BRAIN ON FIRE: TEMPORAL STANDARD DEVIATION OF RESTING STATE BOLD SIGNAL INCREASES IN MAJOR DEPRESSIVE DISORDERS

Masaya Misaki[1], Vadim Zotev[1], Raquel Phillips[1], Kymberly D Young[1], Han Yuan[1], Jonathan Savitz[1,2], Wayne C Drevets[1], and Jerzy Bodurka[1,3]
[1]*Laureate Institute for Brain Research, Tulsa, OK, United States,* [2]*Tulsa School of Community Medicine, University of Tulsa, Tulsa, OK, United States,* [3]*College of Engineering, University of Oklahoma, Tulsa, OK, United States*

Target audience: Researchers utilizing resting state BOLD fMRI to study brain functional abnormalities in major psychiatric disorders.

Purpose: Neuroimaging techniques such as PET, SPECT, and BOLD fMRI have been employed to investigate non-task-driven or resting-state brain activity in order to elucidate the pathophysiology of major depressive disorder (MDD). In the resting-state, PET and SPECT data revealed abnormal metabolism and perfusion in several brain regions in MDD, while most fMRI studies assessed the functional connectivity between regions[1-3] because the BOLD fMRI signal does not provide an absolute measure of brain activity. In this study, we proposed a simple alternative measure derived from resting-state fMRI data that reflects an individual brain region's activity. We used the temporal standard deviation (tSD) of resting-state BOLD time course signals. The tSD reflects both frequency and amplitude of brain region activity changes. Regional increase in tSD indicates higher variability in brain activity during resting state. Due to abnormal metabolic activity in MDD versus healthy control (HC) subjects we expect to identify regional differences in tSDs between these groups.

Methods: Nineteen MDD (age 22–49 years, 15 female) and 19 HC subjects (age 19–60 years, 10 female) participated in the IRB-approved study. Whole brain (axial) resting state fMRI scans with a single-shot gradient-recalled SENSE EPI sequence (TR/TE=2000/30ms, FA=90°, FOV/slice=240/2.9mm, matrix=96×96 image reconstructed to 128x128, SENSE acceleration=2, 225 volumes) were performed using a General Electric Discovery MR750 whole-body 3 Tesla MRI scanner with standard 8ch head array. FMRI data were processed using AFNI[4]. The first 3 volumes were excluded from analysis to allow BOLD signal to reach steady state. The signal time course was normalized to percent change relative to mean signal amplitude. Respiration and cardiac signal modulation were removed, and motion correction and band pass filter (0.01–0.1Hz) were applied. To further reduce physiological noise, and to minimized the nuisance effects irrelevant to neuronal activity, the BOLD signal originating in voxels that predominantly contained white matter or CSF (i.e., in ventricles) were excluded from the signal time course analysis using ANATICOR[5]. For group analysis the images were spatially normalized to the stereotaxic array of Talairach and Tournoux using the Advanced Normalization Tools[9]. The standard deviation of signal time course was calculated on a pixel-wise basis. A two-sample *t* test was employed to compare the tSD between MDD and HC. Age, sex, and amount of motion were entered as covariates in the test to exclude the effect of these variables on the group difference in tSD. Age ($p = 0.84$), sex ($p = 0.17$), and motion size ($p = 0.12$) were not significantly different between MDD and HC.

Results: Fig. 1 shows the group *t* map of tSD difference between MDD & HC overlaid over a T1-weighted template brain. The map was thresholded with voxel-wise $p < 0.001$ (cluster size >50 voxels). Yellow-red regions indicate higher tSD for MDD than HC. The data reveals higher resting-state BOLD tSD in MDD versus HC in multiple brain regions including cerebellum, subgenual and pregenual anterior cingulate cortex (sgACC and pgACC, respectively), thalamus, and anterior/middle insula. Interestingly we did not find any brain regions with significantly lower tSD in MDD versus HC.

Discussion: We found higher temporal standard deviation in MDD as compared to HC. This suggests that resting-state brain activation fluctuated more and with higher amplitude, indicating higher variability in the metabolic activity in MDD than HC. A meta-analysis of MDD resting state PET studies[6] indicated increased metabolic activity in cerebellum, thalamus, and middle frontal regions—which is consistent with the current results—and decreased signal in sgACC, pgACC, middle frontal, superior temporal, and insula. As Drevets et al.[7] suggested, the regions showing decreased PET measures of perfusion and metabolism actually had increased activity when the data were corrected for the partial volume effects of the grey matter volume reduction found in these regions in MDD. Our results suggest that in MDD subjects all these brain regions had more frequent and larger BOLD fMRI activity change in resting-state, suggesting higher abnormal variability in the metabolic activity.

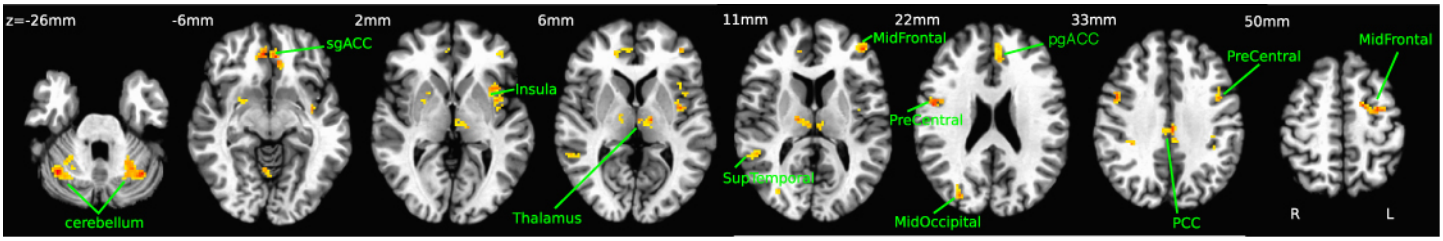

Fig. 1: Group results. The *t* map of tSD difference between MDD and HC.

References: 1) Anand A, et al. Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. *Biol Psychiatry.* 2005;57(10):1079-1088; 2) Greicius MD, et al. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. *Biol Psychiatry.* 2007;62(5):429-437; 3) Zhang J, et al. Disrupted brain connectivity networks in drug-naive, first-episode major depressive disorder. *Biol Psychiatry.* 2011;70(4):334-342; 4) Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res.* 1996;29(3):162-173; 5) Jo HJ, et al., Mapping sources of correlation in resting state FMRI, with artifact detection and removal. *NeuroImage.* 2010;52(2):571-582; 6) Fitzgerald PB, et al.,. A meta-analytic study of changes in brain activation in depression. *Hum Brain Mapp.* 2008;29(6):683-695; 7) Drevets WC. Prefrontal cortical-amygdalar metabolism in major depression. *Ann N Y Acad Sci.* 1999;877:614-637.