

## Multimodal Imaging in Alzheimer's Disease The Relationship between MRI, SPECT, Cognitive and Pathological Changes

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Patients with a clinical diagnosis of Alzheimer's disease were studied using MRI, SPECT, and psychometric tests. Significant correlations between focal perfusion deficits and focal cognitive deficits were found. Significant correlations between regional relaxation time of white matter and psychometric tests of diffuse and focal categories were also found. Pathological examination confirmed Alzheimer's disease as the only diagnosis.

Proton magnetic resonance imaging (MRI) employs the reconstruction of data obtained when mobile protons of a tissue are excited by the application of an oscillating magnetic field in the radio-frequency range, to display an image of that data. An important measure obtained during this process is the spin-lattice relaxation time ( $T_1$ ), the time taken for the nuclei to return to equilibrium after excitation. Most protons available for excitation in tissue are those of water and the  $T_1$  can therefore be altered by changes in the free : bound ratio of water or water content (Mathur de Vre, 1984).

Using MRI, significant increases have been found in the white-matter  $T_1$  in patients with dementia compared with normal controls. This has been a consistent finding at magnetic field strengths of both 0.04T and 0.08T (Besson *et al.*, 1985; Ebmeier *et al.*, 1987). Furthermore, the  $T_1$  changes correlate with severity of the dementia. Selecting specifically patients with Alzheimer's disease (AD),  $T_1$  increases have been confirmed in both studies. Cerebral blood flow measured using carbon-15-labelled  $\text{CO}_2$  and positron emission tomography (PET) has been shown to be reduced in AD (Frackowiak *et al.*, 1981), and such reduction has also been observed using single-photon emission computerised tomography (SPECT) with iodine-132-labelled iodoamphetamine (Gemmell *et al.*, 1984; Sharp, 1986) and more recently with 99m-Tc-hexamethylpropyleneamineoxime (HMPAO) (Gemmell *et al.*, 1987).

The aims of the current study were:

- (a) to determine whether regional changes in white-matter  $T_1$  bear a relationship to focal cognitive deficits measured by psychometric tests in patients with AD
- (b) to determine whether cortical perfusion as measured by HMPAO and SPECT bears a relationship to cognitive deficits in patients with AD

- (c) to determine whether the  $T_1$  values in the white matter are related to perfusion changes in the adjoining grey matter
- (d) to explain what these changes might mean with reference to pathological examination of the patients who have so far come to autopsy.

### Method

Twenty-one right-handed patients (mean age 69, range 57–76 years, 3 men) with a clinical diagnosis of probable AD were studied with MRI, but only the last 13 of these with HMPAO and SPECT (when the technique became available). Diagnostic criteria applied were those of Glen & Christie (1979). In essence, this was progressive dementia in the absence of space-occupying, infective and other neurological disease. Biochemical, haematological and endocrinological abnormalities and vascular disease were also excluded. With respect to the last item, patients who scored greater than four on the Hachinski Ischaemic Scale (Hackinski *et al.*, 1975) were excluded.

All patients received a battery of cognitive tests. The vocabulary and block-design subtests of the Wechsler Adult Intelligence Scale (WAIS) were used to give an indication of general intellectual functioning (Wechsler, 1955; Saville 1971). Verbal and visuospatial memory were assessed using the digit span (digits forwards and backwards) subtest of the WAIS, the visual reproduction (visual recall) and logical memory subtests from the Wechsler Memory Scale (Wechsler, 1945), the Munn test of facial learning (Munn, 1961), an additional test of recognition of famous faces, and the Corsi Block Tapping Test (Milner, 1971). Complex visual-perceptual processing was assessed using the Benton Facial Recognition Test (Benton *et al.*, 1983) and the Raven's Coloured Progressive Matrices (Raven, 1965). Verbal fluency was tested using a controlled oral word-association test (Benton, 1968). Imaging was carried out using the Aberdeen 0.08 T 3.4 MHz resistive system (intercalated SR-IR pulse sequence, TR 1000 ms, TE 200 ms (Redpath *et al.*, 1987)). SPECT imaging was carried out using an IGE400AT rotating gamma camera digitally interfaced to a Link Analytical MAPS 5050 data-acquisition system

15 minutes following intravenous injection of 750mBq Tc-complexed-HMPAO (Sharp *et al.*, 1987).

