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EXAMINATION OF BASAL NEUROENDOCRINE LEVELS IN OIF/ OEF/OND VETERANS

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A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

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Abstract

EXAMINATION OF BASAL NEUROENDOCRINE LEVELS IN OIF/OEF/OND VETERANS

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High rates of combat exposure exist among veterans of the recent conflicts, and are associated with debilitating mental health conditions, including posttraumatic stress disorder (PTSD). Numerous psychosocial and biologic factors are associated with PTSD, including the HPA-axis. The present study aimed to compare baseline neuroendocrine levels by trauma group (PTSD, trauma exposed [TE], and non-trauma controls [NTC]) among a sample of young veterans. An exploratory aim was to examine potential moderators of the relation between PTSD and basal cortisol/ACTH. Group differences in cortisol were nominally significant, with the NTC group having significantly higher cortisol than the PTSD group. Sleep disturbance was the only moderator of this relationship in cortisol, although lifetime trauma load significantly predicted basal cortisol across all models. No significant effects were demonstrated for ACTH.

Examining effects of trauma on basal physiology provides a critical stepping ground for future investigations that may inform targeted prevention and intervention efforts.

Examination of Basal Neuroendocrine Levels in OIF/OEF/OND Veterans

Trauma exposure is extremely common in both civilian and veteran populations (e.g., Breslau et al., 1998; Hoge et al., 2004). Epidemiological studies have shown that trauma exposure is linked to increased risk for posttraumatic stress disorder (PTSD) and other mental health disorders (PTSD; Amstadter, Aggen, Knudsen, Reichborn-Kjennerud, & Kendler, 2013; Pietrzak, Goldstein, Southwick, & Grant, 2011). The hypothalamic-pituitary-adrenal (HPA) axis plays an essential role in the body's neuroendocrine response to stress and trauma. It functions to restore homeostasis by means of a negative feedback loop, wherein high levels of adrenocorticotropic hormone (ACTH), released in response to stress, signal the termination of cortisol production (Handwerger, 2009). The role of these neuroendocrine markers in PTSD has been extensively reviewed in both civilian and veteran populations with PTSD (e.g., Golier, Caramanica, & Yehuda, 2012; Horn, Pietrzak, Corsi-Travali, & Neumeister, 2014; Yehuda, Southwick, & Krystal, 1993). However, the majority of studies have examined neuroendocrine reactivity, as opposed to baseline levels, which may more accurately depict negative feedback loop functioning in trauma exposed and PTSD populations. Furthermore, although several studies have investigated neuroendocrine levels in combat veterans, few have investigated these relationships in service members of the recent conflicts in Iraq and Afghanistan. Veterans are a unique group in need of study, as increasing numbers of men and women return from the current conflicts endorsing high rates of combat-related traumatic events and subsequent mental health outcomes (Hoge, Auchterlonie, & Milliken, 2006; Hoge et al., 2004). In a recent meta-analysis examining the prevalence of PTSD in OIF/OEF veterans, Fulton and colleagues (2015) estimated that as many 23% of returning service members had PTSD.

Following, the present study aimed to compare baseline neuroendocrine levels by trauma group (PTSD, trauma exposed [TE], non-trauma controls [NTC]) among a sample of Operation Iraqi Freedom/Operation Enduring Freedom/Operation New Dawn (OIF/OEF/OND) veterans. A second, exploratory aim of this study was to examine factors (i.e., social support, sleep disturbance, and trauma load) that may moderate the relationship between trauma group and basal neuroendocrine levels. In the upcoming sections, trauma prevalence and related mental health outcomes are discussed for both civilian and veteran populations, with a focus on PTSD, which is the signature trauma-related mental health disorder. Psychosocial and biological correlates of PTSD within these populations are also reviewed, with special emphasis on social support, sleep disturbance, and trauma load, given their particularly robust effects on the measured outcomes. Next, an overview of HPA-axis functioning and its relationship to trauma exposure is provided, followed by an extensive review of the literature on basal cortisol and ACTH functioning in both civilians and veterans. Lastly, aims and hypotheses are presented for the present study.

Trauma Prevalence

Epidemiological studies suggest that upwards of approximately 90% of individuals in the United States will experience at least one traumatic event throughout the course of their lifetime, and that a majority of individuals experience multiple traumatic events, averaging as high as five reported traumatic events per person (Breslau et al., 1998). Findings from other widely cited nationally representative samples suggest lower lifetime prevalence of trauma exposure, with rates ranging from approximately 50% for women to 60% for men (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). Lifetime prevalence rates vary depending on trauma type, ranging from sudden loss of a close relative or friend experienced by 60% individuals, while the lifetime

prevalence rates of military combat exposure reported by less than 2% of individuals (Breslau et al., 1998). These rates are intuitive when considering population proportions (e.g., whereas anyone in the population has the potential to experience the sudden loss of a close one, only a small percentage of the population will be in environments where exposure to combat trauma is possible).

Sociodemographic factors play an influential role in exposure to traumatic events. For example, lifetime prevalence of the majority of traumatic events is slightly higher in men than women (Perkonigg, Kessler, Storz, & Wittchen, 2000). Men are significantly more likely to experience trauma types including witnessing a death or injury, natural disaster, life-threatening accident, physical assault, combat experience, threat with a weapon, and captivity (Kessler et al., 1995). Moreover, men are approximately twice as likely as women to be exposed to forms of physical assaultive violence (e.g., mugging, threat with a weapon, shot or stabbed, severely injured in a fight), whereas women are approximately three times more likely than men to report rape and sexual violence (Breslau et al., 1998; Frans, Rimmö, Åberg, & Fredrikson, 2005; Kessler et al., 1995). Minority racial status, low education, low income, central-city location, and prior marriage have been found to increase the likelihood of experiencing an assaultive traumatic event by two fold (Breslau et al., 1998). Ethnicity is an inconsistent predictor of assaultive violence prevalence, such that some studies indicate an increased risk for exposure among Caucasians (Burnam et al., 1988; Cottler, Compton, Mager, Spitznagel, & Janca, 1992; Norris, 1992), while others demonstrate an increased risk among African Americans (Hanson, Kilpatrick, Freedy, & Saunders, 1995; Kilpatrick, Seymour, & Boyle, 1991), and still others have failed to find any relation between assault risk and ethnicity altogether (Bachman & Saltzman, 1994; Breslau, Davis, Andreski, & Peterson, 1991). Additionally, higher years of education has been

found to significantly lower the likelihood of exposure to interpersonal types of trauma within a national European sample (Amstadter et al., 2013). Age has also been shown to play an important role in trauma exposure, as demonstrated by a drastic increase in prevalence between the ages of 16 and 20 across trauma types, suggesting late adolescence/early adulthood may be a critical risk period for trauma exposure (Breslau et al., 1998). Furthermore, previous exposure to trauma is associated with increased risk for revictimization (Fleming, Mullen, Sibthorpe, & Bammer, 1999; Gidycz, Coble, Latham, & Layman, 1993; Hanson, Kilpatrick, Falsetti, & Resnick, 1997; Walker & Lenore, 2009; Zawitz, 1988).

Considering the alarming rates of trauma found in civilian populations, attention should be given to rates of exposure within military populations, as these individuals are more disposed to experience traumatic events due to the nature of their of their combat experiences and deployment environments. Hoge and colleagues (Hoge et al., 2006; Hoge et al., 2004) conducted a national survey of veterans who served in Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND) and found high rates of combat related exposure (58-95% had been ambushed or attacked, 84-92% had received artillery fire, 66-97% had been shot at, and 25-50% felt in grave danger). Notably, military personnel are first civilians before they enter into the service. Thus, these individuals have the potential to be exposed to both civilian and military traumatic events, potentially increasing the likelihood of experiencing the cumulative effects of multiple traumas. For example, Clancy and colleagues (2006) examined archival data from the medical records of over 400 male veterans diagnosed with PTSD and found that upwards of 90% had endorsed nonmilitary-related trauma (19% met the diagnostic criteria for a trauma for natural disaster prior to military, 15% for motor vehicle or other accident, 19% for death of a loved one, 19% for childhood physical abuse, 9% for childhood sexual abuse,

etc.). Trauma exposure has been demonstrated to increase risk for future trauma exposure (Hanson et al., 1997) and cumulative trauma load is associated with significant medical and mental health problems (Fleming et al., 1999). Thus, investigation into populations that are more likely to be exposed to multiple traumas is crucial to the prevention and intervention of these negative outcomes.

Trauma Exposure and Risk for Mental Health Disorders in Civilians

Although trauma exposure is related to a variety of mental health disorders, PTSD is the "signature" disorder related to trauma exposure and, thus, will remain the primary focus of this study. PTSD is diagnostically unique from most other psychiatric disorders, such that exposure to an environmental event, the traumatic event, is a diagnostic criterion. According to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 2000), exposure to a traumatic stressor is necessary for a PTSD diagnosis, wherein an individual must endorse 1) significant threat to life and/or physical integrity and 2) feelings of helplessness, fear, or horror. The newest edition of the DSM (DSM-V; American Psychological Association, 2013) eliminated the peritraumatic emotional response aspect of criterion A traumatic events within the PTSD diagnosis, such that threat to life and/or physical integrity alone is sufficient for PTSD diagnosis eligibility. Therefore, risk for PTSD can be compartmentalized into 1) risk of exposure to a qualifying event and 2) risk of developing subsequent PTSD. Additional changes have been made in the DSM-V concerning PTSD symptom clusters. In the DSM-IV-TR, PTSD symptoms are grouped into three clusters: (1) re-experiencing of the event (e.g., recurrent and intrusive thoughts, distressing dreams), (2) avoidance and emotional numbing (e.g., avoidance of reminders of the traumatic event, restricted

range of affect), and (3) hyperarousal (e.g., sleep difficulties, exaggerated startle response). The DSM-V, however, now has four symptom clusters, as the avoidance/numbing cluster was further divided into two distinct clusters: avoidance and persistent negative alterations in cognitions and mood. The final cluster, renamed alterations in arousal and reactivity, includes most of the DSM-IV arousal symptoms, with the addition of irritable, aggressive, reckless and self-destructive behavior (American Psychological Association, 2013). As seen within the symptom clusters, sleep disturbances are among the most common symptoms of PTSD (Neylan et al., 1998; Pillar, Malhotra, & Lavie, 2000). An epidemiological study indicated that as many as 91% of PTSD patients experience difficulty falling or staying asleep, with upwards of 71% PTSD patients endorsing nightmares (Maher, Rego, & Asnis, 2006).

Notably, differential responses to trauma in the face of these criteria are vast, and individuals endorsing these experiences may or may not go on to meet full diagnostic criteria. The complex nature of trauma exposure and subsequent developmental outcomes is further exemplified by the stark contrast between the alarmingly high prevalence rates of traumatic exposure and the substantially lower prevalence rates of PTSD. Although diagnostic criteria, sampling, and assessment strategies have varied within the literature, lifetime prevalence estimates across studies using assorted versions of the DSM have been similar. Nationally representative surveys have shown that approximately 3.5% to 9% of individuals will meet lifetime criteria for PTSD (Breslau et al., 1998; Kessler, Chiu, Demier, Merikangas, & Walters, 2005; Kessler et al., 1995), with the highest conditional risk accounted for by those who have experienced interpersonal traumatic events (e.g., physical or sexual assaultive violence; Breslau et al., 1998; Kessler et al., 1995; Kilpatrick & Resnick, 1993).

Exposure to traumatic events has been linked to increased risk for the development of internalizing psychiatric disorders beyond PTSD, such as generalized anxiety disorder, panic disorder, and major depressive disorder (MDD) (Amstadter et al., 2013; Pietrzak et al., 2011), as well as externalizing disorders, including alcohol and substance use disorders (Kilpatrick et al., 2003). However, the relationship between trauma exposure and certain externalizing disorders has not been invariably demonstrated within the literature (Breslau, Davis, & Schultz, 2003). Additionally, the comorbidity between PTSD and these conditions is quite high, with the majority of individuals with lifetime PTSD being diagnosed with at least one other lifetime disorder (Kessler et al., 1995). In a nationally representative sample of U.S. adults, PTSD was associated with nearly all axis I disorders, including MDD, dysthymic disorder, bipolar I and II disorders, GAD, panic disorder, agoraphobia without panic disorder, social and specific phobias, alcohol and drug abuse/dependence, and nicotine dependence (Pietrzak et al., 2011). Furthermore, in a national sample of adolescents ages 12-17, nearly three fourths of all adolescents diagnosed with PTSD had at least one comorbid diagnosis of either major depressive episode (MDE) or substance abuse or dependence (Kilpatrick et al., 2003).

