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Nuclear Magnetic Resonance (NMR)
II. Imaging in Dementia

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Summary: Proton NMR imaging of the brain is rapidly becoming established as a useful investigative tool in medicine. This paper examines the usefulness of the NMR parameters—spin-lattice relaxation time (T_1) and proton density (PD)—in differentiating groups of patients with senile dementia of Alzheimer type (SDAT) and multi-infarct dementia (MID) from each other, and from elderly controls. T_1 values increase with severity of dementia. NMR parameters may also be of use in localising regions of brain damage.

NMR imaging using the Aberdeen method measures two parameters—the proton density (PD) and the spin-lattice relaxation time (T_1); these parameters represent not all protons, but only fairly mobile ones. Protons, (hydrogen nuclei, that are bound inside large molecules such as proteins) generate signals that cannot be detected. Proton density data therefore refers to the protons in water and free lipids, and is a measure of the concentration of such protons. T_1 values represent the water as observed in two states, one 'free', the other a 'bound' state in a hydration sheath around a macromolecule, consisting of water interacting with that molecule. Protons exchange very quickly

between these two states, so that the observed T_1 value is an average of the T_1 values for these states separately.

Pathological studies of patients with multi-infarct dementia (MID) demonstrate changes indicative of infarction (Corsellis, 1969). In the early stage, there is oedema and in the latter stages gliosis or cavitation, while in recent infarcts, the increased water content of the tissue should be reflected in altered T_1 and PD parameters. Such changes would be seen only occasionally, in comparison with the more long-standing lesions, which, because of the gliosis, demyelination, and cavitation, are also likely to be reflected by alteration in the content and state of water in the various tissue compartments. The situation in senile dementia of Alzheimer type (SDAT) is, however, less clear. There is a lack of studies on brain water changes in SDAT, and though animal work (Nagy *et al*, 1982) suggests that brain water declines with age, this says nothing of the situation in SDAT.

The anticipated differences between SDAT and MID in this respect, if reflected in T_1 and PD measures, may differentiate between these two conditions. On this basis, T_1 and PD parameters in MID, SDAT, and normal elderly controls were measured and compared.

Method

The subjects (aged 65–85 years) were all long-term hospital patients suffering from senile dementia. They were divided into two groups, SDAT and MID, on the basis of their scores on the Hachinski Rating Scale (Hachinski, 1975). A score of four or less indicates SDAT, and 8 or more MID.

Clinical history, and physical and biochemical examination based on the MRC diagnostic screen (Glen & Christie, 1979) were used to exclude other causes of dementia. Ultimately, 13 patients were diagnosed as SDAT and 12 as MID. Two patients scored between 5 and 8, and were excluded. Eleven subjects of the same age-range as the patients were selected from a non-patient population as controls.

The severity of dementia was assessed using the MSQ (Kahn *et al*, 1960) and Mattis mental status examination for organic mental syndromes in the elderly (Mattis, 1976). This test measures a number of cognitive tasks, attention, initiation of actions, construction, conceptualisation, and memory, giving both a sub-score for each and an overall score. Patients underwent NMR imaging, using the Mark 1 Aberdeen NMR imager, developed by Hutchison *et al* (1980) and Johnson *et al* (1982), with the special head coil, designed by Redpath & Hutchison (1982), operating at a magnetic field strength of .04 T (Telsa) (proton resonant frequency 1.7 MHz). T_1 and PD values were measured from the supra-ventricular transverse section. T_1 measures were taken from cerebral grey and white matter areas, and PD measures from white matter areas. The pixel volume is 1.95 $mm^2 \times 12$ mm depth, and about 70 pixels were counted in each white matter area, and about 10 in the grey matter areas. The areas examined were left and right, frontal, parietal, and occipital regions. These were obtained by manual mapping of the areas to be examined and a computerised count of the pixel number and T_1 and PD values read back from the initial acquired data.

Results

The control group had a mean MSQ of 8.4 (±1) and a Mattis total score of 118.9 (±16.6). Of the Mattis sub-scores, the main one of relevance to this paper is the constructional sub-score, in which the controls scored a mean of 5.7 (±0.4) out of a total of 6; this test is a reflection of parietal lobe dysfunction. The patients with SDAT scored poorest in all tests of cognitive function, with MSQ scores of 1.4 (±0.5), Mattis total scores of 58.9 (±27.6) and construction sub-scores of 2.8 (±1.9). Patients with MID scored 3.2 (±2.2) on the MSQ, 77.3 (±26.9) on the Mattis and 3.5 (±2.3) on the construction sub-scores.