In the case of MRI,  $T_1$  determinations in the frontal, parietal and temporal regions were carried out on transverse sections 1 cm apart using the three midventricular-cortical sections. Regional  $T_1$  was measured in white matter using the VAX computer system in which a standard area was plotted on each modality of the displayed images,  $T_1$ , inversion-recovery and proton density, avoiding contamination with cerebrospinal fluid (CSF) on the ventricular side and grey matter on the cortical side. The standard areas were selected on the basis of the measured volume on the most atrophic image. Identical volumes were measured in each patient and the means of three consecutive images were used in each calculation. With regard to measuring the perfusion on the HMPAO imaging, the corresponding three sections of the HMPAO images were examined using visual rating of the colour images for each corresponding region as described by Gemmell *et al.* (1987). MRI and SPECT images are on different matrices. Computerised interpolation of images can be achieved by adjusting for their differing centres of gravity, rotational planes and scales. The mean of three blind raters was used to score the severity of the perfusion deficit. A four-point scale was used: normal, mild hypoperfusion, moderate hypoperfusion, and severe hypoperfusion. The raters had a high inter-rater reliability ( $r=0.90$ ,  $P<0.001$ ). This system has previously been successfully used (Reid *et al.*, 1988). Autopsies were carried out on six of the patients and the brains were examined after fixation in formalin.

## Results

### Cognitive test scores and regional white-matter $T_1$

The white-matter  $T_1$  (MS) values in patients with AD were: for the right frontal region, mean 314 (range 293–360); left frontal region, mean 310 (range 290–358); right parietal region, mean 343 (range 301–398); left parietal region, mean 341 (range 297–395); right temporal region, mean 321 (range 303–338); and left temporal region, mean 321 range 301–340).

The results for the correlations between regional  $T_1$  and the scores for the logical memory and delayed recall of logical memory showed a similar profile (Table I). There was a significant correlation with both left and right frontal and parietal, and left temporal white-matter  $T_1$ . This was particularly strong in the frontal region and more so on the left than on the right. The result is in keeping with the fact that this test, which demands attention and organisation as well as memory, reflects diffuse and widespread hemispheric damage, and since it is a verbal task, particularly on the left. A similar pattern of correlation was observed between the visual recall and delayed visual recall subtests and white-matter  $T_1$ . Delayed visual recall showed a stronger correlation overall and, in keeping with the visuospatial nature of this test, a strong relationship with white-matter change in right-sided structures.

The score on the vocabulary subtest of the WAIS (Table I) showed a higher correlation with the  $T_1$  of left-sided structures compared with right, and for the more posterior

TABLE I  
Correlations (Pearson's coefficient) between regional  $T_1$  white matter and cognitive test scores

Region	Logical memory <sup>1</sup>	Logical memory <sup>1</sup> (delayed) <sup>1</sup>	Visual recall <sup>1</sup>	Visual recall <sup>1</sup> (delayed)	Vocabulary <sup>2</sup>	Muniz facial learning	Verbal fluency <sup>3</sup>	Benton facial recognition	Corsi block tapping	Famous faces recognition
Right frontal	0.51**	0.60**	0.54**	0.71***	NS	NS	NS	NS	NS	NS
Left frontal	0.60*	0.67**	0.47*	0.71***	NS	NS	0.42*	NS	NS	NS
Right posterior parietal	0.40*	0.62**	0.50*	0.66**	0.49*	NS	0.61*	NS	0.80**	NS
Left posterior parietal	0.50*	0.56**	0.44*	0.57**	0.52**	NS	0.43*	NS	0.76**	NS
Right temporal	NS	NS	0.57**	0.60**	NS	NS	NS	NS	NS	NS
Left temporal	0.40*	0.59**	NS	NS	0.44*	NS	NS	NS	NS	NS

\* $P<0.05$ , \*\* $P<0.01$ , \*\*\* $P<0.001$ . 1. Subtest of Wechsler Memory Scale. 2. Subtest of WAIS. 3. Controlled oral word-association test (Benton, 1968).

locations (i.e. parietal and temporal). This is in keeping with the expected findings of vocabulary impairment in diffuse left-hemisphere disorder. Scores on both the Munn test of recognition of recently presented novel faces and the Benton Facial Recognition Test correlated with the parietal white-matter change more strongly on the right than on the left, as expected (Damasio *et al*, 1986).

