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14. ABSTRACT Posttraumatic Stress Disorder (PTSD) is a severe disorder that may develop after a person is exposed to one or more traumatic events. Research suggests that approximately 70% of U.S. Military Service Personnel will be exposed to at least one traumatic event during their active duty military service and a significant number of these individuals will develop PTSD as a result of this trauma exposure. Current treatments are effective for many individuals, however, there is a need for new treatment approaches to improve outcomes in PTSD and address the many existing barriers that prevent many individuals from seeking or completing treatment. In this reading study,

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Final Report: Affect Labeling: A Promising New Approach for Mitigating PTSD

ABSTRACT

Posttraumatic Stress Disorder (PTSD) is a severe disorder that may develop after a person is exposed to one or more traumatic events. Research suggests that approximately 70% of U.S. Military Service Personnel will be exposed to at least one traumatic event during their active duty military service and a significant number of these individuals will develop PTSD as a result of this trauma exposure. Current treatments are effective for many individuals, however, there is a need for new treatment approaches to improve outcomes in PTSD and address the many existing barriers that prevent many individuals from seeking or completing treatment. In this seedling study, we tested a novel, brief, partially-automated, computer-based intervention for PTSD utilizing "Affect Labeling" that was inspired by recent advances in neuroscience research. We found that our affect labeling intervention reduced PTSD symptoms as well as hyperreactivity in fear-related brain regions in a sample of Veterans with combat-related PTSD. Results from the seedling study are compelling and suggest that affect labeling training offers significant potential as a novel, cost-effective, computer-based, intervention for PTSD. Specific next steps for further developing this affect labeling intervention are presented.

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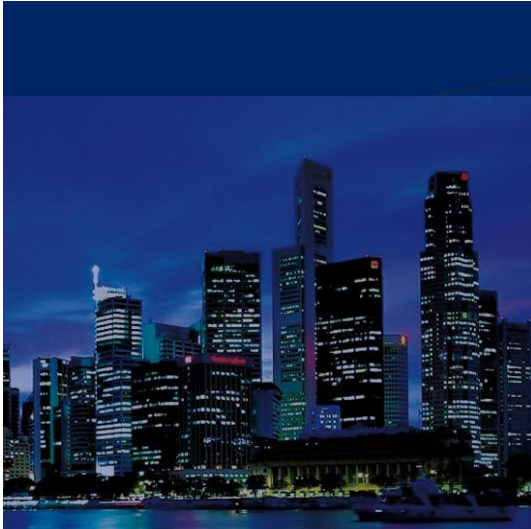
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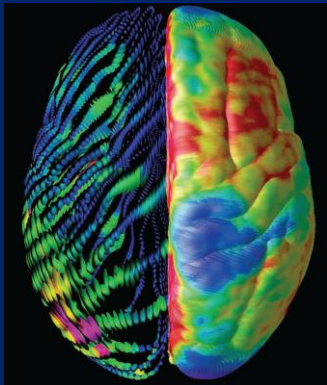
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Affect Labeling: A Promising New Approach for Mitigating PTSD

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Contractor Address:

C. Bryan Gabbard
Defense Group Inc.
429 Santa Monica Blvd., Suite 460
Santa Monica, CA 90401
310-394-8599 | gabbard@defgrp.com

DGI Business Contact:

Lou Elias
Defense Group Inc.
2650 Park Tower Drive, Suite 400
Vienna, VA 22180
571-421-8342 | 571-421-8294 (fax)
lou.elias@defensegrp.com

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1.0 Statement of the Problem Studied

1.1 Posttraumatic Stress Disorder is Widespread and Costly; Additional Effective Treatments are Needed

Posttraumatic Stress Disorder (PTSD) is a severe disorder that may develop after a person is exposed to one or more traumatic events involving actual or threatened physical injury or death. It is theorized that the fear response to the trauma(s) becomes generalized and causes the fear-response system to become hypersensitive, leading to inappropriate or excessive fear responses to trauma-related (and even non-trauma-related) stimuli. Common symptoms involve frequent intrusive thoughts, images, or flashbacks of the event, along with chronic fear and anxiety that may cause the individual to avoid activities, feel emotional numbness, experience negative alterations in thoughts and emotions, and experience states of hyper-vigilance or hyper-arousal.

Research suggests that approximately 70% of U.S. Military Service Personnel will be exposed to at least one traumatic event during their active duty military service (Dedert et al., 2009). Of these individuals, 29% will develop PTSD as a result of this trauma exposure (Hoge et al., 2004), representing a 400-700% increase in the rate of military PTSD since prior to 2001. PTSD is associated with several adverse consequences including significant distress, decreased quality of life, increased unemployment, homelessness, increased substance abuse, and impairments in marital, family, academic, and occupational functioning. PTSD is also strongly linked to physical health problems (Ouimette et al., 2004; Possemato et al., 2010). There is thus a compelling need for PTSD interventions/treatments that can mitigate maladaptive responses to trauma.

1.2 Existing Treatments for PTSD: Need for Alternative Strategies

The gold standard psychosocial treatments for PTSD include cognitive behavioral therapy (CBT) and related exposure-based therapies (e.g., Prolonged Exposure), which fundamentally involve some form of ‘exposure’ to trauma memories, in what is colloquially known as “facing your fears to conquer them” (e.g., Foa, Keane, Friedman, & Cohen, 2008). Cognitive processing therapy (CPT) is another effective treatment for PTSD and, while less emphasized, also typically involves some form of exposure (e.g., in the form of narrative writing). However, non-response rates for even these most effective types of treatment are estimated to be as high as 25-50%. Pharmacotherapy has also shown limited success in treating PTSD, with a similar non-response rate of 40%. Importantly, these treatment failure rates do not take into account the many individuals who do not seek treatment for their PTSD. Barriers to treatment include resistance to cognitive behavioral therapies (Foy et al., 1996), decreased treatment seeking due to the stigma of PTSD (Hoge et al, 2004), negative perceptions among veterans regarding treatment availability and quality (Desai et al., 2005), and logistical issues such as scheduling difficulties and inadequate transportation. Additional issues include the lack of clinicians trained in exposure-based therapies, costs associated with training clinicians, costs associated with one-on-one therapies with trained clinicians, and lack of implementation of effective exposure-based strategies by trained personnel due to

unfounded concerns of iatrogenic effects and contraindications (Becker et al., 2004). Barriers associated with pharmacological treatments are equal if not greater and include resistance to medications, side effects, and contraindications.

