houston, Tex.

Main Outcome Measures: Results of the Wechsler Adult Intelligence Scale–Revised verbal and performance IQ tests, the Western Aphasia Battery sequential commands subtest, the Boston Naming Test, the Halstead-Reitan Finger-Tapping Test, and the calculated Rate of Initial Progression.

Results: We found that left-handed patients had younger ages of onset but unexpectedly lower estimated rates of initial cognitive decline, and their results on language tests did not differ from those of right-handed patients. Regarding asymmetry, left-handed patients were more likely than right-handers to obtain lower verbal IQ than performance IQ scores and to exhibit faster finger-tapping speeds with their nondominant hand, but group differences did not attain statistical significance. There were disproportionately few left-handed patients with AD compared with population norms.

Conclusions: Left-handed patients with AD do not differ from right-handed patients in the severity or pattern of neuropsychological deficits. Left-handedness or some factor associated with it may contribute to the early appearance of cognitive deficits during the development of Alzheimer disease, but may temper the subsequent rate of progression of deficits.

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SUBJECTS AND METHODS

SUBJECTS

A prospectively collected database of 922 patients enrolled in the Alzheimer’s Disease Research Center at Baylor College of Medicine, Houston, Tex, was used to identify subjects diagnosed with probable or possible AD by National Institute of Neurological Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria. A modified version of the Edinburgh Inventory for handedness was used to prospectively classify patients as right- or left-handed based on the following equation, which yields a laterality quotient:

\[ X = \frac{(\text{No. of Tasks Performed With Right Hand} - \text{No. of Tasks Performed With Left Hand})}{(\text{No. of Tasks Performed With Right Hand} + \text{No. of Tasks Performed With Left Hand})} \]

Patients with positive scores are considered right-handed; those with negative scores are classified as left-handed. Using the above equation, 24 patients with AD (2.6%) were determined to be left-handed compared with the 5% to 10% reported in the general population, which is consistent with reports of a reduced frequency of left-handedness among patients with AD.

Of these 24 patients, 18 had complete neuropsychological data sets and were included in the study. All 18 wrote with their left hands, and most were strongly left-handed (Table 1). Fifteen patients were diagnosed with probable AD and 3 with possible AD. These 18 left-handed patients were matched individually with 18 right-handed patients on the following variables, in descending order of importance: Mini-Mental State Examination (MMSE) score at the time of initial evaluation, years of education, and age. With our large database sample of right-handed patients (n = 898), close matches were made on these 3 variables, particularly MMSE scores (Table 2). All 18 right-handed patients in our matched group had a diagnosis of probable AD and scored +1.0 on the Edinburgh Inventory, ie, were completely right-handed. Two of the 18 left-handed patients had one or more left-handed first-degree relatives (parent or sibling), as did 4 of the 18 right-handed patients. We did not include left-handed children as primary relatives since the trait could have come from either parent.

The age of onset of AD was calculated by subtracting the physician’s estimate of disease duration (as determined at the initial visit) from the age of the patient at this visit. The physician’s estimate of AD duration was made according to the established Alzheimer’s Disease Research Center procedure: the patient and all available informants were interviewed, medical records reviewed, and the caregiver asked to estimate the duration of 32 symptoms often associated with AD. The physician then estimated the duration of AD to the nearest half year after discussing and resolving any discrepant information.

PROCEDURE

To evaluate our hypotheses, we examined a small number of neuropsychological test scores selected from the larger neuropsychological test battery given to all patients. These measures included the Wechsler Adult Intelligence Scale–Revised VIQ and PIQ from the Satz-Mogel short form. The PIQ and Block Design age-scaled scores were selected as measures of visuospatial abilities. Block Design was considered individually because it seems to be the most reliable, valid performance subset measure of visuospatial abilities.

The absolute value of the difference between VIQ and PIQ was calculated for each patient as a measurement of cognitive asymmetry. The sequential commands subtest from the Western Aphasia Battery, an 80-point measure that evaluates auditory language comprehension, and the 60-item Boston Naming Test (uncued score) were selected as our measures of language functioning. Possible asymmetry of motor function was analyzed using the Halstead-Reitan Finger-Tapping Test. The dominant-hand tapping advantage was calculated using the following equation:

\[ \text{Percent Advantage} = \frac{(\text{No. of Taps of Dominant Hand} - \text{No. of Taps of Nondominant Hand}) \times 100}{\text{No. of Taps of Dominant Hand}} \]

Finally, the rate of initial disease progression was estimated using the following equation, which reflects MMSE points per year decline prior to the initial clinic visit:

\[ \text{Estimated Rate} = \frac{(\text{MMSE [Expected Score]} - \text{MMSE [Actual Score]})}{\text{Physician’s Estimate of AD Duration}} \]

The MMSE expected score was obtained from a large-scale normative study by Crum et al that stratified MMSE scores by age range and educational level. For each of our patients, the MMSE expected score was the mean score obtained by healthy subjects of the same age and level of education. We have previously shown preliminary data suggesting that the calculated rate of initial MMSE decline may predict the time to subsequent significant clinical deterioration.

