Amygdala Functional Connectivity after Real-time fMRI Neurofeedback Emotional Training in Combat-Related PTSD

Raquel Phillips[1], Vadim Zotev[1], Kymberly Young[1], Chung Ki Wong[1], Brent Wurfel[1], Matthew Meyer[1,2], Frank Krueger[1,3], Matthew Feldner[1,4], and Jerzy Bodurka[1,5]

[1]Laureate Institute for Brain Research, Tulsa, OK, United States, [2]Laureate Psychiatric Clinic and Hospital, Tulsa, OK, United States, [3]Dept. of Psychology, George Mason University, Fairfax, VA, United States, [4]Dept. of Psychological Science, University of Arkansas, Fayetteville, AR, United States, [5]College of Engineering, University of Oklahoma, Tulsa, OK, United States

Target audience: Researchers interested in emotion regulation mechanisms, development of novel approaches to treatment of post-traumatic stress disorder (PTSD), and functional connectivity.

Purpose: Post-traumatic stress disorder (PTSD) is a chronic and disabling psychiatric condition. Individuals with PTSD suffer from the dysregulation of several types of emotion including fear, anxiety, anger, and depression. Neurocircuit models of PTSD emphasize the role of the amygdala [1]. We utilize recent advances in real-time functional magnetic resonance imaging neurofeedback (rtfMRI-nf) to directly target and modulate left amygdala activity [2]. The current analysis aimed to determine left amygdala connectivity to the rest of the brain after undergoing multi-visit rtfMRI-nf procedure with positive autobiographical memory recall, and further to determine neurofeedback specificity. We hypothesized that the LA rtfMRI-nf training will result in specific neuroplastic brain changes in veterans with PTSD.

Methods: The study included 14 unmedicated male U.S. military veterans with a current combat-related PTSD diagnosis (seven in the experimental group (EG) and seven in the control group (CG)). Experiments were performed using a GE MR750 3T MRI scanner with the 8-channel receive-only head coil. BOLD fMRI parameters were: gradient echo EPI with FOV/slice=240/2.9mm, TR/TE=2000/30ms, SENSE=2, 96×96, flip=90°, 34 axial slices. T1-weighted MPRAGE sequence was used for anatomical reference and to define regions of interest (ROIs). Neurofeedback was implemented using a custom real-time fMRI system [3] utilizing AFNI [4] real-time features and a custom GUI software. For each subject, two spherical ROIs (7 mm radius in Talairach space) were centered at the left amygdala (LA) and the left horizontal segment of intraparietal sulcus (HIPS, a region putatively not involved in emotion processing). An average fMRI signal from the target ROI (EG=LA, CG=HIPS), was presented as a red bar, updated every 2s (Fig.1). Each run (except Rest) consisted of 40 s blocks of Rest, Happy, and Count conditions.

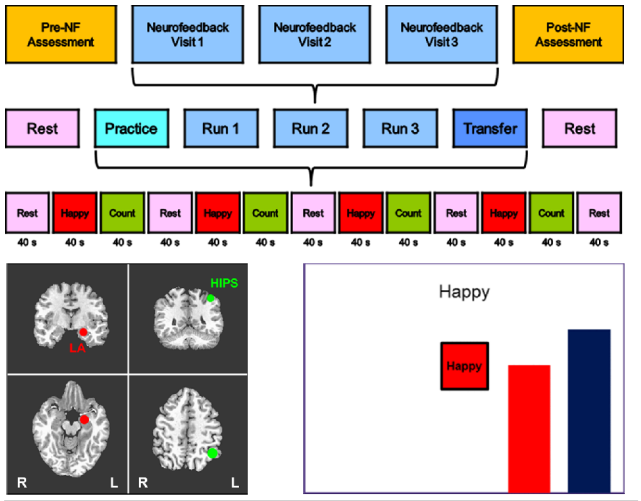

Fig 1: Study design. A) Overview of visits and scans. B) Target ROIs for neurofeedback. C) rtfMRI neurofeedback GUI for Happy condition

