Thalamic Radiodensity and Cognitive Performance in Mild and Moderate Dementia of the Alzheimer Type

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Eighteen patients with mild to moderate dementia of the Alzheimer type underwent cranial computed tomography (CT) and tests of visual attention, recognition and learning. Two subgroups emerged. Subgroup 1 was made up of ten patients who showed impaired visual recognition learning and memory, but intact attention in marked contrast to subgroup 2, which was made up of eight patients, in whom all of these functions were impaired. Planimetric and densitometric CT measurements yielded one significant difference between the two subgroups: a decreased radiodensity in the dorsomedial thalamus of the patients from subgroup 2. Lower radiodensity in the right dorsomedial thalamic area was significantly correlated with impaired performance on the test of attentional set shifting, more specifically, with deficits at the reversal learning stage. These results are interpreted in the context of recent evidence linking reversal learning to a neural network comprising the cholinergic basal forebrain, the amygdala and the orbitofrontal cortex, as well as the mediodorsal nucleus, and recent evidence of cholinergic deficits in this structure in patients with Alzheimer's disease.

Key Words: Alzheimer's disease, thalamus, neuropsychology, computed tomography

INTRODUCTION

The first and most prominent symptom of dementia of the Alzheimer type (DAT) is usually deterioration in memory and learning (McKhann et al 1984; Sahakian et al 1990). Recently, two subtypes, or rather stages of severity, of DAT were described which differ with respect to visual attention (Sahakian et al 1990). Patients with DAT were administered two tests of visual selective attention, as well as tests of spatial and visual recognition memory and visuospatial conditional learning. One set of attentional tests compared visual discrimination learning along intra- and extra-dimensional shifts. In the 12 patients with DAT who were capable of attempting the extra-dimensional shift (subgroup 1), performance was equivalent to that of elderly control subjects matched for age and premorbid level of intelligence. They were also unimpaired at the early stages of the task which included tests of visual discrimination, learning and reversal. In addition, on a second test of attention, a visual search task requiring matching of stimuli on two dimensions (color and shape) with variable numbers of alternatives they were as accurate as the controls. However, subgroup 1 was significantly impaired on tests of recognition memory and learning. In contrast, the other 13 patients (subgroup 2) showed marked impairments on the attentional tasks. This subgroup was also significantly worse than subgroup 1 in performance on the visual recognition and conditional learning tasks and showed greater severity on most of the clinical ratings of dementia.

Deficits in the attentional shift test may be related to frontal lobe dysfunction (Owen et al 1991; Sahakian et al 1990), whereas in contrast the impairments on tests of recognition memory and visuospatial learning are produced by damage, especially to posterior cortical regions, including

temporal lobe and hippocampus (Förstl et al 1992; Mishkin 1982; Sahakian et al 1988).

This study examines potential neuroradiological correlates of the observed neuropsychological differences using quantitative computerized methods for planimetric and densitometric computed tomography (CT) analysis (Beats et al 1991; Förstl et al 1991) in the 18 patients who consented to undergo CT scans. We hypothesized that CT scans from the patients with DAT and deficits on the attentional shift test would show more severe changes in the frontal lobes and functionally related neuroanatomical structures.

METHODS

Patients in the mild and moderate stages (clinical dementia ratings 1 and 2) (Hughes et al 1982) of probable DAT (McKhann et al 1984) underwent extensive neuropsychological tests, including the National Adult Reading Test (NART) (Nelson 1982), the Mini-Mental State Examination (Folstein et al 1975) and tests of visual attention learning and memory from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Sahakian et al 1988; 1990). Eighteen patients (12 males and six females; age range = 53 to 77 years) had given their informed consent to undergo both the testing procedure and a CT scan. They formed a subset of patients from an earlier study (Sahakian 1990).