Clearly, there is a need for new treatment approaches to improve outcomes in PTSD, particularly cost-effective treatment programs that are easily accessible and appealing for individuals who may be otherwise disinclined to pursue formal mental health services. In fact, there has recently been an increase in the development of treatments that attempt to address some of the aforementioned barriers to treatment. Such approaches include exposure-based treatments delivered via brief interventions (e.g., Gunn & Blount, 2009) and distance/home-based telehealth (e.g., through video conferencing, Yuen et al., 2015), both of which appear to represent effective adaptations in preliminary studies with small samples. Another important approach for improving treatment response rates in PTSD requires development of alternative strategies that either replace or augment the “exposure” component of existing treatments. Of the studies to date exploring alternative strategies, some appear to hold promise (e.g., mindfulness: Polusny et al., 2015) and others still lack sufficient data (e.g., art therapy).

In this seedling study, we aimed to address many of these issues by testing a novel, brief, partially-automated, computer-based intervention for PTSD utilizing “Affect Labeling.”

1.3 Using Neuroimaging to Guide Novel Treatment Development

Basic and clinical neuroscience research has provided a unique window into psychopathology and its treatment. With the use of non-invasive tools such as functional magnetic resonance imaging (fMRI) in particular, neuroscience-based approaches have allowed us to examine neural structure and function in patient and healthy populations, thereby yielding invaluable insights into the etiology and mechanisms of clinical disorders and symptoms. As a result, more and more researchers and clinicians have been using neuroscience to guide and validate treatment strategies for a variety of clinical disorders, including PTSD.

As discussed above, a core component of PTSD is an inability to effectively down-regulate negative emotions in response to trauma reminders. An innocuous stimulus may trigger an individual with PTSD to react as if he/she is in danger. This phenomenon is theorized to involve increased reactivity of the primitive neural regions that mediate threat response as well as decreased efficacy of top-down neural regulatory control regions that dampen such responses appropriately. In other words, PTSD can be characterized as involving both a hypersensitive danger “alarm system” as well as a dysfunctional system for shutting off the alarm when there is no real danger present.

Neuroimaging research supports this theoretical framework in that it has shown that individuals with

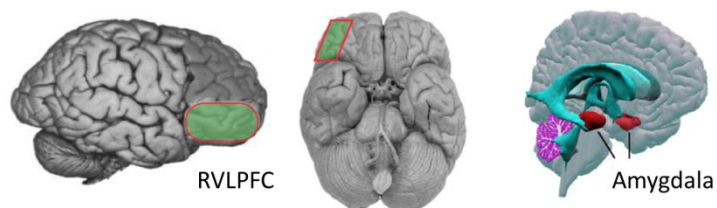


Figure 1. Brain Regions of Interest

PTSD exhibit heightened responsivity of the amygdala during trauma-related and other emotional processing (Hayes et al., 2012). The amygdala is a bilateral structure of the more primitive limbic system involved in the acquisition and detection of learned fear responses such as those that characterize PTSD (LeDoux, 1998). Previous research has also shown PTSD to be associated with impaired down-regulation or ‘extinction’ of amygdala-based fear responses by the ventral medial prefrontal cortex (VMPFC; Milad et al., 2009). The VMPFC is theorized to play a fundamental role in the extinction or suppression of fear-related memories by facilitating the creation of new neural associations that re-characterize the trauma reminder as benign. This process thereby represents a key neural mechanism of CBT and other exposure-based treatments which ostensibly represent the in-vivo application of extinction learning. However, as described above, many PTSD patients fail to respond to existing treatments, and therefore it is essential to explore additional neural pathways.

Recent research suggests that a *distinct lateral PFC route*, involving *ventral lateral PFC* (VLPFC) control over the amygdala, may also be compromised in PTSD. **Our recently-completed DARPA-funded seedling study was the first to specifically target the VLPFC in a PTSD intervention, and has yielded exciting evidence of reduced PTSD symptoms in a sample of Veterans with combat-related PTSD.**

1.4 Affect Labeling via the VLPFC as a Novel Intervention for PTSD

Our recently-completed seedling study was inspired by two distinct lines of neuroimaging research. First, much previous work in the fields of cognitive and affective neuroscience had identified the VLPFC, particularly in the right hemisphere (RVLPFC), as central to *inhibitory regulation* in healthy individuals. Inhibitory regulation or inhibitory control refers to the disruption, suppression, or prevention of prepotent responses to maintain goal-directed behavior, and operates across multiple domains (e.g., emotional, cognitive, motor).

In particular, we pioneered research on *affect labeling* as a form of *emotional* inhibitory regulation (Lieberman et al., 2007). Affect labeling involves labeling the emotional content of a stimulus or labeling how one is feeling in response to a stimulus. Affect labeling is a form of emotional inhibitory regulation in that it engages the RVLPFC and down-regulates the amygdala in healthy individuals (Lieberman et al., 2007), an effect that has been observed many times in both our own and other labs (e.g., Burklund et al., 2014; Foland et al., 2008; Gee et al., 2012; Hariri et al., 2000; Hariri et al., 2003; Lieberman et al., 2005; Payer et al., 2012). Importantly, a seminal study by Lieberman and colleagues (2007) demonstrated the specificity of affect labeling in the RVLPFC-down-regulation of amygdala responses in that other control conditions involving non-emotional linguistic processing (gender labeling) or non-linguistic perceptual processing (affect matching or passive observation) did not yield the same amygdala-modulatory effects. Additionally, a recent study in our lab using dynamic causal modeling confirmed a causal inhibitory role for RVLPFC in down-regulating the amygdala during affect labeling (Torrissi et al., 2013). Additional behavioral studies have provided evidence to

suggest that the emotion modulatory effects of affect labeling may be maintained over time, in terms of psychophysiological and behavioral responding (Kircanski et al., 2012; Tabibnia et al., 2008), however, none had examined the effects of repeated affect labeling training.

It is not particularly surprising that the simple process of affect labeling is effective in down-regulating amygdala/affective responses. Indeed, affect labeling may represent a core process of the long-held folk wisdom that talking about your feelings will make you feel better, and thereby constitute a mechanism of many forms of psychotherapy. Humans are distinctively able to think symbolically and to use language to express and regulate emotion.

