fMRI guided 31P spectroscopy in bipolar disorder

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Introduction: Impulsive symptoms occur in several neuropsychiatric disorders including bipolar disorder (BD). The Balloon Analogue Risk Task (BART) is a novel behavioral measure of risk taking, which correlates with impulsive behavior in BD. In this work, we assessed impulsivity in euthymic bipolar patients and healthy subjects using the BART, fMRI and ^{31}P magnetic resonance spectroscopic imaging (MRSI). Functional MRI activation can identify brain regions that are associated with behavioral impairments. Understanding the metabolic origins of fMRI abnormalities in terms of neurochemistry could clarify the structural and functional neuropathology underlying bipolar disorder. Our goal is to find parallel changes in resting-state high-energy phosphates metabolites and fMRI activation associated with impulsivity in BD patients.

Methods: All MR studies were performed on Varian 4T whole-body MR system. Participants included 6 medicated, euthymic bipolar patients (3 female) with an average age of 34.7 (SD=8.4). Inclusion criteria included no current substance dependence or abuse, Young Mania Rating Scale (YMRS) score <10 (Mean=2.7), and Montgomery-Asberg Rating Scale (MADRS) score <10 (Mean=1.7). Three demographically matched healthy subjects served as controls.

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', which results in a loss of all of the money accumulated on the trial. Subjects may 'bank' accumulated winnings at any time during a balloon trial. The risk of explosion and money loss increases as a balloon expands. 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.

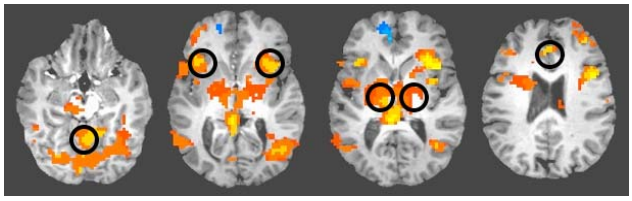
fMRI: fMRI scans were acquired using a T2*-weighted gradient-echo EPI pulse sequence (TR/TE=3000/30 ms, FOV=20.8 x 20.8 cm, matrix 64 x 64 pixels, slice-thickness=2 mm, 1mm gap, flip angle=75°, axial slices angled 30° to AC-PC) while subjects performed the BART. The fMRI analysis employed motion correction, spatial smoothing, normalization and random effects analysis in AFNI.

^{31}P 3-D MRSI : ^{31}P-MRSI were acquired with a ^{1}H/^{31}P double-tuned TEM coil using an one-pulse acquisition utilizing 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 region shown in fMRI data (Figure 1). The regions included the anterior cingulate cortex (ACC), left and right inferior frontal gyrus (IFG), left and right thalamus, and the cerebellar vermis. Reconstructed ^{31}P spectra were curve fitted using the AMARESS method in jMRUI software. Signal loss due to T1 relaxation was corrected using previously published values. ^{31}P MRSI data are presented in metabolite ratios (Pi/PCr, PCr/ATP, and Pi/ATP) and intracellular pH.

Results: Figure 1 displays the summed fMRI activation map from 6 patients' data during balloon pumping. The activation areas were used to select ROIs for ^{31}P spectra reconstruction. There were 2 major findings in the ^{31}P MRSI data. First, the PCr/ATP ratio in the vermis of BD patients is decreased as compared with healthy comparison subjects (1.43±0.49 vs. 2.15±0.50, $p=0.03$). Second, there was a trend towards a decreased PCr/ATP ratio of the right IFG region in the bipolar patient group (1.45±0.25 vs. 1.11±0.22, $p=0.11$).

Discussion: Phosphocreatine provides a reserve supply of rapidly hydrolysable ATP for brain function. The PCr pool is readily interchangeable with ATP under the influence of creatine kinase and PCr/ATP ratio is considered the marker of energy charge. The cerebellum has been associated with emotional modulation and behavioral disorder in BD. Our previous MRI studies also identified the cerebral vermal abnormalities (decreased vermal region V2 and V3 areas) in BD brain[1,2]. However, in this work, the cerebellar voxel included V1 and V2 areas. Since response inhibition engages the right IFG, the patient's lower PCr/ATP ratio of right IFG is particular interesting despite no significant difference from healthy comparison subjects ($p=0.11$). The small number of subjects in this study and medication effects that improve impulsive behavior may contribute to the small effect size. The detection of regional ^{31}P abnormalities in metabolite using fMRI-guided MRSI allows us to link functional brain activation abnormalities to biochemical abnormalities in BD. These links are valuable for understanding the pathopsysiology of BP. Although MRS and fMRI are each important imaging modalities that are increasing the understanding of many disease processes, these two tools have been mainly used exclusively or independently. We believe that integrating these tools will create a new avenue to advance neuroscience. We have demonstrated the concept in patients with bipolar disorder.

Figure 1.



References: 1). Delbello MP. Neuropsychopharmacology 1999;21:63-68. 2). Mills NP. Am J Psychiatry 2005;162:1530-1532.