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The Role of Reflexive Avoidance Behaviors in Posttraumatic Stress Disorder

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The Role of Reflexive Avoidance Behaviors in Posttraumatic Stress Disorder

A dissertation submitted in partial satisfaction of the

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in Psychology

by

Carolyn Darling Davies

2017

ABSTRACT OF THE DISSERTATION

The Role of Reflexive Avoidance Behaviors in

Posttraumatic Stress Disorder

by

Carolyn Darling Davies

Doctor of Philosophy in Psychology

University of California, Los Angeles, 2017

Professor Michelle Craske, Chair

Despite the important role of behavioral avoidance in the maintenance of post-traumatic stress disorder (PTSD), little is known about the role of implicit or reflexive avoidance tendencies in PTSD. The current dissertation examined the role of reflexive avoidance tendencies in individuals with PTSD in a series of three studies. First, we examined avoidance tendencies of trauma-related stimuli in military veterans with PTSD, trauma-exposed military veterans without PTSD, and non-trauma-exposed civilians. Compared to non-trauma exposed civilians, both veterans with and without PTSD showed greater reflexive avoidance of low arousal combat images, but only veterans without PTSD showed heightened reflexive avoidance of high arousal images. Additionally, re-experiencing symptom severity, but not other clusters of PTSD symptoms, was associated with reflexive avoidance of high arousal images and marginally associated with reflexive avoidance of low arousal images among veterans with and without

PTSD. The second study focused on the relationship between automatic avoidance tendencies and neural activity in veterans with and without posttraumatic stress disorder. We found that veterans with and without PTSD exhibited heightened bilateral amygdala, right ventrolateral prefrontal cortex, and medial prefrontal cortex activation in response to combat (versus neutral) images, but this neural reactivity was not associated with avoidance tendencies. Finally, the third study examined the effect of inhibitory regulation training on fear responding, PTSD symptoms, and reflexive avoidance tendencies. Compared to a waitlist control condition, veterans who completed the training experienced significant reductions in self-reported PTSD symptoms and reduced reflexive avoidance of trauma-related images, but did not exhibit changes in physiological reactivity to trauma-related images from pre- to post-training. Our findings suggest that trauma-exposed veterans, regardless of whether they meet criteria for PTSD, exhibit reflexive avoidance of trauma-related stimuli, perhaps representing a behavioral indicator of trauma exposure. Additionally, though reflexive avoidance was not associated with neural activity within regions of the brain involved in emotional responding and inhibitory regulation, our findings do provide evidence that inhibitory regulation-based training may reduce reflexive avoidance behavior. Future research on this topic may elucidate our understanding of how to better address avoidance behaviors in PTSD treatment.

The dissertation of Carolyn Darling Davies is approved.

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Introduction

Nearly one in four veterans returning from military operations in Iraq or Afghanistan has received a diagnosis of posttraumatic stress disorder (PTSD; Fulton et al., 2015). Veterans with PTSD suffer from diminished life satisfaction and well-being, impairments in marital, parental, and occupational functioning, and increased rates of comorbid medical and psychiatric conditions, homelessness, and substance use (Schnurr et al., 2009; Nillni et al., 2014). In addition, the societal costs of PTSD within the military are high; PTSD removes military members from active duty and leads to increased government expenses on treatment and disability benefits. Between 2004 and 2009, the Veterans' Health Administration spent an estimated $1.4 billion on PTSD patients alone (Congressional Budget Office, 2012). Increasing our understanding of PTSD in military veterans and devising accessible, affordable, and effective treatments are imperative steps toward relieving the heavy psychological, financial, and societal burdens of PTSD.

Role of avoidance in PTSD

One of the central features of PTSD is avoidance of trauma-related stimuli (American Psychiatric Association, 2013). Individuals with PTSD report greater avoidance of thoughts and feelings related to their traumatic event, as well as increased avoidance of trauma-related cues, compared to non-PTSD controls (e.g., van Minnen & Hagenaars, 2010). While avoidance strategies can temporarily protect the individual from experiencing overwhelming anxiety, repeated and persistent avoidance maintains anxiety and leads to long-term negative consequences, such as a reduction in quality of life (Kashdan, Morina, & Priebe, 2009; Kashdan, Breen, & Julian, 2010) and an increase in PTSD symptoms (Johnsen, Laberg, & Eid, 1998; North, Spitznagel, & Smith, 2001; Bryant et al., 2000). Avoidance of trauma-related cues, such

as people, places, or situations, is thought to maintain anxiety symptoms by preventing individuals from learning new, non-threatening associations with cues previously associated with trauma (Rachman, 1980), and avoidance of internal cues, including memories, thoughts, or emotions surrounding the traumatic event, similarly maintains anxious responding by hindering the learning of new responses (Salters-Pedneault, Tull, & Roemer, 2004).

The primary function of avoidance is to physically or psychologically distance oneself from threat (Fanselow & Lester, 1988; Arnaudova, 2015). In response to threat, the defensive motivational system prepares the organism for defensive responding, the level of which increases with increasing imminence of threat (predatory imminence model; Fanselow & Lester, 1988). In individuals with PTSD, this defensive system becomes inappropriately activated, such that individuals overestimate the imminence of threat and react with behaviors that are more extreme than the required mode of defense in a given situation (Rau & Fanselow, 2007). Evidence of enhanced defensive responding in PTSD include increased self-reported negative emotional experiences and increased psychophysiological responding in response to threat or trauma-related stimuli (e.g., McFall, Murburg, Ko, & Veith, 1990; Pole, 2007), as well as increased avoidance behaviors (e.g., Badour, Blonigen, Boden, Feldner, & Bonn-Miller, 2012).

Reflexive avoidance in PTSD

Despite the important role of avoidance in the maintenance of PTSD, studies have been limited by methods of measuring avoidance. Current measures of avoidance primarily consist of items on questionnaires and clinician interviews in which participants are asked about how often and what types of stimuli they avoid. While these types of measures of avoidance are helpful for assessing strategies that individuals are well aware of (i.e., explicit avoidance), they do not capture less effortful, intentional, and conscious attempts to avoid anxiety-provoking stimuli (i.e.,

implicit or reflexive avoidance). This is problematic because some patients may be unaware of their avoidance strategies and therefore unable to report them. Additionally, questionnaire data are prone to problems such as self-presentation strategies, demand characteristics, and distortions based on social desirability (Tanaka-Matsumi & Kameoka, 1986). These problems may even be enhanced in military veteran populations; some studies find apparent overreporting of PTSD symptoms among combat veterans (e.g., Frueh, Hamner, Cahill, Gold, & Hamlin, 2000), while others indicate elevated concerns about stigma associated with mental illness, which may lead to underreporting of symptoms (e.g., Hoge et al., 2004). Thus, measurement of implicit or reflexive avoidance in individuals with PTSD could provide additional information that is not impacted by problems of over- or underreporting.

In addition to circumventing issues with reporting of behaviors, reflexive measures also tap into a distinct domain of behavioral expression that consists of fast, automatic, less conscious behavioral tendencies. Research on dual-process models of behavioral selection supports the view of two functional systems that guide behaviors: a *reflexive* (impulsive) system and a *controlled* (reflective) system (Strack & Deutsch, 2004). The reflexive system guides behaviors by activation of a motivational orientation (e.g., defensive motivation) and formed associations between cues and responses, whereas the controlled system steers actions based on individual values, evaluation, and intent. Supporting the notion that behavioral expression is guided by two distinct systems, laboratory studies show more coherence among responses within a single system than responses to the same stimulus across different systems (Huijding & de Jong, 2006; Evers et al., 2014). Thus, while measuring avoidance behaviors under controlled system control provides information about an individual's conscious evaluation of a stimulus, measuring

reflexive avoidance behaviors under control of the impulsive system provides an index of the effects of defensive motivation activation on behavioral tendencies.

As with other modes of defensive responding, a defining feature of reflexive avoidance is an attempt to increase distance from a threatening stimulus (Krieglmeyer, Houwer, & Deutsch, 2013). Reflexive avoidance is generally measured through behavioral tasks that require participants to "approach" positive stimuli and "avoid" negative stimuli (i.e., compatible responses), as well as "approach" negative stimuli and "avoid" positive stimuli (i.e., incompatible responses) based on a feature of the stimulus that is unrelated to its valence (e.g., picture tilt or frame color of photo stimuli). An overall index of reflexive avoidance is then computed by subtracting reaction times of compatible responses from reaction times of incompatible responses. Studies utilizing these types of approach-avoidance tasks have demonstrated greater avoidance tendencies of threat-relevant stimuli in anxious individuals compared to healthy controls, including spider fearful individuals of spider pictures (Klein, Becker, & Rinck, 2011; Rinck & Becker, 2007; Bartoszek & Winer, 2015) and socially anxious people of smiling and angry faces (e.g., Heuer, Rinck & Becker, 2007). However, only one study has examined reflexive avoidance tendencies in PTSD; compared to healthy controls, victims of sexual trauma exhibited greater avoidance tendencies of threatening sexual images (Fleurkens, Rinck, & van Minnen, 2014). Thus, there is a clear need for additional research examining the role of reflexive avoidance in PTSD.

Reflexive avoidance and impaired inhibitory regulation in PTSD

In addition to increased avoidance behaviors, previous research has yielded extensive evidence of altered neural activity in individuals with PTSD, particularly in amygdala and prefrontal cortex regions. PTSD has long been thought to involve

maladaptive fear learning and extinction (Lissek et al., 2005; Craske et al., 2009), processes that are mediated in part by impaired down-regulation of excessive amygdala-based fear responses by the ventromedial pre-frontal cortex throughout the course of extinction (VMPFC; Rosenkranz et al., 2003; Quirk et al., 2006). Impaired VMPFC activity in PTSD patients has been found using symptom provocation paradigms (Lanius et al., 2001; Shin et al., 2004; Hou et al., 2007), as well as paradigms examining cognitive-emotional processes. PTSD patients also exhibit diminished activity in right ventrolateral prefrontal cortex (RVLPFC), a region that mediates inhibitory regulation of responses across multiple domains, during tasks that require inhibitory processing (Falconer, 2008; Aupperle et al., 2012; Hayes et al., 2009). For instance, during a Go-NoGo task, individuals with PTSD exhibited less RVLPFC activity than healthy controls, and this decreased level of RVLPFC was associated with more inhibitory errors and heightened PTSD symptom severity (Falconer, 2008). Similar findings of impaired inhibitory regulation processes in PTSD have been found in studies involving potential emotion regulation (i.e., inhibition of affective responses; Hopper et al., 2007; Morey et al., 2009).

In contrast to deactivation in these prefrontal cortex areas, individuals with PTSD tend to exhibit increased activation in regions that process salient and arousing stimuli (Hayes, Hayes, & Mikedis, 2012). Studies that utilize script-driven imagery paradigms to induce recollections of the trauma (e.g., Pitman et al., 1987) elicit elevated heart rate and skin conductance levels (Orr et al., 1993; Lindauer et al., 2006; Shalev et al., 1992) and heightened amygdala or insula responses in most individuals with PTSD (Rauch et al., 2000; Shin et al., 1997; Shin et al., 2004), reflecting fear or other affective responding. A

meta-analysis of 26 neuroimaging studies of the neural correlates of PTSD concluded that individuals with PTSD generally exhibited hypoactivity of VMPFC and RVLPFC regions, and hyperactivity of amygdala, during both symptom provocation paradigms as well as cognitive-emotional tasks (Hayes et al., 2012). Moreover, this meta-analysis showed that VMPFC and amygdala activity are inversely correlated, supporting the notion that PTSD involves impaired amygdala down-regulation by prefrontal regions.

Such impaired inhibitory regulation processes and enhanced affective responding may underlie reflexive avoidance tendencies in PTSD. Neurobiological studies in animals and humans show that less imminent threat (compared to highly imminent threat) results in greater activation of prefrontal cortex areas associated with decision-making and executive control, regions presumed to be associated with the controlled system (Mobbs et al., 2007; Mobbs et al., 2009; Fanselow, 1994; Arnaudova et al., 2015), whereas more highly imminent threat results in activation of phylogenetically older structures, such as the periaqueductal gray (PAG) and central nucleus of the amygdala (CeA), structures associated with reflexive behaviors (Mobbs et al., 2007; Mobbs et al., 2009). Thus the overestimation of the imminence of threat coupled with the associated neural activity found in PTSD (ie., deficits in VMPFC and RVLPFC activity and increased amygdala activity), suggests that the impulsive system is more likely to dominate in these individuals compared to those who do not exhibit such altered neural activity. Therefore, deficits in VMPFC and RVLPFC activity and increased amygdala activity in the face of threatening stimuli may predict greater reflexive avoidance of such stimuli.

Targeting inhibitory regulation in PTSD

Deficits in regulation of fear responses are potential treatment targets for PTSD. Akin to extinction, exposure therapy is presumed to invoke amygdala down-regulation via the VMPFC

and is one of the most effective and widely used strategies for PTSD treatment. However, a number of PTSD patients fail to respond to conventional exposure-based therapy (Schottenbauer et al., 2008) or drop out early from these treatments (Garcia, Kelley, Rentz, & Lee, 2011). Therefore, it is essential to explore other fear regulatory pathways as potential treatment targets.

