Emotion-Modulated Startle Reactivity in OEF/OIF Veterans with PTSD

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Dedication

Dedicated to my wife, Stephanie, and to my family – Hildy, Joel, Aaron, Michele, Pam, Mark, Randy, and Molly.

Abstract

In addition to an exaggerated startle reflex, the most commonly reported symptoms of post-traumatic stress disorder (PTSD) are intense physiological reactivity and psychological distress, respectively, on exposure to cues that symbolize or resemble an aspect of the traumatic event. While the presence of an objectively measured exaggerated startle reflex in PTSD is firmly established, questions regarding when it is exhibited and what it tells us about the disorder remain unanswered. Furthermore, the data on emotion-modulated startle reactivity in PTSD are especially unclear and need further exploration. This is in large part due to a surprising paucity of data in the literature, as well as the interrelated problems of within-category heterogeneity and diagnostic comorbidity. Given that emotion-modulated startle is such a well-validated measure of emotional processing and defensive system reactivity, the lack of knowledge on this startle blink parameter is striking. The current study explored emotion-modulated startle reactivity in PTSD by investigating startle responses to pleasant, neutral, unpleasant, and trauma-related picture stimuli. Additional information regarding emotional dysregulations in PTSD was obtained through analyses of facial EMG, skin conductance, and heart rate responses. Both categorical (i.e., PTSD vs no-PTSD) and dimensional (i.e., specific symptom cluster) analyses were conducted in order to develop psychophysiological models and measures of the emotional dysregulations in PTSD. Contrary to expectations, categorical comparisons of individuals with and without PTSD did not yield a clear pattern of fruitful differences on any psychophysiological measure other than heart rate. In categorical comparisons, there was no strong indication for a particular physiological model for emotional dysregulations in PTSD and present results provide very little

support for the presence of an objectively-measured exaggerated startle response in PTSD. However, significant relationships between most specific symptom clusters and the startle blink response were observed. The same was true for subjective ratings of the affective valence and arousal of the picture stimuli. Unexpectedly, the most consistent effects were for diminished emotion modulation to pleasant stimuli rather than exaggerated responding to unpleasant or trauma-relevant stimuli. Current results suggest that PTSD is not defined by an abnormality in fear and that an underappreciated and central aspect of PTSD is a limited capacity for positive affect. Implications regarding the coherence of the construct of PTSD as defined in DSM-IV are discussed.

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Introduction

Objective physiological studies of the startle blink reflex in individuals with posttraumatic stress disorder (PTSD) have been reported in the psychophysiology literature over approximately the past twenty years. These investigations began with the inclusion of an exaggerated startle response symptom in the diagnostic criteria for PTSD and have covered a wide range of populations, trauma types, and research designs. And while the presence of an objectively-measured exaggerated startle reflex in PTSD is firmly established, questions regarding how this symptom develops, when it is exhibited, and what it tells us about the disorder remain unanswered.

The data on emotion-modulated startle reactivity in PTSD are especially unclear and need further exploration. This is in large part due to a surprising paucity of data in the literature. It is also due to the interrelated problems of within-category heterogeneity and diagnostic comorbidity that stem from the DSM-IV system of polythetic diagnostic categories. Given that emotion-modulated startle is such a well-validated measure of emotional processing and defensive system reactivity, lack of published data on this startle blink measure is striking. When considered in light of two additional characteristic symptoms of PTSD – physiological reactivity and psychological distress, respectively, on exposure to cues that symbolize or resemble an aspect of the traumatic event – the need to clarify the ambiguous data on emotion-modulated startle in the disorder comes into even starker relief. Dimensional explorations of emotion-modulated startle in PTSD designed to account for both within-category heterogeneity and diagnostic comorbidity have not yet been reported in the literature.

Background and Significance

Nature and Prevalence of Posttraumatic Stress Disorder

Posttraumatic stress disorder is defined in the Diagnostic and Statistical Manual of Mental Disorders as a syndrome marked by the development of characteristic symptoms following exposure to an extreme traumatic stressor (DSM-IV; American Psychiatric Association, 2000). The diagnosis – like all DSM-IV diagnoses – is polythetic and categorical. The diagnosis is polythetic in that multiple symptoms are listed and some certain combination of those symptoms must be met in order to receive the diagnosis. It is categorical in that individuals that do not have symptoms in the specified combination are classified as non-disordered (at least with respect to PTSD), while those with the right combination are classified as disordered.

Due to the polythetic nature of the diagnostic criteria, PTSD is a heterogeneous diagnostic category in which individuals with the disorder have diverse symptom patterns. DSM-IV states that PTSD has four criteria (A-D) that an individual must meet in order to receive the diagnosis. Criterion A defines the type of traumatic events that are officially recognized as those that can cause PTSD. It contains two requirements for such events, both of which must be present in order to meet the criterion. The following three criteria (B, C, & D) each contain different types of symptoms that must be present in varying numbers in order to receive the diagnosis. Criterion B contains symptoms of re-experiencing the trauma; one of five symptoms is needed to meet this criterion. Criterion C contains symptoms both of avoidance and of numbing of general responsiveness (that were not present prior to the trauma). Three of seven Criterion C symptoms are needed and any combination of numbing and/or avoidance symptoms is allowed. Criterion D

contains symptoms of increased arousal (that were not present prior to the trauma); two of five symptoms are needed to meet the criterion. Thus, it is possible that two individuals both meet diagnostic criteria for PTSD while sharing only the Criterion A symptom of having experienced a traumatic event.

Keane, Marx, and Sloan (2009) report that the best estimates of the lifetime prevalence of PTSD in the general population come in around 7%, with women having somewhat higher rates (e.g., about 10%) than men (e.g., about 5%). Rates of PTSD, however, must be considered in the context of exposure to traumatic events. The same authors report estimates that in the general population, approximately 60% of men and 50% of women are exposed to trauma significant enough to cause PTSD during their lifetimes.

However, reported rates of PTSD are generally higher in more specialized populations, such as military veterans, though the data are not as consistent as in the general population. For example, studies of Vietnam veterans estimate the lifetime prevalence of PTSD anywhere from 15-30% for males but only around 9% for females (Keane, et al., 2009). Presumably due to differences in combat experiences relative to Vietnam, PTSD rates for veterans of the first Gulf War were usually lower. Early data on veterans of the wars in Iraq and Afghanistan suggest that rates of PTSD are also lower than in Vietnam veteran samples, in addition to showing differences based on where the deployment was located (Keane et al., 2009). Among those deployed to Afghanistan, conservative estimates suggest that around 6% of Army veterans appear to develop PTSD. Among those deployed to Iraq, conservatively estimated rates of PTSD range between 12-13% for both Army and Marine Corps veterans (Hoge, et al., 2004).

The Construct of Emotion and the Theory of Motivated Attention

Emotion is a construct hypothesized to exist within a two-dimensional affective space containing a valence dimension ranging from pleasant to unpleasant and an arousal dimension that is orthogonal to valence (Lang, Bradley, & Cuthbert, 1992). Affective judgments of the contents of both emotional pictures and emotional narrative imagery texts are dispersed throughout this two-dimensional space in a boomerang-like shape, such that stimuli with greater valence (both pleasant and unpleasant) are judged more arousing than those with a more neutral valence (Bradley, Codispoti, Cuthbert, & Lang, 2001). For the purposes of experimental design and psychophysiological data analysis, the convention has been to divide the space into three levels of valence (pleasant, neutral, and unpleasant) that each contain three levels of arousal (low, medium, and high).

Cuthbert, Bradley, & Lang (1996) and Cuthbert et al. (2000) have proposed a motivated attentional theory of emotional perception. The theory posits that there are three primary brain systems – a defensive system, an appetitive system, and a control system that regulates the other two. The defensive and appetitive motive systems of the brain are fundamental in responding to emotionally arousing stimuli, where defensive activation is associated with stimulus escape/avoidance and appetitive activation is associated with stimulus approach (cf. Panksepp's (2004) FEAR and SEEKING systems). The appetitive motive system is activated by stimulus contents such as erotica, food, and adventure, while the defensive motive system is activated by stimulus contents such as human threat, animal threat, and mutilation. These kinds of emotional stimuli have high evolutionary relevance for the survival of both the individual and the species,

and so elicit more attentional resources to their perception and processing. Physiological measures that covary with valence and arousal are therefore viewed as reflecting motivated attention (Lang, Davis, & Ohman, 2000).

The Psychophysiology of Emotion

The startle blink reflex is the most important physiological measure of emotion and motivated attention for the purposes of the proposed research. It has been shown to be robustly modulated by a variety of emotional and attentional influences (Vaidyanathan, Patrick, & Cuthbert, 2009). And as a key component of the defense cascade, the startle blink reflex is also the most reliable and sensitive index of defense system activation (Davis, Walker, & Lee, 1997; Lang, et al., 2000). In the laboratory, startle blinks are most often elicited by sudden, intense auditory stimuli (termed "startle probes"). These are either short bursts of white noise or high-pitched (e.g., 1000 Hz) tones delivered over headphones. Occasionally, aversive air puffs on the neck are used. Blink reactions to these probes are measured through electromyographic electrodes placed under the eye (Blumenthal, et al., 2005).

Psychophysiological research paradigms for studying motivated attention allow for the examination of affect-modulated startle in response to appetitive stimuli in addition to aversive and neutral cues. These are relatively uncommon in the PTSD literature, but are commonly used in the study of emotion and other internalizing disorders (Vaidyanathan, et al., 2009). The most frequently used paradigms are picture viewing protocols employing the International Affective Picture System (IAPS) (Lang, Bradley, & Cuthbert, 1999) or imagery protocols employing standardized, single-

sentence prompts from the Affective Norms for English Text (Bradley & Lang, unpublished technical manual). The IAPS is a widely used, standardized set of photographs with normed ratings of valence and arousal. Both picture contents and imagery prompts cover the affective space defined by arousal and valence described above.

In a picture-viewing paradigm, participants are instructed to passively view the IAPS images while physiological measures are recorded. In imagery paradigms, subjects are instructed to actively imagine the scenes described in the imagery prompts, either when cued by a tone or when the prompt is read aloud (often by a computer). In both of these paradigms, startle probes are delivered both in the presence of foreground stimuli (i.e., during picture viewing or during active imagining) as well as during inter-trial intervals (ITI's). In these paradigms, baseline startle measures have been operationalized as responses to ITI startle probes and as responses to probes delivered during affectively neutral stimuli.

In affective picture viewing paradigms, the magnitude of the startle blink is potentiated (i.e., increased) when viewing unpleasant contents relative to neutral contents for healthy control subjects (Lang, Bradley, & Cuthbert, 1990). This potentiation of the blink reflex in the presence of unpleasant or aversive stimuli is known as fear-potentiated startle (Davis, 2006). The central nucleus of the amygdala has been reliably shown to be the critical brain region mediating this phasic amplification of startle reactivity (e.g., Davis, et al., 1997). Thus, startle potentiation to unpleasant pictures (i.e., fear-potentiated startle) appears to reflect defense system activation. As such, it has become an accepted and reliable operational measure of fear (Grillon & Baas, 2003).

The startle blink response in affective picture viewing tasks has also been interpreted as indexing both the perceived valence of the stimulus being processed and the motivational system that is consequently activated. This is because in addition to being potentiated by unpleasant contents, the startle reflex is attenuated (i.e., decreased) when viewing pleasant contents and is intermediate when viewing neutral contents (Vrana, Spence, & Lang, 1988). The attenuation of startle reactivity in the presence of appetitive stimuli seems to be mediated by the nucleus accumbens, a critical structure in reward processing that is part of the appetitive motivational system (cf. Panksepp, 2004). Additionally, the blink inhibition observed for pleasant pictures is consistent with prior studies of strong attentional engagement in foreground stimuli (Anthony & Graham, 1985).

The overall pattern of affect-modulated startle reactivity observed in healthy control subjects in picture viewing paradigms (unpleasant > neutral > pleasant) has been explained by a motivational priming hypothesis (Lang, et al., 1990). This model posits that unpleasant stimulus contents prime and activate the defensive system, and because the startle reflex is a defensive reaction, it is enhanced in the presence of aversive stimuli. On the other hand, pleasant stimulus contents prime the appetitive system and elicit an appetitive state, which is inconsistent with the defensive nature of the startle reflex, resulting in its attenuation. Neutral stimulus contents elicit startle reactions that fall intermediate to the other two as they do not elicit activation of either the defensive or appetitive motivational systems.

Several other physiological responses have also been shown to covary strongly with judgments of stimulus valence and arousal and appear to clearly index motivated

attention (e.g., Bradley et al, 2001). In picture-viewing paradigms, facial muscle EMG has been shown to index the valence of the picture being viewed. The corrugator muscle shows greater EMG activity in response to unpleasant contents than to pleasant contents, while its magnitude is intermediate in response to neutral contents. The zygomatic muscle, on the other hand, responds more strongly to pleasant contents than to unpleasant contents, again with intermediate magnitude while viewing neutral contents (e.g., Cuthbert, Bradley, & Lang, 1996). However, with extremely unpleasant and arousing contents, the zygomatic does show increased activation and is usually interpreted as an index of grimacing (Greenwald, Cook, & Lang, 1989; Lang, Greenwald, Bradley, & Hamm, 1993).

The skin conductance response reflects the arousal level of the picture being viewed. Greater responses are seen to emotional contents – both appetitive and aversive – than to neutral contents. As the emotional contents become more arousing, the skin conductance response also becomes larger. Finally, heart rate deceleration is seen to all contents, with the strongest effect in unpleasant pictures, which is interpreted as an orienting response (Cuthbert, Bradley, & Lang, 1996).

Startle Reactivity and Other Physiological Measures in PTSD

The data on emotional processing and emotional responding in PTSD, as indexed by startle reactivity to emotional pictures and imagery scenes, is inconclusive. As a result, the emotion processing dysregulations in PTSD are unclear from a psychophysiological perspective. This is due in large part to a paucity of data. Only five studies have explored emotion-modulated startle reactivity in PTSD – three that

employed a narrative imagery startle paradigm (Cuthbert, et al., 2003; McTeague & Lang, 2012; McTeague, et al., 2010) and two that used affective picture startle paradigms (Elsesser, Sartory, & Tackenberg, 2004; Miller & Litz, 2004).

Cuthbert et al. (2003), in an imagery study containing only fearful and neutral scenes, found that both PTSD and panic disorder patients failed to demonstrate a fear-potentiated startle effect. However, controls as well as individuals with specific phobia and social phobia did demonstrate fear-potentiated startle. This finding was interpreted in light of self-reported symptoms of internalizing distress (i.e., negative affectivity). Those with higher internalizing distress (PTSD and panic disorder patients) had inhibited responding to specific fearful cues relative to those with low levels of internalizing distress (specific and social phobics).

On the other hand, a later imagery study by the same group (McTeague, et al., 2010) found that PTSD participants had greater defensive reflexes (startle blink, heart rate change, skin conductance response, and facial EMG reactivity) than control subjects when imagining their ideographic traumas. Participants with PTSD also had greater responses to generally aversive stimuli than controls, though these were not as great as they were for ideographic trauma stimuli. Digging somewhat deeper, McTeague and colleagues found that individuals in the PTSD group with a single trauma had the largest startle responses while those in the PTSD group with multiple traumas actually showed blunted defensive reactivity in terms of both startle and SCR. Notably, this study also only included fearful and neutral imagery scenes, with no data reported on responses to appetitive stimuli. Additionally, no participants in this sample had experienced a combat trauma.

A third study by this same group (McTeague & Lang, 2012) again compared the startle blink responses of individuals with a variety of primary internalizing disorder diagnoses against control participants using an imagery paradigm. Consistent with the 2003 results (Cuthbert, et al., 2003), participants with fear disorders such as specific phobia demonstrated significant startle potentiation in response to clinically relevant contents. Participants with PTSD and other anxious-misery disorders such as GAD, however, demonstrated inhibited startle responding to all aversive contents. This finding was again interpreted in light of self-reported symptoms of internalizing distress. Those with higher internalizing distress (PTSD and GAD patients) and higher rates of comorbid depression exhibited inhibited responding to specific fearful cues relative to those with low levels of internalizing distress (such as specific and social phobics). Additionally, this relationship between increased internalizing distress and diminished defensive reactivity to aversive stimuli held not only between, but also within disorders (e.g., between participants with PTSD from a single trauma vs multiple traumas). The authors concluded that chronic internalizing distress of the sort found in PTSD and anxious-misery disorders may inhibit adaptive patterns of defensive responding during imagery.

No firm conclusions regarding emotion-modulated startle reactivity in PTSD can currently be drawn from affective picture startle paradigms, either. Miller and Litz (2004) employed a complex picture viewing paradigm that involved three conditions – a baseline condition, a post-shock stressor condition, and a post-trauma stressor condition. It is important to note that none of the picture stimuli were trauma-specific in this study. In the baseline and post-shock stressor conditions, they found no significant differences between groups but did observe normal emotion modulated startle (unpleasant >

pleasant). They only found differential reactivity between PTSD and control groups in response to unpleasant pictures after exposure to the trauma stressor. Following the trauma stressor, the PTSD group exhibited a response pattern in which startles to unpleasant pictures were potentiated relative to pleasant pictures, with ITI startles falling in between. In contrast, control participants' startle responses while viewing pleasant and unpleasant pictures no longer differed from one another but were still attenuated relative to ITI startles.

Miller and Litz (2004) interpret their results as evidence that the PTSD group became much more sensitive to unpleasant foreground stimuli following the trauma stressor. They conclude that this overall pattern of responding is evidence of defensive priming in PTSD caused by trauma-specific stimuli but not generally aversive stimuli (i.e., the shock stressor). However, the other part of their hypothesis – that exposure to the aversive trauma stressor would elicit a phasic numbing response that could be observed in inhibited startle modulation to pleasant pictures – was not supported in the data. These results must be interpreted in light of an experimental context in which the participants knew two significant stressors were to follow the baseline period and that the trauma stressor would be following the shock stressor. It cannot be ruled out that participants were not as engaged with the stimuli during the first two conditions as a result of anticipatory anxiety about the upcoming stressors. Therefore, it is unclear how participants would have responded to the pictures in the absence of these impending stressors. It is also unclear whether the inclusion of trauma-relevant IAPS images would have elicited differential startle reactivity in a different way than generally aversive pictures did.

Elsesser et al. (2004) utilized a more straightforward picture-viewing task and found no differences in startle reactivity to emotional pictures. However, questions about their study design and data analysis preclude drawing firm conclusions from their results. Specifically, the usual linear pattern of affect-modulated startle in picture viewing tasks (unpleasant > neutral > pleasant) was not observed, even for the control group. Failing to find the usual robust pattern of affect-modulated startle even in controls is concerning, and appears to be due to the timing of the startle probes. The authors used three different stimulus onset asynchronies (SOA), delivering startle probes 300 ms, 3500-4000 ms, or 4500-5000 ms after picture onset. Consistent with previous literature (Bradley, Codispoti, & Lang, 2006), the two later SOA's resulted in larger startle responses than the 300 ms SOA. Bradley et al. also found that affective modulation of the startle reflex was not apparent with very early SOA's – such as 300 ms after picture onset – and was elicited only later in the picture-viewing interval. Unfortunately, Elsesser et al. (2004) only reported and analyzed startle responses to the pictures using data averaged across all three SOA's. It seems likely that the inhibited blinks from the 300 ms SOA are therefore driving the lack of affect-modulation that is normally seen in startle responses to emotional pictures. As such, no conclusions regarding emotion-modulated startle in PTSD can be taken from this study.

Similarly, data on general startle reactivity in PTSD are best described as consistently inconsistent (Vaidyanathan, et al., 2009). General startle reactivity is defined as startle responses to probes presented alone, responses to probes during ITI's, and responses across all trial conditions within an individual study. The evidence here is evenly split between the presence and absence of a tonic, heightened reactivity of the

defensive system that is indexed by the startle blink reflex. Consequently, there are enough significant findings to conclude that in some cases of PTSD, there is a tonically exaggerated startle reflex. But there are also enough non-significant findings to conclude that other variables must be examined in order to fully understand this symptom.

On the other hand, the data on context-potentiated startle and fear-potentiated startle from conditioning and threat of shock studies seem quite clear. In these paradigms, the PTSD group usually does not show differentially large fear-potentiated startle in response to specific cues but does show fear generalization and exaggerated startle reactivity in stressful contexts (e.g., Grillon, Morgan, Davis, & Southwick, 1998a, 1998b; Grillon, et al., 2009; Jovanovic, Norrholm, Fennell, et al., 2009; Morgan, Grillon, Southwick, Davis, & Charney, 1995; Pole, Neylan, Best, Orr, & Marmar, 2003). These results are consistent with the argument of Lissek, Pine, and Grillon (2006) that differential responding in individuals with anxiety is best elicited by a weak (i.e., ambiguous) vs a strong (i.e., unambiguous) experimental context. Interestingly, only two of these studies (Jovanovic et al., 2009; Pole et al., 2003) explored the relationship of these startle abnormalities with specific symptoms. Both studies found that self-reported D (hyperarousal) symptoms were unrelated to startle abnormalities, while Jovanovic et al (2009) found that high B (re-experiencing) and C (avoidance) symptoms significantly predicted generalization of fear-potentiated startle in PTSD. Both studies utilized DSM-IV symptom groupings and neither study explored the relationships between specific symptoms of PTSD and responses to pleasant/appetitive stimuli.

Cuthbert et al.'s (2003) emotion-modulated startle results are therefore consistent with conditioning and threat of shock studies. But in contrast to those studies, PTSD

participants in Cuthbert et al.'s imagery study simply did not exhibit a fear-potentiated response at all. This result may indicate that fear-potentiated startle measures in affective imagery studies are not comparable to such measures in conditioning or threat of shock studies. That is, emotion-modulated startle appears to represent a different startle reflex parameter than fear-potentiated startle measured in conditioning and threat of shock studies, but these results have not yet been replicated.

Consistent with the data on emotion-modulated startle, data on other physiological indices of motivated attention are equally unclear, largely due to a lack of data. Facial EMG measures have only been used in three picture-viewing studies. In the first such study (Carlson, Singelis, & Chemtob, 1997), 10 veterans with PTSD and 10 veterans without PTSD viewed neutral and combat-related pictures. Contrary to what the motivated attention literature predicts, the PTSD group exhibited significantly greater zygomatic activity in response to the trauma-related pictures than the control group. This finding may be the result of grimacing, rather than smiling. Corrugator results were in the expected direction (trauma-related > neutral), but no group differences were observed. With the small sample size and only a trauma vs neutral comparison, it is unclear what to make of these results.

Two subsequent studies only serve to further cloud the interpretation of motivated attention data in PTSD. Litz, Orsillo, Kaloupek, and Weathers (2000) found no differences in zygomatic or corrugator EMG between the PTSD group and controls during picture viewing in their baseline (i.e., no-stressor) condition. Following a trauma stressor, however, the PTSD group exhibited less zygomatic reactivity to pleasant stimuli than the control group; there were no significant group differences for corrugator EMG.

In a follow-up study with conflicting results, Miller and Litz (2004) found no significant group differences on zygomatic EMG but did find the PTSD group exhibited significantly greater corrugator responses to unpleasant pictures only following the trauma stressor. It is likely that these data can be clarified with a larger sample size and a study design in which there are no shock or trauma stressors.

The results for skin conductance response and heart rate reactivity are somewhat clearer, as these measures have been employed more often. Pole (2007) reviewed the relevant literature and concluded that there is evidence for exaggerated heart rate reactivity (i.e., faster heart rates) and skin conductance responses in PTSD compared to controls while viewing trauma-relevant stimuli. Across sixteen studies, the unweighted mean effect size for heart rate reactivity in PTSD compared to controls was $d = .40$, which is a medium effect size. The more conservative weighted mean effect size was $d = .27$, which is a small effect size. As the difference between these two statistics suggests, there was significant heterogeneity of effect sizes across studies. Similarly, across nine studies, the unweighted mean effect size for skin conductance responses was medium ($d = .38$) while the weighted mean effect size was small ($d = .21$). Skin conductance response effect sizes were also heterogeneous.

The Inter-related Problems of Within-Category Heterogeneity and Diagnostic Comorbidity

The most significant reason that motivated attention findings in PTSD are so mixed may be that the diagnosis of PTSD suffers from interrelated problems of within-category heterogeneity and diagnostic comorbidity. The problem of within-category

heterogeneity stems from the fact that the diagnosis – like all DSM-IV diagnoses – is polythetic and categorical (American Psychiatric Association, 2000). The diagnosis is polythetic in that multiple symptoms are listed and some certain combination of those symptoms must be met in order to receive the diagnosis. It is categorical in that individuals that do not have symptoms in the specified combination are classified as non-disordered (at least with respect to PTSD), while those with the right combination are classified as disordered.

Due to the polythetic nature of the diagnostic criteria, PTSD is a heterogeneous diagnostic category in which individuals with the disorder have diverse symptom patterns. Indeed, it is possible that two individuals both meet diagnostic criteria for PTSD while sharing only the Criterion A symptom of having experienced a traumatic event. Conversely, it is possible that two individuals have the same number of PTSD symptoms but only one of them gets classified as having the disorder as a result of the combination of symptoms they each have. Such situations are common and confound the interpretation of psychophysiological data when comparing a group of subjects diagnosed with PTSD to controls, as such comparisons hinge on homogeneity within each group.

Researchers have employed factor analysis to empirically investigate the relationships amongst PTSD symptoms in light of the polythetic nature of the diagnosis and the diagnostic heterogeneity that has resulted from it. Their starting point has been the structure implied in the DSM-IV criteria, which have been interpreted as suggesting a three-factor, hierarchical structure for the construct of PTSD. These interpretations usually assume one higher order factor for the syndrome as a whole (i.e., a PTSD factor), with criteria B-D making up three first-order factors – re-experiencing,

avoidance/numbing, and hyperarousal. The models do not include data for Criterion A (presence of a traumatic event), as everyone with the diagnosis meets the entirety of this criterion by definition.

Factor structures for PTSD symptoms have been empirically tested using both exploratory and confirmatory factor analyses. Symptom data for these analyses have almost exclusively been collected using either or both of the Clinician-Administered PTSD Scale (CAPS; Blake, et al., 1995) and the PTSD Checklist (PCL; Blanchard, Jones-Alexander, Buckley, & Forneris, 1996). The CAPS is the gold standard for diagnosing PTSD and is the best instrument available for collecting accurate individual symptom data (Weathers, Keane, & Davidson, 2001). Total scores on the PCL correlate extremely highly with CAPS total scores (r = .929) and it has excellent diagnostic efficiency, but its ability to identify the presence or absence of individual symptoms is not quite as good as the CAPS (Blanchard et al., 1996). The PCL has nonetheless frequently been used in PTSD research mostly as a result of the ease of administering it; unlike the CAPS, the PCL is a self-report questionnaire that does not require a trained interviewer to administer and score. It is not surprising, then, that factor structures based on data from the PCL have differed slightly from those based on the CAPS.

Confirmatory and exploratory factor analyses have been conducted using both CAPS and PCL data from diverse populations, including combat veterans, non-deployed military veterans, motor vehicle accident survivors, sexual and physical assault survivors, and disaster rescue workers from Ground Zero in New York City. All of these analyses, regardless of assessment instrument and sample, agree that there is no empirical support for DSM-IV's implicit three-factor structure (Buckley, Blanchard, & Hickling, 1998;

Palmieri, Weathers, Difede, & King, 2007). The other consensus finding to emerge from this literature is that, paradoxically, the exaggerated startle symptom and the hypervigilance symptom do not appear to covary with the other hyperarousal (Criterion D) symptoms (Simms, Watson, & Doebbeling, 2002).

The models with the strongest support in the literature are all also first-order models with no higher-order "PTSD factor." There is thus compelling evidence for a PTSD syndrome but little to no evidence for a unitary PTSD construct or category. This is a problem for our current nosology, in which individuals meeting criteria for a disorder are understood and assumed to be a homogenous group in the sense that they have a single disorder that presumably has a coherent etiology, course, etc.

The most robust model appears to be the one initially put forward by Simms, Watson, & Doebbeling (2002), which is based on both PCL and structured interview data. Palmieri et al. (2007) confirmed the optimal fit of the Simms et al. model partially by accounting for differences in CAPS and PCL data in their analysis. The four factors in this model are Avoidance, Intrusions, Dysphoria, and Hyperarousal. The Dysphoria factor combines symptoms of what the DSM labels as numbing and hyperarousal, all of which are non-specific to PTSD and are common across other anxiety and mood disorders. It consists of symptoms C3-C7 (all of the DSM-IV numbing symptoms) and D1-D3, which are the hyperarousal symptoms excluding exaggerated startle and hypervigilance (i.e., difficulty sleeping, irritability, and difficulty concentrating). The Intrusions factor is made up of the Criterion B symptoms, labeled "re-experiencing" in DSM-IV. The Avoidance factor contains only the two active avoidance symptoms (C1

and C2) and the Hyperarousal factor contains only the exaggerated startle and hypervigilance symptoms (D4 and D5).

In addition to being cross-validated in multiple samples, the optimal fit of this model was supported with convergent and discriminant analyses utilizing external criteria (Palmieri, et al., 2007; Simms, et al., 2002). These analyses involved correlating scores on individual factors with external measures of negative affectivity, depression, generalized anxiety, and fear symptoms. The results indicate that this model fits better than other models of PTSD, mostly due to the presence of the Dysphoria factor and the specificity of the Intrusions factor. Intrusion symptoms appear to be unique to PTSD while Dysphoria symptoms are non-specific and are common across most internalizing disorders.

Understanding the factor structure of PTSD in this way can clarify psychophysiological research on the disorder. Specifically, knowing that the construct of PTSD is not unitary, it is difficult to justify analyzing the variability of physiological reactivity solely on the basis of the presence or absence of the diagnosis. Instead, factor structures can be utilized in analyses comparing physiological reactivity in relation to scores on empirically derived factors (i.e., on the severity of specific symptom clusters). Such analyses are meaningful because the identified factors are likely to correspond to distinct underlying mechanisms and aspects of the disorder (Palmieri et al., 2007).

