Dissecting Myelin and Axon Abnormalities in Schizophrenia and Bipolar disorder Patients using Novel MRI Approaches

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Target Audience*:* Neuroscientist, Psychiatrist, MR physicist, Neuroimaging Scientist

Purpose: The pathophysiology of schizophrenia (SZ) and Bipolar disorders (BD) is poorly understood but increasing evidence suggested brain tissue microstructure changes especially in the white matter (WM), which was commonly quantified by DTI. However, DTI abnormalities can arise from multiple sources (1-3). Therefore, DTI cannot identify the exact WM abnormalities and distinguish abnormalities of axonal diameter/orientation and myelination. In this study we aimed to measure myelin- vs. axon-related abnormalities separately in a cohort of patients and matched healthy controls by multiparametric MR Imaging methods. Specifically, magnetization transfer ratio (MTR), which is sensitive to myelination changes, and diffusion tensor spectroscopy (DTS), which quantifies diffusion of intracellular metabolites such as N-acetylaspartate (NAA) and is sensitive to axonal changes, were applied. This approach may ultimately allow us to study biological abnormalities in SZ and BD, correlate with clinical presentation/disease progression, and generate biomarkers for novel treatment development aimed at restoring connectivity among brain regions in SZ and BD.

Methods: This study was approved by the McLean Hospital IRB. 23 SZ patients and 22 normal age-gender matched health controls (HC); 21 patients with BD I with psychosis and 24 age- and sex-matched HC, were recruited for this study. Considering NAA sensitivity, we explored the single voxel spectroscopy to detect microstructure changes associated with SZ and BD patents. All ^{1}H MRS and related T_1-weighted brain imaging were acquired on a full-body 4T MR scanner. A single 9cc voxel (1×3×3cm) in pure WM was placed in the PFC of the right hemisphere (see Fig. 1). A standard point-resolved spectroscopy (PRESS) sequence was modified with incorporation of diffusion gradients or a saturation pulse train for DTS and MTR measurements, respectively. All the measurements were conducted on the same position illustrated in the Fig 1. All MRS processing was carried out blind to diagnosis. MTR and DTS constants (axial diffusion-AD, radial diffusion-RD, mean diffusivity-ADC and fractional anisotropy-FA) were calculated using home-grown software on MATLAB.

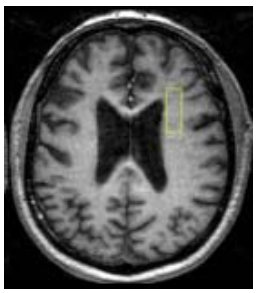

Fig1. T2 weighted brain anatomic imaging and voxel position

Results: When compared with HC, MTR in SZ was significantly reduced by about 10% and diffusion data showed elevated water and NAA ADC in SZ. For BP patients, we found a significant reduction of MTR and significant incensement of water ADC. There was no significant difference between BP patients and controls in NAA ADC.

Discussion and Conclusion: In this study, we examined white matter integrity in SZ and BD using two complementary MRI-based techniques: MTR to probe myelin content and DTS to probe axonal geometry. Our findings suggest that there is a reduction in myelin content in BD but that axonal geometry is not significantly abnormal. This pattern is distinct from what we detected in SZ, where both white matter measures (myelin and axon) showed abnormalities (4). DTI studies have revealed WM abnormalities in both SZ and BD too (1-3). Finding abnormalities in myelin but not axons suggests that WM in BD may be characterized by dynamic abnormalities. The synthesis and maintenance of myelin is an active process throughout life and it is supported by neuronal activity (5-6). Changes in axonal geometry, by contrast, would reflect structural problems in the maintenance of axon biology and perhaps more permanent abnormalities in neuronal function. We did not find evidence for such changes in BD. However, our findings in SZ suggested that abnormalities are present not only in the amount of myelin but also in the structure of the long axons of neurons, whereas our current work indicates that WM abnormalities in BD may be specific to myelin. Myelin has a continuing turnover, and it is possible that the abnormalities in BD, sparing the long axons of neurons, could be more dynamic and potentially mutable. It is intriguing that this difference is similar to the course of the two illnesses, specifically that BD is a recurrent disorder with inter-episode recovery while SZ is typified by chronic symptoms.

In summary, although many previous studies have reported abnormalities in WM integrity in SZ using DTI, the biological nature of these abnormalities cannot be established using DTI alone. We have developed a combined MR approach that examines myelination- vs. axonal-abnormalities separately in the WM in SZ and BP patients. This approach may provide deeper insight into and distinguish the pathophysiology of SZ and BP. It may monitor clinical presentation/disease progression and generate biomarkers for novel treatment development.

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References: 1. Alexander, Neurotherapeutics 2007; 2. Kubicki, Neuroimage 2005; 3. Price, Neuroimage 2010; 4. Du, Biological Psychiatry 2014; 5. Liu, Nat Neurosci 2012; 6. Makinodan, Science 2012