A core component of PTSD is an inability to effectively down-regulate negative affect (i.e., trauma-related distress). As mentioned above, extinction research has identified impairments in the down-regulation of amygdala activity by the ventromedial prefrontal cortex (VMPFC); however, recent research suggests that a lateral prefrontal cortex route involving the ventral lateral prefrontal cortex control over the amygdala may also be compromised in PTSD (Falconer et al., 2008). Thus, therapeutic strategies designed to enhance RVLPFC-based inhibitory regulation may be particularly beneficial for these individuals.

Neuroimaging research suggests that affect labeling may be one way to enhance inhibitory regulation processes. Affect labeling refers to either labeling the emotional content of external stimuli (e.g., labeling a facial expression as 'angry'; Hariri et al., 2000) or labeling personal affective responses to stimuli (e.g., labeling one's response to an aversive stimulus as 'anxious'; Kircanski et al., 2012). Several studies have shown that affect labeling constitutes an inhibitory regulation strategy involving increased activity in RVLPFC, corresponding decreases in limbic emotional response regions including the amygdala (Hariri et al., 2003; Lieberman et al., 2007), as well as reduced self-reported distress (Payer et al., 2012). Affect labeling has also gained evidence as a potential method for enhancing effectiveness of exposure for anxious individuals. For example, in spider phobic individuals, affect labeling during spider picture-viewing led to greater reductions in skin conductance responses to the images one week later (Tabibnia, 2008), and labeling of affect and feared stimuli during exposure therapy led to

significantly greater reductions in skin conductance responses and reduced behavioral avoidance (Kircanski et al., 2012). Additionally, affect labeling plus exposure led to greater reductions in physiological arousal in individuals with public speaking anxiety compared to exposure alone (Niles et al., 2015). Researchers hypothesize that improvements in outcomes following affect labeling procedures are due to enhanced learning of inhibitory regulation during exposure (e.g., Kircanski et al., 2012). Thus, affect labeling procedures may be similarly able to reduce fear responding to trauma reminders in PTSD. Moreover, because the neural circuitry involved in affect labeling overlaps with regions involved in controlled system processing (e.g., Mobbs et al., 2007), affect labeling techniques may also enhance controlled system circuitry (and thereby reduce reflexive avoidance tendencies) among individuals with PTSD.

Another task that has been repeatedly found to elicit RVLPFC activity is the Go-NoGo. During Go-NoGo tasks, individuals are instructed to press a key each time a certain stimulus (e.g., letter, word) appears on the screen, except for a particular pre-identified stimulus (NoGo trial). Correct inhibition of the prepotent motor response during NoGo trials requires activation of inhibitory regulatory networks, including RVLPFC (e.g., Kelly et al., 2004). In individuals with PTSD, activity in inhibitory neural networks are diminished during NoGo trials, and these NoGo inhibitory deficits are correlated with greater symptom severity (Falconer et al., 2008) and enhanced startle reactivity (Jovanovic et al., 2013). Thus, while most studies to date have examined Go-NoGo performance as an assessment of inhibitory regulation ability rather than a training tool, training in Go-NoGo procedures may also lead to enhanced inhibitory regulation in individuals with PTSD.

Current studies

The current dissertation project aimed to enhance understanding of reflexive avoidance

tendencies in individuals with posttraumatic stress disorder in a series of three studies. The first study examined automatic avoidance tendencies of trauma-related stimuli in three groups: military veterans with posttraumatic stress disorder, trauma-exposed military veterans without posttraumatic stress disorder, and non-trauma-exposed civilians. The aims of this study were: (1) to determine whether individuals with posttraumatic stress disorder exhibit enhanced reflexive avoidance tendencies compared to other groups using an automatic approach-avoidance task and (2) to examine the relationship between reflexive avoidance tendencies and posttraumatic stress disorder symptom clusters.

The second study focused on the relationship between automatic avoidance tendencies and neural activity in veterans with and without posttraumatic stress disorder. The aim of the second study was to examine the association between automatic avoidance behaviors and neural activation in response to viewing combat-related stimuli, especially with regard to spontaneous inhibitory regulation.

Finally, the third study examined the effect of inhibitory regulation training on fear responding, posttraumatic stress disorder symptoms, and reflexive avoidance tendencies in veterans with combat-related posttraumatic stress disorder. The aims of the third study were: 1) to examine the effect of inhibitory regulation training (compared to a wait list condition) on subjective symptoms, physiological arousal and reflexive avoidance of combat-related stimuli and 2) to examine performance during affect labeling and Go-NoGo training as predictors of outcome.

Study 1:

How do reflexive avoidance tendencies of combat-related stimuli relate to posttraumatic stress disorder diagnostic status and symptoms?

Reflexive avoidance behaviors provide an index of the effects of defensive motivation activation on individuals' automatic behavioral tendencies. However, little is known about the role of reflexive avoidance in PTSD. As noted above, only one study to date has examined reflexive avoidance tendencies in individuals with PTSD. In this study, victims of sexual trauma exhibited greater avoidance tendencies towards threatening sexual images than healthy controls, and the level of avoidance of threatening sexual images was predicted by self-reported arousal but not self-reported explicit avoidance or symptom severity (Fleurkens et al., 2014). Examining reflexive avoidance and its relationship to PTSD symptoms would provide valuable information about the utility of assessing reflexive avoidance tendencies in this population.

The aims of Study 1 were: (1) to determine whether veterans with combat-related PTSD exhibit enhanced reflexive avoidance tendencies compared to veterans and non-veterans without PTSD and (2) to examine the relationship between reflexive avoidance tendencies and posttraumatic stress disorder symptom clusters (re-experiencing, avoidance, negative alterations in cognitions or mood, and hyperarousal). Based on previous research showing increased reflexive avoidance of threatening stimuli in anxious samples (e.g., Rinck & Becker, 2007), we hypothesized that veterans with PTSD would exhibit greater reflexive avoidance tendencies of threatening combat-related images than veterans and non-veterans without PTSD. We also predicted that PTSD symptoms of hyperarousal and avoidance would be associated with greater reflexive avoidance, based on previous studies examining the relationship between reflexive

avoidance and self-reported arousal (Fleurkens et al., 2014) and behavioral tests of avoidance (Rinck & Becker, 2007).

Method

Participants

Veterans with combat-related PTSD (*n* = 30), combat-exposed veterans without PTSD (VET-HC; *n* = 20), and non-trauma-exposed civilian participants without PTSD (CIV-HC; *n* = 17) were recruited through advertisements in the Los Angeles community, referrals from veteran organizations, and via UCLA undergraduate subject pools. Eligible PTSD and VET-HC participants were between 18 and 45 years old, had deployment experience, and met DSM-5 criterion "A" for PTSD, which requires exposure to a traumatic event involving actual or threatened physical injury or death, or consistent exposure to aversive details of traumatic experience as part of their job (American Psychiatric Association, 2013). PTSD participants met DSM-5 criteria or DSM-5 "Other Specified" criteria for combat-related PTSD, non-dissociative subtype, according to the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5; Weathers et al., 2013) with a clinician severity rating (CSR) of 4 or above. Eligible CIV-HC participants were between 18 and 45 years old and were not trauma-exposed (i.e., did not meet DSM-5 PTSD criterion "A"). Both VET-HC and CIV-HC participants also did not meet DSM-5 criteria for any anxiety, depressive, or trauma/stress-related disorders according to the Structured Clinical Interview for DSM-5 (SCID; First et al., 2015). Exclusion criteria for all participants included serious unstable medical illnesses, pregnancy, intellectual impairment, bipolar disorder, psychosis, current suicidality, more than moderate traumatic brain injury, more than mild

substance use disorder within the past month, and recent changes to psychotropic medication (1 month for benzodiazepines or 3 months for SSRIs/SNRIs) or psychotherapy (3 months).

Demographic data for all participants are reported in Table 1. Three PTSD participants and 3 CIV-HC participants dropped from the study prior to completing the laboratory assessment or scan, and demographic data were not available for four of these participants (1 PTSD and 3 CIV-HC). Additionally, one VET-HC and one PTSD participant did not complete the laboratory tasks due to technical issues.

Procedure

All participants completed a diagnostic assessment to determine eligibility (see below). Advanced graduate students and trained clinicians conducted diagnostic interviews, and diagnostic interviewers confirmed diagnoses with a supervising licensed psychologist. Approximately one week following the diagnostic assessment, eligible participants came into the laboratory for an in-person appointment, during which they completed a joystick automatic approach-avoidance task (AAT, see below; Rinck & Becker, 2007). Participants who were eligible for the fMRI component completed the AAT immediately following an fMRI scan during this assessment, while those who were not eligible for the fMRI component completed the AAT after completing the tasks identical to those done during the fMRI but outside of the scanner. After completing the AAT, healthy control participants were debriefed and dismissed, and PTSD participants were scheduled for their next appointments with the study, as described in Study 3.

Measures

Clinician-Administered PTSD Scale for DSM-5 (CAPS-5; Weathers et al., 2013). All veteran participants completed the CAPS-5. The CAPS-5 is a 30-item structured interview used to assess

PTSD symptoms over the past month in relation to an index trauma. To determine a participant's index trauma, the clinician first administers the Life Events Checklist for DSM-5 (LEC-5; Weathers et al., 2013) to assess exposure to potentially stressful life events, and the index trauma is defined as the "event that currently bothers you the most" if the participant endorses more than one. For each PTSD symptom on the CAPS-5, a severity rating from 0 (absent) to 4 (extreme/incapacitating) is made, with a rating of 2 or above qualifying as a "threshold" level for PTSD diagnosis. CAPS-5 symptom cluster severity scores are calculated by summing the individual item severity scores for each DSM-5 symptom cluster: re-experiencing, avoidance, negative alterations in cognitions or mood, and hyperarousal.

Approach Avoidance Task (AAT; Rinck & Becker, 2007). The AAT is a measure of automatic approach and avoidance tendencies and has been found to exhibit good internal consistency (Cronbach's $\propto$ = .66 to .70; Reinecke, Becker, & Rinck, 2010). In the current study, 28 negatively-valenced combat-related pictures were used to assess automatic avoidance tendencies to trauma-related stimuli. Images were selected from a set of photos used in a previous neuroimaging study examining emotional processing in veterans (Morey, Petty, Cooper, LaBar, & McCarthy, 2008). All images depict combat-related scenes from Iraq and Afghanistan. Valence and arousal rating for images were obtained from a non-veteran sample and used to choose 14 high-arousal images and 14 low-arousal images. Mean arousal ratings (0 = not at all arousing, 9 = extremely arousing) were 5.12 for high-arousal images and 3.15 for low-arousal images. Images were also rated by a subset of our veteran sample; veteran arousal ratings of images correlated very highly with civilian arousal ratings (r = .72). Both high and low arousal images were used in order to determine whether reflexive avoidance is dependent on arousal level of images.

After a brief practice period to gain comfort with the directions and the use of the joystick, one picture at a time appeared on the screen (approximately 20" from the participant) with a resolution of 1,024 x 768 pixels. Participants were instructed to use a joystick to either "pull" or "push" the picture towards or away from themselves using their dominant hand, depending upon the tilt of the picture. Pictures disappeared only upon a full correct movement (not upon a full incorrect one), and the next trial began after the participant pulled the "trigger" on the joystick. To create an unambiguous relationship between joystick movement and approach-avoidance, a zooming effect was used. Thus, when the joystick was pulled, the picture became larger, and when the joystick was pushed, the picture became smaller. Reaction time was based on the time from the time it took to complete a full correct movement of the joystick, regardless of whether participants made an error in the initial joystick movement. Each picture was displayed twice, once in a push trial and once in a pull trial. In addition, trials using an empty frame instead of a combat image were used in order to compare responses to baseline reaction times to the tilted image. In total, there were 84 experimental trials (14 Hi-Pull, 14 Hi-Push, 14 Lo-Pull, 14 Lo-Push, 14 Empty-pull, 14 Empty-push).

Data reduction

Prior to conducting analyses, we examined AAT error rates. Error rates were computed as the percentage of trials in which participants made an initially incorrect movement. One CIV-HC participant had an error rate of 49% (chance performance would predict 50% accuracy) and thus was excluded from analyses. The error rate across remaining participants was low (<1%) and did not significantly differ by group ($p > .15$). We then examined AAT reaction time data and identified and removed latencies below 300ms or above 3000ms in order to minimize the influence of extremely fast or slow responses (Greenwald et al., 1998). For included participants,

less than 2% of the data were above or below these cut-offs. Data from one PTSD participant were excluded from analyses due to >30% of latencies being above 3000ms. Thus, the final analytical sample size was 25 PTSD, 19 VET-HC, and 13 CIV-HC.