Furthermore, exploring PTSD in this way would help to eliminate the problem of within-group heterogeneity that results from polythetic diagnostic criteria. With a factor-based approach, researchers can more accurately determine whether the physiological measures of interest vary with the presence and/or severity of the symptom clusters that

are hypothesized to be related to those measures. That is, the question of whether the symptom of interest (e.g., exaggerated startle) is present in everyone in the diagnostic group would be eliminated and more specific questions regarding which symptoms are related to each physiological measure could be asked and answered. However, no studies have explored physiological reactivity in relation to these empirically derived symptom factors even as more and more investigators are calling for more dimensional approaches in PTSD research (Bovin & Marx, 2010; Suvak & Barrett, 2011).

Comorbidity is also a significant problem for psychophysiological studies of PTSD. The presence of another mental disorder is the rule rather than the exception in individuals with PTSD. Keane and Kaloupek (1997) reviewed the epidemiological literature on this topic and describe consistent findings of high comorbidity in individuals with PTSD across populations, traumatic stressors, patient status, diagnostic measures, and level of interviewer training. Summarizing across epidemiological studies, they report that the most commonly co-occurring disorders are alcohol use, substance use, major depression, and antisocial personality disorder. Anxiety disorders – especially panic disorder and specific phobias – and borderline personality disorder are also highly likely to co-occur with PTSD.

This extensive comorbidity creates several problems for psychophysiological investigations of PTSD. First, just as PTSD modulates physiological reactivity, so do other mental disorders. This makes it very difficult to differentiate between the physiological effects of PTSD and of other comorbid disorders. Second, extensive comorbidity in PTSD makes studying individuals without additional diagnoses substantially less useful. Such individuals are not representative of most PTSD patients

and research findings from studies using this population may not be generalizable to all individuals with PTSD. Third, the comorbidity itself creates heterogeneity in PTSD samples in that each individual will have a somewhat different comorbidity pattern. This additional layer of heterogeneity only confuses the interpretation of physiological data even further.

In response to these high levels of comorbidity, as well as the problem of diagnostic heterogeneity, a growing literature advocates for conceptualizing psychopathology in terms of hierarchical dimensional models in contrast to the polythetic diagnostic categories defined in DSM-IV (Cuthbert, 2005). These models understand psychopathology as a matter of degree rather than as an either/or issue. They empirically account for rates of comorbidity that are far beyond what is expected by chance alone. They also have the advantage of accounting for within-category heterogeneity and extensive symptom overlap across disorders. In other words, dimensional approaches to psychopathology solve the primary and interrelated problems that result from our current diagnostic system – within-category heterogeneity and comorbidity among categories (Krueger & Finger, 2001; Krueger, 1999; Krueger & Markon, 2006).

These models posit two broad dimensions of pathology with underlying liability factors shared amongst the disorders on each one. A personality style characterized by emotional instability and negative affectivity confers risk for a broad internalizing spectrum of unipolar mood and anxiety disorders; when this style is also accompanied by disinhibition, there is elevated risk for a broad externalizing spectrum of substance use and antisocial behavior disorders (Clark, 2005; Krueger, 2005). Furthermore, Krueger and Markon found clear and consistent support for further dividing the internalizing

dimension into distinct but correlated "fear" and "distress" dimensions (2006). The fear disorders, which are marked by intense fear reactions to specific cues, are agoraphobia, social phobia, specific phobia, and panic disorder. The distress disorders, which are marked by generalized distress (or anxious misery), are major depression, dysthymia, and generalized anxiety disorder.

PTSD clearly fits best on the internalizing spectrum, but there is no clear answer as to whether it is a distress disorder or a fear disorder (Cox, Clara, & Enns, 2002; Watson, 2005). This is because the diagnostic criteria for PTSD contain symptoms that are characteristic of both distress disorders and fear disorders. So Watson (2005) argues that dimensional models of psychopathology can take advantage of factor analyses of PTSD to help determine where it fits into the internalizing spectrum. He argues that individual factors of PTSD symptoms should be assessed and modeled separately in future work as a way to explore whether PTSD is truly a fear disorder, a distress disorder, or some combination of the two. Similarly, Simms et al. (2002) argue that factor analyses can illustrate the components of PTSD that are common to all internalizing disorders as well as those that are unique to PTSD. This can be done by comparing patterns of reactivity associated with each symptom factor to patterns of reactivity seen in other disorders. Such an approach would provide richer information that can better define the syndrome of PTSD alone and in the larger context of internalizing pathology.

Startle Reactivity in the Internalizing Disorders

Clark (2005) and Krueger and Markon (2006) argue that the three major dimensions of temperament – positive affect, negative affect, and disinhibition (control) –

are the underlying risk factors for internalizing and externalizing psychopathology. Cuthbert (2005) synthesizes evidence from their lines of work as well as other research and concludes that specific areas of the brain implement each of these aspects of temperament. The evidence suggests that, broadly speaking, the defensive system implements negative affectivity, the appetitive system implements positive affectivity, and the behavioral control system implements disinhibition (cf. Lang, McTeague, & Cuthbert, 2005; Vaidyanathan, et al., 2009). As a consequence of these findings, there is a growing consensus in the literature that anxiety and mood disorders are manifestations of dysregulations of the defensive and/or appetitive motivational systems and that the patterns of these dysregulations match the dimensional models of psychopathology described above (Cuthbert, 2005; Lang, McTeague, & Cuthbert, 2007; Lang, et al., 2000).

Given its ability to index emotional processing, the startle blink reflex is a particularly good measure for identifying similarities and differences in emotional dysregulations across internalizing disorders. Indeed, Vaidyanathan et al. (2009) found that patterns of startle reactivity among internalizing disorders generally mirror structural models of psychopathology and that results were consistent in spite of variations in methodology across studies. Individuals with cue-specific fear disorders – e.g., specific and social phobia – appear to be characterized by increased fear-potentiated startle in response to their feared stimuli. Individuals with distress, or anxious-misery disorders – e.g., depression, generalized anxiety, and panic disorder – are characterized by heightened general startle reactivity or by increased context-potentiated startle.

Individuals with distress disorders may also have a reduced fear-potentiated startle response (Lang & McTeague, 2009).

Yet more work is needed to understand where PTSD fits in these models because it consists of symptoms that characterize both fear and distress disorders. Therefore, in the present study, we built on previous findings of differential emotion-modulated startle reactivity in PTSD by investigating startle responses to pleasant, neutral, unpleasant IAPS stimuli as well as combat trauma-related stimuli obtained from freely available online media. The complete picture of motivated attention deficits in PTSD was also explored through supplementary analyses that included facial EMG, skin conductance, and heart rate responses. By conducting both categorical (i.e., PTSD vs TBI vs Depressed vs Control) and dimensional (i.e., specific symptom factor) analyses, we aimed to develop psychophysiological models and measures of the emotional dysregulations in PTSD. This approach allowed us to also investigate similarities and differences in the emotional dysregulations observed in PTSD as compared to other internalizing disorders.

The Psychophysiology of Emotion in Traumatic Brain Injury

Finally, the issue of traumatic brain injury (TBI) in individuals with PTSD has not yet been addressed in the literature, though there is a limited literature investigating emotion-modulated startle in individuals with TBI. A review of this literature indicated none of these studies included individuals with PTSD and all of these studies examined individuals with moderate to severe TBI. These studies also recruited participants shortly after injury (e.g., days to weeks), while the present study was only able to recruit

participants months to years after injury. Findings are fairly consistent across studies, with several studies reporting that brain-injured participants failed to show emotion-modulated startle effects with respect to both pleasant and unpleasant contents (Buchanan, Tranel, & Adolphs, 2004; Saunders, McDonald, & Richardson, 2006). A third study found that brain-injured participants only showed diminished inhibition of the startle reflex to pleasant contents (Sanchez-Navarro, Martinez-Selva, & Roman, 2005).

Data were mixed with respect to ratings of affective valence and arousal. Some studies found that participants with TBI rated pleasant pictures as more pleasant (Saunders, et al., 2006) and others finding no difference in valence ratings between groups (Buchanan, et al., 2004; Sanchez-Navarro, et al., 2005). Similarly, in these three studies, one found that brain injured participants rated unpleasant pictures as less arousing (Saunders, et al., 2006), one found that brain-injured participants rated pleasant pictures as less arousing (Buchanan, et al., 2004), and one found that brain-injured participants rated all pictures as less arousing than control participants (Sanchez-Navarro, et al., 2005).

By contrast, every study of startle and PTSD reviewed above excluded individuals with a history of head injury, which is standard operating procedure in psychophysiological research studies of psychopathology. However, this severely limits our understanding of many individuals with PTSD, as traumatic incidents often involve a blow to the head. This is especially true for military veterans – a group that bears a disproportionate amount of the cost of PTSD. Indeed, for veterans of the conflicts in Iraq and Afghanistan, closed-head injuries from exposure to explosions or blast waves are the most common type of war-related injury (Warden, 2006). Additionally, these injuries are

strongly associated with PTSD and physical health problems 3-4 months after soldiers return home (Hoge, et al., 2008). The clinical presentations of veterans with PTSD and/or histories of mTBI are often very similar, as well, making differential diagnosis and treatment recommendations challenging. Complicating this picture is emerging evidence that poorer outcomes (psychological, physical, and psychosocial) for individuals who experienced mTBI while deployed may be mostly accounted for by PTSD and other symptoms of psychopathology (Hoge, et al., 2008; Polusny, et al., 2011; Wilk, Herrell, Wynn, Riviere, & Hoge, 2012). There is thus an urgent and pressing need for research investigating the effects of traumatic brain injuries on individuals with and without PTSD (Vasterling, Verfaellie, & Sullivan, 2009).

Specific Aims and Hypotheses

1. The diagnostic criteria for PTSD include symptoms of both increased and diminished emotional reactivity. These include physiological reactivity and psychological distress on exposure to reminders of the trauma, an exaggerated startle response, and hypervigilance, but also anhedonia and emotional numbing. This study employed an emotion-modulated startle paradigm to develop psychophysiological models and measures of emotional dysregulations in PTSD.
    (a) We hypothesized that generally aversive stimuli (i.e., IAPS "unpleasant" stimuli) would elicit larger corrugator but not larger fear-potentiated startle responses in the PTSD group compared to controls, indicating greater perception of unpleasant valence but not sensitivity of the defensive system in response to generally aversive stimuli in PTSD. However, in response to

trauma-relevant aversive stimuli, we predicted that the PTSD group would exhibit both larger corrugator and larger fear-potentiated startle responses, indicating marked sensitivity of the defensive system to trauma reminders.

(b) We hypothesized that the PTSD group would demonstrate inhibited responding to pleasant (i.e., appetitive) stimuli, which would be seen in less startle attenuation and smaller zygomatic EMG responses compared to controls.

(c) We hypothesized that there would be no differences in general startle reactivity between the PTSD and control groups, as measured by the average response across pictures from all affective valence categories. That is, it was predicted that there would be no tonic, heightened sensitivity of the defensive system in individuals with PTSD.

(d) We hypothesized that the PTSD group would exhibit greater heart rate (in beats per minute) in response to trauma-relevant but not generally aversive pictures compared to controls, indicating a dysregulated orienting response specific to trauma-relevant stimuli. We also predicted that the PTSD group would show less heart rate deceleration to pleasant pictures than controls, indicating a smaller allocation of motivated attentional resources to appetitive stimuli.

(e) We hypothesized that both generally aversive and trauma-relevant stimuli would elicit significantly greater skin conductance responses in the PTSD group compared to controls. We also hypothesized that appetitive stimuli

would elicit smaller skin conductance responses in the PTSD group compared to controls, thus mirroring the pattern of results seen in heart rate deceleration.

2. Dimensional explorations of emotion-modulated startle in PTSD designed to account for within-category heterogeneity have not yet been reported in the literature. This study used dimensional approaches that treated PTSD symptoms as continuous variables (i.e., regression) to explore emotion-modulated startle reactivity and other measures in relation to the severity of symptoms within empirically derived symptom clusters.

    (a) We hypothesized that greater overall PTSD symptom severity (i.e., CAPS total severity score) would be associated with greater general startle reactivity, measured as the mean response across all affective valence categories. That is, it was hypothesized that greater PTSD symptom severity would be associated with exaggerated general startle reactivity, reflecting a tonic, heightened sensitivity of the defensive system. This prediction is in contrast to the above prediction of no differences in general startle between the PTSD and no-PTSD groups. It was anticipated that a difference would be found here but not above because CAPS severity is a purer measure of PTSD symptomatology than the diagnostic category and this analysis does not require a comparison between groups. That is, this analysis does not involve the noise in the control group from participants with an exaggerated startle response and other symptoms of PTSD that are not sufficient to meet diagnostic criteria.

(b) We hypothesized that high Dysphoria symptom scores would be related to diminished emotion-modulation effects – meaning less startle potentiation by aversive stimuli and less startle attenuation by appetitive stimuli. We also hypothesized that high Dysphoria symptom scores would be related to diminished emotion modulation in both corrugator and zygomatic EMG. That is, we expected that higher Dysphoria symptom severity scores would significantly diminish corrugator responses to unpleasant contents and zygomatic responses to pleasant contents. We further hypothesized that high Dysphoria symptom scores would be related to significantly smaller skin conductance responses and to smaller heart rate deceleration to affective contents.

(c) It was hypothesized that high Intrusions (i.e., re-experiencing) and high Avoidance symptoms would be related to enhanced defensive responding that was marked by exaggerated fear-potentiated startle responses only to trauma-relevant aversive stimuli. It was also predicted that high scores on these symptom factors would be related to exaggerated corrugator responses only to trauma-relevant aversive stimuli.

(d) High Hyperarousal symptoms, on the other hand, were hypothesized to be associated with exaggerated defensive responding to all aversive stimuli that would be evident in both exaggerated fear-potentiated startle responses and greater corrugator EMG reactivity.

Methods

Participants

Participants were U.S. military veterans recruited approximately equally from two sources. One source was an ongoing Department of Defense-funded project studying risk and resilience for post-traumatic psychopathology in the Minnesota National Guard. A major advantage of this recruitment approach was that data on within-theatre wellbeing and psychopathology were available to target recruiting efforts. Specifically, within-theatre data on PTSD symptomatology were available on over 2,650 MN National Guard soldiers. These data were used to identify individuals for screening and recruitment to obtain an appropriate study sample. Moreover, this sample consisted of individuals who are representative of the population of Minnesota National Guard soldiers who served in Operation Iraqi Freedom (OIF). The second source of participants was patients from the Minneapolis VA Medical Center. Participants were drawn from two clinics within the hospital – the Post-Traumatic Stress Recovery clinic and the Polytrauma Rehabilitation Center. They were also drawn from a list of individuals who were being seen at the medical center and carried current diagnoses of PTSD and/or TBI. Medical documents available to the research team were utilized to target appropriate individuals, all of who served in Iraq and/or Afghanistan as part of OIF, Operation Enduring Freedom (OEF), and/or Operation New Dawn (OND).

Potential participants were screened over the telephone and were asked questions related to current and past physical health, trauma exposures, PTSD symptoms, other current and past Axis I disorders, current and past substance use, and whether they were able to complete an MRI (for another aspect of the larger project of which this study is a

part). While effects of explosive blast were not central to the current study, they are relevant to the larger project of which this study is a part. Therefore, potential participants also answered questions from the Blast Exposure Screen. (The Blast Exposure Screen provides a comprehensive assessment of exposure to blast for the duration of deployment). The current study was primarily focused on comparisons between participants with PTSD and those without, but supplementary analyses were conducted to explore the effect of explosive blast, as well.

Participants were excluded from the study if they manifested 1) a current substance-induced psychotic disorder or psychotic disorder due to a general medical condition (other than TBI), 2) current or past DSM-IV-defined substance dependence other than alcohol, caffeine, or nicotine, 3) current DSM-IV substance abuse other than alcohol, caffeine, or nicotine, 4) a neurologic condition or DSM IV Axis I mental disorder prior to deployment, 5) current or predeployment unstable medical condition that would likely affect brain function (e.g., clear anoxic episode, cardiac arrest, current uncontrolled diabetes) 6) significant risk of suicidal or homicidal behavior, or 7) head injury from a source other than blast that resulted in loss of consciousness for more than 15 minutes, post-traumatic amnesia, skull fracture, or hospitalization. The screening interview included questions to assess subjects with respect to the above exclusion criteria.

Participant demographics and clinical characteristics are reported in Table 1 and Table 2. Overall, 135 participants consented to participate in the startle task. Of those 135 participants, 8 were excluded during the consensus diagnosis process. The data from 3 additional participants was lost due to equipment failure. Participants were included in

the final sample if we obtained usable data from them on any of the dependent variables (i.e., startle blink, SCR, corrugator EMG, zygomatic EMG, heart rate, or affective ratings of the stimuli), yielding a total N = 124. The total sample for the current study included 9 female participants and was 8.80% minority.

Diagnostic Instruments

Structured clinical interviews were utilized to assess DSM-IV Axis I psychopathology and were administered by trained post-bachelors and graduate research staff. The Structured Clinical Interview for DSM-IV-TR (SCID), excluding the PTSD module, was used to assess for Axis I psychopathology other than PTSD (First, Spitzer, Gibbon, & Williams, 2002). The Clinician Administered PTSD Scale (CAPS) was used to assess for PTSD (Blake, et al., 1995). The CAPS is the gold standard for diagnosing PTSD and is the best instrument available for collecting accurate individual symptom data (Weathers, et al., 2001). It also allows clinical judgments to be made regarding the validity of respondents' reports, has excellent reliability, and has good convergent and discriminant validity, diagnostic utility, and sensitivity to clinical change. Due to practical considerations, all participants who reported a Criterion A (traumatic) event were administered the CAPS criterion B module (re-experiencing). If the participant met Criterion B, the rest of the CAPS was administered. If the participant did not meet criterion B, the CAPS was discontinued. Consequently, we only have complete CAPS symptom data for participants who met PTSD Criterion A and Criterion B (N = 93).

To assess blast exposure, research staff first reviewed the questions from the Blast Exposure Screen used during the telephone interview. Then they administered the

MNBEST (Minnesota Blast Exposure Screening Tool), a semi-structured interview developed in our laboratory to accurately characterize explosive blast exposure (Nelson, et al., 2011).

Pre-doctoral graduate students and at least one licensed PhD-level psychologist reviewed CAPS and SCID data for each participant. Final diagnostic decisions were made by consensus of at least two reviewers, one of who was a licensed PhD-level psychologist. MN-BEST interview data were reviewed by licensed clinical neuropsychologists or by post-doctoral fellows in clinical neuropsychology with expertise in head injury and mTBI. Reported head injuries were classified as definite, probable, possible, or unlikely using a group consensus process that included at least two reviewers. At least one of those reviewers was a licensed clinical neuropsychologist. For the purposes of this study, participants were considered to have experienced a blast-related mTBI if they had one or more probable or definite mTBI's. See Table 2 and Table 3 additional information regarding the N's and clinical characteristics of the PTSD and TBI groups in the whole sample and in each data analysis.

IAPS Startle Task

Forty-five pictures were chosen from the IAPS from three emotional valence categories (pleasant, neutral, and unpleasant) based on normative affective ratings (Lang, et al., 1999). Pleasant and unpleasant pictures were balanced for arousal. Fifteen additional pictures were taken from freely available online media and were identified as aversive, OIF combat-related photographs by Minneapolis VA Medical Center employees and research staff. In order to confirm appropriate picture selections were

made, participants made ratings of affective valence and arousal for all of the combat-related pictures as well as a sample of the IAPS stimuli at the end of the study. These dimensional ratings of valence and arousal were made on a computer using the Self-Assessment Manikin (SAM; see Tables 5 and 6 and Figures 1, 2, and 3). Pictures were arranged into two blocks of thirty pictures each such that stimulus contents and arousal were counterbalanced and randomly ordered. A total of three picture orders were created and participants were randomly assigned to a particular order.

The acoustic startle stimulus consisted of a 95 or 103 dB (A) white noise burst presented binaurally for 50 ms, with instantaneous rise time, over stereo headphones. The startle stimulus was increased from 95 to 103 dB during the study after preliminary data analyses revealed a higher than expected number of apparent startle non-responders. [1] The startle probe signal was produced by a Coulbourn S81-02 white noise generator and was gated through a Coulbourn S82-24 amplifier. Probes were presented randomly at either 2500 or 4500 ms following stimulus onset for 48 out of the 60 pictures, such that a probe was presented during 12 pictures in each category (pleasant, neutral, unpleasant,

[1] The following are N's are for participants included in the startle analyses (see *Psychophysiological Data Acquisition and Processing*, below):

- Overall, N = 51 for the 103 dB probe and N=18 for the 95 dB probe.
- For participants with PTSD, N = 5 for the 95 dB probe and N= 38 for the 103 dB probe. For participants without PTSD, N = 13 for the 95 dB probe and N = 13 for the 103 dB probe.
- For participants with TBI, N = 9 for the 95 dB probe and N = 24 for the 103 dB probe. For participants without TBI, N = 9 for the 95 dB probe and N = 27 for the 103 dB probe.
- For participants with depressive disorders, N = 4 for the 95 dB probe and N = 25 for the 103 dB probe. For participants without depressive disorders, N = 14 for the 95 dB probe and N = 26 for the 103 dB probe.

combat). Twelve additional probes were presented during the ITI, at either 8000, 10000, or 12000 ms after stimulus offset.

Consistent with standard picture viewing startle tasks (e.g., Drobes, et al., 2001), pictures were shown for six seconds each on an LCD computer monitor approximately three feet in front of the subject. Each picture was followed by a variable 10-20 second inter-trial interval (ITI). Subjects were instructed to watch each picture for the entire time it was on the screen and to ignore occasional noises heard over their headphones.

Psychophysiological Data Acquisition and Processing

A Dell PC running E-Prime experimental control software (Psychology Software Tools, Inc., Sharpsburg, PA) controlled presentation and timing of the picture stimuli. This computer was linked to another PC running VPM software (Cook III, Atkinson, & Lang, 1987), which controlled presentation and timing of the startle stimuli. The eyeblink component of the startle response to the acoustic probes was measured by recording EMG activity from the orbicularis oculi region beneath the left eye using two Grass Instruments Ag – AgCl electrodes following established guidelines (Blumenthal, et al., 2005). The raw EMG signal was amplified using a Coulbourn S75-01 bioamplifier (bandpass settings of 90–250 Hz), then filtered with a Coulbourn S76-01 contour following integrator using a 125 ms time constant. The digital sampling rate was 1000 Hz from 100 ms prior to the onset of the startle probe until 250 ms after probe onset. A Scientific Solutions Labmaster DPCI A/D converter then digitized the signal.

Heart rate, skin conductance, and facial EMG indices were recorded from one second prior to picture onset through picture offset. For heart rate, the EKG was

amplified with a Coulbourn S75-01 bioamplifier and a Schmitt trigger interrupted the computer to measure each R–R interval to the nearest 1 millisecond. Skin conductance was measured from a pair of electrodes placed on the left hypothenar eminence using Grass Instruments standard electrodes filled with unibase conductance medium. The signal was sampled at 50 Hz and recorded on a Coulbourn S71-23 skin conductance amplifier, calibrated to record a range of 0–20 μS. Data were extracted in 0.5-second intervals. Facial EMG was recorded from the corrugator supercilii and zygomaticus major muscle regions on the left side of the face using guidelines provided by Fridlund and Cacioppo (Fridlund & Cacioppo, 1986). The EMG signals were amplified using Coulbourn S75-01 bioamplifiers with bandpass settings of 90 to 1000 Hz, then filtered with Coulbourn S76-01 contour following integrators using a 500-millisecond time constant. A Scientific Solutions Labmaster DPCI A/D converter then digitized each of these signals. Facial EMG traces were then extracted in 0.5-second epochs.

Scoring of the startle response was accomplished off-line using an interactive program designed to score each blink for onset latency and peak amplitude (VPM). Trials with clear movement artifact or excessive baseline activity were rejected, and trials with no blink were scored as zero amplitude. T-scores for blink magnitudes were computed for each participant using the mean and standard deviation of each participant's responses to the ITI startle probes as the reference distribution. This normalization procedure is designed to reduce the influence of arbitrary, between-subjects variance in reflex size while preserving probe response differences that occur in the context of picture viewing (cf., Drobes, et al., 2001; Lang, Bradley, & Cuthbert, 1998).

Heart rate data were edited off-line with VPM software to correct for missed or extra triggers, were converted to beats-per-minute, and were extracted in 1-second epochs. The average deviation for the entire 6-second viewing period from a 1-second pre-picture baseline was then computed for statistical analyses (cf., Drobes, et al., 2001; Lang, et al., 1998). For corrugator EMG and zygomatic EMG, epochs during which a startle probe was delivered were excluded from further analysis to avoid contamination of the response to the picture with the response to the startle probe. The average deviation for the entire 6-second viewing period from a 1-second pre-picture baseline was then computed for statistical analyses. For skin conductance, each epoch was baseline-corrected by subtracting the mean of the pre-picture epochs. In order to normalize the data and to eliminate trials on which no skin conductance response occurred, these baseline-corrected values were transformed by adding one and taking the base-10 logarithm of that value (Lang, et al., 1993). The skin conductance response (SCR) to each picture was then defined as the maximum of the transformed data during seconds 0-4 of picture viewing in order to avoid SCR's in response to startle probes (Bradley, Codispoti, Cuthbert, et al., 2001; Bradley, Codispoti, Sabatinelli, & Lang, 2001; Schupp, et al., 2004).

For startle data, subjects were included if they had measurable startle responses on 40% or more trials (Cuthbert, et al., 2003). For facial EMG measures, trials were excluded from further analysis if EMG values were greater than 40 μV. Trials in which the standard deviation of the EMG values equaled 0 were excluded, as were trials with excessive noise (i.e., four or more 0.5-second recording epochs that differed from that trial's mean value by more than 3 standard deviations). For the skin conductance

response, trials were excluded from analysis if values were out of range (i.e., greater than 20 μS or less than 0 μS). Trials in which the standard deviation of the SCR equaled 0 were also excluded, as were trials with excessive noise (i.e., three or more 0.5-second recording epochs that differed from that trial's mean value by more than 3 standard deviations). For heart rate, trials were excluded if beats per minute were greater than 133.33 (i.e., a 450 ms inter-beat interval) or less than 40 (i.e., a 1500 ms inter-beat interval). Trials were excluded if the standard deviation of the 1-second recording epochs was zero, as were trials with excessive noise (i.e., more than one epoch that differed from that trial's mean by more than 3 standard deviations). For all measures, participants were then excluded from further analysis if more than 30% of their trials were rejected due to artifact.

Unfortunately, experimenter error also resulted in the loss of data. First, amplifier gains were not recorded for the first 24 subjects, rendering their skin conductance and facial EMG data unusable. Second, gains for the orbicularis oculi were not properly calibrated at the beginning of the study, resulting in a large number of subjects who appear to be "non-responders" with respect to the startle blink response. Third, compounding the problem with the orbicularis gain was the fact that the intensity of the startle probe was also not properly calibrated for the sample and so was increased from 95 dB to 103 dB a short time after the amplifier gains began to be recorded. The result of this was that 30 subjects appear to be startle non-responders; with an additional 15 excluded due to excessive noise and/or movement artifact, a total of 45 subjects have unusable startle data. With an additional 8 subjects having been determined to meet exclusion criteria during the consensus diagnosis process, the final N for subjects with

good startle data is 69 (43 PTSD, 26 without PTSD). The final N's for each measure are reported in Table 1.

There were no significant differences between startle non-responders and those excluded due to artifact with respect to age, gender, ethnicity, PTSD status, or TBI status (p's > .1). When comparing participants who were excluded vs. participants who were included, there were no significant differences with respect to gender, ethnicity, or TBI status. However, participants who were included were significantly younger (mean age 30.36 [sd = 6.82]) than participants who were excluded (mean age 35.42 [sd = 9.09]), $F(1, 111) = 11.411$, $p = .001$. Included participants were also more likely to have PTSD than excluded participants, X^2 (1, N = 113) = 6.051, $p = .0139$.

These differences between included and excluded startle participants are likely explained by two factors related to the timing of recruiting efforts. The age difference is likely explained by the fact that National Guard veterans, who tend to be older than regular activity duty veterans, were recruited before patients from the Minneapolis VAHCS, who are more likely to be regular active duty veterans. The difference in PTSD status is likely explained by the fact that control participants were targeted for recruiting before PTSD participants so that difficulties with data collection could be worked out with the easier-to-recruit and more numerous veterans without PTSD. Given that the problems with data collection were early in the study rather than late, it is unsurprising that the excluded startle participants were slightly older and more likely to have PTSD.

Data Analysis

The first focus of these analyses was the difference in emotional response between participants with and without PTSD and participants with and without TBI. Differences amongst the affective valence categories (pleasant, neutral, unpleasant, and combat) for each physiological response and for ratings of affective valence and arousal were analyzed as manipulation checks.

Each participant's ratings of affective valence and arousal were averaged for each affective valence category (pleasant, neutral, unpleasant, and combat) and were entered into separate 2 (PTSD group) x 2 (TBI group) x 4 (valence category) mixed-effects, repeated measures ANOVA's. As the number of participants meeting criteria for a depressive disorder (i.e., any DSM-IV Axis I unipolar mood disorder; see Table 2) was large enough for statistical analyses, the effect of depressive disorders was also examined via separate 2 (PTSD group) x 2 (depressive disorder group) x 4 (valence category) mixed-effects, repeated measures ANOVA's. Each participant's physiological responses were also averaged for each affective valence category. These data were then entered into separate 2 x 2 x 4 mixed-effects, repeated measures ANOVA's identical to those just described. Multivariate test statistics (Wilks λ and its approximate F statistic) were used to assess the significance of all effects involving the within-subjects factor of affective valence category unless otherwise noted.