In separate clinical work, PTSD had also been associated with impairments in inhibitory processing at the behavioral level (Aupperle et al., 2012; Falconer et al., 2008; Swick et al., 2012; Wu et al., 2010) as well as impairments in inhibitory processing involving the RVL PFC (Falconer et al., 2008; Hayes, 2009; 2012). For example, previous neuroimaging studies had shown that, relative to healthy subjects (trauma-exposed but without PTSD), PTSD subjects exhibited abnormally diminished RVL PFC activity in motor control inhibition tasks (Falconer et al., 2008) and when imagining their trauma (Hayes, 2012). The latter result in particular suggests that individuals with PTSD may be less effective at or less prone to inhibiting negative emotional responses when faced with trauma reminders. However, given that this study did not direct participants to use a specific emotional inhibition strategy when thinking about their traumas, conclusions about what processes they were actually using are limited. Importantly, no previous PTSD studies had directly and quantitatively examined the neural mechanisms of emotional inhibitory regulation of the amygdala-mediated fear response by the RVL PFC prior to our seedling study.

1.5 Aims/Overview of Seedling Study

Synthesizing previous findings, we set out to investigate two primary aims in the seedling study:

Aim #1: Examine whether impaired RVL PFC inhibitory control of the amygdala is one of the mechanisms underlying PTSD symptoms.

Aim #2: Test whether individuals with PTSD exhibit improvements in RVL PFC activation, amygdala down-regulation, or PTSD symptoms following repeated practice with affect labeling, which would ostensibly strengthen RVL PFC-based inhibitory capacity.

To investigate these questions, we had veterans with PTSD and veterans with trauma exposure but no PTSD (“healthy controls” or “HC”) complete a baseline assessment involving a clinical interview, questionnaires, and an fMRI scan. Those with PTSD then underwent 3 weeks of twice-weekly affect labeling training, followed by a post-training assessment similar to the baseline assessment to allow us to assess effects of the training. The affect labeling training in the seedling study involved 6 one-hour sessions during

which participants sat in front of a computer, while an automated program presented several images and the participants used affect labeling and related inhibitory regulation strategies in processing various stimuli.

2.0 Summary of the Most Important Results

2.1 Key Research Methods

A detailed description of the methods and materials used during this research study are given in the Appendix. A brief summary is provided here.

Participants in this study included veterans with PTSD or Other Trauma-Related Disorder as well as veterans with trauma exposure but no PTSD (representing a trauma-exposed healthy control group). Following a phone screening and in-person clinical interview to determine eligibility and diagnostic status, eligible participants underwent a baseline fMRI scanning session during which they completed multiple tasks, including an affect labeling task. Participation was complete for the healthy controls following the baseline fMRI scan. For participants with PTSD, following the baseline fMRI scan, they completed a three-week affect labeling training intervention. The affect labeling training intervention includes six sessions completed over approximately three weeks beginning one week after the baseline fMRI scan. During each affect labeling training session, participants viewed different types of emotionally-evocative images and were asked to describe how they were feeling in response to viewing each image (i.e., use affect labeling to describe their feelings). Images included combat scenes (representing trauma-relevant images), other negative scenes (representing aversive but non-trauma-relevant images), and negative facial expressions. Participants also completed trials of a non-emotional motor inhibition task. Following the three-week training, participants with PTSD underwent a second fMRI scanning session, identical to the first. Participants with PTSD then underwent a second clinical interview one month after completion of the last training session, to assess any changes in clinical status or symptoms.

2.2 Findings

A total of 20 Veterans with PTSD or Other Trauma-Related Disorder (PTSDs) and 20 Veterans without PTSD (healthy controls or HC) were enrolled in the study. Of note, all participants were veterans with deployment experience, mostly to Iraq and/or Afghanistan, and all participants including the HCs must have been exposed to a trauma that was combat-related, satisfying criterion A of DSM-5 criteria. Thus, the HC group is considered a trauma-exposed healthy control group. The HCs had no current or lifetime psychiatric diagnoses whereas PTSDs had to meet DSM-5 criteria for PTSD (N=13) or Other Trauma-Related Disorder (N=7)¹.

As shown in Table 1, HC and PTSD participants were similar in terms of age, gender breakdown, and years of active duty. As expected, the PTSD group has significantly higher scores on the Clinician-Administered PTSD Scale-5 (CAPS-5) as well as the PTSD Checklist-5 (PCL-5). The CAPS-5 reflects a clinician's rating of the severity and frequency of 20 PTSD symptoms as per the DSM-5, whereas the PCL-5 is a self-report

¹ Participants who met criteria for Other Trauma-Related Disorder but not full PTSD typically did not meet full criteria for certain symptoms clusters, but nonetheless had clinically-significant distress or impairment that warranted treatment.

measure asking participants to rate how much they were “bothered” by the same 20 PTSD symptoms.

	HC	PTSD all	PTSD Completers		PTSD Drops	
	Baseline (Time 1)	Baseline (Time 1)	Baseline (Time 1)	Post (Time 2)	Baseline (Time 1)	Post (Time 2)
N	20	20	13		7	
Gender (M/F)	16/4	18/2	12/1		6/1	
Age range	23-44	22-45	22-45		26-35	
Age	31.15 (5.21)	31.40 (6.21)	31.54 (7.47)		31.14 (3.23)	
Yrs Active Duty	4.6 (2.25)	5.60 (3.34)	5.23 (3.53)		6.29 (3.09)	
CSR	.10 (.308)	4.95 (1.64)	5.23 (1.24)	3.73 (1.79)	4.43 (2.23)	n/a
CAPS-5	3.25** (3.02)	26.85** (12.00)	25.62 φ (11.61)	19.42 φ (9.52)	29.14 (13.31)	n/a
PCL-5	11.25** (10.31)	38.68** (19.28)	41.38* (19.83)	28.77* (18.89)	33.65 (18.56)	n/a

Table 1. Demographic and clinical data from the seedling study. ** Significant difference between HCs and PTSDs at baseline ($p < .005$); * Significant reduction from Baseline to Post in Completers ($p < .05$); 3 individuals’ PCL-5 score from post fMRI session rather than one-month post; φ Marginally significant reduction from Baseline to Post ($p = .079$); $N = 12$ for post-CAPS-5 as missing for 1 participant;

With respect to the neural data at baseline, participants with PTSD exhibited amygdala hyperreactivity relative to the healthy controls when passively viewing combat scenes (i.e., trauma-relevant stimuli), consistent with previous related research (see Figure 2).

