In vivo investigation of white matter pathology in schizophrenia with magnetisation transfer imaging

J Foong, M Maier, G J Barker, S Brocklehurst, D H Miller, M A Ron

Abstract

Objectives—This study is the first to use magnetisation transfer imaging (MTI), a technique sensitive to myelin and axonal abnormalities, to investigate the white matter in vivo in patients with schizophrenia.

Methods—MTI was performed in 25 schizophrenic patients and 30 healthy controls. A region of interest (ROI) approach was used to obtain magnetisation transfer ratios (MTRs) in several regions of cerebral white matter.

Results—MTR values were significantly reduced in the right and left temporal regions in schizophrenic patients compared with controls ($p < 0.001$). Clinical variables such as age, duration of symptoms, schizophrenic symptomatology, and soft neurological signs did not predict this reduction in MTR. There were no MTR abnormalities in the other regions sampled. However, the correlation between the left and right frontal MTR values was marginally significantly different in schizophrenic patients compared with controls suggesting that subtle differences in interhemispheric connections may be present.

Conclusions—Subtle white matter pathology, most likely related to myelin and axonal abnormalities, can be detected in the temporal lobes in schizophrenic patients. MTI may be a useful tool in investigating the white matter in schizophrenia. (*J Neurol Neurosurg Psychiatry* 2000;68:70-74)

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Institute of Neurology, London, UK

J Foong
G J Barker
S Brocklehurst
D H Miller
M A Ron

Imperial College School of Medicine, Charing Cross Campus, London, UK

M Maier

Correspondence to:
Dr J Foong, NMR Research Unit, Institute of Neurology, Queen Square, London WC1N 3BG, UK

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It has recently been suggested that schizophrenia may be a disease of brain connectivity, in particular involving frontotemporal connections.^{1,2} However, few studies have examined the white matter in schizophrenia and most volumetric studies have reported normal findings by contrast with widespread grey matter volume reductions.³⁻⁵ Abnormalities in white matter have been reported by Persaud *et al.*⁶ who detected more extensive areas of focal signal hyperintensities, particularly in the frontal lobes, in schizophrenic patients than in controls, although the precise pathological relevance of these abnormalities is uncertain. Some postmortem studies have reported normal axonal density of white matter structures such as the corpus callosum^{7,8} whereas others have reported abnormalities such as a selective

maldistribution of interstitial neurons in prefrontal white matter in schizophrenia.⁹

Magnetisation transfer imaging (MTI) allows the indirect visualisation of protons tightly bound to macromolecular structures, such as myelin and cell membranes in white matter, which are essentially invisible to conventional MRI because of their very short relaxation times. In MTI, the exchange of magnetisation between the bound protons and free water is represented by the magnetisation transfer ratio (MTR), which is considered to be an index of myelin or axonal integrity. Measurements of MTR are reproducible¹⁰ and subtle age related changes but not sex differences have been found in a healthy population.¹¹ Large reductions in MTR have been reported in neurological conditions in which there is significant myelin loss such as multiple sclerosis¹²⁻¹⁴ and central pontine myelinolysis.¹⁵ Postmortem studies in multiple sclerosis have shown that MTR is also reduced in the presence of axonal loss.^{16,17}

In this study, we examined white matter pathology in vivo in a group of schizophrenic patients and controls using MTI, which has not been previously applied to studies of patients with schizophrenia.

Subjects and methods

Twenty five patients (19 men, six women) who fulfilled the DSM IV criteria for schizophrenia were recruited from the Bethlem and Maudsley Hospitals for the study. Their mean age was 37.28 years (range 25-46). Thirty healthy controls (22 men, eight women) with a mean age of 35.03 years (range 25-49) were selected to match the patient group as closely as possible for age, sex, and paternal social class.¹⁸ Any subject with a history of neurological or systemic illness, head injury, drug misuse, or alcohol intake of more than 30 units a week was excluded from the study. Informed consent was obtained from all subjects and the study was approved by the ethics committees of the Maudsley Hospital and Institute of Neurology.

PSYCHIATRIC AND NEUROLOGICAL SIGNS

The subscales for positive and negative symptomatology of the positive and negative syndrome scale (PANSS)¹⁹ were used.

Soft neurological signs ("primitive reflexes", repetitive sequential motor execution, and integration of sensory information) were assessed in all subjects using the "soft signs assessment" section of the Cambridge neurological inventory.²⁰

The Annett questionnaire²¹ was administered to assess hand preference.

Figure 1 ROIs in the white matter of the temporal lobes. (A) T2 weighted image. (B) MTR image.