Trauma Exposure and Risk for Mental Health Disorders in Non-Civilians

Active duty members and veterans embody a crucial demographic when examining pre- and post-trauma PTSD risk factors, largely due to this group's frequent exposure to trauma. Consideration of OEF/OIF/OND veterans is particularly relevant, as increasing numbers of individuals return from the current conflicts endorsing high rates of combat-related traumatic events (Hoge et al., 2006; Hoge et al., 2004). Notably, prevalence estimates for PTSD are much higher among combat veterans than within civilian populations. Findings from the National

Vietnam Veterans' Readjustment Study (NVVRS; Kulka, 1988) suggest that an estimated 15.2% of male and 8.5% female Vietnam veterans met diagnostic criteria for PTSD, but that these rates were significantly higher among men (35.8%) and women (17.5%) with high levels of war-zone exposure (Schlenger et al., 1992). Similarly, in a recent meta-analysis, Fulton et al. (2015) found that PTSD prevalence among OEF/OIF veterans was estimated at 23%. As seen in civilian populations, military population studies demonstrate a high rate of comorbidity of PTSD and internalizing (Hoge et al., 2004) and externalizing (Seal et al., 2011) mental health disorders. For example, combat exposure has been consistently linked to other conditions such as alcohol use (Erbes, Westermeyer, Engdahl, & Johnsen, 2007; Hoge et al., 2006; Hoge et al., 2004; Jacobson et al., 2008; Smith et al., 2008; Wright, Huffman, Adler, & Castro, 2002), depression (Boscarino, 1995; Hoge et al., 2004; Scherrer et al., 2008), and anxiety (Boscarino, 1995; Foy, Sipprelle, Rueger, & Carroll, 1984). These findings elucidate the need for increased understanding of the risk factors that that may predispose veterans to develop negative mental health outcomes following trauma, thus allowing for interventions that are catered specifically to veterans based on these specific targeted risk factors.

Discrepancy between Trauma Exposure and PTSD Prevalence

Although exposure to traumatic events is broadly associated with increased risk for psychopathology (Amstadter et al., 2013), the majority of those exposed do not go on to develop subsequent mental health disorders (Bonanno, 2004). This notable difference between trauma and PTSD prevalence rates raises the compelling question of what risk factors are at play that predispose certain individuals to develop psychopathology following a trauma, but not others. This distinction is most likely the result of multidimensional and interdependent developmental

factors, including psychosocial/environmental (Naeem et al., 2011) and biological risk factors (Amstadter, Sheerin, Lind, & Nugent, in press). Indeed, twin studies suggest an etiological role for both biologic and environmental determinants of PTSD, suggesting that approximately 35% of the etiologic risk for PTSD is biological (i.e., can be attributed to additive genetic factors), with the remaining proportion of the variance accounted for by environmental factors (e.g., Amstadter, Aggen, Knudsen, Reichborn-Kjennerud, & Kendler, 2012; True et al., 1993). Psychosocial/environmental factors (e.g., pre- and post-trauma characteristics, trauma type and severity, early life adversity) and biological factors (e.g., genetic predisposition) are discussed in greater detail in the following sections.

Psychosocial/Environmental Correlates of PTSD

Gender. Interestingly, although men are more likely to experience trauma, women are more than twice as likely as men to develop PTSD. Although rates may vary across studies, the ratio of females to males who develop PTSD is persistently around 2:1 (Breslau et al., 1998; Kessler et al., 1995). Whereas Breslau and colleagues (1998) found that approximately 13% of women develop PTSD, compared to 6.2% of males, Kilpatrick et al.'s findings from the National Survey of Adolescents demonstrated lower rates, (6.3% of females vs. 3.7% of males; Kilpatrick et al., 2003). Kessler and colleagues (1995) reported nearly 20.4% of women and 8.2% of men go on to develop PTSD following exposure to trauma. These variations are likely a complex function of differences in trauma type and rates of revictimization (Johnson & Thompson, 2008; Kessler et al., 1995), as well as sampling and measurement differences across studies. In a meta-analysis examining risk factors for PTSD, Brewin and colleagues (2000) offer a number of potential suggestions for this gender discrepancy. First, they posit that higher PTSD rates among

women could potentially result from an increased willingness to report PTSD symptomatology among women than men. Alternatively, they suggest that higher rates of PTSD in women could result from a cumulative effect of increased exposure to prior trauma. For example, evidence exists to suggest that women's exposure to childhood sexual abuse, as well as sexual revictimization, may account for higher rates of PTSD in adulthood (Arata, 2002; Kaltman, Krupnick, Stockton, Hooper, & Green, 2005; Kaysen, Rosen, Bowman, & Resick, 2010; Mollica, McInnes, Pham, Smith Fawzi, & Murphy, 1998; Shih, Schell, Hambarsoomian, Belzberg, & Marshall, 2010; Wolfe & Kimerling, 1997). Breslau and colleagues also examined these gender differences using data from a broad epidemiological study (1997), but found that higher incidence of PTSD in women could not be attributed to cumulative traumatic events. Instead, after controlling for trauma exposure, Breslau et al. showed that women who had experienced childhood trauma were more likely than men to develop PTSD. Supporting this notion, the Brewin et al.'s 2000 meta-analysis demonstrated a greater effect size for females when studies included childhood traumas as opposed to studies that examined adult traumas exclusively.

Gender differences in PTSD have been demonstrated less consistently in veteran samples. Contrary to many findings within the civilian literature suggesting that women are significantly more likely than men to develop PTSD (Breslau et al., 1998; Kessler et al., 1995; Kilpatrick et al., 2003), a study comparing VA medical records of 1,129 male and female OEF/OIF veterans (Haskell et al., 2010) found that female veterans were significantly less likely to screen positive for PTSD than their male counterparts (21% vs. 33%, respectively). This finding could be explained by higher rates of combat exposure among men than woman, as amount of combat exposure is positively associated with PTSD (Smith et al., 2008). Conversely, however, another study using similar methods (Maguen, Ren, Bosch, Marmar, & Seal, 2010) found that female

veterans were significantly more likely to receive a PTSD diagnosis than their male counterparts, a finding more consistent with the civilian literature. Alternatively, evidence from multiple studies suggests that, although prevalence of probable PTSD may vary between the sexes by type of traumatic event (e.g., sexual harassment vs. combat exposure) occurring during deployment, rates of deployment-related PTSD do not differ significantly between men and women (Street, Gradus, Giasson, Vogt, & Resick, 2013; Vogt et al., 2011; Vogt, Pless, King, & King, 2005). Shared pre- and post-trauma variables could help to explain this lack of gender effects with regards to combat-related PTSD. For example, King et al. (1999) found that men and women shared six variables that were associated with risk for PTSD (early trauma history, abusive violence and perceived threat during deployment, post-deployment stressful life events, hardiness, and functional support). Although men had an additional three variables that were associated with PTSD, including pre-deployment age, adverse war-zone environment, and structural social support post-deployment, early history of exposure to trauma was directly linked to post-deployment stressful life events for both genders, consistent with Bremner et al.'s (1995) conclusion that prior life stress predicts later life stress. To that end, more recent investigations of OEF/OIF veterans have also shown that certain deployment variables, such as perceived threat in the war zone and combat stress, do not differ according to gender (Street et al., 2013; Vogt et al., 2011).

Race. Race is another demographic variable that has been examined throughout the literature in association with PTSD. There is evidence to suggest that minority race status is associated with increased risk for exposure to trauma (Breslau et al., 1998), and minority race was one of the few demographic variables found to be a predictor of greater likelihood of PTSD, albeit with a low effect size, in a meta-analysis of risk factors for PTSD (Brewin et al., 2000).

However, some studies have demonstrated that race, although a significant independent predictor of PTSD, becomes a non-significant predictor when simultaneously accounting for other variables (Breslau et al., 1998; Brewin, Andrews, & Valentine, 2000). Notable, however, is the fact that race was a significantly stronger predictor in military samples than in civilian samples in the meta-analysis. Koenen et al. (2003) found that, compared to male veterans who had never been diagnosed with PTSD, those who had PTSD at any time in their life were more likely to be of a minority race. Although some studies have demonstrated that minority status is associated with increased risk for PTSD, effect sizes are often small and there is little support in the existing literature for race as an independent risk factor for PTSD (Brewin et al., 2000).

Early environment. In addition to demographic correlates, early environmental factors may also confer risk for PTSD. Low childhood socioeconomic status (SES), child abuse, and familial psychiatric history, which could be thought of as an early biologic risk factor, have been repeatedly demonstrated to be associated with increased risk for PTSD within civilian samples (Brewin et al., 2000; Davidson, Hughes, Blazer, & George, 1991; Koenen, Moffitt, Poulton, Martin, & Caspi, 2007; Ozer, Best, Lipsey, & Weiss, 2003; Ozer, Best, Lipsey, & Weiss, 2008). Other early environmental predictors of PTSD include frequent changes in residencies, changes in parental figures, and separation or divorce of parents before age 10 (Brewin et al., 2000; Davidson et al., 1991; Koenen et al., 2007; Ozer, Best, Lipsey, & Weiss, 2003; Ozer et al., 2008). Early environmental influences on development of PTSD are also seen within military populations. In a study on familial and individual risk factors for PTSD, Koenen et al. (2002) found that maternal antisocial behavior, paternal depression, and less than a high-school education at entry into military were significant predictors of PTSD. Moreover, the effects of early family instability have also been shown to negatively affect functioning post trauma

exposure in adulthood within military samples (King et al., 1999). More specifically, a negative association between early familial instability and later social support has been demonstrated in male veterans, both of which serve as risk factors for PTSD (Jones, 1996; King et al., 1999; Main, 1996). The negative effect of early family instability on later social support is an important developmental consideration when attempting to conceptualize the processes in which individuals formulate secure attachments and build social support networks, which may act as buffering agents that protect against the development of PTSD following exposure to trauma (Boscarino, 1995).

Trauma type and frequency. Trauma type may also influence the likelihood that an individual will develop PTSD. Of importance, trauma measures within civilian studies can be highly variable, with trauma severity assessments differing across multiple types of trauma, as well as within trauma types. This heterogeneity is both necessary and unavoidable, as it provides a representative picture of the multiplex nature of trauma exposure and PTSD. In spite of these disparate exposures and responses to trauma, the association between certain trauma types and PTSD have been consistent across the literature (Brewin et al., 2000). For example, several meta-analytic and epidemiological studies have demonstrated that the predictive effects of trauma type on PTSD vary according to gender. Kessler et al. (1995) found in the National Comorbidity Study that males who had experienced combat exposure were at highest risk for PTSD, followed by males who had witnessed someone being killed or who had experienced a serious injury or accident. For females, rape and molestation were most frequently associated with PTSD, followed by physical abuse or threat with a weapon (Kessler et al., 1995). Perkonigg and colleagues (2000) similarly demonstrated that female victims of rape and sexual abuse were at highest conditional risk for PTSD, although the base rate for PTSD among males was too low to

allow interpretation. Another frequently replicated epidemiological finding is the positive association between cumulative effects of trauma and PTSD likelihood, such that individuals exposed to multiple traumatic events experience an enhanced probability of PTSD (Breslau, 2009). Additionally, these cumulative effects have been shown to be predictive of PTSD symptomatology, wherein greater exposure is predictive of greater PTSD symptomatology (Cloitre et al., 2009; Messman-Moore, Long, & Siegfried, 2000).

Combat-specific characteristics that have been shown to increase risk for chronic PTSD include type of trauma, amount of exposure, injury, involvement in atrocities, and perceived life threat (Engdahl, Dikel, Eberly, & Blank, 1997; Green, Grace, Lindy, Gleser, & Leonard, 1990; King, King, Foy, & Gudanowski, 1996; Kulka et al., 1990; Wolfe, Erickson, Sharkansky, King, & King, 1999). Type of combat exposure plays an influential role in the progression of subsequent psychopathology in military samples, such that veterans with direct combat exposure are three times more likely to receive a PTSD diagnosis post-deployment when compared to those without direct combat exposure (Smith et al., 2008). Furthermore, a positive relationship between amount of combat exposure and the development of PTSD has been demonstrated in the extant literature (i.e., more combat exposure is associated with greater risk of PTSD; Dohrenwend et al., 2006; McNally, 2006).