ANALYSIS

Because the right-handed and left-handed patients were matched individually, we used paired t tests to compare continuous variables between the 2 groups. There was substantial heterogeneity of variance on 1 continuous measure (percentage of dominant-hand finger-tapping advantage), which was therefore analyzed using the Wilcoxon signed rank test rather than the paired t test. For discrete variables (sex, anomalous VIQ-PIQ discrepancies, and finger-tapping asymmetry), the McNemar test was used. Power analyses revealed that with an α level of .05 and the use of a 2-tailed paired t test, the probability of detecting an effect size of 0.80 (a large effect, according to Cohen) was .85. Our matching procedure and use of paired t tests contributed to this relatively high power. This effect size would translate to differences of approximately 8 points in PIQ, 9 points on Western Aphasia Battery sequential commands, and 1.2 points on estimated rate of decline on the MMSE. Owing to the small number of variables included in the study and our desire to maximize statistical power, Bonferroni corrections were not applied, and the α level was set at .05.
have tended to contain a disproportionate number of left-handed patients (22% of early- vs 0% of late-onset patients in a small series of 65 male patients), and early-onset patients were more likely to have one or more left-handed family members than late-onset patients.\textsuperscript{3,6} In addition, early-onset patients demonstrated a greater prevalence of language disturbances in verbal intelligence, auditory verbal comprehension, naming, and writing than late-onset patients.\textsuperscript{2,6} Thus, early-onset patients, particularly left-handers (who may have more widely distributed or mixed hemispheric dominance for language\textsuperscript{7}), might have greater risk for language disturbances and/or left hemisphere dysfunction early in the disease course. In addition, there is some agreement that early-onset patients demonstrate more rapid progression of dementia and shorter survival times than late-onset patients.\textsuperscript{3,6,8}

In the present study, we sought to examine these issues using a larger sample of carefully defined left-handed patients with AD (n = 18) and a matched sample of right-handed patients. Based on the results of the studies just reviewed, we hypothesized that left-handed patients would have an earlier age of onset than right-handed patients, more severe language deficits resulting in greater neuropsychological asymmetry manifested by verbal IQ (VIQ) vs performance IQ (PIQ) differences, and right- vs left-hand finger tapping asymmetries, which are an indicator of relative hemispheric involvement.\textsuperscript{9} Finally, we hypothesized that left-handed patients would exhibit a more rapid estimated rate of initial cognitive decline.

### RESULTS

Consistent with the matching procedure used to formulate the groups, there were no significant differences in age, years of education, or MMSE scores (Table 2). The mean MMSE score in both groups was about 20, indicating that most patients were in the mild to moderate stages of dementia. In addition, the sex distributions in the groups did not differ (McNemar test, \(P = .29\)). It should be noted, however, that the percentage of men in the left-handed group (50%) is somewhat higher than that found in all right-handed patients with probable AD in our database (38.5%). Among the left-handed patients, there were 16 whites, 1 Hispanic, and 1 Asian American; and among the right-handers, there were 15 whites, 2 Hispanics, and 1 African American.

The groups’ estimated disease durations did not differ (Table 2), but, in support of our hypothesis, estimated age of onset was significantly younger among left-handed than right-handed patients. Because age was one of the variables used to match patients (although it was the least important matching variable), there was some bias against discovering an age-of-onset difference. Therefore, we also examined the age of onset in all right-handed patients with probable AD in our database, and the mean age of onset was found to be 69.1 years, which is somewhat older than the mean age of onset of 66.4 years among all 24 of our left-handed patients (the 18 study patients plus the 6 patients with incomplete neuropsychological data). Contrary to our prediction, left-handed patients had significantly lower estimated rates of initial decline in MMSE scores than right-handed patients (Table 2).

The groups did not differ significantly in their performances on language tasks (Western Aphasia Battery sequential commands, Boston Naming Test); thus, our
hypothesis of more severe language deficits in left-handed patients was not supported. The groups also did not differ in their scores on visuospatial tasks (PIQ, Block Design). Both groups exhibited mild to moderate deficits on all of the neuropsychological measures. Our matching of subjects on MMSE scores could have contributed to the failure to find significant group differences. Therefore, in a supplementary analysis, we formed another group of 18 right-handed patients matched individually to the left-handers only to years of education and estimated duration of symptoms. Paired $t$ tests again revealed no significant differences on any of the neuropsychological tests. However, despite similar MMSE scores, the left-handed patients again had significantly lower estimated rates of initial decline in MMSE scores than the right-handed patients ($paired t = -5.09; P < .001$).

