ABNORMAL RESTING-STATE DEFAULT MODE NETWORK CONNECTIVITY IN MAJOR DEPRESSIVE DISORDER: MULTIMODAL EEG AND BOLD FMRI STUDY

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

Purpose: Major depressive disorder (MDD) is a psychiatric disease characterized by persistent, pervasive feelings of sadness, guilt, and worthlessness. The tonic nature of depression has prompted functional neuroimaging techniques such as PET, SPECT, and BOLD fMRI to study resting-state brain activity to elucidate the pathophysiology of MDD. In depression, abnormal activity in several brain regions constituting the so-called default mode network (DMN) has been reported[1]. Recent advances in multimodal imaging technique employing simultaneous electroencephalography (EEG) and BOLD fMRI acquisition have allowed neuroimaging capabilities with joint high spatial and temporal resolution. In this study, we acquired simultaneous EEG and BOLD fMRI in groups of unmedicated MDD and healthy control subjects at normal resting state and developed a multimodal analysis approach using EEG microstates[2] to study the abnormal DMN activity in MDD.

Methods: Simultaneous resting-state EEG & fMRI data were acquired from 13 MDD (age 36 ± 12 years, 9 females) and 9 healthy control (HC) subjects (age 33 ± 10 years; one female) at relaxed, eyes-open resting state. Whole-brain resting state fMRI scans with a single-shot gradient-recalled SENSE EPI sequence (TR/TE=2000/30ms, FA=30°, FOV/slice thickness/gap=220/2.9/0.2mm, axial plane, acceleration=2, matrix=96×96 for MDD and 128×128 for HC) were acquired using a General Electric Discovery MR750 whole-body 3 Tesla MRI scanner with a standard 8-channel head array. Structural MRI T1-weighted images were obtained with an MPRAGE sequence. EEG signals were recorded using MRI-compatible BrainAmp MR Plus amplifiers (band width=0.016−250 Hz, resolution=0.1 μV, sampling rate=5000 Hz, 32 channels for MDD and 128 channels for HC). A pneumatic respiration belt and a photoplethysmograph were used to obtain respiration and pulse oximetry measurements, respectively. The severity of depression in MDD was rated using the Hamilton Depression (HAM-D) Rating Scale, the Hamilton Anxiety (HAM-A) Rating Scale. Additionally the Toronto Alexithymia Scale (TAS, identifying and describing emotions) and the Emotional Contagion questionnaire (EC, susceptibility to other's emotions) were used. *fMRI data analysis:* Imaging data were preprocessed using AFNI, including removal of first five volumes, motion correction, removal of cardiac[4] and respiratory noise[5], spatial normalization to Talairach space, and spatial smoothing with FWHM=4 mm. Separate group analysis was performed for the MDD and HC subjects. The preprocessed fMRI data within a group were concatenated across time and analyzed by spatial ICA. For each independent component (IC), the time courses correspond to the waveform of a specific pattern of coherent brain activity, and the intensity of this pattern is expressed in the associated spatial map. Single-subject spatial maps and time courses corresponding to each IC were obtained by a back projection. After ICA separation, the default mode network in each subject was selected by choosing the best-fit component with a template of the DMN[3]. A random effect analysis using the one-sample *t* test was performed on the selected best-fit DMN components separately in the MDD and HC group. The difference between two groups was assessed using the two-sample unpaired *t* test. The brain regions with significant difference (q<0.05, FDR corrected) were identified as regions of interest (ROIs) for combined EEG and fMRI analysis. *EEG data analysis*: after correcting the MRI and cardioballistic artifacts, temporal independent EEG microstates (EEG-ms) were derived using the method described in [2]. The DMN-related EEG-ms were selected by choosing those with significant correlation (p<0.001, uncorrected) with the time course of DMN derived from BOLD fMRI. The time courses of EEG-ms were then used as regressor in a general linear model (GLM) to identify areas where BOLD activity co-varied with the EEG-ms time courses, namely the EEG-ms associated BOLD activity. The EEG-ms-associated BOLD activity at the ROIs was extracted for each subject and compared to the ratings of identifying and describing emotions (TAS), susceptibility to other's emotions (EC), and depressive severity (HAM-A and HAM-D).

