Title: Functional Bold and Functional T1rho Decoupled in Bipolar Disorder

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Synopsis:

Functional T1 relaxation in the rotating frame (fT1ρ) is a new method of functional imaging that is thought to reflect changes in brain metabolism due to pH. FT1ρ may provide a more direct measurement of neuronal activity than the blood-oxygen level dependent (BOLD) contrast that is typically used for functional imaging. Here we applied both methods in order to study brain activation during a flashing checkerboard paradigm in participants with bipolar disorder as compared to controls. Linear mixed effect regression modeling revealed decoupling between the two imaging modalities in bipolar disorder in several brain regions.

Purpose: To test the relationship between fT1ρ and BOLD signals in a clinical population.

Methods:

39 participants with bipolar disorder and 32 healthy controls underwent functional neuroimaging during alternating BOLD and fT1ρ runs of a flashing checkerboard paradigm. Diagnosis was confirmed by a clinician. Participants provided informed written consent in accordance with the University of Iowa Institutional Review Board.

During each run, participants were presented with seven alternating fixation (black screen) and flashing checkerboard (4 Hz) blocks lasting 40s each. Participants confirmed their attention by pressing a button in response to a red square presented every 4 seconds during the flashing checkerboard blocks. Imaging methods alternated between 3 fT1ρ and 2 BOLD runs.

MR imaging was performed on a 3T Siemens Magnetom Tim Trio with a 12-channel receiver head coil. High-resolution T1 (coronal 3D MP-RAGE; field-of-view=256mm^3; matrix= 256×256×256;

resolution=1.0mm^3; TR=2530ms; TE=2.8ms; TI=909ms; flip angle=10°; BW=180Hz/px; and R=2 GRAPPA) and T2–weighted (sagittal 3D SPACE; field-of-view=260×228×176 mm^3; matrix=256×230×176; resolution=1.0 mm^3; TR=4000ms; TE=406ms; BW=592Hz/px; turbo factor=121; slice turbo factor=2; and R=2 GRAPPA) were acquired in order to register functional images to a common atlas space. Functional T1ρ (spin-echo-planar-imaging(SE-EPI) [1]; TR=4s; TSL=10,50ms; SL amplitude($\gamma B_1/2\pi$)=213Hz, field-of-view=240×240mm^2; matrix=64×64(single shot); slice thickness/gap=5.0/1.25mm; TR=2000 ms; TE=15ms; BW=1954Hz/px; partial Fourier=5/8; fat saturation; 140 measurements) and BOLD (T2*-weighted gradient-echo echo-planar-imaging(GRE-EPI); field-of-view=220×220mm^2; matrix=64×64(single shot); 30 slices; slice thickness/gap=4.0/1.0mm; TR=2000ms; TE=30ms; BW=2004Hz/px; fat saturation; 140 measurements) time series were acquired in conjunction with the flashing checkerboard stimulus. in an axial-olique orientation with the most inferior slice positioned at the base of the frontal and occipital lobes.

BRAINS AutoWorkup [2] and Advanced Normalization Tools (ANTS) were used on T1 and T2-weighted anatomical images to generate a deformable transformation to a common atlas space that was used for functional image registration [3]. Functional voxels were masked to exclude non-brain tissue and areas with <95% coverage across participants. Images were transformed to the Montreal Neurological Imaging (MNI) atlas space [4] after analysis for publication.

Functional images were processed using Analysis of Functional NeuroImages (AFNI) [5]. Anatomical registration, skull-stripping, and spatial smoothing(5mmFWHM Gaussian) was performed. T1ρ signal was calculated by fitting the 10 ms and 50 ms spin-lock time images to a mono-exponential signal decay model [1]. Percent signal change for fT1ρ and BOLD were calculated using a general linear model that modelled the timing of the flashing checkerboard blocks, second-order baseline correction, and motion parameters.

Linear mixed effect regression was used to examine the relationship between these two functional imaging modalities and to test whether that relationship was altered in bipolar disorder. A null model that included group and fT1ρ as predictors for the BOLD signal and an experimental model that also included the Group x fT1ρ interaction were compared using a likelihood ratio test [6]. Voxels where these two models were significantly different and where there was a significant effect of the interaction are presented in Figure 2. *3dclustsim* was used to determine a threshold (1.44 cm^3) for cluster-based correction for multiple comparisons (α=0.05).