Median reaction times for each trial type (Hi, Lo, Empty) were used to compute effect scores. Median reaction times are commonly used in reaction time tasks instead of means as they are less sensitive to outliers. To compute effect scores, we subtracted reaction time latencies during pull trials from reaction time latencies during push trials. The effect score reflects the relative strength of approach or avoidance tendencies: a more negative score indicates stronger avoidance (Rinck & Becker, 2007).

Statistical analyses

To examine differences in avoidance tendencies among groups, we conducted multilevel modeling for repeated measures in Stata 12.1, with effect scores for each Trial (High Arousal, Low Arousal, Empty) as the repeated measures dependent variable (level 1 unit) nested within subjects (level 2 unit). Intercept and slope were allowed to vary randomly. Group (PTSD, VET-HC, CIV-HC) and the interaction of Group x Trial were included as predictors. Follow-up comparisons were conducted to examine the effect of group within each trial type.

To examine the relationship between automatic avoidance tendencies and PTSD symptom clusters, linear regression analyses were conducted, with mean-centered scores from each of four symptom clusters from the CAPS (re-experiencing, avoidance, negative alterations in cognition and mood, and hyperarousal) as independent variables and Low Arousal or High Arousal effect score as dependent variable. CAPS scores were available for both PTSD and VET-HC participants, so we examined these groups in the same model to allow for a more powerful examination of the relationship between PTSD symptom severity and reflexive

avoidance and included Group as a covariate in these analyses. Effect score for Empty trials was also included as a covariate to control for response time latencies to non-emotional stimuli.

Results

Preliminary analyses

ANOVA results showed no significant differences among groups on sociodemographic variables (*p*s > .05). Additionally, there were no significant differences on sociodemographic variables between those who did vs. did not complete the laboratory tasks due to dropout or technical issues (*p*s > .07), thus these variables were not included in further analyses. CAPS scores across all symptom domains differed significantly between groups (see Table 2).

Approach-avoidance task (AAT)

There was a significant main effect of Trial ($\chi^2 = 8.53$, $p = .01$); however, this was superseded by a significant Group x Trial interaction ($\chi^2 = 13.2$, $p = .01$; see Figure 1). Follow-up comparisons within each Group showed that there were significant differences in avoidance tendencies across trials for both PTSD ($\chi^2 = 17.3$, $p < .001$) and VET-HC ($\chi^2 = 9.67$, $p = .008$) but not CIV-HC ($p = 0.71$), with the PTSD group showing greater reflexive avoidance during Low Arousal trials ($z = -3.67$, $p < .001$, 95% CI [-170.3, -51.7]), but not High Arousal trials ($p = .68$), compared to Empty, and VET-HCs showing greater reflexive avoidance during both High Arousal ($z = -2.61$, $p = .009$, 95% CI [-142.5, -20.3]) and Low Arousal trials ($z = -2.86$, $p = .004$, 95% CI [-167.2, -31.1]) compared to Empty. Follow-up between-group contrasts showed that, relative to CIV-HCs, both the PTSD group ($z = 2.74$, $p = .006$, 95% CI [40.6, 243.4]) and VETHC group ($z = 2.39$, $p = .02$, 95% CI [23.3, 236.8]) showed greater reflexive avoidance of Low Arousal versus Empty images, and the VETHC group ($z = 2.21$, $p = .03$, 95% CI [12.2,

203.9]), but not PTSD ($p = 0.41$), showed greater reflexive avoidance of High Arousal versus Empty images. There were no significant differences between VETHC and PTSD for Low Arousal images ($p = 0.92$) or High Arousal ($p = 0.09$) images compared to Empty images.

Reflexive avoidance and PTSD symptoms

Controlling for Group, CAPS re-experiencing score was associated with High Arousal trial effect score ($t = -2.16$, $p = .04$) and marginally associated with Low Arousal trial effect score ($t = -1.96$, $p = .06$), such that higher re-experiencing symptom severity was associated stronger avoidance tendencies of High Arousal and Low Arousal images. CAPS avoidance, negative alterations in cognition and mood, and hyperarousal scores did not significantly predict High Arousal or Low Arousal trial effect scores (all *p*s > .27).

Discussion

We examined reflexive avoidance tendencies of negatively-valenced combat images in veterans with and without PTSD, as well as in non-trauma exposed civilians, using a joystick approach-avoidance task. We found that, compared to non-trauma exposed civilians, both veterans with and without PTSD showed greater reflexive avoidance of low arousal combat images, but that only veterans *without* PTSD showed heightened reflexive avoidance of high arousal images. Furthermore, we found that re-experiencing symptom severity was associated with reflexive avoidance of high arousal images and was marginally associated with reflexive avoidance of low arousal images among veterans with and without PTSD. This study represents the first study to our knowledge to examine reflexive avoidance tendencies of trauma-related stimuli in veterans with and without PTSD.

Reflexive avoidance in PTSD

Our findings that both veterans with and without PTSD exhibit greater reflexive avoidance of low arousal combat images compared to civilian healthy controls suggests that reflexive avoidance of trauma-related stimuli is not specific to those with a diagnosis of PTSD. One possibility for this finding is that reflexive avoidance of trauma-related stimuli develops following trauma exposure, regardless of whether individuals go on to develop "full-blown" PTSD. Previous studies have shown that mere trauma exposure can put military veterans at risk for higher rates of depression, substance use, and health problems (Yarvis and Schless, 2009), suggesting that alterations in inhibitory regulation or other regulatory processes may occur following trauma even in individuals who do not meet threshold criteria for PTSD. However, despite exhibiting these initial avoidance tendencies of trauma-related stimuli, trauma-exposed healthy veterans do not report avoidance of internal and external stimuli that is characteristic of individuals with PTSD. Indeed, veteran healthy control participants reported minimal behavioral avoidance on the CAPS (see Table 2). In terms of a dual-process model of behavioral selection (Strack & Deutsch, 2004), our results suggest that while the impulsive system may guide automatic avoidance tendencies in healthy trauma-exposed veterans due to previously formed associations between certain cues and danger, the controlled system is still able to engage, allowing individuals to select behaviors based on their goals and evaluation of their environment. For individuals with PTSD, on the other hand, the controlled system may be unable to engage in order to "override" automatic avoidance tendencies and guide outward behaviors.

This explanation, however, does not account for the surprising finding that veterans with PTSD exhibited reflexive avoidance of low arousal images but *not* high arousal images. This finding is not consistent with the single previous study examining reflexive avoidance in PTSD, which found that individuals with PTSD showed the strongest reflexive avoidance tendencies in

response to the most highly threatening images (Fleurkens et al., 2014). It is possible that in the current study, the high arousal images were not as highly threatening as those used in previous studies (our high arousal images had an average arousal rating of 5.19 out of 9; no arousal ratings are reported in Fleurkens et al. [2014]), which could potentially explain our different pattern of results. However, as avoidance tendencies of high arousal images did not significantly differ between veterans with and without PTSD in between-group comparisons, we cannot conclude whether this pattern of responding represents actual differences in avoidance tendencies or whether this finding is particular to the current sample; thus this is a question that needs to be explored through further study.

Reflexive avoidance and PTSD symptoms

We did not find support for our hypothesis that PTSD symptoms of hyperarousal and avoidance would be associated with greater reflexive avoidance. Re-experiencing symptoms predicted reflexive avoidance of high arousal images and marginally predicted reflexive avoidance of low arousal images across groups, suggesting that re-experiencing symptoms may create distractors and interrupt inhibitory functions (Aupperle et al., 2012). However, no other symptom clusters predicted reflexive avoidance of trauma stimuli. This finding is not consistent with some previous studies showing moderate associations between reflexive avoidance and self-reported avoidance of threatening stimuli (e.g., Rinck and Becker, 2007) or self-reported arousal (Fleurkens et al., 2014). Our lack of association between reflexive avoidance and explicit avoidance could be interpreted as an example of the two distinct behavioral systems (reflexive and controlled) operating to guide behavioral expression. Indeed, laboratory studies have shown that responses to the same stimulus across different systems (such as reflexive avoidance and self-reported avoidance) are less coherent than responses within the same system (Huijding & de

Jong, 2006; Evers et al., 2014). Further study is needed to examine whether reflexive avoidance is associated with other measures within the impulsive system (e.g., eyeblink startle response).

Limitations

One of the limitations of our study was a small sample size. With a larger sample size, we may have had sufficient power to detect small associations between reflexive avoidance and self-reported PTSD symptoms. Second, we did not have information about valence and arousal ratings, or ratings of trauma-relatedness of images, for all participants in the study and thus were unable to examine the relationship between these individual ratings and reflexive avoidance. Finally, as this study was cross-sectional, it was not possible to determine *when* reflexive avoidance behaviors in trauma-exposed veterans developed relative to trauma or the development of PTSD. Though the lack of reflexive avoidance to combat images in non-trauma exposed civilians does suggest that trauma exposure is the important factor in determining the development of reflexive avoidance, future longitudinal studies examining the course of avoidance behaviors prior to and following trauma are needed to answer these questions.

Summary

In summary, the current study found that both veterans with and without PTSD showed more reflexive avoidance of trauma-relevant images than non trauma-exposed civilians, and that these avoidance tendencies were associated with PTSD re-experiencing symptoms. These findings provide preliminary evidence that trauma-exposed individuals exhibit reflexive avoidance of trauma-relevant stimuli and suggest that measuring such reflexive avoidance can provide information that is distinct from that provided by clinician- or self-report measures.

Study 2:

How do reflexive avoidance tendencies relate to neural activity in response to trauma-related stimuli in veterans with and without posttraumatic stress disorder?

In response to threat-related stimuli, individuals with PTSD often exhibit hypoactivity of certain prefrontal regions, including ventromedial prefrontal cortex (VMPFC) and right ventrolateral prefrontal cortex (RVLPFC) regions, as well as amygdala hyperactivity (Hayes et al., 2012). These neurobiological impairments in inhibitory functioning and elevations in affective responding may also be associated with increased reflexive avoidance of threatening stimuli. For example, enhanced amygdala activity was found to be associated with avoidance of aversive events in healthy adults (Schlund & Cataldo, 2010) and children (Schlund et al., 2010). Furthermore, tasks that require inhibition of a pre-potent behavior rely on top-down inhibitory processes that are often impaired in PTSD. For example, inhibition of response during a Go-NoGo task involving negative emotional stimuli elicited greater activity in MPFC compared to "Go" trials and non-emotional "NoGo" trials (Goldstein et al., 2007); successful inhibition of response during a stop-signal task with healthy adults was associated with greater MPFC activity (Li, Huang, Constable, & Sinha, 2006); and more inhibitory errors in a Go-NoGo task in a PTSD sample was associated with decreased RVLPFC activity (Falconer, 2008). However, it is currently unclear whether neural responsivity to threat-related stimuli in individuals with PTSD is associated with reflexive avoidance of threat-related stimuli.

The aim of Study 2 was to examine the association between automatic avoidance tendencies of trauma-related images and neural reactivity in response to trauma-related images, specifically in brain regions responsible for threat processing and inhibitory regulation, including bilateral amygdala and right ventrolateral and ventromedial prefrontal cortex areas. To

investigate this aim, veterans with and without PTSD underwent functional magnetic resonance imaging (fMRI) while completing tasks designed to examine emotional reactivity and spontaneous inhibitory regulation in response to trauma-related stimuli (i.e., combat images) and also completed a behavioral task to assess approach-avoidance tendencies of combat images. We first hypothesized that individuals with PTSD would show heightened activation of amygdala regions and reduced activity in RVLPFC and VMPFC regions compared to healthy control individuals in response to viewing combat compared to neutral images. Second, we hypothesized that reflexive avoidance tendencies of both low and high arousal combat images would be associated with greater amygdala activation and less activation in prefrontal regions during combat image viewing. Results in this direction would suggest that neurobiological processes involved in heightened emotional reactivity and reduced inhibitory regulation may contribute to avoidance tendencies in PTSD.

Method

Participants

Veterans with combat-related PTSD (n = 21) and combat-exposed veterans without PTSD (VET-HC; n = 20) were recruited to complete the fMRI study. Inclusion and exclusion criteria are described in Study 1 above. Due to the fMRI component, additional exclusion criteria for Study 2 included left-handedness, non-removable metal in the body, claustrophobia, more than mild traumatic brain injury, and chronic childhood abuse prior to age 7 due to evidence for adverse brain development and structural abnormalities in this subgroup of individuals (Glaser, 2000).

One PTSD participant dropped from the study prior to completing the scan, and one PTSD participant and one VET-HC did not complete the laboratory tasks due to technical issues. Of remaining participants, one PTSD participant stopped the combat fMRI task early due to heightened distress, and two PTSD participants and one VET-HC participant had to be removed from analyses: one PTSD participant did not comply with the task instructions, one had excessively long reaction times during the AAT (see Study 1 above), and one VET-HC participant was not able to properly view combat images during the fMRI task due to technical difficulties. Thus the final analytical sample included 16 PTSD and 18 VET-HC participants.