Social support. There is strong evidence to suggest that social support is a highly influential predictor of PTSD onset and maintenance (Kaniasty, 2005). Social support, which is typically categorized as received support (actual receipt of help), social embeddedness (quality and type of relationships with others), or perceived support (the belief that help would be available if needed) (Kaniasty, 2005), is based on two dominant theoretical models. The first model, known as the stress buffer (interactive) model posits social support serves as a protective

mechanism from potentially adverse effects of stressful events. The second model, known the main effect (additive) model, refers to social support that is directly beneficial to the recipient (Cohen & Wills, 1985; Wills, Shinar, Cohen, Underwood, & Gottlieb, 2000). Although differences in definition and measurement of social support result in some empirical limitations, reviews of the literature generally point to the beneficial effects that social support has on psychological well-being (Holahan & Moos, 1981) and physical health (Uchino, 2004). Notably, meta-analytic reviews of PTSD risk and protective factors have found that perceived social support is the strongest predictor of PTSD (Brewin et al., 2000; Ozer et al. 2003).

Several studies have examined multiple factors affecting the relationship between social support and PTSD within civilian populations. The association between perceived social support and PTSD has been frequently demonstrated in the literature (Eriksson, Kemp, Gorsuch, Hoke, & Foy, 2001; Fleming, Baum, Gisriel, & Gatchel, 1982; Holeva, Tarrier, & Wells, 2002; Ozer & Weinstein, 2004; Platt, Keyes, & Koenen, 2014). However, Platt et al. (2014) found that low social role diversity (e.g., employee, parent, friend, church member, etc.) was significantly associated with having a current PTSD diagnosis, irrespective of high or low perceived social support. Additionally, Andrew and colleagues (2003) demonstrated both a mediating effect of event-specific negative social support on the association between gender and PTSD, as well as a moderating effect of gender on the relationship between event-specific social support and PTSD. A longitudinal study investigating the relationship between social support and PTSD at 4 weeks and 16 weeks post-trauma showed that, while social support was not associated with PTSD symptom severity at 4 weeks, greater perceived social support and positive social interaction, as well as lower negative social interaction, were each associated with reductions in PTSD symptom severity from 4 weeks to 16 weeks among individuals with elevated PTSD symptom severity at 4

weeks (Robinaugh et al., 2011). Interestingly, the relationship between social support and negative social interaction was no longer significant when analyzed in conjunction with negative post-trauma cognitions, suggesting that perceived social support and negative interactions were associated with maintenance of PTSD symptom severity due to the association with negative posttrauma cognitions.

Examining the buffering effects of social support against PTSD among veterans has enabled a unique look into the influences of social support pre-trauma (pre-deployment), peritrauma (during deployment) and post-trauma (post-deployment). As previously discussed, a negative relationship between early family instability and later social support has been demonstrated among male veterans (Jones, 1996; King et al., 1999; Main, 1996), implicating crucial processes in which the formulation of social attachment and social support networks works to buffer against the effects of trauma exposure (Boscarino, 1995). Interestingly, while temporal restrictions have resulted in very few studies being able to investigate the effects of pre-deployment social support, the one study, to our knowledge, to have investigated this relationship suggests that pre-deployment social support does not have a significant influence on the development of PTSD post-deployment (Han et al., 2014). However, several studies have demonstrated significant influences of deployment unit support and post-deployment support on subsequent PTSD (Koenen et al., 2003; Pietrzak et al., 2010; Pietrzak, Johnson, Goldstein, Malley, & Southwick, 2009; Tsai, Harpaz-Rotem, Pietrzak, & Southwick, 2012). Although the majority of studies have examined this relationship cross-sectionally, Koenen et al. (2003) followed an all male sample of Vietnam veterans longitudinally over a 14-year span and found that, when compared to individuals without a PTSD diagnosis, those with PTSD at any time were more likely to report less perceived social support upon return from deployment. Additionally,

veterans with PTSD at any of the assessed time points were more likely to report perceived negative community attitudes upon returning from deployment than any other group (Koenen et al., 2003). These findings are consistent with much of the extant military literature, which suggests that PTSD is linked to low post-deployment social support, negative homecoming experiences, poor social functioning, lower partner satisfaction, and poor coping and posttraumatic life events (Boscarino, 1995; Engdahl et al., 1997; Green et al., 1990; Han et al., 2014; King, King, Fairbank, Keane, & Adams, 1998; Laffaye, Cavella, Drescher, & Rosen, 2008; Pietrzak et al., 2010; Pietrzak et al., 2009; Solomon, Mikulincer, & Avitzur, 1988; Tsai et al., 2012). Of importance, although the vast majority of research provides strong evidence to suggest that social support plays a buffering role to the deleterious effects of PTSD, Brancu and colleagues (2014) found that the protective effects of social support against psychological distress among veterans with PTSD were minimal, such that levels of psychological distress were alleviated by only approximately 5% by high levels of social support for individuals with PTSD, as compared to the nearly 25% reduction in distress for the TE and NTC groups. These findings, derived from a sample of 1,825 Veterans as part of a multi-site VA study, could be explained by an increased difficulty with interpersonal relationships that accompanies many of the core symptoms of PTSD, such as avoidance, hyperarousal, and emotional numbing (Friedman, 2006).

It is markedly important to consider that, although risk factors for PTSD vary across studies, a small number of variables have been consistently demonstrated to significantly influence PTSD risk, including psychiatric history, early childhood experiences (i.e., abuse, trauma), and family history (Brewin et al., 2000). Some risk factors had larger effect sizes among veteran populations compared to other groups. For instance, effect sizes for severity of trauma and social support following trauma were larger in military than in civilian samples (Brewin et

al., 2000). Additionally, the Brewin meta-analysis found that other important risk factors for veterans included younger age at the trauma, lower education, minority status, and family adversity. Furthermore, although many of these aforementioned risk factors account for relatively little of the variance for PTSD when examined independently, aggregating them could result in a more complete etiologic picture of PTSD. For example, the cumulative effects of pre-trauma factors might outweigh the seemingly larger effect of trauma severity (Brewin et al., 2000). It is crucial, however, to account for the likely intercorrelations among many of these pre-trauma variables (e.g., child abuse and family history). In sum, psychosocial/environmental factors that account for approximately two thirds of variance in PTSD, with the remaining variance being attributed to genetic factors (Amstadter et al., 2012), have begun to be identified.

Biological Underpinnings of PTSD

Although psychosocial and environmental factors, such as early life events and perceived social support, play an influential role in the development of PTSD, investigation into the etiological influences of variables beyond the environment is essential. Biological and genetic mechanisms underlying risk for PTSD are critical and account for approximately one third of the variance in PTSD (Amstadter et al., in press; Mehta & Binder, 2012; Skelton, Ressler, Norrholm, Jovanovic, & Bradley-Davino, 2012; Van der Kolk, 1997; Yehuda, 2001). Because a minimum of 4 weeks following the exposure to trauma is required for a PTSD diagnosis (American Psychological Association, 2013), PTSD is often understood as a maladaptive and continuous stress response, wherein an individual's biological stress response fails to acclimate appropriately to the stressor and instead experiences progressive dysregulation (McFarlane, 2000).

Converging evidence from multidisciplinary research designs has demonstrated a genetic,

and thus biological, role in the development of PTSD. This support is drawn from family, twin, and molecular genetic studies (Koenen, 2007). Family studies have supported the notion that, if PTSD etiology does have genetic influences, then relatives of individuals with PTSD should have a higher prevalence of PTSD than do nonrelatives, indicating increased risk for PTSD in relatives (Amstadter, Nugent, & Koenen, 2009). As previously mentioned, twin studies provide heritability estimates for PTSD, offering insight into the relative contribution of genetic and environmental influences on the variance in PTSD risk (Nugent, Amstadter, & Koenen, 2008). In doing so, twin studies also highlight the importance of gene-environment correlations, wherein selection of environment (and thus, potential for trauma exposure) are partially influenced by genetic factors (Kendler & Eaves, 1986). For example, twin studies have demonstrated that genetic factors influence the likelihood of experiencing a traumatic event, including combat exposure (Lyons et al., 1993) and assaultive violence (Stein, Jang, Taylor, Vernon, & Livesley, 2002). Personality, which is moderately heritable, plays a likely role in an individual's selection into potentially traumatic environments (Nugent et al., 2008). Although twin studies provide support for gene-environment correlations, demonstrate a genetic role in the etiology of PTSD, and offer genetic insight into comorbidity (Nugent et al., 2008), they are unable to identify specific genes associated with the disorder.

Studies of molecular genetics help to identify specific genes related to PTSD risk. Compared to other psychiatric disorders, molecular studies for PTSD are somewhat limited in number, as this research is still in its infancy. Most of the previous research has focused on examining genes in the biological systems associated with the fear response, including the HPA-axis, as well as the dopaminergic and serotonergic systems involving neural pathways underlying emotion and memory consolidation (Logue et al., 2015). However, the field of psychiatric

genetics has made a shift towards genome-wide association studies (GWAS), wherein large sample sizes allow for the detection of unsuspected genes and molecular pathways, as opposed to limiting testing to a small number of hypothesized genes as in candidate gene studies.

Indeed, family, twin, and molecular studies of PTSD have evidenced a genetic role in the etiology of the condition. Additionally, a wealth of literature (e.g., Pervanidou, 2008; Southwick, Rasmusson, Barron, & Arnsten, 2005; Van der Kolk, 1997; Yehuda, 1999; Yehuda, 2001) has investigated the biological underpinnings of the disorder, including physiological, neurological, and neuroendocrine processes. However, when reviewing this literature, it is important to differentiate between biological correlates and risk factors of PTSD. This distinction is based largely on broad differences in study designs. For example, an abundance of literature exists documenting biological correlates of PTSD, which are more clearly identified as markers of the disorder or disease process (aka "PTSD signs"; Amstadter et al., in press). Literature investigating risk factors, or predictors, of PTSD is less prevalent, however, as temporality is paramount in identifying whether certain risk/vulnerability factors (aka "biomarkers") precede the development of PTSD (Amstadter et al., in press). Because the nature of trauma exposure is characteristically unpredictable, identifying risk factors of PTSD proves a methodological challenge. Investigation into biological PTSD correlates, on the other hand, is more feasible, using traditional case-control designs to assess whether certain biological markers appear more prevalently in individuals with PTSD compared to trauma-exposed individuals who do not develop PTSD (Amstadter et al., in press).

HPA-Axis Functioning in PTSD

Findings suggesting that pre-existing PTSD symptomology may be routinely triggered by everyday stressful life events (e.g., a loud car alarm triggers physiological arousal) implies that gradual modification of an individual's stress responsivity may play an important role in the psychobiological dysregulation that is paramount in PTSD (McFarlane, Atchison, Rafalowicz, & Papay, 1994; van der Kolk, Greenberg, Boyd, & Krystal, 1985). Therefore, an individual's immediate response following trauma may not accurately determine the course that is to follow. Naturally, vulnerability and protective factors are both pertinent in this critical period following exposure to trauma. An individual's capability to attune to the acute stressor and recover physiological and biological homeostasis is equally important (McFarlane, 2000). Thus, because the vast majority of trauma-exposed individuals do not go on to develop PTSD (Breslau et al., 1998), the question remains as to what is happening under the skin that makes certain individuals more vulnerable than others to developing psychopathology. Examination of biological correlates of PTSD has led to a large amount of research pointing neuroendocrine system activity (e.g., Golier, Schmeidler, Legge, & Yehuda, 2007; Meewisse, Reitsma, De Vries, Gersons, & Olff, 2007; Miller, Chen, & Zhou, 2007; Morris, Compas, & Garber, 2012; Yehuda, 2002).

The sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) axis are essential elements in the body's neuroendocrine response to stress, be it emotional or physical. Exposure to an acute stressor triggers the SNS to enact a "flight-or-flight" response (Cannon, 1929), which elicits the HPA axis to initiate a process to return the body to homeostasis. This process is conducted by glucocorticoids (e.g., cortisol), the main output of the HPA stress response (Sapolsky, Romero, & Munck, 2000). Glucocorticoids are hormones released by the adrenal cortex that affect bodily responses to stressful stimuli to better enable an individual to deal with stress. In response to a stressor, the hypothalamus activates, resulting in the secretion of

corticotropin-releasing hormone (CRH) and arginine vasopressin. These hormones, in turn, trigger the pituitary release of adrenocorticotropin-releasing hormone (ACTH), which signals the adrenal glands to release glucocorticoids into the bloodstream (Handwerger, 2009). Bodily responses affected by this process include increased cardiovascular tone, concentration of energy to muscles, immune system stimulation, reproductive physiology and appetite inhibition, and increased cerebral perfusion rates and cognition (Sapolsky et al., 2000).

