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14. ABSTRACT

PTSD is a chronic and disabling condition. Neurocircuitry-based models of PTSD emphasize dysregulation of the amygdala, which is involved in the regulation of PTSD-relevant emotions. We are utilizing real-time functional magnetic resonance imaging neurofeedback (rtfMRI-nf) training with concurrent electroencephalography (EEG) recordings to directly target and modulate the emotion regulation neurocircuit. By using multimodal data, we can determine which EEG signals/leads or their combination specifically predicts or correlates with clinical improvement associated with the rtfMRI-nf training. Difficult recruitment is the main reason behind the delayed study schedule (currently 12 months no cost extension). During year 3 of the project we have improved our recruitment and are now finishing rtfMRI-nf and EEG data collection. Preliminary data analysis indicates amygdala training with concurrent EEG recordings in a combat-related PTSD population is feasible, and this procedure resulted in improvements in PTSD symptoms. We identified the variations in frontal upper alpha EEG asymmetry (FEA) during the rtfMRI-nf amygdala training as a promising measure of PTSD severity and treatment response. We will employ this measure together with our already developed stand-alone EEG-only neurofeedback training protocol to evaluate FEA EEG-nf training feasibility in combat-related PTSD.

15. SUBJECT TERMS
PTSD; amygdala; fMRI; EEG; real-time fMRI neurofeedback; simultaneous EEG-fMRI; emotion regulation

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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Our *main objective* is to determine whether rtfMRI- and rtEEG-assisted neurofeedback emotion regulation training protocols can reduce the symptoms of combat-related post-traumatic stress disorder (PTSD), a chronic and disabling psychiatric condition. Individuals with PTSD suffer from the dysregulation of several types of emotion, including fear, anxiety, anger, and depression [1–4]. Neurocircuit models of PTSD emphasize the role of the amygdala and its reciprocal interactions with the ventromedial prefrontal cortex (vmPFC) [5–9]. To advance understanding of the treatment of combat-related PTSD, the current state-of-the-art research aims to test ways to modulate the functions of the emotion circuit implicated in PTSD. We utilize the recent advances in real-time functional magnetic resonance imaging neurofeedback (rtfMRI-nf) to directly target and modulate amygdala activity [10–11]. This technique measures neuronal activity with sufficiently high temporal resolution that information from the amygdala is immediately available to form a feedback loop. In parallel with rtfMRI-nf, we obtain simultaneous measurement of electroencephalography (EEG) signals, which directly reflect brain activity in the cerebral cortex [12]. By using the multimodal imaging data we can determine which EEG signals/leads or their combination specifically predict or correlate with clinical improvement that has been associated with the rtfMRI-nf training [11,13–16]. This knowledge will enable us to establish a translational path toward the development of stand-alone real-time EEG neurofeedback (rtEEG-nf) training for emotion regulation, which can facilitate the widespread implementation of the treatment approach due to the high portability and relatively low cost of EEG systems.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

Combat-related PTSD, fMRI, EEG, emotions, amygdala, neurofeedback

3. **OVERALL PROJECT SUMMARY:** Summarize the progress during appropriate reporting period (single annual or comprehensive final). This section of the report shall be in direct alignment with respect to each task outlined in the approved SOW in a summary of Current Objectives, and a summary of Results, Progress and Accomplishments with Discussion. Key methodology used during the reporting period, including a description of any changes to originally proposed methods, shall be summarized. Data supporting research conclusions, in the form of figures and/or tables, shall be embedded in the text, appended, or referenced to appended manuscripts. Actual or anticipated problems or delays and actions or plans to resolve them shall be included. Additionally, any changes in approach and reasons for these changes shall be reported. **Any change that is substantially different from the original approved SOW (e.g., new or modified tasks, objectives, experiments, etc.) requires review by the Grants Officer's Representative and final approval by USAMRAA Grants Officer through an award modification prior to initiating any changes.**

Difficult and challenging recruitment is the main reason behind the study delay schedule by approximately one year. We therefore requested on Jun 30, 2015 a twelve-month, no-cost extension (beyond the original project completion date of Sep 29, 2015), which was approved. During the third year of the project period we have improved our recruitment, and are now finishing Phase 1 of the study (i.e., real-time fMRI neurofeedback [rtfMRI-nf] and EEG data collection) targeting Aim #1: *Establish rtfMRI-nf training feasibility with concurrent EEG recordings in a combat-related PTSD population*. We already met and have exceeded project Milestone #2: fMRI/EEG data collection of 8 subjects per group (control: veterans with no PTSD; neurofeedback, sham: veterans with PTSD). Preliminary data analysis indicates (as described below) rtfMRI-nf amygdala training with concurrent EEG recordings in a combat-related PTSD population is feasible. In parallel we have also developed the rtfMRI-nf and rtEEG-nf software (Milestone #3) for the purpose of Aim #2: *Develop a stand-alone rtEEG neurofeedback training protocol for PTSD*. We identified the variations in frontal upper alpha EEG asymmetry during the rtfMRI-nf amygdala training as a promising measure of PTSD severity and treatment response. This EEG signal feature is suitable for developing a stand-alone EEG neurofeedback training protocol (Milestone #4). We are currently finishing preparation for Phase 3 of the project and Aim #3: *EEG-only neurofeedback training feasibility in combat-related PTSD*. The Phase 3 subject visit schedule is shown in Figure 1 below.

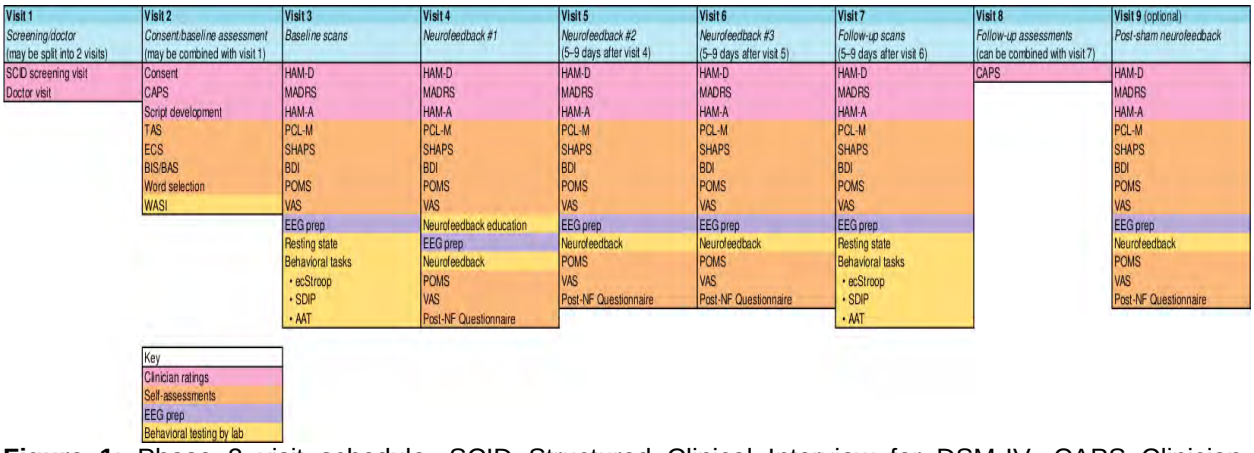


Figure 1: Phase 3 visit schedule. SCID=Structured Clinical Interview for DSM-IV, CAPS=Clinician-Administered PTSD Scale, TAS=Toronto Alexithymia Scale, ECS=Emotional Contagion Scale, BIS/BAS=Behavioral Inhibition System/Behavior Avoidance System, WASI=Wechsler Abbreviated Scale of Intelligence, HAM-D=Hamilton Rating Scale for Depression, MADRS=Montgomery–Åsberg Depression Rating Scale, HAM-A=Hamilton Rating Scale for Anxiety, PCL-M=PTSD Checklist-Military Version, SHAPS=Snaith-Hamilton Pleasure Scale, BDI=Beck Depression Inventory, POMS=Profile of Mood States,VAS=Visual Analog Scales, ecStroop=Emotional Counting Stroop, SDIP=Script-Driven Imagery Procedure, AAT=Approach-Avoidance Task

All necessary computer hardware (1 Ubuntu workstation for running stimulus, 1 Windows laptop for collecting EEG and physiological data) as well as peripheral devices (64-channel EEG caps, additional EEG power supply and amplifiers, respiration belt and GSR leads for collecting physiological data, mechanical keyboard response device for ecStroop task, joystick for AAT, headphones and volume control for the script-driven imagery procedure [SDIP], and a mobile cart for performing the experimental tasks) have been acquired. Modification of the ecStroop and SDIP tasks for phase 3 and programming of the AAT in Python have begun. Setup of stand-alone real-time EEG data collection has been completed. A database for collecting and storing clinician ratings and self-assessment questionnaires has been prepared, which means that phase 3 can be paperless from the start.

