Examining the relationship between computed tomography and neuropsychological measures in normal and demented elderly

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SUMMARY Correlational analysis of CT and neuropsychological measures in patients with dementia revealed more predictive relationships in degenerative and vascular subgroups that in a multi-etiologic group. Normal and dementia patients were then matched for age, sex and educational background, and analysed together. The ventricular/brain ratios of the bodies of the lateral ventricles and of the third ventricle correlated most highly with neuropsychologic performance. Canonical analysis revealed a correlation coefficient of 0.725 between the sets of CT and neuropsychological measures, which increased to 0.78 when a degenerative subgroup only was considered. Discriminant function analysis indicated that the combination of CT and neuropsychological measures was more powerful in discriminating normals from dementia patients than CT or neuropsychological measures alone.

The relationship between brain and behavioural changes in aging and dementia has been the subject of much research and debate. Specifically, the relationship between changes in brain morphology, as reflected by computed tomography (CT), and changes in behaviour, as measured by clinical scales and neuropsychological tests, has been described as relatively weak for both normal elderly and for dementia patients. Nonetheless, several studies have suggested that some correlation exists, albeit moderate between brain atrophy on CT and various behavioural measures. Our contention is that, owing to a variety of methodological reasons, the nature of the relationship has not been fully appreciated in previous studies. For instance, the lack of correlation in a neuropathologically heterogeneous dementia group may mask specific CT-behavioural correlations in more homogeneous subgroups such as those with strictly degenerative or vascular pathology. The commonly used linear measurement of CT features is less likely to reflect volumetric variation that area measurements. The absolute size of brain structures on CT is less likely to reflect intersubject differences than a ratio between the area of brain structure and the area of the whole brain at the same level. Furthermore, there exists a general consensus that measures of cortical atrophy are unreliable, difficult to incorporate into a ratio and less related to mental decline than ventricular measures.

From a neuropsychological standpoint, the common usage of global clinical judgment, gross rating scales, or simple psychometric tests, may fail to provide important differential features of mental decline. A notable exception is the report of de Leon et al describing patients with Alzheimer’s disease. The authors employed a variety of standardized tests and found a number of significant correlations with CT measures.

In a previous study we have established methods of quantitative CT measurement, utilising ratios of ventricular and whole brain areas which discriminated between scans of older normals and dementia patients. Also, we have established that multivariate analysis of objective neuropsychological tests assessing verbal and visual memory, word fluency, tem-
poral orientation and visual perception, discriminated between older normals and dementia patients. Based on these methods of analysis, we considered the nature of the relationship between CT measures and neuropsychological performance in two studies. The first examined a large group of patients with dementia. The second focused on matched groups of normal and demented elderly.

STUDY 1

Method

Subjects

The dementia sample consisted of 64 patients referred to University Hospitals for neurological evaluation because of progressive mental decline. The principal complaints included failing memory, poor judgment and inability to live independently (see table 1 for sample characteristics). We purposefully included various aetiologies of dementia, but simultaneously identified the major subgroups of degenerative disease and vascular disease. Patients who could not satisfactorily complete comprehensive neurological and neuropsychological examinations because of severe mental decline were excluded. The conditions of all patients conformed to Roth's definition of dementia, that is, a condition of progressive deterioration of intellectual and affective faculties in a state of intact consciousness, as well as to DSM III criteria. Each patient had an extensive evaluation, which included neurological examination, comprehensive blood chemistry analyses (complete blood cell count, 6- and 12-factor automated chemical analysis, ESR, VDRL, and determinations of serum vitamin B₁₂, folate, thyroxine, and thyroid-stimulating hormone levels), study of cerebrospinal fluid, computed tomography (CT), and EEG in a standard 20-20 montage. Diagnoses were based on the application of current clinical diagnostic criteria and of Hachinski's ischaemia scale. Aetiology of dementia is summarised in table 1.

