

Relationships between Metabolite Concentrations and Working Memory Performance in Patients with Bipolar Disorder and Schizophrenia

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Target audience – This work should be of interest to psychiatrists and neuroscience researchers who focus on magnetic resonance spectroscopy (MRS).

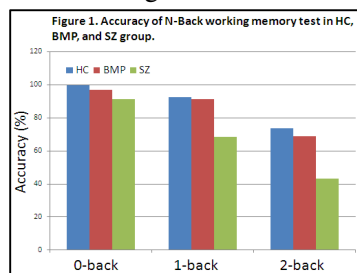
Purpose – We examined correlations between regional brain metabolite levels obtained using *in vivo* MRS and N-back working memory (WM) test accuracy in bipolar disorder (BD), schizophrenia (SZ) and healthy comparison (HC) study groups.

Methods – Thirteen SZ (4F, 32 ±10 yrs.), seven bipolar manic with psychosis (BMP) (3F, 30 ±8 yrs.) and five HC (2F, 31 ±10 yrs.) participants comprised the study groups. **Clinical measurements:** Clinical diagnoses of SZ and BD were verified using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders Patient Edition (SCID-I/P).¹ Schizophrenic patients required a Positive and Negative Syndrome Scale (PANSS) score ≥ 70 to meet inclusion criteria (PANSS: 88 ±10). Bipolar manic patients were required to have a Young Manic Rating Scale (YMRS) score ≥ 20 with psychotic features for inclusion (YMRS: 30 ±5).

MR methods and N-back memory test: Participants were consented and thereafter fMRI with the N-back WM test and MRS was acquired on a 4-Tesla MR scanner using echo planar imaging (EPI). The EPI data were reconstructed immediately after acquisition. The “real-time” fMRI activation map was used for further guiding MRS voxel positioning. In general, the PRESS MR spectra (8 cc, TE/TR=23/2000ms) were acquired in the right and left dorsolateral prefrontal cortex (R-, L-DLPFC) and anterior cingulate cortex (ACC). **Data analysis:** Spectra were analyzed with LCModel and metabolite levels were presented in concentration (mM). The accuracy of the N-back WM test (Figure 1) was compared across the three groups (Table 1).

Correlations between regional metabolite levels and N-back WM accuracy were analyzed using linear regression and presented as *p* values and Pearson’s *r* coefficients (Table 2).

Results – Figure 1 shows that accuracy decreased with increasing difficulty on the N-back WM test, but that only the SZ group



	MI	NAA	Cr	Cho	Glu	Glx
ACC	<i>p</i> =.014 <i>r</i> =-0.741 (1-back)	none	<i>p</i> =.009 <i>r</i> =-0.771 (1-back)	<i>p</i> =.074 <i>r</i> =-0.588 (1-back)	<i>p</i> =.087 <i>r</i> =-0.568 (1-back)	<i>p</i> =.008 <i>r</i> =-0.777 (1-back)
R-DLPFC	none	none	<i>p</i> =.094 <i>r</i> =-0.558 (1-back)	<i>p</i> =.0143 <i>r</i> =-0.492 (1-back)	none	none
L-DLPFC	none	<i>p</i> =.053 <i>r</i> =0.660 (2-back)	none	<i>p</i> =.0008 <i>r</i> =-0.881 (2-back)	none	none

	HC vs. HC	BMP vs. BMP	SZ vs. SZ
0-B vs. 1-B	<i>p</i> =.046	<i>p</i> =.146	<i>p</i> =.006
0-B vs. 2-B	<i>p</i> =.013	<i>p</i> =.015	<i>p</i> =3.3x10 ⁻⁸
1-B vs. 2-B	<i>p</i> =.067	<i>p</i> =.028	<i>p</i> =.010
	BMP vs. HC	BMP vs. SZ	SZ vs. HC
0-B vs. 0-B	<i>p</i> =.255	<i>p</i> =.188	<i>p</i> =.026
1-B vs. 1-B	<i>p</i> =.792	<i>p</i> =7.4x10 ⁻³	<i>p</i> =6.1x10 ⁻³
2-B vs. 2-B	<i>p</i> =.717	<i>p</i> =.037	<i>p</i> =.025

had lower accuracy relative to the HC group. Preplanned pairwise comparisons are summarized in Table 1. We did not find any significant correlations between accuracy vs. regional metabolite levels in the HC or BPM group separately. All significant

correlations were limited to the SZ group only (Table 2).

Discussion – Working memory deficits have long been associated with the dysfunction of the DLPFC and ACC. Table 2 indicates that WM test accuracy decreased with increased Cr and Cho levels in the ACC and R-DLPFC regions of the SZ group. Moreover, the correlations became stronger when test difficulty increased from the 1-back to 2-back condition. In that there were no significant brain tissue differences within MRS voxels between HC and SZ groups, the Cr-related correlations were unlikely due to the gray matter (which has higher Cr level) loss in SZ. Instead, the identified relationships are likely due to bioenergetics abnormalities, such as phosphocreatine level changes in the R-DLPFC region. The Cho-related correlations with R-DLPFC were prominent in the SZ group. This may suggest that WM accuracy is highly sensitive to the subtle Cho changes in the R-DLPFC of the SZ group.

Indeed, a recent review article proposed that choline availability might be one of the factors that contribute to the development of schizophrenia-associated attentional deficits.²

Conclusion – Both HC and BMP groups show similar WM test performance while the SZ group underperformed relative to these two groups. Our data confirm the role of DLPFC in the pathophysiology of SZ. These findings are not likely the result of differences in the severity of psychosis between the patient groups, which was methodologically controlled. The hypothesized role of ventrolateral prefrontal cortex in the neuropathology of BMP might be revealed using similar research procedures in further studies.³

References – (1). First, MB. Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition. New York: Biometrics Research Department, New York State Psychiatric Institute. 1997. (2). Ross, RG. J. Child Psychology and Psychiatry. 2010;51(5):535. (3). Frangou, S. Biol Psychiatry. 2005;58:838.