The HPA axis responds to glucocorticoid release by means of a negative feedback loop, whereby the hippocampus signals the hypothalamus to terminate glucocorticoid release, restoring basal HPA axis functioning and, thus, homeostasis (Handwerger, 2009). It is pertinent that homeostasis be reinstated in order to engender adaptive changes, such as stress recovery and resilience (De Kloet, Joëls, & Holsboer, 2005). Without this termination of glucocorticoid release, the duration of time that bodily tissues are exposed to glucocorticoids can be damaging, underscoring the importance of the HPA axis negative feedback loop system (Habib, Gold, & Chrousos, 2001). Maladaptive functioning of this system may occur by means of unnecessary activation, lack of activation, or lack of termination (Handwerger, 2009). Chronic or severe stress (e.g., trauma) can lead to the perpetuation or failure of the stress system activation, prompting the development of an allostatic load wherein physiologic systems are more vulnerable to stress, resulting in the development of disease (e.g., psychiatric, circulatory, metabolic, gastrointestinal, and immunologic; De Kloet et al., 2005; Flier, Underhill, & McEwen, 1998; Mayer, 2000).

The final product of the HPA axis, cortisol, is typically used to assess HPA functioning. Cortisol follows a diurnal rhythm, peaking in early morning and decreasing throughout the day (Desir et al., 1980). This fluctuation calls relevance to assessment times and methods, especially if HPA functioning is being assessed under basal conditions. Examination of baseline cortisol

levels usually occurs at a standardized point within the diurnal pattern, such as early morning, or late afternoon, when cortisol is highest in intra-individual stability (Pruessner et al., 1997). Some studies examining the modulation of cortisol and ACTH by metabolic inputs relating to blood glucose levels suggest that around 5PM may be the time in which cortisol is most stable (Lovallo, 2006; Van Cauter, Shapiro, Tillil, & Polonsky, 1992). The spike in cortisol levels following morning awakening is referred to as the cortisol awakening response (CAR; Pruessner et al., 1997) and implicates the major role the HPA-axis plays in sleep and awakening. Thus, dysregulation of this system has been demonstrated to have a physiological impact on sleep (Clow, Hucklebridge, Stalder, Evans, & Thorn, 2010). In normal HPA circadian rhythm functioning, the nadir for cortisol occurs around midnight (Buckley & Schatzberg, 2005). Cortisol levels begin to increase approximately 2-3 hours following onset of sleep, and continue to rise throughout the duration of sleep until they peak around 9AM (Turek & Zee, 1999). Following, cortisol levels decline steadily until they again reach their nadir around midnight the following night (Buckley & Schatzberg, 2005). Throughout this circadian process, CRH is concurrently being released in a circadian, pulsatile manner, which in turn controls the subsequent release of ACTH into the bloodstream (Hauger & Dautzenberg, 2000).

Because the HPA-axis works to modulate the secretion of cortisol and ACTH on a diurnal rhythm, frequent abrupt shifts in the sleep period can induce consequential disruptions in neuroendocrine regulation (Buxton, Copinschi, Van Onderbergen, Karrison, & Van Cauter, 2000). Additionally, sleep deprivation and/or reduced quality of sleep have been linked to adjustments of HPA axis activation (Balbo, Leproult, & Van Cauter, 2010). Thus, the bidirectional relationship between sleep and HPA axis functioning serves to either maintain healthy sleep and neuroendocrine regulation or dysregulation. This relationship has been further

evidenced in both animal and human studies, which have confirmed the existence of functional relationships between fear and sleep systems in the brain (Woodward, 2004). Although substantial evidence exists to suggest that HPA axis functioning and sleep disturbances, separately, are associated with PTSD, these interdependent relationships are not well understood.

In addition to sleep, social support has also been shown to affect HPA-axis activity. Previous studies have demonstrated low social support to be associated with significant increases in HPA reactivity, including cortisol secretion, following lab-induced stress (Kirschbaum, Klauer, Filipp, & Hellhammer, 1995; Ozbay, Fitterling, Charney, & Southwick, 2008; Steptoe, Owen, Kunz-Ebrecht, & Brydon, 2004). Similarly, another study using a laboratory-induced stress paradigm demonstrated that individuals who received a combination of oxytocin and social support had the least amount of anxiety and lowest cortisol responses to stress (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003). This is in line with evidence suggesting that oxytocin, a neuropeptide recognized for promoting social behavior, may serve as a physiological link between positive social interactions and suppression of the HPA-axis (DeVries, Glasper, & Detillion, 2003). Furthermore, one study found that, even after controlling for stress, basal cortisol was inversely related to social support among individuals with high social support, indicating a positive effect of social support on the HPA axis (Rosal, King, Ma, & Reed, 2004).

Although the HPA axis is designed to handle transitory stress, effects of extreme or prolonged trauma exposure, resulting in PTSD, have been shown to be associated with long-term HPA axis dysregulation (Olszewski & Varrasse, 2005; Yehuda, 1997). Evidence examining the relationship between PTSD and subsequent HPA activity has been inconsistent in the extant literature. Although the majority of studies suggest that individuals with PTSD resulting from an acute traumatic incident typically exhibit lower basal cortisol when compared to trauma exposed

and non-trauma exposed controls, this has not been consistently demonstrated. Lower cortisol levels might implicate long-term effects resulting from a constant increase in allostatic load (Handwerger, 2009). While, intuitively, greater increases in cortisol are commonly found following a laboratory stressor among subjects with PTSD compared to subjects without PTSD, the question remains as to why the majority of studies examining baseline cortisol find lower basal levels among individuals with PTSD. A growing line of literature is examining genetic variants that affect the HPA axis function (e.g., Mehta & Binder, 2012), but the question further remains as to why, although the minority, other studies demonstrate opposite findings.

A disruption in the HPA axis's homeostatic negative feedback loop could likely account for the acquisition of the physiologic system to a new norm, in which the HPA axis operates as it would in response to stress in healthy individuals at baseline conditions in PTSD positive individuals (Handwerger, 2009; Olszewski & Varrasse, 2005; Yehuda, 1997). More specifically, some studies suggest that elevated cortisol resulting from trauma leads to subsequent sensitization of the nervous system's CRH pathways (Heim & Nemeroff, 1999; Yehuda, 1997). This increase in SNS functioning leads to an escalation of HPA functioning, resulting in elevated cortisol secretion. Higher levels of cortisol secretion consequently exaggerate the negative feedback loop, resulting in lower baseline cortisol levels (Handwerger, 2009; Tucker et al., 2004). The present study aimed to review the current literature on the relationship between PTSD and two HPA axis markers (cortisol and ACTH) at a resting state, and to further examine these markers within a sample of OIF/OEF/OND veterans.

Studies Finding Lower Cortisol

Studies examining basal cortisol levels in relation to PTSD are often contradictory.

However, reports of lower basal cortisol in PTSD-positive individuals are more prevalent within the literature. In a meta-analysis examining basal and reactive cortisol in control, trauma exposed, and PTSD positive adults, some studies reported lower cortisol levels in PTSD patients compared to nonclinical samples (De Kloet et al., 2007; Neylan et al., 2005; Rohleder, Joksimovic, Wolf, & Kirschbaum, 2004; Wessa, Rohleder, Kirschbaum, & Flor, 2006; Yehuda, Golier, & Kaufman, 2005), although cortisol levels did not significantly differ meta-analytically for trauma exposed (TE) vs. PTSD or control vs. PTSD (Klaassens, Giltay, Cuijpers, van Veen, & Zitman, 2012). Additional studies found enhanced cortisol suppression in patients with PTSD (Yehuda, Halligan, Golier, Grossman, & Bierer, 2004; Yehuda, Halligan, Grossman, A Golier, & Wong, 2002; Yehuda, Southwick, Krystal, et al., 1993) but also in trauma-exposed veterans without PTSD (De Kloet et al., 2007), signifying lower levels of cortisol in TE and PTSD individuals assessed at baseline. Notably, basal cortisol levels were lower in military veterans with PTSD in the first hour after awakening compared to non-trauma-exposed civilian controls. However, compared to the TE group, no differences in cortisol measurements were reported (De Kloet et al., 2007; Klaassens et al., 2012). Horn et al. (2014) measured morning plasma cortisol levels in a civilian sample consisting of PTSD, TE, and non-trauma control (NTC) groups. After controlling for Caucasian ethnicity, education, lifetime alcohol use disorder, and current smoking status, the PTSD and TE groups exhibited significantly lower cortisol levels than the NTC group. Cortisol levels between the PTSD and TE groups did not differ. Interestingly, only age and severity of emotional numbing symptoms were significantly associated with cortisol levels in the PTSD group.

Several studies highlight the importance of considering psychiatric comorbidity when examining HPA axis markers. A meta-analysis investigating HPA functioning in PTSD and

PTSD comorbid with MDD found that daily cortisol output was significantly lower for PTSD and comorbid PTSD and MDD groups, compared to the NTCs (Morris et al., 2012). TE and NTC groups did not differ significantly. Morris and colleagues suggest that the inconsistent literature on HPA function in PTSD is due, in part, a failure to consider the commonly occurring psychiatric comorbidities, namely MDD, that often accompany PTSD diagnoses. The authors also argue that including TE individuals in control groups further contributes to inconsistent findings within the literature, such that TE and NTC groups are combined into one comparison group. Newport et al. (2004) also considered comorbidity in their study examining women with childhood abuse diagnosed with PTSD, MDD, or comorbid PTSD and MDD and found that, compared to healthy controls, individuals with early childhood abuse and PTSD had significantly lower baseline plasma cortisol levels and revealed significantly more suppression of morning cortisol.

In their systematic review and meta-analysis, Meewisse and colleagues (2007) found no significant baseline cortisol differences between PTSD and control groups when comparing systematic mean differences, which allowed them to pool across studies that used different types of measurement (i.e., urine, saliva, plasma, or serum). However, subgroup analyses demonstrated that studies assessing cortisol via plasma or serum showed significantly lower levels in people with PTSD when compared to NTC. Additionally, lower basal cortisol levels were seen among PTSD groups in studies that included females, assessed physical and/or sexual abuse, and sampled in the afternoon, where cortisol levels are likely most stable. Significant differences in measurement methodology highlight the need to investigate assessment variability in studies examining neuroendocrine differences in HPA functioning. Furthermore, assessment modality should be taken into consideration when interpreting extant findings, as significant group

differences could be influenced by how the samples were collected. The relationship between lower cortisol demonstrated only in afternoon samples and not demonstrated in any other time points, could elucidate the need to choose time of measurement carefully.

Studies Finding Higher Cortisol

Although the majority of studies within the extant literature have demonstrated overall lower baseline cortisol levels among PTSD-positive individuals, and frequently TE individuals as well, a number of studies have reported higher basal cortisol levels in patients with PTSD (Inslicht et al., 2006; Klaassens et al., 2012; Lindley, Carlson, & Benoit, 2004). Baker et al. (2005) compared CSF, plasma, and urinary cortisol measurements in individuals with combat-related PTSD to healthy controls. Although no group differences were detected in the plasma or urinary free cortisol, mean CSF cortisol concentrations were significantly higher in the PTSD-positive individuals than in the healthy controls. In attempting to explain this incongruence of findings between assessment modalities, the authors posit that CSF cortisol more accurately illustrates brain glucocorticoid exposure. Of additional importance is that CSF, CRH, and CSF cortisol were positively and significantly correlated in this sample.

In a larger study examining HPA response to administration of synthetic corticotrophin-releasing factor (CRF) stimulation in a sample of military veterans (Golier et al., 2012), baseline levels of cortisol were significantly higher in veterans in the PTSD group compared to the TE and NTC groups. Similarly, baseline analyses from a study examining subjective, autonomic, adrenergic, and HPA axis responses in PTSD and TE Vietnam veterans and healthy non-veteran controls (Liberzon, Abelson, Flagel, Raz, & Young, 1999) indicated that PTSD patients, as

compared to TE and NTC groups, had higher subjective distress, skin conductance, NE, and plasma cortisol. TE and NTC groups did not differ significantly on any baseline measures.

Other studies considering psychiatric comorbidity when examining the HPA axis have demonstrated higher levels of baseline cortisol within comorbid groups. Findings from a subsample of a large epidemiological study showed significant elevations in cortisol among individuals with comorbid PTSD and MDD, but not in PTSD or MDD only groups (Young & Breslau, 2004). Young and Breslau compared salivary cortisol between PTSD, TE, and PTSD+MDD groups and found that evening cortisol levels were higher in the PTSD group compared to TE individuals, but that the only statistically significant difference in cortisol was demonstrated within the comorbid group.