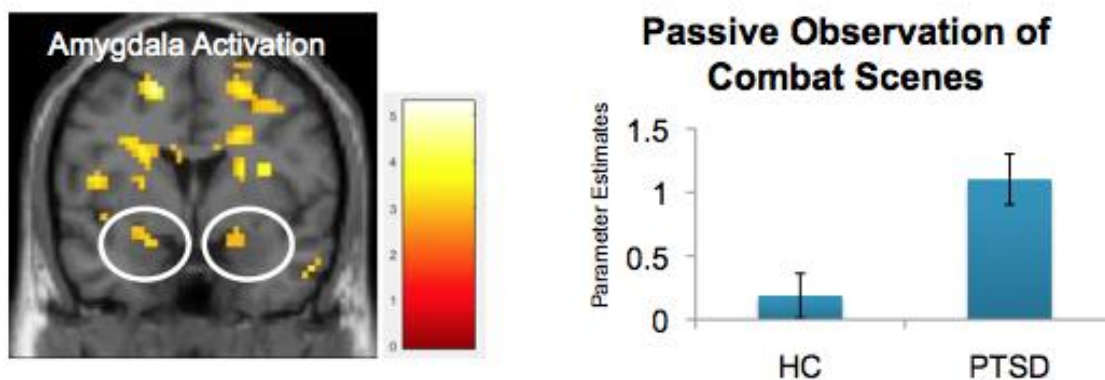


Figure 2. Significantly greater amygdala activity was seen in bilateral amygdala in PTSDs relative to HCs during passive observation of combat scenes ($p < .005$, whole-brain). MR image on the left shows activations clusters, and extracted parameter estimates are plotted on the right.

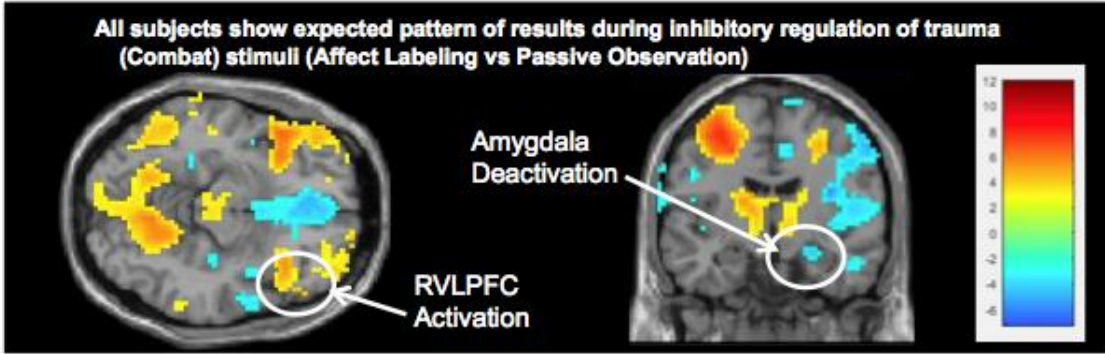


Figure 3. MR images showing results collapsed across all subjects (PTSD&HC) at baseline showing RVL PFC activation and amygdala deactivation ($p < .005$, whole-brain). Patterns for each group individually are similar.

However, when veterans were asked to use affect labeling to describe how they were feeling in response to aversive combat images, also during the baseline fMRI scan, we found that those with PTSD were able to engage the RVL PFC and down-regulate amygdala responses to the trauma images as effectively as the healthy controls. Figure 3 shows the pattern of RVL PFC activation and amygdala deactivation seen in both groups.

These fMRI results at baseline suggest that although individuals with PTSD exhibited hyperreactivity of the amygdala to trauma images when they were left to their own devices to deal with trauma reminders, they appeared to have an intact RVL PFC inhibitory control mechanism for down-regulating amygdala responses to the trauma images when specifically told to use affect labeling.

We next examined what happened when Veterans with PTSD were given repeated practice with inhibitory regulation via six sessions of affect labeling training.

Affect labeling training consisted of 6 one-hour sessions completed approximately twice a week for three consecutive weeks. During each session, participants viewed stimuli presented on a computer screen for 40 minutes per session. There were four types of inhibitory processing tasks included in the training sessions, including affect labeling of combat scenes (see Figure 4 for an example), affect labeling of negative non-combat scenes, affect labeling of emotional faces, and a Go-NoGo motor inhibition task.



Figure 4. Sample screen from Affect Labeling training. Participants are asked to think about how each image makes them feel and then choose an emotion word that best describes how they feel.

Overall, as shown in Table 1, of 20 veterans who completed the baseline assessment, 13 completed all six sessions of the AL training, reflecting a 65% retention rate which is similar to rates for cognitive behavioral therapy (CBT).

Using multiple measures to assess PTSD symptoms, we found **significant reductions in PTSD symptoms following the AL training**. First, we examined clinical severity ratings (CSRs), which represent a trained clinician’s overall assessment of PTSD severity on a scale from 0-8, where 4 or higher represents clinically significant symptom severity, distress, and impairment in functioning. We found that 67% of participants (8/12) showed improvement or decreased PTSD severity, and 42% (5/12) no longer had

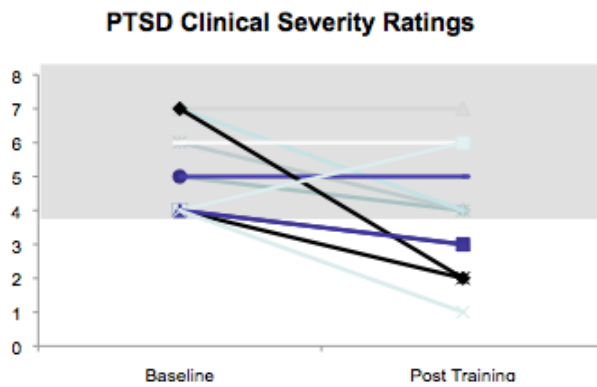


Figure 5. Reduction in PTSD symptoms after AL Training as indexed by Clinical Severity Ratings. Shaded area represents clinically-significant severity, distress, or impairment

clinically-significant PTSD or other Trauma-Related Disorder (see Figure 5). This rate of diagnostic change is remarkable given how minimal this intervention was in terms of both patient and clinician time. Specifically, in our study, Veterans completed a total of 6 one-hour sessions, plus two 1-hour fMRI sessions, all of which involved automated delivery of computer-based stimuli. As a comparison, the rate for standard CBT, which involves 12-16 weekly hour-long sessions with a trained clinician, has been reported as 59%.