We are planning to start recruitment for phase 3 of the project in December of 2015. We are anticipating that for the purpose of Phase 3 of the project (with human subjects research approval already obtained, Milestone #5 reached) recruitment will be easier and faster since there will be no MR-related exclusions (e.g., shrapnel in the body).

To continuously monitor recruitment progress, we have regular weekly meetings with recruitment staff and biweekly research meetings where current project needs, problems, method

and software developments, and relevant activities are discussed with all investigators, including co-investigators Drs. Feldner (University of Arkansas) and Krueger (George Mason University), both joining via video or teleconference.

Preliminary and ongoing data analysis

We have increased the numbers of veterans enrolling in, undergoing, and finishing Phase 1 of the study. Hence, we continue to advance efficient data processing pipelines and conduct preliminary data analysis for Aim #1, which includes the following: (A) to validate whether veterans with PTSD are able to use rtfMRI-nf training to enhance their control of the hemodynamic response of the amygdala, and to further asses specificity of this training; (B) to evaluate possible sustained neuroplastic changes induced by the procedure; and for Aim #2; (C) to conduct preliminary analyses identifying a single EEG feature that is optimally suitable for developing the stand-alone rtEEG-nf training protocol (Phase 2) and experimental evaluation of the protocol (Phase 3); and (D) EEG exploratory analysis focusing on temporally independent EEG microstates.

A. rtfMRI-nf amygdala training. The updated preliminary data analyses were conducted on the 18 veterans in the left amygdala (LA) feedback group and 10 in the control feedback (HIPS) group, and 17 in the healthy (trauma control) group (Fig. A1). These analyses include results from multiple rtfMRI-nf visits.

For each subject, three spherical ROIs (7 mm radius in Talairach space) were centered, respectively, at the left and right amygdala (Fig.1) and the horizontal segment of intraparietal sulcus (HIPS, a region putatively not involved in emotion processing). An average fMRI signal from the target ROI (the left amygdala), was presented as a red bar, updated every 2s

Figure A1

All subjects were male, age 18–55, right-handed U.S. military combat veterans. No significant baseline differences were observed in age, PTSD symptom severity, or depression symptom severity between the two groups (as described in Table A1).

	Experimental (LA)	Control (HIPS)	Healthy (LA)
n	18	10	17
Age	30 (5)	34 (8)	33 (8)
Initial CAPS	54 (15)	61 (22)	5 (5)*
Initial HRSD	17 (6)	16 (9)	2 (2)*

Table A1. Demographic information for experimental, control and healthy (trauma expose) groups. CAPS = Clinician Administered PTSD Scale. HRSD = 21-Item Hamilton Rating Scale for Depression.

ROI analysis results.

A GLM analysis for each of the three visits was performed to determine the training effect of the neurofeedback procedure. The analyses were implemented in AFNI, SciPy, and SYSTAT. Pre-processing included cardiac and respiratory waveform correction, volume registration, and slice timing correction. Standard GLM analysis was then applied separately for each of the five neurofeedback runs on each of the three visits including the following regressors: two block stimulus conditions (Happy Memories, Count), six motion parameters, and five polynomial terms. After deconvolution, percent signal change for Happy vs. Rest conditions was calculated. In preparation for the whole-brain statistical group analysis, the spatially-normalized fMRI percent signal change maps were spatially smoothed using a Gaussian kernel with full width at half maximum (FWHM) of 5 mm. One-sample *t*-tests were performed separately for each run and for each group to determine whether activation was significant.

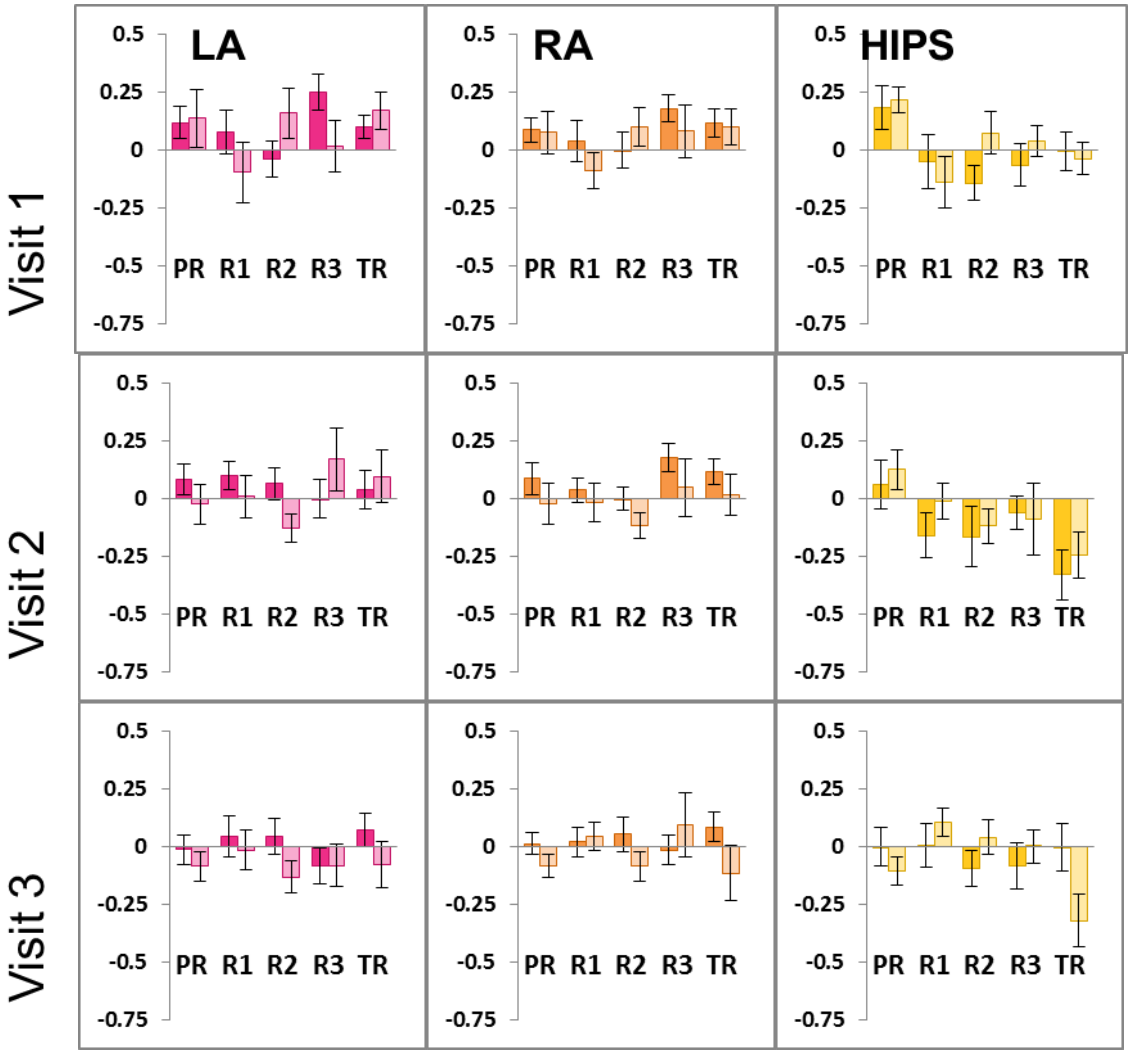


Figure A2. Mean percent signal change between Happy and Rest conditions for each of the neurofeedback runs. LA = left amygdala, RA = right amygdala, HIPS = left horizontal segment of the intraparietal sulcus, PR = practice, R1–3 = training runs 1–3, TR = transfer. Left/dark bar = experimental group, right/light bars = control group.

ROI analysis results are shown below in Figure A2. Each row of graphs represents results from one of the three neurofeedback visits. Each column of graphs shows results for one of three ROIs: left amygdala (target ROI for the experimental group), right amygdala (shown to explore the effects of laterality), and left HIPS (target ROI for the control group). In each graph, bar height represents mean percent signal change between Happy and Rest conditions for a single run. The dark/left bars represent the experimental group while the light/right bars represent the control group.

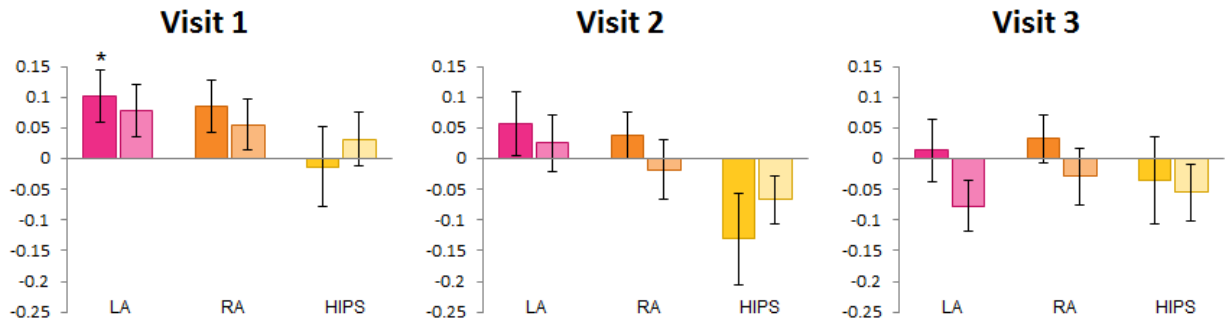


Figure A3. Mean percent signal change between Happy and Rest conditions averaged across all runs (PR, R1-R3,TR) within single visit. Data from all three visits are shown. Left/dark bar = experimental group, right/light bars = control group. (* indicates significant difference from zero at $p<0.05$)

Figure A3 shows for each visit a mean percent signal change between Happy and Rest conditions across all runs (PR,R1-R3,TR) within a single visit for LA, RA, and HIPS (in each bar plot: left, middle, and right columns respectively). For the first visit there is statistically significant difference in ability to upregulate left amygdala in the experimental group.

