Real-time fMRI Neurofeedback with Simultaneous EEG in Combat-related PTSD: Identification of EEG Measures of PTSD Severity and Treatment Response

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Target audience: Researchers employing advanced multimodal fMRI and EEG techniques to study mood disorders, as well as persons interested in emotion regulation mechanisms and development of novel therapeutic approaches for post-traumatic stress disorder (PTSD).

Purpose: Real-time fMRI neurofeedback (rtfMRI-nf) is an emerging technique for researching novel treatments of neuropsychiatric disorders [1-3]. EEG performed simultaneously with rtfMRI-nf makes it possible to examine electrophysiological correlates of the rtfMRI-nf training [3] and even provide simultaneous multimodal rtfMRI-EEG-nf [4]. Frontal EEG asymmetry (FEA) [5] has been widely used as a measure of emotion/motivation, sensitive to symptoms of depression and anxiety [6]. Resting FEA has been shown to exhibit an inverse correlation with PTSD severity [7]. Here we report results of the first study using rtfMRI-nf with simultaneous EEG in PTSD patients. We show that FEA changes during rtfMRI-nf training targeting the left amygdala (LA) [8] correlate with PTSD severity ratings as measured by the Clinician-Administered PTSD Scale for DSM-IV (CAPS) and may provide information about patients' response to treatment.

Methods: Twelve male patients with a primary diagnosis of PTSD related to combat trauma have completed the study (the research is in progress and more patients are enrolled). Six patients (age 31±8) were randomly assigned to the experimental group, and six (age 33±10) to the control group. The study included 8 sessions (visits): an initial psychological assessment, an initial CAPS evaluation, an fMRI session with an emotional Stroop task, three rtfMRI-nf training sessions with simultaneous EEG, a final fMRI session with an emotional Stroop task, and a final CAPS evaluation. The experiments were performed on a GE Discovery MR750 3T MRI scanner with an 8-channel receive-only head coil. A single-shot gradient echo EPI sequence with FOV/slice=240/2.9 mm, *TR/TE*=2000/30 ms, SENSE *R*=2, image matrix 96×96, 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. The rtfMRI-nf was implemented using a custom real-time system with a neurofeedback GUI (Fig. 1A). It was based on fMRI activation in the LA target ROI (Fig. 1D) for the experimental group, and the LHIPS target ROI for the control group. The rtfMRI-nf experimental protocol (Fig. 1B, see [2,3] for details) included seven runs, and each run (except Rest) consisted of 40-s blocks of **R**est, **H**appy Memories, and **C**ount conditions. For each Happy Memories condition, the participant was instructed to feel happy by evoking happy autobiographical memories, while trying to raise the level of the red bar on the screen. EEG data analysis was performed using BrainVision Analyzer 2. MR and cardioballistic artifacts were removed using the average artifact subtraction method. Residual artifacts were removed using ICA. Time-frequency analysis was conducted with 8 ms temporal and 0.25 Hz frequency resolution using a continuous wavelet transform. The upper alpha EEG band was defined individually for each subject as [IAF…IAF+2] Hz, where IAF is the individual alpha peak frequency. Signals from frontal EEG channels F3 and F4 with Cz reference (Fig. 1E) were used to define FEA=ln(*P*(F4))–ln(*P*(F3)), where *P* is the EEG power in the upper alpha band. Average FEA changes between Happy Memories and Rest conditions were examined. EEG-informed fMRI analysis was performed as in [3,4].

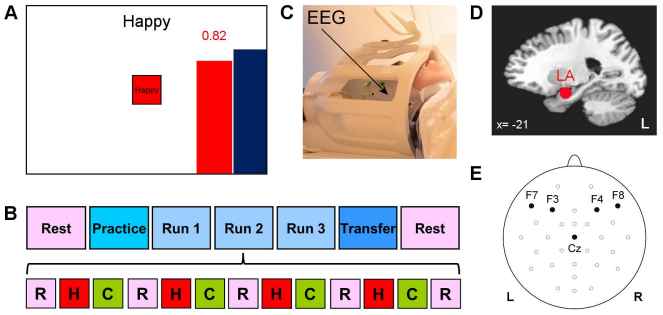

Fig. 1. Overview of an rtfMRI-nf training session. A) GUI screen with rtfMRI-nf bar (red) and target bar (blue). B) Experimental protocol with **R**est, **H**appy, and **C**ount condition blocks. C) EEG-fMRI setup. D) Left amygdala (LA) target ROI for rtfMRI-nf. E) Frontal EEG channels for FEA analysis.