Significant main effects of group were indicative of differences in overall emotional reactivity between groups. Significant interactions of groups (i.e., PTSD x TBI or PTSD x Depression) were indicative of overall differences in emotional reactivity between participants with and without PTSD as a function of either TBI or depression.

Significant interactions of group x valence category were indicative of between-group differences in response to at least one affective valence category.

No post-hoc tests were necessary for significant main effects of group, as each group only contained two levels. Differences among each valence category were tested by Fisher's least significant difference (LSD) tests regardless of main effects of valence category, as these comparisons were planned a priori. Similarly, simple effects of PTSD and of TBI within each valence category were tested regardless of the significance of the interaction of PTSD or x valence category, as these comparisons were also planned a priori. Significant interactions of valence category with depression were followed up by tests for simple effects of depression within each valence category using between-subjects ANOVA's.

The second focus of these analyses was exploring PTSD as a dimensional construct. To achieve this aim, a measure of overall PTSD symptom severity (i.e., CAPS Total score) was used to predict physiological responses as well as ratings of valence and arousal using bivariate linear regression. Severity scores for each empirically-derived symptom cluster (Palmieri, et al., 2007; Simms, et al., 2002) were also used to predict physiological responses as well as ratings of valence and arousal using bivariate linear regression. Models with significant regression coefficients were indicative of the severity of PTSD symptoms significantly predicting changes in physiological responses or ratings.

Results

Demographic and Clinical Characteristics of the Sample

Participant demographics and clinical characteristics are reported in Table 1 and Table 2. To examine differences between participants with and without PTSD, TBI, and depression, separate between-subjects ANOVA's were run with relevant demographic and clinical characteristics of the sample as dependent variables. The first was a 2 (PTSD) x 2 (TBI) between-subjects ANOVA with age as the dependent variable. There were no main effects for either PTSD or TBI on age, *p*'s > .21. However, there was a statistically significant interaction of PTSD x TBI, $F(1,120) = 4.05$, $p = .046$, *partial* $\eta^2 = .03$. This interaction was followed up with simple effects ANOVA's testing the effect of TBI on participants with and without PTSD. For participants without PTSD, age did not vary as a function of TBI, $F(1,59) = .26$, $p = .61$. For participants with PTSD, age did vary as a function of TBI, $F(1,61) = 5.95$, $p = .02$, *partial* $\eta^2 = .09$. Participants with PTSD and TBI were significantly younger (*mean* = 29.29, *sd* = 6.36) than participants with PTSD and no TBI (*mean* = 34.07, *sd* = 9.19). However, the literature does not suggest any reason to think that this five-year age difference will have any significant effect on other variables of interest. A separate between-subjects ANOVA was run to examine differences in age between those with depressive disorders and those without. Age did not significantly differ between those participants with a current depressive disorder and those without, $F(1,122) = 2.77$, $p = .10$.

To examine differences in CAPS total severity between groups, separate between-subjects ANOVA's were run. Severity for each symptom was calculated as the sum of the frequency (0-4) and intensity (0-4) of each PTSD symptom, consistent with the

standard CAPS scoring procedure. Individuals without completed CAPS (see Methods) were excluded from these analyses. A total of 93 participants in the final sample had complete CAPS protocols (63 with PTSD, 30 without PTSD; 49 with TBI, 44 without TBI; and 49 with depressive disorders, 44 without depressive disorders).

A 2 (PTSD) x 2 (TBI) between-subjects ANOVA revealed a main effect of PTSD on CAPS total severity, $F(1,89) = 108.67$, $p < .01$, *partial* $\eta^2 = .55$. As expected, participants with PTSD had significantly greater CAPS total severity scores than participants without PTSD. There was no main effect of TBI and PTSD and TBI did not significantly interact, p's > .11. This indicates that CAPS total severity scores successfully distinguished between participants with PTSD and those without and that there was no effect of TBI on CAPS total severity.

A second 2 (Depression) x 2 (PTSD) between-subjects ANOVA was run to explore the effect of Depression on CAPS total severity. The main effect of PTSD is reported above. There was a significant main effect of Depression, $F(1,89) = 21.21$, $p < .01$, *partial* $\eta^2 = .19$. Not surprisingly, participants with depressive disorders had significantly greater CAPS scores than participants without depressive disorders. Depression and PTSD did not significantly interact, $p = .18$. These results indicate that depressive disorders were also a significant driver of elevated CAPS scores, though the effect was not nearly as large as it was for PTSD, likely reflecting both the overlap in symptoms between the two disorders as well as the differences between the two.

A significant issue in PTSD research is comorbidity of Axis I psychopathology. It is the rule rather than the exception in individuals meeting diagnostic criteria for PTSD and complicates psychophysiological investigations of the disorder, as described above.

To examine rates of comorbidity in the current sample, the total number of Axis I disorders assigned to each participant was calculated, inclusive of PTSD. Comparing the number of diagnoses each participant was assigned provided a rough estimate of comorbidity within each diagnostic group in the present study.

To examine whether the total number of DSM-IV Axis I diagnoses (inclusive of PTSD) differed between those with and without PTSD and TBI, a 2 (PTSD) x 2 (TBI) between-subjects ANOVA was run with the total number of Axis I diagnoses as the dependent variable. There was a significant main effect of PTSD, such that participants with PTSD had significantly more Axis I diagnoses than participants without PTSD, $F(1,120) = 13.84$, $p < .01$, *partial* $\eta^2 = .10$. There was also a significant main effect of TBI, such that participants with TBI had significantly more Axis I diagnoses than participants without TBI, $F(1,120) = 6.23$, $p = .01$, *partial* $\eta^2 = .05$. The interaction of PTSD and TBI was not significant, $p = .18$.

A second 2 (Depression) x 2 (PTSD) between-subjects ANOVA was run to examine the influence of Depression on the number of total Axis I diagnoses (inclusive of Depression). Notably, when Depression was included in the model (rather than TBI), there was no longer a main effect of PTSD, $F(1,120) = 1.06$, $p = .31$, *partial* $\eta^2 = .01$. There was, however, a significant main effect of Depression, $F(1,120) = 121.36$, $p < .01$, *partial* $\eta^2 = .50$. The interaction of PTSD and Depression was not significant, $p = .736$. When comparing the effect sizes of PTSD from the first model and Depression from the second model, the effect of Depression was significantly larger (*partial* $\eta^2 = .10$ for PTSD and *partial* $\eta^2 = .50$ for Depression). Given that the significant main effect of

PTSD also disappears when Depression is included in the ANOVA, these results suggest that Depression was the driving force behind the increased comorbidity in the sample.

In examining the distribution of female participants in the sample, it was notable that all 9 of them are in the no-PTSD group. Unsurprisingly, there was a significant difference between the PTSD and no-PTSD groups, $\chi^2 = 10.02$, $p < .01$. There was no significant difference in the number of females with and without TBI, $\chi^2 = 2.20$, $p = .14$. There was also no significant difference between the number of females with and without depressive disorders, $\chi^2 = 1.55$, $p = .21$.

It was also important to examine the differences in the comorbidity of depressive disorders amongst participants with and without PTSD and TBI, as these conditions are known to co-occur at higher than chance rates. As expected, there were significantly more participants with depressive disorders in the PTSD group than the no-PTSD group, $\chi^2 = 17.77$, $p < .01$. Also as expected, there were significantly more participants with depressive disorders in the TBI group than the no-TBI group, $\chi^2 = 11.04$, $p < .01$.

Similarly, it was important to examine the differences in the comorbidity of TBI amongst participants with and without PTSD and depressive disorders. While every attempt was made to balance the co-occurrence of TBI and PTSD in recruiting for the current study, we were unable to obtain equal groups in the final sample for the present study. Results indicated there were significantly more participants with TBI in the PTSD group than in the no-PTSD group, $\chi^2 = 4.74$, $p = .03$. The significantly greater number of participants with TBI in the depressed group than in the non-depressed group is reported above.

Because the volume level of the startle probe was changed during the study, analyses were run to explore how this may have influenced the data. Significantly more participants with PTSD received the 103 dB probe than the 95 dB probe, $\chi^2 = 12.37$, $p < .01$. This is likely due to the fact that control participants were initially targeted during recruiting and participants with PTSD were targeted later so that any issues in data collection could be worked out. The number of participants with and without TBI did not differ across the two probe levels, $\chi^2 = 0.046$, $p = .83$. Participants with depressive disorders were significantly more likely to have received the 103 dB probe, $\chi^2 = 3.91$, $p = .047$. Participants who received the 103 dB probe (*mean age* = 31.19, *sd* = 7.50) were significantly younger than participants who received the 95 dB probe (*mean age* = 34.33, *sd* = 8.97), $F(1,67) = 5.71$, $p = .02$. This is likely due to the shift from older National Guard veterans to younger regular army veterans at approximately the same time as the change in probe intensity. There were no differences in gender between those who received the 95 dB vs 103 dB probes, $\chi^2 = 0.54$, $p = .46$. Importantly, there was no main effect of startle probe intensity on startle blink magnitude, $F(1,67) = .09$, $p = .77$. Probe intensity also did not significantly interact with Valence Category, $F(3,65) = .06$, $p = .98$.

Specific Aim 1: Develop psychophysiological models and measures of emotional dysregulations in PTSD.

Ratings of Affective Valence and Arousal

Means and standard deviations for valence and arousal ratings are reported in Table 5, Table 6, and Figure 1. Mean ratings of affective valence for each picture were analyzed with a 2 (PTSD) x 2 (TBI) x 4 (Valence Category) mixed-effects, repeated-

measures ANOVA (see Figures 2 and 4). As expected, there was a main effect of valence category, $F(3, 113) = 190.13$, $p < .01$, *partial* $\eta^2 = .84$. Follow-up LSD pair-wise comparisons of valence categories indicated that ratings for each valence category significantly differed from all other valence categories, p's $< .01$. Pleasant pictures were rated as most pleasant, followed by neutral, then unpleasant, and finally combat. These results successfully checked the study's manipulation of the affective valence of the picture stimuli, including successfully choosing combat-related images that were viewed as significantly less pleasant (i.e., more unpleasant) than the "unpleasant" IAPS images.

There was a nominal main effect of TBI status, $F(1, 115) = 3.21$, $p = .08$, *partial* $\eta^2 = .03$. Participants in the TBI group rated the picture stimuli as being overall somewhat more pleasant than those in the no-TBI group. There was no significant main effect of PTSD and there was no significant interaction of PTSD x TBI, p's $> .31$. Valence category did not significantly interact with PTSD, TBI, or their interaction, p's $> .10$.

Pre-planned one-way ANOVA's were run to explore between group effects of PTSD and TBI within each valence category. There was an effect of PTSD only for pleasant pictures, where participants with PTSD rated the pleasant pictures as significantly less pleasant than participants without PTSD, $F(1, 117) = 8.07$, $p = .01$. This finding was partially unexpected in that differences in ratings of combat pictures as a function of PTSD were also expected.

There was an effect of TBI for unpleasant pictures, where participants with TBI rated the unpleasant pictures as significantly more pleasant than those without TBI, $F(1, 117) = 3.99$, $p = .048$. There was also an effect of TBI for combat pictures where

participants with TBI rated the combat pictures as significantly more pleasant than participants without TBI, F (1, 117) = 5.13, p = .03. These findings were notable for the participants with TBI rating aversive stimuli, including combat-related stimuli that may be related to their injuries, as more pleasant than those without TBI.

Mean ratings of affective valence for each picture were also analyzed with a 2 (PTSD) x 2 (Depression) x 4 (Valence Category) mixed-effects, repeated-measures ANOVA (see Figure 5). Effects of Valence Category and PTSD are reported above. Depression did not significantly interact with Valence Category, p = .16. The three-way interaction of Depression, PTSD, and Valence Category was also not significant, p = .98. There was no main effect of Depression and it did not interact with PTSD, p's > .61. Thus, Depression did not appear to have an independent effect on ratings of affective valence.

Mean ratings of arousal for each picture were analyzed with a 2 (PTSD) x 2 (TBI) x 4 (Valence Category) mixed-effects, repeated-measures ANOVA (see Figures 3 and 6). As expected, there was a significant main effect of valence category, F(3,113) = 107.33, p < .01, *partial* η^2 = .74. Follow-up LSD pair-wise comparisons of valence categories indicated that arousal ratings for each valence category significantly differed from all other valence categories, p's < .02. Combat pictures were rated as the most arousing, followed by pleasant pictures, then unpleasant pictures, and finally neutral pictures. These results partially confirmed the study's manipulation of the arousal level of the different valence categories. Our aim was to balance the arousal level of the pleasant and unpleasant pictures so as to be able to clearly interpret effects of valence independent of arousal. However, it appears that the introduction of the combat pictures – which were

rated as most arousing – altered the affective space in which the ratings were made (i.e., altered perceptions of the relative arousal levels of the stimuli). As a result, the arousal ratings of pleasant and unpleasant pictures significantly differed. Caution must therefore be used in interpreting measures that are normally associated with affective valence because of the potential role of differing arousal levels.

The only other significant effect was a significant interaction of PTSD x Valence Category, $F(3,113) = 5.34$, $p < .01$, *partial* $\eta^2 = .12$. There were no main effects of PTSD or TBI and they did not significantly interact, p's > .51. Valence category did not significantly interact with TBI and the three-way interaction was not significant, p's > .79.

Follow-up one-way ANOVA's were run to explore between group effects of PTSD on arousal ratings within each valence category. The only significant finding was a main effect of PTSD for combat pictures in which participants with PTSD rated the combat pictures as significantly more arousing than participants without PTSD, $F(1,117) = 5.20$, $p = .02$. PTSD did not have a significant effect on ratings of arousal within the other valence categories, p's > .14.

Pre-planned one-way ANOVA's were run to explore between group effects of TBI on arousal ratings within each valence category. No significant effects were observed, p's > .33.

Mean ratings of arousal for each picture were also analyzed with a 2 (PTSD) x 2 (Depression) x 4 (Valence Category) mixed-effects, repeated-measures ANOVA to examine effects of Depression (see Figure 7). Effects of Valence Category and PTSD are

reported above. The main effect of Depression was not significant and Depression did not significantly interact with PTSD or with valence category, *p*'s > .23.

Startle Blink Magnitude

Means and standard deviations for startle blink magnitude T-scores are reported in Table 7 and Table 8. Mean startle blink magnitudes for each picture were analyzed with a 2 (PTSD) x 2 (TBI) x 4 (Valence Category) mixed-effects, repeated-measures ANOVA (see Figure 8 and Figure 9). As expected, there was a significant main effect of Valence Category, $F(3, 63) = 23.19$, $p < .01$, *partial* $\eta^2 = .53$. Follow-up LSD pair-wise comparisons of valence categories indicated that startle blink responses for each valence category significantly differed from all other valence categories (*p*'s < .03), with the exception of unpleasant and combat ($p = .23$). Combat pictures elicited the largest startle responses, followed by unpleasant, then neutral, and finally pleasant. These results successfully checked the study's manipulation of the affective valence of the IAPS stimuli. Contrary to expectation and contrary to the finding that participants rated the combat pictures as more unpleasant than the IAPS unpleasant stimuli, startle blink responses did not differ between the two categories.

There were no significant main effects of PTSD or TBI and they did not significantly interact, *p*'s > .31. Valence Category did not significantly interact with PTSD or TBI and the three-way interaction was also non-significant, *p*'s > .40.

Pre-planned one-way ANOVA's were run to explore between group effects of PTSD and TBI within each valence category. No significant effects of PTSD (*p*'s > .09) or TBI (*p*'s > .52) were observed within any valence category. Of note, the difference in

response to neutral pictures between participants with and without PTSD trended toward significance (p = .09), with participants with PTSD exhibiting nominally larger startle responses.

Mean startle blink magnitudes for each picture were also analyzed with a 2 (PTSD) x 2 (Depression) x 4 (Valence Category) mixed-effects, repeated-measures ANOVA to examine effects of Depression (see Figure 10). Effects of Valence Category and PTSD are reported above. There was no significant main effect of Depression and Depression did not significantly interact with PTSD or with Valence Category, p's > .25.

However, the three-way interaction of Depression x PTSD x Valence Category was significant, $F(3,63) = 3.57$, p = .02, *partial* η^2 = .15. In order to explore the differential effect of Depression on participants with and without PTSD, this interaction was followed up by separate 2 (Depression) x 4 (Valence Category) mixed-effects, repeated-measures ANOVA's for participants with PTSD and participants without PTSD. Of note, the "No-PTSD, Depressed" group was very small (N=5). Therefore, results should be interpreted cautiously.

For participants with PTSD, there was no significant main effect of Depression and Depression did not significantly interact with Valence Category, p's > .34. For participants without PTSD, there was no significant main effect of Depression. There was a nominal interaction of Depression x Valence Category, $F(3,22) = 2.51$, p = .09, *partial* η^2 = .255. Follow-up simple effects ANOVA's were run to explore between group effects of Depression within each valence category for participants without PTSD in light of the significant three-way interaction. The only significant finding was a main effect of Depression for neutral pictures, where participants with depression exhibited larger

startle responses to neutral pictures than non-depressed participants, $F(1,24) = 6.28$, $p = .02$. There were no significant effects of Depression within other valence categories for participants without PTSD, p's > .30. Thus, the significant three-way interaction of PTSD x Depression x Valence Category seems to have been driven by differences between depressed and non-depressed participants without PTSD.

To address the basic question of whether participants' reports of an exaggerated startle response (symptom D5) predict an objectively measurable increase in startle response reactivity, mean startle blink magnitudes were analyzed with a 2 (Symptom D5 Present) x 4 (Valence Category) mixed-effects, repeated-measures ANOVA (see Figure 11). There was no main effect of reporting an exaggerated startle response, and the presence of symptom D5 did not significantly interact with Valence Category, p's > .17. Pre-planned one-way ANOVA's were also run to examine between group effects within each valence category. No significant effects of the presence of symptom D5 were observed within any valence category, p's > .41.

Skin Conductance Response

Means and standard deviations for the skin conductance response (SCR) are reported in Table 9 and Table 10. Mean SCR's for each picture were analyzed with a 2 (PTSD) x 2 (TBI) x 4 (Valence Category) mixed-effects, repeated-measures ANOVA (see Figure 12 and Figure 13). As expected, there was a significant effect of Valence Category, $F(3,71) = 7.30$, $p < .01$, *partial* $\eta^2 = .24$. Follow-up LSD pair-wise comparisons of valence categories indicated that SCR's elicited by neutral pictures significantly differed from all other valence categories (p's < .01), while SCR's elicited

by the other valence categories did not significantly differ from each other (p's > .46). Combat pictures elicited the largest SCR's, followed by unpleasant, then pleasant, and finally neutral. These results successfully checked the study's manipulation of the affective valence and arousal of the picture stimuli in that the SCR's elicited by affective pictures (pleasant, unpleasant, and combat) differed significantly from those elicited by neutral pictures.

Contrary to expectations, there were no significant main effects for PTSD or TBI and they did not significantly interact, p's > .23. Also contrary to expectations, Valence Category did not significantly interact with PTSD or TBI and their three-way interaction was also non-significant, p's > .26.

Pre-planned one-way ANOVA's were run to explore between group effects of PTSD and TBI within each valence category. Again contrary to expectations, no significant between group effects were found for PTSD within any valence category, p's > .31. No significant between group effects were found for TBI within any valence category, p's > .20.

Mean SCR's for each picture were also analyzed with a 2 (PTSD) x 2 (Depression) x 4 (Valence Category) mixed-effects, repeated-measures ANOVA to examine effects of Depression (see Figure 14). Effects of Valence Category and PTSD are reported above. There was no significant main effect of Depression (p = .87). Depression did not significantly interact with Valence Category and the three-way interaction of Depression x PTSD x Valence was also non-significant, p's > .64. There was a nominal interaction of Depression x PTSD, $F(1,73) = 3.41$, p = .07, *partial* η^2 =

.05. This nominal interaction was not followed up in light of the non-significant statistical test result and the very small effect size.

The lack of between group effects for the SCR was unexpected and likely reflects the heterogeneity of the PTSD group as well as the presence of sub-threshold PTSD and depressive symptoms in the no-PTSD and no-Depression groups, respectively. Additionally, in most psychophysiological studies of PTSD, the comparison group would not contain individuals with depression (which it did in the above analyses); and in most psychophysiological studies of depression, the comparison group would not contain individuals with PTSD (which it did in the above analyses). Therefore, the presence of pathology in the comparison groups likely obscured any between group effects that would have been observed with "cleaner" comparison groups.

Corrugator Supercilii

Means and standard deviations for corrugator EMG are reported in Table 9 and Table 10. Mean corrugator responses for each picture were analyzed with a 2 (PTSD) x 2 (TBI) x 4 (Valence Category) mixed-effects, repeated-measures ANOVA (see Figure 15 and Figure 16). As expected, there was a significant effect of Valence Category, $F(3,77) = 8.67$, $p < .01$, *partial* $\eta^2 = .25$. Follow-up LSD pair-wise comparisons of valence categories revealed that responses elicited by pleasant pictures significantly differed from all other valence categories, p's $< .01$. Corrugator responses elicited by neutral pictures significantly differed only from pleasant and combat pictures, p's $< .01$. Responses elicited by unpleasant pictures significantly differed only from pleasant pictures, $p < .01$. And responses elicited by combat pictures significantly differed only from pleasant and

neutral pictures, *p*'s < .01. Combat pictures elicited the largest responses, followed by unpleasant, then neutral, and finally pleasant. These results successfully checked the study's manipulation of the affective valence of the picture stimuli. The corrugator responses elicited by the picture stimuli corresponded to ratings of affective valence such that the most unpleasant pictures elicited the greatest corrugator responses, followed by the next most unpleasant pictures eliciting the next greatest corrugator response, etc.

However, there were no significant main effects of PTSD or TBI and they did not significantly interact, *p*'s > .78. Contrary to expectations, Valence Category did not significantly interact with either PTSD or TBI and their three-way interaction was also non-significant, *p*'s > .28.

Pre-planned one-way ANOVA's were run to explore between group effects of PTSD and TBI within each valence category. Contrary to expectations, there were no significant effects of PTSD within any valence category, *p*'s > .15. There were also no significant effects of TBI within any valence category, *p*'s > .65.

Mean corrugator responses for each picture were also analyzed with a 2 (PTSD) x 2 (Depression) x 4 (Valence Category) mixed-effects, repeated-measures ANOVA to examine effects of Depression (see Figure 17). Effects of Valence Category and PTSD are reported above. There was no significant main effect of Depression, $p = .13$. Depression did not significantly interact with Valence Category and the three-way interaction of Depression x PTSD x Valence Category was also non-significant, *p*'s > .75. There was a nominal interaction of Depression x PTSD, $F(1,79) = 3.27$, $p = .07$, *partial* $\eta^2 = .04$. In light of the nominal interaction and very small effect size, this interaction was not followed up.

Zygomaticus Major

Means and standard deviations for zygomatic EMG are reported in Table 9 and Table 10. Mean zygomatic responses for each picture were analyzed with a 2 (PTSD) x 2 (TBI) x 4 (Valence Category) mixed-effects, repeated-measures ANOVA (see Figure 18 and Figure 19). Contrary to expectations, no significant effects were observed. The main effect of Valence Category was not significant, $F(3,75) = 0.64$, $p = .59$, *partial* $\eta^2 = .03$. Valence Category did not significantly interact with PTSD or TBI and their three-way interaction was not significant, p's > .43. There were no main effects for either PTSD or TBI and their interaction was not significant, p's > .10. Unfortunately, these results raise questions regarding the manipulation of the affective valence of the picture stimuli, as we expected significantly greater zygomatic responses to pleasant pictures than to unpleasant, neutral, or combat pictures. Also notable was the fact that the combat pictures elicited the largest zygomatic response, consistent with a grimacing response (see Table 9).

Pre-planned one-way ANOVA's were run to explore between group effects of PTSD and TBI within each valence category. Contrary to expectations, there were no significant effects of PTSD within any valence category, p's > .35. There were also no significant effects of TBI within any valence category, p's > .13.

Mean zygomatic responses for each picture were also analyzed with a 2 (PTSD) x 2 (Depression) x 4 (Valence Category) mixed-effects, repeated-measures ANOVA to examine effects of Depression (see Figure 20). Effects of Valence Category and PTSD are reported above. There was no significant main effect of Depression, $p = .64$.

Depression did not significantly interact with Valence Category, and the three-way interaction of Depression x PTSD x Valence Category was non-significant, *p*'s = .88. There was a nominal interaction of PTSD x Depression, $F(1,77) = 3.22$, $p = .08$, *partial* $\eta^2 = .04$. Given the non-significant test result and the very small effect size, this interaction was not followed up.

Heart Rate Change

Means and standard deviations for heart rate change are reported in Table 9 and Table 10. Mean heart rate changes for each picture were analyzed with a 2 (PTSD) x 2 (TBI) x 4 (Valence Category) mixed-effects, repeated-measures ANOVA (see Figure 21 and Figure 22). As expected, there was a significant effect of Valence Category, $F(3,89) = 8.84$, $p < .01$, *partial* $\eta^2 = .23$. Follow-up LSD pair-wise comparisons of valence categories revealed that responses elicited by unpleasant pictures significantly differed from all other valence categories, *p*'s < .02. Responses elicited by the other valence categories did not significantly differ from each other, *p*'s > .14. Unpleasant pictures elicited the greatest heart rate deceleration, followed by pleasant, then neutral, and finally combat. These results partially checked the study's manipulation of the affective valence of the picture stimuli. The main effect of affective valence was expected, and it was also expected that more pleasant contents would elicit less heart rate deceleration (Lang, et al., 1993). However, the finding that combat-related pictures elicited the least heart rate change and that those responses did not differ from pleasant or neutral contents was unexpected. As seen below, this is likely due to the significant differences between participants with and without PTSD in their responses to combat pictures.

There were no main effects of PTSD or TBI and they did not significantly interact, *p*'s > .10. Valence Category did not significantly interact with TBI and the three-way interaction of PTSD x TBI x Valence Category was non-significant, *p*'s > .26. There was a significant interaction of PTSD x Valence Category, $F(3,89) = 2.90$, $p = .04$, *partial* $\eta^2 = .09$.

This significant interaction of PTSD x Valence Category was followed up by between-groups ANOVA's to explore the effect of PTSD within each valence category. There was a significant main effect of PTSD on heart rate responses to unpleasant pictures such that those with PTSD had significantly less heart rate deceleration in response to unpleasant pictures than those without PTSD, $F(1,93) = 4.80$, $p = .03$. There was also a significant main effect of PTSD on heart rate responses to combat pictures such that those with PTSD actually experienced heart rate acceleration in response to combat pictures, while those without PTSD experienced heart rate deceleration, $F(1,93) = 7.66$, $p < .01$. This is consistent with past work in which participants with PTSD exhibited faster heart rates in response to standardized trauma cues (see the meta-analysis by Pole, 2007).

Pre-planned between-groups ANOVA's were also run to explore the effects of TBI within each valence category. There was a significant effect of TBI for pleasant pictures such that those with TBI had significantly less heart rate deceleration than those without TBI, $F(1,93) = 4.93$, $p = .03$. This may represent a diminished orienting response to appetitive stimuli in individuals with histories of TBI, though no other psychophysiological measures indicated diminished processing of appetitive stimuli in

the TBI group. There were no significant effects of TBI within the other valence categories, *p*'s > .13.

Mean heart rate responses for each picture were also analyzed with a 2 (PTSD) x 2 (Depression) x 4 (Valence Category) mixed-effects, repeated-measures ANOVA to examine effects of Depression (see Figure 23). Effects of Valence Category and PTSD are reported above. There was no main effect of Depression and it did not significantly interact with PTSD, *p*'s > .67. The three-way interaction of Depression x PTSD x Valence Category was not significant, $p = .65$. The interaction of Depression x Valence Category was nominally significant, $F(3,89) = 2.39$, $p = .07$, *partial* $\eta^2 = .08$. This nominal interaction was not followed up in light of the non-significant statistical test and very small effect size.

Specific Aim 2: Explore emotion-modulated startle reactivity and other measures of emotion in relation to empirically derived symptom clusters.

Ratings of Affective Valence and Arousal

To explore any continuous or dimensional effects of PTSD symptom severity on valence ratings, separate bivariate linear regression analyses were conducted (see Table 12 and Figure 29). Each subject's mean valence ratings for each category were the dependent variables in separate regressions, while, respectively, CAPS total severity, Dysphoria symptom severity, Intrusions symptom severity, Avoidance symptom severity, and Hyperarousal symptom severity were the independent variables.

Significant negative relationships were observed between valence ratings of pleasant pictures and CAPS total severity, Dysphoria symptom severity, Intrusions

symptom severity, and Avoidance symptom severity. CAPS total severity significantly predicted valence ratings of pleasant pictures (b = -1.17, $t(83)$ = -4.07, $p < .01$) and explained a significant proportion of variance in those ratings, R^2 = .17, $F(1,83)$ = 16.60, $p < .01$. Dysphoria symptom severity significantly predicted valence ratings of pleasant pictures (b = -1.97, $t(83)$ = -3.46, p = .01) and explained a significant proportion of variance in those ratings, R^2 = .13, $F(1,83)$ = 11.99, $p < .01$. Intrusions symptom severity also significantly predicted valence ratings of pleasant pictures (b = -3.76, $t(83)$= -3.95, $p < .01$) and explained a significant proportion of the variance in those ratings, R^2 = .15, $F(1,83)$ = 15.59, $p < .01$. Avoidance symptom severity also significantly predicted valence ratings of pleasant pictures (b = -6.38, $t(83)$ = -3.94, $p < .01$) and accounted for a significant proportion of the variance in those ratings, R^2 = .16, $F(1,83)$ = 15.50, $p < .01$. Hyperarousal symptoms were also nominally predictive of valence ratings of pleasant pictures in the same way (b = -3.69, t = -1.93, p = .06) and explained a nominal proportion of the variance in those ratings, R^2 = .04, $F(1,83)$ = 3.73, p = .06.