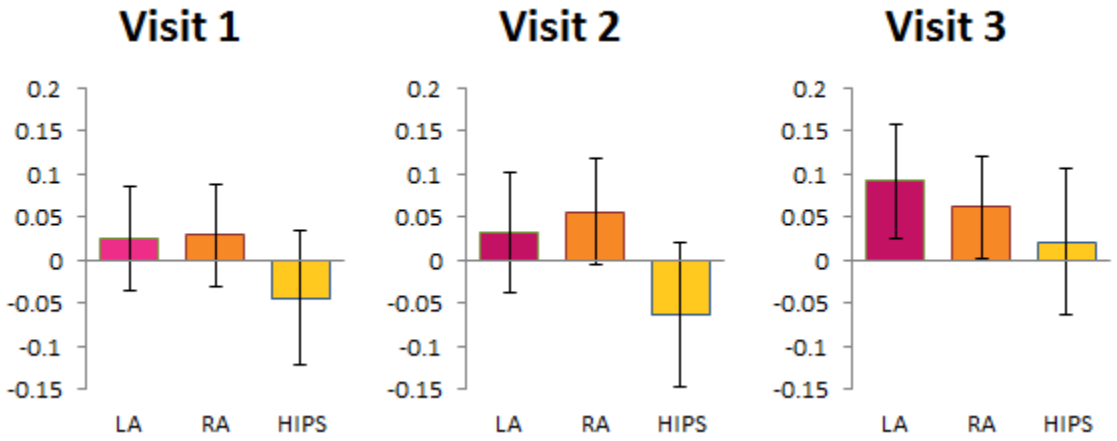


Figure A4. Group difference (EG-CG) average Happy vs. Rest signal (from LA,RA,HIPS) across practice, run 1, run 2, run 3, and transfer, for all visits.

Interestingly the difference between mean left amygdala percentage change (averaged across all runs) in experimental and control conditions is progressively increasing with each visit (Fig. A4), although this trend is not significant. These results indicate that across each of the three visits subjects in the experimental group were able to better elevate activity in the left

amygdala during neurofeedback scans as compared to the control group. Also, a large degree of variability across subjects exists, resulting in a lack of consistent statistically significant differences between the experimental and control groups. A similar activation pattern occurred in the right amygdala, though the effect for the experimental group was not as strong as in the left amygdala. Neither group was able to up regulate activity in the left HIPS.

Clinical score change results.

Clinical ratings were taken at the beginning of each visit and used to assess the effects of the neurofeedback training on PTSD and depression symptoms (Table A2). Subjects in the experimental group showed decreased PTSD and depression symptoms that were both statistically and clinically significant. Significant reduction in depression symptoms (according to the HRSD) were seen after only one neurofeedback visit and significant PTSD symptom reductions (according to the PCL-M) were observed after two neurofeedback visits.

	Experimental (LA)			**Control (HIPS)**			**HC (LA)**		
Scale	Initial score	Mean change	t	Initial sore	Mean change	t	Initial score	Mean change	t
CAPS	55	**–14****	t(14)=3.7	62	–9	t(7)=1.7	4	–1	t(14)=0.5
PCL-M	47	**–10****	t(17)=4.1	52	–9	t(8)=2.1	19	0	t(15)=–0.3
HRSD	17	**–5****	t(18)=4.6	17	**–6***	t(8)=2.7	2	+1	t(15)=–0.7
MADRS	21	**–8****	t(18)=3.6	19	–6	t(8)=1.4	1	+2	t(15)=–0.8
HRSA	17	**–6****	t(18)=4.1	19	**–5***	t(8)=2.4	2	+1	t(15)=–0.7

Table A2. Clinical score change results for both experimental and control groups. CAPS = Clinician Administered PTSD Scale (0–136). PCL-M = PTSD Checklist – Military Version (17–85). HRSD = 21-Item Hamilton Rating Scale for Depression (0–52). MADRS = Montgomery–Åsberg Depression Rating Scale (0–60). HARS = Hamilton Anxiety Rating Scale (0–56). Initial ratings taken before first neurofeedback scan. Final ratings taken at final Stroop scan (after 3rd neurofeedback scan). A significant change from pre- to post-scan ratings at $p < 0.05$ marked with *, and at $p < 0.01$ marked with **.

Functional connectivity results

To better understand the degree to which LA neurofeedback is yielding results specific to activity in the LA, we have examined amygdala functional connectivity after completing multiple sessions of amygdala-focused rtfMRI-nf training. A GLM-based functional connectivity analysis was applied using a seed ROI in the left amygdala region to determine functional connectivity of the amygdala network (Figure A2). 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 experimental group neurofeedback (21, 5, −16). The volume-registered and slice-timing-corrected single-subject fMRI data from the 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.

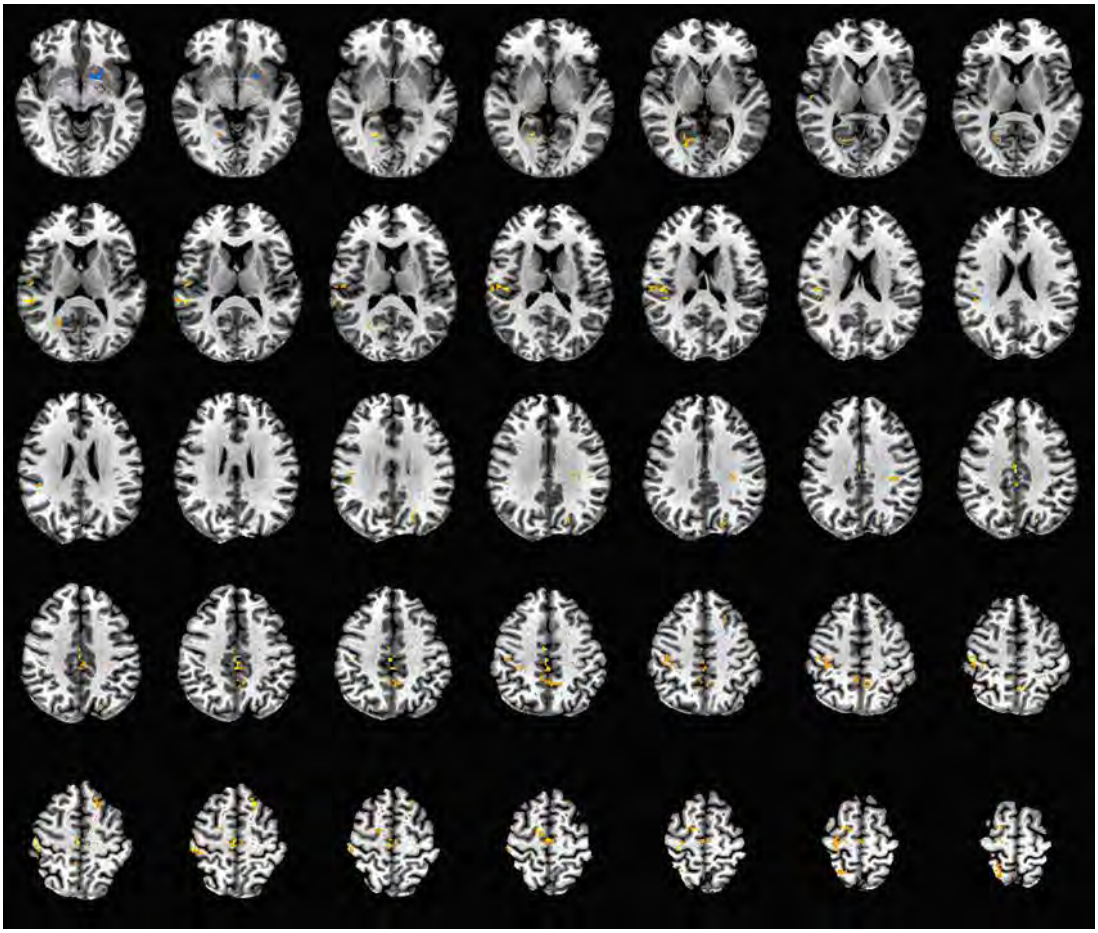


Figure A5. Functional connectivity analysis (visit 3 transfer run) using a seed ROI in the left amygdala (experimental vs. control). The connectivity maps are projected on a representative single-subject T1 template in the Talairach space. The red crosshairs mark the center of the seed ROI for the connectivity analysis (21, 5, −16). Warm colors indicate greater connectivity in the

experimental group, cool colors indicate great connectivity in the control group. $p < 0.05$, cluster size ≥ 30.