Table I shows the T_1 and PD values for right and left frontal, parietal, and occipital white and grey areas (RFW, LFW, RFG, LFG, RPW, LPW, RPG, LPG, ROW, LOW, ROG, LOG).

The T_1 and PD values of all areas in the three groups were compared using analysis of variance. The T_1 values of white matter of all areas were significantly greater in SDAT and MID subjects than in controls, and there was no significant difference between the SDAT and MID groups. The T_1 results for grey matter are variable, probably due to the greater error in mapping because of the small volumes. With regard to the PD measures of white matter, however, SDAT patients had significantly greater values than controls, though there is no difference between controls and MID patients. SDAT patients also had significantly greater values than MID patients. Using a combination of PD and T_1 measures in white matter, it is therefore possible to differentiate between the SDAT and MID groups, and both these from normal controls.

The mean T_1 value for all white areas of the section was calculated for each subject, and plotted against the MSQ score. The scattergram (see Figure) illustrates this.

Pearson's correlations of mean T_1 for all white areas with MSQ score shows that for the whole group, there is a significant negative correlation between the two (Table II); in other words, the greater the degree of dementia, the greater the T_1 value. Within groups, however, the correlation does not reach significance, which may reflect the narrow range of MSQ scores within each group. The mean T_1 data for grey areas also shows a significant negative correlation with MSQ scores for all groups taken together, but there are no significant differences when each is taken separately. Significant correlations are not achieved for the mean PD value for white area, for the groups taken separately or together. As might be expected, a similar result is obtained when the Mattis total scores are correlated with the mean T_1 values for white and grey matter and the PD for white matter. Severity of

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TABLE I

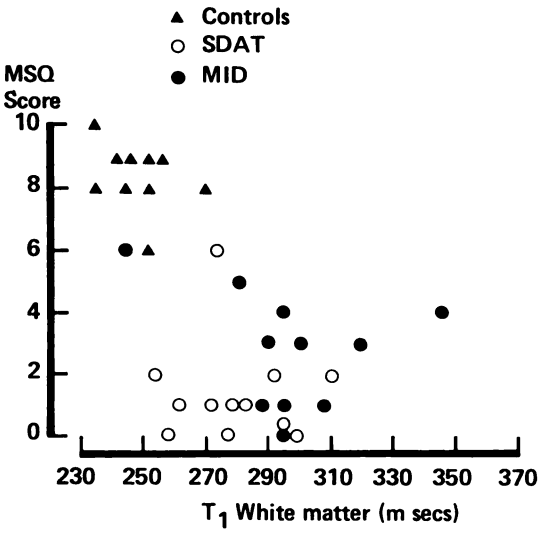
T_1 and proton density (PD) values for patients with SDAT, MID and elderly controls

	Area	Control n = 11 (Mean ± SD)	SDAT (n = 13) (Mean ± SD)	MID (n = 12) (Mean ± SD)	Control vs. SDAT (P)	Control vs. MID (P)	MID vs. SDAT (P)
T_1 (m sec)	RFW	246 ± 14	271 ± 17	283 ± 26	0.001	0.005	NS
	LFW	241 ± 18	280 ± 27	285 ± 31	0.001	0.0007	NS
	RPW	246 ± 10	277 ± 15	298 ± 43	0.0001	0.009	NS
	LPW	250 ± 17	278 ± 13	312 ± 71	0.0002	0.01	NS
	ROW	260 ± 6	284 ± 17	294 ± 33	0.0001	0.0004	NS
	LOW	251 ± 13	282 ± 24	292 ± 29	0.001	0.0004	NS
T_1 (m sec)	RFG	307 ± 19	330 ± 28	331 ± 22	0.04	0.02	NS
	LFG	298 ± 10	321 ± 19	340 ± 20	0.002	0.0001	0.03
	RPG	309 ± 10	322 ± 12	318 ± 16	0.02	NS	NS
	LPG	300 ± 11	324 ± 24	325 ± 34	0.007	0.04	NS
	ROG	302 ± 16	316 ± 16	315 ± 16	NS	0.06	NS
	LOG	296 ± 18	309 ± 22	312 ± 36	NS	NS	NS
PD Arbitrary Units	RFW	168 ± 12	187 ± 10	169 ± 20	0.0007	NS	0.01
	LFW	170 ± 12	194 ± 25	168 ± 22	0.01	NS	0.01
	RPW	170 ± 9	186 ± 7	166 ± 20	0.0002	NS	0.004
	LPW	171 ± 11	191 ± 10	169 ± 26	0.0001	NS	0.008
	ROW	170 ± 10	187 ± 10	166 ± 24	0.0005	NS	0.01
	LOW	172 ± 10	187 ± 9	169 ± 18	0.0007	NS	0.004