Studies Finding No Differences in Cortisol

Some studies failed to find any significant differences in basal cortisol between study groups. Results from several meta-analyses indicate no significant differences in basal cortisol levels between individuals with PTSD and controls (Klaassens et al., 2012; Meewisse et al., 2007; Miller et al., 2007). However, as previously mentioned, subgroup analyses within these samples typically did reveal significant differences, depending on considered variables. In addition to these meta-analyses, Savic et al. (2012) compared 400 individuals by group (current PTSD, lifetime PTSD, TE, NTC) and found no significant differences in basal cortisol, measured in blood and taken hourly from 10PM to 9AM, between study groups. In another study, Hockings et al. (1993) compared 13 Vietnam Veterans with PTSD to 7 healthy controls and found no significant differences in baseline plasma cortisol levels. Another study by Lindley and colleagues (2004) additionally found no significant differences in baseline salivary cortisol levels,

assessed at multiple time points over two consecutive days, in a sample of 17 individuals with PTSD resulting from various types of trauma and 17 matched controls.

Studies Finding Higher ACTH

Studies examining baseline ACTH have also demonstrated mixed findings, but are overall less variable than those examining basal cortisol levels. In behavioral medicine, ACTH is assayed less frequently than it's neuroendocrine counterpart, cortisol, largely because it is blood-based biomarker. Unlike cortisol, which can be assessed via several biological specimens (e.g., saliva, blood, hair), ACTH is limited to serum-based assessment, resulting in fewer studies investigating its association with PTSD. However, whereas the literature on the association between PTSD and cortisol is highly variable, standardization of ACTH assessment results in a more consistent literature. Overall in the literature, basal ACTH has been found to be significantly higher in individuals with PTSD, or to not differ significantly altogether. In a study by Kloet et al. (2012) analyzing HPA axis, immunological, and SNS system responses to cognitive stress in combat exposed PTSD veterans and combat TE controls, basal ACTH levels were significantly higher in PTSD patients compared to controls. Another study examining baseline HPA functioning and biological correlates of PTSD in Gulf War veterans, Golier and colleagues (2007) found significantly higher basal levels of ACTH in the PTSD compared to the TE group. Interestingly, ACTH levels were also significantly higher in the NTC group compared to the TE group. Significant differences between PTSD and NTC groups were not discussed.

Studies Finding No Differences in ACTH

The majority of studies investigating ACTH levels in relation to PTSD have failed to find significant differences in baseline ACTH between groups. In Savic et al.'s (2012) study comparing 400 individuals with current PTSD, lifetime PTSD, TE, or NTC, no significant differences in basal ACTH were found between study groups. Additionally, Baker and colleagues (2005) demonstrated no significant group differences in basal plasma ACTH between males with combat related PTSD and NTC. In another military sample investigating HPA functioning among several generations of veterans, Golier and colleagues (2012) found no significant differences in baseline ACTH between PTSD, TE, and NTC groups. Similarly, a study by Liberzon et al. (1999) examining HPA axis, subjective, autonomic, and adrenergic responses in Vietnam veterans showed no significant differences in baseline ACTH levels between PTSD, TE, and NTC groups.

Possible Explanations of Contradictory Findings

The disparate findings implicating lower levels of cortisol, yet higher levels of ACTH in the majority of individuals with PTSD is likely a function of the HPA Axis's negative feedback loop. Stress-induced hypothalamic activation triggers CRH and arginine vasopressin to signal pituitary release of ACTH. This increase in ACTH then leads the hippocampus to signal the hypothalamus to halt glucocorticoid (e.g., cortisol) production (Handwerger, 2009). Thus, because the negative feedback loop works to restore homeostatic functioning, sustained levels of increased ACTH leads to decreased cortisol production. Hence, chronic or severe exposure to trauma, including combat exposure, may produce enduring physiological effects, whereby continuous effort of the HPA axis to respond to trauma/stress and restore homeostatic functioning results in chronically high levels of ACTH, which in turn, result in lower levels of cortisol at

resting states. Furthermore, maladaptive functioning of the HPA system has been shown to occur via numerous mechanisms, including unnecessary activation, lack of activation, or lack of termination (Handwerger, 2009). These differential responses in physiological functioning could potentially account for the contradictory findings regarding baseline ACTH and cortisol within the extant literature.

Variation in assessment methodology is a likely contributor to the conflicting results concerning neuroendocrine activity in individuals with and without PTSD. Cortisol and ACTH fluctuate on a diurnal rhythm, wherein healthy individuals, levels peak in the early morning and become lowest when nearing the beginning of the sleep period (Desir et al., 1980). Consideration of this fluctuation with regard to assessment is crucial, as assessments conducted at differing times of day may result in misleading variations in baseline results. While both cortisol and ACTH should ideally be assessed at a standardized point within the diurnal pattern (e.g., early morning, when levels are highest in intra-individual stability; Pruessner et al., 1997), external factors, such as participant scheduling, study design, and methodology do not always allow for such control. Therefore, samples obtained at varying time points may result in inconsistent results, particularly when neuroendocrine activity is being assessed under basal conditions.

In addition to the temporal issues surrounding the assessment of HPA axis activity, variations in assessment mediums may account for some of the contradictory findings within the cortisol/ACTH literature. Unlike ACTH, which is restricted to blood-based assessment only, cortisol may be assessed via several pathways. Cortisol is most commonly assessed via saliva, urine, or plasma, but may also be assessed via cerebrals spinal fluid (CSF). Each of these pathways, however, do not reflect cortisol in a standardized manner. For example, whereas plasma and saliva samples mediate cortisol levels 1-2 hours prior to the assessment (Baum &

Grunberg, 1995), urine samples are usually collected over a 24-hour period to account for diurnal variation (Handwerger, 2009). Consequently, results may vary depending on the sample method used. For example, Levine and colleagues (Levine, Zagoory-Sharon, Feldman, Lewis, & Weller, 2007) caution researchers when comparing salivary measurements to other sampling methods, demonstrated by the decrease in salivary cortisol when converted to cortisone by 11-beta-hydrosteroid dehydrogenase type 2.

Another possible explanation for the contradictory findings suggesting higher levels of baseline cortisol in individuals with PTSD could be described by time elapsed since trauma. For example, some studies demonstrate increases in cortisol in the period directly following exposure to trauma (Bremner, 2001). Cortisol has additionally been shown to increase in response to acute stress among individuals with PTSD (Bremner et al., 2003). Thus, studies examining PTSD-positive individuals who have experienced multiple or sustained traumas have not found evidence for a significant relationship between PTSD-positive status and lower baseline levels (Lemieux & Coe, 1995; Pitman & Orr, 1990). This evidence could help explain why PTSD-positive individuals with consistent exposure to trauma or acute stress fail to display lower baseline cortisol levels. Handwerger and colleagues (2009) offer a physiological explanation for this for lack of lower basal cortisol output among PTSD individuals exposed to multiple traumas/stressors. They posit that, although the majority of studies report lower basal cortisol in PTSD, individuals with PTSD often display decreased hippocampal volume, typically associated with increased exposure to glucocorticoids, as evidenced by previous research (e.g., Bremner, Randall, et al., 1995; Gurvits et al., 1996). Thus, although PTSD may result in lower output of cortisol over time, sustained exposure to stress or trauma will continue to result in higher glucocorticoid (e.g., cortisol) output, even at baseline.

Handwerger et al. (2009) acknowledge that some evidence in the literature demonstrates lower cortisol levels in the "immediate aftermath" of trauma (McFarlane, Atchison, & Yehuda, 1997; Yehuda, Resnick, Schmeidler, Yang, & Pitman, 1998), but counter argue that obtaining neuroendocrine samples *immediately* following trauma is impossible and, thus, that cortisol samples collected during medical examination following a trauma may not actually be representative of cortisol levels present at the actual time of trauma. Hence, individuals who go on to develop PTSD may exhibit significantly higher cortisol levels immediately following exposure to trauma and, additionally, may exhibit significantly higher cortisol levels during traumatic reminders. These sustained or repeated high levels of cortisol may result in lasting glucocorticoid assault on the hippocampus (Handwerger, 2009).

Another explanation for inconsistent findings regarding HPA functioning in relation to PTSD involves issues concerning control groups. As previously discussed, Morris et al. (2012) propose the inclusion of TE individuals into control groups could be contributing to the inconsistent findings. Studies that have analyzed separate TE and NTC groups have reported conflicting results. Some studies have found neuroendocrine alterations following trauma irrespective of psychopathological diagnosis (De Kloet et al., 2007; Klaassens, Giltay, van Veen, Veen, & Zitman, 2010; Klaassens et al., 2009; Klaassens, van Veen, et al., 2010), whereas other studies have demonstrated changes in HPA functioning following trauma in relation to PTSD (Griffin, Resick, & Yehuda, 2005; Klaassens et al., 2012; Wessa et al., 2006; Yehuda et al., 2002).

Statement of the Problem

Ubiquitous rates of trauma exposure are seen in both civilian and veteran populations (e.g., Breslau et al., 1998; Hoge et al., 2004), and are associated with a number of debilitating mental health conditions, including PTSD (Amstadter et al., 2013). Numerous psychosocial factors, such as sleep (Maher et al., 2006), social support (Tsai et al., 2012), and trauma load (Dohrenwend et al., 2006) are related to risk for PTSD, and may also be related to HPA axis function. Indeed, biological factors are also essential in understanding PTSD etiology, accounting for approximately one third of the variance (Amstadter et al., 2012). Of biologic systems investigated in relation to PTSD, the HPA axis has received much attention and is a commonly implicated system in the etiology of PTSD (Yehuda, 2000). Although the extant literature provides an abundance of important data on HPA axis biomarkers in relation to PTSD, studies examining basal cortisol and ACTH in a three group design (PTSD, TE, NTC) are less common and findings are highly variable. Additionally, cortisol and ACTH are infrequently assessed within the same sample and few studies have investigated these associations in OIF/OEF/OND veterans. The disparate findings stemming from a plethora of investigations is likely the result of several methodological issues (e.g., standardization, various assessment mediums, study design), but could also potentially be explained by a lack of examination of key moderators that may influence the relationship between PTSD and neuroendocrine markers.

Although previous researchers have examined the associations between PTSD and key psychosocial and environmental variables such as social support, sleep, and trauma load, no studies to our knowledge have simultaneously investigated these factors as potential moderators of the relationship between PTSD and basal neuroendocrine levels. For example, although social support has been evidenced as a dominant risk factor for PTSD, as well as an influential factor in neuroendocrine reactivity following stress (Kirschbaum et al., 1995; Ozbay et al., 2008; Steptoe

et al., 2004), no studies to our knowledge have examined the influence of social support on the relationship between PTSD and HPA-axis activity.

The present study utilized data from an ongoing R01 (AA020179; PI Amstadter), which examines the effects of trauma on stress reactivity and subsequent drinking behavior in OIF/OEF/OND veterans aged 21-40 years old, to test whether genetic variation mediates these relationships. This unique sample provides valuable data on psychosocial factors and basal neuroendocrine activity among a young military population, one which is largely comprised of individuals at highest risk for combat exposure (Hoge et al., 2004).

Aims and Hypotheses

The present study aimed to compare baseline neuroendocrine levels by trauma group (PTSD, TE, NTC) among a sample of OIF/OEF/OND veterans. More specifically, the main aim was to examine basal cortisol and ACTH to test whether levels differ significantly by trauma group. Based on the effects of the HPA axis negative feedback loop, wherein chronically elevated levels of ACTH may result in lower basal cortisol, it was hypothesized that individuals in the PTSD group will demonstrate significantly lower cortisol levels at baseline, compared to both TE and NTC groups. Considering the HPA axis among individuals with PTSD may operate as it would in response to stress in healthy individuals at resting conditions suggests a sustained production of ACTH, even at baseline. Therefore, it was hypothesized that individuals in the PTSD group would demonstrate significantly higher baseline ACTH levels than those in the TE and NTC groups. However, due to the negative feedback loop within the HPA axis, wherein increased ACTH should signal the termination of cortisol release to return to homeostasis, it was hypothesized that lower levels of cortisol at resting state among individuals with PTSD may be

found. Based on common findings in the extant literature, it was hypothesized that basal neuroendocrine levels would not differ between the TE and NTC groups, suggesting a unique contribution of HPA axis activity to PTSD.