The average age of participants was 31.5 (*SD* = 5.6), and the majority of the sample was male (84.2% male, 15.8% female). 42.1% of participants were Hispanic/Latino, 26.3% White, 13.2% mixed race, 10.5% Asian, and 7.9% Black. In terms of education level, 63.2% of participants had completed some college, 15.8% had completed a college degree, 10.5% had completed a graduate school degree, 7.9% had completed some graduate school, and 2.6% had completed a high school diploma or less.

Procedure

All participants completed a diagnostic assessment to determine eligibility (see below). Approximately one week following the diagnostic assessment, eligible participants came into the laboratory for an in-person appointment, during which they completed an fMRI scan and joystick automatic approach-avoidance task (AAT, see below; Rinck & Becker, 2007). Prior to entering the scanner, participants were led through detailed instructions and practice trials for all fMRI tasks. After completing the scan and AAT, healthy control participants were debriefed and dismissed, and PTSD participants were scheduled for follow-up appointments as described in Study 3.

Measures

Clinician-Administered PTSD Scale for DSM-5 (CAPS-5; Weathers et al., 2013). The CAPS-5 is a 30-item structured interview used to assess PTSD symptoms over the past month. For each PTSD symptom, a severity rating from 0 (absent) to 4 (extreme/incapacitating) is made, with a rating of 2 or above qualifying as a "threshold" level to be counted towards a PTSD diagnosis. A total symptom score is calculated by summing the individual item severity scores for items 1-20, which include ratings for symptoms of re-experiencing, avoidance, negative alterations in cognitions or mood, and hyperarousal. Thus CAPS-5 total scores range from 0 (all symptoms absent) to 80 (all symptoms present and extreme/incapacitating).

Joystick Approach Avoidance Task (AAT; Rinck & Becker, 2007). Participants completed the AAT as described above in Study 1. Scoring and data reduction for the AAT is described above in Study 1. Low Arousal, High Arousal, and Empty effect scores were used in the current analysis.

fMRI tasks

While in the scanner, participants completed blocks of trials including: combat-observe, neutral-observe, combat-affect label, and shape-match. For all combat trials, combat images consisted of genuine war photos from the Military Affective Picture Set (MAPS; Dretsch et al., 2012), the majority of which were taken in Iraq and Afghanistan. Neutral images were taken from the International Affective Picture Set (IAPS; Lang, Bradley, & Cuthbert, 2008). For each type of trial, participants viewed two blocks consisting of five images each across two runs, for a total of four blocks per trial type. Each image was presented for 5 seconds. Following each block, participants rated their distress viewing the previous block of images on a scale of 1 (no distress)

to 9 (extreme distress). All stimuli were presented using Matlab (Mathworks, Inc.) software and high resolution goggles, and the order of tasks was counterbalanced across participants.

During combat-observe and neutral-observe trials, participants were instructed to observe the images presented and respond as they normally would. The combat-observe task was designed to measure emotional reactivity and spontaneous inhibitory regulation (i.e., emotional responses in the absence of any directions to use any specific inhibitory regulation) in response to trauma-relevant stimuli, while the neutral-observe task was used to control for processing related to perception of visual stimuli. Thus we used the contrast of combat-observe *vs* neutral-observe to provide an index of emotional reactivity and spontaneous inhibitory regulation controlling for processing of visual material.

Regions of interest were defined functionally from combat-affect label minus shape-match contrasts. During combat-affect label trials, participants viewed combat images and chose (using a button box) one of three labels at the bottom of the screen that best corresponded with their current emotion. During shape-match trials, participants viewed a target shape and chose from one of three shapes at the bottom of the screen that matched the shape at the top of the screen. See Figure 2 below for examples of each trial type. The contrast of combat-affect label vs. shape-match provided an index of emotional processing and inhibitory regulation in response to trauma-relevant images, controlling for neural activity associated with response selection and motor processing (Lieberman et al., 2007).

Image acquisition and data processing

Magnetic resonance images depicting blood oxygen level dependent (BOLD) signal were collected using a Trio 3.0 Tesla MRI scanner at the UCLA Staglin Center for Cognitive Neuroscience. A functional scan was acquired for each task (gradient-echo, TR=2000ms,

TE=30ms, flip angle=90°, matrix size=64x64, resolution 3.1 x 3.1 x 4.0mm, FOV=200mm, 33 axial slices, 4mm thick).

All fMRI data pre-processing was completed using Statistical Parametric Mapping 8 (SPM8; London, UK). Preprocessing included slice-timing to correct for order of slice acquisition, realignment to correct for head motion, segmentation to facilitate normalization, normalization to Montreal Neurological Institute standard stereotactic space, and smoothing (5mm Gaussian kernel, full width at half maximum) to increase the signal-to-noise ratio. First level contrast images were computed for each participant and used in group-level analyses.

ROI definition

In order to constrain analyses to regions involved in emotional processing and inhibitory regulation of trauma-related stimuli, we defined functional ROIs from the combat-affect label vs. shape-match contrast. This approach allowed us to examine functionally relevant ROIs in our contrast of interest while also limiting bias by using a separate contrast to define the ROIs (Friston et al., 2006). Regions of left and right amygdala, RVLPFC, and VMPFC showing greater activation in combat-affect label > shape-match were identified. For group-level analyses, we used a mask image of these defined regions to examine the combat-observe vs. neutral-observe contrast. We then used Matlab to extract parameter estimates from the combat-observe > neutral-observe contrast within each ROI (defined by the combat-affect label > shape-match contrast), and these parameter estimates were used in subsequent analyses.

Statistical analyses

Group-level analyses were implemented using SPM8. We examined the combat-observe vs. neutral-observe contrast between groups (VETHC vs. PTSD), using a mask image

comprising right and left amygdala, RVLPFC, and MPFC regions as defined above, small volume-corrected with an error rate of .05.

To examine the relationship between neural activation and reflexive avoidance tendencies, we employed a series of multiple regression analyses with Low Arousal and High Arousal effect scores as dependent variables. Empty effect scores were included as covariates in all analyses to control for baseline response latencies. Parameter estimates for ROIs (right and left amygdala, RVLPFC, and VMPFC) were examined separately as predictors of High Arousal and Low Arousal effect scores. Group (VETHC or PTSD) was also included as a predictor, as well as the Group x ROI interaction in order to examine whether the association between neural activity and reflexive avoidance depended on Group.

Results

Preliminary analyses

We first examined demographic differences between groups and found no significant differences across age, gender, or ethnicity (ps > 0.12); thus, these variables were not included in further analyses.

Behavioral results

VETHC and PTSD groups both reported significantly higher distress ratings during the combat-observe task compared to the neutral-observe task (ps < .001). Distress ratings did not significantly differ between groups for either combat-observe nor neutral-observe (see Table 3).

Combat-observe vs. *neutral-observe comparison*

The contrast of combat-observe vs. neutral-observe revealed no differences between groups that reached threshold significance level within our defined ROIs. Thus, we combined

VETHC and PTSD groups to examine brain activity during combat-observe vs. neutral-observe activity across groups. In this analysis, there was heightened activation in combat-observe > neutral-observe in regions within right amygdala, left amygdala, RVLPFC, and MPFC (small volume corrected, $p < .05$; see Table 4 and Figure 3).

Neural activity as a predictor of reflexive avoidance

Neural activity in right and left amygdala, RVLPFC, and MPFC during combat-observe vs. neutral-observe did not significantly predict High Arousal (*p*s > .16) or Low Arousal (*p*s > .21) effect scores. There were no significant Group x ROI interactions across analyses of either High Arousal or Low Arousal effect scores (all *p*s > .28).

Discussion

In this study we examined neural activity in veterans with and without PTSD in response to viewing trauma-related combat (versus neutral) images, as well as the association between neural reactivity and reflexive avoidance of trauma-related images. We focused particularly on brain regions involved in threat processing and inhibitory regulation, including bilateral amygdala, right ventrolateral prefrontal cortex, and ventromedial prefrontal cortex. In a blocked design, veterans with and without PTSD observed combat images and neutral images while undergoing fMRI. We defined our regions of interest using a separate contrast designed to index emotional processing and inhibitory regulation in response to trauma-related images. Following the fMRI, participants completed an approach-avoidance task in order to examine reflexive avoidance of combat images. Overall, we found that both veterans with and without PTSD exhibit heightened bilateral amygdala, right ventrolateral prefrontal cortex, and medial prefrontal cortex activation in response to combat (versus neutral) images. Additionally, we found no

significant associations between reflexive avoidance of combat images and neural reactivity to combat versus neutral images within our regions of interest.

Neural reactivity to combat versus neutral images

While we had hypothesized that veterans with PTSD would show heightened activation of amygdala regions and reduced activity in right ventrolateral prefrontal cortex and ventromedial prefrontal cortex regions in response to viewing combat compared to neutral images, our results did not support this hypothesis. Across both groups (veterans with and without PTSD), bilateral amygdala, right ventrolateral prefrontal cortex, and medial prefrontal cortex activation was greater while observing combat versus neutral images, with no significant between-group differences observed. This pattern of results mirrored participants' behavioral data, which showed no significant differences between the groups' distress ratings while viewing combat images but significantly heightened distress across both groups while viewing combat compared to neutral images. Overall, these results are not consistent with findings from prior neuroimaging studies showing that individuals with PTSD generally exhibit hypoactivity of VMPFC and RVLPFC regions, and hyperactivity in amygdala regions, during symptom provocation or emotion-cognition tasks (see Hayes et al., 2012).

Our distinct findings may in part be due to methodological differences. For example, several previous studies examining neural reactivity in PTSD have used non-veteran trauma samples, such as individuals who developed PTSD after a motor vehicle accident (e.g., Lanius et al., 2007; Frewen et al., 2008) or following sexual or physical assault (Lanius et al., 2001; Protopopescu et al., 2005). It is possible that veterans with combat-related trauma may exhibit different patterns of neural activity in response to trauma reminders than individuals who have experienced other types of trauma. For studies that have examined combat veterans specifically,

some have found that veterans with PTSD exhibit hyperactivity in amygdala regions and hypoactivity in prefrontal regions in response to trauma stimuli (e.g., Shin et al., 2004), while others have not (e.g., Britton et al., 2005). A recent study found that combat veterans with and without PTSD did not exhibit distinct neural responses while viewing aversive images but that those with PTSD showed reduced engagement of dorsolateral prefrontal cortex regions during an emotion regulation task (Rabinak et al., 2014). Thus, it is possible that differences in neural reactivity in combat veterans with and without PTSD are more evident during emotion regulation versus passive viewing tasks. Further research is needed to examine this question. Additionally, further research examining neural responses to trauma-relevant images within not only combat veterans with and without PTSD, but also non-combat exposed healthy controls, would help tease apart differences in reactivity that are due to trauma exposure or the occurrence of PTSD.

Neural reactivity and reflexive avoidance

While we had hypothesized that reflexive avoidance tendencies of combat images would be associated with greater amygdala activation and less activation in prefrontal regions during combat image viewing, we found no significant associations between reflexive avoidance and neural reactivity within amygdala, right ventrolateral prefrontal cortex, or ventromedial prefrontal cortex regions. As no previous studies have directly examined the association between reflexive avoidance and neural reactivity, it is difficult to determine whether our results are specific to the current study. However, previous studies have shown that avoidance of aversive stimuli is associated with heightened amygdala activity (Schlund and Cataldo, 2010), and that deficits in controlled processing in PTSD are associated with decreased activity in prefrontal cortex regions (e.g., Falconer, 2008). Our results suggest that emotional reactivity and deficits in

controlled processing, insofar as they are measured by neural activation while viewing trauma-related stimuli, are not associated with reflexive avoidance of trauma-related stimuli.

One possibility for our finding is that the neural circuitry involved in reflexive avoidance behaviors is distinct from the patterns of neural activity that occur while passively viewing trauma-related stimuli. As reflexive avoidance behaviors occur very quickly, it may be that neural reactivity to trauma stimuli presented briefly (rather than over a block of time as in the current study) would be more closely associated with reflexive avoidance tendencies. Presenting combat images over a block of time may allow individuals to regulate their responses, which may then provide an index of neural reactivity that is incongruent with that which may occur during quick reflexive responding. In order to better examine this question, future studies should implement event-related designs with shorter stimulation presentations or should examine neural responses *during* the AAT, perhaps using a version of the AAT that requires less movement.

Limitations

There are a number of limitations to the current study. First, as the AAT was conducted outside the scanner, we were not able to examine participants' neural reactivity to images while completing the task. Second, we did not include non-trauma-exposed healthy controls in the current study, and this it was not possible to determine whether results were specific to trauma-exposed individuals. Finally, our analyses were limited to certain regions of interest rather than a whole-brain analysis approach. However, we felt that a region-of-interest approach was most suitable to this analysis as it allowed to identify certain regions that were functionally related to our cognitive processes of interest.