Of the remaining participants who completed the treatment, 25% (3/12) had no change in their overall clinical rating, and 8% (1/12) experienced an increase in PTSD symptoms. (N=12 for these data as Post-AL training clinician-rated data was missing for one participant.)

The pattern of improvement was similar for both the CAPS-5 and PCL-5 (see Figure 6).

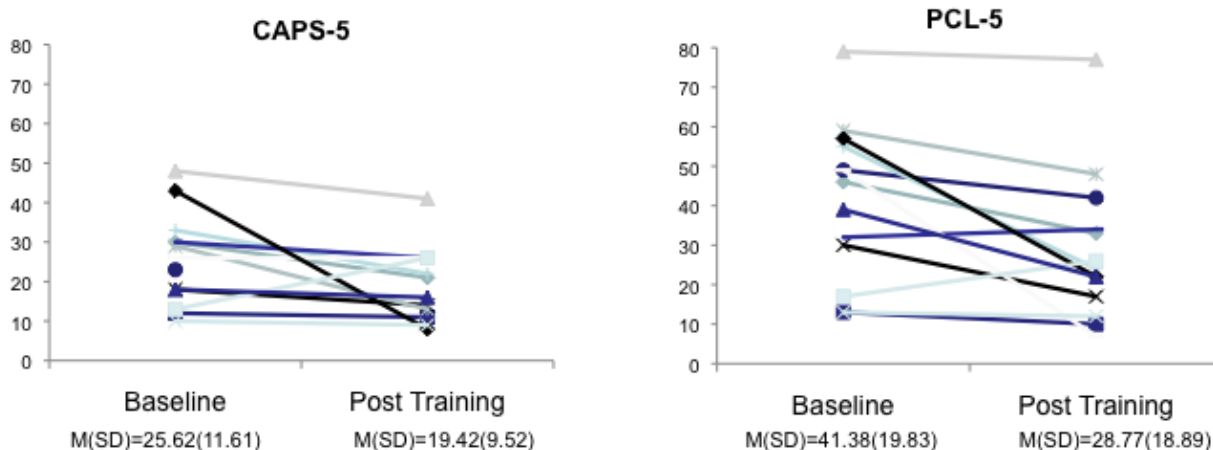


Figure 6. Reduction in PTSD symptoms after AL Training as indexed by clinician-rated CAPS-5 scores (left) and participant-rated PCL-5 scores (right).

Looking at changes in neural activity following training, we found that there was a significant reduction in amygdala reactivity (during passive viewing of combat images) from pre to post AL training. Importantly, we also found that this decrease in amygdala reactivity from pre to post AL training was correlated with reduction in PTSD symptoms (using CAPS-5 scores; see Figure 7). Thus, **to the extent that AL training reduced amygdala reactivity, there was a proportionate reduction in PTSD symptoms**, which suggests that in addition to changes in PTSD symptoms, AL training also appears to lead to meaningful changes in the brain. A manuscript detailing results from the seedling study is in preparation for publication in a peer-reviewed journal.

2.3 Key Remaining Unknowns and Future Directions

Results from the seedling study are compelling and suggest that AL training as a treatment for PTSD warrants further investigation. The seedling study was an initial proof-of-concept study involving a relatively small sample of Veterans with PTSD. An examination of the seedling study limitations and remaining unknowns will help guide our next steps.

One of the key remaining unknowns is the precise neural and psychological mechanisms by which AL training is effective. This is important to understand in order to refine and optimize the intervention to increase effects. The AL training included an exposure element in that participants were instructed to practice affect labeling while observing trauma-relevant images. Thus, some may argue that despite the theoretical emphasis on affect labeling, the seedling intervention may be merely another form of exposure therapy. If so, then this intervention nonetheless has value, primarily in its brief, standardized, cost-effective approach to exposure therapy. However, we hypothesize that the affect labeling component constitutes an important augmentation and plan to tease apart the additive effects of affect labeling in future work.

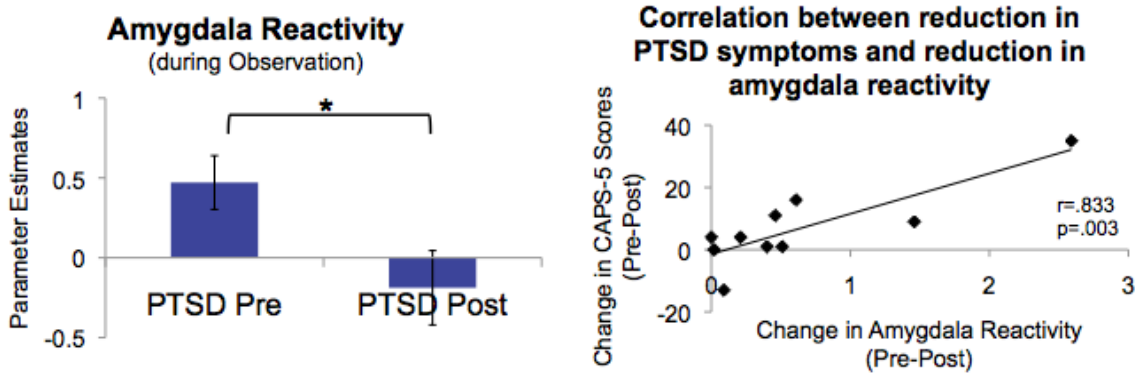


Figure 7. Amygdala activity is significantly reduced from pre to post AL training for Veterans with PTSD during passive observation of combat images (Left); and this reduction in amygdala activity is significantly correlated with reduction in PTSD symptoms (Right).

One possibility is that affect labeling increases participants’ engagement with the trauma stimuli (i.e., attention to and encoding of), thereby increasing meaningful exposure to feared stimuli (in the absence of the feared outcome) and facilitating extinction learning. Previous research on exposure-based interventions suggests that enhanced engagement during exposure is associated with better outcomes. During each session of our affect labeling intervention, participants had to perceive the stimuli, think about how they were feeling in response to it, and then produce an observable behavioral response to characterize their responses (e.g., selecting “I am anxious” from possible options on a computer screen), which clearly requires more attention and engagement with the stimuli than if they instead had to simply view it. In the latter case (which would represent exposure alone), one could easily distract oneself with other thoughts or even close his/her eyes and avoid the stimuli altogether since compliance would not be clearly reflected by participants’ behavioral responses.