CT analysis

CT measurements followed the method of Damasio et al. Two neurologists, blind to the clinical and behavioural profiles of the subjects, independently traced onto translucent paper, the following cerebral structures: (1) the third ventricle at the level of the foramina of Monro; (2) the frontal horns at the level at which they were largest; (3) the bodies of the lateral ventricles at the first level in which they were fully seen; and (4) the interhemispheric fissure at the same level as the bodies of the ventricles. At each level, the entire perimeter of the brain was also traced. The surfaces circumscribed by those tracings were then retracted with a magnetic digitiser pen, directly connected to a Hewlett-Packard graphics computer. By means of a specifically designed program, the area subtended by each tracing was determined, and a percent ratio between the ventricular or interhemispheric fissure area and the corresponding brain area was calculated. The mean of the two neurologists’ tracings served as the dependent measure.

Neuropsychological tests

The neuropsychological battery, administered by a neuropsychologist blinded to both CT and neurological evaluation, included the following tests:

1 Temporal Orientation

This test assesses the accuracy of identification of the year, month, day of month, day of week and time of day according to the standardised method of Benton. A perfect score is zero and increasing scores represent increasing disorientation.

2 Digit span

Administration and scoring of this immediate memory test was similar to the WAIS Digit Span subtest except that the raw score represents the number of digit sequences correctly repeated (forwards and backwards) rather than the number of digits per se. This method results in a more reliable estimate of performance.

3 Digit sequence learning ("Digit supraspan")

This test of short-term auditory-verbal memory requires the subject to learn an eight or nine digit sequence, depending upon education level, over repeated trials. Testing is terminated after 12 trials or two consecutive correct repetitions. Administration and scoring followed the method of Hamsher et al.

4 Logical memory (Wechsler Memory Scale)

Scores on this test of verbal recall represent the average number of items correctly recalled from two stories. Administration and scoring followed the method of Wechsler.

5 Associate learning (Wechsler Memory Scale). Scores on this test of learning 10 word pairs over three trials were obtained through the standard method of Wechsler.

6 Visual retention test

Number correct and error scores on this test of short-term visual memory for designs were obtained through administration A (immediate reproduction after 10 second exposure of each design) of Form C. Though highly correlated, number correct and error scores were treated separately in analysis.

7 Controlled oral word association ("Word Fluency")

This test requires the oral production of words beginning with a given letter of the alphabet over a one minute period. Three letters are successively presented, and scores represent the cumulative number of correct responses.

8 Facial recognition

Subjects are required to recognise unfamiliar faces in a standardised matching to sample scores.
Examining the relationship between computed tomography and neuropsychological measures

paradigm. Scoring represents number of correct matches to a total of 54.

9 Spatial judgment Subjects here are required to judge the orientation of lines in a matching to sample paradigm. There are a total of 30 trials and scoring represents the number of correct matches with correction for sex differences to a maximum score of 30.

Results

Pearson product-moment correlation coefficients were calculated for all pairs of CT-neuropsychological measures. Correlations ranged from $-0.19$ to $+0.13$, with none significant at the $p < 0.05$ level. We then submitted the data to canonical analysis. This multivariate procedure computes the maximal correlation possible between the composite set of CT measures and the composite set of neuropsychological scores. The composite sets are represented by the optimal linear weighted combinations of the CT measures and the neuropsychological scores. Although the canonical correlation was $0.47$, it did not reach a level of statistical significance ($p > 0.05$).

Finally, CT-neuropsychological correlations were calculated for the neuropathological subgroups of degenerative disease, vascular disease and the broad miscellaneous other/mixed category. Several correlations and correlational trends now became evident. For the degenerative subgroup ($n = 29$), a significant correlation was found between Facial Recognition and the Frontal Horns ($r = 0.44$, $p < 0.02$), and four other coefficients suggested a trend ($0.05 < p < 0.10$). For the vascular subgroup ($n = 15$), two significant correlations were evident ($r = 0.60$, $p < 0.02$, between Visual Retention—No. Correct score and the Frontal Horns; $r = 0.55$, $p < 0.04$, between Logical Memory score and the Interhemispheric Fissure), and eight others suggested a trend ($0.05 < p < 0.10$). However, in the other/mixed aetiology subgroup, no significant correlations or trends emerged.

