Impaired Brain Circuitry and High-Energy Phosphates in Bipolar Disorder

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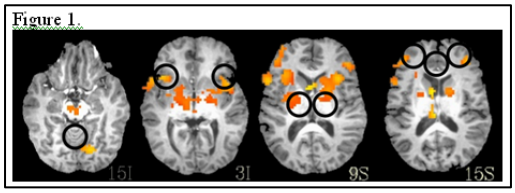
Introduction: In this work we used fMRI with the Balloon Analogue Risk Task (BART)[1] in order to investigate the functional neuroanatomy of impulsivity in bipolar disorder. Then, to extend this work to understand the neurophysiological underpinnings of the activation patterns, in the same regions that are associated with brain activation abnormalities identified by functional MRI, we assessed regional bioenergetics using whole brain ^{31}P MRSI. Our goal was to find parallel differences in resting-state high-energy phosphate metabolites and fMRI activation in BD patients and healthy subjects.

Methods: All MR studies were performed on Varian 4T whole-body MR system. Participants included 13 medicated, euthymic bipolar patients (7 women) with an average age of 33 years. Inclusion criteria included no substance dependence and no substance abuse within the past 3 months, Young Mania Rating Scale score <10 (Mean=2.7), and Montgomery-Asberg Rating Scale score <10 (Mean=1.7). Thirteen demographically matched healthy subjects served as comparisons (HC; 6 women, average age 29). Behavioral Paradigm (BART): During the fMRI scan, participants were instructed to "pump up" a balloon presented on the screen by pressing a specific key on a button box. Participants were instructed that, for each balloon pump, they would earn 2 cents. After an unpredictable number of 'pumps' the balloon may 'explode' resulting in a loss of money accumulated on that balloon trial. However, subjects may 'bank' accumulated winnings at any time during a trial. The risk of explosion and money loss increases as the balloon inflates. Participants are considered more impulsive if they pump more before banking, i.e., exhibit a greater willingness to risk money loss. Three 8 minute scanning runs each included 15 balloon trials for a total of 45 trials. fMRI: fMRI scans were acquired using a T2*-weighted gradient-echo EPI pulse sequence (TR/TE=3000/30 ms, FOV=20.8 x 20.8 cm, matrix 64 x 64 pixels, slice-thickness=2 mm, 1mm gap, flip angle=75°, axial slices angled 30° to AC-PC) while subjects performed the BART. The fMRI analysis employed motion correction, spatial smoothing, normalization and random effects analysis in AFNI. ^{31}P MRSI : ^{31}P-MRSI were acquired with a ^{1}H/^{31}P double-tuned TEM coil and a one-pulse acquisition based on a 3-D spherical sampling scheme (13x13x13; FOV, 24x24x24 cm, TR 0.5 sec). Total acquisition time was 46 minutes. These 3D-MRSI data were overlaid on a 3D MDEFT anatomical image for visualization and interpretation. ^{31}P spectra were reconstructed from the activated brain regions that differed between BD and HC as shown in Figure 1. Regions of interest for ^{31}P spectral reconstruction included the anterior cingulate cortex (ACC), cerebellar vermis, thalamus, dorsolateral prefrontal cortex, putamen, amygdala (amyg), ventrolateral prefrontal cortex (VLPFC), lateral orbitofrontal cortex (BA10), and thalamus. Reconstructed ^{31}P spectra were curve fitted using the AMARES method in jMRUI software. Signal loss due to T1 relaxation was corrected using previously published values.



Results: Figure 1 displays the difference in fMRI activation between 13 patients and 13 comparison subjects during BART performance and indicates the approximate location of some of the ROIs used for ^{31}P spectra reconstruction. Table 1 summarizes the ^{31}P MRSI data that were found significantly different in several brain regions between HC and BD groups. Significant differences were observed in amygdala, VLPFC and BA10.

Table 1.

Ratios	Regions	HC	BD	Note
Pi/PCr	R-amyg	0.384±0.215	0.217±0.168	*P*=0.032
	R-BA10	0.669±0.238	0.384±0.234	*P*=0.018
PDE/PCr	L-VLPFC	0.409±0.235	0.816±0.312	*P*=0.002
PDE/total_phosphates	L-VLPFC	0.125±0.059	0.207±0.074	*P*=0.008
Pi/total_phosphates	R-amyg	0.088±0.045	0.049±0.025	*P*=0.010
PCr/total_phosphates	L-VLPFC	0.333±0.063	0.260±0.045	*P*=0.002
	R-BA10	0.198±0.030	0.250±0.043	*P*=0.005

Pi: Inorganic phosphate; PCr: Phosphocreatine; PDE: Phosphodiester

Discussion: A dysfunctional anterior limbic network results in dysregulation of mood.[2] The regions indicated by the fMRI activation differences between HC and BD include components of the anterior limbic network. In ^{31}P MRSI data, the reduced Pi/total-phosphate and Pi/PCr in patients in the amygdala could reflect medication effects, which facilitate the regulation of phosphorylation/dephosphorylation reactions and may favor phosphorylation. Eleven of 13 patients were medicated. The increased PDE/total-phosphates and PDE/PCr are consistent with previous reports, which found increased PDE in the frontal lobe of BD patients.[3] Kato et al. report PDE is significantly higher in medication-free BD patients with white matter hyperintensity (WMHI) than in those without WMHI and healthy controls.[4] The increased PDE suggest the alterations in membrane phospholipid metabolism could alter membrane composition and fluidity and affect the healthy status of neurons.

References: 1). J. Exp. Psychol. Appl. 2005; 8:75. 2). Molecular Psychiatry 2005;10:105. 3). Am. J Psychiatry 1995;152:615. 4). Eur Arch Psychiatry Clin Neurosci 1998;248:301.