REAL-TIME FMRI NEUROFEEDBACK TRAINING OF AMYGDALA ALTERS RESTING-STATE DEFAULT MODE NETWORK CONNECTIVITY IN MAJOR DEPRESSIVE DISORDER

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Target audience: Researchers utilizing fMRI, real-time fMRI neurofeedback (rtfMRI-nf) to study brain functional organization in particular emotion regulation, and brain functional abnormalities in major psychiatric disorders, and those seeking development of novel therapeutic approaches for neuropsychiatric disorders.

Purpose: Pharmacological and psychological treatments of patients with major depressive disorder (MDD) show some promise[1], however many patients do not respond well to such approaches. The rtfMRI-nf training targeting elements of emotion regulation circuit of the brain, such as the amygdala, has been suggested as potential new therapeutic approach[2]. A recent pilot rtfMRI-nf study has shown that MDD subjects were able to increase the amygdala activity during recalling happy autobiographical memories[3]. However, it remains unknown if there is any plasticity effect present in the brain due to rtfMRI-nf. In the present study we employed BOLD fMRI resting state scans and default-mode network (DMN) functional connectivity analysis to investigate the plasticity effect of rtfMRI-nf training of amygdala in MDD.

Methods: 19 MDD subjects (15 female subjects) were recruited and randomly assigned into active (12 subjects) and sham (7 subjects) groups. The experiment was performed on a General Electric Discovery MR750 whole-body 3 Tesla MRI scanner with a standard 8-channel head array. Whole brain fMRI scans were acquired with a single-shot gradient-recalled SENSE EPI sequence (TR/TE=2000/30ms, FA=90°, FOV/slice =220/2.9mm, 34 axial slices, acceleration=2, matrix=96×96, 263 volumes). T1-weighted MPRAGE sequence was used for anatomical reference and to define ROIs. A pneumatic respiration belt and a photoplethysmograph were used to obtain respiration and pulse oximetry measurements, respectively. The rtfMRI-nf was implemented using a custom real-time fMRI system utilizing AFNI real-time features and a custom GUI software. In the respective active and sham group, the neurofeedback was based on fMRI activation in the left amygdala (LA) and the horizontal segment of intraparietal sulcus (HIPS) region[2]. Subjects were instructed to feel happy by evoking positive autobiographical memories, while trying to raise the level of a red bar on the screen that is proportional to the activation of the targeted ROI. Three neurofeedback sessions were performed on the subjects following the published protocol[2]. Two resting state fMRI scans were recorded in the subjects while they rested with their eyes open and looked at a fixation cross on the screen. The 1st resting scan (D1) was conducted right before the first neurofeedback session and the 2nd resting state scan (D2) was acquired on a different day before any task/neurofeedback sessions. No scanning was performed between the two recoding days. On each visit day, and before scanning, the severity of depression in MDD subjects was rated using the Hamilton Depression (HAM-D) Rating Scale and the Hamilton Anxiety (HAM-A) Rating Scale. Additionally subjects' state of mood was self-evaluated using the Trait Anxiety questionnaire and the Profile of Mood States (POMS) questionnaire. Subjects also scored their level of happiness (i.e. happiness score) and how successful they recalled happy memory (i.e. memory score) during neurofeedback sessions. In this work, only resting-state fMRI data were analyzed. The data were preprocessed using AFNI, including removal of first five volumes, motion correction, removal of cardiac[5] and respiratory noise[6], spatial normalization to Talairach space and spatial smoothing with FWHM=4 mm. Separate group analysis was performed for the active and sham groups and for different days. 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 was obtained by a back projection. After ICA separation, the default model network in each subject was selected by choosing the best-fit component with a template of the DMN[4]. A random effect analysis using the one-sample *t* test was performed on the selected best-fit DMN components separately per group and per day. The difference between two visit days in each group was assessed using the two-sample paired *t* test. The brain regions with significant difference (q<0.05, FDR corrected) were identified as regions of interest (ROIs), where the individual functional connectivity was extracted and compared to the happiness scores and memory scores during rtfMRI-nf sessions.

