Real-time fMRI Neurofeedback Training of Amygdala Modulates Frontal EEG Asymmetry in MDD Patients

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Target audience: Researchers employing advanced multimodal fMRI and EEG techniques to study human emotions, as well as everybody interested in emotion regulation mechanisms and in the development of novel therapeutic approaches for neuropsychiatric disorders, particularly depression.

Purpose: Real-time fMRI neurofeedback (rtfMRI-nf) is a promising approach for training of emotional self-regulation both in healthy subjects [1,2] and in patients with major depressive disorder (MDD) [3]. EEG performed simultaneously with rtfMRI-nf can provide new insights into the underlying mechanisms of neurofeedback training. Frontal EEG asymmetry has been extensively explored as an electrophysiological characteristic of affective style and emotional processing [4]. MDD patients have been shown to exhibit elevated activity (reduced alpha EEG power) over the right frontal brain regions compared to the left [5]. Here we report results of the first study utilizing rtfMRI-nf with simultaneous EEG. We demonstrate for the first time that rtfMRI-nf training of left amygdala (LA) fMRI activation in MDD patients performing a positive mood induction task is accompanied by task-dependent variations in frontal EEG asymmetry.

Methods: Eleven unmedicated MDD patients (7 females) participated in the study. The experiments were performed on a GE Discovery MR750 3T MRI scanner with an 8-channel receive-only head coil array. A single-shot gradient echo EPI sequence with FOV/slice=240/2.9mm, *TR*/*TE*=2000/30ms, SENSE *R*=2, image matrix 96x96, flip=90°, 34 axial slices, was employed for fMRI. Concurrent EEG recordings were performed using a 32-channel MR-compatible EEG system (Brain Products GmbH) in 0.016–250 Hz band with 0.1 μV resolution and 5 kS/s sampling rate. The rtfMRI-nf was implemented using a custom developed real-time system with a custom neurofeedback GUI software (Fig. 1a). It was based on fMRI activation in a left amygdala ROI (LA, Fig. 1e) as in [2]. The experimental protocol (see [2] for details) included seven runs, and each run (except Rest) consisted of 40 s long blocks of **R**est, **H**appy Memories, and **C**ount conditions (Fig. 1b). For each Happy Memories condition, the subject was instructed to feel happy by evoking positive autobiographical memories, while trying to raise the level of the red bar on the screen. EEG data analysis was performed in BrainVision Analyzer 2. MRI and cardioballistic artifacts were removed using the average artifact subtraction method. Intervals with motion artifacts were excluded. Residual artifacts were removed using ICA. Time-frequency analysis was conducted using continuous wavelet transform with Morlet wavelets. The EEG alpha band was defined individually for each subject as [IAF–2…IAF+2] Hz, where IAF is the individual alpha peak frequency. Signals from EEG electrodes F3 (left) and F4 (right) with FCz reference were used to determine the frontal EEG power asymmetry (Fig. 1d). The asymmetry was defined at each time point as $A=[P(\mathrm{F4})-P(\mathrm{F3})]/[P(\mathrm{F4})+P(\mathrm{F3})]$, where P is the EEG power in the alpha band. Normalized asymmetry was computed as $An=\mathrm{atanh}(A)=[\ln(P(\mathrm{F4}))-\ln(P(\mathrm{F3}))]/2$, converted to z-scores and convolved with HRF to yield an EEG-asymmetry-based regressor. fMRI data processing was performed in AFNI [6]. Psychophysiological interaction (PPI) analysis [7] was conducted within the GLM framework to evaluate task-dependent correlations between the EEG-asymmetry-based regressor and fMRI data.