Additionally, Hyperarousal symptom severity significantly predicted valence ratings of neutral pictures (b = -2.61, $t(83)$ = -2.29, p = .03) and explained a significant proportion of the variance in those ratings, R^2 = .06, $F(1,83)$ = 5.23, p = .03. As Hyperarousal symptoms increased, valence ratings of neutral pictures decreased. There were no other significant relationships between symptom clusters and ratings of affective valence for any valence category. Thus, greater PTSD symptom severity, both overall and in terms of individual symptom clusters, predicted significantly lower perceptions of the pleasantness of appetitive stimuli.

To explore any continuous or dimensional effects of PTSD symptom severity on arousal ratings, separate bivariate linear regression analyses were conducted (see Table 12 and Figure 30). Each subject's mean arousal ratings for each valence category were the dependent variables in separate regressions, while, respectively, CAPS total severity, Dysphoria symptom severity, Intrusions symptom severity, Avoidance symptom severity, and Hyperarousal symptom severity were the independent variables.

Significant negative relationships between ratings of arousal for pleasant pictures and PTSD symptom severity were also observed (all relationships reported here are negative unless otherwise noted). CAPS total severity significantly predicted arousal ratings of pleasant pictures (b = -1.44, $t(83)$ = -3.19, $p < .01$) and explained a significant proportion of variance in those ratings, R^2 = .11, $F(1,83)$ = 10.17, $p < .01$. Dysphoria symptom severity significantly predicted arousal ratings of pleasant pictures (b = -2.57, $t(83)$ = -3.08, $p < .01$) and explained a significant proportion of variance in those ratings, R^2 = .10, $F(1,83)$ = 9.46, $p < .01$. Intrusions symptom severity significantly predicted arousal ratings of pleasant pictures (b = -4.47, $t(83)$ = -3.02, $p < .01$) and explained a significant proportion of variance in those ratings, R^2 = .10, $F(1,83)$ = 9.10, $p < .01$. Finally, Avoidance symptom severity significantly predicted arousal ratings of pleasant pictures (b = -6.00, $t(83)$ = -2.34, p = .02) and explained a significant proportion of variance in those ratings, R^2 = .06, $F(1,83)$ = 5.47, p = .02.

In a positive relationship, Dysphoria symptom severity also significantly predicted arousal ratings of combat pictures (b = 2.01, $t(83)$ = 2.13, p = .04) and explained a significant proportion of variance in those ratings, R^2 = .05, $F(1,83)$ = 4.52, p = .04. There were no other significant relationships between symptom clusters and ratings

of affective valence for any valence category. Overall, greater PTSD symptom severity, both overall and in terms of individual symptom clusters, predicted significantly lower perceptions of the arousal of appetitive stimuli. This is consistent with ratings of valence, described above. Interestingly, greater Dysphoria symptoms predicted greater perceptions of arousal of combat stimuli while other symptom clusters did not.

Startle Blink Magnitude

To explore any continuous or dimensional effects of PTSD symptom severity on startle blink magnitudes, separate bivariate linear regression analyses were conducted (see Table 11 and Figure 24). Each subject's mean startle blink magnitudes for each valence category and general startle reactivity were the dependent variables in separate regressions, while, respectively, CAPS total severity, Dysphoria symptom severity, Intrusions symptom severity, Avoidance symptom severity, and Hyperarousal symptom severity were the independent variables. General startle reactivity was defined as each subject's mean response across all picture-viewing trials. For CAPS total severity, N = 54, as only 54 of the 69 startle subjects completed the entire CAPS (see Methods).

In a positive relationship, Dysphoria symptom severity significantly predicted startle blink responses to pleasant pictures ($b = .14$, $t(51) = 2.16$, $p = .04$) and explained a significant proportion of variance in those responses, $R^2 = .08$, $F(1,51) = 4.65$, $p = .04$. Also in a positive relationship, Intrusions symptom severity significantly predicted startle blink responses to pleasant pictures ($b = .26$, $t(51) = 2.09$, $p = .04$) and explained a significant proportion of variance in those responses, $R^2 = .08$, $F(1,51) = 4.35$, $p = .04$. In another positive relationship, Hyperarousal symptom severity significantly predicted

startle blink responses to pleasant pictures (b = .58, t(51) = 2.59, p = .01) and explained a significant proportion of variance in those responses, R^2 = .12, F(1,51) = 6.72, p = .01. Also in a positive relationship, Hyperarousal symptom severity significantly predicted startle blink responses to neutral pictures (b = .52, t(51) = 2.06, p = .04) and explained a significant proportion of variance in those responses, R^2 = .08, F(1,51) = 4.25, p = .04. There were no other significant relationships between symptom clusters and startle blink magnitude for any valence category. Additionally, general startle reactivity was not related to CAPS total severity or to the severity of any symptom clusters.

Overall, these results indicate that increasing PTSD symptom severity (excepting Avoidance symptoms) led to increased startle reactivity in response to pleasant stimuli. That is, the more severe a participant's symptoms of Dsyphoria, Intrusions, or Hyperarousal, the less startle attenuation there was to pleasant stimuli. Similarly, Hyperarousal symptom severity predicted increased startle responding to neutral stimuli.

Skin Conductance Response

To explore any continuous or dimensional effects of PTSD symptom severity on SCR's, separate bivariate linear regression analyses were conducted (see Table 11 and Figure 25). Each subject's mean SCR's for each valence category were the dependent variables in separate regressions, while, respectively, CAPS total severity, Dysphoria symptom severity, Intrusions symptom severity, Avoidance symptom severity, and Hyperarousal symptom severity were the independent variables.

The only significant finding was that increasing Avoidance symptom severity significantly predicted increasing SCR's to combat pictures, (b = .003, t(60) = 2.31, p =

.02) and explained a significant proportion of variance in those SCR's, R^2 = .08, F(1,60) = 5.32, p = .02. There were no other significant relationships between symptom clusters and SCR's for any valence category. Contrary to expectations, PTSD symptom severity generally did not predict changes in SCR's to affective picture stimuli.

Corrugator Supercilii

To explore any continuous or dimensional effects of PTSD symptom severity on corrugator EMG, separate bivariate linear regression analyses were conducted (see Table 11 and Figure 26). Each subject's mean corrugator responses for each valence category were the dependent variables in separate regressions, while, respectively, CAPS total severity, Dysphoria symptom severity, Intrusions symptom severity, Avoidance symptom severity, and Hyperarousal symptom severity were the independent variables.

Only two of the regressions models indicated that PTSD symptoms significantly predicted corrugator responses. In a positive relationship, Intrusions symptom severity significantly predicted corrugator responses to combat pictures, (b = .03, t(65) = 2.48, p = .02) and explained a significant proportion of variance in those responses, R^2 = .09, F(1,65) = 6.16, p = .02. In a negative relationship, Avoidance symptom severity significantly predicted corrugator responses to neutral pictures, (b = -0.02, t(65) = -2.12, p = .04) and explained a significant proportion of variance in those responses, R^2 = .06, F(1,65) = 4.48, p = .04. There were no other significant relationships between symptom clusters and corrugator responses for any valence category. Contrary to expectations, PTSD symptom severity generally did not predict changes in corrugator responses to affective picture stimuli.

Zygomaticus Major

To explore any continuous or dimensional effects of PTSD symptom severity on corrugator EMG, separate bivariate linear regression analyses were conducted (see Table 11 and Figure 27). Each subject's mean corrugator responses for each valence category were the dependent variables in separate regressions, while, respectively, CAPS total severity, Dysphoria symptom severity, Intrusions symptom severity, Avoidance symptom severity, and Hyperarousal symptom severity were the independent variables. Contrary to expectations, none of these regression models indicated that any PTSD symptom cluster significantly predicted zygomatic responses to stimuli in any valence category. Zygomatic EMG does not appear to be significantly related to PTSD symptom severity.

Heart Rate

To explore any continuous or dimensional effects of PTSD symptom severity on heart rate change, separate bivariate linear regression analyses were conducted (see Table 11 and Figure 28). Each subject's mean heart rate responses for each valence category were the dependent variables in separate regressions, while, respectively, CAPS total severity, Dysphoria symptom severity, Intrusions symptom severity, Avoidance symptom severity, and Hyperarousal symptom severity were the independent variables.

Only one symptom cluster significantly predicted heart rate change. Increasing Avoidance symptom severity significantly predicted increasing heart rate responses to combat pictures, (b = .14, $t(71) = 2.61$, p = .01) and explained a significant proportion of variance in those responses, R^2 = .09, $F(1,71) = 6.80$, p = .01. Increasing Avoidance

symptom severity also nominally predicted increasing heart rate change to unpleasant pictures, (b = .08, $t(71)$ = 1.97, p = .05) and explained a nominal proportion of variance in those responses, R^2 = .05, $F(1,71)$ = 3.87, p = .05. There were no other significant relationships between symptom clusters and corrugator responses for any valence category. Thus, Avoidance symptom severity seems to have the greatest effect on heart rate responses to aversive stimuli, with increasing symptom severity predicting increased heart rate reactivity (in beats per minute).

Discussion

The primary goals of the current project were twofold – to develop psychophysiological models and measures of emotional dysregulations in PTSD and to explore PTSD as a dimensional construct by examining the relationships between the severity of specific symptom clusters and psychophysiological measures of emotional reactivity. Secondary goals included investigating the roles of blast-related mTBI and comorbid depression, respectively, in veterans with and without PTSD.

Contrary to expectations, the pattern of emotion-modulated startle blink responses to affective stimuli did not differ between participants with and without PTSD and/or TBI. Depressive disorders were found to have an effect only on the startle blink magnitudes of participants without PTSD in response to neutral pictures, though this isolated finding should be interpreted cautiously due to the very small number of participants with Depression but not PTSD diagnoses (N=5). Of particular note, results demonstrated that participants who reported an exaggerated startle response (PTSD symptom D5 in DSM-IV-TR) did not exhibit significantly greater startle magnitudes than those who did not report this cardinal symptom of PTSD, either overall or in response to any particular valence category.

However, the severity of several empirically-derived symptom clusters did significantly predict modulation of the startle blink response. The increasing severity of symptoms of Dysphoria, Intrusions, and Hyperarousal were all independently predictive of an increased magnitude of the startle blink in response to pleasant picture contents. That is, as the severity of those symptoms increased, startle blink magnitude became less modulated by pleasant contents (as pleasant contents attenuate the startle blink response

in healthy controls). These results suggest that more severe symptoms of Dysphoria, Intrusions, and Hyperarousal independently diminished the activation of participants' appetitive systems in response to pleasant contents. Additionally, increased severity of Hyperarousal symptoms was predictive of increased startle blink magnitude in response to neutral contents. Consistent with the nature of these self-reported symptoms, this appears to reflect a generalization of defensive/fear responding to stimuli with no appetitive or defensive value.

The patterns of emotion-modulated skin conductance responses (SCR's), corrugator EMG responses, and zygomatic EMG responses to affective stimuli did not differ between participants with and without PTSD and/or TBI. There were also no significant effects of Depression on any of those three measures (SCR, corrugator, and zygomatic).

The severity of individual symptom clusters was predictive of SCR's and corrugator EMG responses in just a few isolated instances. Zygomatic responses to all valence categories were not significantly related to the severity of any symptom clusters. Increasing SCR's to combat pictures were significantly predicted by increasing Avoidance symptom severity. Increasing corrugator responses to combat pictures were significantly predicted by increasing Intrusions symptoms and decreasing corrugator responses to neutral pictures were significantly predicted by increasing Avoidance symptoms. Thus, overall, PTSD symptom severity had little influence on any of those three measures and no consistent relationships with overall or specific symptom cluster severity emerged.

Patterns of emotion-modulated heart rate change did vary between participants with and without PTSD. Unexpectedly, participants with PTSD evidenced significantly less heart rate deceleration (i.e., faster heart rates) in response to unpleasant stimuli than participants without PTSD. As expected, participants with PTSD also evidenced heart rate acceleration to combat pictures, while those without PTSD evidenced deceleration. These results are suggestive of a failure of participants with PTSD to orient adaptively to aversive stimuli, as heart rate deceleration in response to aversive stimuli in healthy research participants is a robust phenomenon (e.g., Bradley, Codispoti, Cuthbert, et al., 2001). As heart rate deceleration is an initial step of the defense cascade (Davis, et al., 1997; Lang, et al., 2000; Panksepp, 2004), these results may be indicative of a failure to prepare the defensive system to respond adaptively to aversive stimuli in PTSD. Additionally, participants with TBI had significantly less heart rate deceleration to pleasant contents than those without TBI, perhaps indicating a diminished capacity to orient to pleasant stimuli in participants with histories of blast-related TBI. There were no significant effects of depressive disorders on heart rate change.

Heart rate change was only significantly related to the severity of one PTSD symptom cluster. Avoidance symptom severity was positively related to heart rate responses to both combat and unpleasant stimulus contents. As Avoidance symptoms increased, heart rate deceleration was diminished, suggesting that Avoidance symptoms were driving the differences between participants with and without PTSD in heart rate responses to those stimulus contents.

Subjective ratings of the affective valence of the picture stimuli confirmed our successful selection of combat-related images, as these were rated as the least pleasant

valence category and significantly differed from the unpleasant pictures. Participants with PTSD rated aversive stimuli similarly to those without PTSD but rated pleasant contents as less pleasant, perhaps reflecting anhedonia and emotional numbing in PTSD participants. These results were unexpected, however, in that ratings of unpleasant and combat pictures did not differ between those with and those without PTSD. Contrary to expectations, participants with TBI rated unpleasant and combat pictures as significantly more pleasant than those without TBI. This puzzling result may be suggestive of participants with a history of TBI having positively skewed subjective perceptions of the hedonic value of aversive cues. Notably, there were no significant effects of Depression on ratings of affective valence.

Ratings of affective valence were strongly influenced by PTSD symptom severity. Increased severity of overall PTSD symptoms (i.e., CAPS total severity) was negatively related to valence ratings of pleasant pictures. Furthermore, each of the four empirically-derived symptom clusters were independently negatively related to valence ratings of pleasant pictures. Thus, all aspects of PTSD symptom severity were related to diminished subjective perceptions of the pleasantness of appetitive stimuli. That symptom severity was not at all related to ratings of combat stimuli was striking, as the DSM-IV B (re-experiencing) symptoms of PTSD imply that core features of PTSD are subjective sensitivity and reactivity to trauma-relevant cues.

Hyperarousal symptoms were also negatively related to valence ratings of neutral pictures, reflecting a diminished perception of the pleasantness of affectively neutral stimuli. This is consistent with the significant relationship between increasing Hyperarousal symptom severity and startle blink magnitudes to neutral contents, where

increasing symptom severity predicted greater blink magnitudes. It thus appears that as Hyperarousal symptoms increase, subjective appraisals of affectively neutral stimuli become less pleasant, which may be driving the positive relationship between Hyperarousal symptoms and startle blink magnitudes to neutral contents.

Ratings of arousal also confirmed our successful selection of combat related images, as these were rated as the most arousing and significantly differed from the IAPS unpleasant images. However, these stimuli appear to have altered participants' perceptions of the relative arousal levels of the other stimuli, as the ratings of arousal significantly differed between pleasant and unpleasant pictures. Due to this difference in arousal levels between pleasant and unpleasant images, effects of affective valence must be interpreted cautiously because the influence of arousal cannot be ruled out.

With respect to between-subjects effects, participants with PTSD rated combat images as significantly more arousing than participants without PTSD. While this was as expected, it was in contrast to the lack of between-groups differences in valence ratings of combat pictures. There were no effects of TBI or depression on arousal ratings.

Ratings of arousal were also strongly influenced by PTSD symptom severity. Increased overall symptom severity (i.e., CAPS total severity) significantly predicted diminished ratings of arousal for pleasant contents. Similarly, the severity of Dysphoria symptoms, Intrusions symptoms, and Avoidance symptoms were each independently negatively related to ratings of arousal for pleasant images. Thus, increasing overall symptom severity and increasing severity of three of four symptom clusters (excepting Hyperarousal) significantly predicted diminished subjective perceptions of the arousal of appetitive stimuli. In contrast, only Dysphoria symptom severity was significantly related

to arousal ratings for combat pictures. As Dysphoria symptoms increased, arousal ratings for combat stimuli also increased. Overall, then, PTSD symptom severity was most predictive of reductions in the perceived arousal of pleasant stimuli rather than combat or unpleasant stimuli. Indeed, only one symptom cluster (Dysphoria) predicted increased subjective perceptions of the arousal of combat stimuli.

Specific Aim 1: Develop psychophysiological models and measures of emotional dysregulations in PTSD.

Contrary to expectations, categorical comparisons of individuals with and without PTSD did not yield a clear pattern of fruitful differences on any psychophysiological measure other than heart rate. Affective picture viewing startle paradigms thus do not appear to hold particular promise for the study of emotional dysregulations in PTSD, at least from the perspective of making categorical comparisons between individuals with and without PTSD. Additionally, because of this lack of clear and consistent findings in the psychophysiological data, there was no strong indication for a particular physiological model for emotional dysregulations in PTSD.

Hypothesis 1a: Generally aversive stimuli (i.e., IAPS "unpleasant" stimuli) would elicit larger corrugator but not larger fear-potentiated startle responses in the PTSD group compared to the no-PTSD group, indicating greater perception of unpleasant valence but not sensitivity of the defensive system in response to generally aversive stimuli in PTSD. However, in response to trauma-relevant aversive stimuli, the PTSD group would exhibit

both larger corrugator and larger fear-potentiated startle responses, indicating marked sensitivity of the defensive system to trauma reminders.

This hypothesis was not supported. There were no differences in either startle blink magnitude or corrugator EMG responses between the PTSD and no-PTSD groups when viewing either unpleasant or combat stimuli. There was no support for a greater perception of unpleasant valence in the absence of an increased sensitivity of the defensive system in response to generally aversive stimuli in PTSD. There was also no evidence of a marked sensitivity of the defensive system (as indexed by greater startle blink magnitude) to trauma reminders in individuals with PTSD.

One would have expected differential sensitivity and defensive responding to trauma-relevant vs. generally aversive stimuli in participants with PTSD given the specificity of symptoms such as B4 and B5 (intense psychological distress and intense physiological reactivity, respectively, to trauma-relevant cues). However, objective measures of such sensitivity (corrugator EMG) and defensive responding (startle blink) did not support these predictions. These findings were consistent with most past work, including both imagery studies (Cuthbert, et al., 2003; McTeague & Lang, 2012) and picture-viewing studies (Carlson, et al., 1997; Elsesser, et al., 2004; Litz, et al., 2000; Miller & Litz, 2004). These two objective measures were also consistent with the subjective reports of perceived valence of these stimuli, as ratings of affective valence of combat and generally aversive stimuli did not differ between groups. In categorical comparisons, individuals with PTSD and individuals without PTSD demonstrated the same subjective perceptions of, sensitivity to, and defensive responding to trauma-relevant stimuli as generally aversive stimuli.

Hypothesis 1b: The PTSD group would demonstrate inhibited responding to pleasant (i.e., appetitive) stimuli, which would be seen in less startle attenuation and smaller zygomatic EMG responses compared to the no-PTSD group.

This hypothesis was not supported. There were no differences between participants with and without PTSD in their zygomatic EMG or startle blink magnitudes in response to pleasant contents. Results from the current study thus do not support, in a categorical comparison, inhibited responding to pleasant stimuli in individuals with PTSD as compared to those without PTSD.

Notably, while the differences were not significant, the largest zygomatic response was actually for combat stimuli. While the zygomatic is most commonly interpreted as an index of pleasant affective valence, it has also been shown to index grimacing for extremely unpleasant contents (Greenwald, et al., 1989; Lang, et al., 1993). It does appear to index pleasant valence within the standard IAPS stimuli, as the order of responses from greatest to least was pleasant > neutral > unpleasant. However, in response to combat pictures, the zygomatic response most likely represents grimacing. This result is consistent with the findings of Carlson et al. (1997) and Litz et al. (2000). They both found greater zygomatic reactivity to trauma-relevant cues than neutral cues but no significant differences between participants with and without PTSD. The lack of differences between groups is also consistent with Miller & Litz (2004).

In contrast to these objective measures, subjective ratings of pleasant stimuli did differ between groups. Participants with PTSD rated pleasant contents as less pleasant

(but not less arousing) than participants without PTSD. This points to the possibility of a deviant association between the subjective experience of appetitive stimuli and the activation of the appetitive system in the brain in individuals with PTSD. It may be that individuals with PTSD are able to recognize the motivational relevance of such stimuli (as seen in arousal ratings) but not experience the hedonic pleasure normally associated with them (as seen in valence ratings), perhaps as a result of emotional numbing (i.e., Dysphoria symptoms).

Hypothesis 1c: There would be no differences in general startle reactivity between the PTSD and no-PTSD groups, as measured by the average response across pictures from all affective valence categories. That is, it was predicted that there would be no tonic, heightened sensitivity of the defensive system in individuals with PTSD.

This hypothesis was supported. There was no difference between individuals with and without PTSD in general startle reactivity. This is consistent with past work that found no differences in general startle reactivity between individuals with and without PTSD (see, e.g., Grillon, Morgan, Southwick, Davis, & Charney, 1996; Jovanovic, Norrholm, Sakoman, Esterajher, & Kozaric-Kovacic, 2009; Ross, Ball, Cohen, Silver, & et al., 1989). Present results therefore do not support the presence of a tonic, heightened sensitivity of the defensive system in individuals with PTSD as compared to individuals without PTSD.

Hypothesis 1d: The PTSD group would exhibit greater heart rate (in beats per minute) in response to trauma-relevant but not generally aversive pictures compared to the no-

PTSD group, indicating a dysregulated orienting response specific to trauma-relevant stimuli. Also, the PTSD group would show less heart rate deceleration to pleasant pictures than the no-PTSD group, indicating a smaller allocation of motivated attention resources to appetitive stimuli.

This hypothesis was not supported. Results indicated that participants with PTSD exhibited diminished heart rate deceleration in response to unpleasant IAPS stimuli and heart rate acceleration in response to combat stimuli. There was no support for a dysregulated orienting response specific to combat stimuli in participants with PTSD. These results, however, are generally consistent with the findings of Pole's (2007) meta-analysis, which found a small effect for greater HR reactivity in individuals with PTSD while viewing trauma-relevant stimuli.

Present results, as discussed above, are in fact suggestive of a failure of participants with PTSD to orient adaptively to aversive stimuli. As orienting is an initial step in the mammalian defense cascade, it is possible that this failure of initial orientation disrupts the entire cascade of defensive responses in individuals with PTSD. However, if this were the case, we would have likely observed significant group differences in other indices of defensive reactivity, such as SCR's, startle blink responses, and facial muscle EMG in response to unpleasant and trauma-relevant stimuli.

Additionally, there were no differences in heart rate responses to pleasant pictures between participants with and without PTSD. Participants with and without PTSD oriented equally to appetitive stimuli. There was thus no evidence of a smaller allocation of motivated attention resources to appetitive stimuli in PTSD.

Hypothesis 1e: Both generally aversive and trauma-relevant stimuli would elicit significantly greater skin conductance responses in the PTSD group compared to the no-PTSD group. Also, appetitive stimuli would also elicit smaller skin conductance responses in the PTSD group compared to the no-PTSD group.

This hypothesis was not supported. There were no differences in SCR's to any valence category between participants with and without PTSD. This is inconsistent with the results of Pole's (2007) meta-analysis, which found a small effect size for SCR's in response to trauma-relevant stimuli. However, effect sizes were very heterogeneous and all of the studies included compared only responses to trauma vs neutral stimuli. Therefore, it is not clear that the present study, which also included generally aversive and pleasant stimuli, is directly comparable to past work. Either way, present results do not support, in a categorical comparison, any differences in objective measures of emotional arousal between individuals with and without PTSD in response to any affective valence category.

Additionally, this objective measure is mostly consistent with subjective ratings of the arousal of the picture stimuli. It is consistent in that there were no group differences in arousal ratings for unpleasant or pleasant pictures. But it is inconsistent in that participants with PTSD rated combat images as more arousing than participants without PTSD. That there was no difference in SCR where there was a significant difference in subjective ratings of arousal for combat pictures suggests an abnormal association between the subjective experience of the motivational relevance of the combat stimuli and the physiological response generated based on that appraisal. This

abnormal association appears to indicate a maladaptive perception of, but not response to, trauma-relevant stimuli in individuals with PTSD.

Specific Aim 2: Explore emotion-modulated startle reactivity and other measures of emotion in relation to empirically derived symptom clusters.

This specific aim was achieved but yielded mixed results. Significant relationships between most specific symptom clusters and the startle blink response were observed. The same was true for ratings of affective valence and arousal with respect to the picture stimuli. However, other physiological measures did not demonstrate strong relationships to more than one or two symptom clusters.

Hypothesis 2a: Greater overall PTSD symptom severity (i.e., CAPS total severity score) would be associated with greater general startle reactivity, measured as the mean response across all affective valence categories. That is, it was hypothesized that greater PTSD symptom severity would be associated with exaggerated general startle reactivity, reflecting a tonic, heightened sensitivity of the defensive system.

This hypothesis was not supported, as CAPS total severity was unrelated to general startle reactivity. This prediction was in contrast to the above prediction of no differences in general startle between the PTSD and no-PTSD groups. It was anticipated that a difference would be found here but not above because CAPS total severity is a measure of PTSD symptomatology that does not require specific numbers or combinations of symptoms in the way that the diagnostic category itself does. This analysis also did not require a comparison between groups, which eliminated the noise in

the control group from participants with an exaggerated startle response and other symptoms of PTSD that were not sufficient to meet diagnostic criteria. However, neither of those factors ended up making a significant difference. Consistent with the categorical comparison reported above, these results support the conclusion that there is no tonic, heightened sensitivity of the defensive system associated with PTSD symptoms.

Hypothesis 2b: High Dysphoria symptom scores would be related to diminished emotion-modulation effects – meaning less startle potentiation by aversive stimuli and less startle attenuation by appetitive stimuli. High Dysphoria symptom scores would also be related to diminished emotion modulation in both corrugator and zygomatic EMG. That is, higher Dysphoria symptom severity scores would significantly diminish corrugator responses to unpleasant contents and zygomatic responses to pleasant contents. High Dysphoria symptom scores would also be related to significantly smaller skin conductance responses and to less heart rate reactivity to affective contents.

This hypothesis was marginally supported. Dysphoria symptom severity was positively related to startle blink magnitudes in response to pleasant stimuli, as predicted. But it was unrelated to startle blink responses elicited by aversive stimuli. Dysphoria symptom severity was unrelated to corrugator responses, zygomatic responses, SCR's, and heart rate changes. In sum, Dysphoria symptom severity did not have the predicted across-the-board influence on emotion-modulation effects that was predicted, instead having only an isolated effect on startle blink responses to pleasant contents.

By contrast, Dysphoria symptom severity was significantly negatively related to subjective appraisals of the valence and arousal of pleasant pictures. This is consistent

with the anticipated suppression of emotion-modulation effects with respect to pleasant stimuli, but only in the subjective experience of them. Dysphoria symptom severity was also significantly positively related to subjective appraisals of the arousal level of combat stimuli, which was unexpectedly in the direction of amplifying perceptions arousal.

The Dysphoria symptom cluster has been shown to be a non-specific set of symptoms that overlaps considerably with most internalizing disorders (Palmieri, et al., 2007). As such, it was predicted to have a broad suppressing effect on emotion modulation given past results (e.g., Lang, et al., 2007; Larson, Nitschke, & Davidson, 2007). Present results suggest that these symptoms alone are not sufficient for broad suppression of psychophysiological emotion-modulation during picture viewing tasks and that these symptoms most strongly influence subjective perceptions of the valence and arousal of pleasant stimuli.

Hypothesis 2c: High Intrusions (i.e., re-experiencing) and high Avoidance symptoms would be related to enhanced defensive responding that was marked by exaggerated fear-potentiated startle responses only to trauma-relevant aversive stimuli. It was also predicted that high scores on these symptom factors would be related to exaggerated corrugator responses only to trauma-relevant aversive stimuli.

This hypothesis was not supported with respect to startle blink magnitudes, as neither Intrusions symptom severity nor Avoidance symptom severity were related to startle blink magnitudes to trauma-relevant stimuli. Indeed, the startle blink response was not related to Avoidance symptom severity at all. It was only related to Intrusions symptom severity with respect to pleasant stimuli such that increasing Intrusions

symptom severity predicted increased responses to pleasant stimuli (i.e., less attenuation). This was unexpected given the nature of these symptoms (active avoidance and intrusive re-experiencing). Individuals who actively avoid trauma reminders and who re-experience the trauma intrusively were expected to exhibit enhanced defensive responding concomitant with the severity of their avoidance/re-experiencing. However, there was no evidence that heightened defensive system responding, as measured by the startle blink response to trauma-relevant cues, was related to the severity of either Avoidance or Intrusions symptoms.

This hypothesis was partially supported with respect to corrugator responses, however. Corrugator responses to combat stimuli were positively related to Intrusions symptom severity but were unrelated to Avoidance symptom severity. As the corrugator is a measure of unpleasant affective valence, this suggests that increasing severity of Intrusions symptoms – but not Avoidance symptoms – is positively related to an increasing experience of trauma-relevant stimuli as aversive. This finding was unexpected, as it was predicted that increasing active avoidance of trauma reminders would be in part driven by an increased perception of trauma stimuli as aversive.

Also unexpectedly, Avoidance symptom severity, while unrelated to corrugator or startle responses to combat stimuli, was significantly positively related to SCR's and heart rate responses to combat pictures. It was also significantly positively related to heart rate responses to unpleasant pictures. Thus, Avoidance symptom severity was predictive of changes in measures that index physiological arousal and orienting but was not predictive of heightened sensitivity to the unpleasantness of trauma-related stimuli (i.e., corrugator). This suggests that active avoidance of trauma reminders and other aversive

stimuli may be driven by a desire to avoid the drain on attentional resources and the arousal caused by those stimuli rather than by the desire to avoid their perceived unpleasantness.