	Active	Sham
Gender (female/male)	8/4	7/0
Age (Mean ± SD Years)	38.8 ± 9.8	35.4 ± 9.3
HAM-D (Mean ± SD)	22.0 ± 5.0	24.7 ± 5.3
HAM-A (Mean ± SD)	20.2 ± 5.6	22.7 ± 8.0
Trait Anxiety Change (Mean ± SD)	-2.4 ± 3.6 *	-0.9 ± 1.8
Depression Change (Mean ± SD)	-4.3 ± 8.8 *	-2.6 ± 5.7

Table 1 Demographic and clinical characteristics of the active and sham groups. *indicate significant (p<0.05) difference between two visit days.

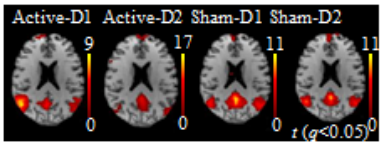

Fig. 1 Group DMN functional connectivity in the active and sham groups on the first (D1) and second (D2) resting state scans.

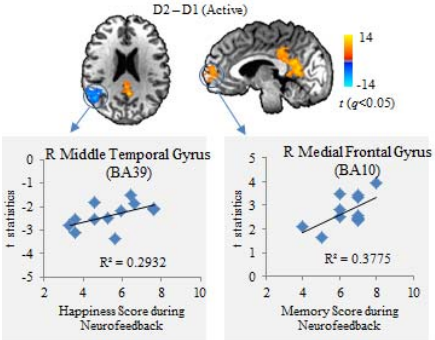

Fig. 1 Difference of DMN functional connectivity between two resting state scans before and after rtfMRI-nf. The connectivity differences are correlated with the happiness and memory scores during rtfMRI-nf sessions.

Results: The demographic and clinical characteristics are listed in Table 1 for the groups receiving active and sham neurofeedback. The two resting state scans were separated by 2-14 days (7 ± 3 days). There is no significant difference (p>0.05) between active and sham groups in the age, Ham-D and Ham-A scores. In the active group, subjects reported significant decrease (p<0.05) in the Trait Anxiety score and the depression score of the POMS questionnaire for the 2nd resting state scan. Fig.1 shows the respective spatial pattern of the DMN in the active and sham group on the first and second resting state scans (one sample t-tests: q<0.05, FDR corrected). In both group and on both days significant functional connectivity was found in the bilateral middle temporal gyri (MTG), posterior cingulate cortex (PCC), medial prefrontal cortex (MPFC) and bilateral superior frontal cortex which correspond to the typical pattern of DMN. Note the similar pattern yet different strength of functional connectivity between two visits in the active group. The two-sample *t* test (q<0.05, FDR corrected) identified significant differences between DMN from the two resting state scans before and after rtfMRI-nf (Fig. 2, upper row), only in the active group but not in the sham group. Compared with the 1st resting state session, the 2nd session showed increased resting functional connectivity in the in the PCC and MPFC, but decreased connectivity in the right MTG. The differences of resting functional connectivity in the right middle temporal gyrus (BA39) were found positively correlated with the happiness score during neurofeedback, while the differences in the right MPFC (BA10) were positively correlated with the memory score, i.e. how successful subjects reported to recall happy memory during the neurofeedback.

Discussion & Conclusion: We demonstrate in the MDD subjects, rtfMRI-nf training of amygdala during happy autobiographical memory recall induced changes of resting state DMN functional connectivity. Subjects reported decreased depressive feelings after rtfMRI-nf amygdala training. In the resting state scan after rtfMRI-nf session, increased functional connectivity was found in MPFC and PCC, and decreased connectivity in MTG, which are the key brain regions found to show abnormal activity in the MDD. The within-group, correlation analysis found positive correlation between the resting state connectivity difference and the happiness/memory score during neurofeedback. Our results suggest sustainable plasticity effect in the brain of MDD due to the amygdala-targeted rtfMRI neurofeedback.

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