Do Differences in Myelin Underlie the the Schizotypal Personality Spectrum?

K. McMullen[1], S. Kolind[1,2], E. Barkus[3], and S. C. Deoni[1]
[1]Centre for Neuroimaging Sciences, Institute of Psychiatry, London, England, United Kingdom, [2]Centre for Functional Magnetic Resonance Imaging of the Brain, Oxford University, Oxford, England, United Kingdom, [3]Department of Psychiatry, University of Wollongong, NSW, New South Wales, Australia

INTRODUCTION: Increasing evidence suggests that schizophrenia spectrum disorders lie at the extreme end of a continuum of psychosis proneness, ranging in severity from mild (non-clinical) schizotypy, through to schizophrenia. Individuals with schizotypal traits can be identified in the general population and display a constellation of cognitive perceptual disturbances; disorganised thought; and cognitive deficits [1]. These deficits are similar to those found in clinical schizophrenia, but in an attenuated form. Prior structural imaging studies in schizotypy and schizotypal personality disorder have demonstrated widespread disruption in regional brain volumes, with consistent findings of reduced cortical grey matter volume in frontal and left temporal lobes [2]. Functional MRI studies in schizotypy have shown an increased left hemisphere activation during verbal tasks [3], suggestive of either inefficient or hyper-responsive processing. Evidence for inefficient processing has been provided through analysis of resting state fMRI data, showing reduced functional connectivity [4], and DTI analysis showing altered fractional anisotropy throughout frontal, white matter [5]. Functional connectivity of the disparate brain regions implicated in psychosis is mediated by myelin (both content and integrity). In this study, we sought to specifically investigate myelin content across the schizotypal personality spectrum (as measured using the schizotypal personality questionnaire, SPQ). We also investigated correlations between verbal working memory performance, a core deficit in schizotypy [6], evaluated through the N-Back fMRI paradigm. To measure myelin content, we used the multi-component Driven Equilibrium Single Pulse Observation of T1 and T2 (mcDESPOT) [7], which isolates the MR signal associated with the water trapped within the myelin sheath, and quantified as the myelin water fraction, MWF.

METHODS: 33 individuals were recruited into the study. The SPQ was administered to each participant, and individuals were grouped as either those with medium schizotypy personalities (SPQ scores: mean 25.7 (SD = 4.40), out of a range from 21-35), or high schizotypy personalities (mean 48.6 (4.83); range 43-58). All imaging data was acquired at 3T on a GE Signal HDx scanner. Sagittally-oriented whole-brain mcDESPOT data, which consists of SPGR (spoiled FLASH) and SSFP (FIESTA, TrueFISP) imaging data acquired over a range of flip angles were acquired of each individual with a 22x22x16cm FOV and 128x128x92 acquisition matrix. For the SPGR data, TE/TR=1.7ms/4.3ms, α={4,5,6,7,8,11,14,18}°, BW=±32kHz. For the SSFP data, TE/TR=1.6ms/3.2ms, α={10,16,21,27,33,40,50,60}°, BW=±83kHz. The SSFP data were acquired with phase-cycling increments of 0 and 180° in order to correct for off-resonance effects [8]. A reduced resolution inversion prepared (IR-) SPGR image was also acquired with TE/TR/TI/α = 1.7ms/4.3ms/450ms/5° in order to correct for flip angle inhomogeneity [9]. fMRI data, using an N-back task, were also acquired. This comprised whole-brain EPI data with 24cm^2 FOV; 64x64 matrix; α=75°;3mm; slice thickness (with 3.3mm gap) and TE/TR = 3ms/2000ms.

Imaging data for each participant were linearly co-registered and non-brain parenchyma removed prior to voxel-wise estimation of the MWF (calculated as detailed in [7]). Tract-based spatial statistic (TBSS) analysis [10] was then employed to investigate possible differences in white matter myelin content between the low and high schizotypes, as well as a basis for correlation analysis comparing MWF with SPQ scores (with both low and high schizotypes pooled) and latency measures from the 0,1,2 and 3-back tasks. The tract-baed t-Tests and correlation analysis were performed using Randomise, part of the FSL suite of neuroimaging analysis tools.