Cognitive asymmetry, as assessed by the absolute value of the difference between VIQ and PIQ test scores, did not differ significantly between groups (Table 2). Because PIQ subtests involve timed, novel tasks, and most of the VIQ subtests do not, patients with AD typically display higher VIQ than PIQ scores (in our database sample $N = 922$), the mean VIQ-PIQ score difference among right-handed patients was about 6 points). Therefore, we also examined how many patients in our 2 groups had lower VIQ than PIQ scores, which would represent an atypical pattern of performance. Eight (44%) of 18 left-handed patients scored lower in VIQ than PIQ subtests, whereas only 4 (22%) of 18 right-handed patients did so, but this group difference, while suggestive, was not significant (McNemar test, $P = .34$). In the complete database sample, only 28% of right-handed patients had lower VIQ than PIQ scores. For the 8 left-handed patients with lower VIQ than PIQ scores in the current study, these discrepancies were generally small; only 1 patient had a difference score greater than 15 (none of the right-handed patients had a difference score this large).

Regarding motor speed asymmetry, as given in Table 2, the median right-hand finger-tapping advantage in right-handers was 12.8%, and the median left-hand advantage for left-handers was only 1.6%, but this group difference was not quite statistically significant (Wilcoxon signed rank, $P = .07$). Eight of the 18 left-handed patients had a right-hand tapping advantage, whereas only 3 of the 18 right-handed patients had a left-hand advantage, but this difference was not statistically significant (McNemar test, $P = .23$). The VIQ-PIQ difference scores of the 8 left-handed patients with a right-hand tapping advantage did not differ significantly from these difference scores in the 10 patients with left-handed tapping advantages ($2$-tailed $t$ test, $P = .90$). A normative study by Thompson et al found right-hand dominant normal subjects had a mean right-hand tapping advantage of 10.8%, while left-hand dominant normal subjects had a significantly smaller left-hand advantage of 5.2%. It was also found that finger-tapping discrepancies were not correlated with age. The left-hand advantage in our left-handed patients was lower than that in normal left-handers, suggesting possible loss of the left-hand advantage.

Previous studies have suggested that left-handed patients with AD may differ from right-handed patients neuropsychologically or with respect to the course of their disease. In the present study, we attempted to address some of the limitations of previous studies of handedness and AD by using a larger subject population, standardized criteria for the diagnosis of AD, a standardized assessment of handedness (the Edinburgh Inventory), and groups of left-handed and right-handed patients closely matched for severity of dementia, age, and educational background.

Some of our hypotheses based on the literature were not supported by statistically significant group differences: specifically, the neuropsychological profiles of right- and left-handed patients did not differ, and there was no evidence that the initial disease progression of left-handed patients was faster. Our findings supported the hypothesis that left-handed patients would have younger ages of onset than right-handed patients (both in the small matched sample and in our larger database sample). Perhaps because cognitive abilities are more widely distributed in the brains of some left-handed persons (as suggested by reduced or reversed lateralization on dichotic listening and tachistoscopic tasks, for example), the AD process can more easily disturb their cognitive functioning so that they manifest neuropsychological deficits earlier in the disease course than right-handers.

Despite earlier average age of onset, estimated rate of initial (prior to diagnosis) decline in MMSE scores was significantly lower for left-handed patients, an unexpected finding. Perhaps the more widely distributed nature of some left-handed patients' cognitive abilities places them at greater risk for manifesting deficits in the first place, but helps to mitigate the subsequent rate of deterioration of these abilities.

Contrary to our literature-based prediction, left-handers did not display more severe language deficits than right-handers, and overall, neuropsychological test scores were very similar in the 2 groups, consistent with a previous study. That study differs from ours because it included only 7 left- and 7 right-handed patients, and it did not explore onset or progression characteristics. A supplementary analysis within the current study, in which the left-handed patients were matched individually with right-handed patients only in years of education and estimated duration of symptoms (not MMSE scores) also failed to reveal significant differences (left-handers still showed lower estimated rates of initial decline in MMSE scores, however). So our failure to demonstrate neuropsychological test differences in left- and right-handed patients was not due to the matching on this highly language-based measure.

Assessment of potential cognitive asymmetry by examining VIQ-PIQ score discrepancies did not reveal significant group differences. Still, it is notable that a greater proportion of left-handed patients obtained lower VIQ than PIQ scores, an atypical pattern suggestive of greater language dysfunction, but the group difference was not statistically significant. This could reflect greater vulnerability of language skills secondary to more highly dis-
ttributed language dominance. Regarding possible anomalous motor asymmetry, there was a nonsignificant statistical trend toward the left-handed patients exhibiting a smaller dominant-hand finger-tapping advantage than right-handed patients. If this were due to greater right- than left-hemisphere dysfunction in left-handers, one would expect this hemispheric asymmetry to be evident on cognitive tests, but it was not. An alternative explanation is that left hemisphere motor system functioning is more resistant to decline in AD, regardless of handedness. Functional neuroimaging may provide a means to test these hypotheses, as neurocognitive asymmetries are common in AD and may have pathophysiological significance.24

Further studies are necessary to confirm and extend our results. Although we used a large database of patients with AD to identify left-handers, the low prevalence of left-handedness in general, which may be compounded in AD, still resulted in a small number of left-handed subjects. Our analyses need to be repeated with larger groups, likely requiring a multicenter effort. Future analysis of progression would benefit by inclusion of patients with frequent assessment points over a long follow-up period using multiple cognitive and staging measures.

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REFERENCES