Summary

Overall, our results suggest that veterans with and without PTSD exhibit similar levels of distress and similar patterns of neural reactivity in amygdala, right ventrolateral prefrontal cortex, and ventromedial prefrontal cortex regions in response to passively viewing trauma-related stimuli compared to neutral stimuli. Furthermore, these patterns of response do not appear to be related to reflexive avoidance tendencies, perhaps due to different types of neural circuitry responsible for responding in passive viewing versus reflexive avoidance tasks. Future studies should investigate neural reactivity during approach avoidance tasks to evaluate how these processes are related to reflexive avoidance in real-time.

Study 3:

Can reflexive avoidance be modified through inhibitory regulation training?

Enhancing inhibitory regulation processes may help improve treatment outcomes for individuals with PTSD. Neuroimaging research has helped identify two methods that may be particularly effective for enhancing inhibitory regulation circuitry: affect labeling and Go-NoGo. Affect labeling in combination with exposure leads to reductions in psychophysiological responding and behavioral avoidance of feared stimuli in spider-phobic individuals (Tabibnia, 2008; Kircanski et al., 2012) and reduced physiological arousal in individuals with social anxiety disorder (Niles et al., 2015). The Go-NoGo, while primarily used as an assessment task, strongly recruits inhibitory networks (e.g., Kelley et al., 2005) and thus has the potential to modify or strengthen individuals' inhibitory regulation abilities through repeated training.

The current study aimed to examine the effects of affect labeling and Go-NoGo as a novel inhibitory regulation-based training protocol. In particular, this study aimed to investigate the effects of affect labeling and Go-NoGo training on subjective, physiological, and reflexive avoidance outcomes in veterans with combat-related PTSD. We hypothesized that, compared to a wait list condition, training in affect labeling and Go-NoGo would lead to reductions in subjective ratings of PTSD symptoms and reduced physiological arousal and reflexive avoidance of combat-related stimuli.

A secondary aim of the study was to examine training variables as predictors of outcome. Prior studies of affect labeling in anxious samples have found that increased usage of anxiety-related labels during affect labeling trials predicted greater follow-up reductions in skin conductance responsivity (Kircanski et al., 2012; Niles et al., 2015). Thus, we expected that increased usage of negative emotion labels during affect labeling training would be associated

with greater reductions in skin conductance reactivity. In addition, as successful inhibition during NoGo trials recruits inhibitory regulation networks, we also investigated performance during NoGo trials as a predictor of outcome. Finally, we examined whether heightened arousal and variability in arousal levels during training sessions predicted superior outcome (e.g., Culver, Stoyanova, & Craske, 2012; Kircanski et al., 2012).

Method

Participants

Participants (n = 30) with combat-related PTSD were recruited through advertisements in the Los Angeles community and through referrals from veteran organizations. Eligible veteran participants were between 18 and 45 years old, had deployment experience, and met DSM-5 or DSM-5 "Otherwise specified" criteria for PTSD, non-dissociative subtype, according to the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5; Weathers et al., 2013) with a Clinician Severity Rating (CSR) of 4 or higher. Additional inclusion and exclusion criteria are described above.

Three participants dropped from the study prior to completing the Pre assessment, and demographic data were not available for one of these participants. For remaining participants, the mean age was 32.34 (SD = 6.49), 93% were male, 48.3% Hispanic/Latino, 27.6% White, 10.3% Black/African-American, and 13.8% other or mixed race.

Procedure

All participants first completed a phone screener to determine their initial eligibility for the study. Initially eligible participants were invited to complete the diagnostic assessment, including the CAPS-5 and SCID-5, to determine their full eligibility. Eligible participants then

completed a physiological assessment (see below) during which skin conductance and heart rate were recorded while participants complete several tasks, followed by a joystick approach-avoidance task (JAAT, see below; Rinck & Becker, 2007). For neuroimaging participants, the physiological assessment took place during the scan (though the tasks completed were identical). Following the baseline assessment, participants were assigned to either the Training or Waitlist (WL) condition. As this study was part of a larger study examining the effects of the training on outcome, we had to allocate the first 20 participants to the training condition; thus only a small subset of participants were randomized to WL or Training. A diagram of participant flow through the study is below (see Figure 4).

Participants in the Training condition completed 6 training sessions as described below (twice per week for 3 weeks), followed by a post-physiological assessment and AAT approximately one week later. WL participants received weekly phone calls for 3 weeks, followed by a post-physiological assessment and AAT (see Figure 5 below).

Physiological assessment

At Pre and Post, participants completed a brief physiological assessment. To examine physiological reactivity to trauma-related stimuli, participants viewed a series of twenty combat-related images (4 blocks of 5 images each) while their skin conductance was recorded. The images used were taken from a set of actual photos taken in Iraq and Afghanistan (Dretsch et al., 2012); each image appeared on a computer screen one at a time for 5 seconds. Skin conductance and heart rate recordings were collected to examine physiological reactivity (see Outcome Measures below).

Joystick approach avoidance task

Participants completed the joystick approach-avoidance task (AAT; Rinck & Becker, 2007) at Pre and Post as described above in Study 1. Scoring and data reduction for the AAT is described above in Study 1. Low Arousal, High Arousal, and Empty effect scores were used in the current analysis.

Training sessions

Training sessions were conducted in a partially automated, computerized format; a graduate-level clinician or highly-trained bachelor-level research assistant guided the participant through instructions at the beginning of each session and then the participant was guided through the session by prompts and instruction slides that appeared on a computer screen. The researcher remained in the room throughout the session to gauge the participants' progress and assess the participants' emotional distress before and after each training session. Each session lasted approximately one hour.

Each session began with instructions and a physiological baseline, during which the participant remained still for two minutes to obtain baseline readings of physiological measures (heart rate and skin conductance level). Participants then viewed a series of combat-related and non-combat related negative images and complete a series of tasks designed to enhance participants' inhibitory regulation processes. Participants completed 4 types of tasks during each training session: 1) combat affect/content labeling (Combat AL), 2) faces affect labeling (Faces AL), 3) IAPS content/affect labeling (IAPS AL), and 4) a Go-NoGo task. Trials were separated into 2 blocks; 13 trials each of Combat AL, Faces AL, and IAPS AL tasks, and 200 Go-NoGo trials were completed in each block. Trial order was counterbalanced across participants.

Combat affect/content labeling (Combat AL). During Combat AL trials, participants viewed a combat-related images for 8 seconds, followed by a 5-second labeling period, during

which they chose a label word at the bottom of the screen that best matched either their current emotion or the content of the image. Emotion labels were followed by the prompt "I feel…" and label choices always included two emotions words (anxious, sad, guilty, angry, or disgusted) and "other" as options (see Figure 6). Participants were instructed to choose the emotion word that most closely matched the emotion they were experiencing at that moment or to choose "other" if neither of the words is fit their current emotion. Content labels were followed by the prompt "I see…" and participants were instructed to choose one of three words displayed at the bottom of the screen that best described the image content. Content labels included one negative relevant option, one negative irrelevant option, and one neutral option. AL trials included 50% affect label trials and 50% content label trials.

IAPS affect/content labeling. (IAPS AL). IAPS AL trials were identical to Combat AL trials except that images comprised negatively valenced images from the IAPS set.

Faces affect labeling (Faces AL). During Faces AL trials, participants viewed images of negative facial expressions taken from the NimStim set (Tottenham et al., 2009) for 8 seconds, followed by a 5-second labeling period, in which they chose a label word at the bottom of the screen that best matches the facial expression portrayed in the image. Label choices included two emotion words (anxious, sad, guilty, angry, or disgusted).

Go-NoGo. During the Go-NoGo task, participants were presented with a letter on the screen at a rate of once per second. Participants were instructed to press a key on the keyboard each time they see a letter ("Go" trials), except for the letter identified on the instruction slide prior to the task ("NoGo" trials). 80% of trials were Go trials, and 20% were NoGo trials.

Outcome measures

PTSD Checklist for DSM-5 (PCL-5; Weathers et al., 2013*)*. The PCL-5 is a 20-item self-report questionnaire that assesses DSM-5 symptom criteria for PTSD (see Appendix A). Participants rate each symptom on a scale of 0 ("Not at all") to 4 ("Extremely"). The PCL-5 has been shown to exhibit good internal consistency, test-retest reliability, and validity (Bovin et al., 2015).

Skin conductance level (SCL). SCL while viewing combat images was used as a physiological measure of arousal. BIOPAC Acqknowledge software was used for all SCL data extraction. To measure skin conductance, two AgCl electrodes attached to a BIOPAC recording device (Biopac Systems Inc., Goleta, CA) were placed on the middle and ring fingers of the participants' left hand at the beginning of the physiological assessment. SCL across each 20s block of viewing combat images was extracted and averaged for further analyses.

Heart rate (HR). HR while viewing combat images was used as a second measure of physiological arousal. HR was collected from electrodes placed on the right clavicle and below the bottom left front rib or from a pulse oximeter finger cuff places on the left index finger. HR was defined as the number of heart beats per minute and was extracted across each 20s block of viewing combat images and averaged for further analyses.

Reflexive avoidance. Effect scores for each type of trial (high-arousal, low-arousal, and empty) were computed as described in Study 1. The effect score reflects the relative strength of approach or avoidance tendencies: a more negative score indicates stronger avoidance (Rinck & Becker, 2007).

Predictor variables

Word choice. During Combat AL trials, participants chose from a set of labels displayed on the computer screen. The number of emotion words chosen, as well as the number of "anxiety" label chosen, were recorded for each participant and examined as a predictor of outcome.

Go-NoGo performance. Correct response inhibition (no response during NoGo trials) and commission errors (responses during NoGo trials) were collected to create an index of the percentage of correct NoGo responses. Percentage of correct NoGo responses served as a measure of successful response inhibition and was examined as a predictor of outcome.

Physiological reactivity. Skin conductance level (SCL) was measured throughout all training sessions using a BIOPAC recording device via two AgCl electrodes attached to participants' chest and abdomen. Changes in arousal level from the first to last training session were computed as mean SCL during Training session 1 minus mean SCL during Training session 6 (not including the physiological baseline). Variability in arousal was computed as the standard deviation of skin conductance level during each training session (not including the physiological baseline), averaged across the six training sessions.

Statistical analyses

To examine the effect of inhibitory training on outcome, we conducted multilevel modeling for repeated measures in Stata 12.1, with outcome variable (PCL, SCL, HR, or AAT effect score) as the repeated measures dependent variable (level 1 unit) nested within subjects (level 2 unit). Intercept and slope were allowed to vary randomly. Group (Training or WL), Time (Pre and Post), and the interaction of Group x Time were included as predictors. For the AAT analysis, Trial (High Arousal, Low Arousal, Empty) was also included as a predictor variable, along with the three-way interaction of Group x Time x Trial. Follow-up comparisons were conducted to examine simple effects. For significant findings, effect sizes were calculated using the "multilevel tools" (mlt) package in Stata 12.1 (Mohring & Schmidt, 2012), which computes effect sizes according to the Snijders & Bosker (1994) method. Between-subject effects (R_2^2) are reported as the proportion of the between-subject variance accounted for by the effect. The effect

size of Time (R_1^2) is reported as the proportion of within-subject variance accounted for by Time.

To examine the effects of training predictor variables on outcome, we conducted a series of regression analyses with either Post PCL score or Post SCL as the dependent variable. For these analyses, Pre PCL score or Pre SCL was always included as a covariate. Number of emotion words, number of correct NoGo responses, change in SCL, and SCL variability were each examined separately as predictors of outcome.

Results

Preliminary analyses

There were no significant differences in demographic or outcome variables between those in the Training versus WL condition (*p*s > .05), with the exception of SCL at Pre; WL participants had higher mean SCL at Pre than those in the Training condition ($t = 2.14$, $p = .04$). There were no significant differences in demographic variables or outcome variables at Pre (PCL, SCL, HR, and AAT effect scores) between participants who completed the Training or WL compared to those who did not (*p*s > .38).

Outcome results

PCL. There was a significant Time x Group interaction ($z = -2.62$, $p = .009$, 95% CI [-31.7, -4.6]; $R_2^2 = 0.28$; $R_1^2 = 0.29$; see Figure 7), such that those in the Training condition experienced a significant reduction in PTSD symptoms from Pre to Post ($z = -2.91$, $p = .004$), whereas the Waitlist condition showed a slight increase in PTSD symptoms from Pre to Post ($z = 2.29$, $p = .02$). The PCL within-group effect size for the Training condition was 0.39 (computed as $(M_{pre} - M_{post})/[(SD_{pre}^2 + SD_{post}^2)/2]^{1/2}$).

SCL. There was no significant Time x Group interaction for SCL (p = .58). SCL in response to combat images showed no significant change from Pre to Post in either the Training or Waitlist condition (p > .59).

HR. There was no significant Time x Group interaction for HR (p = .79), with HR responses to combat images showing no significant change from Pre to Post in either the Training or Waitlist condition (ps > .76).