A second, exploratory aim of this study was to examine factors that may moderate the relation between PTSD symptom severity and basal neuroendocrine levels. Given the robust effect sizes for social support demonstrated in the PTSD literature, which suggest that social support is among the strongest predictors of PTSD following trauma (e.g., Brewin et al., 2000), as well as the evidenced effects of social support on neuroendocrine activity (e.g., Ozbay et al., 2008), it was hypothesized that deployment unit social support and post-deployment social support would moderate the relationship between PTSD symptom severity and basal cortisol and ACTH, serving as a buffer between PTSD and neuroendocrine activity, such that higher levels of social support would weaken the inverse relationship between PTSD and basal cortisol and weaken the positive relationship between PTSD and ACTH.

Additionally, given the distinct relationships between both sleep and PTSD, as evidenced by the high prevalence of sleep disturbance symptoms among individuals with PTSD, and sleep and the HPA-axis, as evidenced by the importance of the HPA-axis in sleep onset, maintenance, and awakening, sleep is a discernable variable which may act to influence the relationship between PTSD severity and HPA-axis activity. If disturbed, sleep is associated with both increased PTSD severity and HPA-axis dysregulation; poor sleep quality may serve to influence the relationship between PTSD and HPA-axis activity. Thus, it was hypothesized that sleep disturbance would moderate the relationship between PTSD symptom severity and cortisol and ACTH, such that higher sleep disturbance would strengthen the inverse relationship between

PTSD and basal cortisol and strengthen the positive relationship between PTSD and symptom severity ACTH.

Furthermore, as demonstrated in the literature, cumulative effects of trauma have profound effects on psychopathology and physiological functioning. Therefore, given the low conditional risk for PTSD, examination of trauma exposure, regardless of psychological diagnosis, is critical in elucidating whether the effects of PTSD symptom severity on HPA-axis activity are influenced by cumulative trauma load. To that end, as a result of the powerful influence of cumulative trauma load on subsequent physical and mental health functioning, it was hypothesized that trauma load would moderate the relationship between PTSD and basal cortisol and ACTH, such that higher levels of combat severity and lifetime trauma load would strengthen the inverse relationship between PTSD and cortisol and strengthen the positive relationship between PTSD and ACTH.

Method

Overview of the Study

The present study included data from 155 participants from a larger ongoing study examining the effect of trauma on stress reactivity and subsequent drinking behavior in OIF/OEF/OND veterans (R01 AA020179; PI Amstadter). Data collection began in the winter of 2011, and will continue until June 2016. Potential participants were screened via telephone or REDCap. REDCap is a secure web-based application designed exclusively to support data capture for research studies (Harris et al., 2009). Individuals meeting basic eligibility criteria completed an office visit assessment, and those meeting final eligibility criteria were brought to

the Clinical Research Services Unit (CRSU) to complete the lab visit. Half of participants from each group were randomized to receive the Trier Social Stress Test (TSST); the other half received a no-stress control condition. Baseline and post-stress objective and subjective measures of stress reactivity were collected. Following the stress task, all participants received a "priming dose" of alcohol, followed by a deceptive "taste test" task, where amount of alcohol consumed served as the primary dependent variable for the parent study. The Virginia Commonwealth University and Richmond McGuire VA Institutional Review Boards approved all study procedures and informed consent was obtained from all study participants. Data for the present study included information from the clinical interview and self-report assessments administered in the office session, as well as the baseline neuroendocrine assessments from the lab session.

Recruitment

Participants were recruited through the community, as well as the university and Veteran's hospitals, by advertising (e.g., flyers, internet), and through collaborations with other researchers. Mailings were distributed to local veterans within the 21-40 year old age range via the local Veteran's hospital. Mailed materials included study brochures and an "Initial Contact" cover letter, used to inform potential participants that they may be called by research staff and provide a phone number that the recipient could call to confirm that the study constitutes VA research, as well as a phone number that recipients could call to "opt out" of future contact. Individuals who "opted out" were removed from future mailing and calling lists for the parent study. In addition to the mailings, calls to potential participants were made after sending the brochure and the initial contact letter. Interested individuals completed an eligibility screener for major inclusion and exclusion criteria via the telephone or online through REDCap.

Inclusion/Exclusion Criteria

Inclusion criteria for the parent study included an age between 21-40 years old and the ability to provide informed consent. Because alcohol was administered in the parent study, participants had to be regular drinkers (i.e., drink alcohol on at least 4 days in the month prior to the screener) and drink beer, but could not meet DSM-IV criteria for current alcohol dependence nor be seeking treatment for alcohol dependence. Exclusion criteria included history of a moderate or severe traumatic brain injury (TBI), the presence of a condition that affected HPA-axis functioning (e.g., individuals taking psychoactive medications, antihistamines, or anti-inflammatory medications; alcohol dependence; Major Depressive Disorder; hypertension, chronic pain, Addison's disease) and factors that would affect stress or stress hormones (e.g., smokers who could not abstain from smoking for at least 4 hours, severe obesity [i.e., BMI $\geq$ 40]). With the exception of nicotine and caffeine, and possibly marijuana (if the participant could abstain), participants could not be dependent on other drugs. Additionally, pregnant or nursing women, or women who suspected they may be pregnant were excluded from participation. Individuals with any blood clotting disorder were also excluded due to the blood draw component of the study.

Eligibility Screening

The eligibility screener, which was administered via telephone or via an online screening tool, assessed for age, past month drinking status and preference, potential alcohol dependence, presence of a TBI, presence of conditions that affect HPA-axis functioning, factors that affect stress or stress hormones, and disorders that affect blood clotting. The screener also assessed

potential substance use disorder and past month drug use. Women were queried about the potential of pregnancy or nursing. In total, 863 screeners have been conducted to date, with 275 individuals qualifying for the office visit. Major reasons for disqualification include use of psychoactive medications and MDD.

Participants

Descriptive statistics for the parent study sample. The parent study sample (i.e., participants who completed at least the office visit) was comprised of 236 participants (89.6% male; M_{age}=29.28, SD=4.28). The sample was comprised of participants who self-identified as White (76.2%), Black (15.8%), and Other (7.9%). 48% of participants had never been married at the time of assessment, 13.4% were separated/divorced, 34.2% were married or cohabitating, and 0.5% were widowed. 7.4% of participants were high school or GED graduates. Over half of the sample had completed some college (55.4%), 24.9% were college graduates, and 8.4% had completed more than a bachelor's degree. The majority of the sample had an annual income of $50,000 or less (71.3%).

Descriptive statistics for the present study sample. Not all participants who complete the office visit qualify for the laboratory visit. In order to be included in the present study, participation in both sessions was required, as neuroendocrine data are collected at the second study visit. Descriptive statistics from the present study sample closely mirror those from the parent study sample, as they represent a proportion of the larger parent sample. The sample for the present study was comprised of 155 participants (90.3% male; M_{age}=29.36, SD=4.31). Because stricter criteria were used to determine group status, analyses examining the effects of trauma group will have a smaller sample size (N=117). Said groups were categorized as PTSD

(n=32), TE (n=51), or NTC (n=34). Additionally, PTSD symptom severity was determined using the DSM-IV diagnostic criteria, rather than the extreme discordant severity score criteria to determine group status. Therefore, analyses examining the predictive effects of PTSD symptom severity will be conducted with a more inclusive sample (N=155).

The restricted sample used for analyzing trauma group differences (N=117) was comprised of participants who self-identified as White (75.0%), Black (15.4%), and Other (9.6%). 46.3% of participants had never been married at the time of assessment, 16.9% were separated/divorced, 35.3% were married or cohabitating, and 1.5% were widowed. 8.8% of participants were high school or GED graduates. Over half of the sample had completed some college (52.9%), 28.7% were college graduates, and 9.6% had completed more than a bachelor's degree. The majority of the sample had an annual income of $50,000 or less (75.7%). The majority of the sample had an annual income of $50,000 or less (74.6%). The majority of individuals in the total sample had served in the Army (58.8%), followed by Marines (14.0%) and Navy (8.8%). Most participants in the total sample had served as Enlisted soldiers, with the majority ranked from E-4 to E-6 (81.6%).

The more inclusive sample used for analyzing PTSD symptom severity (N=155) was comprised of participants who self-identified as White (76.7%), Black (14.0%), and Other (9.3%). 45.3% of participants had never been married at the time of assessment, 14.7% were separated/divorced, 39.3% were married or cohabitating, and 0.7% were widowed. 8% of participants were high school or GED graduates. Over half of the sample had completed some college (56%), 26.7% were college graduates, and 9.3% had completed more than a bachelor's degree. The majority of the sample had an annual income of $50,000 or less (74.6%). The majority of individuals in the total sample had served in the Army (57.3%), followed by Marines

(17.3%) and Army National Guard (8.7%). Most participants in the total sample had served as Enlisted soldiers, with the majority ranked from E-4 to E-6 (80.7%). Data for the present study was frozen on 08/21/2015.

Procedures

Office session. Individuals meeting preliminary criteria came in for an office visit. The office visit included the provision of informed consent, a clinical interview, and a battery of self-report measures to assess combat exposure, traumatic event exposure history, alcohol use, lifetime and past month PTSD, and other psychopathology and psychological characteristics. The majority of the structured clinical interviews were conducted by post-doctoral fellows; however, some interviews were conducted by MSWs and advanced doctoral psychology students. All interviews were recorded on audiotape and will be assessed to determine inter-rater reliability. Following the office visit, participants who did not meet criteria for the second session were compensated for their time. Reasons for disqualification following the office session included a diagnosis of past but not current PTSD or other comorbidities, such as a diagnosis of any Axis I disorder. Of the 297 individuals who completed the eligibility screen and qualified for the office session, 234 completed the office session. Of the participants who completed the office session, 71% qualified for the laboratory visit, and 68% completed the laboratory session. Of the participants who qualified for the laboratory visit, 96% completed it. Of the 4% of participants who qualified for the laboratory visit but did not participate in it, 1 declined to participate due to a family conflict, 1 was called to Active Duty, 1 decided to quit drinking alcohol, and 4 were lost to follow-up.

Group assignment. To be eligible for the Non-Trauma Control (NTC) group,

participants could not have a history of a Criteria A traumatic event (combat or otherwise; DSM-IV Criteria A requires that the person has experienced, witnessed, or been confronted with an event or events that involve actual or threatened death or serious injury, or a threat to the physical integrity of oneself or others, and that the person's response involved fear, helplessness, or horror; American Psychiatric Association, 1994).

To be eligible for the Combat Trauma Exposed group (TE), participants must have had a history of a Criteria A combat traumatic event during OIF/OEF deployment, but not have met the DSM-IV criteria for PTSD (Current or Lifetime), as defined by a Clinician Administered PTSD Scale (CAPS) score of ≤ 19. If individuals endorsed more than one form of combat traumatic event exposure, the combat event personally deemed the "worst" was used as the index trauma. Other than the time frame of OIF/OEF deployment, there was no restriction on the timing of the "worst" trauma. No restriction on the timing of the trauma was decided based on data that clearly indicates that PTSD can result from both recent (within the past year) and distant (greater than one year) TE exposure (Teicher et al., 2003; Waldrop, Santa Ana, Saladin, Brady, & McRae, 2007; Weems & Carrion, 2007).

To be eligible for the PTSD group, participants must have had a history of combat trauma, meeting Criteria A, and have met current criteria for PTSD, as defined by DSM-IV (exposure to a Criteria A event, endorsement of at least 1 cluster B symptom, 3 or more cluster C symptoms, at least 2 cluster D symptoms, and functional impairment) and a CAPS severity score of ≥ 45.

Laboratory session instructions. Eligible participants were instructed not to eat after noon on the day of their scheduled laboratory visit, and to avoid caffeine on that day, as both food and caffeine can introduce noise variability to the neuroendocrine response to the stressor. If the individual was a smoker, he/she was asked to smoke his/her last cigarette between 3:00 and 4:00

pm on that day, to prevent nicotine withdrawal that might influence neuroendocrine activity. Participants were also instructed to avoid alcohol in the 48 hours prior to the test date. Additionally, participants were cautioned to abstain from use of drugs in the weeks prior to the challenge day, as they would need to pass a urine drug test on the challenge day. Women were scheduled for the laboratory session during the follicular phase of their menstrual cycle, which is the period of the menstrual cycle when both estrodial and progesterone are low; testing all women during this phase served to reduce variability within women and between the genders.

