Longitudinal Study of First-Episode Schizophrenia using 4.0T ^{1}H MRS and Voxel-Based Morphometry

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Introduction

Glutamatergically linked components of the basal ganglia thalamo-cortical circuit, such as the anterior cingulate (AC) and thalamus, have been implicated by models of schizophrenia (1). Our previous studies reported increased levels of glutamine (Gln) in the medial prefrontal cortex/AC area and thalamus of never-treated patients (2, 3) compared to controls. In chronic schizophrenia (4) we found decreased levels of Gln in the AC compared to controls and glutamate (Glu) + Gln levels that decreased with duration of illness (5). These changes can be interpreted as signs of neurodegeneration in schizophrenia. This prompted a longitudinal study of a group of first-episode schizophrenic patients over the early course of antipsychotic treatment. In this study, we present levels of Glu, Gln, NAA and other short echo time ^{1}H MRS metabolites in the left AC and left thalamus of patients, as well as voxel-based morphometry (VBM) measurements, at three time points: never-treated first-episode, after stabilization on medication, and after two and a half years of treatment. Control subjects were also scanned at two time points two and half years apart. We hypothesised that the patient's Glu+Gln levels would decrease in both regions as time progresses in agreement with the observed changes in large groups of never-treated patients (2) and chronic patients (4, 5). Decreases of grey matter volumes are expected in the AC, thalamus and other regions of the brain connected to them via glutamatergic projections.

Method

Nine never-treated, first-episode schizophrenic patients were scanned and followed up ten months (10M) and 30 months (30M) after the start of antipsychotic treatment. Healthy control subjects were matched for handedness, gender, age and parental education and were scanned twice, an average of 30 months apart. All scans were performed using a Varian/Siemens Unity Inova 4.0 Tesla system. Two in vivo short echo ^{1}H STEAM spectra in the left AC and left medio-dorsal thalamus (1.5 cc, TR = 2000ms, TE = 20ms, TM = 30ms, dwell time = 500µs, Acq. Time = 1.5 sec., 256 water suppressed averages, 16 unsuppressed averages) and a 3-dimensional MP-FLASH T1-weighted volume (TI=500ms, TR=11.4ms, TE=6.2ms, 64 slices, thickness=2.75mm, FOV=20cm, matrix=256x256) were obtained from all subjects. Lineshape corrected and water subtracted spectra were fitted in the time domain using a priori knowledge from 12 metabolite solutions in a constrained Levenberg-Marquardt minimisation algorithm (6). Metabolite levels were normalised to the amplitude of the water unsuppressed acquisition and corrected according to grey matter, white matter and CSF content within each voxel. Only metabolites that showed group standard deviation smaller than 75% were included in the statistical comparisons. Patient levels and control levels were compared among themselves using paired t-tests. Patient levels were compared to control levels using heteroschedastic t-tests.

VBM maps were obtained using SPM2 (Wellcome Institute, London, UK) (7). Images were spatially normalized to the T1-weighted SPM2 template, segmented into grey matter / white matter / CSF images with the modified model cluster analysis technique from SPM2 including the correction for image intensity non-uniformity, modulated by the Jacobian determinants from the normalization step, and finally smoothed using an isotropic Gaussian kernel (12mm FWHM). SPM2's general linear model was used to produce statistical parametric maps of the between-group *t* statistic for grey matter "concentrations" thresholded at a corrected p<0.05.

Results

Quantified metabolites included in the statistical analysis are plotted in Figure 1 (Tau = taurine, Cho = choline, Syl = Scyllo-Inositol). Levels of thalamic total-creatine (tCr) (p<0.001) and Glu+Gln (p=0.009) were lower in 30M patient repeats than 10M patient repeats. VBM maps showed no significant differences between the two control groups or between never-treated and 10M as well as 10M vs 30M. Significant grey matter volume differences were found between the never-treated group and 30M repeat group (Figure 2). Of specific interest are volume changes within the hippocampus/hippocampal sulcus and dorsolateral prefrontal cortex. Glu+Gln was nearly, but not significantly reduced in controls (p=0.056) and no tCr or VBM differences were observed between control and control-repeat subjects.