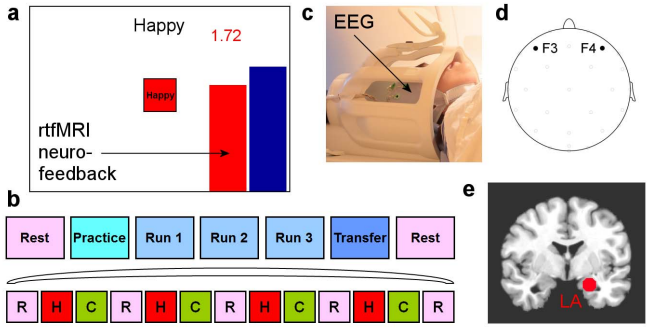

Fig. 1. a) GUI screen with neurofeedback bar (red) and target bar (blue); b) experimental protocol with **R**est, **H**appy, and **C**ount condition blocks; c) EEG-fMRI setup; d) EEG F3 and F4 electrode positions; e) left amygdala ROI for rtfMRI neurofeedback.

Results: Fig. 2a shows average values of the frontal alpha EEG asymmetry for 11 MDD patients. The asymmetry increases toward zero during the Happy condition blocks and decreases during the Count blocks. Average resting asymmetry varies similarly from run to run. Fig. 2b shows a group statistical map of the PPI interaction term describing the difference in correlations with the EEG-asymmetry-based regressor between the Happy and Count conditions (p<0.05, uncorrected, min. cluster size 200 voxels). One neurofeedback run (among Runs 1-3) with the highest amygdala activation was included in the analysis for each subject. The crosshaires mark the center of the LA ROI at (–21,–5,–16). A significant effect is observed in the left parahippocampal gyrus (PHG) area, including LA. Fig. 2c exhibits a map of Happy vs Count activation contrast (p<0.02, uncorrected, min. cluster size 200 voxels) showing a significant effect in the same left PHG region.

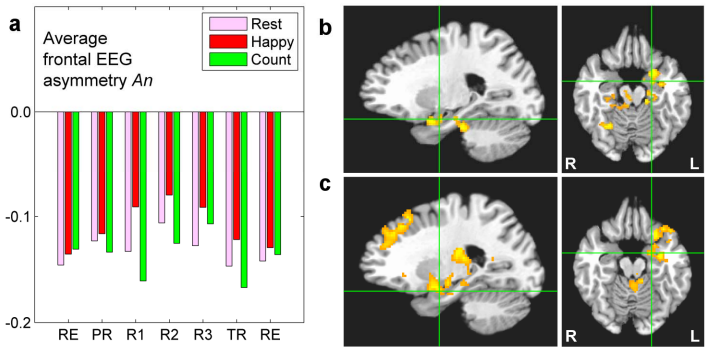

Fig. 2. a) Average frontal alpha EEG power asymmetry during neurofeedback training; b) PPI interaction [EEG-asymmetry-based regressor] x [Happy – Count] maps; c) Happy vs Count fMRI activation contrast maps (see text for details).

Conclusion: Our results demonstrate, for the first time, that rtfMRI-nf training of amygdala self-regulation using positive mood induction is accompanied by changes in frontal EEG alpha power asymmetry in MDD patients. The changes are consistent with those expected for reduced MDD symptoms [5]. Moreover, variation in the frontal EEG asymmetry correlates with fMRI activation in the left PHG region including LA. Our data indicate that frontal asymmetry-based EEG neurofeedback [8] may naturally complement rtfMRI-nf in training of emotional self-regulation. Our results further suggest that multimodal simultaneous rtfMRI-EEG neurofeedback [9,10] may become a viable cognitive therapeutic approach for neuropsychiatric disorders, particularly depression.

References: [1] S.J. Johnston et al. *NeuroImage* 2010, 49:1066. [2] V. Zotev et al. *PLoS ONE* 2011, 6:e24522. [3] D.E.J. Linden et al. *PLoS ONE* 2012, 6:e38115. [4] R.J. Davidson. *Brain Cogn.* 1992, 20:125. [5] R. Thibodeau et al. *J. Abn. Psychol*. 2006, 115:715. [6] R.W. Cox. *Comput. Biomed. Res.* 1996, 29:162. [7] K.J. Friston et al. *NeuroImage* 1997, 6:218. [8] J.J.B. Allen et al. *Psychophysiol.* 2001, 38:685. [9] V. Zotev et al. *Proc. 20th ISMRM* 2012, 3704. [10] J. Bodurka et al. *Proc. 20th ISMRM* 2012, 3627.