A 30-Month ^{31}P MRS Follow Up Study of First Episode Schizophrenia

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Introduction Membrane phospholipid abnormalities within the thalamocortical circuit have been implicated in the pathophysiology of schizophrenia. (1) Our previous ^{31}P MRS studies of schizophrenia revealed an increase in phosphodiesters (PDE - glycerophosphocholine and glycerophosphoethanolamine) in the frontal regions of first episode schizophrenic patients (3) and a decrease in PDE and phosphomonoesters (PME - phosphocholine and phosphoethanolamine) in the prefrontal(AC) and thalamic(TH) regions in chronic schizophrenic patients [length of illness = 21.6 +/-7.3 yrs] (2). These two studies suggest an interruption in phospholipid turnover as the illness progresses. In addition, regional deficits in grey matter have been revealed in the left superior temporal gyrus(STG) in schizophrenia as the disease progresses(5). To further explore these findings we have performed a longitudinal study to detect changes in the phospholipid turnover as the disease progresses through the early stages of psychosis. We hypothesized a change in PDE will occur in the AC, left and right TH and left and right STG over time.

Study Design First-episode schizophrenic patients(S) and healthy matched controls(C) were scanned at two separate time points, a first scan at onset (0M) and again 30 months later (30M). To date 30 first-episode patients & 30 matched controls have undergone the first scan and 15 first-episode and 13 controls have undergone 30M.

Methods Thirty never-treated first-episode schizophrenic patients were scanned at onset of the symptoms and again at 30 months (30M). 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 and to exclude psychopathology in control subjects. Of the first-episode subjects, 6 were drug naïve at 0M and all patients except for 3 were on atypical antipsychotics at 30M.

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 fraction 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 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)). All statistics were performed using SPSS version 10.0 for Windows for only the membrane breakdown and synthesis products, in the hypothesized regions. A 2x2 Split-Plot Factorial design with measurement–period as the 2 level within-subjects factor and group the 2 level between-subjects factor, was used for the 2 measurement 2 time point data. For the changes over time in synthesis and breakdown products a 2 level repeated measures design was used to compare 0M and 30M.

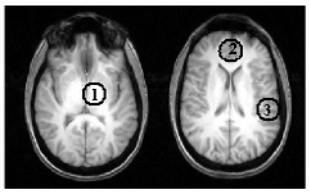

Figure 1. Transverse images displaying effective volume positions(15cc) on regions where significant changes were observed. 1) left thalamus 2) anterior cingulate 3) left superior temporal gyrus

	Anterior Cingulate			Left Thalamus			Left STG		
	Within		Between	Within		Between	Within		Between
Metabolite/Design	**t**	**G*t**	**G**	**t**	**G*t**	**G**	**t**	**G*t**	**G**
GPch									
2x2 SPF	ns	ns	**p=0.043**	ns	ns	ns	**p=0.009**	ns	ns
2-level RM	ns	ns		ns		ns	**p=0.041**		ns
Univar. S0 vs C0			**p=0.005**			ns			ns
Univar. S30 vs C30			ns			ns			ns
GPeth						ns			ns
2x2 SPF	ns	ns	ns	ns	**p=0.040**	ns	ns	ns	ns
2-level RM	ns	ns		**p=0.023**		ns	ns		ns
Univar. S0 vs C0			ns			ns			ns
Univar. S30 vs C30			ns			**p=0.020**			ns
Peth									
2x2 SPF	ns	ns	**ns(p=0.11)**	ns	ns	ns	ns	ns	ns
2-level RM	**ns(p=0.06)**			ns		ns	ns		ns
Univar. S0 vs C0			ns			ns			ns
Univar. S30 vs C30			ns			ns			ns

Table 1. Summary of all statistics performed on the data and significant results. A 2X2 split plot factorial (SPF) was performed on the 2 measurement-2 timepoint data(2 level btn subjects factor and 2 level within subjects factor) For the changes over time a 2 level repeated measures(RM) design was used to compare 0M and 30M. A univariate design was used to compare controls and patients at each time point (0M and 30M). **t** = time, **G** = group, **GPCh** = glycerophosphocholine, **GPeth** = glycerophosphoethanolamine, **Peth** = phosphoethanolamine

Results In the anterior cingulate a main effect of group was observed between subjects with increased levels of membrane breakdown in the patients as compared to controls at disease onset (S0vsC0, table 1). In the left thalamus a main effect of group*time was observed within subjects and a decrease in membrane breakdown products is observed over time in patients (0M & 30M). In this same region a decrease in breakdown products was observed between groups at the 30 month scan (S30&C30). In the left superior temporal lobe a main effect of time was observed within patients with a significant increase in membrane breakdown products in this region over time. Also notable was a trend observed in the anterior cingulate of a decrease in synthesis products observed in patients over time (p=0.059).

Discussion These preliminary results reveal an increase in membrane breakdown in the anterior cingulate of patients as compared to controls at disease onset, in keeping with our first episode study (3). In the left thalamus a decrease in breakdown products is seen over time in patients, initially this concentration is similar to controls at onset and lower than the breakdown products concentration observed in controls at 30M. In the left superior temporal lobe an increase in breakdown products over time was observed in the patients (0M vs 30M). These changes may represent an interruption in phospholipid membrane turnover as the disease progresses.

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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