Scores on the Corsi Block Tapping Test correlated with right parietal white-matter change, an observation which supports the finding of De Renzi *et al* (1977) that lesions in this region seriously impair performance on this task. The verbal fluency test, where subjects must produce as many words as possible beginning with a selected letter of the alphabet within a specified time, bore the expected relationship to the left frontal white-matter  $T_1$ .

No significant correlations were found with: orientation (WAIS block-design and Raven's tests); digits forward, which is a left inferior parietal function (highly focal changes may not be detected in the relatively large volumes of tissue measured); and digits backwards, which is influenced by more diffuse and predominantly left-hemisphere disturbance.

#### Cognitive test score and regional grey-matter perfusion

With regard to the correlations between perfusion deficit and performance on cognitive tests (Table II), the digits forwards and digits backward subtest scores correlated predominantly with right-sided changes posteriorly and anteriorly. No such correlation was found between these test scores and white-matter  $T_1$ . The logical memory and delayed logical memory subtests did not show any correlation with cerebral perfusion. It is to be noted that there was a relationship with white-matter  $T_1$ . Scores on the Corsi Block Tapping Test show a significant correlation with right but not left posterior parietal perfusion. The block-design subtest of the WAIS also showed correlation with posterior right parietal perfusion. With regard to the Munn test of facial learning, the score showed a correlation with right parietal perfusion. Overall, the visuospatial tasks appear to correlate more highly with perfusion deficit than do auditory verbal tasks.

To summarise:

- the Corsi Block Tapping Test, Munn facial learning test, Benton Facial Recognition test, and vocabulary subtest of the WAIS all showed strong correlations with cerebral blood-flow deficits in the grey matter as well as increased  $T_1$  in the white matter, predominantly in the parietal regions (the visual recall subtest just failed to reach significance with perfusion deficits)
- The digits forward and digits backwards subtest, the famous faces recognition test, the Raven's Coloured Progressive Matrices and the block-design subtest correlated with cerebral perfusion only
- the logical memory subtest of the Wechsler Memory Scale and the verbal fluency test correlated with white-matter  $T_1$  only.

TABLE II  
Correlations (Kendall's coefficient) between regional perfusion deficits and cognitive test scores

Region	Digits forwards <sup>1</sup>	Digits backwards <sup>1</sup>	Vocabulary <sup>1</sup>	Logical memory <sup>2</sup>	Logical memory (delayed) <sup>2</sup>	Corsi block tapping	Block design <sup>1</sup>	Ravens colour matrices	Famous faces recognition	Munn facial learning	Visual recall <sup>2</sup>	Benton facial recognition
Left frontal	-0.06	-0.28	-0.29	-0.06	-0.39	0.07	0.12	-0.18	-0.47*	-0.37	-0.24	0.57
Right frontal	-0.06	-0.38	-0.38	-0.04	-0.35	-0.01	-0.04	-0.20	-0.48*	-0.42*	-0.30	0.35
Left posterior	-0.12	-0.21	-0.10	-0.14	-0.29	-0.14	-0.38	-0.26	0.06	0.13	-0.40	-0.68*
parietal												
Right posterior	-0.53*	-0.49*	-0.48*	-0.22	0.14	-0.50*	-0.58*	-0.49*	0.27	-0.47*	-0.40	-0.72*
parietal												

\* $P < 0.05$ . 1. Subtest of WAIS. 2. Subtest of Wechsler Memory Scale.

