Relationship Between Cognitive and Morphological Asymmetry in Dementia of the Alzheimer Type: A CT Scan Study

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RELATIONSHIP BETWEEN COGNITIVE AND MORPHOLOGICAL ASYMMETRY IN DEMENTIA OF THE ALZHEIMER TYPE: A CT SCAN STUDY

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In this study we investigated the association between morphological asymmetry and patterns of cognitive ability in dementia of Alzheimer's type (DAT). Digitized CT scans were used to estimate volumetric parameters of the brain. The volume of the cranium, brain parenchyma, the subarachnoid space, and lateral ventricles was computed. The volume of the subarachnoid space was used as an index of cortical atrophy, while the ventricular volume served as an estimate of subcortical atrophy. Asymmetry indices were computed for all structures as the difference between left and right volume divided by their average and multiplied by 100. Cognitive asymmetry index was computed by dividing the difference between VIQ and PIQ of the Wechsler Adult Intelligence Scale (WAIS) by their average and multiplying by 100. After statistically controlling for cranial asymmetry, hemispheric asymmetry was found to correlate positively with cognitive asymmetry. The correlation was somewhat greater for male than for female patients. Asymmetry of both cortical and subcortical atrophy correlated negatively with cognitive asymmetry.

Keywords: Alzheimer's disease, cerebral asymmetry, computer assisted tomography, sex differences

Address correspondence to the first author.

Parts of this investigation were presented at the Fourteenth Annual Meeting of the International Neuropsychological Society at Denver, February 1986.
Dementia of Alzheimer type (DAT) is a complex neuropathological entity, and considerable intersubject variability in patterns of cognitive deficits is one of its most salient features. Thus, although intellectual deterioration is the hallmark of DAT, there is no agreement on the pattern of this deterioration. Some reports suggest that visuospatial skills are affected in the earliest stages of the disease, when verbal aptitude is still quite intact (Koss, Friedland, Ober, & Jagust, 1985), while others surmise that aphasic changes may be more prevalent in the early-onset DAT (Seltzer & Sherwin, 1983; Filley, Kelly & Heaton, 1986). DAT patients, relatively homogeneous in their behavioural pathology, may nevertheless show diverse patterns of response to pharmacological intervention (Vroulis, Johnson, Morgan, Little, Mauldin, & Affas, 1985). Postmortem neurochemical investigations of cholinergic system in brains of DAT patients have also revealed fundamental heterogeneity in this disease (Bird, Stranahan, Sumi, & Raskind, 1983). Although heterogeneity of expression is well established, all attempts to specify a clear taxonomic system for classification of dementias of the Alzheimer type have been unsuccessful (Jorm, 1985).

Recently, PET scan studies (Friedland, Koss, Jagust, & Ober, 1985; Duara, Grady, Haxby et al., 1986) have shown that glucose utilization in DAT declines asymmetrically, suggesting that the disease may affect cerebral hemispheres unequally. Grady, Haxby, Sundaram et al. (1985) have reported that in DAT, lateraled cognitive abilities show significant impairment later than global skills (e.g., memory), which may be related to the differential effects of progressive disease on the hemispheres. In DAT, unlike normal aging, regional metabolic decline appears to be accompanied by structural degeneration of the same areas of the brain (De Leon, George, Ferris, et al., 1985). This suggests that morphological measures obtained using CT images may shed some light on the patterns of lateraled changes in DAT brains, and further, that such changes may be linked with the pattern of deterioration of cognitive skills. Asymmetry in atrophy may be related to the specific pattern of cognitive deficits.