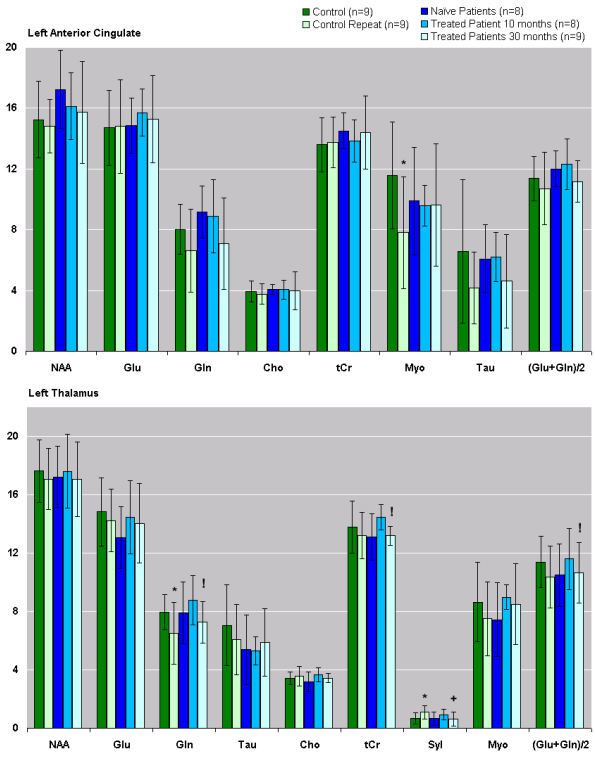

Figure1. 1H MRS Metabolite levels (arbitrary units) measured from a 1.5 cc voxel in the anterior cingulate and thalamus of schizophrenic patients (never-treated, treated 10 months, treated 30 months) and control subjects (intial scan, repeat scan 30 months later). * = significant difference on paired t-test with the control group (p<0.05, 2-tailed). ! = significant difference on paired t-test with 10 month group (p<0.05, 2-tailed). + = significant difference on heteroschedastic t-test (p<0.05, 2-tailed).

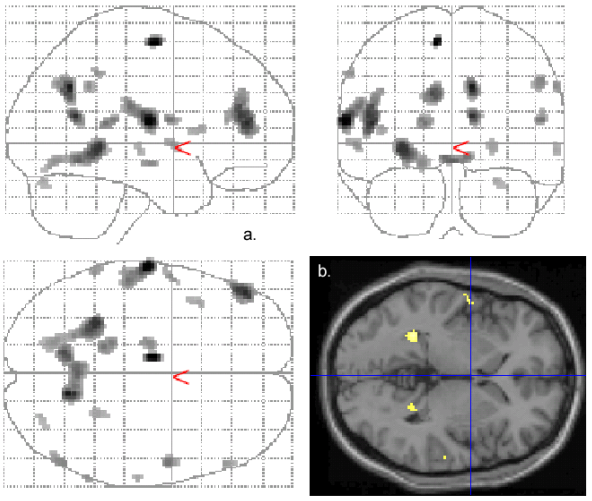

Figure2. a. Glass-brain representation of a SPM{t} map of local grey matter differences between the never-treated group and same group after 30 months of antipsychotic treatment (never-treated > 30M, corrected p<0.05 , T=7.7, k=10). b. Selected transverse slice showing reduced grey matter volumes in the hippocampal sulcus (never-treated > 30M, corrected p<0.05 , T=7.7, k=10).

Discussion

These preliminary results showed no evidence of Glu+Gln decreases with time in the AC. Glu+Gln levels underwent a significant reduction in the thalamus after 30M of treatment, which supports the idea of neurodegeneration of glutamatergic neurons. The very significant reduction of tCr in the same group may represent abnormal energy metabolism in this area. Grey matter volume reductions within the hippocampus and dorsolateral prefrontal cortex of the 30M group, regions connected to the AC and thalamus via glutamatergic pathways, further support the idea of neurodegeneration. Although trends toward decreased Glu+Gln were observed in control-repeat spectra (perhaps due to normal ageing), tCr levels and VBM showed no changes over time in the control subjects. The study of a larger group should clarify the spectroscopy findings.

References

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