AAT. There was a significant Time x Group x Trial interaction (χ^2 = 7.15, p = .028; R_2^2 = 0.10; R_1^2 = 0.21; see Figure 8). Examination of the simple effects of each Trial type over Time within each Group indicated that those in the Training condition showed a significant reduction in reflexive avoidance of High Arousal (z = -2.15, p = .03) and Low Arousal (z = -2.56, p = .01) images but not Empty images (p = .44), whereas the WL condition showed no change in reflexive avoidance from Pre to Post for High Arousal, Low Arousal, or Empty trials (ps > .08). Contrasts examining High Arousal vs. Empty and Low Arousal vs. Empty effect scores from Pre to Post indicated a significant increase in reflexive avoidance of Low Arousal vs. Empty images for those in the Waitlist condition (p = .023), but not for High Arousal vs. Empty images (p = .13), and no significant change for participants in the Training condition (ps > .19).

Predictor results

Word choice. Number of emotion words chosen during Combat AL was not a significant predictor of PCL outcome (p = .70) or SCL at Post (p = .77).

Go-NoGo performance. Percentage correct NoGo trials was not a significant predictor of PCL outcome (p = .78) or SCL at Post (p = .18).

Physiological reactivity. SCL variability significantly predicted PCL outcome such that greater variability in SCL during training sessions was associated with better outcome (t = -3.29, p

= .009, *CI* [-35.94, -6.64]). Change in SCL from the first to last training session was not a significant predictor of PCL outcome (p = .95). Neither SCL variability nor change in SCL from the first to last training session was a significant predictor of SCL at post (ps > .28).

Discussion

In this study we examined the effect of an inhibitory regulation-based training on self-reported PTSD symptoms, reflexive avoidance, and physiological reactivity in veterans with PTSD. Participants completed six hour-long training sessions that included affect labeling tasks - viewing combat images, other aversive images, and images of faces while labeling their own emotions or the content of the images – as well as Go-NoGo tasks. Compared to the waitlist condition, veterans who were assigned to the training condition reported a significant reduction in self-reported PTSD symptoms and exhibited reduced reflexive avoidance of trauma-related images, but did not exhibit changes in physiological reactivity to trauma-related images from pre- to post-training. In addition to examining outcome variables, we analyzed several potential predictors of outcome. We found that greater variability in physiological reactivity throughout the training sessions significantly predicted better outcome. Affect labeling word choice, Go-NoGo performance, and change in physiological reactivity from the first to last training session were not significant predictors of outcome.

Training outcome

Results partially supported our hypotheses, with veterans in the training condition experiencing significant reductions in self-reported PTSD symptoms and reflexive avoidance, but not physiological arousal, compared to those in the wait list condition. These findings provide initial evidence that a brief intervention targeting inhibitory regulation functioning can

lead to improvements in PTSD symptoms and reflexive avoidance in combat veterans. While effect sizes in the current study ($d = 0.39$ for the PCL) are not as large as those in studies examining individualized PTSD treatment such as prolonged exposure (e.g., PCL effect size $d = 2.09$; Tuerk et al., 2011), they do suggest that a semi-automated, computerized intervention can produce moderate improvements in PTSD symptoms. Notably, those in the wait list condition experienced a slight worsening of symptoms, consistent with previous findings that PTSD symptoms can increase over time, especially among veterans exposed to combat (Orcutt, Erickson, & Wolfe, 2004; Bonanno et al., 2012). Though in the current study, wait list condition participants were called weekly and were given the option of completing the training following the wait list period, future studies using combat veteran samples may consider utilizing active control treatment conditions in order to help prevent symptom worsening.

Our finding that the training did not lead to reductions in physiological arousal is in contrast to previous studies that have found greater reductions in physiological arousal when exposure was paired with affect labeling compared to exposure alone (Kircanski et al., 2012; Niles et al., 2015). In the current study, those in the training condition did not experience reductions in skin conductance level or heart rate in response to viewing combat images, suggesting that improvements in their self-reported symptoms occurred without congruent changes in physiological arousal. Previous studies have only examined affect labeling in combination with exposure to disorder-relevant stimuli, while the current study examined affect labeling in combination with both disorder-relevant and other stimuli, as well as Go-NoGo tasks, in order to target inhibitory regulation. Thus, it is possible that physiological arousal in response to viewing disorder-relevant stimuli (ie., combat images) was less targeted in the current study.

With regard to reflexive avoidance, those in the training condition experienced a significant reduction in reflexive avoidance of both high arousal and low arousal images from pre to post training, though this effect was no longer significant after controlling for changes in reflexive avoidance of empty images from pre to post training. In contrast, those in the wait list condition experienced a significant *increase* in reflexive avoidance of low arousal images after controlling for changes in reflexive avoidance of empty images, a finding that parallels the wait list group's slight worsening of self-reported PTSD symptoms. These findings show that an intervention targeting inhibitory regulation can effectively reduce reflexive avoidance behaviors, suggesting that the neural circuitry strengthened through inhibitory regulation training may also improve reflexive avoidance behaviors. Furthermore, our findings corroborate other evidence that reflexive avoidance is a malleable construct that can show change through intervention (e.g., Reinecke et al., 2012). Further studies are needed to replicate these findings, and future research should examine whether changes in reflexive avoidance from pre to post treatment predict maintenance of gains or further improvement during follow-up period.

Predictors of outcome

We examined the number of emotion labels, Go-NoGo performance, physiological arousal, and variability in arousal during training sessions as predictors of outcome. Only variability in arousal emerged as a significant predictor of outcome, with greater variability in skin conductance level during training sessions predicting superior outcome on self-reported PTSD symptoms. This is consistent with previous findings showing that variability in emotional responses during exposure leads to improved outcomes (Culver, Stoyanova, & Craske, 2012; Kircanski et al., 2012) and suggests that variability in one's internal state (ie., physiological arousal) may enhance the retrievability of inhibitory learning during exposure and help

generalize learning such that individuals can tolerate exposure to anxiety-provoking stimuli in a variety of internal states (Craske et al., 2008). Furthermore, our results suggest that variability in physiological arousal is more important than between-session differences in physiological arousal as change in skin conductance level from the first to last training session was not a predictor of outcome.

Regarding word choice during affect labeling and Go-NoGo performance, neither of these measures predicted training outcome. There are several potential explanations for these findings. First, both previous studies showing a beneficial effect of greater usage of anxiety-related words during exposure found this effect using skin conductance reactivity as an outcome variable (Kircanski et al., 2012; Niles et al., 2015). Given that we did not observe significant changes in skin conductance reactivity from pre to post training, it is possible that there may not have been enough variability in this outcome variable from pre to post to be accounted for by additional predictor variables. Second, it is possible that the beneficial effects of the affect labeling and Go-NoGo tasks during the training sessions were not due to the particular word choices selected during affect labeling or participants' performance during the Go-NoGo but rather to other mechanisms. For example, the act of applying a label to an aversive image during the training (regardless of the content of that label) may have served to enhance engagement and attention toward the aversive image, thereby facilitating exposure; and the inclusion of the Go-NoGo task may have served to increase variability in physiological arousal during the training sessions, thereby improving outcomes regardless of an individual's performance during the task. These questions must be examined through further research. Finally, there is also the possibility that the usage of affect labeling and Go-NoGo did not significantly enhance outcomes beyond the effect of exposure alone. The current study was designed to examine the overall effects of an

inhibitory regulation-based training paradigm on outcomes, and thus the effects of each singular component of the training cannot be parsed apart. This is certainly a limitation of the study, and future research should examine the effects of this training compared to an exposure-only condition.

Limitations

There are several limitations to the current study. First, our sample size was small, especially for the wait list comparison group. Second, only a subset of participants were randomized to the training or wait list condition, and thus between-group effects may not be generalizable to the larger population. Third, we had no exposure-only control group and thus we are not able to determine whether the affect labeling and Go-NoGo components of the training improved outcomes beyond the effect of exposure alone.

Summary

Our findings provide initial evidence that individuals with PTSD can experience an improvement in PTSD symptoms and reflexive avoidance behaviors through a relatively simple inhibitory regulation-based intervention involving six sessions of a semi-automated, computerized protocol. Though further studies using larger samples are needed to more thoroughly examine the effectiveness of the training and to investigate which components of the training are the key ingredients for producing change, these initial results are promising. Current treatments for PTSD such as prolonged exposure and cognitive processing therapy can be highly effective, but they require relatively intensive clinician training, and not all patients are willing to undertake these treatments. A recent review of treatment provided for veterans with PTSD found that only 41% of returning veterans with PTSD receive minimally adequate care (Hoge et al., 2004). Thus, developing alternatives that are easy to disseminate, such as the current training

program, could broaden patients' treatment options and potentially allow patients to have greater access to interventions.

Summary and Implications

Avoidance of trauma-related stimuli is a central feature of PTSD. Reflexive avoidance, the fast, automatic, and less deliberate attempts to avoid trauma-related stimuli, has been understudied in PTSD. The current dissertation project aimed to elucidate the role of reflexive avoidance in individuals with PTSD across three studies. The first study examined reflexive avoidance tendencies of trauma-related stimuli in military veterans with PTSD, trauma-exposed military veterans without PTSD, and non-trauma-exposed civilians, using an automatic approach-avoidance task. Compared to non-trauma exposed civilians, both veterans with and without PTSD showed greater reflexive avoidance of low arousal combat images, suggesting that the impulsive system may guide automatic avoidance tendencies in both veterans with and without PTSD, but only veterans without PTSD showed heightened reflexive avoidance of high arousal images. Additionally, re-experiencing symptom severity, but not other clusters of PTSD symptoms, was associated with reflexive avoidance of high arousal images and marginally associated with reflexive avoidance of low arousal images among veterans with and without PTSD. These findings provide initial evidence of reflexive avoidance behaviors and their correlates in veterans with PTSD.

The second study focused on the relationship between automatic avoidance tendencies and neural activity in veterans with and without posttraumatic stress disorder. We examined neural activity in veterans with and without PTSD in response to viewing trauma-related combat (versus neutral) images and examined the relationship between this neural reactivity and

reflexive avoidance of trauma-related images. We found that veterans with and without PTSD exhibited heightened bilateral amygdala, right ventrolateral prefrontal cortex, and medial prefrontal cortex activation in response to combat (versus neutral) images. However, we found no significant associations between reflexive avoidance of combat images and neural reactivity to combat versus neutral images within these regions. Thus we did not find evidence that reflexive avoidance of trauma-related stimuli is associated with emotional reactivity and deficits in controlled processing, as measured by neural activity in relevant brain regions while viewing trauma-related stimuli.

Finally, the third study examined the effect of inhibitory regulation training on self-reported PTSD symptoms, reflexive avoidance, and physiological reactivity in veterans with PTSD. Compared to a waitlist control condition, veterans who completed the training experienced significant reductions in self-reported PTSD symptoms and reduced reflexive avoidance of trauma-related images, but did not exhibit changes in physiological reactivity to trauma-related images from pre- to post-training. These findings provide initial evidence that individuals with PTSD can experience benefits from a relatively simple inhibitory regulation-based intervention. Greater variability in skin conductance level throughout the training sessions significantly predicted better outcome, whereas affect labeling word choice, Go-NoGo performance, and change in physiological reactivity from the first to last training session did not.

Overall, this set of studies suggests that trauma-exposed veterans, regardless of whether they meet criteria for PTSD, exhibit reflexive avoidance of trauma-related stimuli. Whether heightened reflexive avoidance simply represents a change that developed following trauma or a risk marker that signals a vulnerability to developing other problems is a topic for future research. Though we found that reflexive avoidance was not associated with neural activity within regions

of the brain involved in emotional responding and inhibitory regulation, our findings do provide evidence that reflexive avoidance in veterans with PTSD can decrease after training that includes inhibitory regulation-based tasks. Given the important role of avoidance in the maintenance of PTSD, assessing both reflexive avoidance and behavioral avoidance in these individuals will elucidate our understanding of how treatments address avoidance and potentially help improve outcomes for those seeking treatment.

Table 1. Demographic variables across groups in Study 1.

	PTSD (*n* = 29)	VET-HC (*n* = 20)	CIV-HC (*n* = 14)
Age (years)	32.3 (SD = 6.5)	31.2 (SD = 5.2)	26.9 (SD = 9.3)
Gender (% male)	93.1% (27/29)	80.0% (16/20)	71.4% (10/14)
Ethnicity			
Hispanic/Latino	48.3% (14/29)	30.0% (6/20)	7.1% (1/14)
White	27.6% (8/29)	35.0% (7/20)	7.1% (1/14)
Black	10.3% (3/29)	5.0% (1/20)	21.4% (3/14)
Asian	3.5% (1/29)	15.0% (3/20)	35.7% (5/14)
Other/Mixed	10.3% (3/29)	15.0% (3/20)	28.7% (4/14)

Note. PTSD = veterans with posttraumatic stress disorder; VET-HC = veteran healthy controls; CIV-HC = civilian healthy controls.

Table 2. Clinician Administered PTSD Scale (CAPS) symptom cluster scores and total scores.

