Trait and State-Dependent Abnormalities of Bipolar Disorder Detected by Quantitative T1rho Mapping

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Purpose: Bipolar I disorder (BD) is a debilitating psychiatric disease that afflicts ~1% of the United States population. People with BD experience discrete mood states of depression, euthymia (i.e., normal mood), and mania. The pathophysiological mechanisms of BD and triggers of mood state change are largely unknown. In a recent exploratory study, we applied whole-brain quantitative mapping of T1 relaxation in the rotating frame (T1ρ) as a new tool to study participants with BD in the euthymic state [1]. T1ρ is sensitive to a number of factors that have been implicated in BD, including altered pH [2-4], glucose levels [5,6], and cellular density [7], and thus may provide new information about the disease mechanisms and regions of interest in the brain. We found that T1ρ was significantly elevated in the cerebral white matter and the cerebellum in the euthymic bipolar group compared to a group of normal control participants [1]. The cerebellar finding is particularly interesting since this region has received little attention in BD research and the observed effect was not seen in those participants using lithium. The aim of this study was to determine if these findings were preserved or changed with mood state, suggesting either trait or state-dependent abnormalities of the illness, respectively. To this end, we expanded our exploratory T1ρ study of BD to include participants in the depressed and manic mood states. The same T1ρ mapping technique was used as in the prior study, enabling comparison of T1ρ values across all three mood states.

Methods: People with BD in either a euthymic (Montgomery-Asberg Depression Rating Scale (MADRS)<10 and Young Mania Rating Scale (YMRS)≤12), depressed (MADRS≥20), or manic (YMRS≥20) mood state and healthy controls without a history of psychiatric illness were recruited for participation in this study and provided written informed consent in accordance with our local IRB. In total, 27 participants with BD and 25 controls balanced for age and gender were imaged with the quantitative T1ρ mapping technique. Seven of the participants with BD were imaged in multiple mood states, providing sample pools of 9 depressed, 15 euthymic, and 11 manic participants. Imaging was performed on a 3T Siemens TIM Trio MRI system. First, 1.0 mm isotropic T1- and T2-weighted brain scans were acquired for anatomical alignment. Next, the whole-brain 3D T1ρ map was acquired with a coronal 3D FLASH sequence and parameters: FOV=22×22×20 cm^3; sampling matrix=128×128×40; spin-lock times (TSLs)=10 and 55 ms; and spin-lock frequency=330 Hz. Data from each imaging session were processed as follows: (i) the T1ρ map was calculated from the TSL images using the signal model: $S(TSL)=S(0)\cdot e^{-TSL/T1\rho}$; (ii) the T1ρ map was aligned to the T1 image; and (iii) the T1 and T2 images were used to transform the T1ρ map to a common brain atlas with tissue labels for group-wise comparisons. T1ρ maps for each of the three bipolar groups (depressed, euthymic, and manic) were then compared to the normal control group maps. Two group-wise analyses were performed: (i) average T1ρ maps for each group were compared voxel-wise with significance threshold $p<0.05$ and cluster threshold $\alpha=0.05$ to correct for multiple comparisons; and (ii) median T1ρ values for each participant in regions of interest (ROIs) identified by the voxel-wise comparison and defined by the common brain atlas tissue labels were averaged by group and compared with significance threshold $p<0.05$. Note that the euthymic bipolar and normal control group data have been previously reported [1].

Results: Using the voxel-wise comparison, we found that cerebellar T1ρ was significantly elevated in all three bipolar groups vs. the control group, suggesting that the cerebellar abnormality may be a trait of the illness (Fig. 1). We also found T1ρ in the putamen was reduced in the depressed vs. euthymic group, which points to a mood-state-dependent abnormality. These findings are further supported by analyses of the median T1ρ values in the identified ROIs. Average T1ρ values in cerebellar white and gray matter ROIs were significantly elevated in the depressed ($p=0.027$ and 0.009, respectively) and euthymic ($p=0.039$ and 0.032, respectively) groups compared to the control group. When comparing the euthymic and depressed groups, the T1ρ difference in a bilateral putamen ROI was not statistically significant ($p=0.101$), but the finding was significant when limiting the ROI to the left putamen ($p=0.022$). The cerebellar and putamen ROI findings were not significant when comparing the manic group to the control and depressed groups, respectively.

Discussion: Using whole-brain T1ρ mapping, we found evidence for both trait and mood-state-dependent abnormalities in bipolar disorder. Interestingly, the cerebellum finding is seen in all three mood states, which emphasizes the potential importance of this under-appreciated structure in bipolar disorder. The putamen finding in the depressed state is also intriguing and suggests that this region may be involved in perpetuating depression. Although the source of these T1ρ abnormalities has yet to be determined, in our prior work we argued that abnormal metabolism is a likely contributor to the cerebellar finding [1]. Similarly, dynamic changes in metabolism may be responsible for the mood-state-dependent findings reported here. This study points to roles of the cerebellum and putamen in BD and motivates further investigation of these regions of interest to determine their significance in the pathophysiology of BD.

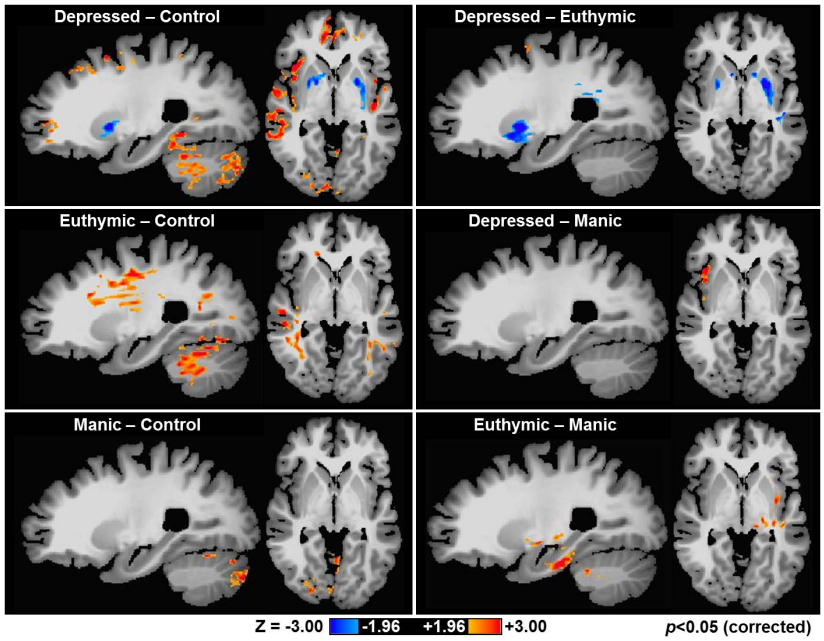

Fig. 1: T1ρ abnormalities were seen in all three mood states of BD. Identified ROIs include the cerebellum (all three groups) and putamen (depressed group).

References:

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