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. The GLM-based R-squared statistics were converted to correlation coefficient values *r*. A paired samples *t*-test was then used to compare connectivity between the experimental and control groups.

	Peak region	Peak	Size
	R. postcentral gyrus	(-45,25,50)	97
	R. medial frontal gyrus (BA6)	(-11,9,58)	77
	R. insula (BA13)	(-43,25,18)	73
	L. precuneus	(3,53,50)	70
	R. posterior cingulate	(-23,61,14)	62
	R. medial frontal gyrus (BA6)	(-3,23,54)	58
	R. postcentral gyrus (BA3)	(-25,29,62)	52
EG>CG	R. paracentral lobule (BA31)	(-5,13,44)	47
	L. middle frontal gyrus (BA6)	(19,-17,54)	39
	R. cingulate gyrus	(-1,33,40)	33
	R. postcentral gyrus (BA7)	(-23,51,64)	33
	R. insula	(-41,35,22)	32
	L. precuneus	(21,65,26)	32
	R. superior temporal gyrus	(-55,35,10)	30
	L. postcentral gyrus	(31,27,34)	30
CG>EG	L. putamen	(19,-5,-4)	39

Table A3. Functional connectivity analysis of visit 3 transfer run using a seed ROI in the left amygdala as function of group (experimental [EG] vs. control [CG]).

Correction for multiple comparisons was based on FDR. Results of the functional connectivity analysis showed that activity in the left amygdala was significantly more correlated with activity in other brain regions during happy memory recall for the subjects in the experimental group receiving LA neurofeedback than it was for subjects in the control group receiving left HIPS neurofeedback. In fact, only one region showned to be more connected with the left amygdala in the control group vs. the experimental group (Figure A5, Table A3).

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.

B. Functional connectivity analysis pre- and post-rtfMRI-nf procedure to assess sustained neuroplastic changes induced by rtfMRI-nf training.

We utilized rtfMRI-nf to increase amygdala activity while recalling happy autobiographical memories in veterans with combat-related PTSD. Here we aimed to determine whether such training induces sustained brain plasticity effects. We employed resting-state fMRI and functional connectivity analysis to investigate the changes in the default mode network (DMN) involved in self-referential and internal emotion processing [17], and to determine changes in amygdala connectivity.

Method: Male veterans with PTSD were recruited and assigned to active (experimental) amygdala-focused (EG, n = 19) and control HIPS-focused (CG, n = 9) groups. Seventeen healthy veterans (HG) were also recruited and received active amygdala-focused neurofeedback. Subjects went through three repetitions of rtfMRI-nf in the same protocol as described previously (above and 11,18). Subjects in the active group were instructed to feel happy by evoking positive autobiographical memories while trying to raise the activation level of the targeted ROI (i.e., LA in the active group and the HIPS region in the control group). Participant characteristics by experimental group and pre- and post- clinical ratings changes are shown in Table B1. Resting-state fMRI data were collected on separate visits before and after the rtfMRI-nf training with subjects' eyes open. Single-shot gradient-recalled SENSE EPI (FOV/slice=240/2.9mm, TR/TE=2000/30ms, 96×96, R=2, FA=90°) was used for fMRI on a GE MR750 3T MRI scanner. T1-weighted MPRAGE sequence was used for structural imaging. Resting state networks were derived from preprocessed imaging data using spatial independent component analysis [19], separately for each visit. The DMN was selected by choosing the best-fit component with a template of the DMN [20]. The before-and-after difference of DMN connectivity was assessed using a two-sample paired t test.

Results: As shown in Table A2 above, the experimental (active) group compared to the control group reported significantly decreased PTSD symptoms (CAPS, PCL-M) and anxiety (HARS) after rtfMRI-nf training. Changes resulting from rtfMRI-nf amygdala training in DMN and amygdala functional connectivity are shown in Figures B1, and B2, respectively.

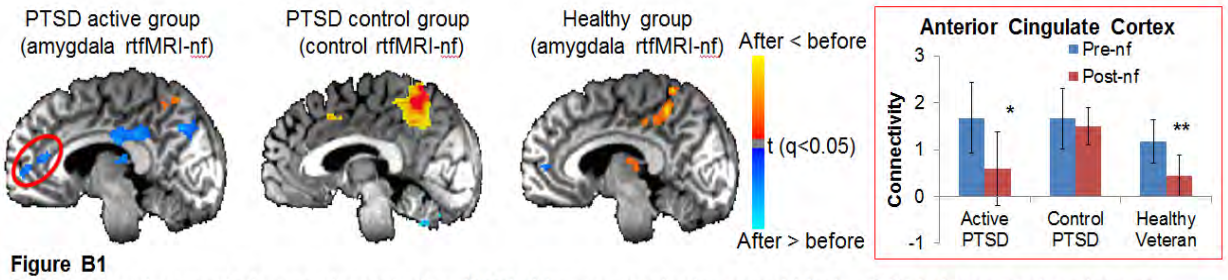


Figure B1
DMN functional connectivity was changed after rtfMRI-nf training. * indicates paired t-test p<0.05 between post- and pre-nf.

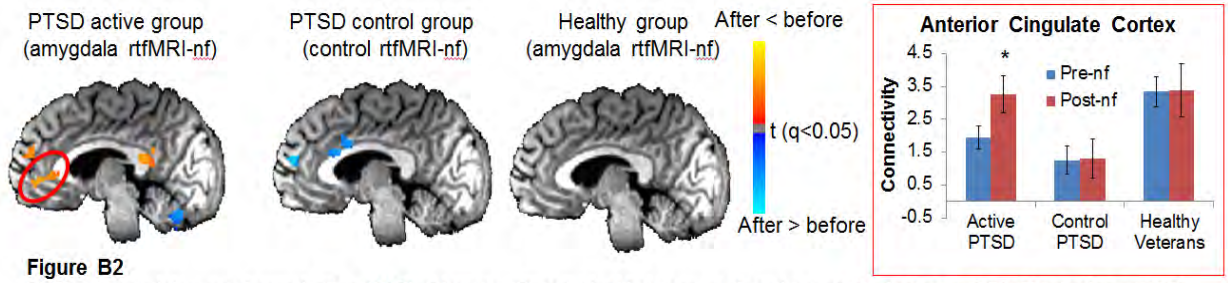
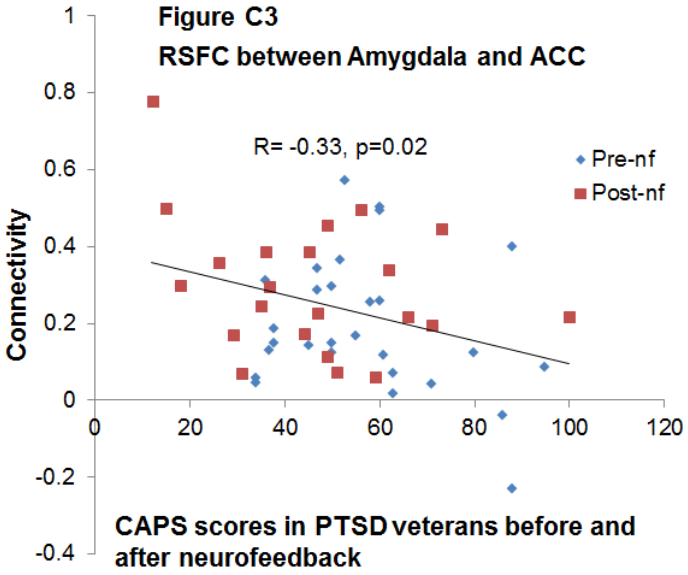


Figure B2
RSFC of amygdala was changed after rtfMRI-nf training. Paired t-test between post- and pre-nf, * indicates p<0.05, ** indicates p<0.01.

Figure B3 shows an inverse relationship between amygdala and ACC resting state functional connectivity obtained pre- and post-neurofeedback with corresponding CAPS scores.

Discussion and Conclusions: Our results reveal plastic, lasting brain changes after the rtfMRI-nf training during positive autobiographical memory recall in veterans with combat-related PTSD. Moreover, self-reported PTSD symptoms, anxiety, and depression were all significantly reduced after the amygdala training. We found that resting-state functional connectivity (RSFC) between amygdala and ACC inversely correlates with CAPS scores, suggesting a measure of PTSD severity and treatment response. Post-neurofeedback imaging results show that the abnormal hypo-connectivity between left amygdala and anterior cingulate cortex [21,22] was reversed, suggesting a therapeutic effect of rtfMRI-nf using positive AM recall in PTSD. Moreover, abnormal hyper-connectivity of ACC in the default mode network [22] was also reversed after



receiving active neurofeedback. These findings have implications for our understanding of PTSD pathophysiology and mechanisms involved in neurofeedback, as well as for efforts to enhance existing, and to develop new and more effective, treatments for PTSD.