#### Correlations between perfusion deficits and adjacent white matter

If the perfusion score in the posterior parietal region is plotted against regional posterior parietal white-matter  $T_1$  lying adjacent to that area of cortex, significant correlations are found (on the right,  $r=0.46$ ,  $P<0.03$ ; on the left  $r=0.63$ ,  $P<0.003$ ). The greater the  $T_1$ , the greater the perfusion deficit on the adjoining grey matter, and the lower the blood flow in the areas. When similar comparisons were made for other regions, no significant correlations were obtained.

#### Pathological findings

The brains of six patients studied by both MRI and SPECT were examined at autopsy both macroscopically and microscopically by the same neuropathologist (PVB) in accordance with the criteria laid down in the Report from the Medical Research Council's (1987) AD workshop. AD was confirmed as the only diagnosis. In none of the cases were there significant atherosomatous changes in the major arteries or macroscopically identifiable infarcts. Microscopically, those areas of the brain that had shown reduced cerebral perfusion with HMPAO were not detectably different from areas that had not shown such change. Rarefaction in the central white matter was found in five of the six cases, but there was no macrophage infiltration or other acceptable evidence of ischaemic damage. Small arteries showed mild fibrous sclerosis in three cases, in one of which there was also mild amyloid angiopathy; in none of the affected vessels was the lumen significantly narrowed and neither old nor recent thrombosis was identified.

#### Discussion

The results suggest that, where the strongest correlations between one of the image characteristics (perfusion or  $T_1$ ) and cognitive test score occurs, there also tends to be a significant correlation between the other image characteristic and that cognitive test score. Thus tests including the Benton Facial Recognition, the Munn facial learning, the Corsi Block Tapping and the vocabulary subtest of the WAIS all show correlations with  $T_1$  and blood flow. It is also of interest that tests which place demands on specific areas of the brain (e.g. Corsi Block Tapping and facial memory tasks) tend to show relationships with both imaging techniques, unlike those reflecting diffuse damage. Such specific focal abnormalities are particularly located in the parietal regions. However, such relationships between white-matter  $T_1$  and grey-matter perfusion have not been found when the other brain regions are considered. While it is possible that this may be an incidental finding, it is noted that perfusion deficits in this region have been identified by a number of studies as a hallmark of AD

(Risberg & Gustafson, 1983; Gemmell *et al.*, 1984). It is interesting that the perfusion score in the parietal cortex correlates with the  $T_1$  of the adjacent white matter on both left and right. It might be argued on the basis of the above data that the disruption of cognitive processes which require the support of mechanisms focused in specific cortical regions can be detected by changes in both regional  $T_1$  and cerebral perfusion. However, failure on tasks which require a wide network of neural interconnections may be indicated only by degenerative changes in the white matter (which carries the brain communication tracts); then changes would only be detected by the  $T_1$  index. Tasks on the verbal fluency test, finding the appropriate definition for a word or constructing a schema to remember a short sequence of events for example, are all extremely complex activities which require the integrity of a number of specialised processors. Integrity of the brain's inter-regional connections may be particularly important for the adequate performance of these tasks.

The histological appearances in the six brains so far examined suggest that the increased  $T_1$  values in the white matter are not associated with ischaemia resulting from vascular disease. It seems that the rarefaction in the central white matter encountered in most of these cases (Besson *et al.*, 1988) is more likely to be secondary to changes in the grey matter than to result from ischaemia (Englund *et al.*, 1988). It is possible that axonal changes associated with nerve-cell degeneration may give rise to an increased water content in the white matter. The elevated  $T_1$  may therefore be a reflection of the raised free : bound ratio of water consequent upon the alteration in myelin structure. A further possible explanation is that fluid increase in glial cells or in the extracellular compartment occurs in areas with loss of nerve fibres.

#### Conclusion

There are links between regional changes in white-matter  $T_1$  values in AD and cognitive deficits. These indices of morphological change are associated with functional change (as indexed by reduction in regional cerebral perfusion). The regions of reduced perfusion and the region of increased  $T_1$  are not due to recognisable vascular disease. The relationships between  $T_1$  change and pathological change may allow the *in-vivo* interpretation of  $T_1$  on images of patients with AD. Furthermore, these can be linked to functional impairment as measured by perfusion deficits and cognitive deficits.

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