Results:

The relationship between fT1ρ signal and BOLD signal was weaker in bipolar disorder in left caudate, thalamus, occipital pole, and middle and superior temporal gyri; right lateral occipital cortex and inferior temporal gyrus; and bilateral visual cortex and cerebellum (Figure 2). The relationship was stronger in bipolar disorder in left inferior and middle temporal gyri.

Conclusions:

Decoupling between fT1ρ and BOLD in bipolar disorder was present, suggesting that distinct mechanisms underlie these signals. BOLD contrast reflects changes in blood oxygenation that occur following neuronal activation [7-9]. Blood flow changes are indirect, requiring the involvement of astrocytes [10, 11] and are delayed by 4-6 seconds after stimulation [9]. FT1ρ is sensitive to changes in pH [12, 13], with increased signal reflecting increased acidity and is thought to reflect metabolic activity and/or the release of acidic signaling molecules such as lactate or glutamate [14].

A weaker relationship between fT1ρ and BOLD was present in bipolar disorder within most of the regions identified in this study, but a stronger relationship was observed in others. These regions have been implicated in bipolar disorder by prior BOLD imaging studies [15-22], which suggests that our results reflect disease-related differences. However, our findings may also change the interpretation of prior studies, calling into question whether these prior findings reflect an actual change in neuron activity or instead reflect a decoupling between brain activity and blood flow. These findings suggest an altered relationship between metabolism and blood flow in bipolar disorder and suggest that combined BOLD and may provide an additional form of imaging contrast.

