Assessment of white matter integrity and subregional myelination in first-episode psychosis patients using Myelin Water Imaging

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Background: Schizophrenia and schizophrenia spectrum illnesses (i.e. schizoaffective disorder, general psychotic disorder, schizotypal personality disorder) are severe, chronic debilitating complex disorders with unknown etiology and limited treatments. Both developmental and degenerative processes may be involved. The most prominent features of schizophrenia include frank psychosis (hallucinations, delusions), affective instability and cognitive deficits (thought disorder, memory deficits and deficits of executive functioning or problem solving and learning). Structural imaging studies have overwhelmingly demonstrated the presence of subtle to moderate abnormalities of normal brain asymmetry, ventricular volume, reductions in thalamic and hippocampal volumes and loss of cortical grey matter in schizophrenia-related psychosis patients (1). While these observations are intriguing, no single brain defect parsimoniously explains the wide diversity of symptoms seen in these patients, nor are anatomic brain defects readily visible in all cases of the illness. Cognitive deficits may involve more complex interconnected functional circuits in the brain, for which newer imaging approaches in white matter are more informative. Our group has developed a novel technique to measure the integrity of white matter by assessing the myelin-associated water fractions (MWFs) in white matter (2). In a previous study, we reported decreased frontal lobe MWFs in chronic schizophrenia patients compared to healthy volunteers (3). The current study of first-episode psychosis (FEP) patients and age-matched healthy volunteers underwent myelin water imaging to investigate potential myelin-related abnormalities early in the presentation of illness. To investigate the underlying integrity of these circuits, we conducted a naturalistic longitudinal study of first-episode psychosis (FEP) to assess symptom severity, cognition and white matter integrity of fronto-temporal and fronto-medial regions. Baseline data are presented here.

Subjects: FEP subjects, who had received a mean of 5.8 weeks of antipsychotic medications at time of baseline intake, were recruited from the South Fraser Healthy Authority catchment area which covers a population of 620, 000 people. A total of 132 FEP subjects and 73 healthy matched volunteers were recruited for the entire study. A subpopulation of 78 FEP subjects (mean age 21.7 yrs; range 13.6-49.9 yrs) and 31 healthy volunteers (mean age 23.7; range 15.9-41.8 yrs) were included in analyses of white matter integrity.

Methods: All FEP subjects were clinically assessed at intake by a trained clinician. Symptom severity was assessed with the Positive and Negative Symptoms Scale (PANSS). All subjects underwent a full demographics interview and IQ assessment with the North American Adult Reading Test (NAART). Additional clinical measures for the FEP subjects included medication histories and family histories for psychiatric disorders. All subjects received baseline MRs with the following protocols:

Imaging MR images were acquired on a 1.5 T GE Signa EchoSpeed scanner (software version 5.7). A 3D SPGR sequence (graphic prescription, minimum TR, TE=5 ms, FOV = 22 cm, matrix 256 x 256, 124 continuous 1.5 mm thick slices, flip angle = 45°) was acquired for volumetric assessments and single-slice myelin water imaging data were acquired using a 48-echo CPMG sequence, consisting of 90° slice selective pulse followed by 32 rectangular composite 180° pulses flanked by slice-selective crusher gradient pulses for elimination of stimulated echos (TR=3800 ms, TE = 10 ms, BW = 31 kHz, FOV = 22 cm, thickness = 10 mm, matrix 256 x 128, averages = 4). The myelin water image slice was placed transversely to the slice parallel to the AC-PC line to optimize simultaneous visualization of frontal white matter, basal ganglia structures, thalamic nuclei and posterior white matter.

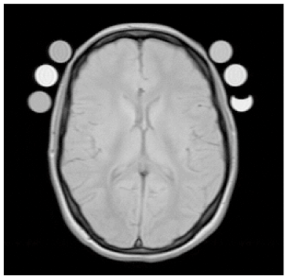
Image Analysis Six bilateral white matter regions of interest- ROIs- (genu, minor forceps, anterior internal capsule, posterior internal capsule, splenium and major forceps) were manually selected by a trained rater and averaged over 3 trials. T_2 relaxation decay curves from these regions were decomposed into an unspecified number of exponentials by using a non-negative least squares algorithm (2) and myelin water fraction was defined as the signal with T_2 below 50ms divided by the total signal in the T_2 distribution. All ROIs were analyzed using a pixel-by-pixel analysis based on MWF maps and then taking the average of the pixels within each ROI to obtain a MWF value for each ROI.

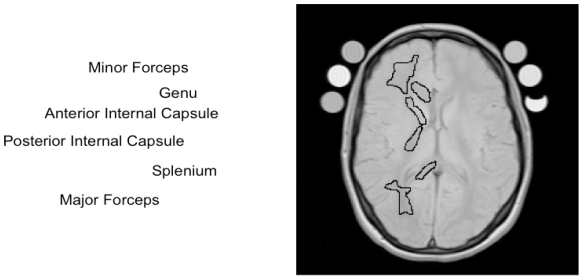
Statistics: Pearson's correlations were used to investigate potential relationships between age, education, NAART score, brain volume, sub-regional white matter volumes in our ROIs to MWFs. As this is preliminary data from an ongoing study, these initial exploratory statistics are presented here without Bonferroni corrections. Subsequent between group comparisons were performed with omnibus ANOVAs without co-variates, as no significant relationships between potential co-variates and any dependent variable were observed.

Results: FEP subjects had significantly lower MWFs in the right and left genu compared to healthy controls (Right genu: $F(1, 107) = 6.1$, $p. = 0.015$, left genu: $F(1, 107) = 4.6$, $p. = 0.035$) and showed a trend towards reduction In the right posterior internal capsule in FEPs compared to controls ($F(1,107 = 3.4$, $p. = 0.067$).

Conclusions: FEP subjects have bilateral reductions in MWFs in the genu, a major inter –hemispheric bridge between the frontal lobes and may be contributing to the emergence of psychotic disorders and concomitant cognitive dysfunction. These results are in agreement with some of our earlier work in chronic subjects. Additional subjects may demonstrate clearer relationships to other factors such as age and gender.

Figure 1 - Raw T2 Image → **T2 Image with Selected Regions of Interest**





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