TABLE II

Correlations (Pearson's) between MSQ scores and mean T_1 and PD values for grey and white matter in MID, SDAT and elderly controls

	MID	SDAT	Controls	All groups
T_1 mean white—all areas	−0.49 P = 0.054	−0.08 NS	−0.35 NS	−0.63 P = 0.0001
T_1 mean grey—all areas	−0.03 NS	−0.04 NS	−0.38 NS	−0.47 P = 0.002
PD mean white—all areas	0.22 NS	0.29 NS	−0.07 NS	−0.2 NS



FIG—MSQ scores vs T_1 white matter—all groups.

dementia is therefore reflected in T_1 scores for grey and white areas, but not in PD scores for white areas.

We have considered the relationship between overall state of mental deterioration, as measured by psychological measures of cognitive functioning, and changes in T_1 and PD. Do T_1 and PD changes also reflect regional pathology? To answer this, we looked at the constructional sub-scores of the Mattis scale, and correlated them with the T_1 and PD values of both parietal lobes. There was a significant negative correlation between the Mattis constructional scores and the T_1 scores for white matter in the parietal regions (−0.47, P = 0.003 on the left; and −0.34, P = 0.03 on the right), when all groups were taken together. This implies bilateral pathology, but suggests that it might be more prominent on the left. Highly significant correlations were also obtained when measures of T_1 for grey parietal areas were considered. All subjects appeared to be right-handed.

Discussion

The diagnostic value in SDAT of morphological changes in the brain observed by CAT scan is much debated. Ford & White (1981) have shown that advancing age is associated with increased cerebral atrophy in both normal persons and in those with

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dementia, while Tomlinson *et al* (1970) have indicated that although patients with dementia show more atrophy than non-demented persons of equal age, there is considerable overlap between the two groups. The degree of atrophy provides little information about degree of cognitive impairment. Soininen *et al* (1982) have shown, however, that ventricular dilatation may be of more value as a diagnostic and severity parameter, being increased in SDAT subjects, as opposed to MID subjects and normals, and larger the more severe the dementia.

In addition to looking at the size of cortical and cerebral tissue as an index of change in dementia, it is possible to look at the physico-chemical characteristics of the tissues, e.g. the X-ray density of the tissue during CAT scanning. However, these studies have yielded conflicting results. Wilson *et al* (1982) showed no change in CT density between patients with SDAT and normal age-matched controls. On the other hand, Bondareff *et al* (1981) demonstrated reduced density in the medial temporal lobe, anterior frontal lobe, and head of the caudate nucleus in patients with SDAT.

Farbas *et al* (1982), using ^{18}F-2-deoxy-2-fluoro-D-glucose as a tracer in positron emission studies in SDAT, demonstrated reduced utilisation of glucose, and correlated this with the degree of cognitive impairment.

The present study demonstrates that it is possible, given the relevant T_1 and PD values, to distinguish between SDAT, MID, and non-demented elderly patients. These changes can be measured even when lesions cannot be detected visually on the images. This could have potential in differentating, for example, patients with dementia from those with pseudo-dementia due to functional psychoses. Furthermore, severity of dementia bears a relationship to the T_1 of white matter, and we have also demonstrated that where there is psychometric evidence of a regional deficit, the degree of deficit is reflected in changes in the T_1 and PD measures of that region.

T_1 values which are observed clinically will depend on several factors. In the first place, total water content and water structure may interact in a complex way; generally speaking, the more free water, the higher the T_1, while free lipid protons have a lower T_1 than water protons. Membrane lipids and proteins are too structured to give observable signals, but influence observed T_1 by structuring adjacent water molecules. By and large, the T_1 data are representative of the state of protons in water and free lipids. The PD values predominantly represent the proton concentration of water and free lipids, so that two tissues that have very different water/fat ratios may have the same PD but different T_1 values.

In SDAT, for a given volume of white matter, there is an increased total proton concentration; this is presumably associated with a reduction in other (large molecular) structures, consistent with the observed increased T_1. However, this finding cannot be readily accommodated with the known pathological changes in SDAT. In MID, on the other hand, total water proton concentration is unchanged, but the T_1 is increased. This may be explained by the presence of a large proportion of the water in a more 'free' state (perhaps related to the cysts observed pathologically) or by a reduction of free lipids (perhaps a late consequence of the demyelination which is also observed pathologically). These questions, though, will have to await neuropathological confirmation.

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