C. rtfMRI-nf amygdala training effect on simultaneously collected EEG data. We have developed data analysis methods for simultaneously collected EEG data during rtfMRI-nf experiments (Fig. C1.A,B,C,D) alongside preliminary combined analysis of EEG and fMRI. To evaluate electrophysiological correlates of the rtfMRI-nf training targeting the amygdala, we examined task-specific changes in frontal EEG asymmetry (FEA), defined as $\ln(P(\text{right}))-\ln(P(\text{left}))$, where P is EEG signal power in an individual upper-alpha EEG band. **Method:** The analysis followed the procedure employed in our previous study on MDD patients (described in Appendix 1) [23]. The analysis was conducted for 15 PTSD patients who underwent the rtfMRI-nf training with the active nf condition (target: left amygdala, Fig. C1.D) and completed the whole study, including the final CAPS evaluation.

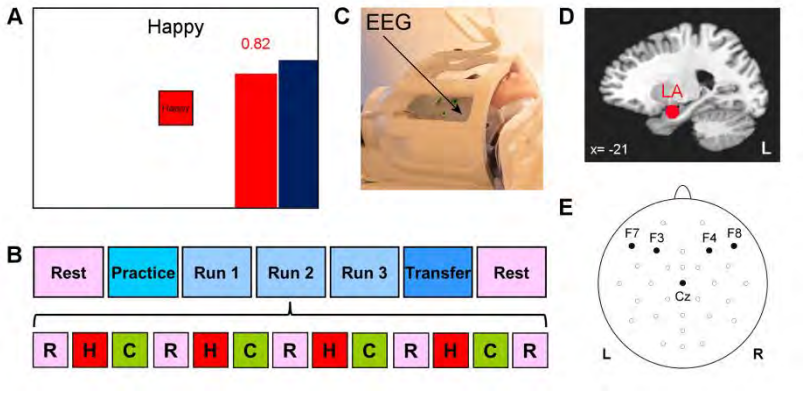


Figure C1. A. rtfMRI-nf amygdala training experimental condition screen (red bar left amygdala BOLD signal) **B.** rtfMRI-nf training session imaging protocol; **C.** EEG was collected during the rfMRI-nf procedure; **D.** Left amygdala region of interest; **E.** Schematic representation of EEG channels location.

The average FEA changes for the Happy conditions with rtfMRI-nf relative to the Rest conditions for EEG channels F3 (left) and F4 (right) (Fig. C1.E) were determined for each run, and further averaged for the four rtfMRI-nf runs (Practice, Run 1, Run 2, Run 3, Fig. C1.B) in a given training session.

Results: Figure C2.A and B reports the FEA analyses examining individual variations in patients' PTSD severity ratings (CAPS) and MDD severity ratings (HDRS).

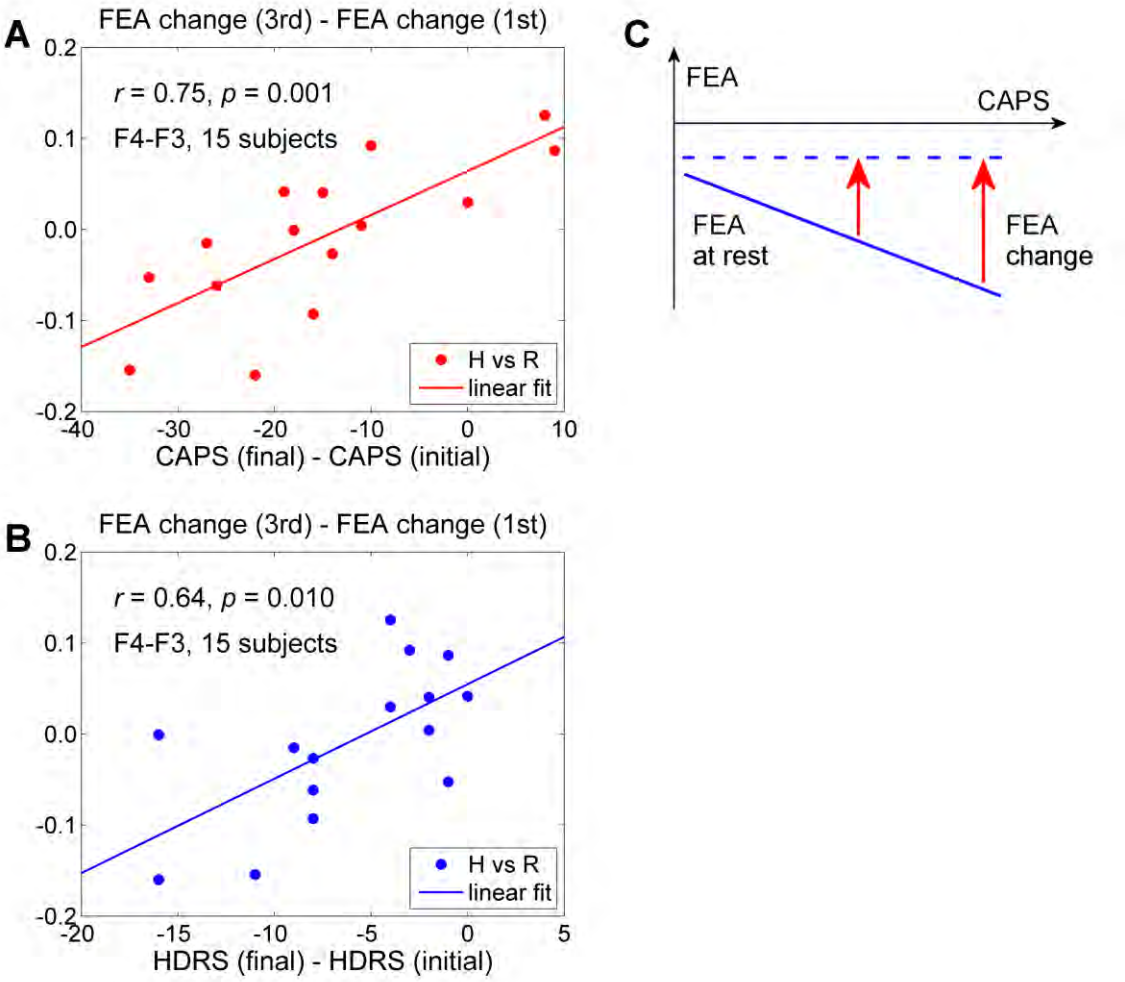


Figure C2. Relation between individual FEA changes between the last and the first rtfMRI-nf training sessions and **A.** CAPS ratings changes and **B.** HDRS rating changes. **C.** Interpretation of the observed FEA changes.

Fig. C2.A displays correlations between individual differences in the average Happy vs Rest FEA changes between the last (3rd) and the first (1st) rtfMRI-nf sessions (y-axis) and individual differences in the CAPS ratings from the final and initial CAPS evaluations (x-axis). The results show a significant positive correlation (r=0.75, p=0.001) between the two measures. A partial correlation between the ΔFEA and ΔCAPS when controlling for ΔHDRS is also significant ($r(12)$=0.71, p=0.004). Notably, the individual variations in these ratings (ΔCAPS and ΔHDRS) were uncorrelated (r=0.38, p=0.157).

Fig. C1.B displays correlations between individual differences in the average Happy vs Rest FEA changes between the last (3^{rd}) and the first (1^{st}) rtfMRI-nf sessions and individual differences in the HDRS ratings from the final and initial HDRS evaluations. The results show a significant positive correlation (r=0.64, p=0.010) between these two measures as well. A partial correlation between ΔFEA and ΔHDRS when controlling for ΔCAPS is also significant ($r(12)$=0.58, p=0.031). A multiple regression analysis indicated that the variations in the FEA changes (ΔFEA) were significantly predicted by the variations in the CAPS ratings (ΔCAPS) and HDRS ratings (ΔHDRS) ($F(2,12)$=14.74, p=0.001, R^2=0.711), with the partial correlations specified above.

Discussion: Our tentative interpretation of the FEA results is illustrated in Fig. C1.C. The FEA at rest is known to exhibit inverse correlations with both CAPS ratings and HDRS ratings [24]. The FEA values during the Happy conditions with rtfMRI-nf appear to be less dependent on the PTSD and MDD symptom severity (dashed line in Fig. C1.C), because the rtfMRI-nf task used in our study is associated with enhanced happy emotion and approach motivation [23]. Therefore, larger positive Happy vs Rest FEA changes can be expected in the patients with more severe PTSD and/or MDD symptoms, reflecting their lower baseline FEA levels. The results in Fig. 1.A and B suggest that normalization in the PTSD patients' symptom levels is associated with reduction in the average FEA changes during the rtfMRI-nf task. The fact that both partial correlations above are significant and close to the corresponding zero-order correlations indicates that the variations in the CAPS and HDRS scores may have essentially independent effects on the variations in the FEA changes, in agreement with [24].