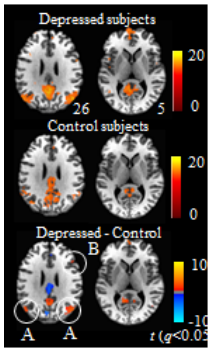

Fig. 1 DMN activity of the MDD and HC and the group difference. A and B label regions of interest.

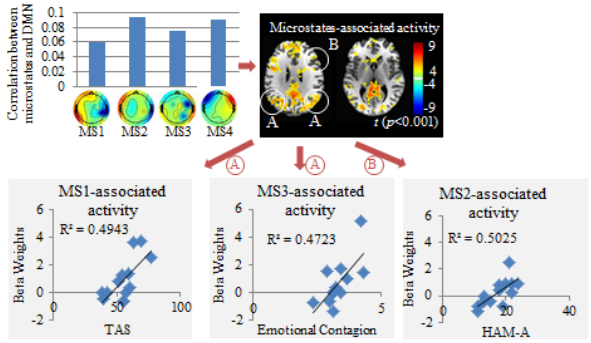

Fig. 2 Four temporal independent EEG microstates were found to be correlated with BOLD fMRI DMN. The microstate-associated activities were identified using GLM analysis and correlated to the TAS score, the EC score, and the HAM-A score.

Results: Fig.1 shows the respective spatial pattern of the DMN in the MDD and HC subjects (one-sample *t* test: q<0.05, FDR corrected). In both groups significant functional connectivity was found in the bilateral angular/middle temporal gyri, posterior cingulate cortex (PCC), medial prefrontal cortex (MPFC), and bilateral superior frontal cortex which correspond to the typical pattern of DMN. The two-sample *t* test (q<0.05, FDR corrected) identified significant differences between DMN of the two groups (Fig. 1, lowest row). Compared with HC subjects, the MDD subjects showed increased resting functional connectivity in the left superior frontal cortex, bilateral angular/middle temporal gyri, and MPFC, but decreased functional connectivity in the PCC. In the depressive subjects, four different EEG-ms (MS1, MS2, MS3 and MS4) are found to be correlated (p<0.001, uncorrected) with the time courses of DMN measured by BOLD fMRI (Fig. 2, upper row). GLM analysis identified regions (labeled A,B on Fig. 1,2) where BOLD signals are correlated with the microstate time courses (Fig.2 bottom row). In the left superior frontal cortex, MS2-associated activity was found to be correlated with the HAM-A score. In the bilateral angular/middle temporal gyri, MS1-associated activity was found to be correlated with the TAS and MS3-associated activity was found to be correlated with the EC score. In these regions of interest no significant correlation with any of the ratings was found in the functional connectivity of DMN derived from BOLD fMRI alone.

Discussion & Conclusion: We developed a multimodal approach to study the abnormal activity in MDD. Using spatial ICA methodology, our study demonstrated altered resting state DMN in unmedicated MDD. Compared with healthy controls, the depressed subjects showed increased resting functional connectivity in the left superior frontal cortex, bilateral angular/middle temporal gyri, and MPFC and decreased functional connectivity in the PCC, implicating these regions as dysfunctional nodes in a distributed limbic and paralimibic neural network[1]. Furthermore, in joint analysis with EEG, the EEG microstates-associated BOLD activity was found to be positively correlated with the rating scores of depressive severity, which are not correlated with the DMN connectivity derived from BOLD fMRI alone. Our results indicate abnormal activity of the brain resting-state DMN in MDD subjects and show that multimodal imaging approach can unravel additional functional information. Our results show that multimodal EEG & fMRI is a very promising method in the search of neuroimaging biomarkers for psychiatric disorders.

References: 1) Greicius MD, et al. Biol Psychiatry. 2007;62(5):429-437; 2) Yuan H, et al. Neuroimage 2012;60(4):2062-2072; 3) Laird AR, et al. J Neurosci. 2009;29(46):14496-14505. 4) Glover GH, et al. Magn Reson Med. 2000;44(1):162-167. 5) Birn RM, et al. Neuroimage 2006;31(4):1536-1548.