For Happy condition, subjects were asked to feel happy by recalling positive autobiographical memories so as to raise the level of the red bar displayed on the screen. The target level (blue bar) was adjusted and raised from run to run. No neurofeedback was provided (no bars displayed) during Rest and Count conditions or during Transfer run. Subjects underwent this procedure three times over three separate visits, each approximately one week apart. To determine functional connectivity of the amygdala network, a GLM-based functional connectivity analysis was applied using a seed ROI in the left amygdala region. The seed ROI was defined as a sphere of 5 mm radius in the Talairach space with the same central point as the target ROI for the EG neurofeedback (21, 5, −16). The volume-registered and slice-timing-corrected single-subject fMRI data from the third visit transfer run were high-pass filtered at 0.01 Hz and low-pass filtered at 0.08 Hz. The time course of the mean fMRI signal from the seed ROI only during the Happy condition was used as a stimulus regressor. The GLM model for each run also included six motion parameters, five polynomial terms for modeling the baseline, and time courses from two additional ROIs defined, respectively, within the deep white matter and the CSF of the lateral ventricles.

The resulting maps were transformed into Talairach space and spatially smoothed at 5 mm FWHM. An unpaired t-test was then used to compare connectivity between the experimental and control groups. Correction for multiple comparisons was based on FDR.

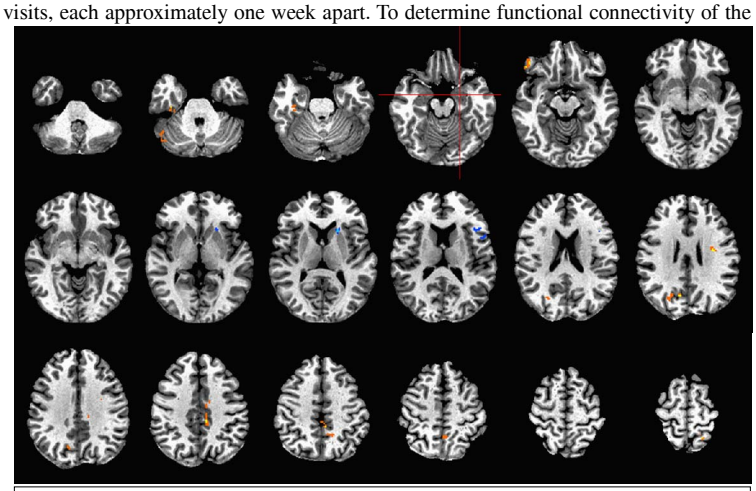

Fig 2: Functional connectivity analysis of visit 3 transfer run using a seed ROI in the left amygdala EG vs. CG. The connectivity maps are projected on a representative single-subject T1 template in the Talairach space. The red crosshairs mark the center of the seed ROI for the connectivity analysis (21, 5, −16). Warm colors indicate greater connectivity in EG, cool colors indicate great connectivity in CG. $p<0.05$, cluster size > 20.

Results: Results of the functional connectivity analysis are show in Figure 2. Clusters where connectivity with LA was significantly greater in EG were centered in the follow regions: L. precuneus, R. precuneus, L. Brodmann area 7, R. tuber, L. cingulate gyrus, R. inferior frontal gyrus, R. Brodmann area 31, R. middle frontal gyrus, L. precentral gyrus, L. cingulate gyrus. Clusters where connectivity with the LA was significantly greater in CG were centered in the follow regions: L. inferior frontal gyrus, L. insula, L. caudate.

Discussion and Conclusion: Activity in the LA was significantly more correlated with activity in other brain regions during happy memory recall without neurofeedback (transfer run) for the EG than the CG. This also shows that the connectivity effects are specific to LA neurofeedback and persist even in the absence of neurofeedback.

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References: [1] Rauch, S. L.(2006) 'Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research--past, present, and future', Biol. Psychiatry 60, pp. 376-82. [2] Zotev, V. (2011), 'Self-regulation of amygdala activation using real-time fMRI neurofeedback', PloS ONE, vol. 6, no. 9, e24522 [3] Bodurka, J. (2008), 'Real time software for monitoring MRI scanner operation', Neuroimage, 41 (Supp. 1), pp. S85. [4] Cox, R.W. (1996), 'AFNI: software for analysis and visualization of functional magnetic resonance neuroimages' Computers and Biomedical Research, Vol. 29, pp. 162-173.