Comment

Despite multiple quantitative CT and neuropsychological measures, no overall correlations were evident in this large sample of patients with dementia from various aetiologies. Most studies in which CT-behavior correlations have been reported utilized more homogeneous groups of dementia patients, namely those afflicted with Alzheimer's disease. Thus, the multiple etiology dementia group we evaluated may have been too heterogeneous anatomically, pathologically and behaviourally to permit a clear correlation of CT measures with neuropsychological scores. The emergence of significant correlations and correlational trends in the specific degenerative and vascular subgroups, as well as the continuing lack of correlations in the miscellaneous other/mixed etiology subgroup, offers support for this hypothesis and may help explain some of the discrepancies among published studies, as others have suspected.

STUDY 2

We examined the question of CT-neuropsychological correlations from another perspective, namely the analysis of normal elderly and dementia patients together. Specifically, we were interested in determining if CT-behaviour relationships within this type of analysis were any clearer or more useful for the evaluation of pathological states. We determined this through the multivariate procedures of canonical correlation and linear discriminant function.

Method

Subjects

The dementia sample consisted of 26 patients chosen from among the larger dementia group of study 1 so as to match

Table 2 Characteristics of matched normal and dementia samples (Study 2)

<table>
<thead>
<tr>
<th>Normal</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>sample size</td>
<td>26</td>
</tr>
<tr>
<td>male:female</td>
<td>7:19</td>
</tr>
<tr>
<td>mean age (yr)</td>
<td>74-50</td>
</tr>
<tr>
<td>(SD)</td>
<td>(5-62)</td>
</tr>
<tr>
<td>age range (yr)</td>
<td>64-88</td>
</tr>
<tr>
<td>mean years of education</td>
<td>13-15</td>
</tr>
<tr>
<td>(SD)</td>
<td>(3-13)</td>
</tr>
</tbody>
</table>

* $t$ test not significant ($p > 0.05$)

Table 3 CT and neuropsychological scores of normal and dementia samples

<table>
<thead>
<tr>
<th>CT Measures</th>
<th>Normal $x$ (SD)</th>
<th>Dementia $x$ (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>bodies of ventricle</td>
<td>7-94 (2-86)</td>
<td>15-34 (4-35)*</td>
</tr>
<tr>
<td>interhem. fissure</td>
<td>1-23 (0-60)</td>
<td>1-50 (0-66)†</td>
</tr>
<tr>
<td>third ventricle</td>
<td>2-93 (1-01)</td>
<td>4-89 (1-56)*</td>
</tr>
<tr>
<td>third ventricle</td>
<td>0-58 (0-23)</td>
<td>1-15 (0-44)*</td>
</tr>
</tbody>
</table>

Neuropsychological Measures

<table>
<thead>
<tr>
<th></th>
<th>Temporal orientation</th>
<th>Digit span</th>
<th>Digit seq. learning</th>
<th>Logical memory</th>
<th>Paired associates</th>
<th>Visual retention</th>
<th>No. correct</th>
<th>No. errors</th>
<th>Word fluency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0-34 (1-02)</td>
<td>1-04 (0-91)</td>
<td>14-73 (7-14)</td>
<td>8-94 (2-99)</td>
<td>14-23 (3-49)</td>
<td>2-07 (1-67)*</td>
<td>6-27 (3-44)</td>
<td>38-62 (11-04)</td>
<td>43-65 (3-61)</td>
</tr>
<tr>
<td>Dementia</td>
<td>20-77 (32-13)*</td>
<td>7-89 (2-52)*</td>
<td>5-46 (8-12)*</td>
<td>3-58 (2-89)*</td>
<td>7-27 (3-93)*</td>
<td>2-07 (1-67)*</td>
<td>16-73 (5-45)*</td>
<td>17-34 (12-36)*</td>
<td>31-46 (13-52)*</td>
</tr>
</tbody>
</table>

* $t$ test ($p < 0.01$)
† $t$ test ($0.05 < p < 0.10$)
normal controls as closely as possible for age, sex and educational background. Aetiology included: degenerative disease (46% of cases), vascular disease (15%) and miscellaneous other/mixed causes (39%). Distribution according to age, sex and educational level is summarised in Table 1.

