Metabolite levels in hippocampus and anterior cingulate of 29 patients with recent-onset schizophrenia, as measured with single-voxel PRESS at 4 Tesla

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Introduction

There are at least 64 published studies that measure metabolite levels in brain tissue of patients with schizophrenia (SZ), using ^{1}H magnetic resonance spectroscopy (MRS). Roughly 88% of these studies were done at 1.5T and 77% focused on patients with chronic SZ. Consensus has emerged that NAA levels are reduced ~5% in hippocampus and in cortical gray matter of frontal lobe, among chronic patients. Yet it is not known if metabolite levels are also reduced among newly-diagnosed patients.

Methods

We did a study at 4T, to characterize MRS measurement precision and to determine if NAA levels are reduced in newly-diagnosed SZ patients. We used a 4T whole-body scanner (GE LX 8.3) with a PRESS sequence (PROBE-P) and a standard quad head coil. Single-voxel ^{1}H spectra were acquired from left (L) and right (R) hippocampus (VOI=4cc), and L and R anterior cingulate (AC) (VOI=6cc), with: TR = 3000 ms, TE = 30 ms, NEX = 64, automated higher-order and linear shims, and CHESS suppression. Precision was characterized by measuring metabolite coefficient of variation (CV) in a volunteer in 4 different brain regions in 10 exams. The clinical study includes 20 newly-diagnosed SZ patients, 9 established patients (diagnosis made 6 months ago), and 17 healthy controls (we continue to accrue and will double our sample size in ~6 months). All spectra were processed with LCModel, and were discarded if the S/N ratio was <4.

Results

The average CV was 13.2% (± 1.9% SD) in 20 hippocampal VOIs, and was 6.5% (± 2.9% SD) in 20 AC VOIs of the control, so measurement precision of major metabolites (tNAA, tCho, Cr) is acceptable.

Ave. CV	tNAA	NAA	tCho	Cr	Glu	Glx	NAA/Cr	tCho/Cr	Glx/tNAA
R Hippo.	13.8	13.0	13.2	15.3	17.4	19.5	18.2	4.2	18.5
L Hippo.	15.0	12.1	10.3	11.6	27.6	26.6	12.1	13.1	34.5
R AC	7.5	21.8	11.5	2.9	4.0	9.0	20.6	9.3	11.3
L AC	4.3	15.20	6.4	6.20	11.90	8.1	20.10	8.90	10.50
Overall CV=	10.2	15.5	10.4	9.0	15.2	15.8	17.8	8.9	18.7

Data are more reliable in AC, and some metabolites are more reliably measured than others. Certain metabolites with high CV should not be evaluated until a large sample is accrued (*e.g.*, glutamate). The CV of ratios is 18% higher than the CV of metabolites. Despite good precision, there was substantial variation in metabolite levels among 17 controls (data not shown), and NAA levels broadly overlap between patients and controls. There was a trend for new patients to be more like controls than like established patients.

Conclusions

Study reliability is a problem, as most published studies are under-powered. With simple assumptions about the inherent difference in NAA levels between SZ patients and controls, it was calculated that at least 39 patients and 39 controls are required for adequate statistical power. Only 3 of 64 published MRS studies had enough subjects to have 80% power to detect a 10% NAA reduction in patients, and no studies at all were adequately powered to detect a 5% NAA reduction with 80% power. There appears to be little or no change from normal in metabolite levels among SZ patients at diagnosis.