In another unexpected finding, the severity of both Intrusions and Avoidance symptom severity were negatively related to ratings of the valence and arousal of pleasant stimuli only. There were no effects of Intrusions or Avoidance symptom severity on ratings of unpleasant or combat stimuli. As such, it is notable that neither symptom cluster was significantly related to a measure of pleasant valence or to a physiological response to pleasant stimuli. This suggests that these symptoms have a strong influence on the subjective appraisal of appetitive stimuli but not the motivational response to them.

Hypothesis 2d: High Hyperarousal symptoms would be associated with exaggerated defensive responding to all aversive stimuli that would be evident in both exaggerated fear-potentiated startle responses and greater corrugator EMG reactivity.

This hypothesis was not supported. Neither startle blink responses nor corrugator responses to aversive stimuli were related to the severity of Hyperarousal symptoms. Findings instead indicated that Hyperarousal symptom severity was positively related to startle blink responses to pleasant and neutral contents and was unrelated to corrugator responses. Furthermore, Hyperarousal symptoms were significantly negatively related to ratings of the affective valence of pleasant and neutral stimuli.

This symptom cluster therefore appears to underlie a generalization of defensive responding to non-aversive stimuli rather than an exaggeration of defensive responding to

aversive stimuli. Notably, the text of the symptoms in the DSM-IV-TR does not specify whether they are in response to trauma-relevant cues. Indeed, the text could be interpreted as intentionally implying that Hyperarousal symptoms (an exaggerated startle response and hypervigilance) are explicitly not in response to trauma cues, given that they are grouped separately from the symptoms of psychological and physiological reactivity to trauma cues (B symptoms). The current results support this latter interpretation and are consistent with data indicating that exaggerated startle in PTSD is the result of fear generalization and is thus best elicited in context-potentiated startle paradigms (e.g., Grillon, et al., 1998a, 1998b; Grillon, et al., 2009; Jovanovic, Norrholm, Fennell, et al., 2009; Morgan, et al., 1995; Pole, et al., 2003).

Implications and Conclusions

Results from the present study provide very little support for the presence of an objectively measured exaggerated startle response in individuals with PTSD. We found no evidence of an exaggerated general startle response in either a categorical comparison of individuals with PTSD vs those without PTSD or in a novel dimensional exploration of whether the severity of PTSD symptomatology predicted an exaggerated general startle response. Whether participants reported an exaggerated startle response also had no bearing on their general startle reactivity. There were also no significant group differences in startle responses to specific valence categories.

With respect to specific symptom clusters, the most consistent effects were for diminished emotion modulation to pleasant stimuli rather than exaggerated responding to unpleasant or trauma-relevant stimuli. However, the severity of Hyperarousal symptoms

predicted increased startle reactivity to neutral stimuli, consistent with past work that is indicative of fear generalization in individuals with PTSD.

There are several reasons why significant group differences may not have emerged. First, there may simply not be an exaggerated general startle response in individuals with PTSD. Second, it is possible that our control group was not "clean" enough, due to sub-threshold symptomatology and comorbid disorders, for group differences to emerge in general startle or emotion-modulated startle reactivity. However, statistical analyses of the presence of sub-threshold PTSD symptoms in the control group did not yield significant results. Similarly, statistical analyses to explore the effect of current alcohol use disorders did not yield significant results. Third, the startle blink reflex may not be a good measure for comparing individuals with and without PTSD. Several past studies using imagery paradigms, for example, have found a lack of emotion-modulated startle in response to aversive stimuli in individuals with PTSD (Cuthbert, et al., 2003; McTeague & Lang, 2012). Fourth, it is possible that the loss of data from experimenter error led to sample sizes that did not generate enough statistical power to detect group differences. However, as the sample size in the current study was larger than most published studies, this explanation does not seem likely. And fifth, as discussed both above and below, the construct may be too heterogeneous for clear differences to emerge between individuals meeting and not meeting criteria for the disorder.

Indeed, the most striking results in the present study are those that indicate deficits in the subjective appraisal of, processing of, and responses to appetitive stimuli in individuals with increasingly severe symptoms of PTSD. These results seem to suggest

that an underappreciated aspect of the disorder is a limited capacity for positive affect. They also seem to suggest, consistent with Suvak and Barrett (2011), that PTSD is not defined by an abnormality in fear. This is not to say that there are no abnormalities in fear in PTSD, but rather that other aspects of the disorder may be equally or more prominent in many, if not most, symptom presentations. In other words, PTSD may be more similar to anxious-misery disorders (depression, GAD) than to fear disorders (specific phobia, social phobia).

Consistent with factor analytic results of PTSD symptoms, the failure to find consistent between-group differences in the present study suggests that there is no coherent overall PTSD syndrome as defined by the symptoms in DSM-IV (i.e., there is no higher-order PTSD factor). Individuals with PTSD are heterogeneous and their pathology is better understood through the four empirically-derived symptom clusters that factor analytic models support (Intrusions, Avoidance, Dysphoria, and Hyperarousal). In the present study, these clusters were more predictive of subjective ratings of the affective valence and arousal of emotional stimuli as well as of the psychophysiological responses to such stimuli. This suggests that the diagnosis can be better understood through a careful examination of the severity of these symptoms independently and as a whole than it can by looking for the DSM-IV-defined number and combination of individual symptoms.

A novel aspect of the current study was the investigation of the psychophysiology of emotion in individuals with histories of blast-related mTBI. Fortunately for the participants with such a history, present results lead to the clear conclusion that a history of mTBI has little to no effect on current emotional processing. There were no significant

effects of mTBI other than for heart rate responses to appetitive stimuli. It is hard to know what to make of such an isolated finding and any conclusions should be drawn cautiously. This finding may be indicative of a failure to orient to appetitive stimuli in individuals with histories of mTBI, but the absence of findings in other measures of pleasant affect argues against this. Additionally, the lack of significant interactions between PTSD and mTBI indicates that there are no differences in emotional reactivity between individuals with PTSD alone and individuals with PTSD and mTBI. While these findings need to be replicated, they are encouraging news for professionals treating combat veterans with both PTSD and a history of mTBI as it helps to clarify the diagnostic picture.

Finally, the role of depressive disorders was also investigated at every step of the current study. Unexpectedly, there were no significant differences between individuals with and without depressive disorders in their SCR, corrugator, zygomatic, or heart rate responses to the picture stimuli. The same was almost uniformly true for the startle blink response, with the lone exception being an interaction of depression and PTSD in the response to neutral pictures. This effect is difficult to interpret, however, given the small N of participants with depression but not PTSD (5). These results were unexpected given past findings regarding the psychophysiology of depression (see, e.g., Vaidyanathan, et al., 2009).

There are several possible explanations for our failure to observe differences between participants with depressive disorders and those without. It is possible that the current sample, being predominantly non-treatment seeking, did not have sufficiently severe depression symptoms for differences between groups to emerge. Similarly, as the

sample was not uniformly composed of individuals with, e.g., single episode MDD, the mix of depressive disorders may have obscured group differences. It is also possible that the non-depressed group, given its other comorbidities, was not "clean" enough for group differences to emerge. As above with respect to PTSD, the role of current alcohol use disorders was investigated but did not have a significant influence on current results.

Limitations

A primary limitation of the current study was the loss of data from experimenter error. This resulted in smaller than anticipated sample sizes as well as different (but overlapping) groups of subjects included the analyses for each measure. With larger sample sizes, it is possible that group differences would have been observed. As mentioned above, however, the sample size in the current study was larger than that of nearly all published studies, indicating that it was sufficient to observe any effects that were present.

Additionally, we did not have information regarding current psychotropic medications being taken by participants. While many psychophysiological studies screen out individuals currently taking such medications, that was not possible in this population. As such, we cannot rule out the possibility that medication use obscured differences between individuals with and without PTSD. However, review of the literature indicated that six studies of the startle blink in PTSD investigated the influence of current use of psychoactive medications and found it had no effect on their results (Carson, et al., 2007; Cuthbert, et al., 2003; Jovanovic, Norrholm, Fennell, et al., 2009; Metzger, et al., 1999; Orr, Lasko, Shalev, & Pitman, 1995; Pole, et al., 2003).

Another limitation is that we had a small and novel set of combat-related stimuli to choose from. While the stimuli performed well in terms of subjective ratings of valence and arousal, as well as in terms of the physiological reactivity elicited across the whole sample, it is unknown how the sample used fit into the wider universe of such stimuli. It may have been possible to obtain stimuli that were more unpleasant and/or more arousing than those chosen. It is also unclear precisely how specific the images chosen were to the traumas experienced by our participants. Presumably the more specific they were, the more differential reactivity they would have elicited in comparison to generally unpleasant stimuli.

Finally, a significant limitation of the current study is that the no-PTSD group contained a substantial number of participants with other current Axis I disorders, current sub-threshold symptoms of PTSD, and lifetime (but not current) Axis I diagnoses. That is, they were not "super controls." This may have obscured group differences in the categorical comparisons that then emerged in the dimensional analyses. It is possible that if the comparison group were free of psychopathology, group differences between individuals with and without PTSD would have emerged.

Future Directions

With this novel dimensional approach to exploring the psychophysiology of emotion in individuals PTSD, the present picture-viewing paradigm appears to hold promise for understanding emotional dysregulations in the disorder. While physiological responses to these stimuli did not consistently differ between individuals with and without PTSD, examining physiological responses to these stimuli in relation to the

severity of specific PTSD symptom clusters was a successful approach. This approach should be replicated with combat veterans and with the current stimuli.

In addition, future work should expand this dimensional approach to exploring the emotional dysregulations in PTSD to other specialized populations, including sexual assault survivors, motor vehicle accident survivors, policemen/firemen, and disaster survivors. It is possible that different types of traumas will result in different symptom presentations and different emotional dysregulations. If so, this dimensional approach to studying PTSD will be valuable in understanding any differences that may exist.

Future work should also expand this approach into other startle paradigms, including emotional imagery paradigms, fear-potentiated startle paradigms, and context-potentiated startle paradigms. This can help to clarify which symptoms are driving the effects seen in each of these paradigms and which symptoms underlie the dysregulations that are observed in individuals with PTSD.

Similarly, future work can incorporate additional and broader measures of internalizing psychopathology consistent with the approach of Lang and colleagues (Cuthbert, et al., 2003; Lang & McTeague, 2011; McTeague & Lang, 2012; McTeague, et al., 2010). This can help to distinguish symptomatology that is unique to PTSD from that which is common to all internalizing disorders. It can also open avenues to explore physiological reactivity in relation to these broader measures (such as the BDI, STAI, etc) and to compare those patterns of reactivity to those that covary with specific symptoms of PTSD and other disorders.

We were able to successfully identify a set of trauma-relevant combat stimuli that were distinct from the IAPS unpleasant images. However, additional investigations of the

stimuli used should be conducted. Additionally, the sample of stimuli should be broadened to include a wider array of combat stimuli that will more accurately represent the range of traumas experienced by soldiers who fought in Iraq and Afghanistan. As the stimuli improve and become standardized across samples, firmer conclusions can be drawn from research results.

Finally, future work should focus on comparing individuals with PTSD to so-called "super controls" to help clarify whether differences between individuals with and without PTSD can be observed when the comparison group is as close to a true control as is possible. This can help to eliminate the limitation of comparing individuals with PTSD to individuals without PTSD but with symptoms of the disorder and other disorders that may obscure differences between groups.

Tables

Table 1. Participant demographics.

	All Participants	Included in Startle Analyses	Included in SCR Analyses	Included in Corr. Analyses	Included in Zygo. Analyses	Included in EKG Analyses	Included in SAM Ratings Analyses
N (female)	124 (9)	69 (5)	78 (3)	83 (3)	81 (2)	95 (7)	119 (9)
Percent minority	8.80%	7.25%	7.69%	9.64%	9.64%	7.37%	8.40%
Age	32.20 ± 8.10	30.36 ± 6.82	32.19 ± 8.17	32.05 ± 8.00	31.57 ± 7.64	32.45 ± 8.29	32.44 ± 8.18

Note: "All Participants" includes all participants whose data are used in at least one analysis (i.e., their data is included in at least one of: ratings, startle, SCR, corrugator [corr.], zygomatic [zygo.], or EKG).

Table 2. Diagnostic and clinical characteristics of the whole sample.

			N (female)	Mean Age (sd)	Mean Number of Diagnoses (sd) [c]	Mean CAPS Total Severity [a] (sd)
PTSD Status	**Depressive Disorder [b]**	**Blast-TBI**				
No PTSD	**Non-depressed**	**No**	32 (6)	31.91 (7.896)	1.09 (0.296)	19.73 (14.595)
		Yes	15 (1)	34.47 (8.331)	1.27 (0.458)	25.38 (11.587)
		Total	47 (7)	32.72 (8.037)	1.15 (0.360)	22.11 (13.370)
	Depressed	**No**	7 (1)	35.86 (10.189)	2.86 (1.345)	33.40 (14.011)
		Yes	7 (1)	32.14 (7.244)	2.29 (0.756)	32.50 (13.157)
		Total	14 (2)	34.00 (8.709)	2.57 (1.089)	32.91 (12.857)
	Total No PTSD	**No**	39 (7)	32.62 (8.343)	1.41 (0.910)	24.00 (15.401)
		Yes	22 (2)	33.73 (7.905)	1.59 (0.734)	28.43 (12.340)
		Total	61 (9)	33.02 (8.139)	1.48 (0.849)	26.07 (14.000)
PTSD	**Non-depressed**	**No**	16 (0)	34.88 (10.658)	1.19 (0.403)	53.13 (14.282)
		Yes	9 (0)	32.89 (7.167)	1.56 (0.726)	53.00 (12.083)
		Total	25 (0)	34.16 (9.437	1.32 (0.557)	53.08 (13.273)
	Depressed	**No**	12 (0)	33.00 (7.084)	2.58 (0.669)	71.42 (22.573)
		Yes	26 (0)	28.04 (5.681)	2.69 (0.736)	73.38 (12.413)
		Total	38 (0)	29.61 (6.495)	2.66 (0.708)	72.76 (16.014)
	Total PTSD	**No**	28 (0)	34.07 (9.189)	1.79 (0.876)	60.96 (20.147)
		Yes	35 (0)	29.29 (6.360)	2.40 (0.881)	68.14 (15.145)
		Total	63 (0)	31.41 (8.044)	2.13 (0.924)	64.95 (17.761)
Total	**Non-depressed**	**No**	48 (6)	32.90 (8.909)	1.13 (0.334)	39.52 (21.892)
		Yes	24 (1)	33.88 (7.792)	1.38 (0.576)	40.00 (18.269)
		Total	72 (7)	33.22 (8.511)	1.21 (0.442)	39.70 (20.348)
	Depressed	**No**	19 (1)	34.05 (8.202)	2.68 (0.946)	60.24 (26.799)
		Yes	33 (1)	28.91 (6.161)	2.61 (0.747)	65.72 (20.373)
		Total	52 (2)	30.79 (7.336)	2.63 (0.817)	63.82 (22.680)
	Total All Participants	**No**	67 (7)	33.22 (8.669)	1.57 (0.908)	47.52 (25.713)
		Yes	57 (2)	31.00 (7.263)	2.09 (0.912)	56.80 (23.071)
		Total	124 (9)	32.20 (8.098)	1.81 (0.943)	52.41 (24.666)

Notes. [a]CAPS Total Score is only available for subjects who completed the entire CAPS (see Methods); N for the whole sample = 93. [b]Depressive disorders include any DMS-IV unipolar mood disorder diagnosis (e.g., MDD, Dysthymia, etc). [c]Mean number of diagnoses includes diagnoses of PTSD and/or depression.

Table 3. PTSD status and TBI status of participants included in each statistical analysis.

	PTSD Status								Total N
	No PTSD			PTSD					
	TBI Status		Total No PTSD	TBI Status		Total PTSD			
	No TBI	TBI		No TBI	TBI		Total No TBI	Total TBI	
Startle	N = 18	N = 8	N = 26	N = 18	N = 25	N = 43	N = 36	N = 33	N = 69
SCR	N = 16	N = 14	N = 30	N = 21	N = 27	N = 48	N = 37	N = 41	N = 78
Corr.	N = 18	N = 13	N = 31	N = 24	N = 28	N = 52	N = 42	N = 41	N = 83
Zygo.	N = 17	N = 13	N = 30	N = 22	N = 29	N = 51	N = 39	N = 42	N = 81
EKG	N = 23	N = 19	N = 42	N = 26	N = 27	N = 53	N = 49	N = 46	N = 95
SAM Ratings	N = 38	N = 22	N = 60	N = 27	N = 32	N = 59	N = 65	N = 54	N = 119

Note: TBI status was determined using a consensus diagnosis approach. Participants were considered to be in the blast-related TBI group if they had one or more definite or probable blast-related mTBI. See Methods for additional details.

Table 4. PTSD status and depression status of participants included in each statistical analysis.

	PTSD Status								Total N
	No PTSD			PTSD					
	Depression Status		No PTSD Total	Depression Status		PTSD Total			
	- Depr.	+ Depr.		- Depr.	+ Depr.		– Depr. Total	+ Depr. Total	
Startle	N = 21	N = 5	N = 26	N = 19	N = 24	N = 43	N = 40	N = 29	N = 69
SCR	N = 20	N = 10	N = 30	N = 21	N = 27	N = 48	N = 41	N = 37	N = 78
Corr.	N = 20	N = 11	N = 31	N = 20	N = 32	N = 52	N = 40	N = 43	N = 83
Zygo.	N = 19	N = 11	N = 30	N = 21	N = 30	N = 51	N = 40	N = 41	N = 81
EKG	N = 29	N = 13	N = 42	N = 23	N = 30	N = 53	N = 52	N = 43	N = 95
SAM Ratings	N = 46	N = 14	N = 60	N = 23	N = 36	N = 59	N = 69	N = 50	N = 119

Notes. Depressive disorders include any DMS-IV unipolar mood disorder diagnosis (e.g., MDD, Dysthymia, etc).

Table 5. Evaluative judgments of IAPS picture stimuli by content, PTSD status, and TBI status.

	PTSD Status						Total		
	No PTSD			PTSD					
	TBI Status		Total No PTSD	TBI Status		Total PTSD			
	No TBI	TBI		No TBI	TBI		Total No TBI	Total TBI	
Affective Valence Ratings									
Pleasant	433.26	440.90	436.06	407.66	400.30	403.67	422.62	416.84	420.00
	(57.89)	(60.28)	(58.38)	(66.97)	(65.78)	(65.86)	(62.62)	(66.15)	(64.04)
Neutral	327.71	331.45	329.08	326.83	316.70	321.34	327.34	322.71	325.24
	(50.69)	(26.23)	(43.12)	(25.11)	(36.05)	(31.68)	(41.73)	(32.97)	(37.92)
Unpleasant	244.18	268.26	253.01	253.76	269.68	262.40	248.16	269.10	257.66
	(57.01)	(50.78)	(55.62)	(55.28)	(63.34)	(59.82)	(56.06)	(58.04)	(57.69)
Combat	185.18	208.92	193.89	196.19	221.75	210.06	189.75	216.52	201.90
	(56.87)	(68.00)	(61.70)	(71.14)	(64.68)	(68.33)	(216.53)	(65.72)	(65.31)
Arousal Ratings									
Pleasant	316.22	313.30	315.15	300.55	275.57	287.00	309.71	290.94	301.19
	(107.55)	(124.36)	(112.96)	(95.78)	(93.02)	(94.31)	(102.35)	(107.42)	(104.65)
Neutral	172.98	172.92	172.96	200.78	180.50	189.78	184.53	177.41	181.30
	(87.18)	(87.78)	(86.65)	(100.84)	(83.78)	(91.73)	(93.35)	(84.69)	(89.22)
Unpleasant	285.50	276.84	282.33	280.17	276.63	278.25	283.29	276.71	280.30
	(81.50)	(88.49)	(83.49)	(86.70)	(72.66)	(78.71)	(83.07)	(78.68)	(80.83)
Combat	356.65	349.68	354.09	386.53	409.57	399.03	369.06	385.17	376.37
	(110.17)	(120.82)	(113.22)	(107.01)	(96.56)	(101.25)	(109.04)	(110.09)	(109.35)

Notes. Ratings of affective valence and arousal were collected by computer using the Self-Assessment Manikin (SAM). The computer captured the location of the mouse on the x-axis of the screen. Ratings are on a 0 to 639 scale, where 0 is least arousing and least pleasant, respectively.

Table 6. Evaluative judgments of IAPS picture stimuli by content, PTSD status, and depression status.

	PTSD Status						Total		
	No PTSD			PTSD					
	Depression Status		Total No PTSD	Depression Status		Total PTSD			
	- Depr.	+ Depr.		- Depr.	+ Depr.		– Depr. Total	+ Depr. Total	
Affective Valence Ratings									
Pleasant	434.48 (55.73)	442.26 (68.40)	436.06 (58.38)	405.23 (73.36)	402.67 (61.66)	403.67 (65.86)	424.73 (63.16)	413.48 (65.30)	420.00 (64.04)
Neutral	329.38 (40.47)	328.12 (52.61)	329.08 (43.12)	326.86 (24.45)	317.81 (35.41)	321.34 (31.68)	328.54 (35.76)	320.70 (40.64)	325.24 (37.92)
Unpleas-ant	248.32 (57.36)	268.44 (48.12)	253.01 (55.62)	254.20 (51.22)	267.63 (64.87)	262.40 (59.82)	250.28 (55.08)	267.86 (60.17)	257.66 (57.69)
Combat	194.31 (63.15)	192.48 (58.92)	193.89 (61.70)	210.09 (51.71)	210.04 (77.83)	210.06 (68.33)	199.57 (59.67)	205.12 (72.88)	201.90 (65.31)
Arousal Ratings									
Pleasant	317.84 (113.32)	306.30 (115.57)	315.15 (112.96)	286.82 (97.02)	287.12 (93.93)	287.00 (94.31)	307.50 (108.44)	292.49 (99.61)	301.19 (104.65)
Neutral	176.06 (87.27)	162.77 (86.99)	172.96 (86.65)	194.52 (97.17)	186.75 (89.35)	189.78 (91.73)	182.21 (90.40)	180.04 (88.48)	181.30 (89.22)
Unpleas-ant	279.27 (90.31)	292.38 (57.07)	282.33 (83.49)	272.05 (77.19)	282.20 (80.49)	278.25 (78.71)	276.86 (85.66)	285.05 (74.25)	280.30 (80.83)
Combat	339.69 (114.39)	401.41 (98.71)	354.09 (113.22)	381.67 (91.82)	410.11 (106.60)	399.03 (101.25)	353.69 (108.55)	407.68 (103.53)	376.37 (109.35)

Notes. Ratings of affective valence and arousal were collected by computer using the Self-Assessment Manikin (SAM). The computer captured the location of the mouse on the x-axis of the screen. Ratings are on a 0 to 639 scale, where 0 is least arousing and least pleasant, respectively.

Table 7. Startle blink magnitudes (T-scores) for each affective valence category by PTSD status and TBI status.

	PTSD Status						Total		
	No PTSD			PTSD					
	TBI Status		Total No PTSD	TBI Status		Total PTSD			
	No TBI	TBI		No TBI	TBI		No TBI Total	TBI Total	
Pleasant	50.16	48.31	49.59	50.29	51.65	51.08	50.22	50.84	50.52
	(5.64)	(6.67)	(5.89)	(5.64)	(5.59)	(5.59)	(5.56)	(5.93)	(5.71)
Neutral	52.14	51.78	52.03	54.36	54.64	54.52	53.25	53.94	53.56
	(4.27)	(5.73)	(4.65)	(7.26)	(5.98)	(6.46)	(5.97)	(5.96)	(5.93)
Unpleasant	55.45	53.50	54.85	56.00	55.56	55.74	55.73	55.06	55.41
	(8.17)	(6.24)	(7.56)	(5.76)	(7.16)	(6.53)	(6.97)	(6.91)	(6.90)
Combat	56.04	55.86	55.99	54.99	56.59	55.92	55.52	56.41	55.94
	(5.39)	(7.03)	(5.80)	(5.41)	(6.14)	(5.83)	(5.35)	(6.25)	(5.77)
All Valences	53.53	52.35	53.17	53.87	54.61	54.30	53.70	54.06	53.87
	(4.70)	(4.95)	(4.71)	(5.22)	(5.46)	(5.31)	(4.90)	(5.35)	(5.08)

Notes. Startle blinks were scored in A/D units and were standardized for each subject using the distribution of their ITI startle blink magnitudes. See Methods for additional details.

Table 8. Startle blink magnitudes (T-scores) for each affective valence category by PTSD status and depression status.

	PTSD Status								Total
	No PTSD			PTSD					
	Depression Status		Total No PTSD	Depression Status		Total PTSD			
	- Depr.	+ Depr.		- Depr.	+ Depr.		– Depr. Total	+ Depr. Total	
Pleasant	49.95 (5.39)	48.06 (8.29)	49.59 (5.89)	49.61 (5.62)	52.25 (5.39)	51.08 (5.59)	49.79 (5.43)	51.53 (6.03)	50.52 (5.71)
Neutral	51.02 (3.89)	56.29 (5.63)	52.03 (4.65)	54.12 (7.81)	54.89 (5.31)	54.52 (6.46)	52.49 (6.19)	55.10 (5.30)	53.56 (5.93)
Unpleasant	54.43 (8.32)	56.63 (2.52)	54.85 (7.56)	55.12 (6.65)	56.24 (6.55)	55.74 (6.53)	54.75 (7.49)	56.31 (6.01)	55.41 (6.90)
Combat	55.41 (5.93)	58.41 (5.00)	55.99 (5.80)	55.57 (5.32)	56.20 (6.31)	55.92 (5.83)	55.49 (5.58)	56.58 (6.08)	55.94 (5.77)
All Valences	52.80 (5.09)	54.73 (2.29)	53.17 (4.71)	53.57 (5.50)	54.88 (5.20)	54.30 (5.31)	53.16 (5.23)	54.85 (4.79)	53.87 (5.08)

Notes. Startle blinks were scored in A/D units and were standardized for each subject using the distribution of their ITI startle blink magnitudes. See Methods for additional details.

Table 9. Means and standard deviations of autonomic and somatic measures for each affective valence category by PTSD status and TBI status.

	PTSD Status								Total
	No PTSD			PTSD					
	TBI Status		Total No PTSD	TBI Status		Total PTSD			
	No TBI	TBI		No TBI	TBI		No TBI Total	TBI Total	
SCR (µS)									
Pleasant	0.0155 (0.0208)	0.0240 (0.0320)	0.0196 (0.0267)	0.0142 (0.0143)	0.0201 (0.0243)	0.0175 (0.0206)	0.0147 (0.0171)	0.0214 (0.0268)	0.0175 (0.0206)
Neutral	0.0087 (0.0113)	0.0167 (0.0273)	0.0126 (0.0206	0.0103 (0.0135)	0.0119 (0.0238)	0.0112 (0.0198)	0.0096 (0.0125)	0.0136 (0.0248)	0.0117 (0.0200)
Unpleas-ant	0.0175 (0.0301)	0.0214 (0.0276)	0.0193 (0.0285)	0.0169 (0.0156)	0.0235 (0.0316)	0.0206 (0.0258)	0.0171 (0.0224)	0.0228 (0.0300)	0.0201 (0.0267)
Combat	0.0118 (0.0152)	0.0210 (0.0420)	0.0162 (0.0309)	0.0191 (0.0201)	0.0291 (0.0467)	0.0247 (0.0375)	0.0161 (0.0184)	0.0263 (0.0448)	0.0215 (0.0352)
Corr. (µV)									
Pleasant	-0.0814 (0.3453)	-0.1140 (0.3712)	-0.0951 (0.3507)	-0.1464 (0.4458)	-0.0615 (0.4996)	-0.1007 (0.4729)	-0.1186 (0.4025)	-0.0781 (0.4587)	-0.0986 (0.4290)
Neutral	0.0947 (0.3490)	0.1436 (0.3604)	0.1152 (0.3487)	0.0040 (0.1946)	0.0248 (0.3356)	0.0152 (0.2772)	0.0429 (0.2717)	0.0625 (0.3437)	0.0525 (0.3076)
Unpleas-ant	0.1332 (0.1104)	0.1104 (0.3974)	0.1236 (0.4063)	0.1784 (0.6811)	0.1280 (0.3806)	0.1512 (0.5353)	0.1590 (0.5790)	0.1224 (0.3811)	0.1409 (0.4887)
Combat	0.2202 (0.4253)	0.1830 (0.5624)	0.1409 (0.4887)	0.4279 (0.9154)	0.3100 (0.6556)	0.2046 (0.4789)	0.3389 (0.7456)	0.2697 (0.6234)	0.3047 (0.6846)
Zygo. (µV)									
Pleasant	0.3260 (0.1099)	0.0253 (0.0906)	0.0295 (0.1003)	0.0112 (0.0668)	0.0131 (0.0572)	0.1227 (0.0609)	0.0205 (0.0875)	0.0169 (0.0683)	0.0186 (0.7769)
Neutral	0.0099 (0.0547)	0.0110 (0.0690)	0.0106 (0.0626)	0.0010 (0.0547)	0.0110 (0.0690)	0.0106 (0.0626)	0.0143 (0.0604)	0.0179 (0.0785)	0.0162 (0.0700)
Unpleas-ant	0.0194 (0.0647)	0.0358 (0.0960)	0.0260 (0.0787)	-0.0045 (0.1384)	0.0258 (0.0793)	0.0127 (0.1086)	0.0055 (0.1117)	0.0289 (0.0838)	0.0176 (0.0983)
Combat	0.0044 (0.0869)	0.0918 (0.0167)	0.0423 (0.1327)	0.0245 (0.1166)	0.0431 (0.0138)	0.0351 (0.1282)	0.0157 (0.1039)	0.0582 (0.1471)	0.0377 (0.1291)
Heart Rate (Δ BPM)									
Pleasant	-0.7645 (1.5531)	-0.4461 (1.2077)	-0.6204 (1.4001)	-1.1096 (1.1144)	-0.3742 (0.8876)	-0.7349 (1.0624)	-0.9476 (1.3352)	-0.4039 (1.0198)	-0.6843 (1.2177)
Neutral	-0.7452 (1.0380)	-0.3223 (0.8966)	-0.5540 (0.9881)	-0.9111 (1.7141)	-0.5357 (1.1132)	-0.7198 (1.4381)	-0.8332 (1.4252)	-0.4477 (1.0241)	-0.6465 (1.2557)
Unpleas-ant	-1.6224 (1.0335)	-1.0612 (1.0458)	-1.3685 (1.0645)	-0.7813 (1.6084)	-0.8095 (1.2057)	-0.7957 (1.4039)	-1.1761 (1.4201)	-0.9135 (1.1372)	-1.0489 (1.2909)
Combat	-1.0308 (1.5181)	-0.6700 (1.1838)	-0.8676 (1.3729)	0.5253 (2.1567)	-0.3.046 (1.5822)	0.1026 (1.9140)	-0.2051 (2.0235)	-0.4555 (1.4283)	-0.3263 (1.7559)

Notes. All scores reflect change from a 1-second pre-stimulus baseline.

