Neurometabolic changes observed in the anterior cingulate cortex and the thalamus in schizophrenia and in unipolar mood disorder relative to healthy controls at 7T

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Introduction: Proton magnetic resonance spectroscopy (^{1}H-MRS) is a useful tool for evaluating the health of a small volume in the brain based on the concentrations of the metabolites that make up its spectra. It can provide clues towards the potential causes of the symptomatology of neuropsychiatric disorders. ^{1}H-MRS studies of Schizophrenia (SZ), for example, have implicated the main excitatory neurotransmitter glutamate (Glu) and its metabolic precursor, glutamine (Gln) in the dorsal anterior cingulate cortex (dACC) and the thalamus (TH)[1,2] as a potential cause of the symptoms of SZ. Furthermore, ^{1}H-MRS studies of unipolar mood disorder (MD) have discovered a reduction in myo-inositol (MI), a sugar alcohol that can represent glial integrity, concentrations relative to controls in the dACC[3]. Most of these studies have been in comparison to a sample of healthy controls, but it would be ideal to have a psychiatric control group as well to account for some of the symptomatic overlap. This helps to isolate problems specific to the disorder. Therefore, MD and SZ groups will be examined concurrently in the same study as psychiatric control groups for each other to determine metabolic abnormalities that are specific to each disorder. It is expected that glutametergic (Glu, Gln) abnormalities will be present dACC and TH of the SZ group relative to the healthy controls and the MD group. It is also expected that MI concentrations will be significantly different in the MD group in comparison to the other two groups. It has been demonstrated that there are important improvements in spectral quality with higher external magnetic field strength MRIs, such as increased SNR and improved spectral dispersion[4], so to ensure reliable data, a high-field 7T MRI will be employed in this study.

Methods: There were sixteen participants with schizophrenia within two years of diagnosis, seventeen patients with unipolar mood disorder, and seventeen healthy controls that all gave informed written consent to be involved in the study. They were scanned on an Agilent/Magnex 7-T head-only scanner with Siemens AC84 head gradient coil, located at the Center for Functional and Metabolic Mapping (CFMM) at the University of Western Ontario with a 15ch-transmit/receive head coil described in the literature[5]. 8cm^3 (2cm x 2cm x 2cm) angled voxels were placed in the left thalamus and left dorsal anterior cingulate cortex using anatomical landmarks to ensure consistent voxel placement. A STEAM sequence based on the literature[6] was applied with nt=64, TE=10ms, TM=32ms, and TR=3s with VAPOR water suppression and OVS. Prior to acquisition, the voxel was B1 shimmed, followed by a B0 shimming using rastamap A 16 average water suppressed spectrum was also acquired, along with a 64 average metabolite suppressed spectrum[7] to account for the macromolecules, which would later be modeled into the fitting of the metabolites. Spectra were acquired individually and then frequency and phase corrected prior to being combined. Post-processing included QUECC lineshape correction[8] prior to the spectra being fit by our time domain fitting algorithm, fitMAN[9]. There were 21 metabolites in the fitting template (Glu, Gln, GSH, NAA, NAAG, Cr, PCr, MI, PC, GPC, Cho, Tau, PE, Glc, Gly, Scy, Asp, Ala, Ser, Lac, GABA) . Student t-tests were employed to test significance ($p<0.05$, two-tailed).

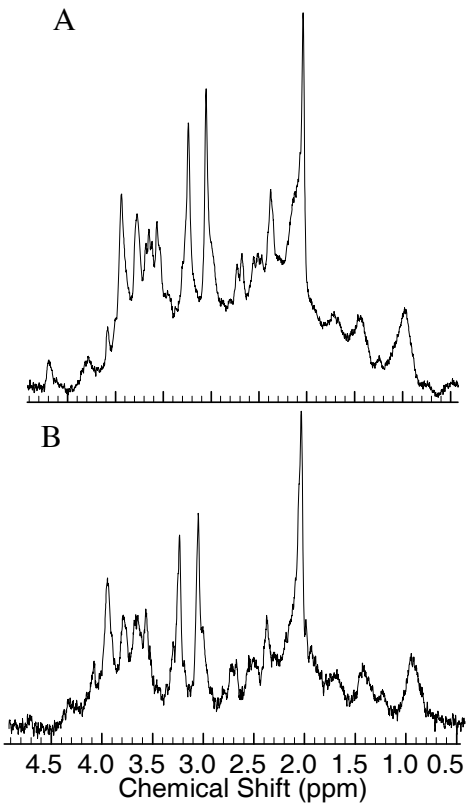

Figure 1. Example 64 average spectra from the dorsal anterior cingulate (A) and the thalamus (B), (8cm^3) with 1Hz Lorentzian line broadening.

Results and Discussion: High quality spectra were acquired in both the ACC and TH (Fig.1) with average water linewidths being 12.9Hz and 16.5Hz, respectively. It is expected that the TH would have higher linewidths due to the increased iron content. In the TH, Gln concentrations were significantly higher in the participants with SZ relative to the healthy controls but not to the MD group. This is in agreement with previous reports on Gln concentrations in the TH of participants early in their illness[1,2]. Gln concentrations were not significant between any groups in the ACC, but Glu concentrations were significantly elevated in the ACC of the SZ group relative to the healthy controls. Neither Glu nor Gln were significant when comparing the MD group to the other groups. It would be expected that the Glu and Gln concentrations would be on par with the healthy controls, so perhaps there is some involvement of the metabolites in the disorder but not enough to induce a significant concentration difference between the groups. In addition to Glu and Gln, glycine was also significantly lower in the SZ group relative to both the HC ($p<0.05$) and MD groups ($p<0.01$) in the TH. This is perhaps not surprising given the role of glycine as a coagonist to Glu and the NMDA receptors[10] thus providing further support for glutamatergic involvement in SZ. MI levels were significantly lower in the MD group when compared to the SZ group in the TH and both groups in the ACC. It was also a trend ($p<0.1$) when compared to the TH in the controls. It has been previously shown that the MI levels can normalize after treatment[3]. Of the participants in our study, 11 of the 17 were medicated, and the medicated ones showed less MI than the non-medicated. This is interesting, but is likely due to the variety of medications the participants were using and due to the relatively early stage of illness of the MD group.

Conclusions: Using a high field MRI significant concentration differences between a sample of people with SZ, MD, and healthy controls were discovered. These differences are specific to each disorder as they act as psychiatric control groups for each other. This study provides further support to the Glu theory of SZ through significant Glu, Gln, and Gly differences specific to SZ.

References: [1] Théberge et al. *Br. J. Psychiatry* 2007; 191:325-334. [2] Théberge et al. *Am J Psychiatry.* 2003;160(12):2231-2233. [3] Chen et al. *Psychiatry Clin Neurosci.* 2014;68(5): 357-364. [4] Tkac et al. *Magn Reson Med.* 2001; 46:451-456. [5] Gilbert et al. *NMR Biomed.* 2011; 24:815-823. [6] Tkac et al. *Appl Magn Reson* 2005;29(1):139-157. [7] Penner et al. *Proc Intl Soc Magn Reson Med* 18(2010). [8] Bartha et al *Magn Reson Med* 2000;44:541-545 [9] Bartha et al. *NMR Biomed* [10] Kleckner et al *Science*1988;241(4867):835-7