All patients were examined with unenhanced CT scans using a GE 9800 scanner. A series of horizontal images was acquired parallel to the orbitomeatal line. The data were stored on a tape for post-hoc analysis on an independent viewing console by an examiner who was blind to the clinical findings. A slice 40 mm to 50 mm above the orbitomeatal line was selected for standardized planimetric and densitometric measurements. This slice was chosen to demonstrate the following structures: head of the caudate, thalamus, anterior horns of lateral ventricles and third ventricle. Tissue density (in Hounsfield units) was measured in "regions of interest" with 200 ± 30 pixels, which were placed over the heads of the caudate, the dorsomedial thalamic area and the periventricular white matter (Beats et al 1991; Förstl et al 1991). Statistical comparisons were performed using both the raw data and the values corrected with a multiple regression analysis which took into account differences in head size and age (Förstl et al 1991). The means of the subgroups were compared using a 2-tailed t-test for unrelated samples.

One-tailed tests were used to estimate the significance of the correlation between the CT measurements and the test scores, since the observed differences were expected from previous findings (Förstl et al 1991). Kendall's r was used to estimate the correlations between the CT measurements and the neuropsychological scores.

RESULTS

All patients with mild and moderate DAT showed impaired visual recognition learning and memory. Subgroup 1 (ten patients) had completely normal visual attention. These patients were able both to perform a complex visual search task along two independent perceptual dimensions and to focus their attention to achieve a correct match. In addition, they were able to perform intra- and extra-dimensional shifts

Table 1

Planimetric measurements of the third ventricle and the anterior horns of the lateral ventricles (in cm^2); densitometric measurements of the left and right dorsomedial thalamus, caudate head and frontal periventricular white matter (in Hounsfield units) of the patients with DAT without (subgroup 1) and with visual attention deficits (subgroup 2)

	Subgroup 1		Subgroup 2		Correlations with
	Mean	SD	Mean	SD	the attentional shift test[a]
Third ventricle	1.6	0.7	1.9	0.6	−0.21
Right anterior horn	3.5	1.1	3.7	2.5	0.04
Left anterior horn	3.6	1.3	4.2	2.4	−0.10
Right thalamus	36.0	1.1	34.6	1.2[b]	0.44[c]
Left thalamus	35.1	0.8	33.8	2.1[b]	0.23
Right caudate nucleus	38.3	1.5	38.5	1.4	0.15
Left caudate nucleus	38.0	1.5	37.5	2.2	−0.09
Right frontal white matter	31.0	1.2	30.7	1.9	0.14
Left frontal white matter	31.0	0.8	31.0	2.8	−0.13

[a]Kendall's r, [b]$p < 0.05$, [c]$p < 0.01$

as well as the normal control subjects. Out of a possible nine stages, they attained a mean stage of 8.8 (± 0.5 SD). On the attentional shift test, there was no overlap with subgroup 2 (eight patients), who were severely impaired and attained a mean stage of 3.0 (± 2.0; $p < 0.001$). Subgroup 2 was also impaired on the complex visual search task. The majority of these failed at the reversal stages, which precluded their attempting the more difficult set shifting phases.

Premorbid intelligence was estimated using the NART and was found to be identical in the two subgroups (IQ in subgroup 1 = 115.9 ± 9.2; IQ in subgroup 2 = 115.4 ± 8.6). The Mini-Mental State Examination score was higher in subgroup 1 than in subgroup 2 (21.4 ± 3.9 compared with 14.3 ± 6.1; maximum = 30; $p < 0.01$). Although differences did not reach statistical significance, subgroup 1 was slightly older (age range = 58 to 77 years; median = 72; five males and three females) than subgroup 2 (age range = 53 to 75 years; median = 69; seven males and three females) and the duration of illness was somewhat shorter in subgroup 1 (mean = 4.6 ± 2.3 years) than in subgroup 2 (mean = 5.1 ± 2.4).

Table 1 shows the planimetric measurements of the third ventricles and of the anterior horns of both lateral ventricles (in cm^2) for subgroups 1 and 2. The ventricular areas were consistently but insignificantly larger in subgroup 2. The densitometric measurements (in Hounsfield units) showed a significantly decreased radioattenuation in the left and right dorsomedial thalamic regions in the patients with attentional disturbance (subgroup 2; $p < 0.05$). This difference was significant when the raw or the corrected data were compared.