Alternatively, or in addition to increasing engagement with the stimuli, affect labeling may yield effects entirely independent of exposure/extinction learning processes. Given that individuals with PTSD appeared to have an intact mechanism for using affect labeling to inhibit amygdala responses on demand, it may be the case that AL training is effective by increasing participants’ spontaneous use of affect labeling or RVL PFC inhibitory regulation at either a conscious or unconscious level. This may then result in more effective management of anxiety symptoms or prevention of initial threat responses from escalating into excessive anxiety.

Alternatively, AL training may directly increase the efficiency or efficacy of the RVL PFC to dampen amygdala responses when necessary via changes in the timing of neural responses or functional or structural connectivity. Although in the seedling study we did not observe significantly less engagement of RVL PFC or down-regulation of the amygdala during affect labeling in individuals with PTSD at baseline compared with healthy controls, there may still be impairments in the neural mechanisms of affect labeling that are either mended or overcome with compensatory changes following affect

labeling training. For example, the observed RVL PFC engagement in PTSD individuals, although similar in average magnitude to the healthy controls, may have been insufficient to handle their exaggerated fear responses. There may also be differences in the time course of neural patterns during affect labeling. In the seedling study, fMRI stimuli were modeled using a blocked design wherein several trials were lumped together in order to maximize signal to noise ratio and thus increase our chances of observing differences in activations across the two groups of participants. However, differences in the timing of activations, such as the speed with which the RVL PFC dampens the amygdala on an individual trial basis, is obscured by a blocked-design approach. In fact, research with social anxiety disorder has found that during emotional regulation in particular, there are differences in the timing of neural responses more so than differences in overall activation magnitudes such that prefrontal regulatory responses were slower in the anxiety-disordered group (e.g., Goldin et al., 2009). Such differences may have profound impacts on resulting processes. For example, down-regulation of the amygdala may be too delayed in individuals with PTSD to prevent the full expression of fear responses (e.g., behavioral, autonomic, and neuroendocrine responses) that are initiated by the amygdala. Consistent with this finding, research with phobic participants has shown that the duration of amygdala activation to threat stimuli is extended relative to that of healthy controls (Larson et al., 2006). Finally, there may be differential neural connectivity patterns between the groups that render affect labeling more effective in those without PTSD despite similar overall activation patterns.

Other factors that remain unknown include the extent to which we can increase the effects of the intervention by personalizing or enhancing intervention components, whether we can predict who will respond to this particular intervention, and whether the intervention can be effectively and safely adapted into a remote/web-based intervention in order to increase access to treatment.

Finally, there are important limitations of the seedling study worth noting. Although the participants' PTSD severity ranged from mild to severe, most participants' PTSD was mild to moderate, likely in part due to the study being advertised as a research study rather than a treatment study. Thus, in follow up work, it will be essential to enroll a much larger sample of veterans across the full range of severity in order to insure generalizability across the full range of severity. Nevertheless, there is value in a treatment that may be effective for only mild and moderate PTSD. For example, in Kessler et al., 2005, which presents results from the US National Comorbidity Survey Replication, a breakdown of PTSD severity showed that approximately 2/3 of PTSD cases would be considered mild to moderate. Additional limitations include the strict exclusion criteria of the seedling study (e.g., no more than mild TBI, exclusion for fMRI contraindications such as shrapnel injuries and metallic implants), the lack of an AL training control group, and the small sample size. All of these limitations will be addressed in follow-up work.

3.0 Recommended Next Steps

Affect Labeling training offers significant potential as a novel, cost-effective, computer-based, intervention for PTSD. In follow-up work, we plan to build upon the seedling study by developing and testing an enhanced AL Training intervention that can be delivered in person as well as via a remote/web-based interface. We plan to refine the AL intervention itself by personalizing the images shown to each participant in order to optimize responses during the intervention and thereby improve outcomes. We will also enhance the general potency of the AL intervention by determining which intervention components are most potent and subsequently maximize these elements. We will also test the feasibility of a remote/web-based version of the AL intervention and further pinpoint psychological and neural mechanisms of the intervention in order to maximize its effects.

The key benefits of the proposed enhanced affect labeling intervention include significantly reduced overall patient and clinician time, and, thus, a reduction in treatment cost. Other benefits include minimal training for staff implementing the intervention, and a remote web/app-based format that can reach many more individuals suffering with PTSD. Additionally, our follow up work will also identify markers that predict who will respond best to an affect labeling intervention.

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APPENDIX – METHODS AND MATERIALS

Overview and Participants

General Procedures and Timing of Sessions.

Following a phone screening and in-person clinical interview to determine eligibility, eligible participants underwent a baseline fMRI scanning session during which they completed multiple tasks, including a Combat Affect Labeling task. Participation was complete for HCs following the baseline fMRI scan. For participants with PTSD, following the baseline fMRI scan, they completed a three-week affect labeling training intervention. Following the three-week training (described below), participants with PTSD underwent a second fMRI scanning session, identical to the first, 1-2 weeks following the last training session. Participants with PTSD then underwent a second clinical interview one month after completion of the last training session, to assess any changes in clinical status or symptoms.

Participants Overview.

Participants (Ps) were Veterans with PTSD or other Trauma-Related Disorder (PTSDs) as per DSM-5 or Veterans with trauma exposure but no PTSD (healthy or “HCs”). The use of a healthy trauma-exposed veteran group allowed us to control for the effects of the trauma exposure itself, and thereby isolate differences due to PTSD (i.e., maladaptive response to trauma). Such an approach is consistent with previous studies examining the neural and behavioral mediators of PTSD.

Inclusion Criteria.