The normative sample was selected from a well-studied population of healthy, community-dwelling volunteers, 64-88 years of age, who were recruited through local organisations and received comprehensive neurological evaluations (including CT, EEG and clinical examination) and neuropsychological tests. Those with any history or finding compatible with neurological abnormality, psychiatric disorder requiring hospitalisation or debilitating medical illness were excluded from the study. Members of the normative sample considered themselves to be in good physical and mental health, and constituted a group of unequivocally normal persons. The final sample of 26 subjects was selected so as to match the dementia sample as closely as possible for age, sex and educational level. The two samples did not differ in age or education and 21 of 26 pairs did not differ in sex (Table 2).

**Results**

Data were analysed for basic group differences, relationship between CT and neuropsychological measures, and accuracy of discrimination between groups. To facilitate an overview of group performances, we summarised all measures in table 3. On CT measures, the dementia sample exhibited significantly higher values (p < 0.01) for the Bodies of the Lateral Ventricles, the Frontal Horns and the Third Ventricle—indicating that ventricular structures occupied a relatively larger area of brain than in normals. Measures of the Interhemispheric Fissure suggested only a trend in group differences, (0.05 < p < 0.10). Neuropsychological differences were also prominent with significantly poorer scores on each behavioural variable (p < 0.01). Overall, these measures establish clear differences between groups.

**Correlational analysis**

Correlational analysis was undertaken for the single combined group of normal and dementia cases. First, the Pearson product-moment correlation coefficients computed for all pairs of CT and neuropsychological measures revealed many significant correlations (Table 4). The CT measures of Bodies of the Ventricles and Third Ventricle correlated most highly and consistently with neuropsychological scores. The highest correlations were evident between Spatial Judgment and Bodies of the Lateral Ventricles (r = 0.63), Digit Span and the Bodies of the Lateral Ventricles (r = 0.62), Digit Span and the Third Ventricle (r = 0.58), and between Paired Associates and the Third Ventricle (r = 0.57). The Frontal Horns also correlated significantly with all neuropsychological scores, though to a generally lesser degree. The Interhemispheric Fissure demonstrated no significant correlations at all.

We considered next the multivariate dimensions of the CT and neuropsychological relationship by submitting the data to canonical analysis. This procedure computes the maximal correlation between sets of variables, in this case the CT measures and the neuropsychological scores. The sets are defined as composites on the basis of standard regression weights representing the independent contribution of each variable to the optimal composite. (Note: Temporal Orientation was omitted because of its highly skewed distribution and Visual Retention — No. Errors was omitted because of its very high correlation with Visual Retention — No. Correct score, r = 0.89). The results are presented in Table 5. The
Discriminant function analysis

In previous separate studies, we have established through discriminant function analysis that a very high percentage of normals and dementia patients can be correctly classified on the basis of these quantitative CT measures and these neuropsychological tests. We now applied the same multivariate procedures to our current normal and dementia samples for the purpose of examining the comparative efficacy of CT and neuropsychological measures in the detection of dementia. We compared specifically the accuracy of dichotomous classification (that is, normal or dementia) when stepwise linear discriminant function analyses were performed on (1) only the CT measures, (2) only the neuropsychological measures, and (3) both the CT and the neuropsychological measures together.

The results are based on the following variables chosen by the stepwise linear discriminant function analysis: CT—Bodies of the Ventricles, with no other CT measure reaching significance with the F statistic; Neuropsychologic tests—Visual Retention Test (number correct), Spatial Judgment and Word Fluency, with no other measure reaching statistical significance; CT/Neuropsychological measures—Bodies of the Lateral Ventricles, Visual Retention Test (number correct) and Word Fluency, with no other measure reaching statistical significance. Accuracy of the dichotomous classification improved slightly from 90-5% (CT) and 92% (neuropsychologic tests) to 94% when CT and neuropsychological scores were combined for a single composite. We then used the posterior probability levels to classify each case into one of three interpretative categories: (1) “highly probable” normal or dementia (≥70% probability level of belonging to respective group), (2) “borderline” (31-69% probability level of belonging to respective group) and (3) “misclassified” (0-30% probability level of belonging to respective group). This procedure essentially separates those cases that more clearly fall into their respective group (“highly probable”) from those that hover about the discriminant criterion (“borderline”) and those clearly misclassified by the procedure. Correct classification of cases into the “highly probable” normal and dementia categories increased from 73% (CT formula) and 83% (neuropsychological formula) to 92% when CT and neuropsychological variables were combined for a single composite (table 6). In addition, the number of “borderline” cases decreased markedly to 2%, while “misclassified” cases remained in the 4-6% range. Thus, the combination of CT and neuropsychological measures would seem to discriminate more clearly older normals and dementia subjects than either set of measures alone, although the two sets of measures share a high degree of overlap in accuracy of overall classification.

