Longitudinal ^{31}P Magnetic Resonance Spectroscopy of Membrane Metabolism in Schizophrenia

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Introduction Schizophrenia is a debilitating neuropsychiatric disease, characterized by auditory hallucinations, delusions, lack of motivation and thought disorder. In our previous studies of schizophrenia, we used ^{31}P MRS to non-invasively measure membrane phospholipid and high-energy metabolism within the brain (1). Our results revealed changes in ^{31}P brain in the prefrontal regions of first episode schizophrenic patients (3) and in the prefrontal, thalamic, and hippocampal regions in chronic schizophrenic patients [length of illness = 21.6 +/-7.3 yrs] (2). The prefrontal region measurements were significant in both studies and trends were observed in the thalamus of the first-episode patients, where significant results were also revealed in the chronic patients. However, to determine the location of significant changes in ^{31}P MRS metabolites as the disease progresses more time points are required between the onset and chronic stages.

Study Design Patients and healthy matched controls undergo a ^{31}P MRS scan at onset of symptoms (S1), at medication stabilization (~ 6 months)(S2) and again at 30 months (S3). To date 23 first-episode patients & 18 matched controls have undergone S1, 4 first-episode patients and 1 control have undergone S2 and 2 first-episode patients and 2 controls have undergone S3.

Methods Informed, written consent according to the guidelines of the Health Sciences Research Ethics board at the University of Western Ontario was obtained from all subjects participating in this study. Patients and controls were matched for age, handedness, and parental education. The Structural Clinical Interview for DSM-IV (SCID) was used to establish the DSM-IV diagnosis of schizophrenia to exclude psychopathology in control subjects. The 4 first-episode subjects, drug-naïve for S1, were on ziprasidone, quetiapine and olanzapine, all atypical antipsychotics, at the time of S2.

Scans were performed using a 4.0 T whole body research scanner (Varian/Siemens/UnityINOVA). A ^{1}H quadrature head-coil was used for shimming and to acquire sagittal, coronal images (2D-FLASH-TR=11ms, TE=6ms, 256 phase-encodes, 0.93x0.93 mm pixels) and 32 T_1-weighted transverse images (3D-FLASH-TR=11 ms, TE =6.2 ms, nominal slice thickness = 4.375 mm and 1.09X1.09 mm in-plane resolution) for ^{31}P voxel location and to determine the grey matter, white matter and CSF ratios within these voxels. The ^{1}H coil was replaced with a ^{31}P quadrature head-coil, without moving the patient. Localized ^{31}P spectra were acquired from 15cc effective spherical voxels using an optimized 3D chemical shift imaging sequence with a spherically bound, random point omission, weighted k space. (TR = 500ms; pre-acquisition delay time = 1.905 ms; tip angle = 32°; matrix size (x, y, z) = 14X14X14 (zero-filled to 16X16X16); FOV (x, y, z) = 280 mm; data readout time = 400 ms)(4). Spectra were analyzed from the left and right prefrontal cortex, thalamus, hippocampus and cerebellum and the anterior and posterior cingulate. After left shifting 5 time domain points to remove the broad membrane baseline component, unfiltered spectra were fit in the time-domain using a non-linear, iterative fitting program based on the Marquardt-Levenberg algorithm using prior spectral knowledge (4). There was no T_2 weighting in the fitted data, since the fitting algorithm automatically extrapolated metabolite amplitude values back to t=0. Millimolar concentrations for each metabolite were determined after correction with literature T_1 values and an external reference standard (methylene diphosphonic acid (270mM).

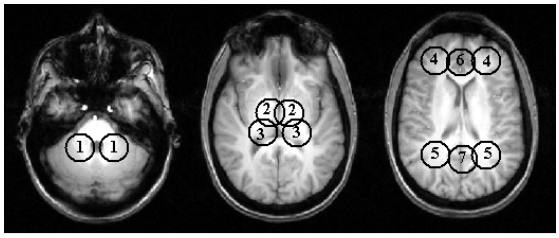

Figure 1 - Transverse images displaying effective volume positions (15cc) on regions from which spectra are acquired. 1- cerebellum; 2- thalamus; 3- hippocampus; 4- prefrontal;

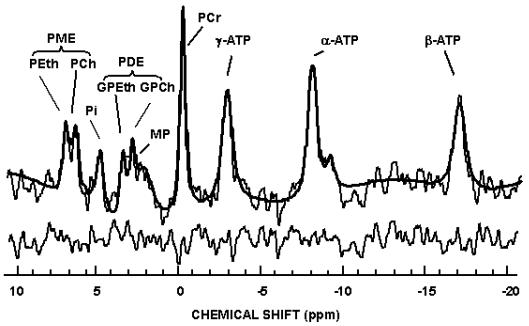

Figure 2 – Raw and fitted spectrum (10 Hz exponential filter for display) and residuals, from a 15cc effective volume in the anterior cingulate. Peth – phosphoetholamine; PCh – phosphocholine; Pi - inorganic phosphate; GPEth – glycerophosphoethanolamine; GPCh – glycerophosphocholine; MP = mobile phospholipid; PCr - phosphocreatine.

Results Statistics were performed on the schizophrenic patients between S1 and S2 (n=4) using SPSS version 10.0 for Windows. The MANOVA was significant for the left hippocampus (Wilk's Lambda = 0.001, F =578.051, df = 6, $p < 0.032$ and the ANOVA revealed a decrease in Peth ($p < 0.05$), PCh ($p < 0.014$) and MP ($p < 0.003$). Although the MANOVA was not significant in the anterior cingulate ($p < 0.30$), the ANOVA revealed a significant decrease in GPCH ($p < 0.026$). At present, the patient and control groups for S3 are too small for statistical analysis.

Discussion Preliminary results suggest a possible decrease in membrane precursors in the anterior cingulate and breakdown products in the left hippocampus between the drug-naïve scan (S1) and the medication stabilization scan (S2). These results could reflect either the effects of medication stabilization or disease progression. The decrease in membrane precursors in the anterior cingulate is consistent with the decrease observed in our first-episode and chronic studies (2,3), however, the difference in breakdown products observed in the left hippocampus is not consistent with these studies. Further assessment of subjects at 30 months (S3) will be needed to see the effect of disease progression. Within the next 5 months, 10 schizophrenic patients and 10 controls are scheduled for a 30-month repeat scan to determine the location of significant changes in phosphorous metabolites during disease progression. Limitations of this study include exposure to different types of atypical antipsychotic medications, which may have a different effect on phosphorous membrane metabolism at the time of scan. In addition, the phosphorous spectra are T_1 weighted due to the short repetition time, which could be a potential source for the observed changes in metabolite concentrations in schizophrenia. Other limitations of this study are described in Jensen et al, 2002 (2).

References

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