Based on our EEG data analysis we have already identified frontal asymmetry in the alpha band (FA-alpha) as a target for rtEEG-nf experiments (Aim #3). In addition, our preliminary results suggest that variations in FEA during rtfMRI-nf training might independently provide valuable information about PTSD severity and treatment response.

D. Tracking Resting State Connectivity Dynamics in Veterans with PTSD: New Insights from EEG-fMRI. In PTSD, abnormal connectivity of spontaneous activity in several brain regions constituting the "default mode network" (DMN) in a resting state has been reported [4,25-26]. However, the mechanisms underlying these abnormalities in neurobiological activity are not well understood. Simultaneous EEG and BOLD fMRI have allowed for examining brain

activity with joint high spatial and temporal resolution. Here, we developed a novel multimodal analysis approach using temporally independent EEG microstates [16] to study DMN activity.

Method: Simultaneous EEG and fMRI data were acquired from 34 veterans with combat-related PTSD and 17 healthy control (HC) veterans in an eyes-open resting state. Whole-brain fMRI with a single-shot gradient-recalled SENSE EPI (TR/TE=2000/30ms, R=2, FA=30°) were acquired using a GE MR750 3T MRI scanner. EEG signals were recorded using MRI-compatible 32-channel BrainAmp MR Plus amplifier. BOLD fMRI RSNs were derived from preprocessed imaging data using spatial independent component (ICA) analysis separately for PTSD and HC groups. The default mode network was selected by choosing the best-fit component with a template of the DMN [20]. The difference between groups was assessed using an independent samples *t* test. After correcting for MRI and cardioballistic artifacts, temporally independent EEG microstates (EEG-ms) were derived using the method described in [16]. The DMN-related EEG-ms was selected by choosing one EEG-ms of correlated time course with BOLD fMRI DMN. The complete time courses of DMN-related EEG-ms were obtained by back-projection and determined via a winner-take-all approach. The occurrence ratio of DMN-related EEG-ms was calculated for each subject and then compared across groups and against the clinical ratings.

Results: Figure D1 shows the respective spatial patterns of the DMN in the PTSD and HC veterans and the difference between groups.

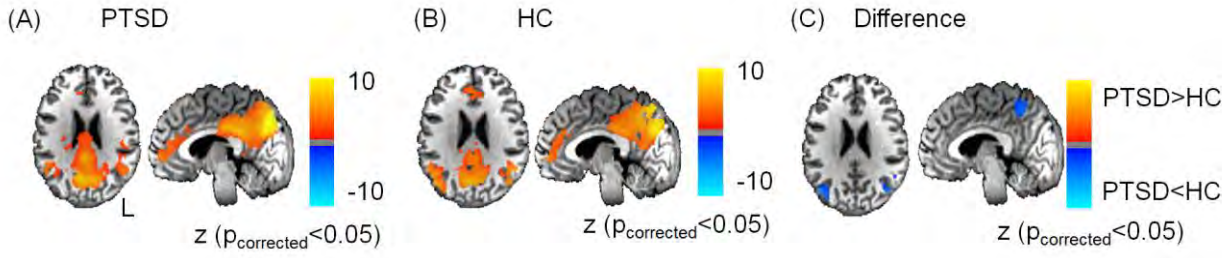


Figure D1. Resting state functional connectivity of the default mode network in the groups of veterans with PTSD and healthy control (HC) veterans.

In both groups significant functional connectivity in the DMN was found in the bilateral middle temporal gyri (MTG), posterior cingulate cortex (PCC), and medial prefrontal cortex (MPFC) as consistent with [4,25-26]. Compared with HC, the PTSD subjects showed decreased

connectivity in the bilateral MTG and the PCC. Next we examined the EEG resting state activity to investigate the fast temporal dynamics underlying connectivity.

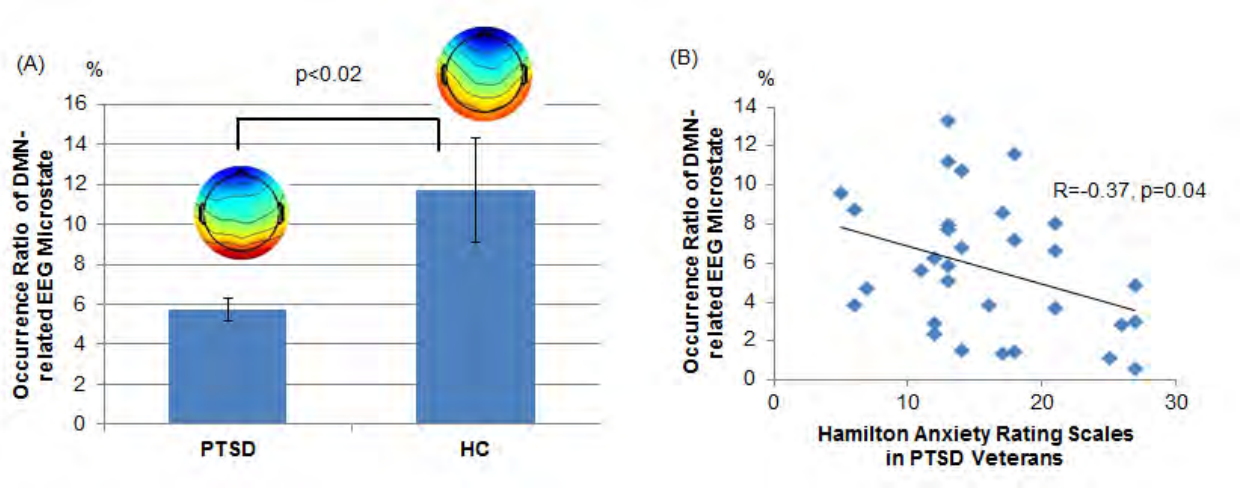


Figure D2. Occurrence ratio of the temporally independent EEG microstates that are associated with the DMN observed by BOLD fMRI. **A)** PTSD and HC group differentiation; **B)** Correlation with Hamilton Anxiety Rating Scale scores.

The temporally independent EEG-ms that exhibit the strongest relation with the DMN was identified in both the PTSD and HC groups. For both groups this EEG-ms features consistent topology of electrical potentials (Fig. D2.A). However, the occurrence ratio of the DMN-related EEG-ms was significantly different between the PTSD and HC groups ($p < 0.05$, Fig. D2.A), and was negatively correlated with Hamilton Anxiety Rating Scale scores ($p = 0.04$, Fig. D2.B).

Discussion: Resting state functional connectivity at the bilateral MTG and the PCC was reduced in veterans with combat-related PTSD as compared to the healthy veterans. From simultaneously acquired EEG-fMRI data we identified temporally independent EEG microstates whose temporal dynamics evolve at a much faster scale and yet were correlated with the fMRI DMN. The occurrence ratio of the EEG microstate statistically differentiates PTSD and HC groups. Importantly, the abnormally decreased functional connectivity in veterans with PTSD observed via fMRI was associated with a decreased occurrence ratio of DMN-related EEG-ms, which suggests PTSD is related to a relocation of neural processing resources during rest.

Summary of preliminary data analyses

Taken together, preliminary analyses of our rtfMRI-nf amygdala training results demonstrate that veterans with PTSD can learn to self-regulate their amygdala BOLD responses during recall of positive autobiographical memories (i.e., confirmation of Aim #1). Notably, rtfMRI-nf training of the left amygdala resulted in improvements in PTSD and depression symptoms. Significant reduction in depression symptoms (according to the HRSD) were seen after just one neurofeedback visit and significant PTSD symptom reductions (according to the PCL-M) were seen after just two neurofeedback visits in veterans with PTSD in the experimental group but not in controls. Functional connectivity analysis of the amygdala during the neurofeedback procedures revealed substantial differences between the experimental (feedback from LA) and control groups (feedback from HIPS), proving additional evidence of a specific neuromodulatory effect induced by the LA neurofeedback procedure during positive memory recall. Brain regions co-activated with the LA feedback procedure (forming an amygdala-related network) were consistent with the broader literature regarding the amygdala-related neural network involved in emotion processing.

Evaluation of brain effects induced by the rtfMRI-nf procedure revealed changes in resting state DMN connectivity in veterans with PTSD. The LA rtfMRI-nf training procedure reversed abnormal connectivity observed in subjects with PTSD and as compared to healthy controls. Specifically in the post-training session, functional connectivity decreased in insula, pregenual ACC, BA31, precuneus, and thalamus. Veterans in the experimental group reported significantly reduced PTSD symptoms (PCL-M), anxiety, and depression after rtfMRI-nf training. This analysis also suggests sustained neuroplastic changes induced by the rtfMRI-nf LA training and happy autobiographical memory recall.

