Measurements of glutamatergic pathway in patients with schizophrenia using 7T MRSI

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Introduction Schizophrenia (SCZ) is a mental disorder characterized by excessive (positive) and absent (negative) normal function, and patients with SCZ mostly have poor quality of life. The cause of the disease is still unclear. The primary antipsychotic medicine for SCZ acts by blocking the dopamine D2 receptors but fails to improve the negative symptoms of the disease. Alternative medicines that target the N-methyl-D-aspartate receptor (NMDAR) are based on the evidences that Glu antagonist, such as ketamine, can mimic some of the symptoms of SCZ [1], and Glu itself can also affect dopamine pathways. Changes in Glu, glutamine (Gln), γ-aminobutyric acid (GABA), glutathione (GSH) and glycine (Gly) can be detected noninvasively using proton magnetic resonance spectroscopic imaging (H-1 MRSI). The availability of ultra high field MR systems offer advantages in studying these metabolites because it provides higher SNR and improved spectral resolution. The purpose of this study was to compare levels of Glu, Gln, GABA, GSH and Gly in patients with SCZ to those in healthy controls using 3D short-echo MRSI at 7 Tesla.

Methods The population studied comprised 7 patients (2F/5M, 24±4years) who had recent onset SCZ or schizoaffective disorder based on DSM-IV criteria and were on stable doses of an antipsychotic medication, as well as 13 age- and gender-matched healthy controls (4F/9M, 23±4years). All MR studies were performed using a 32-channel receive-only array with a volume transmit head coil on a GE 7 Tesla scanner (GE Healthcare, Waukesha, WI). Anatomical imaging consisted of a T1-weighted sagittal scout and T1-weighted fast spoiled gradient echo images. The 3D H-1 MRSI data were obtained using spectrally-selective adiabatic inversion recovery lipid suppression, CHESS water suppression, 8 automatically-prescribed VSS outer volume suppression, spin echo slice selection with TE/TR=20/2000ms, spectra array=18-20x22x8 and spatial resolution = 1cm^3 [2]. The total acquisition time was about 10 min after applying an interleaved flyback echo-planar trajectory in the A/P direction. The slice selection for the 3D MRSI data was placed parallel to the AC-PC-line with almost full coverage of the thalamus (see Figure 1). The 32 channels of data were combined and processed as described previously, and quantified using LCModel. Regions of interest (ROIs) were automatically segmented on the T1-weighted SPGR images using the Harvard-Oxford cortical and subcortical structural atlases within FSL (see Figure 1). Rank-sum tests were utilized to compare metabolite ratios between the two subject groups.

Results Figure 1 illustrates ROIs and H-1 MRSI data acquired from a patient with SCZ. As shown in Table 1, there were significant differences in metabolite ratios between patients and controls. The patients had significantly increased GSH/Cr in the cingulate cortex and frontal lobe but decreased GSH/Cr in posterior SMG, left PT and left insula. Glu/Cr was lower in MFG (including dorsolateral prefrontal cortex, DLPFC) but higher in the angular gyrus, cuneus cortex, LOG superior and subcortical regions. The relative levels of GABA/Cr were reduced in left para-cingulate gyrus, insula and putamen, and decreased Gly/Cr was found in the Heschl gyrus and posterior SMG.