The results obtained on the attentional shift test were significantly correlated with thalamic density on the right side, a finding which is consistent with the visuospatial nature of the test material.

DISCUSSION

Performance on the attentional shift test yielded a clear distinction between the patients with DAT, thereby dividing them into two subgroups. While performance in subgroup 1 was no different from normal control subjects and they were able to successfully complete both intra- and extra-dimensional shifts, none of the patients in subgroup 2 successfully passed the intra-dimensional shift stage and failed at the earlier stages of simple and compound visual discrimination reversal (Sahakian et al 1990). Both subgroups were impaired on tests of visual learning and memory. However, subgroup 1 was affected to a lesser extent, suggesting that both subgroups represent different stages of illness. This is reflected by differences in global (Mini-Mental State Examination) and more specific (for example, attentional set shifting) estimates of cognitive functioning and by different CT findings. This would also be compatible with the observation of very similar durations of illness in subgroups 1 and 2, since it has been repeatedly demonstrated that patients of similar age, education and global intellectual function at the onset of illness may develop largely disparate rates of symptom progression (Mann et al 1989; Salmon et al 1990).

The patients in subgroup 2 patients with impaired reversal learning and attentional dysfunction showed a significantly lower radioattenuation in the dorsomedial thalamic region than the patients with preserved attention (subgroup 1). The correlation of performance on the visual discrimination/attentional set shifting paradigms with right-sided thalamic radiodensity was consistent with the non-verbal, visuospatial nature of the test material. A similar result was obtained in an independent sample of patients with moderate to severe DAT who had a lower thalamic radiodensity than healthy age-matched controls (Förstl et al 1991). A detailed neuropsychological assessment could not be carried out on these patients, who had more advanced dementia. The lower density was not related to the enlargement of the adjacent third ventricle and could therefore not be explained as a partial volume effect, as suspected in an earlier study (Gado et al 1983). Densitometric CT measurements are subject to numerous artifacts, which we either tried to avoid or to correct for (Förstl et al 1991; Jacobson et al 1985). Nonetheless, these observations must be interpreted with caution, even though they are based on the examination of independent samples.

The thalamus shows neuronal loss, neurofibrillary changes amyloid deposition in the course of neurophathologically verified Alzheimer's disease (AD) (Braak and Braak 1991; Xuereb et al 1991). A reduction in thalamic volume was described in patients with AD who were studied with magnetic resonance imaging (Jernigan et al 1991). The authors suggested that this finding may have neuropsychological implications (Jernigan et al 1991). Recently, Brandel et al (1991) demonstrated differential vulnerability of cholinergic projections to the mediodorsal nucleus of the thalamus in patients with AD and progressive supranuclear palsy. The patients with AD showed a more severe loss of the cholinergic innervation of the patch compartment of the mediodorsal nucleus, which is innervated by cholinergic neurons originating in the basal forebrain and itself projects to the orbital surface of the prefrontal cortex.

The dorsomedial thalamic region, examined with our technique, comprises specific relay nuclei (for example, the dorsomedial nucleus receiving afferents from the amygdaloid complex and projecting to the prefrontal cortex) and non-specific intralaminar and reticular nuclei, which modulate thalamic activity mediating attentional function (Singer 1977). The deficits described here may depend on the disruption of both types of circuitry. The patients in subgroup 2 failed mainly at the attentional shift task at early stages that required the reversal of the stimulus-reward associations, rather than shifting between different dimensions (Sahakian et al 1990). Such deficits are known, from research on

animals, to be crucially dependent on neural circuitry that includes the amygdala and orbitofrontal cortex (Jones and Mishkin 1972). It is therefore significant that basal forebrain lesions that result in cholinergic depletion in the orbitofrontal cortex and amygdala — and probably the mediodorsal thalamus — also produces deficits in reversal learning using very similar stimulus material (Roberts et al 1990; 1992). In view of these considerations, inferior performance on this task may well be related to structural changes in the dorsomedial thalamic area, disrupting function in a network comprising the cholinergic basal forebrain, amygdala and orbitofrontal cortex.

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