Laboratory Session

Participants meeting inclusion criteria were urn randomized by gender and at-risk drinking to receive either the stress condition or the no-stress condition for the aims of the parent study. Urn randomization allows for equal distribution between experimental conditions, as it decreases the probability of being assigned to a certain experimental group if the group is overrepresented and vice versa (i.e., the more individuals in the stress condition, the less likely the next participant is to be randomized into that condition; Schulz & Grimes, 2002).

The individual arrived at the clinical research services unit (CRSU) at 4:00 pm on the challenge day, at which time, (s)he was breathalyzed and asked to provide a urine sample, which was tested for presence of marijuana, opiates, barbiturates, benzodiazepines, and stimulants. For female participants, a pregnancy test was administered (to ensure safety of the alcohol administration component of the parent study). When both tests came back negative, the participant was fitted with an indwelling catheter to facilitate blood draws (which were assayed for ACTH and cortisol) and a blood pressure cuff at approximately 4:15 pm. The participant acclimated for one hour to the testing room (4:00 to 5:00pm). Two baseline assessments of stress

response measures were collected: one at approximately 4:40pm and the second at approximately 4:55pm. Subjective units of distress (SUDS), blood pressure and heart rate were also assessed at baseline.

Parent study procedures. Figure 1 shows the experimental procedures and assessments collected at each time point during the laboratory visit for the full parent study. Notably, however, only data from the baseline assessments collected at 4:55pm were used in the present study. The decision to use the second baseline assessment was made to allow for further acclimation following the fitting of the indwelling catheter, with the aim of obtaining data that most closely resembles cortisol and ACTH at "resting state".

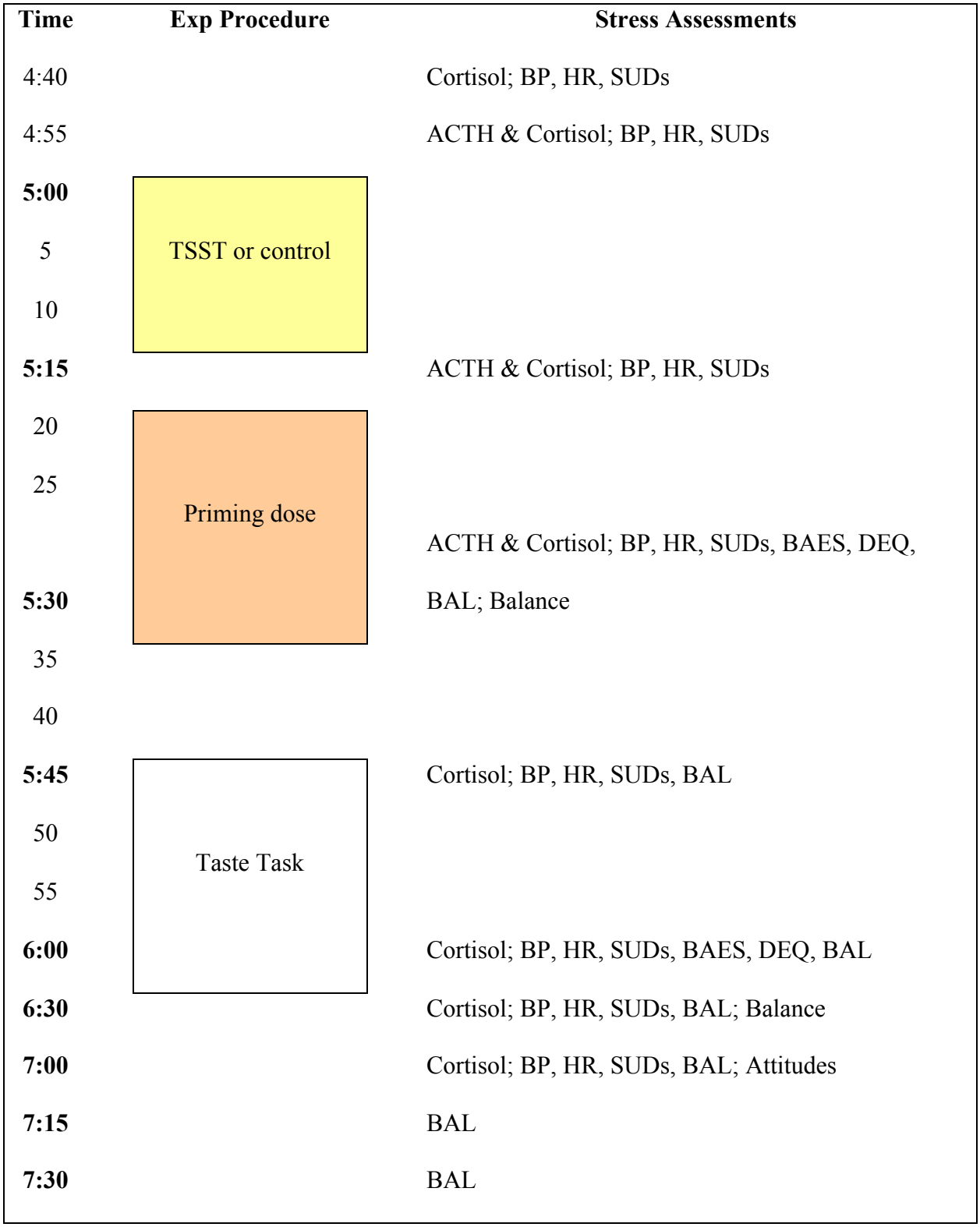


Figure 1. Overview of Laboratory Session Procedures

Dismissal. A breath alcohol analyzer was used to confirm that the reading was 10 mg% or lower prior to dismissal. All participants were given an information packet that includes information about services related to assessment and treatment of PTSD and related conditions.

Measures

Demographics. A demographics form was used to assess participant gender, race, ethnicity, marital status, education, annual income, employment status, military status, and smoker status. Age, weight, and height were also assessed, in addition to military branch, rank, and status. Information regarding participant deployments was obtained in the demographics form, as well as information regarding post-deployment difficulties and resources. Race and ethnicity were dummy coded into a "White, Non-Hispanic vs. other" variable, which was entered into the model.

Clinician Administered PTSD Scale (CAPS) (Blake et al., 1990). The CAPS is a diagnostic interview for current and lifetime PTSD. The CAPS demonstrates high inter-rater reliability (i.e., above .86) and internal consistency on each of the three PTSD symptom clusters (range .63 to .89), and correlates strongly (i.e., above .61) with other measures of PTSD (Hovens et al., 1994; Hyer, Summers, Boyd, Litaker, & Boudewyns, 1996). Since the beginning of the study, the APA released the DSM-V that included changes to the PTSD criteria. However, eligibility was still based on DSM-IV criteria. Total internal consistency for this measure within the present sample was .87. Internal consistency for the re-experiencing subscale within the present sample was .73. Internal consistency for the avoidance subscale within the present sample was .78. Internal consistency for the hyper-arousal subscale within the present sample was .65.

Mini-International Neuropsychiatric Interview (MINI) (Lecrubier et al., 1997). The clinician-delivered structured clinical interview (MINI version) using DSM-IV criteria was used to assess potential participants for presence of exclusionary major Axis I disorders as well as to confirm eligibility for individuals in the PTSD group. This measure demonstrates excellent inter-rater reliability, with all kappa values above 0.75 and the majority over 0.90 or higher. Furthermore, the majority of kappas for test-retest reliability were above 0.75, indicating very good test-retest reliability (Sheehan et al., 1997).

The Life Events Checklist (LEC) (Gray, Litz, Hsu, & Lombardo, 2004). The LEC assesses trauma exposure history, including a list of 17 potentially traumatic events (e.g., sexual assault, physical assault). Participants indicate whether they have experienced each event, have witnessed the event happening to someone else, or have learned about the event happening to someone close to them. The LEC has been shown to have a mean kappa of .61 and a retest correlation of $r = .82$, $p < .001$ (Gray et al., 2004).

The Deployment Risk and Resiliency Inventory (DRRI) (King, King, & Vogt, 2003). The DRRI is a series of scales assessing 14 key deployment-related risk and resilience factors with demonstrated implications for veterans' long-term health including the veteran's exposure to various combat-related experiences, level of social support prior to and following deployment and the effect of deployment on family life. Estimates of internal consistency reliability were .85 or higher for all DRRI scales (Vogt, Samper, King, King, & Martin, 2008). The Unit Social Support Scale (USS) and Post-deployment Social Support Scale (PSS) was used to examine deployment and post-deployment social support in the moderation analyses. Internal consistency for the USS subscale in the present sample was .90. Internal consistency for the PSS subscale in the present sample was .85. The Combat Experiences Scale (CES) was used to examine combat trauma load

and the Pre- and Post-deployment stressful event scales were aggregated to assess lifetime trauma load in the moderation analyses. Internal consistency for the Combat Experience Scale (CES) within the present sample was .88. Internal consistency for Lifetime Trauma Load within the present sample was .73.

Pittsburg Sleep Quality Index (PSQI) (Buysse et al., 1989). The PSQI is a self-report instrument that measures sleep quality and disturbance over a 1-month period (Carpenter & Andrykowski, 1998). The PSQI has 9 questions and 19 items. All scores are combined to derive a Global PSQI Score. There are seven subscales: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime functioning. The PSQI has an item that queries nightmares. Clinically meaningfully disturbed or poor sleep of the insomnia type is indicated with Global PSQI Scores above 5 ($\leq$5 are considered normal, 6-10 = moderately impaired sleep; $\geq$11 = severely impaired sleep). The Global PSQI score was be used to examine sleep disturbance in the analyses. Internal consistency for this measure within the present sample was .76.

Subjective Units of Distress (SUDs) (Wolpe, 1958) is a self-report instrument designed to measure subjective distress levels on a scale of no distress at all (0) to extreme distress (10) following a potentially anxiety provoking stimuli. The measure was assessed numerous times throughout the study. SUDs was examined as a potential covariate if trauma groups differ at baseline.

ACTH and cortisol assays. Blood samples for buffy coat and plasma storage were collected in 1 x 10 ml standard EDTA tubes. Plasma was separated from cells by centrifugation, and the serum samples were stored at -80 C until thawed for assay. Cortisol and ACTH were assayed using the ELISA immunoassay system (ALPCO Diagnostics, Salem, NH).

Data Analytic Plan

Post hoc statistical power analyses were conducted using G*Power software (Faul, Erdfelder, Buchner, & Lang, 2009) for the proposed hypotheses. The power to detect a medium-sized effect (f=.25; Cohen, 1988) for the MANOVA at an alpha level of .05 in the present sample was determined to be >.99. Considering tests of moderation are traditionally low in power, a power analysis was also conducted for the exploratory aim, with the effect size anticipated for the moderator effect (i.e., the anticipated incremental variance explained by the joint effect above and beyond the additive effects). The power to detect a medium-sized moderator effect (f^2=.15; Cohen, 1988) at an alpha level of .05 in the present sample was determined to be >.99.

First, all variables were assessed for univariate normality and for outliers. Second, key demographic variables (e.g., age, race/ethnicity, sex) were examined in relation to cortisol and ACTH levels to test for inclusion as possible covariates in the tests of group differences and in the regression analyses. To address the primary aim, two one-way analyses of variance (ANOVAs) were conducted, one with cortisol as the dependent variable and one with ACTH as the dependent variable. The independent variable in both ANOVAs was trauma group (PTSD, TE, NTC). In the presence of a nominally significant ANOVA, post-hoc testing was conducted to determine which groups were driving the effects.

To address the exploratory aims, ten separate hierarchical regression analyses were conducted within the more inclusive sample (N=155), one regression for each potential moderator for each neuroendocrine marker. First, two hierarchical regression analyses were conducted to evaluate the hypothesized influence of unit social support during deployment on the relation between PTSD and basal neuroendocrine levels with cortisol and ACTH as the dependent

variables. Second, two hierarchical regression analyses examined the influence of post-deployment social support on the relation between PTSD and cortisol and ACTH. Third, two hierarchical regression analyses were conducted to evaluate the hypothesized influence of sleep disturbance on the relation between PTSD and basal neuroendocrine levels with cortisol and ACTH as the dependent variables. Fourth, four hierarchical regression analyses were conducted to evaluate the hypothesized influence of trauma load (two regressions examining combat severity and two regressions examining lifetime trauma load) on the relation between PTSD and basal neuroendocrine levels with cortisol and ACTH as the dependent variables. Prior to the analyses, the independent and moderator variables were centered and a product term created from the centered variables (Baron & Kenny, 1986). Significant demographic variables were controlled for in step 1, PTSD symptom severity was entered independently in step 2, the additive effects were entered in step 3, and the product term was entered in step 4 of the model. Correction for multiple testing was done via a Bonferroni adjustment.