- (1) All Ps were veterans with deployment experience.
- (2) Ps met DSM-5 criterion “A” for PTSD, which requires exposure to a traumatic event. This trauma must have been combat-related and during military service, but may have taken a variety of forms (e.g., injury to self, witnessing death of another, etc.).
- (3) Ps were 18-45 years old since normal age-related structural and functional variations in participants above and below this age range could prevent accurate comparison of neural activity across participants.
- (4) Ps were English-speaking as translation of all study materials into other languages would be cost-prohibitive.
- (5) Both male and female participants were allowed.
- (6) Ps were right-handed in order to allow comparison of neural activity across participants.
- (7) PTSD participants only: PTSD Ps met DSM-5 criteria for PTSD or other Trauma-Related Disorder with a combat-related trauma related to their military service, as assessed by the CAPS, and did not meet criteria for the Dissociative subtype.
- (8) HC participants only: HC Ps must not have met DSM-5 criteria for current/lifetime PTSD or any other current Axis I disorders.

Exclusion Criteria for All Participants.

- (1) Ps had no metallic implants or other non-removable metal in the body (e.g., shrapnel, surgical staples or screws, etc.) as this would preclude them from undergoing any

MRI scanning.

- (2) Ps must not have been claustrophobic in order to be able to complete all fMRI procedures.
- (3) Ps must not have been pregnant.
- (4) Ps must not have had any serious unstable medical illnesses, intellectual impairment, bipolar disorder, psychosis, delusional disorder, suicidality, organic brain damage, or more than mild traumatic brain injury.
- (5) Ps must not have met DSM-IV criteria for Moderate-Severe Substance Use Disorder within the last six months.
- (6) Ps must not have made any recent modifications to psychotropic medication status (i.e., within the last 1 month for benzodiazepines and within the last 3 months for SSRI and SNRIs).
- (7) Ps must not have recently initiated or made changes to any psychotherapy (within the last 3 months).
- (8) Ps must not have had any chronic or repeated neglect/maltreatment, sexual abuse, physical abuse, emotional abuse, or domestic violence prior to the age of 7, given evidence for adverse brain development and structural abnormalities in this subgroup of individuals.

Note: we did not exclude PTSD Ps with comorbid disorders such as depression, other anxiety disorders, or personality disorders, mild substance abuse, or stable psychotropic medication use as such conditions are very common in PTSD and therefore exclusion for such factors would not only make recruitment prohibitive, but it would also significantly limit the generalizability of our findings.

Recruitment and Screening

Recruitment.

Participants were recruited from the greater Los Angeles area via flyers and other postings in the community and through the internet and Veteran organizations. Participants were compensated for their participation.

Screening and Diagnostic Procedures.

Ps underwent a brief telephone screening to ensure they satisfied basic inclusion and exclusion criteria (e.g., right-handed, no metallic implants, etc.). Telephone screenings were conducted by trained research staff following an IRB-approved script. Potentially eligible Ps were invited for an in-person diagnostic interview using the Clinician-Administered PTSD Scale 5 (CAPS-5) (Blake et al., 1995), SCID-5, Research Version, Patient Edition (First et al., 2002), and Ohio State Traumatic Brain Injury Interview. Participants provided informed consent prior to beginning the in-person interview. Interviewers included graduate students and research staff who were certified as reliable diagnosticians.

Self-Report Questionnaires.

Immediately following the initial in-person clinical interview, Ps completed several questionnaires, including the PTSD Checklist (PCL-5).

fMRI Combat Task

Overview of fMRI Testing Sessions.

Prior to entering the scanner, participants practiced the fMRI tasks and asked any questions they may have had. The fMRI scanning lasted approximately 60 minutes, and included structural scans to facilitate data analysis as well as functional scans corresponding to task-related activity. The post-training fMRI session was identical to the baseline fMRI session.

Combat Stimuli.

Stimuli for the Combat Affect Labeling task were chosen from the Military Affective Picture System (MAPS; Dretsch et al., 2012). Combat images consisted of genuine war photos, the majority taken in Iraq and Afghanistan. Examples include photos of caskets, masked insurgents, and pictures of soldiers and civilians with flesh wounds, and thereby constituted trauma-relevant stimuli. Images assigned to each condition within each run were matched on average valence and arousal ratings, as well as image content (e.g., mutilation, deceased soldiers, surgeries, injured or deceased children). Affect labels were chosen from the following pool of labels: angry, anxious, sad, disgusted, guilty, and other. For each affect labeling trial, two emotion words and “other” were offered as choices.

Images for the Neutral condition were chosen from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2008). Neutral images were selected from the IAPS image set with images rated as low in arousal and around the midpoint in valence representing neither a highly positive nor highly negative average valence rating. Images were balanced to ensure average valence and arousal ratings remained relatively similar across runs.

Experimental design.

Tasks were presented via the Psychophysics Toolbox (Brainard, 1997; Kleiner et al., 2007) in the MATLAB environment version 7.4. Instructions were provided to subjects during a pre-scan session along with practice trials to familiarize subjects with each task. Each subject confirmed an understanding of task procedures. Additionally, experimenters reminded subjects of the task instructions just prior to administration in the fMRI scanner via verbal communication. Participants viewed the task via MR-compatible LCD goggles while in-scanner responses were made via a button response box held in the subject’s right hand.

Combat Affect Labeling Task. Participants were administered an affect labeling task in the scanner that was comprised of five conditions: Affect Label, Common Label, Observe, Neutral, and Shape Match. For Affect Label, Common Label, and Observe, participants were shown aversive images from the Military Affective Picture System (MAPS; Dretsch et al, 2012) and asked to perform one of three operations corresponding to the conditions. In the affect labeling condition (‘Affect Label’), a modified version of the affect labeling task (Hariri et al., 2000; Lieberman et al., 2007) was performed.

Participants were shown aversive images of combat scenes presented simultaneously with two negatively valenced emotion labels (e.g. ‘Anger’, ‘Anxious’) and a third option ‘Other.’ Participants were instructed to select via a button box the label that ‘best describes the emotion you feel while viewing the scene depicted’. The option ‘Other’ was presented for the participants to select if they were feeling another emotion other than the two presented with the image or they felt no emotional response at all. During the other labeling condition (‘Common Label’), participants were also presented with images of combat scenes and performed a task similar to the ‘Affect Labeling’ condition except they were instructed instead to ‘choose the label that best represented what the typical or most common emotional reaction would be among others to the scene depicted’. No option for ‘other’ was presented with the emotion labels for in this condition and participants were instructed to make their best guess. During the ‘Observe’ condition, subjects were instructed simply to look at the images of combat scenes presented and respond naturally so as to allow experience of a typical emotional reaction to the image. During the ‘Neutral’ condition, participants were shown images from the International Affective Picture System (IAPS; Lang et al., 2008) that were rated as low arousal with neutral valence. Participants were likewise instructed to respond naturally and were not required to make responses during these trials. Finally, during the ‘Shape Match’ condition, participants were presented with an image of a shape in the center of the screen with three smaller shapes at the bottom, one of which was an identical but smaller version of the shape in center-screen. Participants were instructed to select via the button box which shape at the bottom matched the shape in center-screen.

