

## Altered Magnetic Resonance White-Matter $T_1$ Values in Patients with Affective Disorder

R. J. DOLAN, A. M. POYNTON, P. K. BRIDGES and M. R. TRIMBLE

The MRI  $T_1$  proton relaxation values were assessed in 14 patients with bipolar affective disorder and 10 with a unipolar disorder and a matched normal control group. The  $T_1$  values in the frontal white matter of patients significantly exceeded those of the controls. This difference was accounted for by an increase in  $T_1$  values in the frontal white matter of unipolar patients: the values for bipolar patients alone did not differ from those for controls. These preliminary findings support a hypothesis of frontal lobe dysfunction mediating pathological changes in mood.

Morphological brain changes in patients with affective disorders are supported by neuropathological and neuroradiological evidence. Corsellis (1962), reporting 300 consecutive post-mortem investigations from a single mental hospital, included 40 patients (mean age 69 years) with affective disorders. Within this group 22% had moderate to severe cerebral atrophy in the absence of significant numbers of plaques or neurofibrillary tangles. Early neuro-radiological investigations, based on findings from pneumoencephalography (PEG), indicating morphological brain changes in affectively ill patients (Braftos & Sagedal, 1960; Haug, 1962; Nagy, 1963), are supported by reports of the use of computerised tomography (CT) and air ventriculograms in patients undergoing subcaudate tractotomy (Van Boxel *et al*, 1978; Standish-Barry *et al*, 1982). Further CT findings have confirmed that patients with affective disorders, both bipolar and unipolar, show significant ventricular enlargement and sulcal widening compared with controls (Jacoby & Levy, 1980; Pearlson & Veroff, 1981; Dolan *et al*, 1985, 1986). Using a CT index of brain tissue density (Hounsfield units), patients suffering affective disorders were found to differ from both controls and patients with dementia (Jacoby *et al*, 1983).

Magnetic resonance imaging (MRI) represents a further technological advance in the study of brain structure. It is sensitive to pathological changes (Bydder *et al*, 1984) and has the potential to examine physicochemical changes. The proton relaxation parameters,  $T_1$  and  $T_2$ , are sensitive to pathophysiological change, particularly shifts in water distribution. As yet, this potential of MRI has been little used in the study of so-called functional psychoses. However, in one study of patients with bipolar affective disorder an increase in  $T_1$  values in frontal and temporal white matter, which normalised following lithium therapy, was reported (Rangel-

Guerra *et al*, 1983). The present study was undertaken to explore further the relationship between regional brain  $T_1$  values of patients with affective disorders by comparison with an age- and sex-matched control group.

### Method

Patients were selected from the acute in-patient population of a teaching hospital, the Royal Free Hospital, and a large mental hospital, Friern Barnet Psychiatric Hospital. A further sample was recruited from patients undergoing evaluation for psychosurgery at the Geoffrey Knight Unit for Affective Disorders. All patients fulfilled Research Diagnostic Criteria (RDC) for current major depressive disorder (Spitzer *et al*, 1978). Exclusion criteria included a history of significant past or concurrent medical illness or of alcohol abuse. Normal control subjects, matched with the patients for age and sex, were recruited from hospital staff and from the general public by advertisement. None of the controls had a past or present history of significant physical illness, alcohol abuse, or a family history of psychiatric disorder. All patients and controls gave written informed consent.

Twenty-four patients (12 men, 12 women) and 13 control subjects (6 men, 7 women) were included in the study. Fourteen patients had a bipolar illness (8 men, 6 women) while the remainder had a unipolar disorder. Three of the bipolar and four of the unipolar women were menopausal. Six patients were recruited from the Geoffrey Knight Unit for Affective Disorders.

A detailed psychiatric history obtained by interview was supplemented by information from psychiatric case records. Attention was given to the following: lifetime pattern of illness; a family history of depression or major psychosis; and present and past medication, including type and duration. Severity of depression was determined using the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1967).

The MRI scanning was carried out using an MD800 scanner with field strength 0.08 T and resonance frequency of 3.4 MHz. A standard pulse sequence employing

alternating saturation-recovery and inversion-recovery sequences with repetition times (TR) of 1 s and an inversion-recovery time (TI) of 200 ms was utilised. A calculated  $T_1$  image was generated from a computed algorithm.

Ten slices, in three planes, one coronal (through the external auditory meatus), one sagittal (mid-line) and eight 12 mm transaxial slices parallel to the orbital-meatal line, were obtained in each subject.  $T_1$  values were measured from 17 pixel regions of interest (ROIs) from the transaxial slices using a cursor controlled by a joystick. Representative areas were sampled from the grey and white matter of the frontal, temporal and parietal regions of both hemispheres, as well as the caudate and thalamic nuclei. Anatomical landmarks were identified from the scans and by reference to a stereotactic atlas. Similar axial slices were used for ROI measurements in all subjects. All measures were taken blind to whether the subject was a patient or a control by a single investigator (RJD).

