Myelination in First-Episode Psychosis Patients Measured by Myelin Water Imaging

D. J. Lang[1], H. M. Emmerton[2], C. Laule[3], G. W. MacEwan[2], A. L. MacKay[1,3], W. G. Honer[2]

[1]Radiology, University of British Columbia, Vancouver, BC, Canada, [2]Psychiatry, University of British Columbia, Vancouver, BC, Canada, [3]Physics, University of British Columbia, Vancouver, BC, Canada

Background: Patients with psychosis and schizophrenia-related psychosis suffer from a combination of motor, cognitive and affective deficits. These various deficits often appear concurrently with the most salient features of psychosis (hallucinations and delusions), but respond less readily to currently available antipsychotic medications. Imaging studies of first-episode psychosis and schizophrenia-related psychosis have shown that psychosis patients may have a wide range of structural and functional deficits compared to healthy volunteers. In particular, some brain structures appear to be preferentially affected in patients with schizophrenia-related psychosis, including the frontal lobes, the amygdalo-hippocampal formation, the basal ganglia and the ventricular system (1,2). Abnormalities in specific brain regions, while part of the psychosis phenotype, do not fully explain the underlying brain abnormalities that would give rise to the full spectrum of observed cognitive and clinical symptoms. More recent imaging studies of white matter abnormalities in psychotic patients have suggested abnormalities in myelin contribute to the schizophrenia-related psychosis syndrome (3). In a recent MR study, decreased frontal lobe myelin water fractions were found in patients with chronic psychosis when compared to normal volunteers (4). ***In the current pilot study, first-episode, minimally treated patients and age-matched controls underwent myelin water imaging to assess regional myelin water abnormalities and variations within patients and controls.***

Methods: ***Subjects –*** A total of 18 first-episode psychosis patients (mean age: 19.2yrs (range 15.1-28.9yrs), mean education: 11.4yrs (range 9.0-16.0yrs)) and 17 healthy age matched volunteers (mean age: 22.8yrs (range 15.1-41.8yrs), mean education: 13.7yrs (range 11.0-16.0yrs)) were included in this pilot analysis. ***MR Experiments –*** MR images were acquired using a 1.5T GE Signa EchoSpeed scanner operating at the 5.7 software level. MR experiments included an axial 3D spoiled gradient echo sequence (graphic prescription, minimum TR, TE=5ms, 1 average, FOV=22cm, matrix = 256x256, 124 1.5mm contiguous slices, flip angle = 45 degrees) for volumetric measurements and single slice myelin water imaging data were acquired using a 48 echo CPMG sequence, consisting of a 90^o slice selective pulse followed by 32 rectangular composite 180^o pulses flanked by slice-selective crusher gradient pulses for elimination of stimulated echoes. (TR=3800ms, TE=10ms, BW=31kHz, FOV=22cm, thickness=5mm, matrix=256x128, averages=4). The location of the myelin water imaging experiment was a transverse slice parallel to the anterior-commissure posterior-commissure line to optimize simultaneous visualization of frontal white matter, medial basal ganglia structures, thalamic nuclei and posterior white matter. ***Data Analysis –*** Six white matter structures (genu and splenium of the corpus callosum, posterior and anterior internal capsule, minor forceps, major forceps) were outlined in the subjects. T_2 relaxation decay curves were decomposed into an unspecified number of exponentials by using a non-negative least squares algorithm (5), and myelin water fraction (MWF) was defined as the signal with T_2 below 50 ms divided by the total signal in the T_2 distribution. ***Statistical Analysis –*** Initial omnibus ANOVAs were performed to examine overall group differences in MWF in specific subregions. Additional Pearson's correlations were performed to examine relationships of MWF, age and educational attainment. As this was a pilot study with a restricted sample size and range, post-hoc Bonferroni corrections were not applied to reduce the probability of type II error.