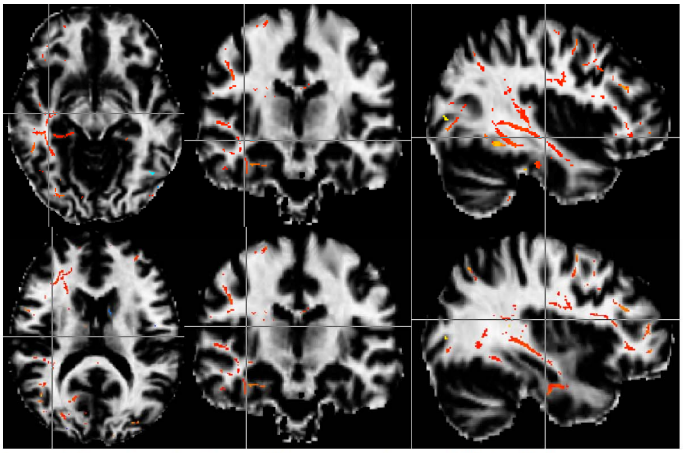

Figure 1: Areas of significant group difference in myelin content (High > Medium).

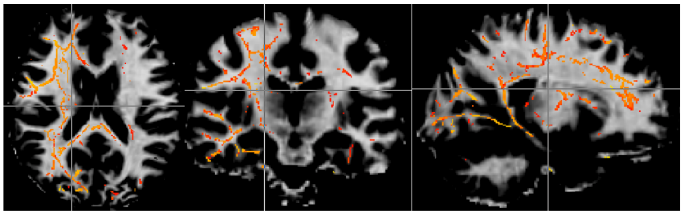

Figure 2: Areas with significant positive correlation between MWF and SPQ Score.

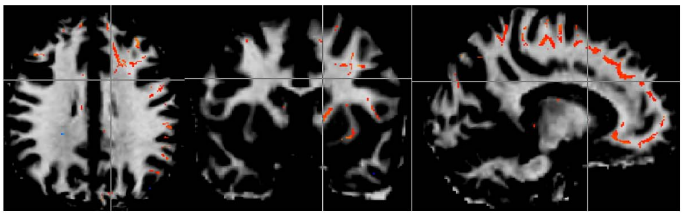

Figure 3: Areas with significant positive correlation between MWF and 3-Back Task Latency.

RESULTS: Figure 1 contains comparative results of myelin content between the medium and high schizotypy groups (red colourscale = high > medium), Significant (p<0.05, corrected) differences found in the left temporal and frontal lobes Brain regions displaying significant (p<0.05) MWF vs. SPQ score correlations (red colourscale = positive) are highlighted in Figure 2 and include most of the white matter of the left hemisphere as well as bilateral splenium and body of the corpus callosum. Finally, brain areas displaying significant (p<0.05) between MWF vs. 3-back task performance correlation (red colourscale = positive) are shown in Fig. 3 and include right frontal white matter. No significant correlations were noted on the 0, 1 or 2-back tasks, likely owing to "floor" effects (i.e. the task was not difficult enough to elicit performance differences across the subjects).

DISCUSSION / CONCLUSIONS: A perhaps surprising result of this study is the association of high schizotypal personality with significantly increased MWF throughout the left hemisphere. However, these results are consistent with prior fMRI studies that show increased activation in the left hemisphere. Increased activity may be indicative of inefficient neural networks and this may be related to increased but inefficient MWF. It has been shown that there is a positive correlation between white matter maturation and increased brain activation during working memory tasks. As mcDESPOT provides a measure of the water bound between the lipid bilayers of the myelin sheath, increased MWF could correspond to an increased number of myelin wraps around the axon, or increased intra-wrap space. We hypothesize that an increased intra-wrap space reduces the myelin efficiency. The negative correlation between increased myelin water fraction and performance on the working memory task seen in this cohort supports this explanation. However, further work is required before firm conclusions can be drawn. In addition to MWF, mcDESPOT provides other measures reflecting micro-structural integrity, which may play in an important role in disambiguating between these effects. Furthermore, connectivity analysis of the N-Back fMRI data would allow us to further determine the efficiency of the working memory network in high schizotypes.

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