Preliminary analysis of the concurrently acquired EEG data during rtfMRI-nf revealed that modulation of BOLD LA activity during the neurofeedback procedure was accompanied by changes in frontal EEG asymmetry (FEA) in the upper alpha band (power(F4)-power(F3) electrodes). The direction of change in the FEA (e.g., more positive FEA) induced by the rtfMRI-nf LA training was consistent with more approach-oriented responses and traits as well as more positive emotions.

Indeed we observed that reduction in CAPS ratings was associated with reduction in the average FEA changes during the rtfMRI-nf task, indicating that variations in FEA during

rtfMRI-nf training might independently provide valuable information about PTSD severity and treatment response. Those preliminary results identified the FEA as a promising target for EEG-only neurofeedback training among veterans with combat-related PTSD (Aim #3).

Recruitment efforts description

During the third year of the grant (October 2014 through October 2015) radio advertising continued to be our most successful recruitment effort. We ran 28 ads on 9 different radio stations across multiple genres (country, rock, hip-hop, top 40, and contemporary hits) and two metropolitan areas (Oklahoma City and Tulsa). Radio stations were chosen based on previous success as well as Nielson ratings procured during the last year. In addition to trying new radio stations in order to target a wider population, we also tweaked the airing schedule. Radio ads are now played from Monday through Friday with the first ad starting Monday at 5am and last one at 6am on Friday. Then we continue the final ad for the week on Saturday from 12am to 1am.

We also found that advertisements run during patriotic holidays (e.g. Independence Day) seem to be especially effective. The study coordinator was interviewed about the study on a Tulsa hip op radio station in May 2015. Furthermore, we have run additional advertisements on online radio stations, Facebook, and Craigslist.

Beginning in October 2014, in order to help with recruitment, LIBR decided to have veterans who were excluded from the study participate in a LIBR-funded single-visit version of the study. We hoped this would help LIBR staff build rapport with veterans, thereby increasing recruitment via word of mouth. We continue to allow flexible scheduling, including visits on evenings and weekends to accommodate as many veterans as possible.

We have also continued our community outreach efforts during the last year. We have an on-going monthly relationship with certain medical and veteran organizations such as the Veterans Initiative, Family and Children Services, Veteran's Advisory Council, and Laureate Psychiatric Clinic and Hospital. Each month, our recruitment-focused staff attended meetings and provided presentations provided study-focused literature to various social workers, mental health counselors, psychologists, and physicians. These recruitment efforts included meetings and presentations with selected clinicians who work directly with the target population. We also continued our efforts directly targeting recruiting patients/potential participants from Family and

Children Services monthly and the Laureate Psychiatric Clinic and Hospital weekly. LIBR also hosted a barbecue for employees and patients at Family Children Services in May of 2015.

In November of 2014, LIBR had an open house for the community. The open house allowed professionals in the community, including the VA, to come to LIBR and learn about ongoing research studies. Research scientists gave presentations about their studies, and study-related material for the current study was displayed for professionals to freely take. The professionals were also given a tour of the research facility. To help with recruitment, recruitment staff invited clinicians that directly work with the study population. In the last year we have also provided tours and study information specifically for staff of veteran and mental health organizations, including the Coffee Bunker (a local organization that provides a gathering place for veterans and their families), the Wounded Warriors (a program that provides hyperbaric oxygen therapy to veterans to treat TBI and PTSD), and the Mental Health Association of Tulsa.

Our recruitment staff was able to obtain a list of zip codes where many veterans reside. Staff attended community organizations in those areas to build partnerships that will help with recruitment. For example, organizations we connected with were apartment complexes and recruitment staff was able to distribute 250 study related materials in the Claremore and Sandsprings area. LIBR had a strong presence at several community events, including Live Great 918 in August of 2015 and the Zarrow Mental Health Symposium (September of 2015).

Though our efforts to recruit through Jack C. Montgomery VA Medical Center in Muskogee, OK, our initially planned primary recruitment source, have not been successful, we have continued to maintain a relationship with their staff. The center recently hired two new staff members for full-time research positions, and we hope that through them we may be able to establish a referral mechanism.

LIBR is currently working on creating a video advertisement to air on local television stations. We hope in the next quarter to begin airing these ads, which have the potential to reach a very large number of veterans.

Enrollment information

Beginning in January of 2015 our institution began using a new system for storing subject data. The new system is paperless, which will not only make it easier to track subjects but will facilitate the intake of veterans who contact LIBR through streams other than our study-focused

recruitment efforts. During this period of transition, however, it has been a challenge to integrate the tracking of subjects who began the process before and after the implementation of our new system.

Since January of 2015, 210 veterans have completed the LIBR phone screening. Of those, 93 came in for in-person assessments. 21 of those subjects were found eligible for the study, 9 of whom were consented to the study. There are currently 21 veterans pending in-person assessments.

Below are the total participant numbers since the beginning of the study.

· 65 consented to the study

· 57 completed the 1st scan

· 53 completed the 2nd scan

· 49 completed the 3rd scan

· 47 completed the 4th scan

· 45 completed the final scan

· 36 completed the final CAPS

In the upcoming months, recruitment will continue to research new ways to help recruit the target population. Current recruitment possibilities include recruiting in areas where there is a large veteran population. We were able to obtain a list of zip codes where many veterans reside. We will be attending community organizations in those areas to build partnerships that will help with recruitment. For example, new organizations we would like to connect with are post offices, tag agencies, unemployment agencies and laundry facilities in each of these areas.

We also are continuing to hand out surveys to the veterans that participate in the study. The surveys ask the veterans for recruitment suggestions. One recent idea we received from a survey was to attend drill weekend at the National Guard. A veteran suggested for us to teach a class about PTSD during drill weekend, which would allow us to have direct contact with veterans and directly recruit from the base. We are currently trying to connect with bases in the area to see if this may be a possibility.

4. **KEY RESEARCH ACCOMPLISHMENTS:** Bulleted list of key research accomplishments emanating from this research. Project milestones, such as simply completing proposed experiments, are not acceptable as key research accomplishments. Key research accomplishments are those that have contributed to the major goals and objectives and that have potential impact on the research field.

Due to recruitments delays, and continuing data collection, there is nothing to report for the period covered by this report.

5. **CONCLUSION:** Summarize the importance and/or implications with respect to medical and /or military significance of the completed research including distinctive contributions, innovations, or changes in practice or behavior that has come about as a result of the project. A brief description of future plans to accomplish the goals and objectives shall also be included.

Recruitment of veterans continued to be challenging which has resulted in data collection delays, and resulted in our request on June 30, 2015 for a 12-month no-cost extension, which was approved (beyond the original project complete date of Sep 29, 2015). During the last year we have improved our recruitment. We secured even more institutional support for our already very substantial recruitment efforts to further increase our recruitment campaign focused on the veteran population in Oklahoma. Those substantial efforts (as described in this report) improved subject enrollment rate. We anticipate that those efforts will be sufficient and realistic to accomplish our pending aims of this project.

Our other efforts during year 3 have resulted in substantial progress toward accomplishing our aims for this project. With substantial efforts and investments our recruitment efforts improved, and bring us close to completing rtfMRI-nf and EEG experimental Phase 1 of the study. We have further advanced necessary methodological aspects of the study, with a current primary focus on developing and implementing data analysis pipelines, and conducting data analysis on collected multimodal fMRI and EEG data. Preliminary data analysis suggests rtfMRI-nf feasibility, and clinical relevance in reducing PTSD symptoms. For the purpose of accomplishing Aim #2, we have developed a software environment for real-time EEG neurofeedback (rtEEG-nf). Feasibility of rtfMRI-nf amygdala training (with simultaneous EEG recordings) in the combat-related PTSD population (Aim #1), allowed for identification of an EEG signal feature (frontal EEG asymmetry) for the purpose of establishing rtEEG neurofeedback. We have developed and are currently implementing an EEG-nf training paradigm (Aim #3 and Phase 3), and establishing its feasibility among veterans with PTSD. We anticipate that our accomplishments in Years 1 through 3 have situated our successfully collaborating team for further satisfactory progress throughout the remainder of the project period. Therefore, we remain well-positioned to develop and initially test a novel intervention that has the potential to advance both understanding of PTSD and our ability to successfully treat this chronic and costly condition.

6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

a. List all manuscripts submitted for publication during the period covered by this report resulting from this project. Include those in the categories of lay press, peer-reviewed scientific journals, invited articles, and abstracts. Each entry shall include the author(s), article title, journal name, book title, editors(s), publisher, volume number, page number(s), date, DOI, PMID, and/or ISBN.

