A 4.0 T ^{31}P Magnetic Resonance Spectroscopy Study of Chronic and First-Episode Schizophrenia

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Introduction Schizophrenia is a lifelong debilitating disorder characterized by auditory hallucinations, delusions, lack of motivation, and thought disorder. A number of brain imaging techniques have been applied with the hope of understanding this puzzling disorder. One such method, ^{31}P-MRS, can non-invasively measure membrane phospholipid and high-energy metabolism within the brain (1). Previously, we found changes in ^{31}P brain metabolism in the prefrontal, thalamic, and hippocampal regions in a study of chronic schizophrenic patients (2). Evidence suggests brain abnormalities in schizophrenia may also exist in the following regions: the inferior parietal cortex (IP), associated with the attentional system; the superior temporal cortex (ST), associated with hallucinations; and the basal ganglia (BG), associated with cognitive, sensory and motor processing (3). In this study, in-vivo 31P-MRS is used to determine if significant changes in 31P-MRS metabolites exist within these regions.

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 taking part in this study. Thirteen first-episode schizophrenic patients and 13 matched controls plus 8 chronic schizophrenic patients and 8 matched controls were recruited. Patients and controls were matched for age, handedness, and parental education. The DSM-IV diagnosis of schizophrenia was established with the Structured Clinical Interview for DSM-IV (SCID), and was also applied to controls to exclude psychopathology. Ten of the first episode patients were neuroleptic naïve, but 1 had received benzodiazepine for sedation at the time of the scan and 3 had prior exposure to a specific serotonin re-uptake inhibitor. Two of the remaining patients were on atypical and 1 on conventional neuroleptics, 2 of which had prior exposure to a specific serotonin reuptake inhibitor. The estimated mean duration of exposure to antipsychotic medication at the time of scan was 0.4 +/- 0.4 years. Of the chronic patients, 6 were on olanzapine, 2 were taking conventional neuroleptics, 1 was taking clozapine, 1 was taking quetiapine and 1 ziprasidone at the time of the scan and all had been on conventional medications prior to going on atypical neuroleptics.

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 (2D-FLASH) and transverse (3D MPRAGE) images for ^{31}P voxel location and to determine the grey matter, white matter and CSF ratios within these voxels. A ^{31}P quadrature head-coil was swapped for the ^{1}H coil without moving the patient. Localized ^{31}P spectra were acquired from 15cc effective 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 BG, IP, and ST. 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 (2). There was no T2 weighting in the fitted data, since the fitting algorithm automatically extrapolated metabolite amplitude values back to t=0. Combined with T1 values for each metabolite and an external reference standard (methylene diphosphonic acid (270mM), millimolar concentrations for each metabolite were determined.

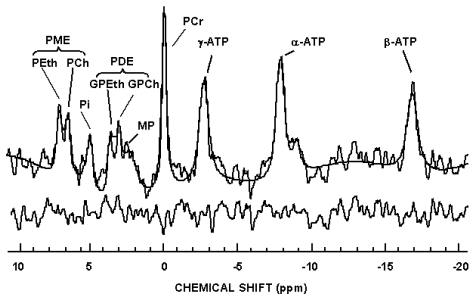

Figure 1 – Raw and fitted spectrum (10 Hz exponential filter for display) from a 15cc effective volume in the right inferior parietal lobe. PEth=phosphoetholamine, PCh=phosphocholine, PI=inorganic phosphate, GPEth=glycerophosphoethanolamine, GPCh=glycerophosphocholine, MP=mobile phospholipid, PCr=phosphocreatine

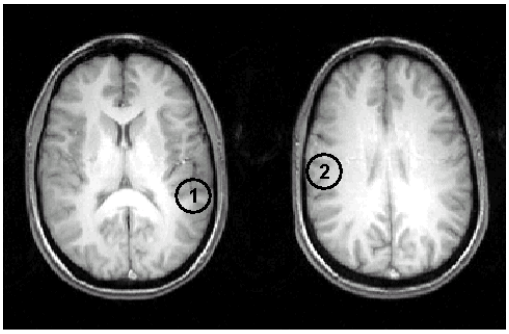

Figure 2 – Transverse images displaying regions where significant changes between schizophrenics and controls were observed. 1-In first episode, left superior temporal lobe: an increase in PCh. 2-In chronic, right inferior parietal lobe: a decrease in GPEth.

PATIENT	LOC.	MET.	CONT.(SD)	SCHIZ.(SD)	p
1st EPISODE	L_BG	GPETH	0.35(0.20)	0.55(0.20)	0.024
	L_STE	PCH	0.19(0.13)	0.37(0.15)	0.003
CHRONIC	L_BG	GPETH	0.72(0.47)	0.25(0.22)	0.024
	R_IP	GPETH	1.00(0.47)	0.43(0.20)	0.007
		PCH	0.63(0.33)	0.29(0.15)	0.020
		PCR	3.83(0.68)	2.87(0.88)	0.028

Table 1 - ANOVA (NAÏVE) and ANCOVA (CHRONIC) results for 31P metabolite concentrations, expressed as a ratio to external reference standard in mM/L brain tissue. (SD=standard deviation). BG=basal ganglia, STE=superior temporal lobe, IP=Inferior parietal lobe

Results Significant results (SPSS version 10.0 for Windows) are summarized in Table 1. The MANOVA/MANCOVA results were not significant for all regions, although the MANOVA analysis on the first-episode and matched control data revealed a trend in the left superior temporal lobe (Wilk's Lambda = 0.393, F = 1.963, df = 11,14, p = 0.107). The MANCOVA (covariate for age) analysis on the chronic and matched control data yielded a trend in the right inferior parietal lobe (Wilk's Lambda = 0.023, F=7.768, df = 11, 3, p = 0.119). An ANOVA, of first-episode and control data, revealed an increase in PCh (p=0.003) in the left superior temporal lobe in first-episode patients as compared to their matched controls. An ANCOVA, of chronic and control data, revealed a decrease in GPEth (p=0.007) in the right inferior parietal lobe as compared to matched controls.

Discussion In the left superior temporal lobe, the observed increase in PCh in first-episode patients as compared to matched controls, are consistent with previous volumetric findings in association with hallucinations in this region (5). The decrease in GPEth in the right inferior parietal lobe, displayed in the chronic patients as compared to matched controls, are consistent with previous volumetric findings within this region (5). Furthermore, this decrease is consistent with previous chronic schizophrenia findings, in which a decrease in GPEth was found in other regions associated with the attentional system, including the anterior cingulate and right prefrontal cortex (2). From these results it can be suggested that schizophrenic patients may have altered membrane metabolism in the superior temporal lobe at the onset of illness, with further alterations in phosphorous metabolism occurring in the inferior parietal lobe as the disease progresses. Limitations of this study include present or previous exposure to medication, which may have altered phosphorous membrane metabolism at the time of scan. In addition, the phosphorous spectra are T1 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

[1]Williamson, PC and Drost DJ, Phospholipid Spectrum Disorder in Psychiatry: Peet, Glen and Horrobin, Marius Press,UK,45-55, (1999)
[2]Jensen JE, et al, *Br. J. Psychiatry*, 180:39-44 (2002)
[3]Shelton ME, et al, *Schiz Research*, 49:1-52 (2001)
[4]Jensen JE, et al, *NMR Biomed*,15:338-347(2002)
[5]Schlaepfer TE, et al, *Am. J. Psychiatry*, 151:842-848 (1994)

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