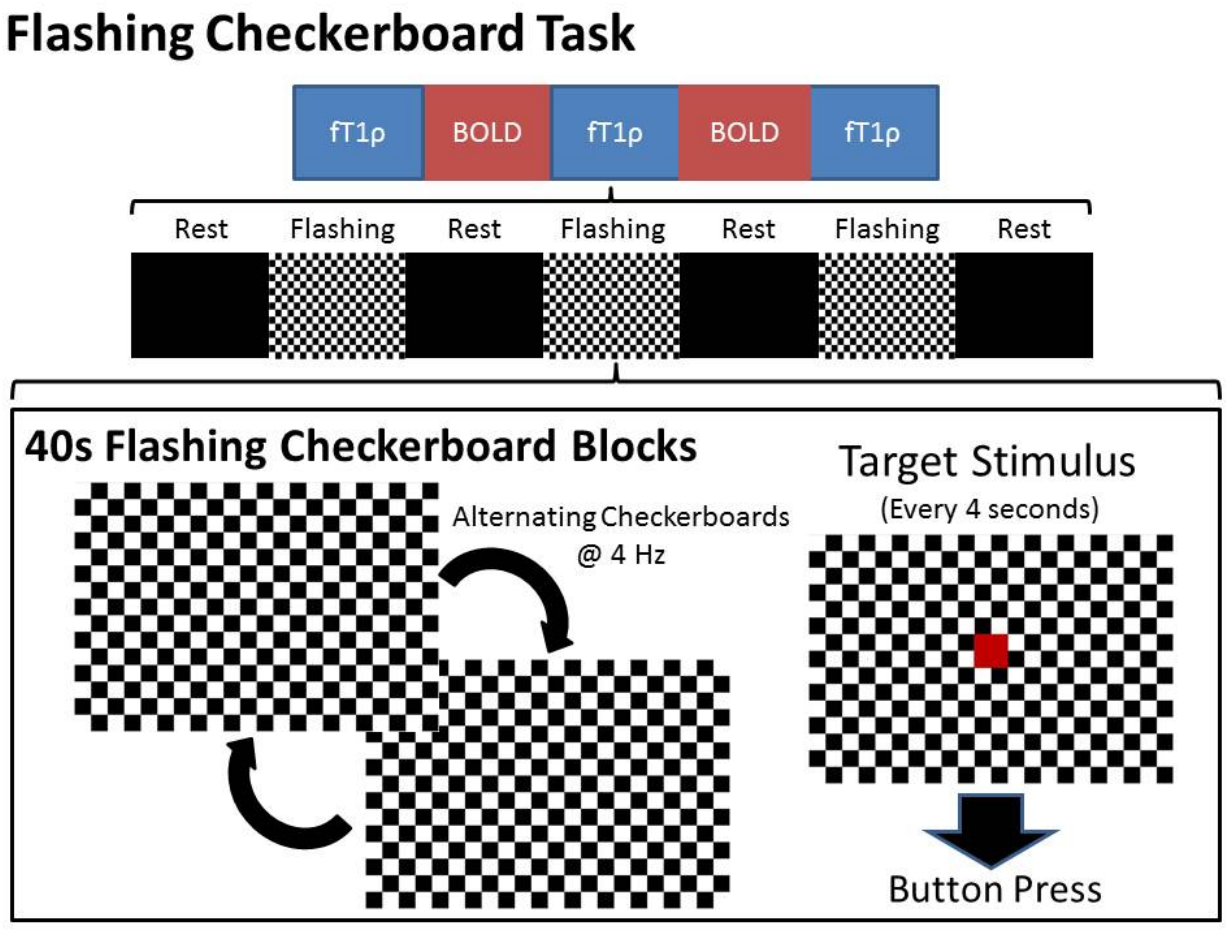

Figure 1: Diagram of imaging runs and flashing checkerboard task.

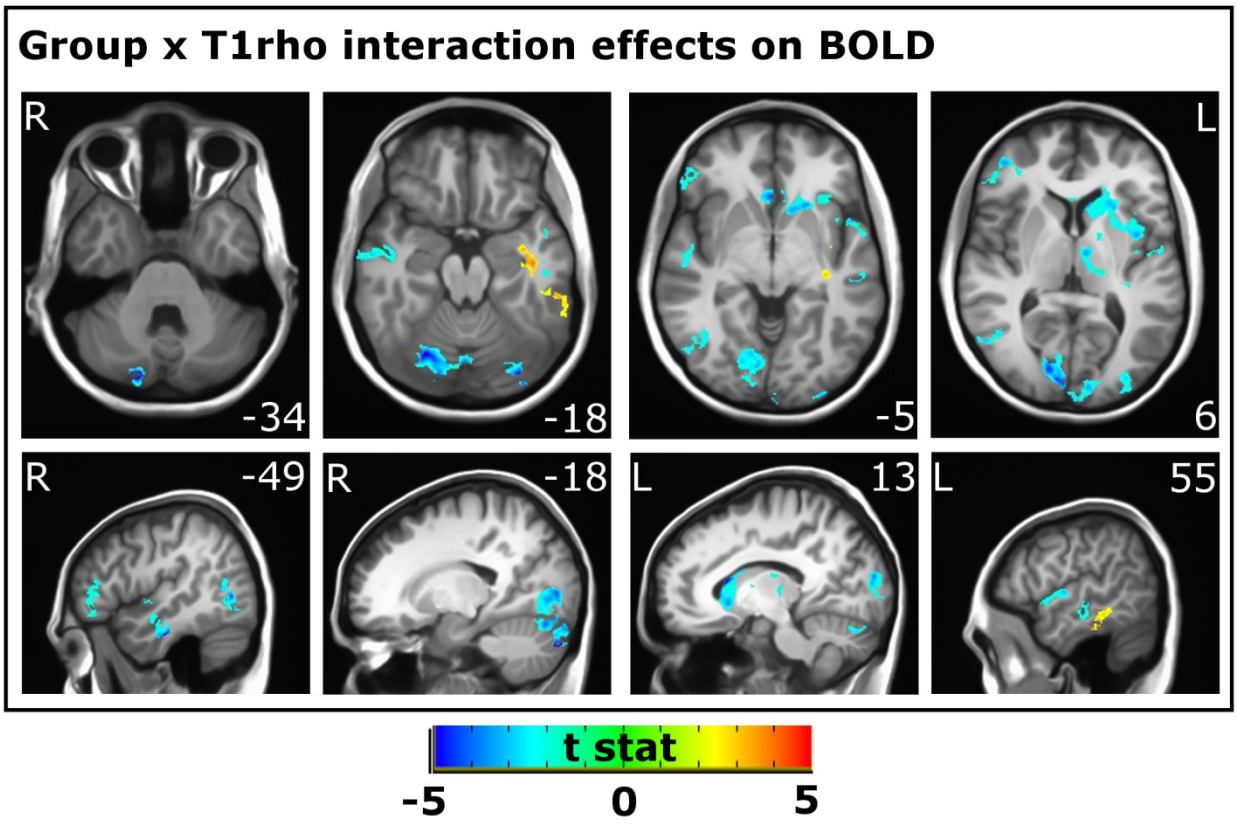

Figure 2: Clusters with significant Group x T1ρ on BOLD signal. Weaker relationships between T1ρ and BOLD are shown in blue; stronger relationships are shown in red/yellow. Slice number (MNI coordinates) for axial and sagittal images are provided for the Z and X planes respectively. L: Left, R: Right

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