(1) Lay Press:
(2) Peer-Reviewed Scientific Journals:
(3) Invited Articles:
(4) Abstracts:

b. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.

a. Submitted manuscripts:
Peer-Reviewed Scientific Journals:
1) Wong, C.K., Zotev, V., Yuan, H., Misaki, M., Phillips, R., Luo, Q., Bodurka, J. (2015). An automatic EEG-assisted retrospective motion correction for fMRI (aE-REMCOR) NeuroImage (under revision).
2) Misaki, M., Barzigar, N., Zotev, V., Phillips, R., Cheng, S., Bodurka, J. Real-time fMRI processing with physiological noise correction – Comparison with off-line analysis. (2015) J. Neurosci Methods 356:117-121.

b. Conference abstracts:
1) *Wong, C.K., Zotev, V., Yuan, H., Misaki, M., Phillips, R., Luo, Q., Bodurka, J. (2015). An automatic EEG-assisted retrospective motion correction for fMRI (aE-REMCOR). Poster presented at the 23rd Annual Meeting of the International Society of Magnetic Resonance in Medicine, Toronto, CA. In: Proc. Intl. Soc. Magn. Reson. Med. 23, 2562.

2) Phillips, R., Zotev, V., Young, K., Masaya, M., Wong, C.K., Wurfel, B., Meyer, M., Krueger, F., Feldner, M., Bodurka, J. (2015). Amygdala connectivity after real-time fMRI neurofeedback emotional training in combat-related PTSD. Poster presented at the 23rd Annual Meeting of the International Society of Magnetic Resonance in Medicine, Toronto, CA. In: Proc. Intl. Soc. Magn. Reson. Med. 23, 1360.

3) Zotev, V., H., Phillips, R., Misaki, M., Wong, C.K., Wurfel, B., Meyer, M., Krueger, F., Feldner, M., Bodurka, J. (2015) rtfMRI neurofeedback with concurrent EEG in combat-related PTSD: EEG measure of treatment response. Poster presented at the 23rd Annual Meeting of the International Society of Magnetic Resonance in Medicine, Toronto, CA. In: Proc. Intl. Soc. Magn. Reson. Med. 23, 1366.

4) Mayeli, A., Zotev, V., Refai, H., Bodurka, J. (2015) Evaluation of real-time removal of cardiobalistic artifacts from EEG data acquired during fMRI. Poster presented at the 21st Annual Meeting of the Organization for Human Brain Mapping, Honolulu, USA, In: Conf. Proc. 1830

5) Mayeli, A., Zotev, V., Refai, H., Bodurka, J. (2015) ICA-based automatic artifacts detection and removal from EEG data recorded simultaneously with fMRI. Poster presented at the 21st Annual Meeting of the Organization for Human Brain Mapping, 1831, Honolulu, USA. In: Conf. Proc. 1831.

6) Yuan, H., Phillips, R., Zotev, V., Misaki, M., Wong, C.K., Wurfel, B., Meyer, M., Krueger, F., Feldner, M., Bodurka, J. (2015) Role of anterior cingulate cortex in fMRI neurofeedback training of amygdala in veterans with PTSD. Poster presented at the 21st Annual Meeting of the Organization for Human Brain Mapping, Honolulu, USA. In: Conf. Proc. 1024.

7) Yuan, H., Phillips, R., Zotev, V., Misaki, M., Wong, C.K., Wurfel, B., Meyer, M., Krueger, F., Feldner, M., Bodurka, J. (2015) Tracking resting state connectivity dynamics in veterans with PTSD: new insights from EEG-fMRI. Poster presented at the 21st Annual Meeting of the Organization for Human Brain Mapping, Honolulu, USA. In: Conf. Proc. 1931.

c. Conference presentation:

1) Bodurka, J. (2015). Emotional regulation training of amygdala using real-time fMRI and EEG-assisted neurofeedback in combat-related PTSD. Talk at the 31st Annual Meeting of the International Society for Traumatic Stress Studies, New Orleans, Louisiana, USA.

2) Bodurka, J. (2015). Emotional regulation training for treating warfighters with combat-related PTSD using real-time fMRI and EEG-assisted neurofeedback. Progress report presented at the MOMRP PTSD Biomarkers IPR annual meeting, Ft. Detrick, MD.

7. **INVENTIONS, PATENTS AND LICENSES:** List all inventions made and patents and licenses applied for and/or issued. Each entry shall include the inventor(s), invention title, patent application number, filing date, patent number if issued, patent issued date, national, or international.

Nothing to report.

8. **REPORTABLE OUTCOMES:** Provide a list of reportable outcomes that have resulted from this research. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. This list may include development of prototypes, computer programs and/or software (such as databases and animal models, etc.) or similar products that may be commercialized.

1) Enhanced an automated implementation of EEG-assisted retrospective motion correction (E-REMCOR), which utilizes EEG motion artifacts to correct the effects of head movements in simultaneously acquired fMRI data on the slices-by-slice basis [27]. The automated implementation of E-REMCOR, referred to as aE-REMCOR, was developed to facilitate the application of E-REMCOR in multimodal brain research and in particular in large-scale clinical EEG-fMRI studies. The aE-REMCOR algorithm, implemented in MATLAB, enables automated preprocessing of the EEG data, ICA decomposition, and, importantly, automatic, computer-based, identification of motion-related ICs. We evaluated our automatic and novel algorithm on 305 EEG & fMRI data sets. We found that aE-REMCOR is capable of substantially reducing head motion artifacts in fMRI data. We applied the method on all currently acquired fMRI and EEG data from veterans with combat-related PTSD.
2) We have developed a stand-alone real-time EEG neurofeedback system, which includes a novel algorithm for better detection and correction of motion artefacts in real-time EEG data. We utilized moving window standard deviation and spline interpolation for better detection and correction of motion artefact in EEG data. This algorithim will be an important addition to the real-time EEG data correction pipeline for the purpose EEG neurofeedback experiments (Aim #3).
3) Abnormal brain resting state connectivity dynamics in PTSD: novel insights from simultaneous EEG and fMRI. We have conducted an exploration multimodal analysis on the

EEG-fMRI data collected during resting scans in groups of unmedicated veterans with combat-related PTSD and healthy veterans. This novel analysis approach using temporal independent EEG microstates (EEG-ms) [16] to study default mode network activity (DMN) activity. We found that resting state functional connectivity at the bilateral middle temporal gyrus and the posterior cingulate cortex was reduced in veterans with combat-related PTSD as compared to the healthy veterans. From the simultaneously acquired EEG-fMRI data we identified temporal independent EEG microstates whose temporal dynamics evolve at much faster scale and yet we found EEG-ms that is correlated with the fMRI DMN network. The occurrence ratio of this EEG-ms statistically differentiates between PTSD and HC group. Additionally the occurrence ratio negatively correlates with Hamilton Anxiety Rating Scale scores in veterans with PTSD. Importantly, the abnormally decreased functional connectivity in veterans with PTSD observed via fMRI was associated with a decreased occurrence ratio of DMN-related EEG-ms, which suggests the relocation of neural processing resources associated with the PTSD condition.

9. **OTHER ACHIEVEMENTS:** This list may include degrees obtained that are supported by this award, development of cell lines, tissue or serum repositories, funding applied for based on work supported by this award, and employment or research opportunities applied for and/or received based on experience/training supported by this award.

   Nothing to report.

10. REFERENCES: List all references pertinent to the report using a standard journal format (i.e., format used in *Science*, *Military Medicine*, etc.).

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11. **APPENDICES:** Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

NOTE:

TRAINING OR FELLOWSHIP AWARDS: For training or fellowship awards, in addition to the elements outlined above, include a brief description of opportunities for training and professional development. Training activities may include, for example, courses or one-on-one work with a mentor. Professional development activities may include workshops, conferences, seminars, and study groups.

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on this eReceipt System https://cdmrp.org/Program_Announcements_and_Forms/ and under "Forms" on https://www.usamraa.army.mil) should be updated and submitted with attachments.

MARKING OF PROPRIETARY INFORMATION: Data that was developed partially or exclusively at private expense shall be marked as "Proprietary Data" and Distribution Statement B included on the cover page of the report. Federal government approval is required before including Distribution Statement B. The recipient/PI shall coordinate with the GOR to obtain approval. REPORTS NOT PROPERLY MARKED FOR LIMITATION WILL BE DISTRIBUTED AS APPROVED FOR PUBLIC RELEASE. It is the responsibility of the Principal Investigator to advise the GOR when restricted limitation assigned to a document can be downgraded to "Approved for Public Release." DO NOT USE THE WORD "CONFIDENTIAL" WHEN MARKING DOCUMENTS. See term entitled "Intangible Property – Data and Software Requirements" and https://mrmc.amedd.army.mil/index.cfm?pageid=researcher_resources.technical_reporting for additional information.

1) Zotev, V., Yuan, H., Misaki, M., Phillips, R., Young, K.D., Feldner, M.T. Bodurka J.. Correlation between amygdala BOLD activity and frontal EEG asymmetry during real-time fMRI neurofeedback training in patients with depression. 2015 *NeuroImage Clinical* (under review),

Preprint available at: http://www.arxiv.org/abs/1409.2046