MRI

Brain MRI was performed on a GE Signa 1.5 Tesla scanner using a standard quadrature head coil. T2 weighted and proton density images were acquired initially using a dual echo sequence (TE 15/90 ms, TR 3000 ms, 28 contiguous 5 mm axial slices, 256×256 pixel image matrix, 24×24 cm² FOV). A spin echo sequence (TE 30/80 ms, TR 1720 ms, 28 contiguous 5 mm axial slices, 256×128 pixel image matrix, 24×24 cm² FOV) was the acquired with and without a MT saturation pulse (16 ms, 23.2uT Hamming apodised 3 lobe sinc pulse, applied 1kHz from water resonance). The data were collected in an interleaved manner allowing MT images to be inherently coregistered with the T2 weighted and proton density images.¹⁰ MTR was calculated on a pixel by pixel basis from the formula:

$$\text{MTR} = [M_0 - M_s] / [M_0] \times 100$$

where M_s and M_0 are the mean signal intensities determined for a given region with and without the saturation pulse respectively.

IMAGE ANALYSIS

In consultation with a neuroradiologist, a protocol was defined for selecting regions of interest (ROIs) in the white matter based on the standard neuroanatomical divisions of the frontal, temporal, parietal, and occipital lobes. The ROIs in the corpus callosum and white matter of the frontal, temporal, parietal, and occipital regions of both hemispheres were sampled with reference to this protocol. Specifically, the temporal ROI was placed in the middle temporal gyrus and the frontal ROI was placed in the middle frontal gyrus to ensure that ROIs were strictly in white matter. The ROIs were standardised at 35.2 mm² and outlined by a single rater (JF) on the T2 weighted images and not directly on the MT images to avoid any bias in placing them. Adjacent slices were checked to ensure that all ROIs were surrounded by white matter to minimise partial volume effects from grey matter and CSF. As MT images were coregistered with T2

weighted images, the ROIs were automatically transferred onto the MT images and mean MTR measurements were obtained in these regions (fig 1).

We did not attempt to perform a global analysis (MTR histogram) of the data as our aim was to examine subtle regional differences that may have been missed.

Results

There were no significant differences in age, sex, or paternal social class between the schizophrenic patients and controls. Subjects were right handed apart from one schizophrenic patient and two controls.

The mean duration of psychiatric symptoms in schizophrenic patients was 14.32 years (range 3–22 years) and all patients were on neuroleptic medication at the time of the study. Schizophrenic patients had significantly greater scores than controls on the soft neurological signs scale (mean scores of 8.84 and 1.67 respectively, $z = -5.17$; $p < 0.001$). This score correlated significantly with the negative symptoms score ($r = 0.480$; $p < 0.01$) but not with age or duration of illness.

Mean MTR values in the white matter were more variable and lower in almost all the regions in the schizophrenic group (fig 2). A generalised linear mixed modelling (GLMM) approach²² was used to investigate group differences and to examine the interactions between the variables avoiding multiple comparisons. The results of the GLMM analysis are shown in the table. Initially, a full GLMM was applied with fixed within subject factors region (frontal/parietal/occipital/temporal/corpus callosum) and side (left/right), a fixed between subjects factor group (control/schizophrenic) and a random factor subject (nested within group). The full model showed that the MTR values, when all regions were considered together, were significantly different between schizophrenic patients and controls. The group×region interaction was highly significant ($p < 0.001$) indicating that the group differences in MTR were dependent on the

p Values for main effects and interactions from GLMM analyses

	<i>p</i> Values for effects						
	Group	Region	Side	Group× region	Group× side	Region× side	Group× region ×side
Full GLMM	0.012	0.000	0.024	0.000	0.664	0.031	0.784
Region by region GLMMs:							
F	0.768		0.019		0.856		
P	0.938		0.988		0.521		
O	0.437		0.543		0.342		
T	0.000		0.004		0.704		
CC	0.717						

F=Frontal, P=parietal, O=occipital, T=temporal, CC=corpus callosum.

Figure 2 Mean (SEM) MTR values in white matter. CC=corpus callosum; LF=left frontal; RF=right frontal; LP=left parietal; LT=left temporal; RT=right temporal; LO=left occipital; RO=right occipital.

region. The region×side interaction was also significant ($p<0.031$) indicating that to a lesser extent, differences between right and left MTR values were dependent on the region. There was no significant group×side interaction indicating that the group differences in MTR were not dependent on the side.

Separate GLMMs were then applied to individual regions with one fixed within subject factor side (left/right), a fixed between subjects factor group (control/schizophrenic) and a random factor subject (nested within group). The individual region analyses showed a highly significant group effect for MTR values in the temporal regions ($p<0.001$). This difference in mean MTR values represented about a 2% reduction in the schizophrenic group compared with the controls for the right temporal region (mean MTR 38.58 and 39.51 respectively) and left temporal region (mean MTR 39.07 and 39.89 respectively) as shown in fig 2. There was a significant effect of side for the temporal regions ($p<0.004$) but the group×side interaction was not significant indicating that right temporal MTR values were significantly different from the left in both the schizophrenic and control groups. There were no significant differences in frontal or other regional MTR values between schizophrenic patients and controls. There was a significant effect of side for the frontal region ($p<0.019$) but the group×side interaction was not significant indicating that right frontal MTR values were significantly different from the left in both schizophrenic patients and controls.