The daily reproducibility of  $T_1$  measurements, utilising standard phantoms of copper sulphate in the relevant  $T_1$  range, had a standard deviation of less than 5% of the mean. The test-retest intraclass correlation was satisfactory (0.91) for all white matter and thalamic and caudate nuclei but less so (0.82) for grey matter. As grey-matter  $T_1$  values could not be measured reliably these were excluded from further analysis.

The distribution of  $T_1$  values for the regions sampled conformed to the normal and therefore parametric statistics were performed using the SPSS computer package. Correlations between variables were examined using Pearson product-moment correlations. For each brain region a two-way analysis of variance was performed using the MANOVA procedure. Age was used as a covariate and the main effects examined were subject status (control, unipolar, or bipolar) and laterality. Two comparisons were used to distinguish more clearly between the main effects of subject status, namely control v. patient and unipolar v. bipolar.

### Results

There was no significant difference in the mean age of the patients (42 years, s.d. 10) and control subjects (46 years, s.d. 7). The mean age of the bipolar patients was 39 years (s.d. 9) and of the unipolar patients was 47 years (s.d. 11). In the patient group, the mean age of onset of illness was 31 years (s.d. 9), the mean duration of illness 11 years (s.d. 7), and the mean overall HRSD score was 23 (bipolar 24, unipolar 21). None of the patients displayed psychotic symptoms.

The patients were all taking some form of psychotropic medication. All but two of the 14 bipolar patients were receiving lithium at the time of the study compared with four of the ten unipolar patients. The patients were, at the time of the study, receiving a variety of other psychotropic agents: tricyclics 75% (bipolars 57% v. unipolars 100%), neuroleptics 30% (bipolars 35% v. 20% unipolars), benzodiazepines 20% (bipolars 14% v. 33% unipolars).

The mean  $T_1$  values by brain region and side, for patients and controls, are presented in Table I. There were no relationships between age and the  $T_1$  values in either the control or the two patient groupings. Furthermore, within the patient sample there were no correlations between age of onset, duration, or HRSD score and the  $T_1$  values.

TABLE I  
 $T_1$  values in patients and control subjects by brain site and side

	Controls Mean (s.d.)	Unipolar patients Mean (s.d.)	Bipolar patients Mean (s.d.)
Frontal			
right	288 (16)	313 (27)	288 (16)
left	289 (11)	315 (24)	293 (18)
Parietal			
right	279 (10)	296 (26)	287 (22)
left	282 (12)	293 (23)	282 (12)
Temporal			
right	325 (16)	346 (27)	335 (13)
left	331 (11)	341 (22)	338 (22)
Caudate			
right	379 (23)	392 (24)	375 (25)
left	370 (23)	368 (18)	361 (20)
Thalamus			
right	328 (13)	330 (34)	323 (32)
left	325 (13)	327 (24)	319 (30)

The patients recruited from the Unit for Affective Disorders did not differ in terms of the  $T_1$  values from the remaining patients. There was no evidence of an effect of sex on  $T_1$  values across all subjects or with respect to the individual subject groupings.

There were no effects of laterality nor any significant interaction between laterality and subject status in any brain region. Significant differences in  $T_1$  values were, however, apparent between patients and controls in the frontal white matter. The mean  $T_1$  values in frontal white matter (FWM) of the total patient sample were significantly greater than those of control subjects ( $P < 0.05$ , d.f. = 1,  $F = 6.13$ ). Furthermore, within the patient group, the FWM  $T_1$  values of the unipolar patients significantly exceeded those of the bipolar patients ( $P < 0.01$ , d.f. = 1,  $F = 9.63$ ). For FWM the  $T_1$  values of bipolar patients did not differ significantly from those of controls. These comparisons are presented

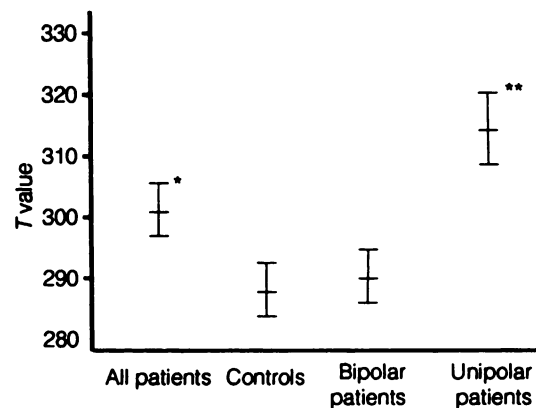


Fig. 1 Plot of mean ( $\pm$  s.e.)  $T_1$  relaxation values for frontal white matter in patients and control subjects (\* $P < 0.05$ , \*\* $P < 0.01$ , relative to controls).

graphically in Fig. 1. No differences were noted between patient and controls or unipolar and bipolar patients for  $T_1$  values in the thalamic or caudate nuclei.