Discussion

There is no doubt that significant morphological and neurochemical brain alterations occur in patients with progressive dementing illnesses. The fact that neuropsychological tests can detect mental decline associated with those pathologic processes commands little debate. However, the confidence in CT as an accurate indicator of pathologic mental decline has been uncertain. Nonetheless, several studies have supported a predictable relationship, albeit a moderate one, between CT changes and neuropsychological changes in dementia.

Table 6 Classification of cases based on Linear Discriminant Function Analysis

<table>
<thead>
<tr>
<th></th>
<th>Normal sample</th>
<th>Dementia sample</th>
<th>Combined samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥70% probability level (Highly Probable)</td>
<td>81%</td>
<td>65%</td>
<td>73%</td>
</tr>
<tr>
<td>1LDF-CT</td>
<td>85%</td>
<td>81%</td>
<td>83%</td>
</tr>
<tr>
<td>1LDF-NP</td>
<td>88%</td>
<td>96%</td>
<td>92%</td>
</tr>
<tr>
<td>31-69% probability level (Borderline)</td>
<td>15%</td>
<td>27%</td>
<td>21%</td>
</tr>
<tr>
<td>LDF-CT</td>
<td>11%</td>
<td>13%</td>
<td>2%</td>
</tr>
<tr>
<td>LDF-NP</td>
<td>4%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>0-30% probability level (Misclassified)</td>
<td>4%</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>LDF-CT/NP</td>
<td>4%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>LDF-NP/NP</td>
<td>8%</td>
<td>4%</td>
<td>6%</td>
</tr>
</tbody>
</table>

*Linear Discriminant Function classification based on one CT measure.
†Linear Discriminant Function classification based on composite of 3 neuropsychological (NP) measures.
‡Linear Discriminant Function classification based on composite of 1 CT and 2 neuropsychological measures (NP).
The strongest indication of this relation has come from de Leon et al. and Brinkman et al. who reported several significant correlations (0.4–0.6 range). Unlike most previous studies, their experimental groups were restricted to patients with a presumed diagnosis of Alzheimer’s disease. Soininen et al. reported similar findings with their sample of Alzheimer’s disease patients.

Dementia, as defined by criteria such as those of Roth or DSM III, is a heterogeneous syndrome associated with different neuropathological features and with variable neuropsychological profiles. The lack of correlation between CT and neuropsychological measures in study 1 must have been due, at least in part, to this heterogeneity. The fact that correlations and trends emerged in the degenerative and vascular subgroups supports that explanation and argues for a more consistent approach to the study of dementias, particularly to the importance of considering the possible aetiology of the syndromes under analysis. Even within the category of degenerative disease, it is becoming clear that the patterns of brain dysfunction and behavioural disturbance are variable and need to be further studied and refined.

Our second finding is that when CT and neuropsychological measures are considered in older normal and dementia patients together, a highly significant correlation becomes evident, which has rarely been appreciated. We found that 53% of the variance in behavioural parameters could be accounted for by the measured CT changes. This correlation increased further when a specific degenerative subgroup and their matched controls were analysed, showing that CT measures accounted for 61% of the variance among neuropsychological scores. The unusual strength of this correlation, as compared to previous studies, was in all likelihood due to the use of multiple quantitative measures analysed with multivariate statistical procedures. When considering a heterogenous disease process such as dementia, it appears more prudent to consider neuroanatomical and behavioural changes across a variety of measures, providing a more global quantitative analysis rather than attempting to relate a single CT measure with a single behavioural measure. This would appear to be true even when considering major subgroups such as degenerative and vascular disease. Since both CT and neuropsychological measures are gathered in the evaluation of dementia, applying an objective, multivariate method of combined analysis should prove especially useful in the distinction between normal and dementia patients, and possibly pseudodementia patients which is often difficult to achieve on clinical grounds alone.

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