Results: The majority of white matter regions investigated showed a significant decrease in MWF of patients with psychosis when compared to controls (Table 1). Certain regions of interest showed correlation between MWF and age: Left genu (R=0.54, p=0.02); right minor forcep (R=0.57, p=0.02); left minor forcep (R=0.59, p=0.01), left anterior internal capsule (R=0.68, p=0.002) and right major forceps (R=0.48, p=0.05). A correlation was also found between MWF and years of education for the right genu (R=0.51, p=0.03); right anterior internal capsule (R=0.55, p=0.02) and the right posterior internal capsule (R=0.62, p=0.007), as demonstrated in Figures 1 and 2.

Table 1: Omnibus Comparisons (ANOVAs) of Myelin Water Fraction in First-Episode Psychosis Patients and Healthy Volunteers

Region	f value	p value
Genu (right)	3.60	0.06
Genu (left)	10.51	0.003
Splenium (right)	7.52	0.01
Splenium (left)	10.17	0.003
Minor Forceps (right)	5.13	0.030
Minor Forceps (left)	5.85	0.021
Major Forceps (right)	8.02	0.008
Major Forceps (left)	10.12	0.003
Ant. Int. Capsule (right)	10.59	0.003
Ant. Int. Capsule (left)	1.30	0.26
Post. Int Capsule (right)	0.69	0.41
Post. Int. Capsule (left)	0.71	0.41

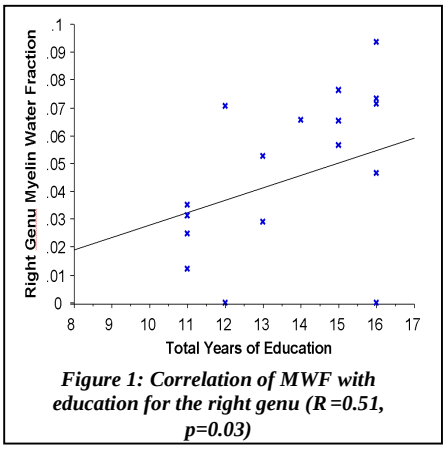

Figure 1: Correlation of MWF with education for the right genu (R =0.51, p=0.03)

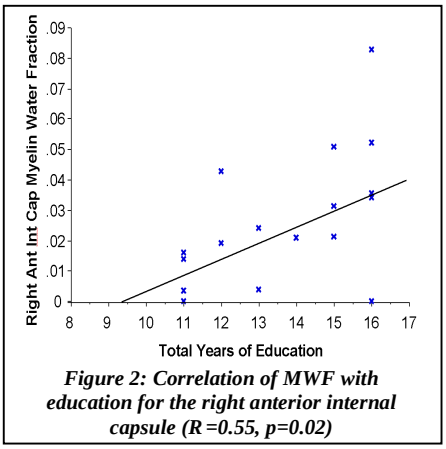

Figure 2: Correlation of MWF with education for the right anterior internal capsule (R =0.55, p=0.02)

Conclusion: Significant decreases in myelin-associated water fractions were observed in the frontal white matter (left genu, right and left minor forceps), the medial white matter (right anterior limb of the internal capsule), and in the posterior white matter (right and left splenium, right and left major forceps) compared to healthy volunteers. Significant correlations between MWF and age, and MWF and years of education, were found for various white matter regions in controls, but not in patients. Preliminary findings from this study support the previous reports of both decreased MWF in psychosis patients compared to healthy volunteers and a loss of normal age and educational attainment relationships with MWF in frontal white matter (genu, minor forceps), medial white matter tracts (anterior and posterior limbs of the internal capsule), and posterior white matter tracts (major forceps). Overall, these findings suggest that underlying white matter circuitry between functional nodes of the brain are affected in psychosis and that normal age and learning processes do not affect brain development in psychosis patients in the same manner as in a healthy population. Current and future treatments for patients with psychosis may need to be revised with consideration to these factors.

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