	PTSD (*n* = 25)	VET-HC (*n* = 19)	*t*	*p*
CAPS Re-experiencing (*SD*) mean score (Range: 0-20)	6.72 (3.61)	0.68 (1.05)	56.47	<.001
CAPS Avoidance (*SD*) mean score (Range: 0-8)	3.64 (1.80)	0.11 (0.32)	82.85	<.001
CAPS Negative cognitions/mood (*SD*) mean score (Range: 0-28)	8.64 (6.04)	0.68 (1.06)	39.87	<.001
CAPS Hyperarousal (*SD*) mean score (Range: 0-24)	8.88 (3.98)	1.58 (1.64)	57.22	<.001
CAPS Total (*SD*) mean score (Range: 0-80)	27.88 (12.51)	3.05 (2.97)	--	--

Table 3. Distress ratings during Combat-observe and Neutral-observe trials across groups.

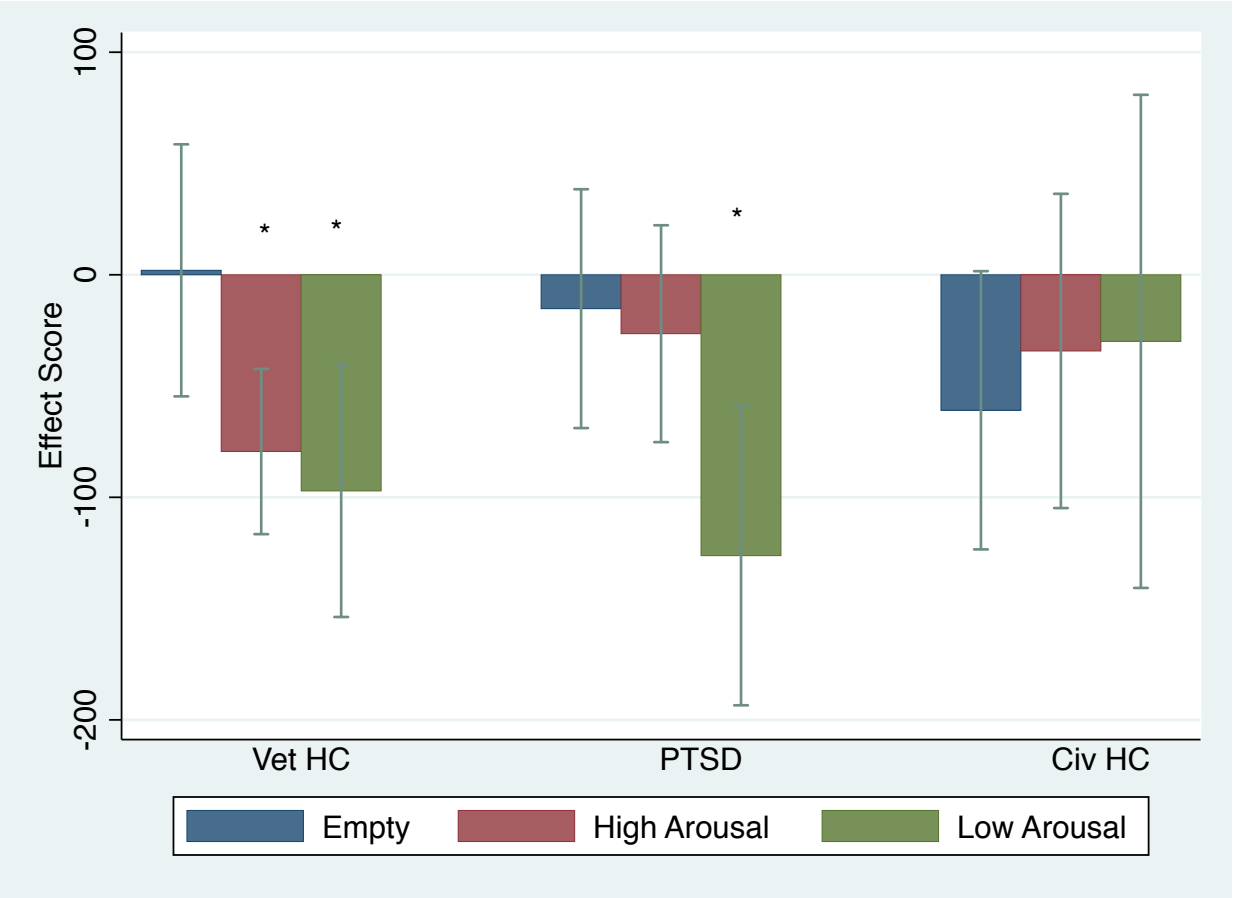
	PTSD (*n* = 16)	VET-HC (*n* = 18)	*t*	*p*
Combat-observe mean (*SD*) distress rating (Range 1-9)	5.72 [1.99]	4.49 [2.39]	1.70	.10
Neutral-observe mean (*SD*) distress rating (Range 1-9)	2.19 [1.27]	1.68 [1.03]	1.34	.19

Table 4. Regions showing greater activity during combat-observe compared to neutral-observe tasks (small volume corrected, $p < .05$).

Region	MNI coordinates			Size (voxels)	*t*
	x	*y*	*z*		
R amygdala	21	-1	-14	11	4.61
L amygdala	-21	-4	-14	17	6.03
RVLPFC	54	38	13	21	4.72
Ventromedial PFC	3	50	-11	67	4.60

Note. RVLPFC = right ventrolateral prefrontal cortex; PFC = prefrontal cortex.

Figure 1. Approach avoidance task effect scores across groups and trial types. Asterisks indicate significant within-group differences between Low or High Arousal vs. Empty trials.



Note. PTSD = veterans with posttraumatic stress disorder; Vet HC = veteran healthy controls; Civ HC = civilian healthy controls.

Figure 2. Examples of a) Combat-observe, b) Neutral-observe, c) Combat-affect label, and d) Shape-match trials.

a) 

b) 

c) 

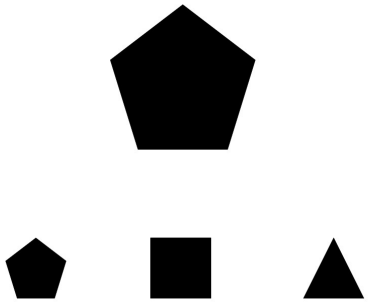
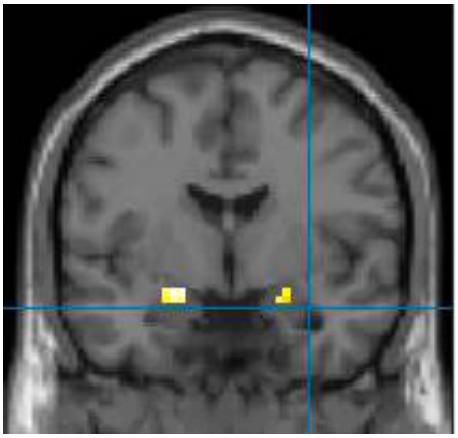
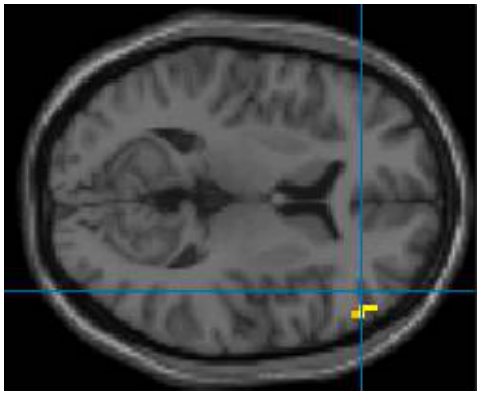
d) 

Figure 3. Regions within a) right and left amygdala, b) right ventrolateral prefrontal cortex, and c) medial prefrontal cortex showing elevated activity during combat-observe compared to neutral-observe tasks across groups.

a) 

b) 

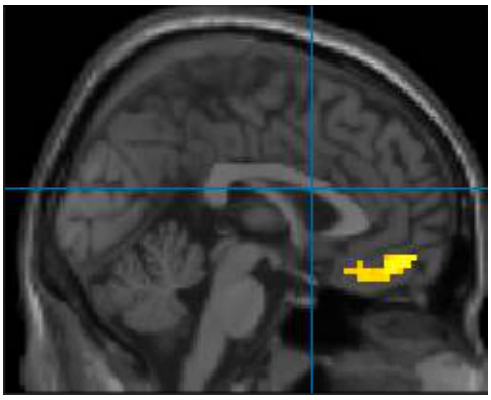
c) 

Figure 4. Diagram of participant flow through Study 3.

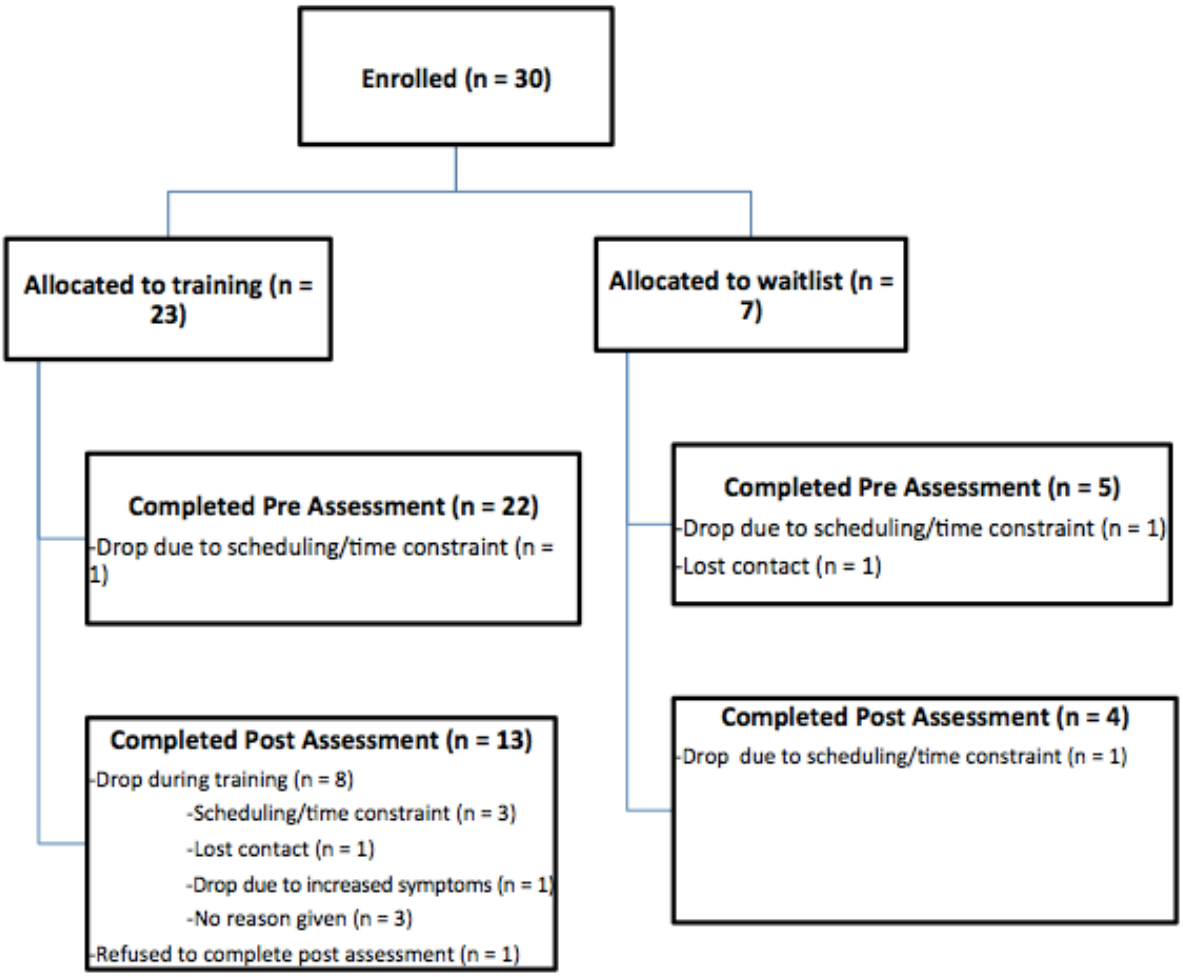


Figure 5. Diagram of Study 3 procedure.

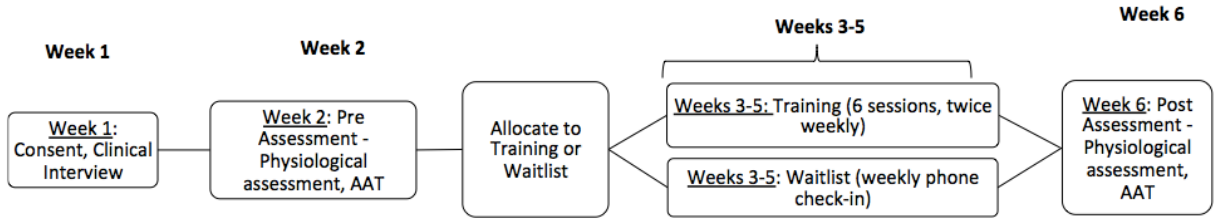


Figure 6. Example of Combat Affect Labeling training trial.