Table 10. Means and standard deviations of autonomic and somatic measures for each affective valence category by PTSD status and depression status.

	PTSD Status								Total
	No PTSD			PTSD					
	Depression Status		Total No PTSD	Depression Status		Total PTSD			
	- Depr.	+ Depr.		- Depr.	+ Depr.		- Depr. Total	+ Depr. Total	
SCR (µS)									
Pleasant	0.0228	0.0135	0.0196	0.0090	0.0242	0.0175	0.0157	0.0213	0.0175
	(0.0303)	(0.0177)	(0.0267)	(0.0108)	(0.0239)	(0.0206)	(0.0244)	(0.0226)	(0.0206)
Neutral	0.0157	0.0067	0.0126	0.0070	0.0145	0.0112	0.0111	0.0124	0.0117
	(0.0244)	(0.0087)	(0.0206	(0.0122)	(0.0238)	(0.0198)	(0.0192)	(0.0210)	(0.0200)
Unpleasant	0.0237	0.0112	0.0193	0.0144	0.0255	0.0206	0.0188	0.0216	0.0201
	(0.0319)	(0.0194)	(0.0285)	(0.0137)	(0.0317)	(0.0258)	(0.0242)	(0.0294)	(0.0267)
Combat	0.0190	0.0111	0.0162	0.0177	0.0301	0.0247	0.0183	0.0250	0.0215
	(0.0367)	(0.0153)	(0.0309)	(0.0251)	(0.0446)	(0.0375)	(0.0308)	(0.0396)	(0.0352)
Corr. (µV)									
Pleasant	-0.1486	0.0021	-0.0951	-0.0753	-0.1166	-0.1007	-0.1119	-0.0863	-0.0986
	(0.3813)	(0.2767)	(0.3507)	(0.3202)	(0.5517)	(0.4729)	(0.3495)	(0.4956)	(0.4290)
Neutral	0.0095	0.3075	0.1152	0.0072	0.0201	0.0152	0.0084	0.0936	0.0525
	(0.3008)	(0.3604)	(0.3487)	(0.2197)	(0.3110)	(0.2772)	(0.2600)	(0.3441)	(0.3076)
Unpleasant	0.0153	0.3205	0.1236	0.1503	0.1518	0.1512	0.0828	0.1950	0.1409
	(0.4412)	(0.2438)	(0.4063)	(0.3362)	(0.6341)	(0.5353)	(0.3931)	(0.5626)	(0.4887)
Combat	0.0956	0.4028	0.1409	0.4025	0.3407	0.2046	0.2490	0.3566	0.3047
	(0.4597)	(.4686)	(0.4887)	(0.6596)	(0.8565)	(0.4789)	(0.5823)	(0.7711)	(0.6846)
Zygo. (µV)									
Pleasant	0.0354	0.0193	0.0295	0.0053	0.0171	0.1227	0.0196	0.0177	0.0186
	(0.1039)	(0.0979)	(0.1003)	(0.0459)	(0.0698)	(0.0609)	(0.0793)	(0.0770)	(0.7769)
Neutral	0.0392	0.0023	0.0106	0.0101	0.0109	0.0106	0.0239	0.0086	0.0162
	(0.0678)	(0.0996)	(0.0626)	(0.0638)	(0.0629)	(0.0626)	(0.0665)	(0.0732)	(0.0700)
Unpleasant	0.0402	0.0014	0.0260	0.0012	0.0208	0.0127	0.0197	0.0156	0.0176
	(0.0800)	(0.0734)	(0.0787)	(0.1470)	(0.0727)	(0.1086)	(0.0120)	(0.0725)	(0.0983)
Combat	0.0509	0.0274	0.0423	0.0142	0.0497	0.0351	0.0316	0.0437	0.0377
	(0.1458)	(0.1114)	(0.1327)	(0.1258)	(0.1299)	(0.1282)	(0.1352)	(0.1243)	(0.1291)
Heart Rate (Δ BPM)									
Pleasant	-0.6336	-0.5910	-0.6204	-0.9181	-0.5945	-0.7349	-0.7594	-0.5935	-0.6843
	(1.4199)	(1.4114)	(1.4001)	(1.0218)	(1.0886)	(1.0624)	(1.2560)	(1.1779)	(1.2177)
Neutral	-0.3899	-0.9202	-0.5540	-0.4712	-0.9104	-0.7198	-0.4259	-0.9134	-0.6465
	(0.9375)	(1.0368)	(0.9881)	(0.9650)	(1.7074)	(1.4381)	(0.9412)	(1.5232)	(1.2557)
Unpleasant	-1.4804	-1.1189	-1.3685	-0.7209	-0.8530	-0.7957	-1.1445	-0.9334	-1.0489
	(1.0672)	(1.0567)	(1.0645)	(1.5193)	(1.3323)	(1.4039)	(1.3289)	(1.2489)	(1.2909)
Combat	-1.0544	-0.4508	-0.8676	-0.1371	0.2863	0.1026	-0.6486	0.0634	-0.3263
	(1.4634)	(1.0821)	(1.3729)	(1.4163)	(2.2286)	(1.9140)	(1.5009)	(1.9700)	(1.7559)

Notes. All scores reflect change from a 1-second pre-stimulus baseline.

Table 11. R^2 for regression models in which the severity scores for each symptom cluster were used to predict the respective physiological responses for each affective valence category.

	Dysphoria Severity	Intrusions Severity	Avoidance Severity	Hyperarousal Severity
Startle				
General	.015	.025	.003	.066
Pleasant	**.084**	**.079**	.024	**.116**
Neutral	.004	.015	.001	**.077**
Unpleasant	.021	.017	.009	.035
Combat	.008	.000	.009	.003
SCR				
Pleasant	.018	.017	.023	.021
Neutral	.005	.024	.040	.035
Unpleasant	.034	.019	.012	.045
Combat	.013	.047	**.082**	.044
Corrugator				
Pleasant	.001	.011	.017	.002
Neutral	.060	.023	**.064**	.010
Unpleasant	.001	.018	.001	.002
Combat	.001	**.087**	.051	.008
Zygomatic				
Pleasant	.019	.004	.001	.016
Neutral	.008	.002	.000	.006
Unpleasant	.001	.035	.003	.003
Combat	.004	.025	.000	.001
Heart Rate				
Pleasant	.000	.003	.003	.008
Neutral	.001	.001	.029	.000
Unpleasant	.015	.017	*.052	.011
Combat	.031	.023	**.087**	.022

Notes. **Bold** indicates significant R^2 values ($p<.05$) and * indicates $p = .053$. Independent variables are in the columns and dependent variables are in the rows.

Table 12. R^2 for regression models in which the severity scores for each symptom cluster and CAPS total severity were used to predict ratings of affective valence and arousal for each affective valence category.

	CAPS Total Severity	Dysphoria Severity	Intrusions Severity	Avoidance Severity	Hyperarousal Severity
Valence Ratings					
Pleasant	**.167**	**.126**	**.158**	**.157**	* .043
Neutral	.030	.010	.038	.015	**.059**
Unpleasant	.013	.028	.004	.000	.006
Combat	.005	.012	.000	.001	.005
Arousal Ratings					
Pleasant	**.109**	**.102**	**.099**	**.062**	.025
Neutral	.008	.014	.013	.005	.003
Unpleasant	.000	.001	.000	.016	.004
Combat	.041	**.052**	* .043	.006	.004

Notes. **Bold** indicates significant R^2 values (p<.05). Values with a * have p < .06. Independent variables are in the columns and dependent variables are in the rows.

Figures

Figure 1. Mean valence and arousal ratings for each picture (0-100 scale).

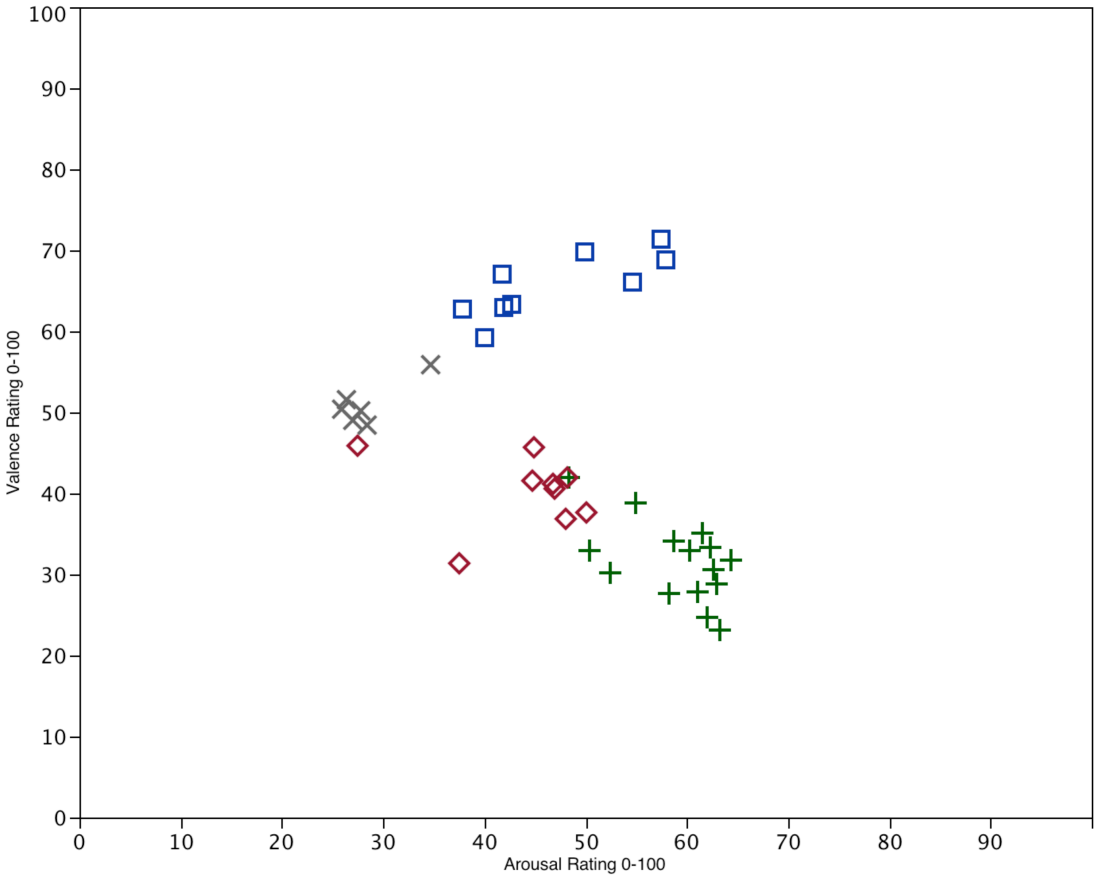

Figure 1. Pleasant pictures are indicated by squares, neutral pictures by *x*'s, unpleasant by diamonds, and combat by crosses. Ratings of affective valence and arousal were collected by computer using the Self-Assessment Manikin (SAM). The computer captured the location of the mouse on the x-axis of the screen, with scores ranging from 0 (least arousing/pleasant) to 639 (most arousing/pleasant). For graphing, scores were converted to a scale of 0 to 100.

Figure 2. Mean valence ratings for each affective valence category (0-100 scale).

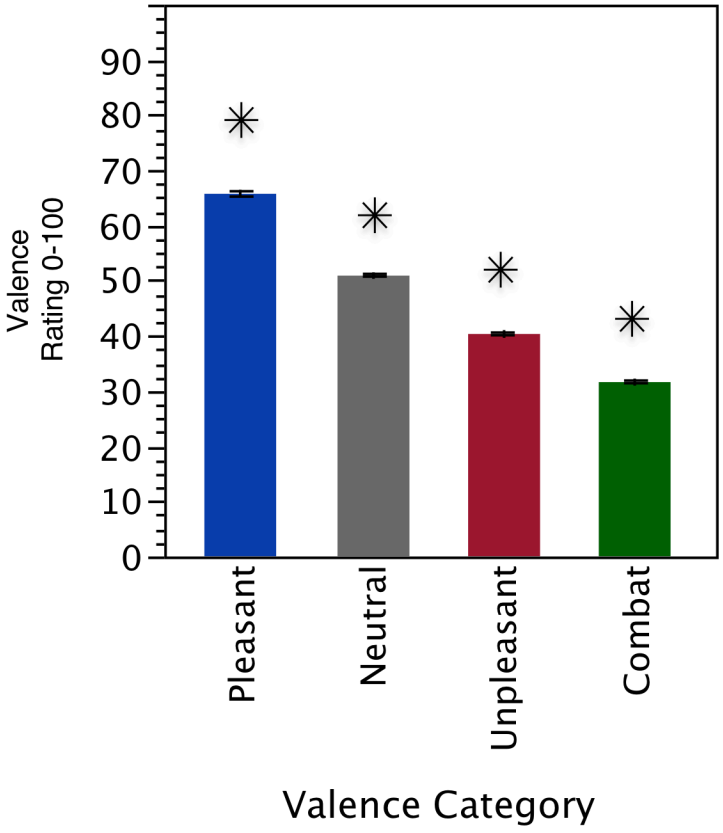

Figure 2. Valence categories marked with an * differ significantly from all other categories, *p*'s < .01.

Figure 3. Mean arousal ratings for each affective valence category.

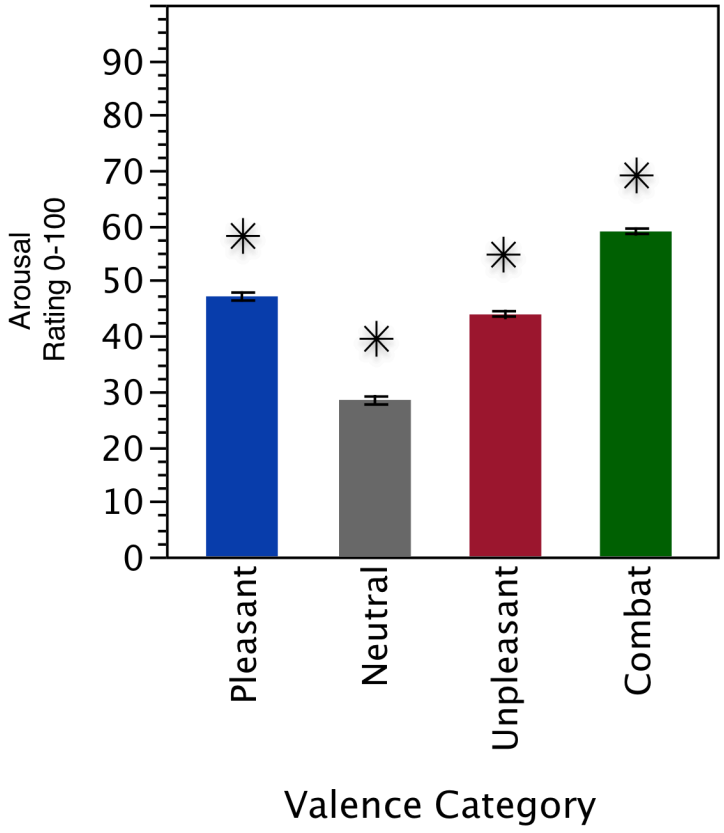

Figure 3. Valence categories marked with an * differ significantly from all other categories, *p*'s < .02.

Figure 4. Mean valence ratings for each affective valence category by PTSD and TBI status.

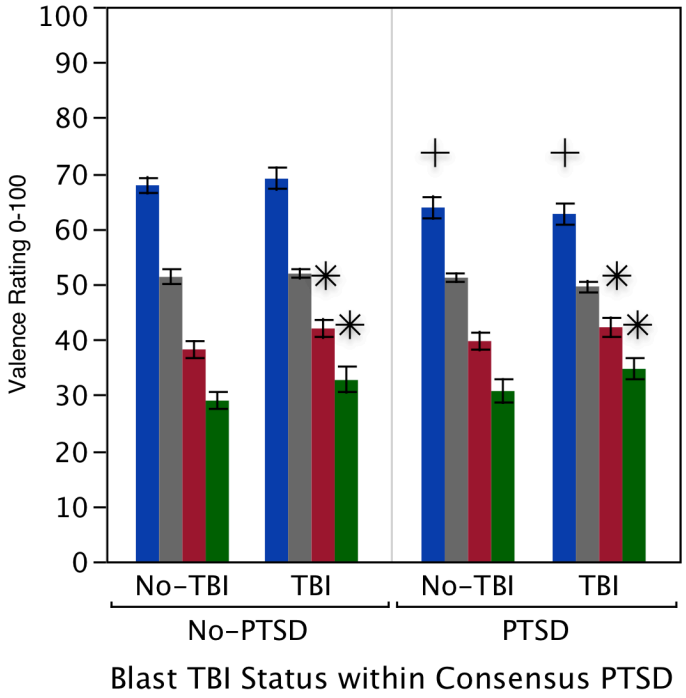

Figure 4. Columns within each set of four are ordered as follows from left to right: Pleasant, Neutral, Unpleasant, Combat. Crosses indicate significant differences in the marked valence categories between the PTSD and no-PTSD groups, $p < .01$. Asterisks (*) indicate differences in the marked valence categories between the TBI and no-TBI groups, *p's* < .05. There were no significant main effects of PTSD or TBI and they did not significantly interact. The main effect of valence category is depicted in Figure 2.

Figure 5. Mean valence ratings for each affective valence category by PTSD and depression status.

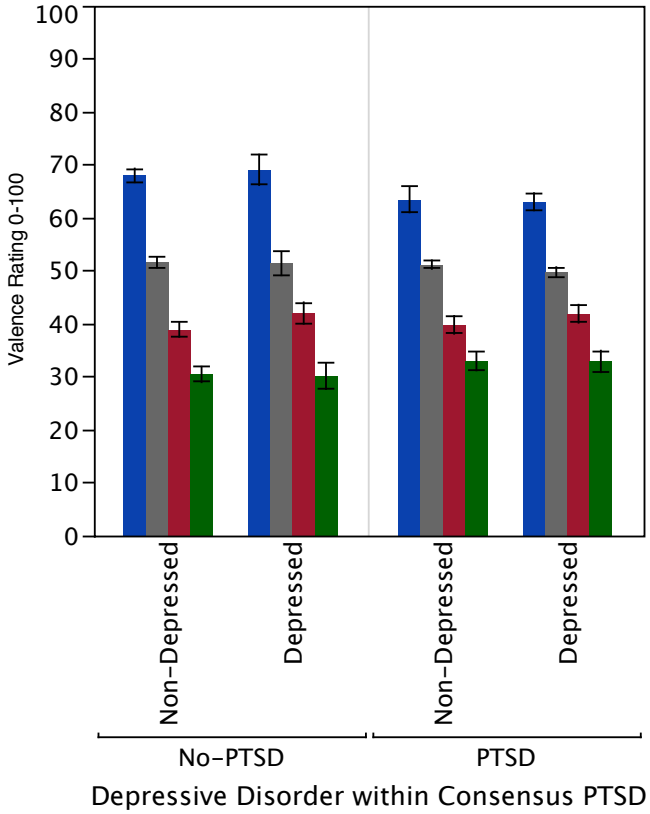

Figure 5. Columns within each set of four are ordered as follows from left to right: Pleasant, Neutral, Unpleasant, Combat. There were no significant effects of depression on mean valence ratings. Effects of valence and PTSD are depicted in Figures 2 and 4.

Figure 6. Mean arousal ratings for each affective valence category by PTSD and TBI status.

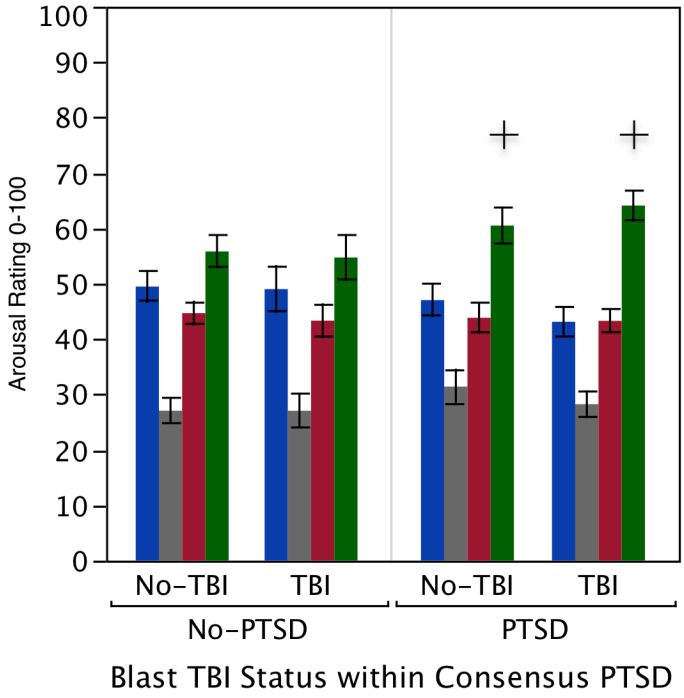

Figure 6. Columns within each set of four are ordered as follows from left to right: Pleasant, Neutral, Unpleasant, Combat. Crosses indicate significant differences in the marked valence categories between the PTSD and no-PTSD groups, $p = .02$. TBI did not significantly interact with valence category. There were no significant main effects of PTSD or TBI and they did not significantly interact. The main effect of valence is depicted in Figure 3.

Figure 7. Mean arousal ratings for each affective valence category by PTSD and depression status.

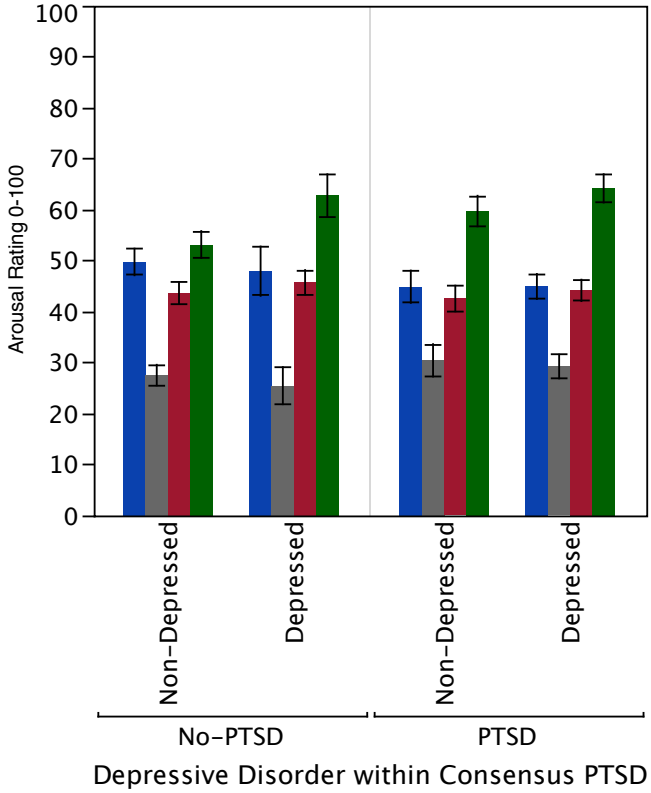

Figure 7. Columns within each set of four are ordered as follows from left to right: Pleasant, Neutral, Unpleasant, Combat. There was no main effect of depression and depression did not significantly interact with PTSD or with Valence Category. Interactions of PTSD and valence category are depicted in Figure 6. Main effects of valence category are depicted in Figure 3.

Figure 8. Startle blink magnitude (T-score) by affective valence category.

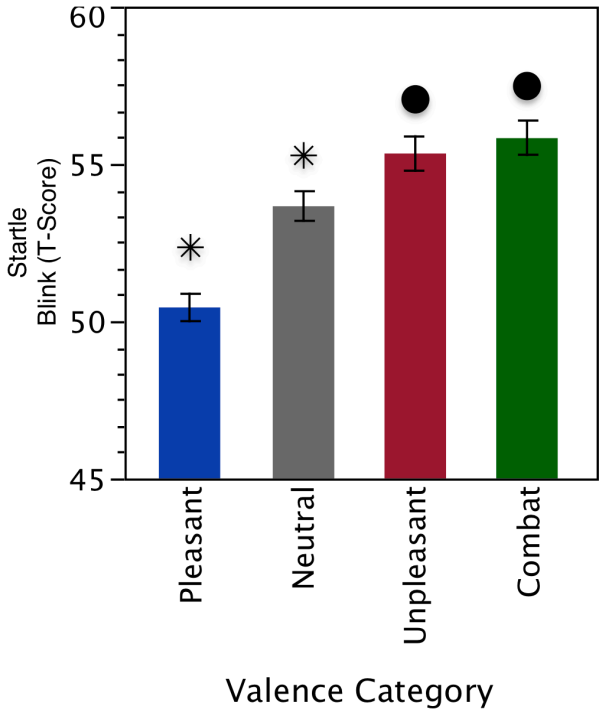

Figure 8. Valence categories marked with an * significantly differ from all other valence categories, while valence categories marked with a circle significantly differ from valence categories not marked with a circle, *p*'s < .03.

Figure 9. Startle blink magnitude (T-score) for each affective valence category by PTSD status and TBI status.

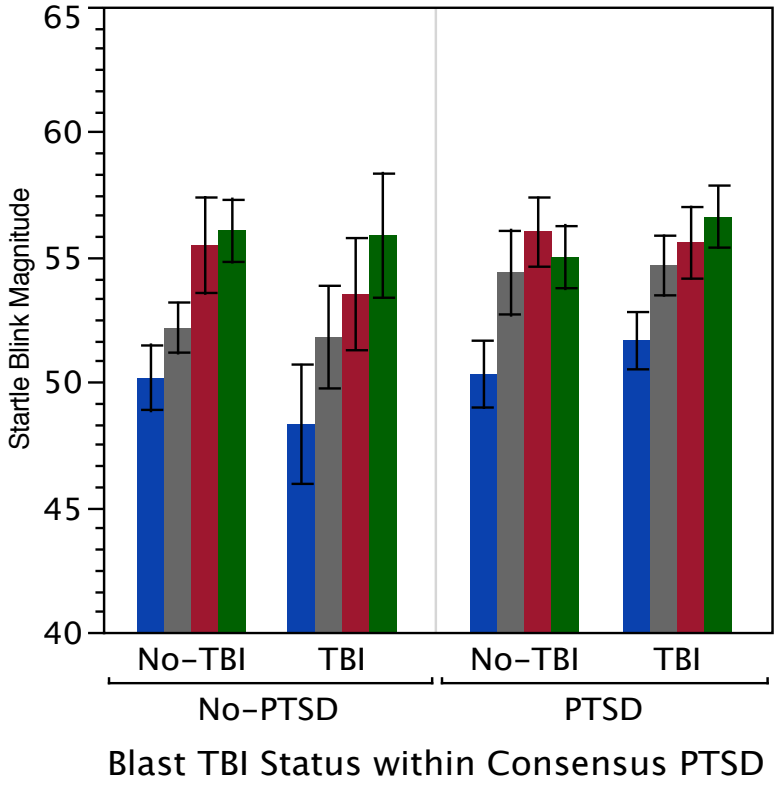

Figure 9. Columns within each set of four are ordered as follows from left to right: Pleasant, Neutral, Unpleasant, Combat. Valence category did not significantly interact with PTSD or TBI. There were no main effects of PTSD or TBI and they did not significantly interact. The main effect of valence category is depicted in Figure 8.

Figure 10. Startle blink magnitude (T-score) for each affective valence category by PTSD status and depression status.

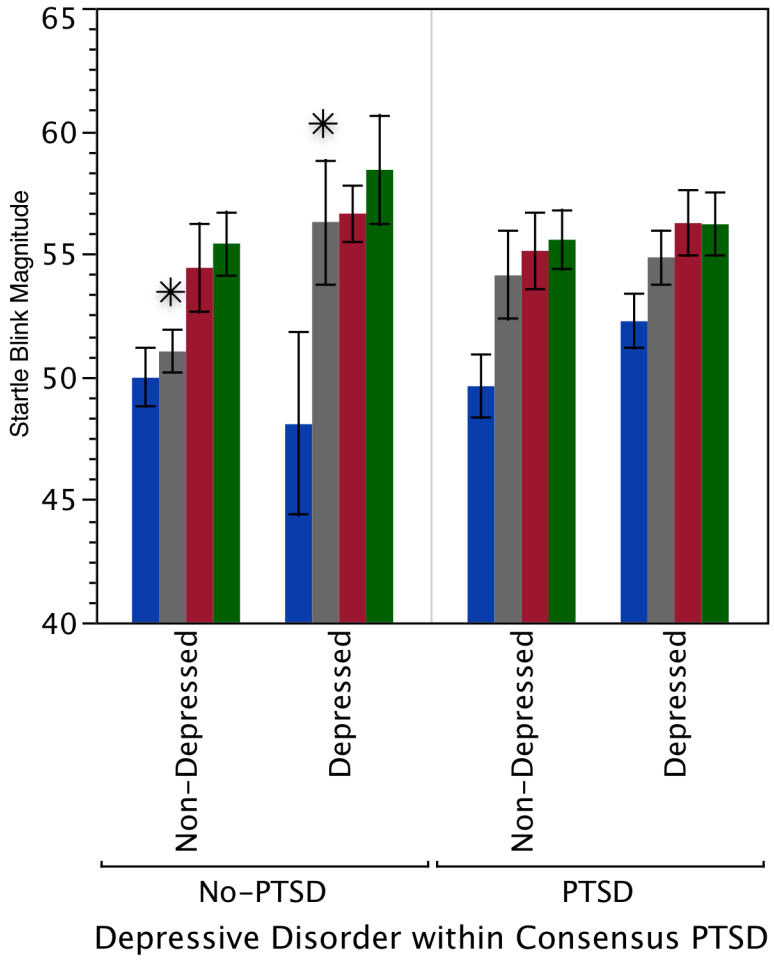

Figure 10. Columns within each set of four are ordered as follows from left to right: Pleasant, Neutral, Unpleasant, Combat. Asterisks indicate significant differences in the marked valence categories between depressed and non-depressed participants within the no-PTSD group, $p = .02$. There was no main effect of depression. Depression and PTSD did not significantly interact in the absence of valence category. There was no main effect of PTSD (see Figure 9). The main effect of valence is depicted in Figure 8.