Pearson's correlation coefficient was used to examine the association between regional

MTR values within each group and to determine whether this association differed between the schizophrenic and control groups. There were some differences in the correlations between MTR values in the different white matter regions between the two groups; in particular, there were greater left frontal-right frontal and left frontal-left occipital correlations in the schizophrenic group compared with controls. A statistical test²³ of whether the correlations differed for the two groups indicated that only the left frontal-right frontal correlation was significantly different ($p<0.047$) suggesting that there may be subtle changes in frontal interhemispheric connections in the schizophrenic patients.

Using forward regression analysis, none of the clinical variables of age, duration of symptoms, PANSS scores, and soft neurological signs predicted the temporal MTR values in the patient group. In addition, age did not predict MTR values in the control group.

Sample size calculations were performed retrospectively to estimate the number of patients that would have been required to detect significant MTR changes in the different brain regions based on the total sample mean and SD of the regional MTRs in this study, with a power of 80% and 5% level of significance. We estimated that a sample size of 16 in each group would have been sufficient to detect statistically significant MTR changes in the temporal regions whereas at least 2000 subjects in each group would have been required to detect significant MTR changes in the frontal regions. Sample size estimations for the other regions were similar to those for the frontal regions. This suggests that MTR abnormalities may be localised to the temporal regions and that if they are present in the other white matter regions we sampled, they are very subtle and their detection using MTR impractical.

Discussion

This study introduces a novel approach in investigating white matter abnormalities in schizophrenia and our results to date indicate a significant reduction of MTR in temporal white matter in schizophrenic patients compared with controls which is likely to reflect myelin or axonal disruption.

Large reductions in MTR are found in lesions with major myelin or axonal loss such as in multiple sclerosis but smaller reductions could be due to more subtle abnormalities in either myelin or axons. Some studies of the temporal lobes in schizophrenic patients have reported changes in neuronal density in the hippocampus^{24, 25} and this could lead to axonal disruption. There is also evidence of a reduction in N-acetyl aspartate (NAA), considered to be a marker of neuronal or axonal integrity, in the temporal lobes^{26, 27} and hippocampus.^{28, 29} More recently, Lim *et al*³⁰ reported a reduction in NAA signal intensity in brain white matter without any volumetric change in a group of schizophrenic patients and suggested that this may reflect a disruption of axonal connections. In addition, there is

indirect evidence that myelin abnormalities may be present in the hippocampus^{31, 32} and the high incidence of psychosis in patients with metachromatic leukodystrophy³³ gives further support to this possibility. It is therefore possible that subtle changes in axonal and myelin structure or chemistry could have contributed to the MTR reduction in our schizophrenic patients.

The idea that functional connectivity may be abnormal in schizophrenia has originated from PET studies, which have demonstrated a failure of deactivation in the temporal lobes normally associated with activation of DLPF cortex during a verbal fluency task in schizophrenic patients.² Woodruff *et al.*³⁴ reported a dissociation between frontal and temporal lobe volumes in schizophrenic patients compared with controls and others have suggested that the correlation between thalamic volumes and prefrontal white matter is abnormal in schizophrenia.³⁵ These findings have been interpreted as suggesting that the abnormalities in schizophrenia may be in the connections between different brain regions and not only within the regions themselves. Our finding of MTR abnormalities circumscribed to temporal lobe white matter and the absence of any significant correlation between frontal and temporal MTR values gives little support to this interpretation. However, it remains possible that MTR abnormalities may be present in other regions not sampled in this study. It is difficult to draw firm conclusions from our finding of significantly different correlations between frontal MTR values in schizophrenic patients compared with controls. Subtle changes in interhemispheric connections may be responsible, but it is possible that the greater variability of MTR values in the schizophrenic patients may have accounted for the difference.

Age and duration of illness failed to predict MTR changes in the schizophrenic patients suggesting that these changes are unlikely to be progressive although this would need to be confirmed in longitudinal studies. Neither the positive nor negative schizophrenic symptoms predicted the MTR changes in patients, suggesting that they may be common to the different clinical subtypes. The same applies to the presence of soft neurological signs, which were significantly more common in schizophrenic patients and associated with the presence of negative symptoms.

We used the ROI approach as we were interested in examining regional abnormalities in white matter, particularly the frontal and temporal areas that have been suggested to be abnormal in schizophrenia. Future research using extensive sampling and different methods of analysis capable of examining the whole brain may be able to determine if more widespread changes are present. In addition, the use of other techniques such as diffusion tensor imaging (DTI), which may be more sensitive to axonal loss than myelin changes,³⁶ could provide more information about fibre density and directionality.

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