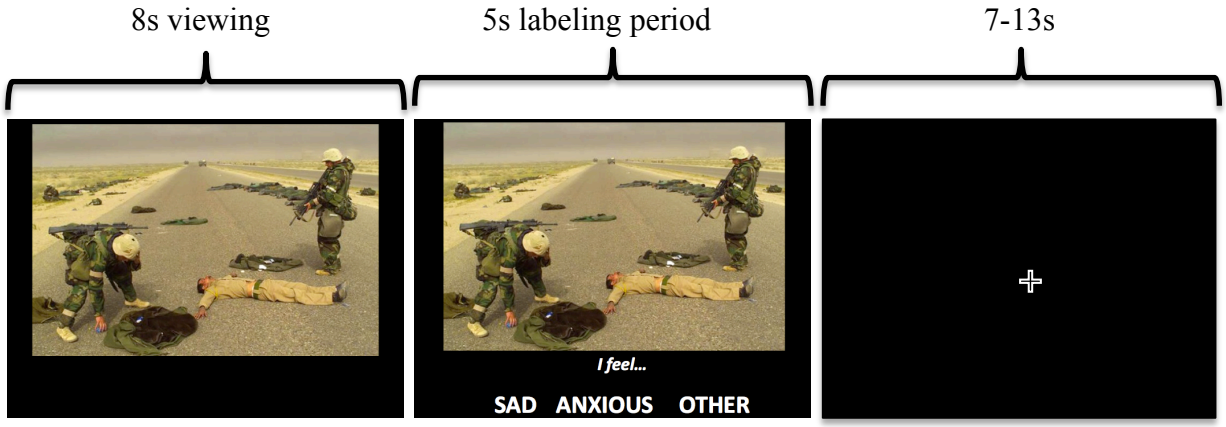


Figure 7. PCL-5 score at Pre and Post assessment across Waitlist and Training conditions.

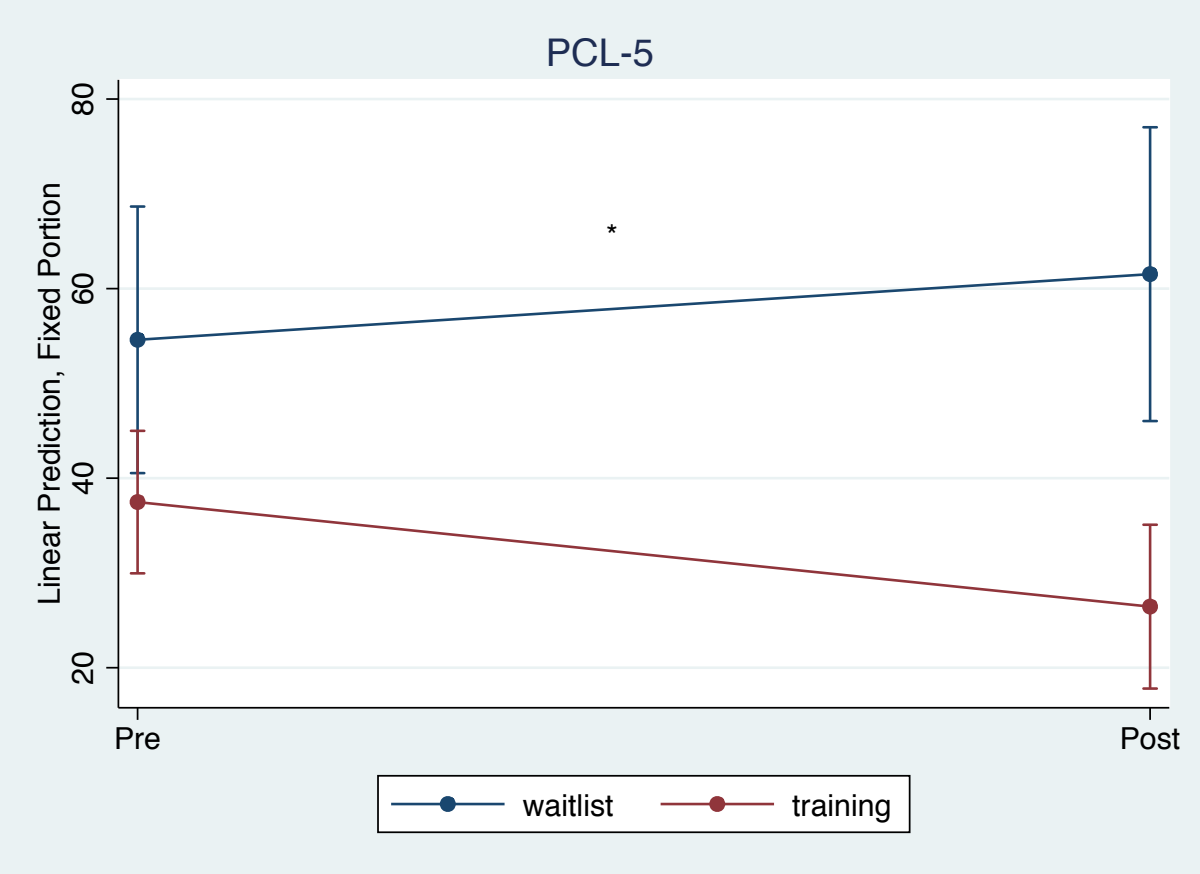
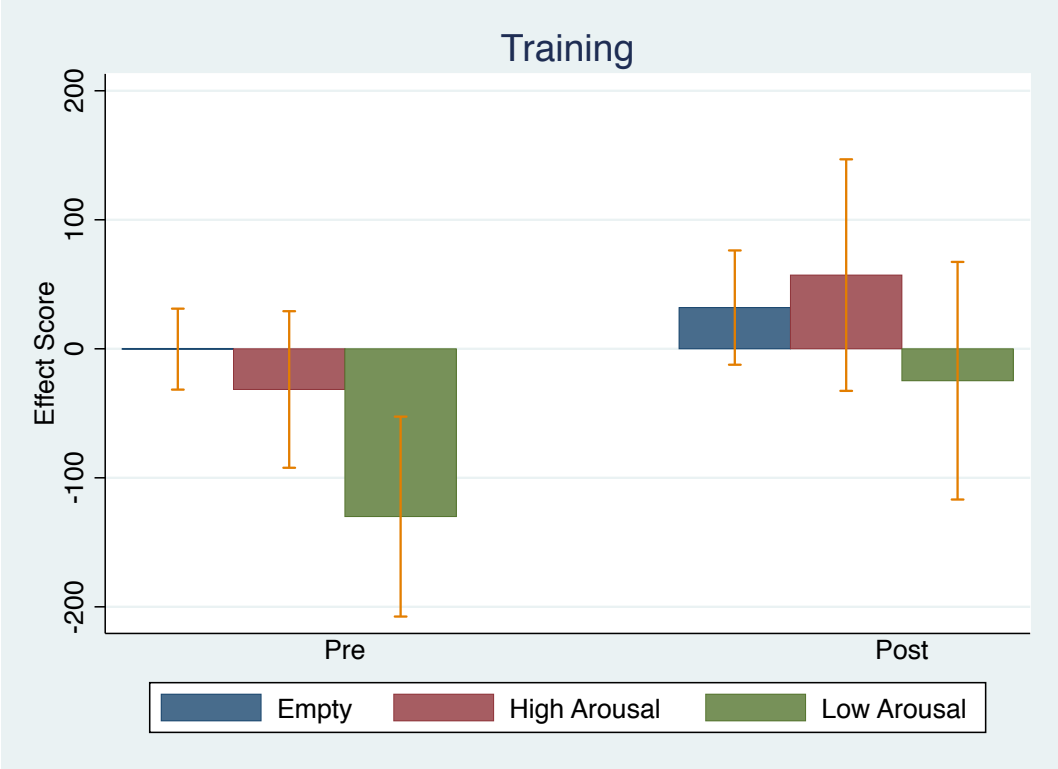
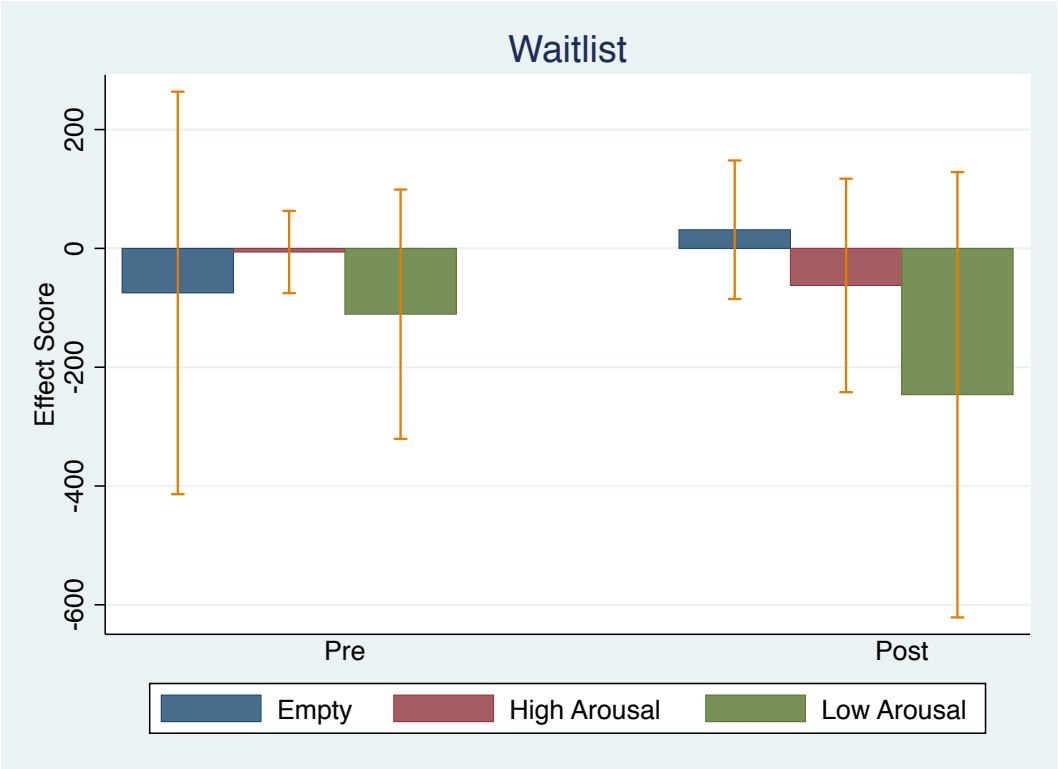


Figure 8. Approach avoidance task results from Pre to Post in a) Training condition and b) Waitlist condition.



a)



b)

Appendix A

PCL-5

Instructions: Below is a list of problems that people sometimes have in response to a very stressful experience. Please read each problem carefully and then circle one of the numbers to the right to indicate how much you have been bothered by that problem in the past month.

In the past month, how much were you bothered by:	*Not at all*	*A little bit*	*Moderately*	*Quite a bit*	*Extremely*
1. Repeated, disturbing, and unwanted memories of the stressful experience?	0	1	2	3	4
2. Repeated, disturbing dreams of the stressful experience?	0	1	2	3	4
3. Suddenly feeling or acting as if the stressful experience were actually happening again *(as if you were actually back there reliving it)*?	0	1	2	3	4
4. Feeling very upset when something reminded you of the stressful experience?	0	1	2	3	4
5. Having strong physical reactions when something reminded you of the stressful experience *(for example, heart pounding, trouble breathing, sweating)*?	0	1	2	3	4
6. Avoiding memories, thoughts, or feelings related to the stressful experience?	0	1	2	3	4
7. Avoiding external reminders of the stressful experience *(for example, people, places, conversations, activities, objects, or situations)*?	0	1	2	3	4
8. Trouble remembering important parts of the stressful experience?	0	1	2	3	4
9. Having strong negative beliefs about yourself, other people, or the world *(for example, having thoughts such as: I am bad, there is something seriously wrong with me, no one can be trusted, the world is completely dangerous)*?	0	1	2	3	4
10. Blaming yourself or someone else for the stressful experience or what happened after it?	0	1	2	3	4
11. Having strong negative feelings such as fear, horror, anger, guilt, or shame?	0	1	2	3	4
12. Loss of interest in activities that you used to enjoy?	0	1	2	3	4
13. Feeling distant or cut off from other people?	0	1	2	3	4
14. Trouble experiencing positive feelings *(for example, being unable to feel happiness or have loving feelings for people close to you)*?	0	1	2	3	4
15. Irritable behavior, angry outbursts, or acting aggressively?	0	1	2	3	4
16. Taking too many risks or doing things that could cause you harm?	0	1	2	3	4
17. Being "superalert" or watchful or on guard?	0	1	2	3	4
18. Feeling jumpy or easily startled?	0	1	2	3	4
19. Having difficulty concentrating?	0	1	2	3	4
20. Trouble falling or staying asleep?	0	1	2	3	4

PCL-5 (8/14/2013) Weathers, Litz, Keane, Palmieri, Marx, & Schnurr -- National Center for PTSD

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