Quantitative T1rho Mapping of Bipolar Disorder: Basal Differences in Euthymia

Casey P. Johnson[1], Robin L. Follmer[2], Ipek Oguz[3], Lois A. Warren[2], Gary E. Christensen[3], Jess G. Fiedorowicz[2], Vincent A. Magnotta[1,2], and John A. Wemmie[2,4]
[1]*Radiology, University of Iowa, Iowa City, IA, United States,* [2]*Psychiatry, University of Iowa, Iowa City, IA, United States,* [3]*Electrical and Computer Engineering, University of Iowa, Iowa City, IA, United States,* [4]*Veteran Affairs Hospital Center, Iowa City, IA, United States*

PURPOSE: Patients with bipolar disorder suffer from volatile changes in mood between euthymic (i.e., neutral), depressive, and manic states. The mechanisms of this prevalent, costly, and potentially dangerous mental illness are poorly understood. A leading hypothesis is that bipolar disorder may be due in part to abnormal metabolism [1]. Evidence supporting this hypothesis includes observed acidosis in euthymic patients vs. manic patients and normal controls as measured by ^{31}P MR spectroscopy (MRS) [1]. To further investigate a potential role for altered pH and/or metabolism in euthymic bipolar disorder, we employed 3D quantitative T1ρ mapping [2,3]. The spin-lock-based T1ρ relaxation parameter has been shown to be sensitive to pH and metabolite concentrations and may thus be a marker for abnormal metabolism [4,5]. T1ρ mapping is able to image the whole brain with high spatial resolution, which cannot be obtained using MRS. In this study, we hypothesized that whole-brain basal differences in euthymic participants with bipolar disorder would be observed with T1ρ mapping, adding support to the abnormal metabolism hypothesis. Additionally, consistent with an observed acidosis in euthymia, we hypothesized that T1ρ values would be elevated in these participants.

METHODS: 13 participants with bipolar disorder (case group: 7 male, 6 female, mean age 40.7 yr, range 21-66 yr) and 18 healthy participants (control group: 9 male, 9 female, mean age 42.3 yr, range 22-62 yr) were recruited for this IRB-approved and HIPAA-compliant study. All participants provided written informed consent. Patients were evaluated by a psychiatrist to confirm diagnosis of bipolar I disorder and euthymia (Young Mania Rating Scale ≤12, Montgomery-Asberg Depression Rating Scale <10). Psychiatric and medication history were recorded for all participants. Imaging was performed on a Siemens 3T MRI system with a vendor-provided 12-channel head coil. High resolution (1.0 mm isotropic) T1- and T2-weighted images were acquired for group level anatomical registration. A whole-brain quantitative T1ρ map was then acquired with a segmented 3D GRE sequence with imaging parameters: FOV=22×22×20 cm^3; matrix=128×128×40; TR/TE/block time=5.6/2.5/1500 ms; lines/segment=24; R=2 GRAPPA; 7/8 partial Fourier; TSLs=[10,55] ms; and $B1_{SL}$ frequency=400 Hz. A Biopac physiological monitoring system was used to record respiratory rate (RR) and heart rate (HR) during imaging. T1ρ maps were calculated using a log-linear fit of the two TSLs assuming a mono-exponential model. For group-level analysis, T1ρ maps were aligned to the companion anatomical T1-weighted image using AFNI [6] and then transformed to a common atlas space using BRAINS AutoWorkup [7]. Voxel-wise differences between the mean T1ρ maps for the case and control groups were assessed using AFNI with a two-tailed *t*-test (p<0.05) and multiple comparisons cluster threshold of α=0.05. Tissue-specific differences were also assessed using BRAINS AutoWorkup-derived tissue classification labels for cerebral and cerebellar white and gray matter for each participant. The median T1ρ values within each label were averaged for each group, and these mean values were then compared using a two-tailed *t*-test (p<0.05). Group mean RR and HR were also compared using a two-tailed *t*-test (p<0.05).

RESULTS: T1ρ relaxation times were observed to be elevated in the case group compared to the control group (Fig. 1). Voxel-wise differences were observed throughout the brain with statistically significant clusters observed in the temporal lobes, cerebellum, and cingulate. Differences were nearly significant for both the cerebellar (p=0.042) and cerebral white matter (p=0.054) labels but not for the gray matter labels. RR and HR were elevated for the case vs. control group, but only the HR elevation was statistically significant (p=0.003).

DISCUSSION: Global elevation of T1ρ was observed in euthymic participants with bipolar disorder vs. normal controls, supporting our hypotheses. Additionally, significant focal changes were identified, which provide regions of interest to probe in future studies. These results support that metabolism is abnormal in bipolar disorder, and mitochondrial or other metabolic dysfunction is a plausible mechanism given the whole-brain effect observed. Elevated RR in the case group may reflect hyperventilation, which has been observed to decrease T1ρ values and is thus not likely the source of the observed differences [8]. The potential effect of elevated HR is less clear. Other potential confounds include differences in medication and T1- and T2-dependent effects such as water content. Further investigation of quantitative T1ρ mapping as tool is warranted to study bipolar disorder and a number of other psychiatric illnesses for which abnormal metabolism has been implicated. Metabolism-sensitive quantitative mapping techniques may lead to new biomarkers of psychiatric illness and insight into disease mechanisms.

REFERENCES: [1] Kato T, Kato N. Bipolar Disord 2000. [2] Borthakur A, et al. JMRI 2003. [3] Li X, et al. MRM 2008. [4] Kettunen MI, et al. MRM 2002. [5] Jin T, et al. MRM 2011. [6] Cox RW. Comput Biomed Res 1996. [7] Pierson R, et al. NeuroImage 2011. [8] Magnotta VA, et al. PNAS 2012.

ACKNOWLEDGMENTS: This work was partially supported by a gift from Roger Koch.

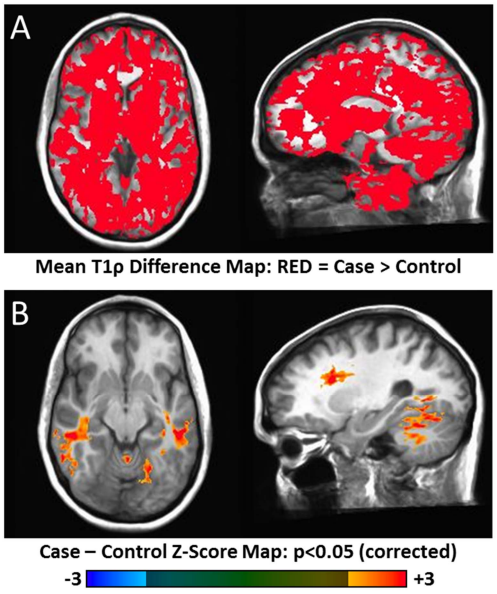

Fig. 1: (**A**) Mean T1ρ was elevated in the cases with bipolar disorder during euthymia vs. a control group in a majority of voxels (red), indicating a whole-brain effect. (**B**) Statistically significant clustered mean T1ρ differences were seen in the temporal lobes, cerebellum, and cingulate.