Configured as a block design, this task included these five conditions each beginning with a 3-second cue prompt indicating the upcoming block and task followed by five 5-second trials. Each block was preceded and followed by a 12-second fixation presentation. Each of the five conditions was presented twice per run in pseudo-random order with two runs administered, totaling four blocks of each condition per subject. No stimuli were repeated within this task including across runs. Following each block, a 9-item Likert sliding scale was displayed for 5 seconds. Participants were instructed to use the button box on the sliding scale to indicate how much distress they felt overall while viewing the preceding block of images. The scale ranged from 1 (‘Not at all distressed’) to 9 (‘Extremely distressed’). The primary contrasts of interest included comparing affect labeling of aversive combat images against passive observation of aversive combat images (Affect Label > Observe) in order to assess the emotion inhibitory effects of affect labeling (e.g., RVL PFC activation and amygdala de-activation) and passive observation of aversive combat stimuli against passive observation of neutral stimuli (Observe>Neutral) in order to assess general emotion reactivity to the aversive combat stimuli.

Image Acquisition.

Imaging data were acquired via a Siemens Tim Trio 3 tesla MRI scanner at the UCLA Staglin Center for Cognitive Neuroscience. We acquired functional T2*-weighted echo planar image volumes (EPIS; slice thickness = 4 mm, gap = 1 mm, 33 oblique axial slices, TR = 2000 ms, TE = 30 ms, flip angle = 75°, matrix = 64x64, FOV = 220 mm). Two structural scans were acquired including a matched bandwidth high-resolution T2-

weighted echo-planar image (spin echo; slice thickness = 4 mm, no gap between slices, 34 slices, TR = 5000 ms, TE = 34 ms, flip angle = 90°, matrix = 128 x 128, FOV = 196 mm) and a T1-weighted, magnetization prepared, rapid-acquisition, gradient echo anatomical scan (MPRAGE slice thickness = 1 mm, gap = .5 mm, 160 slices, TR = 1900 ms, TE = 3.43 ms, flip angle = 9°, matrix = 256 x 256, FOV = 256 mm) to facilitate image normalization.

Image Analysis.

Preprocessing. Imaging data were analyzed using SPM8 (Wellcome Department of Cognitive Neurology, Institute for Neurology, London, UK). All images were first manually reoriented to align brains along a horizontal AC-PC line with the image origin at the anterior commissure; structural images were reoriented independently but functional images were reoriented using parameters from the first run's first image applied to each subsequent volume within that task. All functional images were then realigned to the first volume within the appropriate run to correct for head motion. High resolution MPRAGE structural images were co-registered to a mean EPI using the T2-weighted echo planar structural as a mediating co-registration step. MPRAGE anatomical images were then normalized using the New Segmentation routine in SPM8 to warp them into Montreal Neurological Institute space (resampled at 3x3x3mm; Mazziotta et al., 2001). Resulting normalization parameters were applied to functional images which were then subsequently smoothed using an 8-mm Gaussian kernel, full-width half-max. Finally, visual inspection was employed assessing EPI alignment to structural images after co-registration and accurate warping to the MNI standard space after normalization to assure quality of the preprocessing pipeline for images from all subjects and runs.

Statistical Analysis. General linear models were defined separately for each participant. For the Combat Affect Labeling task, the model included five regressors of interest: Affect Label, Common Label, Observe, Neutral, and Shape Match. Blocks were modeled as box car functions spanning from onset of the first stimulus in the block to the offset of the last stimulus convolved with the canonical double-gamma hemodynamic response function (HRF). Six motion parameters were included as covariates of no interest. Additionally, regressors identifying individual volumes as representing global signal intensity change (thresholded at 2.5 standard deviations from average global signal intensity within the run) were similarly included. High pass filters were set at SPM8 default values of 128s. Regressors were replicated across runs adjusted for new condition timing, motion parameters, and volumes identified by our custom scripts. Contrast images were created at the subject-level for contrasts of interest.

To investigate group-level effects for each task, the resulting contrast images from subject-level analyses described above were used in a random-effects analysis using a one sample t-test in the GLM Flex statistical software package (<http://mrtools.mgh.harvard.edu>, June 22, 2014). Voxels with missing data from subjects were analyzed using degrees of freedom adjusted to the number of subjects contributing to that data point. Reported p-values are adjusted automatically within the GLM Flex software to reflect the equivalent p-value for the degrees of freedom dependent upon the

full model. Voxels missing data from more than 10% of the subjects in the full model were eliminated from the analysis.

Affect Labeling Training

PTSDs completed six sessions of AL training. The training program was presented via a computer with headphones and Ps made responses via keyboard button presses. Training was conducted in a private room with only the P and a research staff member present at all times. Training consisted of a total of six 1-hour sessions, completed twice a week for three consecutive weeks, beginning one week after the baseline fMRI scan. Each 1-hour session included 40 minutes of actual training, and the remaining 20 minutes were spent setting up and completing administrative tasks. We selected six sessions because common treatments for PTSD typically employ at least 6 sessions to see results, if any.

Ps completed eight five-minute blocks of inhibitory regulation training, each comprised of multiple trials of one of four different types of inhibitory processing, with two five-minute blocks of each type. In the first type of trial, participants were shown a combat-relevant image for 10 seconds. After 10 seconds, two affect labels appeared on the screen at the bottom of the image and participants chose one of the labels that best described how they felt while viewing the image. The second and third types of trials involved a similar format and procedure, but instead of trauma-relevant images, generally aversive images and negative facial expressions were presented for affect labeling. The final type of inhibitory processing involved completion of a Go-NoGo motor inhibition task.

Post-training Clinical Interviews

One week following the post-training fMRI session, PTSDs completed a second clinical interview using the CAPS-5 to assess any changes in clinical status and symptoms as a result of the training. PTSDs also completed the PCL-5 at post to provide self-reported indices of changes in PTSD symptoms.

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