Figure 11. Startle blink magnitude (T-Score) for each affective valence category and general startle by whether participants report symptom D5 (exaggerated startle).

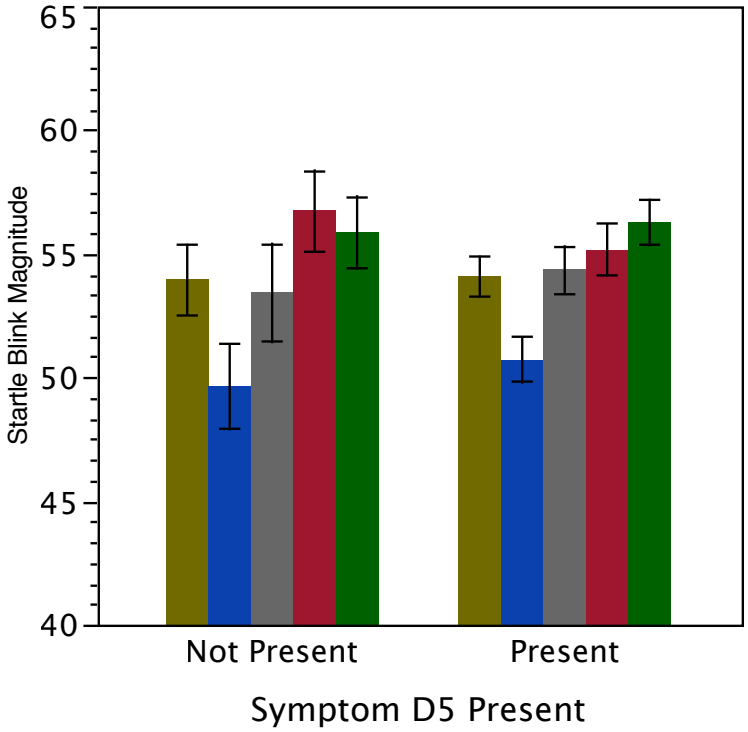

Figure 11. Columns within each set of five are ordered as follows: General, Pleasant, Neutral, Unpleasant, Combat. There was no main effect of whether participants reported symptom D5 (exaggerated startle). There were no interactions with valence.

Figure 12. Skin conductance response by affective valence category.

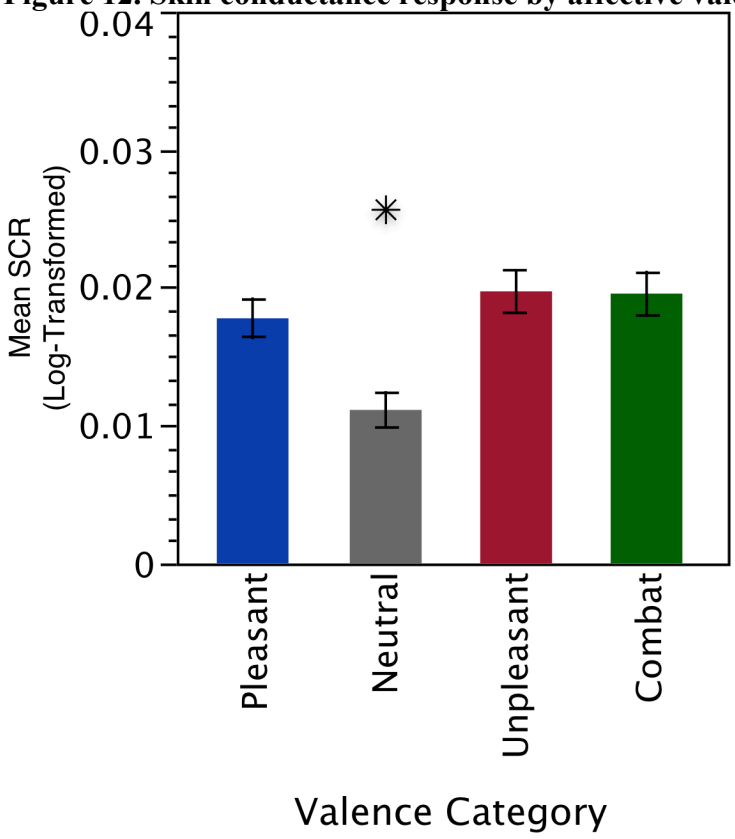

Figure 12. Valence categories marked with an * significantly differ from all other valence categories, *p*'s < .002. Unmarked valence categories did not significantly differ.

Figure 13. Skin conductance response for each affective valence category by PTSD status and TBI status.

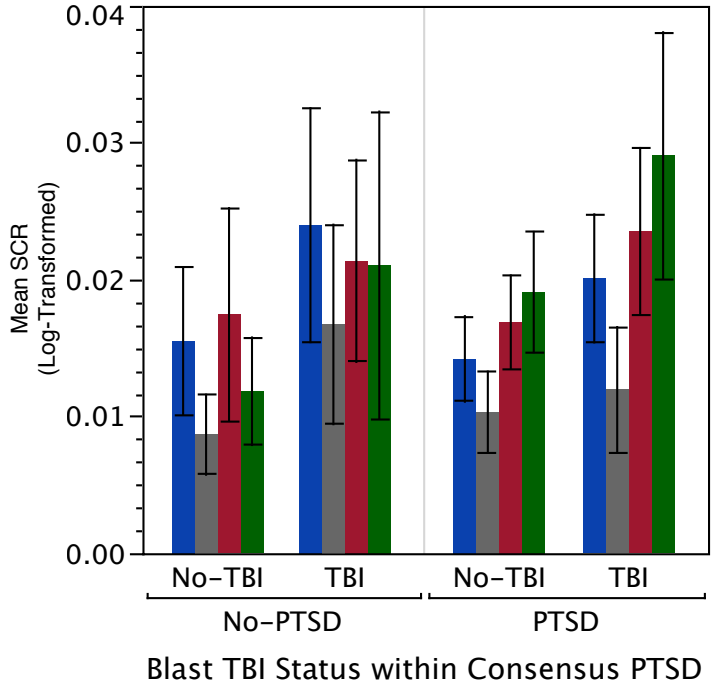

Figure 13. Columns within each set of four are ordered as follows from left to right: Pleasant, Neutral, Unpleasant, Combat. There were no significant interactions of PTSD or TBI with valence category. There was no main effect of either PTSD or TBI and they did not significantly interact. The main effect of valence is depicted in Figure 12.

Figure 14. Skin conductance response for each affective valence category by PTSD status and depression status.

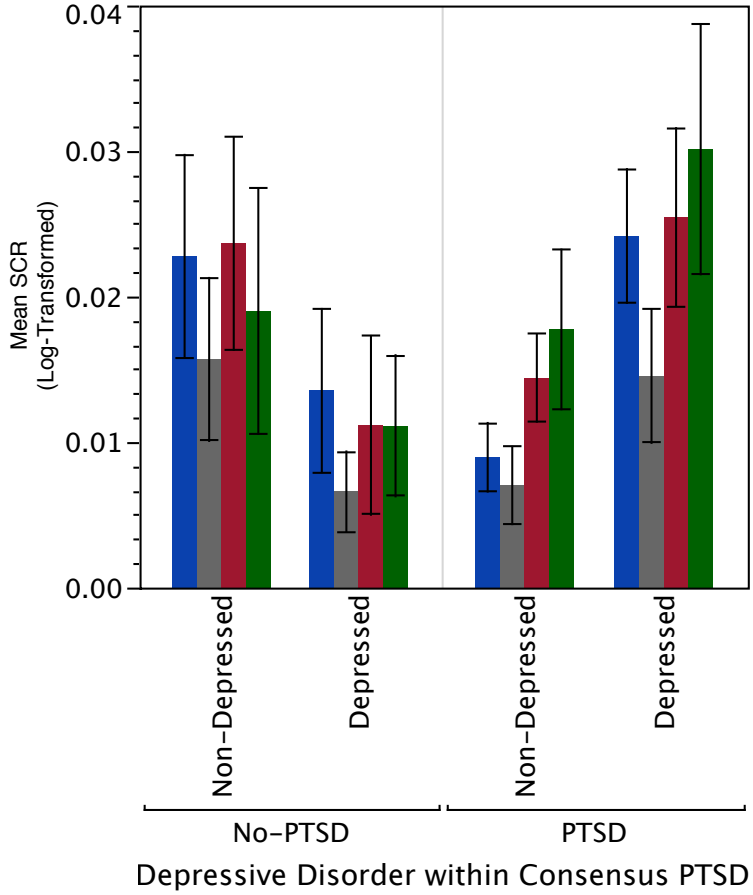

Figure 14. Columns within each set of four are ordered as follows from left to right: Pleasant, Neutral, Unpleasant, Combat. Depression did not significantly interact with valence category. There was no significant main effect of depression and it did not significantly interact with PTSD. Effects of PTSD are described in Figure 13 and the main effect of valence is depicted in Figure 12.

Figure 15. Corrugator response by affective valence category.

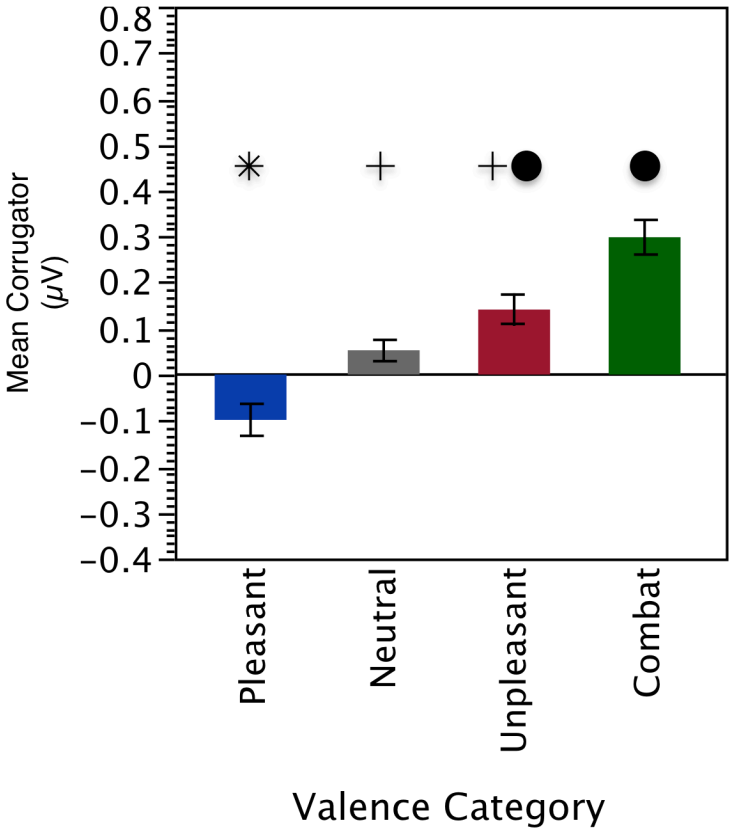

Figure 15. Valence categories that do not share a symbol significantly differ, *p*'s < .01. Unpleasant and combat nominally differ, *p* = .06.

Figure 16. Corrugator response for each affective valence category by PTSD status and TBI status.

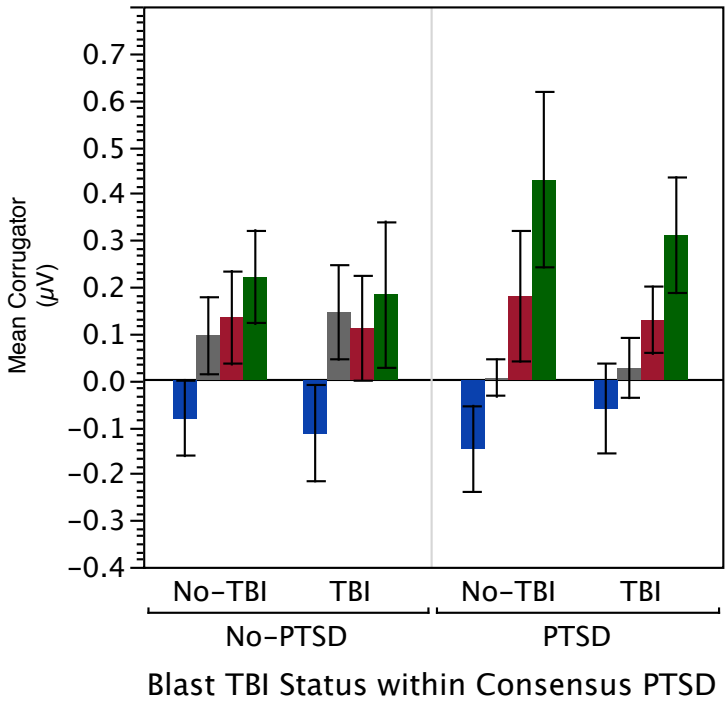

Figure 16. Columns within each set of four are ordered as follows from left to right: Pleasant, Neutral, Unpleasant, Combat. There were no significant interactions of PTSD or TBI with valence category. There were no significant main effects of PTSD or TBI and they did not significantly interact. The main effect of valence is depicted in Figure 15.

Figure 17. Corrugator response for each affective valence category by PTSD status and depression status.

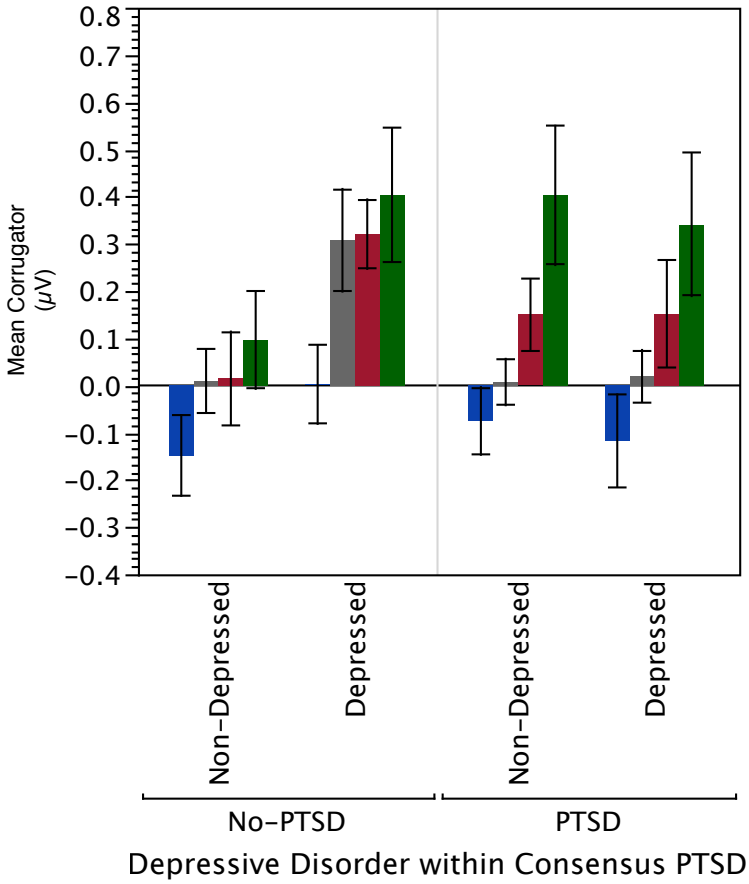

Figure 17. Columns within each set of four are ordered as follows from left to right: Pleasant, Neutral, Unpleasant, Combat. Depression did not significantly interact with valence category. There was no significant main effect of depression and it did not significantly interact with PTSD. Effects of PTSD are described in Figure 16 and the main effect of valence is depicted in Figure 15.

Figure 18. Mean zygomatic response by affective valence category.

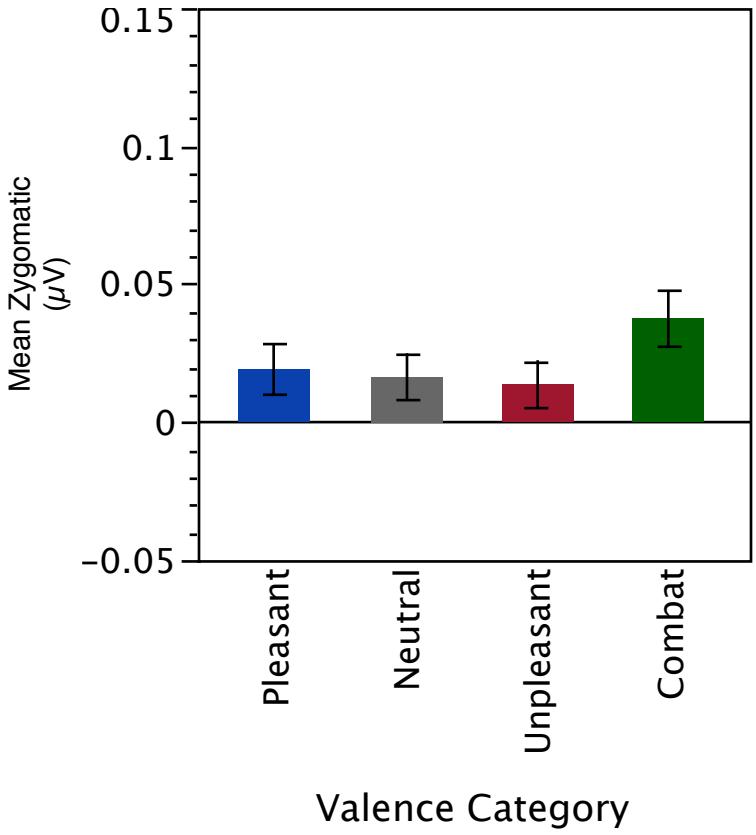

Figure 18. There were no significant differences among zygomatic responses elicited by the four valence categories.

Figure 19. Mean zygomatic response for each affective valence category by PTSD status and TBI status.

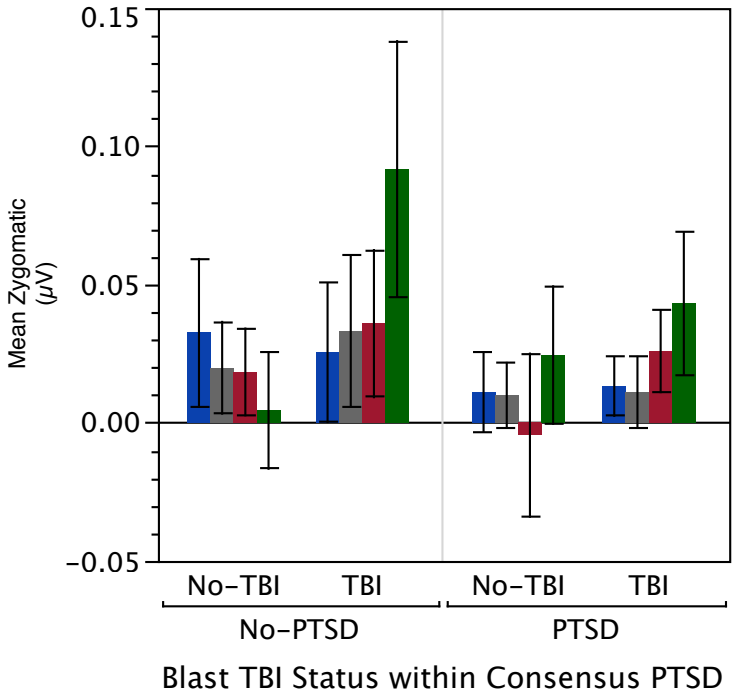

Figure 19. Columns within each set of four are ordered as follows from left to right: Pleasant, Neutral, Unpleasant, Combat. There were no significant main effects of PTSD or TBI and they did not significantly interact. Effects of valence are depicted in Figure 18.

Figure 20. Mean zygomatic response for each affective valence category by PTSD status and depression status.

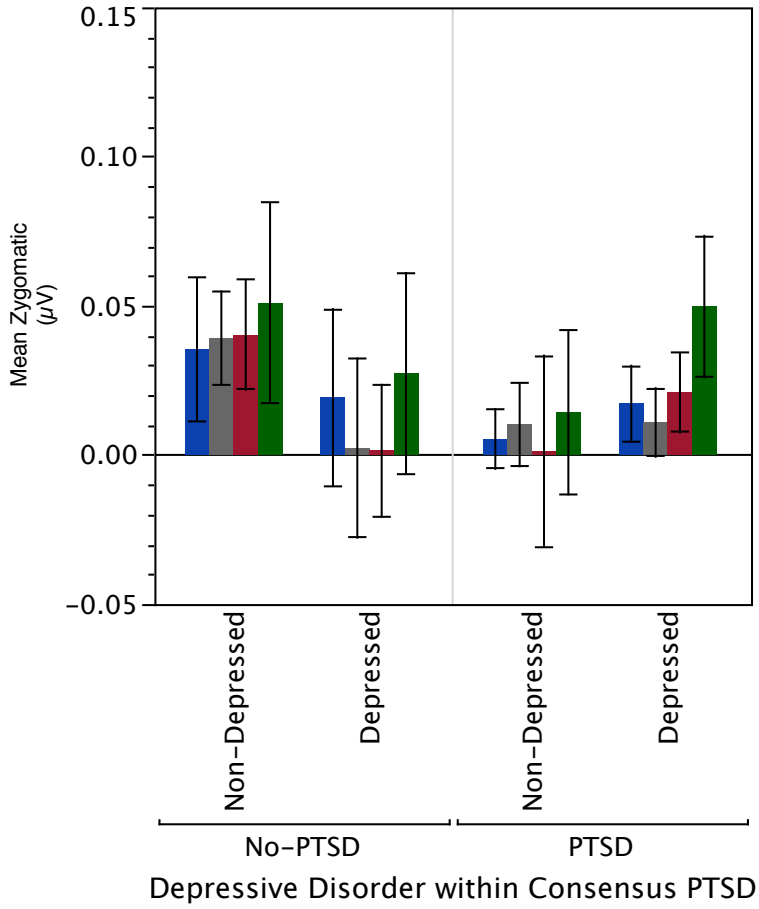

Figure 20. Columns within each set of four are ordered as follows from left to right: Pleasant, Neutral, Unpleasant, Combat. Depression did not significantly interact with valence category. There was no significant main effect of depression and it did not significantly interact with PTSD. Effects of PTSD are described in Figure 19 and the main effect of valence is depicted in Figure 18.

Figure 21. Mean heart rate change (BPM) by affective valence category.

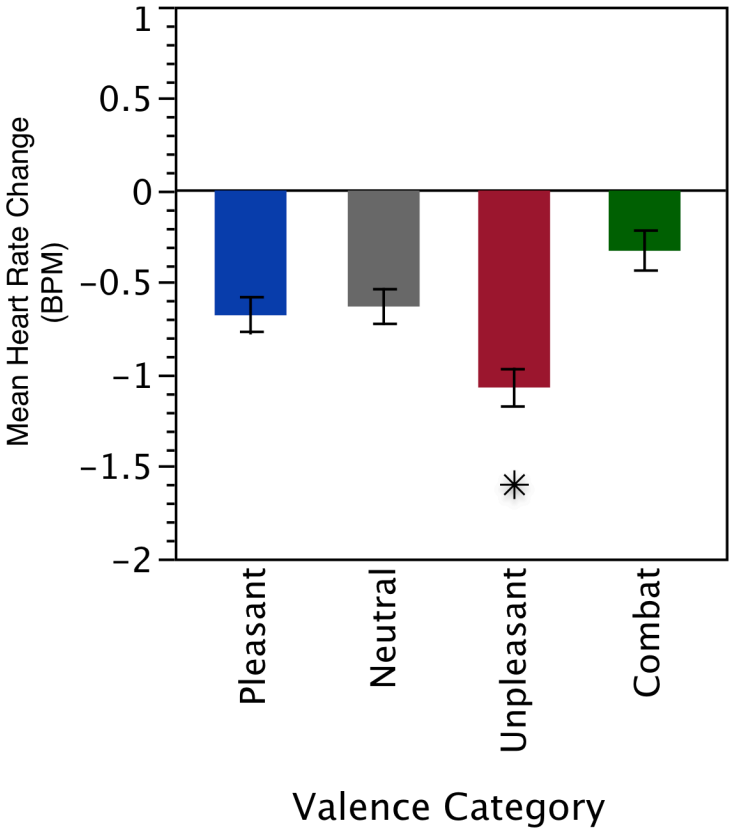

Figure 21. Valence categories marked with an * significantly differ from all other valence categories, *p*'s < .02. Unmarked valence categories did not significantly differ.

Figure 22. Mean heart rate change for each affective valence category by PTSD status and TBI status.

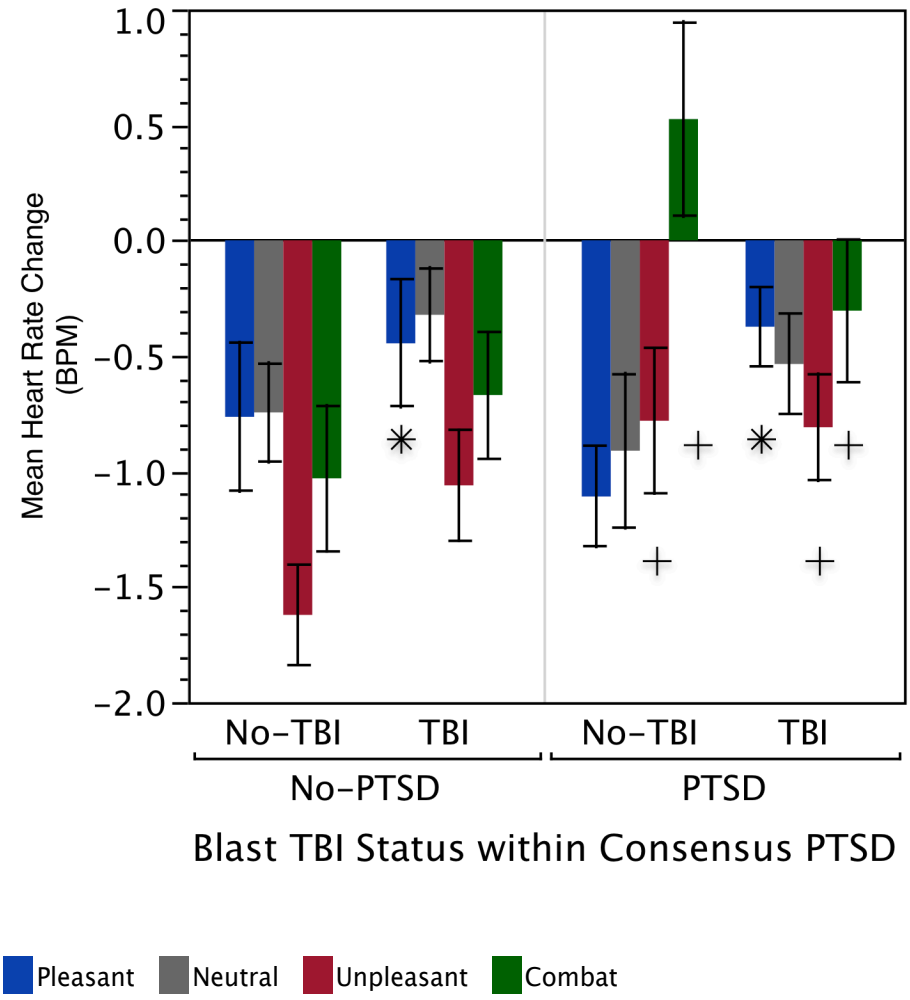

Figure 22. Columns within each set of four are ordered as follows from left to right: Pleasant, Neutral, Unpleasant, Combat. Crosses indicate significant differences in the marked valence categories between the PTSD and no-PTSD groups, *p*'s < .04. Asterisks indicate significant differences in the marked valence categories between the TBI and no-TBI groups, $p < .03$. There were no significant main effects of PTSD or TBI and they did not significantly interact. The main effect of valence is depicted in Figure 21.

Figure 23. Mean heart rate change for each affective valence category by PTSD status and depression status.