There was no relationship between family history and regional  $T_1$  values. No significant effect of neuroleptic, antidepressant or benzodiazepine drugs on regional  $T_1$  values were apparent in the total patient population or in the unipolar or bipolar groups analysed separately. It was not possible to ascertain the effect of lithium on the  $T_1$  values as such treatment was strongly associated with bipolar patient status. However, the mean  $T_1$  values in the two bipolar patients not taking lithium were similar to other bipolar patients and normal controls.

### Discussion

This study has demonstrated significant alterations of  $T_1$  values in the frontal white matter of patients with affective disorders compared with age- and sex-matched normal control subjects. These differences were accounted for by increased  $T_1$  values in the unipolar patients, as the values for the bipolar patients were close to those of the controls.

Before discussing the significance of these findings it is necessary to consider sources of bias that could account for the observed changes. An important consideration is the possibility of systematic alterations in the measurement of  $T_1$  values due to machine error or 'drift' over time. This does not seem a likely explanation as the scanner gave consistent  $T_1$  phantom readings, obtained daily, over the course of the study. Furthermore the subjects, both patients and controls, were frequently studied within a single scanning session and no group was preferentially scanned at particular times. A statistical consideration is the fact that in the data analysis a relatively high number of different group comparisons were computed, thus increasing the likelihood of chance significant findings. This possibility cannot be entirely dismissed although the observed significant differences remained even after correcting for multiple comparisons. No effects of sex were apparent on  $T_1$  values and in women menopausal status was not associated with altered values. Finally, the patient groupings were far from ideal in that they all had established illness and all were taking various psychotropic medications. Nevertheless, apart from lithium in bipolar patients, no medication was exclusive to any particular diagnostic group.

The basis of the observed altered  $T_1$  values in the white matter of unipolar patients is not immediately obvious. Relaxation parameters are reported as altered in a variety of pathophysiological states, including experimentally induced oedema, in apparently normal white matter in multiple sclerosis, in the basal ganglia of patients with Parkinson's disease, in

epilepsy, and in schizophrenic patients with tardive dyskinesia (Barnes *et al*, 1986; Ormerod *et al*, 1986; Besson *et al*, 1985, 1987; Conlon *et al*, 1988). Therefore, the finding of altered relaxation values would appear to lack pathological specificity.

An important source of alteration in MRI relaxation parameters is variation in the distribution of 'free' and 'bound' tissue water (Mathur-De Vre, 1984). A strong correlation between the water content of white matter and  $T_1$  values has been demonstrated (Bell *et al*, 1987). In patients with affective disorders alterations in membrane transport of sodium, potassium and water distribution have been reported, with an increase in intracellular sodium levels during depressive episodes (Coppen & Shaw, 1963; Coppen *et al*, 1966). These changes may reflect alterations in membrane  $\text{Na}^+ - \text{K}^+ - \text{ATPase}$  activity (Naylor *et al*, 1973, 1976). Furthermore, lithium has been shown to increase enzymatic  $\text{Na}^+ - \text{K}^+ - \text{ATPase}$  activity in manic-depressives but not in controls (Naylor *et al*, 1974). The findings of increased  $T_1$  values in this study might reflect such dysregulation of intracerebral ionic and water distribution in depression, although such an explanation is highly speculative.

In the present study the  $T_1$  values of bipolar patients approximated those of normal controls. Two explanations can be suggested for this. The fact that most of the bipolar patients were taking lithium could mean that these patients had  $T_1$  values 'normalised' by such therapy. This explanation would be consistent with a previously reported finding that lithium 'normalised'  $T_1$  values of the white matter in bipolar patients without having any effect on normal white matter (Rangel-Guerra *et al*, 1983). However, the mean  $T_1$  values of the two bipolar patients not taking lithium were similar to those of normals. Alternatively, the absence of changes in bipolar patients in the present study might reflect a different pathophysiology in this condition.

Abnormalities of white matter are not usually associated with affective illness. However, an early neuropathological biopsy study of five patients with affective disorder reported such abnormalities, in particular, swelling of the oligodendroglia (Elvidge & Reed, 1938). As the present study gave no reliable data on cortical grey matter, one interpretation of the finding of abnormalities in the white matter is that they reflect a generalised abnormality in frontal lobe function in affective disorders. The frontal lobes are important components of the limbic system, the primary mood-regulating system, and it is established that pathology in the frontal lobes may result in affective change (Hecaen & Ajuriaguerra, 1956; Direkze *et al*, 1971; Robinson *et al*, 1984). More

