Changes in Upper Alpha EEG Power Predict Performance in Real-time fMRI Neurofeedback Training of Amygdala

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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: Training of emotional self-regulation using real-time fMRI neurofeedback (rtfMRI-nf) is a promising area of neuroscience research with potential applications in treatment of neuropsychiatric disorders [1-3]. Neurofeedback training requires attention and cognitive engagement on the part of a participant. EEG performed concurrently with rtfMRI-nf is a sensitive tool for studying attentional and cognitive processes during such training. It has been shown that EEG power variations in the lower alpha band (~6-10 Hz) reflect attentional demands, while variations in the upper alpha band (UA, ~10-12 Hz) reflect cognitive and memory performance [4-6]. Here we report results of the first study utilizing rtfMRI-nf with simultaneous EEG. We demonstrate for the first time that changes in relative UA EEG power, presumably reflecting cognitive effort, inversely correlate with left amygdala (LA) fMRI activation during rtfMRI-nf training of LA in MDD patients performing a positive mood induction task.

Methods: Eleven unmedicated patients (7 females) with major depressive disorder (MDD) 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 acceleration=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 together with dedicated neurofeedback GUI software (Fig. 1a). It was based on fMRI activation in a left amygdala ROI (LA, Fig. 1d) 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. Following [4], the upper alpha (UA) band was defined individually for each subject as]IAF…IAF+2] Hz, and the extended alpha (EA) band was defined as [IAF–4…IAF+2] Hz. Here, IAF is the individual alpha peak frequency determined from each subject's posterior EEG spectra averaged across Rest blocks in four neurofeedback runs (Practice and Runs 1-3). Relative UA power was defined for each channel at each time point as $R=P(\mathrm{UA})/P(\mathrm{EA})$. Normalized relative UA power was computed as $Rn=\ln(R/(1-R))$. *Z*-scores of *Rn* were determined within each Happy and Count block using mean and std values of *Rn* for the preceding Rest block. Because the neurofeedback bar height was updated during the first half of each *TR* interval, only *z*-scores corresponding to the second half of each *TR* during Happy condition were included in the analysis. fMRI data processing was performed in AFNI [7] using GLM analysis as in [2].

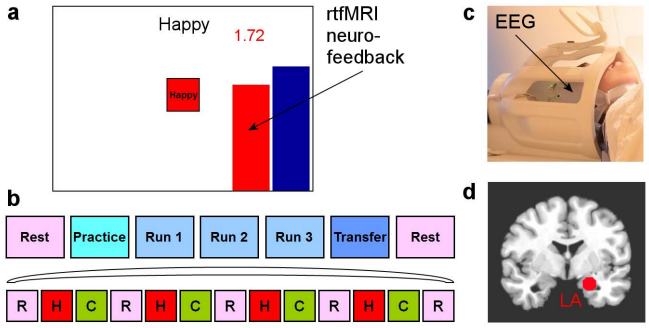

Fig. 1. a) GUI screen with neurofeedback bar (red) and target bar (blue); b) experimental protocol with **R**est, **H**appy, and **C**ount condition blocks; c) EEG-fMRI setup; d) left amygdala ROI for rtfMRI neurofeedback.

Results: Fig. 2a shows a significant increase in relative UA power for both Happy and Count conditions, particularly in parietal regions (average reference). Fig. 2b exhibits significant anti-correlations, for Happy condition, between average LA activation levels and relative UA power *z*-scores for the average EEG signal (Avg) and signals from channels O1, P3, and P4 (with the average reference). Four data points per subject are included in each subplot of Fig. 2b, corresponding to four neurofeedback runs (Practice and Runs 1-3). The slopes are negative for all the EEG channels, and many channels exhibit significant anti-correlation effect ($p<0.05$). The results for nine MDD patients are included in Fig. 2a,b (two patients, who were unable to achieve positive average LA activation across Runs 1-3, were classified as non-responders and excluded from further analysis).

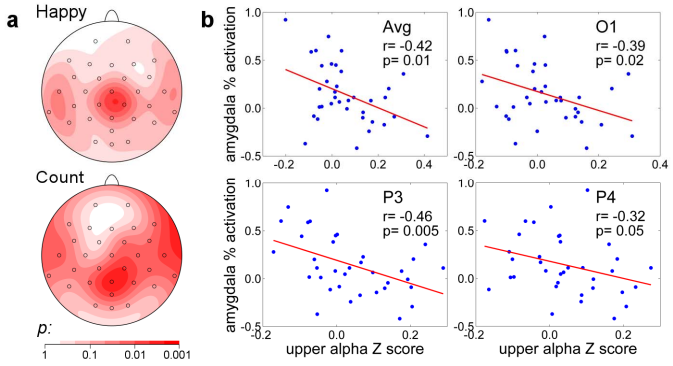

Fig. 2. a) Increase in relative upper alpha (UA) power (group *p*-values) during neurofeedback training (Run 2); b) anti-correlation between amygdala fMRI activation and relative upper alpha power *z*-scores during Happy condition.

Conclusion: Our results demonstrate, for the first time, that an increase in relative upper alpha power, presumably reflecting increasing cognitive effort, is associated with a reduction in average LA activation during rtfMRI-nf training with positive mood induction. This is consistent with the fact that the increase in relative UA power is even stronger during the Count condition, which is known to reliably reduce the LA fMRI activation [2]. Our results indicate that proper balance between emotional and cognitive aspects of rtfMRI-nf training is essential for successful learning of emotional self-regulation. Our results further suggest that the UA-based EEG neurofeedback [8] may be helpful in training of down-regulation of emotional networks (after sad or aversive stimuli) through the use of cognitive strategies such as reappraisal [3].

References: [1] S.J. Johnston et al. *NeuroImage* 2010, 49:1066. [2] V. Zotev et al. *PLoS ONE* 2011, 6:e24522. [3] M. Hampson et al. *J. Vis. Exp*. 2012, 59:e3535. [4] W. Klimesch. *Brain Res. Rev*. 1999, 29:169. [5] W. Klimesch et al. *Brain Res. Rev*. 2007, 53:63. [6] A. Fink et al. *Cogn. Brain Res.* 2005, 24:252. [7] R.W. Cox. *Comput. Biomed. Res.* 1996, 29:162. [8] B. Zoefel et al. *NeuroImage* 2011, 54:1427.