Across diverse populations, a relatively large left hemisphere has been associated with relatively greater verbal intelligence, whereas relatively large right hemisphere was indicative of relatively increased nonverbal intelligence. Although asymmetries in atrophy have not been examined, the relationship between other morphological asymmetries of the brain and lateralization of cognitive functions has been explored in a variety of clinical and normative populations. In recent studies, morphological asymmetry of the brain was assessed in vivo from CT scan images, while the degree of cognitive asymmetry was inferred from the differences between Verbal and Performance IQ scales (VIQ–PIQ). For instance, it has been reported that hemispheric asymmetry in the width of the occipital lobes correlated \((r = .38)\) with VIQ–PIQ difference scores in a group of learning disabled children (Rosenberger & Hier, 1980). Schizophrenics whose left hemisphere cross-section was wider than right tended to have greater VIQ–PIQ split than those with a reversed pattern of asymmetry (Luchins, Weinberger & Wyatt, 1985). A correlation between morphological (hemispheric) and cognitive asymmetry \((r = .57)\) was recently reported by Yeo, Turkheimer, Raz, and Bigler (in press) in neurologically normal subjects.

In this study, we investigated patterns of anatomic and cognitive asymmetry and the relationship amongst different aspects of anatomic cerebral asymmetry in DAT. First, we examined the relationship between asymmetrical atrophy (cortical as well as subcortical) and patterns of cognitive abilities. Second, we investigated the relationship between volumetric asymmetry of brain parenchyma and patterns of cognitive abilities.
METHOD

Subjects

A total of 47 right-handed patients (24 females) was selected from the files of Austin Neurological Clinic. The decision to restrict this sample to right-handers was dictated by the uncertainty surrounding cerebral dominance in left-handers (Geschwind & Galaburda, 1985) and the possibility of an association between left-handedness and distinctive types of dementia (Seltzer & Sherwin, 1983). All patients were diagnosed by a board certified neurologist, following exclusion of other neurological diseases on the basis of standard neurological examination, electroencephalographic and serological studies. Since definitive diagnosis of AD can be made only by histopathological examination, these patients should be considered, strictly speaking, as suffering from a probable AD, or dementia of Alzheimer's type (DAT).

The mean age of the patients was 66.9 years (SD = 10.2 years). This can be taken as a rough estimate of the average age of onset of DAT in this sample, since all measurements were obtained in the context of the first diagnostic work-up.

Psychometrics

Wechsler Adult Intelligence Scale—Revised (WAIS-R) was administered to all patients by an experienced technician as part of a neuropsychological evaluation. Short forms of the WAIS including at least four verbal and four performance subtests were administered to 16 patients (nine females). Cognitive asymmetry index (CAI) was obtained by dividing the difference between the VIQ and PIQ by their average and multiplying by 100%.

CT Scan Analysis

All CT scans were performed without contrast medium on an EMI 1010 scanner obtaining nine 10 mm slices per scan parallel to the orbitomeatal line. CT films were subsequently digitized on a Summagraphics Bitpad, and analyzed using volumetric software implemented in APLSF on the DEC-20 computer. The details of this highly reliable method are available in Yeo, Turkheimer and Bigler (1983) and Turkheimer, Cullum, Hubler et al. (1984). As a result of this analysis, we obtained volumetric estimates of intracranial space, brain parenchyma, and lateral ventricles. All indices were computed for four quadrants delineated by right–left and anterior–posterior axes.

Hemispheric asymmetry index (HAI) was computed as the difference between left and right hemispheric volumes (without the ventricles) divided by their average and multiplied by 100. Cranial asymmetry index (CRAI), and ventricular asymmetry index (VAI) were calculated using the same method. Asymmetry index for cortical atrophy (CTAI) was obtained by computing the subarachnoid volume for the left and right halves (total hemicranial capacity minus hemispheric volume), then dividing the difference in subarachnoid fluid volumes of the hemispheres by their mean and multiplying by 100%.

RESULTS

The asymmetry indices for brain tissue, cortical atrophy, lateral ventricles, and the cranium, as well as cognitive asymmetry indices and demographic data for the total
sample and both genders separately are presented in Table 1 along with $t$ values for comparisons between males and females. Each asymmetry index was also tested for significance of its departure from zero. All asymmetry indices for the total sample and for the females were found to be significantly left-biased, whereas only cognitive, hemispheric, and cranial asymmetry indices differed from zero in the male subsample. All nonzero indices were positive, indicating that brain structures were larger on the left than on the right.

### TABLE 1
Demographic data and asymmetry indices

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total $n=47$</th>
<th>Males $n=23$</th>
<th>Females $n=24$</th>
<th>$t$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample description</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>66.9 (2.94)</td>
<td>67.2 (3.93)</td>
<td>66.7 (4.44)</td>
<td>0.16</td>
</tr>
<tr>
<td>Education (years)</td>
<td>13.3 (0.95)</td>
<td>13.5 (1.12)</td>
<td>13.0 (1.53)</td>
<td>0.54</td>
</tr>
<tr>
<td>FSIQ</td>
<td>89.9 (4.21)</td>
<td>91.7 (6.86)</td>
<td>88.2 (5.05)</td>
<td>0.82</td>
</tr>
<tr>
<td>VIQ</td>
<td>94.4 (4.04)</td>
<td>97.8 (6.57)</td>
<td>91.9 (4.89)</td>
<td>1.33</td>
</tr>
<tr>
<td>PIQ</td>
<td>85.1 (4.70)</td>
<td>85.4 (4.17)</td>
<td>84.9 (5.94)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Asymmetry indices</strong></th>
<th>Total $n=47$</th>
<th>Males $n=23$</th>
<th>Females $n=24$</th>
<th>$t$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive</td>
<td>21.9 (7.81)*</td>
<td>28.5 (10.29)*</td>
<td>15.5 (11.40)*</td>
<td>1.68*</td>
</tr>
<tr>
<td>Hemispheric</td>
<td>3.3 (1.35)*</td>
<td>3.4 (1.82)*</td>
<td>3.2 (2.06)*</td>
<td>0.93</td>
</tr>
<tr>
<td>Cortical atrophy</td>
<td>8.7 (5.74)*</td>
<td>5.1 (8.72)</td>
<td>12.2 (7.44)*</td>
<td>-1.75*</td>
</tr>
<tr>
<td>Lateral ventricles</td>
<td>8.8 (5.56)*</td>
<td>3.9 (7.65)</td>
<td>13.5 (7.76)*</td>
<td>-1.24</td>
</tr>
<tr>
<td>Cranium</td>
<td>4.1 (1.27)*</td>
<td>3.6 (1.57)*</td>
<td>4.6 (1.98)*</td>
<td>0.79</td>
</tr>
</tbody>
</table>

* $p<.1$, two-tailed.
* $*$significantly different from zero, $p<.05$, two-tailed $t$-test, 95% confidence limits are presented in parentheses.

Correlation between cognitive and hemispheric asymmetry indices in the total sample are presented in Table 2. Note that hemispheric asymmetry correlated only $r=.19$ (ns) with cognitive asymmetry. When males and females were considered separately, however, the correlations were $r=.57$ ($p<.005$) for males and $r=-.08$ (ns) for females. This difference was tested using Fisher's $Z$ transformation and found to be significant ($z=2.33$, $p<.01$, two-tailed).

The fact that the left hemicranium was found to be significantly larger than the right, suggested a possibility that parenchymal and ventricular asymmetries might be determined to a substantial degree by cranial asymmetry. The correlations between cranial and other anatomic asymmetry indices (Table 2) showed that at least hemispheric asymmetry might be very closely related to the asymmetry of the cranial cavity. To assess the association between the asymmetry indices of brain parenchyma and cortical atrophy, independently of cranial asymmetry, we computed first-order partial correlations among the variables featuring in Table 2, using cranial asymmetry index (CRAI) as the control variable. The results of this analysis are presented in Table 3.
TABLE 2
Correlation matrix of CT and cognitive asymmetry indices for total sample

<table>
<thead>
<tr>
<th></th>
<th>Cognitive</th>
<th>Cortical</th>
<th>Ventricular</th>
<th>Skull</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAI</td>
<td>0.19</td>
<td>-0.25</td>
<td>-0.02</td>
<td>0.89*</td>
</tr>
<tr>
<td>CAI</td>
<td>-0.44*</td>
<td>-0.31*</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>CTAI</td>
<td></td>
<td>0.68*</td>
<td>0.17</td>
<td>0.32*</td>
</tr>
<tr>
<td>VAI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p<.05, two-tailed.

TABLE 3
Partial correlations among CT and cognitive asymmetry indices, controlling for cranial asymmetry

<table>
<thead>
<tr>
<th></th>
<th>Cognitive</th>
<th>Cortical</th>
<th>Ventricular</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAI</td>
<td>0.42*</td>
<td>-0.91*</td>
<td>-0.71*</td>
</tr>
<tr>
<td>CAI</td>
<td>-0.45*</td>
<td></td>
<td>-0.33</td>
</tr>
<tr>
<td>CTAI</td>
<td></td>
<td></td>
<td>0.67*</td>
</tr>
</tbody>
</table>

*p<.05, two-tailed.

As evident from Table 3, cranial asymmetry acted as a suppressor variable (Pedhazur, 1982) obscuring the relationship between hemispheric and cognitive asymmetry. The difference in the magnitude of correlations between hemispheric (HAI) and cognitive (CAI) asymmetry indices for males and females was reduced after cranial asymmetry was partialled out. The first-order partial correlations were $r=.55$ ($p<.01$) for males, and $r=.21$ (ns) for females. These correlations were compared using Fisher's $Z$ transformation, and the difference fell short of statistical significance, although the trend for males to have stronger relationship between hemispheric and cognitive asymmetry was preserved ($z=1.30$, $p<.1$, one-tailed).

The correlations in Table 3 also suggest that asymmetries of cortical and periventricular degeneration are negatively related to the cognitive asymmetry index. Thus, when atrophy in the left hemisphere was greater than in the right one, the relative difference between verbal and performance IQ was small. With regard to asymmetry indices of cortical and subcortical atrophy, they did not differ significantly in the strength of their association with cognitive asymmetry.

DISCUSSION

Cognitive variability among DAT patients was found to be associated with cerebral hemispheric asymmetry and with asymmetry in cerebral atrophy. Specifically, moderately strong associations were observed between cognitive and anatomic cerebral asymmetries in male, but not female DAT patients. Relatively greater left-side atrophy was associated with lower verbal ability. Also, left-side volumes of
brain parenchyma, cortical and periventricular atrophy, were found to be consistently larger than respective right-side volumes. This finding is especially interesting in light of recently reported PET scan findings: in DAT patients with moderate and severe form of the disease, reduction of cerebral metabolism was greater in the left hemisphere than in the right (Duara et al., 1986).

Relatively larger left hemispheres were associated with relatively greater verbal skills, whereas relatively larger right hemisphere predicted relative strength of nonverbal abilities. This pattern is consistent with previous observations in neurologically normal subjects (Ye0 et al., in press), but the magnitude of the relationship was reduced in DAT patients relatively to normals.

This association is not a result of having more brain volume committed to a specific domain of cognitive skills. If this were true, and an absolute increase in left hemispheric volume were associated with an increase in verbal ability, then we would have found significant correlations between the right and left hemispheric volumes and Performance and Verbal IQ, respectively. This has been found in neither our neurologically normal sample (Ye0 et al., in press) nor in this study: the correlations were \( r = .06 \) and .19 (both ns) for left hemispheric volume and VIQ, and right hemispheric volume and PIQ, respectively.