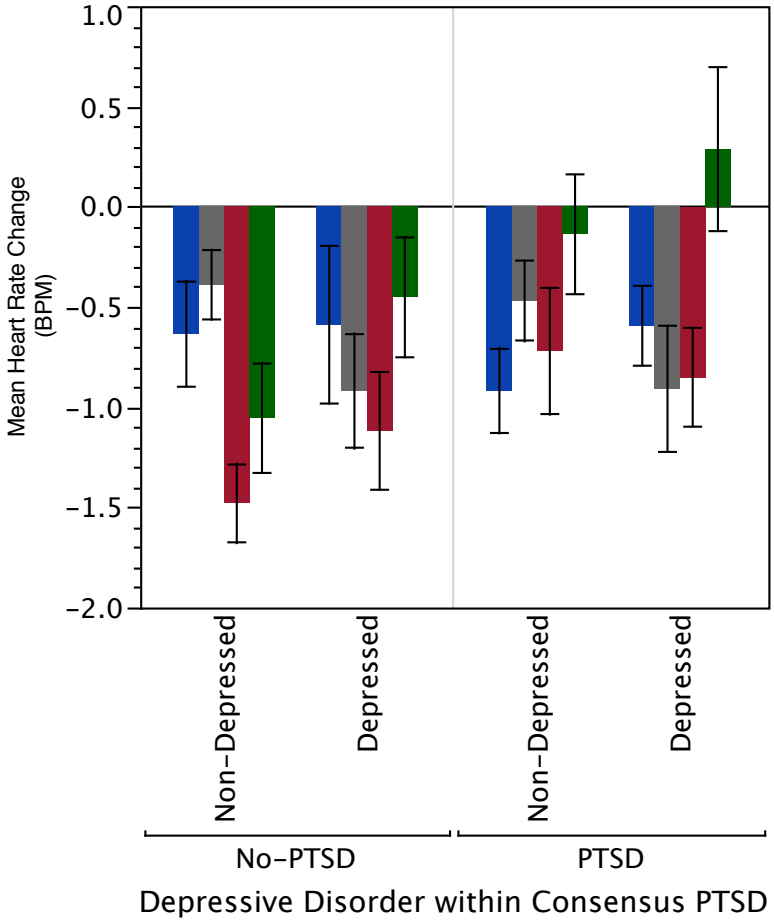

Figure 23. Columns within each set of four are ordered as follows from left to right: Pleasant, Neutral, Unpleasant, Combat. There was no significant main effect of depression and it did not significantly interact with PTSD or with valence category. Effects of PTSD are depicted in Figure 22 and the main effect of valence is depicted in Figure 21.

Figure 24. Mean startle blink magnitude (T-score) by CAPS total severity and PTSD symptom cluster severity.

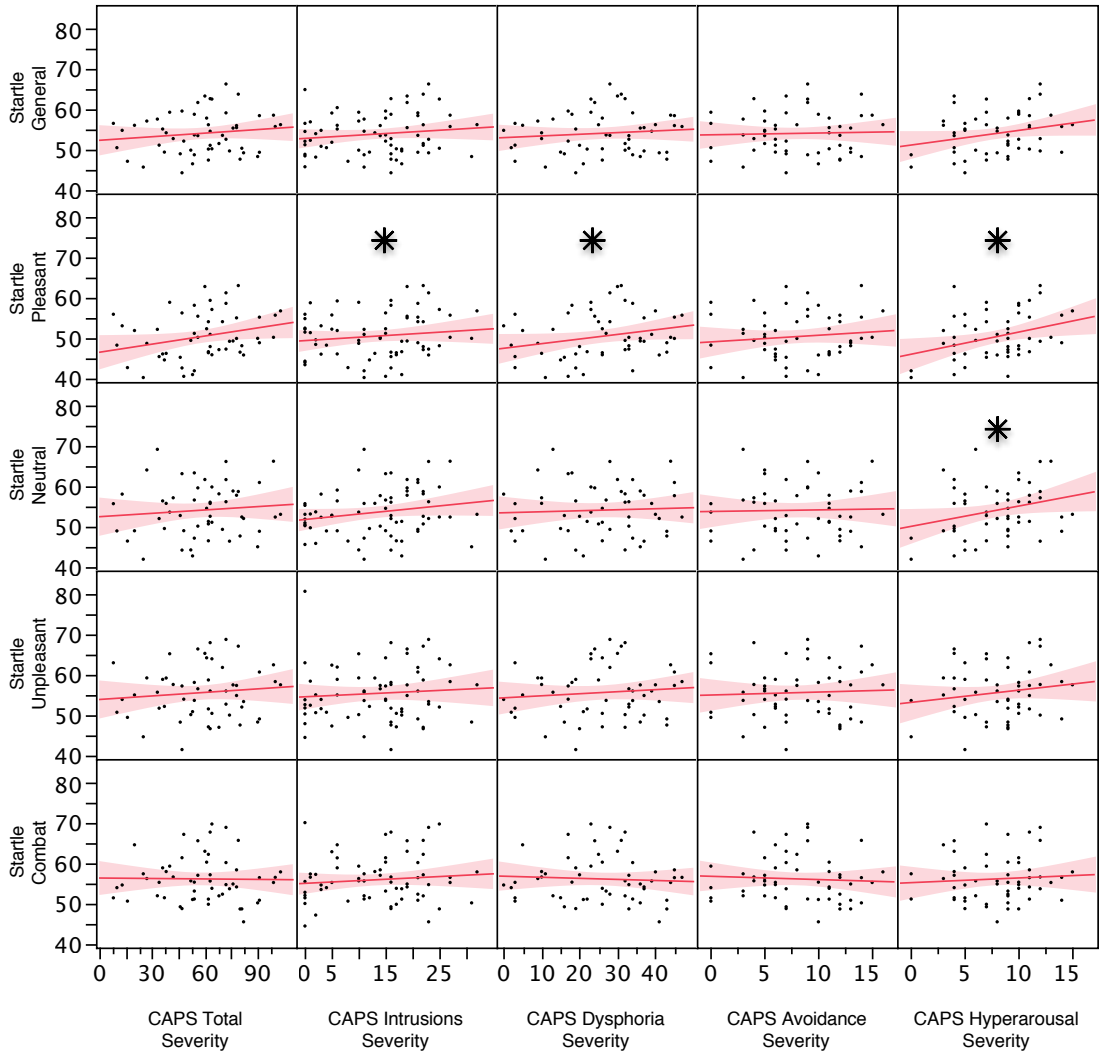

Figure 24. Asterisks indicate significant R^2 values, *p*'s < .05.

Figure 25. Mean skin conductance response by PTSD symptom cluster severity.

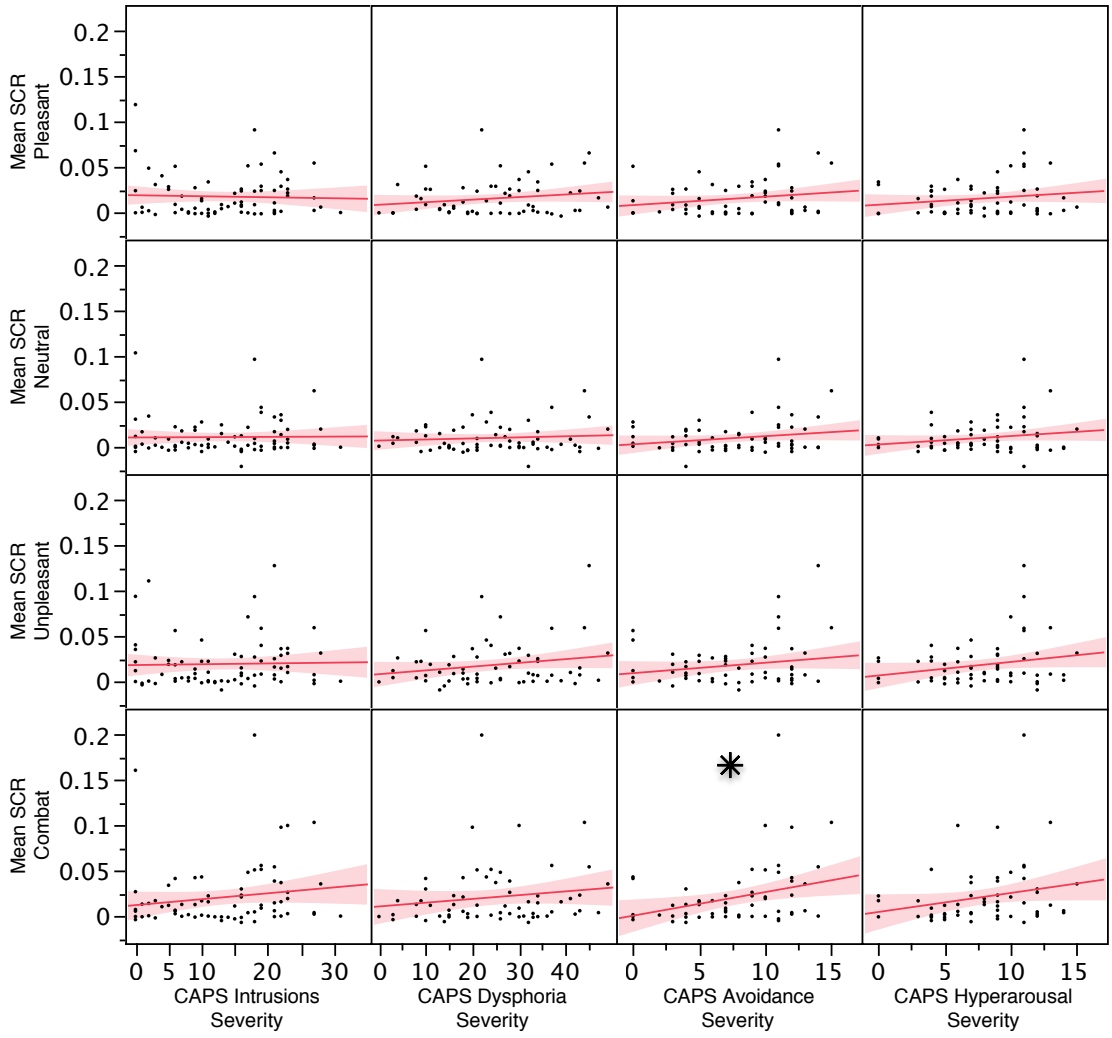

Figure 25. Asterisks indicate significant R^2 values, *p*'s < .05.

Figure 26. Mean corrugator response by PTSD symptom cluster severity.

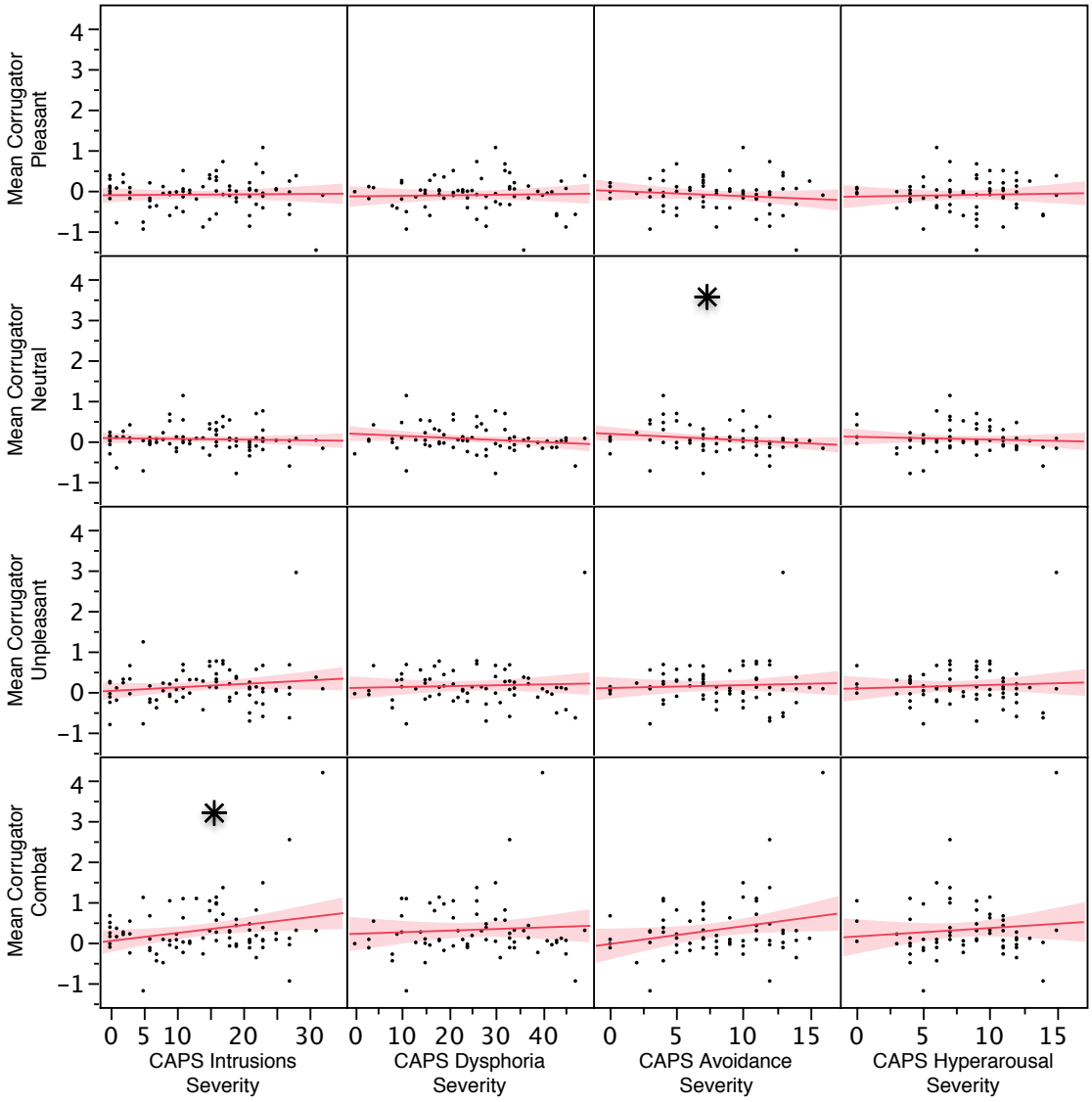

Figure 26. Asterisks indicate significant R^2 values, *p*'s < .05.

Figure 27. Mean zygomatic response by PTSD symptom cluster severity.

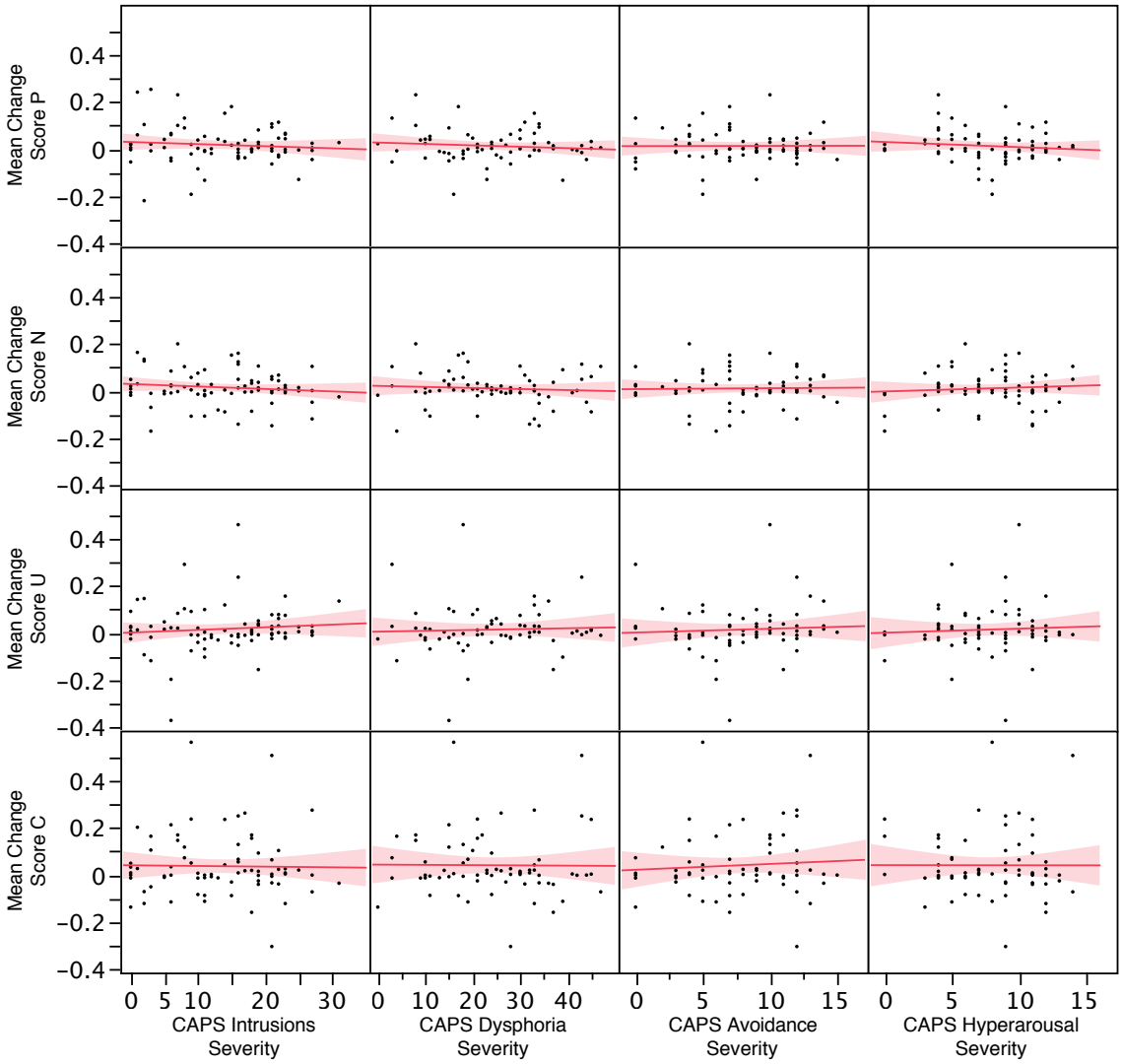

Figure 27. Zygomatic responses to any valence category did not differ as a function of any PTSD symptom cluster.

Figure 28. Mean heart rate change by PTSD symptom cluster severity.

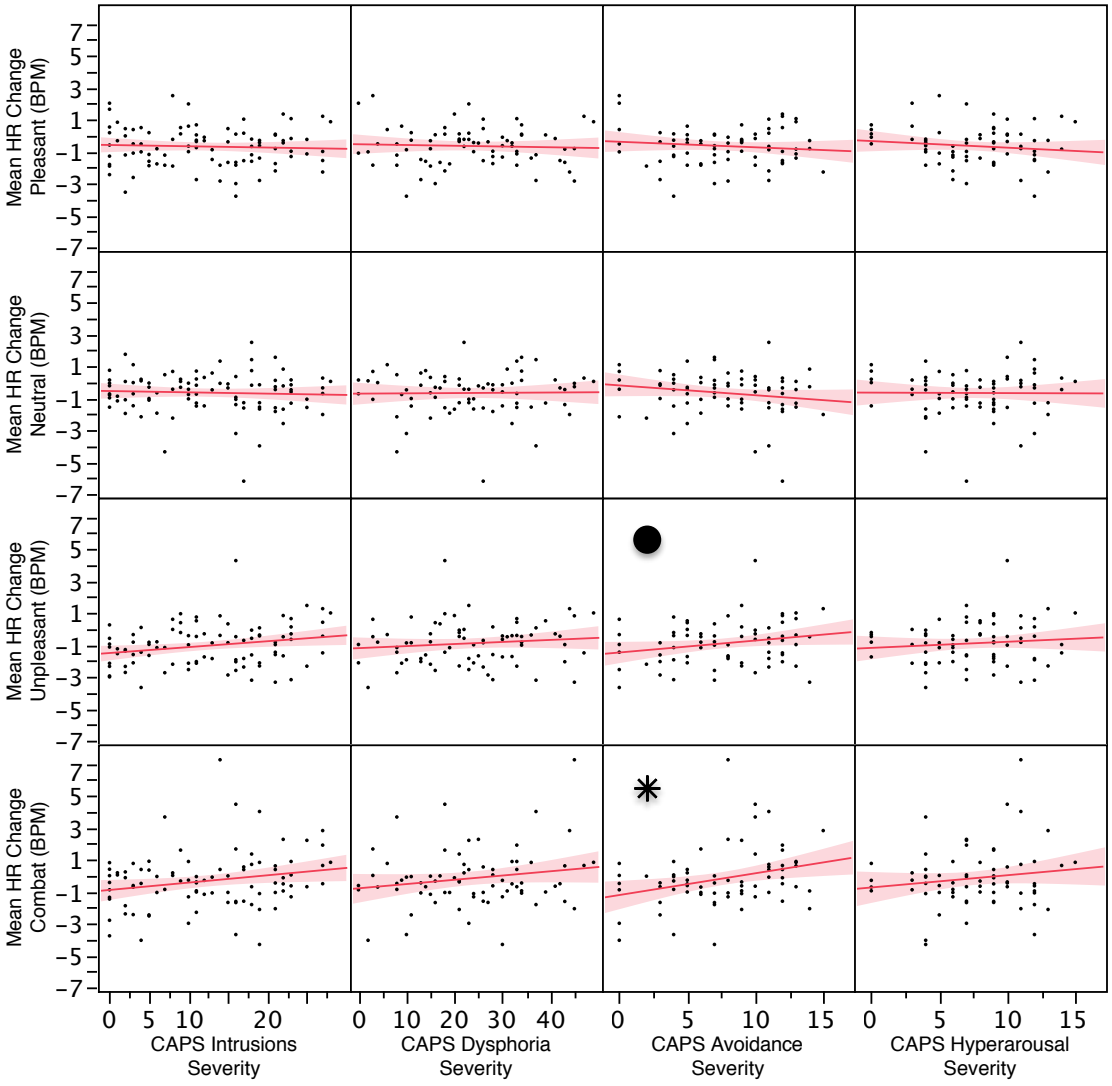

Figure 28. Asterisks indicate significant R^2 values, *p*'s < .05. The circle indicates an R^2 value with $p = .053$.

Figure 29. Valence ratings by PTSD symptom cluster severity.

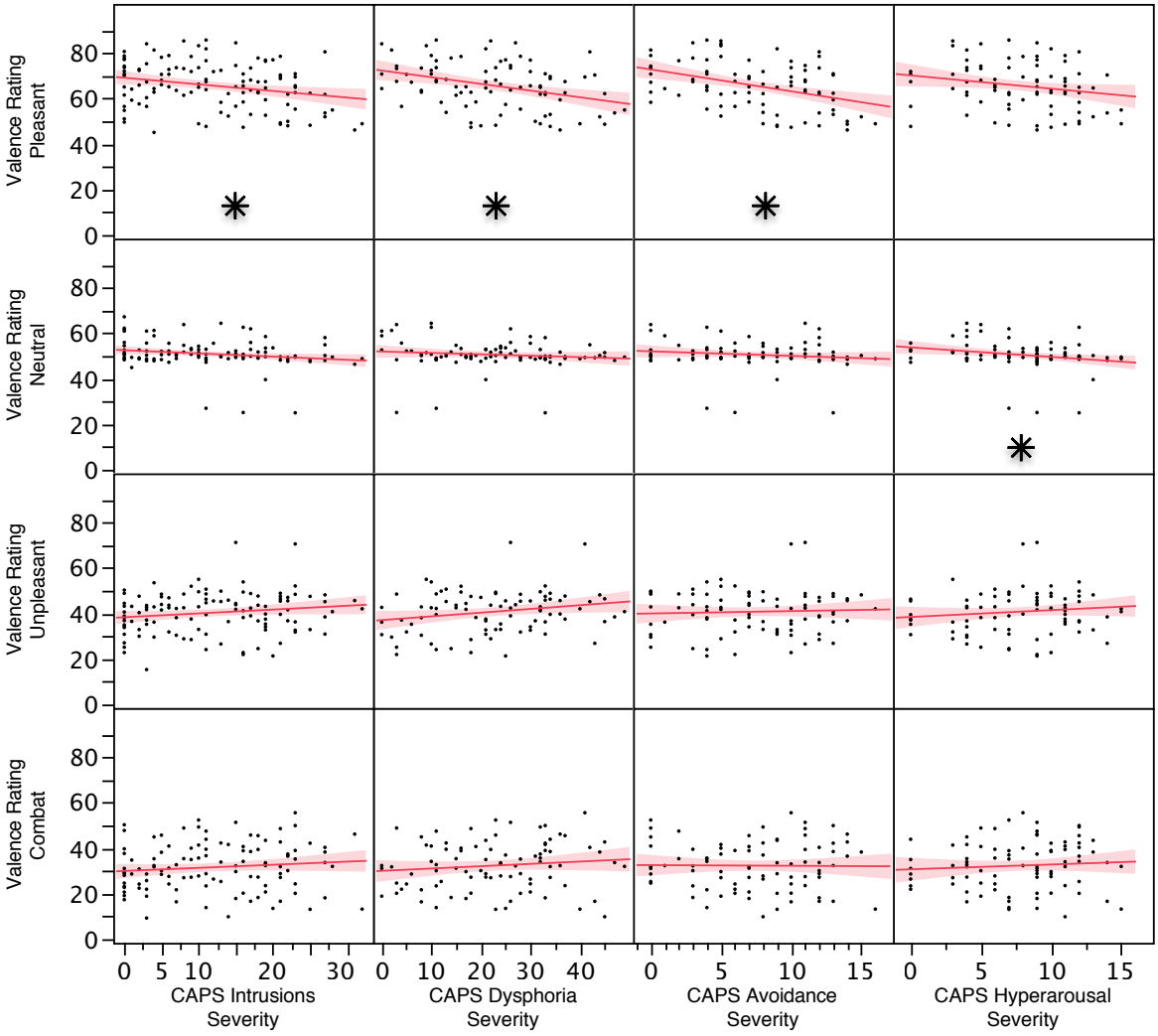

Figure 29. Asterisks indicate significant R^2 values, *p*'s < .05.

Figure 30. Arousal ratings by PTSD symptom cluster severity.

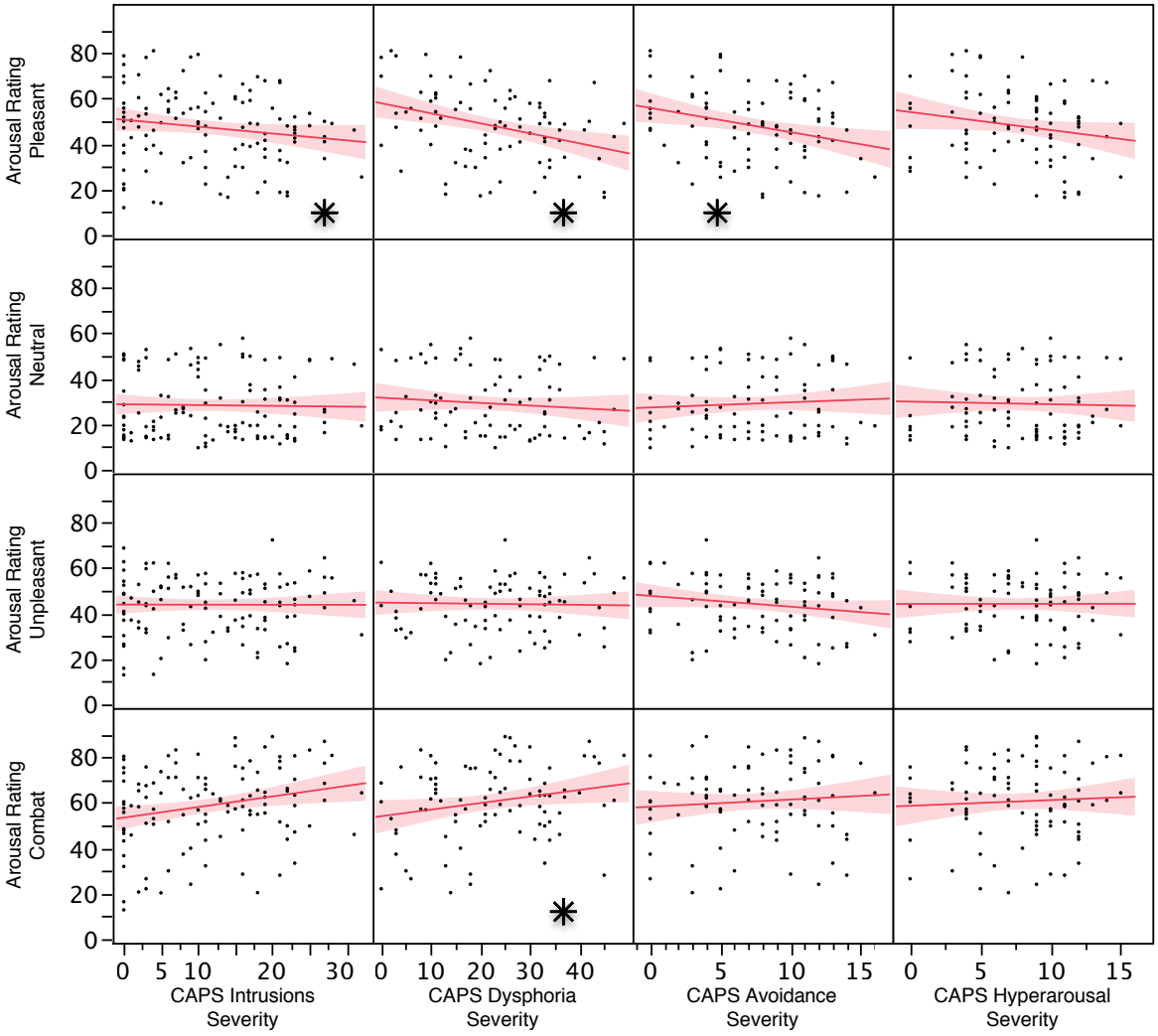

Figure 30. Asterisks indicate significant R^2 values, *p*'s < .05.

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Appendix 1: IAPS Images and Combat Picture Stimuli

The IAPS images used were: 1051, 1270, 1300, 1930, 2095, 2383, 2516, 2880, 2980, 4606, 4611, 4651, 4653, 4687, 4694, 5531, 5740, 6022, 6200, 6243, 6244, 6260, 7050, 7080, 7095, 7170, 7175,7179, 7205, 7330, 7410, 7450, 7470, 7488, 7550, 7705, 8034, 8117, 8480, 8499, 8502, 9042, 9290, 9342, and 9592.

The following are the 15 OEF/OIF combat-related images used in the present study. They were obtained through freely available online media.

Combat 1:

Combat 2:

Combat 3:

Combat 4:

Combat 5:

Combat 6:

Combat 7:

Combat 8:

Combat 9:

Combat 10:

Combat 11:

Combat 12:

Combat 13:

Combat 14:

Combat 15: