Correlations Among fMRI, MRS and Working Memory in Healthy, Bipolar and Schizophrenic Subjects

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Target audience – This work is of interest to psychiatrists and neuroscience researchers with interests in fMRI and MRS.

Purpose – Magnetic resonance spectroscopy (MRS) and functional magnetic resonance imaging (fMRI) have been widely but separately used in studies of bipolar disorder (BD) and schizophrenia (SZ). In the present work we studied BD, SZ and healthy comparison (HC) participants during an N-back working memory test using fMRI-guided MRS to investigate the correlations among the fMRI activation and neurochemical levels.

Methods – Thirteen SZ (9M/4F, 32 ± 10 yrs.), seven BD manic with psychosis (4M/3F, 30 ± 8 yrs.) and five HC (3M/2F, 31 ± 10 yrs.) participants comprised the study groups. ***Clinical measurements:*** Diagnoses of SZ and BD were made and excluded using the Structured Clinical Interview for DSM-IV (SCID).[1] Schizophrenic patients required a Positive and Negative Syndrome Scale (PANSS) score ≥ 70 to meet inclusion criteria (PANSS: 87.5 ± 9.9). Bipolar manic patients were required a Young Manic Rating Scale (YMRS) score ≥ 20 with psychotic features for inclusion (YMRS: 29.6 ± 5.2). ***MR methods and cognitive task***: Participants provided informed consents and thereafter fMRI with the N-back working memory test and MRS was acquired on a 4-Tesla MR scanner using echo planar imaging (EPI). The EPI data was reconstructed immediately after acquisition. The "real-time" fMRI activation map was used for further guiding MRS voxel positioning. In general, the PRESS 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. Functional MR activation signals were analyzed using previously published procedures.[2] The averaged fMRI signal extracted from each of the three MRS voxels was compared to the resting-state metabolite level. The fMRI data were processed using various contrasts to reflect the different cognitive functions required for task performance. For example, the contrast of 2-back *minus* 0-back is to isolate working memory from monitoring processes. The contrast of 2-back *minus* 1-back is to isolate high from low processing demands. The contrast of 2-back *plus* 1-back *minus* 0-back is to isolate working memory from monitoring regardless of processing demands.

Results – Figure 1 illustrates the correlation between fMRI activation in the 2-back *minus* 0-back condition and Glx concentrations [the summed term of glutamate (Glu), glutamine (Gln), and γ-amino butyric acid (GABA)] in the L-DLPFC of the BD group. Table 1 provides a further summary of significant correlations observed at various regions in the BD group. In the HC group, only the correlation between N-acetyl aspartate (NAA) and the contrast of 2-back *minus* 1-back was significant (*p=.046; r=-0.089)* in the ACC. No such correlations were present in the ACC of the BD or SZ groups.

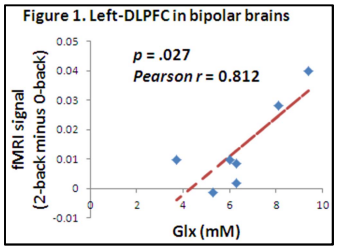

Table 1. Correlations between fMRI signals and metabolite level at various regions in bipolar brain.

	NAA	Glx
0-back	*P=.027, r=-0.811 (L-DLPFC)*	
2-back ***minus*** 0-back		*P=.027, r=+0.812 (L-DLPFC)*
2-back ***plus*** 1-back ***minus*** 0-back		*P=.050, r=+0.752 (L-DLPFC)*
2-back ***minus*** 1-back	*P=.032, r=+0.797 (L-DLPFC)*	*P=.025, r=-0.867 (ACC)* *P=.050, r=+0.753 (L-DLPFC)* *P=.034, r=-0.845 (R-DLPFC)*

Discussion – The balance between glutamatergic excitatory neurons and GABA-ergic inhibitory interneurons is believed to have relevance to fMRI activations.[3] We noticed that none of Glx or Glu-related correlations were found in the HC group. Only one NAA-related correlation was found in healthy ACC. This is inconsistent with the patient data, especially for the BD group. Our data show that working memory and processing demand are correlated with Glx in DLPFC regions in the BD group. Although we did not find similar significant correlations in the SZ group, some of the regions showed trend-level relationships, such as the correlation between 2-back *minus* 1-back activation and Glx in R-DLPFC (*p=.119*) with a positive r (*r=+0.558*), which is opposite to the negative *r* value in the same region of BD group.

Conclusion – Glutamatergic abnormalities in DLPFC of BD group may provide insight into how regional neurochemicals regulate the fMRI activation induced by cognitive tasks. An improved MR method allowing the simultaneous measurement of Glu, Gln and GABA is needed for shorter scan times and more accurate measurement to address the correlations among fMRI activation, neurochemicals and cognitive dysfunction in psychiatric disorders.

References – (1). First, MB. Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition. New York State Psychiatric Institute. 1997. (2). Strakowski, SM. Biol Psychiatry. 2011;69(4):381. (3).Figley, CR. Eur. J. Neuroscience. 2011;33:577.