ROI		Metabolite	+/-	SCZ	HC	P-value
Limbic	rh ACC	GSH/Cr	+	0.31±0.03	0.26±0.05	0.0369
	lh PCG	GABA/Cr	-	0.35±0.03	0.41±0.08	0.0420
		GSH/Cr	+	0.35±0.08	0.27±0.06	0.0365
Cortical	MFG	Glu/Cr	-	1.26±0.27	1.54±0.23	0.0449
	SFG	GSH/Cr	+	0.33±0.06	0.24±0.09	0.0202
		Gln/Cr	-	0.30±0.07	0.59±0.24	0.0303
	SMG posterior	Gly/Cr	-	0.13±0.03	0.17±0.04	0.0426
	rh angular	Glu/Cr	+	1.95±0.44	1.57±0.15	0.0369
	Heschl	Gly/Cr	-	0.15±0.05	0.29±0.19	0.0221
	lh PT	GSH/Cr	-	0.29±0.07	0.35±0.05	0.0393
	Cuneus Cortex	Glu/Cr	+	1.47±0.22	1.03±0.21	0.0055
	LOG superior	Glu/Cr	+	1.53±0.26	1.31±0.22	0.0456
Insular	lh insula	GABA/Cr	-	0.28±0.03	0.32±0.05	0.0297
		GSH/Cr	-	0.28±0.03	0.32±0.04	0.0293
Subcortical	lh putamen	GABA/Cr	-	0.26±0.05	0.34±0.07	0.0225
		Gln/Cr	-	0.40±0.13	0.60±0.19	0.0477
	lh caudate	Glu/Cr	+	1.11±0.13	0.96±0.22	0.0432
	lh thalamus	Glu/Cr	+	1.14±0.08	0.97±0.22	0.0357

Table 1. Summary of the significant difference in metabolite ratios by brain regions.
lh = left hemisphere; rh = right hemisphere; ACC = anterior cingulate cortex; PCG = para-cingulate gyrus; MFG = medial frontal gyrus; SFG = superior frontal gyrus; SMG = supramarginal gyrus; PT = planum temporale; LOG = lateral occipital gyrus.

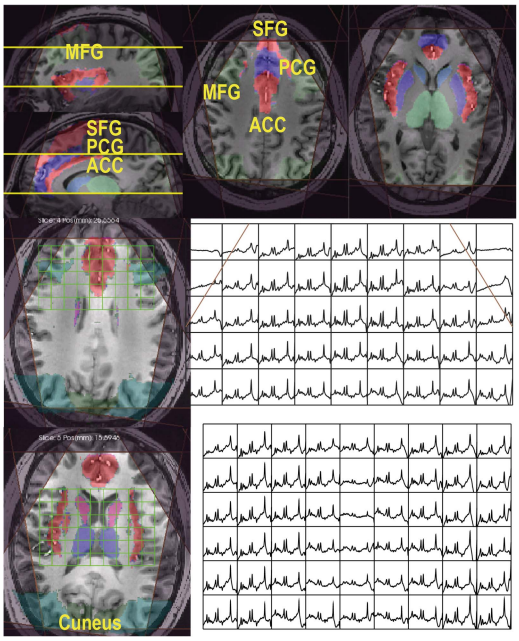

Figure 1. MRSI data (w/ baseline) from a patient with SCZ.

Discussion This study evaluated in vivo levels of Glu, Gln, GABA, GSH and Gly from different brain regions in patients with SCZ using a single MRSI acquisition. The NMDAR is an ion channel involved in controlling synaptic plastic and memory function. The activation of NMDAR requires binding of both Glu and Gly/d-serine, and is modified by antioxidant GSH. NMDAR antagonist blocks the activation of NMDAR resulting in excessive extracellular Glu and could induce SCZ-like symptoms [1]. The level of Glu was reported increased in the early stage of SCZ and decreased after treatment [4]. The findings of changes on Gly/tCr and GSH/tCr suggest that they have complicated roles in controlling the activation of NMDAR in brain regions for patients with SCZ. Disturbance and hyperactivity of dopamine systems in the limbic loop could also contribute to some of the symptoms of SCZ [3]. The presynaptic release of dopamine is inhibited by GABAergic neurons and activated by NMDAR [4]. This may explain that the significantly lower GABA/Cr were found in the PCG, putamen and insula. In summary, this study has found abnormalities of the glutamatergic system in different brain regions and suggests that future study should examine these metabolite ratios in drug-naïve/free subjects, as well as examine the correlations between metabolites and symptoms.

References 1. Javitt DC, et al. Am J Psychiatry 1991; 2. Li Y, et al. ISMRM 2012; 3. Jocyce JN, Psychopharmacology 1993; 4.Poels EMP, et al. Mol Psychiatry 2013.

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