Consistent leftward asymmetry of the cranium and the ventricles (Table 1) replicates Zatz, Jernigan and Ahumada’s (1982) findings obtained with a different volumetric technique. Why asymmetric CT images of the skull have been repeatedly observed is unclear at present. One possibility is that right-handed patients may tend to tilt their heads to the right within the CT scanner gantry. Such a tilt, if it occurs consistently, may result in asymmetric distortion of the CT image, creating the impression of left hemispheric enlargement (Zatz et al., 1982). Alternatively, asymmetry of the skull may be a result of asymmetric growth of the brain, since early skull development is affected by the brain growth (Davis & Wright, 1977). If the latter is true, skull asymmetry in DAT patients may reflect premorbid anatomic asymmetry which is highly correlated with hemispheric asymmetry measured after the onset of the disease, but exhibits little or no association with the patients’ asymmetric pattern of cognitive skills (see Table 2).

Variability of individual patterns of DAT-related cognitive and morphological deterioration may be of explanatory value for some of the findings reported here. Inspection of Table 1 reveals tremendous variability of indices of atrophic asymmetry. These indices correlate negatively with both hemispheric and cognitive asymmetry. What hypothesis can be advanced concerning the processes resulting in this pattern? One, admittedly speculative, possibility is discussed below.

Suppose the left hemisphere is larger than the right, as suggested by our findings and others with neurologically normal subjects (Zatz et al., 1982; Ye0 et al., in press). Given that the left hemicranium may be somewhat larger than the right, it is quite reasonable to assume that in the intact brain, left and right subarachnoid spaces occupy equal shares of the volumes of their respective hemicrania. This implies that the left subarachnoid space is larger than the right. Atrophic processes of DAT may affect cerebral hemispheres asymmetrically, resulting in a disproportional increase of right or left subarachnoid space. In individuals with greater left atrophy, indices of atrophic asymmetry will increase, while in those with greater right atrophy a tendency toward negative indices of atrophic asymmetry will be evident. Deterioration of the right hemisphere will result in decreased atrophy indices, since the difference between the left ventricular and subarachnoid spaces and their right counterparts will decrease. It will also result in deterioration of right-hemispheric functions heavily represented in PIQ subtests, in a decrease in
PIQ scores and in increased cognitive asymmetry indices. This would explain the negative correlations between the cognitive and atrophic asymmetries found in this study. Although causal inference in correlational analysis is not usually warranted, it is probably safe to assume that asymmetry in brain atrophy is an antecedent of reduction in cognitive asymmetry and not vice versa.

The results reported here leave a few issues unresolved. The nature of volumetric asymmetries of the brain and the underlying mechanisms are unclear. CT scanners do not allow good differentiation amongst cell types and will therefore provide no answer to the question of whether volumetric asymmetries result from greater numbers of neurons, denser connections, or proliferation of glial cells in the left hemisphere.

The sex differences in the pattern of association between hemispheric and cognitive asymmetry, are difficult to interpret. Differences in regional brain morphology of males and females are quite well established (Geschwind & Galaburda, 1985), as are differences in cognitive processing (McGlone, 1980). The relationship between cognitive and cerebral morphological asymmetries within the two sexes has not been as extensively explored.

In neurologically intact subjects the relationship between cognitive and morphological asymmetry was somewhat stronger in males \((r = .72)\) than in females \((r = .51)\), although this difference did not reach the conventional significance level. In patients with DAT, the association of hemispheric and cognitive asymmetry was stronger for males. The magnitude of this sex difference was somewhat stronger than in normals. A possible explanation of this finding may be that females exhibit weaker association between hemispheric and cognitive asymmetries because they use more uniform (less hemisphere-specific) strategies in solving problems of WAIS Verbal and Performance subscales (Inglis & Lawson, 1982).

In summary, we have been concerned with the cognitive variability observed in DAT patients and have related this variability to asymmetric patterns of atrophy and those of intact hemispheric parenchyma. We believe that the data reinforce the notion that DAT is not a global or diffuse disorder in either its pathology or patterns of cognitive deficits.

REFERENCES