Results: Figs. 2A,B compare average individual Happy vs Rest FEA changes across four rtfMRI-nf runs (Practice, Runs 1-3) for 6 PTSD patients in the experimental group and their CAPS ratings. Both figures reveal positive correlations between the average FEA changes during the rtfMRI-nf sessions (1st and 3rd) and the corresponding CAPS scores. Fig. 2C further demonstrates that the individual reductions in CAPS ratings significantly correlate with the reductions in FEA changes between the two sessions. The proposed interpretation of these results is illustrated in Fig. 2D.

Discussion: Our results suggest that average individual changes in FEA during the rtfMRI-nf training targeting the amygdala may be sensitive to severity of PTSD symptoms. Furthermore, the FEA changes may also provide a measure of an individual response to emotion regulation training in PTSD patients. The more positive FEA changes in the patients with higher PTSD severity (greater CAPS) can be interpreted as a consequence of an inverse correlation between FEA values at rest and CAPS [7]. This effect may be similar to the one observed in patients with depression [3]. Clearly, a larger experimental group is needed to replicate and verify these findings.

Conclusion: Using concurrent rtfMRI-nf and EEG during the emotion regulation training, we identified the frontal upper alpha EEG asymmetry as a promising measure of PTSD severity and treatment response. The asymmetry-based EEG-nf [4,9] may complement and enhance the rtfMRI-nf training in PTSD.

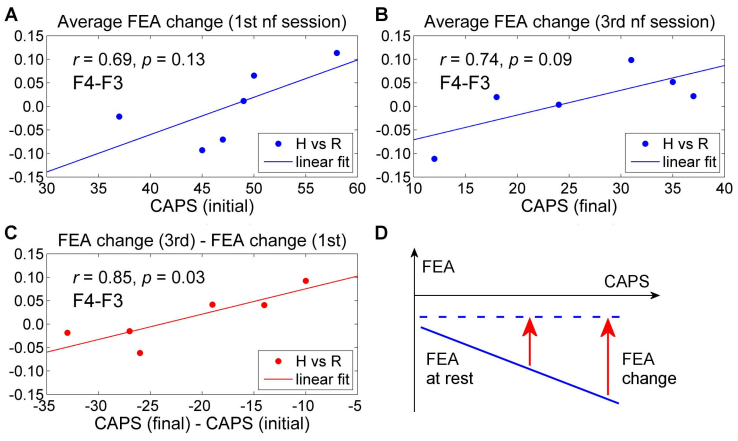

Fig. 2. Average Happy vs Rest changes in FEA=ln(*P*(F4))–ln(*P*(F3)) vs CAPS ratings of PTSD severity. A) For the 1st rtfMRI-nf session vs initial CAPS. B) For the 3rd rtfMRI-nf session vs final CAPS. C) Variation in average FEA changes vs reduction in CAPS scores. D) Our tentative interpretation of the results.

Acknowledgment: This research was supported by W81XWH-12-1-0697 award from the US Department of Defense.

References: [1] S. Ruiz et al. *Hum. Brain Mapping* 2013, 34:200. [2] K.D. Young et al. *PLoS ONE* 2014, 9:e88785. [3] V. Zotev et al. *ArXiv*:1409.2046. [4] V. Zotev et al. *NeuroImage* 2014, 85:985. [5] R.J. Davidson. *Brain Cogn.* 1992, 20:125. [6] R. Thibodeau et al. *J. Abn. Psychol*. 2006, 115:715. [7] A.H. Kemp et al. *Biol. Psychol*. 2010, 85:350. [8] V. Zotev et al. *PLoS ONE* 2011, 6:e24522. [9] F. Peeters et al. *PLoS ONE* 2014, 9:e91837.