Results

Descriptive Statistics

Descriptive statistics by group can be found in Table 1. The mean age of participants in the total sample (N=155) was 29.36 (*SD*=4.31), and the majority of participants were male (90.3%), and 74.2% were white/non-Hispanic.

The NTC (n=34), TE (n=51), and PTSD (n=32) groups did not differ among any demographic variables, but were significantly different with regards to a number of other variables. By design of the inclusion and exclusion criteria, the group means differed

significantly for PTSD symptom severity, F (2, 97 = 137.43, $p < .001$, partial η^2=.75, with the NTC (M = 9.83, SD = 5.36) and TE (M = 10.12, SD = 8.32) groups having significantly lower scores than the PTSD group (M = 52.18, SD = 17.11, $p < .001$). Expectedly, mean scores of PTSD symptom severity did not differ significantly between NTC and TE groups ($p = .997$). Trauma group means also differed significantly for post-deployment social support, F (2, 120) = 6.93, $p = .001$, partial η^2=.10. Notably, lower scores on the PSS subscale indicated greater endorsement of support. Thus, individuals in the TE (M = 30.37, SD = 8.58) group endorsed significantly higher levels of post-deployment social support than the PTSD group (M = 35.58, SD = 9.23, $p = .021$). NTC post-deployment social support levels (M = 29.17, SD = 6.66) did not significantly differ from those of the PTSD group ($p = .075$) or from the TE group ($p = .901$).

Additionally, trauma group means differed according to combat exposure severity, F (2, 120) = 8.35, $p < .001$, partial η^2=.12, with individuals in the TE (M = 5.54, SD = 3.44) group reporting significantly lower combat exposure severity than the PTSD group (M = 8.18, SD = 3.92, $p = .005$). Notably, however, combat exposure severity levels in the NTC group (M = 6.0, SD = 3.95) did not significantly differ from those in the PTSD group ($p = .188$). Mean scores of combat exposure severity did not differ significantly between NTC and TE groups ($p = .919$). Furthermore, group means differed significantly for lifetime trauma load, F (2, 120) = 11.45, $p < .001$, partial η^2=.16, with the NTC (M = 3.08, SD = 2.31) and TE (M = 6.31, SD = 3.82) groups endorsing significantly lower lifetime trauma load than the PTSD group (M = 8.45, SD = 3.30, $p < .001$, $p = .019$, respectively). Mean scores of lifetime trauma load also differed significantly between NTC and TE groups ($p = .014$). Lastly, trauma group mean scores for sleep disturbance differed significantly, F (2, 120) = 13.19, $p < .001$, partial η^2=.18, such that individuals in the NTC (M = 4.08, SD = 1.98) and TE (M = 6.0, SD = 3.66) groups endorsed significantly lower

sleep disturbance than individuals the PTSD group ($M = 9.42$, $SD = 3.41$, $p < .001$ for both comparisons). Mean scores of sleep disturbance did not differ significantly between NTC and TE groups ($p = .192$).

Table 1.

Descriptive Statistics by Trauma Group

	Control (n=34)	TE (n=51)	PTSD (n=32)	Total	
Variable	Mean (SD)	Mean (SD)	Mean (SD)	*F*	*p*
Age	29.50 (3.93)	30.76 (4.32)	29.78 (5.00)	.874	.421
PTSD Symptom Severity	9.83 (5.36)	9.6 (7.55)	52.97 (16.76)	154.28	.000[b,c]
Trauma Load	4.65 (3.41)	6.31 (3.85)	8.56 (3.29)	11.14	.000[a,b,c]
PSQI	5.35 (3.09)	5.92 (3.65)	9.50 (3.44)	15.43	.000[b,c]
PSS	29.53 (7.33)	30.25 (8.62)	36.00 (9.04)	5.21	.007[b]
USS	28.41 (10.04)	31.45 (10.76)	30.34 (10.82)	1.18	.312
CES	4.50 (3.57)	5.49 (3.46)	8.03 (3.88)	4.81	.010[b]
SUDS	0.21 (0.23)	0.19 (0.23)	0.31 (0.24)	2.58	.081
	%	%	%	Total	
				X^2	*p*
Gender				5.95	.051
Males	100	85.0	87.2		
Race				5.57	.234
White	83.3	66.1	79.5		
African American	8.3	23.7	10.3		
Other	8.3	10.2	10.3		
Ethnicity				3.92	.141
Hispanic	5.4	5.0	15.4		
Non-Hispanic	94.6	95.0	84.6		
Education				1.147	.979
High School	8.3	8.5	10.3		
Some College	52.8	49.2	56.4		
College	30.6	32.2	23.1		
More Than College	8.3	10.2	10.3		
Marital Status				5.0	.544
Never Married	44.4	42.4	53.8		
Separated /Divorced	11.1	23.7	12.8		
Married or Cohabitating	41.7	32.2	33.3		
Widowed	2.8	1.7	0.0		
Military Branch				8.84	.841
Army	55.6	50.8	71.8		
Marine Corps	13.9	16.9	10.3		
Navy	8.3	11.9	5.1		
Air Force	5.6	3.4	2.6		
Army National Guard	5.6	8.5	10.3		
Army Reserves	2.8	1.7	0.0		
Marine Reserves	5.6	5.1	0.0		
Military Rank				16.14	.583
Enlisted	89.0	91.6	84.7		
Officer	11.0	8.4	15.3		

Note:
[a] Significant difference between NTC and TE

[b] Significant difference between TE and PTSD
[c] Significant difference between NTC and PTSD
PSQI=Pittsburg Sleep Quality Index
PSS= Post-deployment Social Support Scale
USS= Unit Social Support Scale
CES= Combat Experiences Scale
SUDs= Subjective Units of Distress
*p<.05;**p<.01;***p<.001

Tests of Univariate Normality

Prior to analyses, all variables were assessed for univariate normality. Variables with violations in skewness or kurtosis, as defined by having an absolute z-value (skewness or kurtosis/standard error) over 3.29, were log-transformed (Kim, 2013). Log-transformations were conducted for cortisol, ACTH, and SUDs. Following log-transformation, one outlier on ACTH was removed for having a value that exceeded 3 standard deviations beyond the mean. Notably, because the number of participants in each group was not equal and tests of ANOVA assume equal variances across groups, a hypothesis test was performed to validate the assumption, (i.e., Levene's Test) and showed that the assumption of homogeneity of variance was met for each group for both cortisol and ACTH, F (2, 117) = 2.772, p = .067; F (2, 115) = 2.189, p = .117, respectively. Notably, these tests are not powerful to detect small deviations; however, they are able to detect larger deviations. Additionally, deviation from heterogeneity of variance was checked by inspecting residual plots, which showed that all group variances approximated normality.

Determination of Covariates for Trauma Group Difference Analyses

The determination if covariates should be used (i.e., ANCOVA vs. ANOVA) was done in a two-step process. First, variables found to be significantly correlated with either cortisol or

ACTH within the restricted sample (n=117) were entered into two hierarchical linear regressions in order to determine the unique contribution of each potential covariate on both cortisol and ACTH. Age was negatively associated with cortisol, $r(115) = -.21$, $p = .025$. White/Non-Hispanic status was negatively associated with ACTH, $r(115) = -.16$, $p = .04$. Conversely, post-deployment social support was positively associated with ACTH, $r(115) = .20$, $p = .029$. Lifetime trauma load was negatively associated with cortisol $r(115) = -.20$, $p = .03$. Lastly, SUDS was positively associated with cortisol, $r(115) = .20$, $p = .027$. Second, significantly correlated variables (i.e., age, white/non-Hispanic status, post-deployment social support, lifetime trauma load, and SUDs) were entered in the first step and trauma group was entered in the final step of each hierarchical regression (one predicting basal cortisol and one predicting ACTH). Partial correlation coefficients were examined to determine the amount of variance estimated by each variable, independent of the variance estimated by other variables in the model. Because all variables demonstrated small effect sizes (Cohen, 1988), no covariates were included and ANOVAs were conducted.

Aim 1 Results: Examine Whether Baseline Cortisol and ACTH Differ by Trauma Group

ANOVAs. Two one-way analyses of variance (ANOVAs) were conducted, one with cortisol as the dependent variable and one with ACTH as the dependent variable. The independent variable in both analyses was trauma group (NTC, TE, PTSD). The difference in levels of basal cortisol between trauma groups was nominally significant, $F(2, 119) = 2.996$, $p = .054$. Because difference in basal cortisol showed a nominally significant p-value, post-hoc comparisons were conducted to determine from where the effect was driven. Post-hoc comparisons using the Tukey HSD test indicated that the mean basal cortisol level for NTC

individuals (M = 9.94, SD = 5.33) was significantly higher than the mean basal cortisol level for individuals in the PTSD group (M = 7.01, SD = 2.34, p = .049). The TE group (M = 8.34, SD = 5.24) did not differ significantly from either the NTC (p = .18) or PTSD (p = .70) groups. A second one-way ANOVA indicated that there was not a significant effect of trauma group on ACTH, F (2, 117) = .045, p = .96.

Table 2.

Correlations Between Study Variables Within the Total Sample

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1) Age	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2) ACTH	-.036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3) Cortisol	-.156	.305**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4) USS	-.143*	.052	-.049	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5) PSS	-.117	.174*	.044	.422**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6) CES	-.087	-.033	-.035	-.183**	.047	-	-	-	-	-	-	-	-	-	-	-	-	-	-
7) Lifetime	.090	-.084	-.243**	.075	.174**	.120	-	-	-	-	-	-	-	-	-	-	-	-	-
8) PSQI	-.112	.091	-.144	.144*	.291**	.118	.223*	-	-	-	-	-	-	-	-	-	-	-	-
9) CAPS	-.096	-.003	-.201*	.080	.376**	.345**	.304**	.528**	-	-	-	-	-	-	-	-	-	-	-
10) SUDS	-.114	-.014	.119	-.002	.189*	.083	-.006	.182*	.300**	-	-	-	-	-	-	-	-	-	-
11) Gender	.029	-.064	-.114	-.044	-.046	-.226**	.038	.097	.019	-.022	-	-	-	-	-	-	-	-	-
12) Race	.093	.130*	-.022	-.059	-.067	-.106	.059	.011	-.015	-.049	.078	-	-	-	-	-	-	-	-
13) Ethnicity	-.064	.012	.222**	-.017	-.059	.109	-.057	-.082	-.109	.124	.052	-.037	-	-	-	-	-	-	-
14) Marital Status	.267**	-.096	-.183**	-.033	-.081	-.069	-.059	-.051	-.034	-.093	.036	-.052	-.097	-	-	-	-	-	-
15) Education	.245**	-.071	-.046	-.108*	-.131*	.028	-.077	-.089	-.030	-.087	.048	-.021	.140	.029	-	-	-	-	-
16) Income	.299**	-.030	-.092	-.050	-.061	.115*	.030	-.117*	.015	-.076	.046	-.119*	-.024	.224**	.206**	-	-	-	-
17) Employment	-.236**	-.026	.113	.078	.051	-.060	-.084	.063	-.014	.093	.018	.033	-.041	-.175**	-.032	-.453**	-	-	-
18) Branch	.001	.073	-.003	-.011	.032	-.217**	-.070	-.059	-.092	.073	.033	.065	-.104	.022	-.086	-.120*	.095	-	-
19) Rank	.242**	-.019	-.086	-.185**	-.108*	.013	-.033	-.075	-.104	-.131	.059	-.082	-.124*	.126*	.331**	.364**	-.141*	-.076	-

*p<.05;**p<.01;***p<.001
Note: USS= Unit Social Support Scale
PSS= Post-deployment Social Support Scale
CES = Combat Experiences Scale
PSQI= Pittsburg Sleep Quality Index
CAPS = Clinician Administered PTSD Scale

Aim 2 Results: Examine Potential Moderators of the Relation between PTSD Symptom Severity and Neuroendocrine Activity

Correlations among study variables are shown in Table 2. Variables significantly correlated with cortisol were controlled for in Step 1 of all of the models examining cortisol as the outcome variable (i.e., marital status and lifetime trauma load). Lifetime trauma load was excluded as a covariate in the analysis examining lifetime trauma load as a potential moderator.

Similarly, factors significantly correlated with ACTH were controlled for in Step 1 of all of the models examining ACTH as the outcome variable (i.e., post-deployment social support).

Social support. Hierarchical regression analyses evaluated the hypothesized influence of social support on the relation between PTSD symptom severity and both basal cortisol and ACTH. Neither unit social support nor post-deployment social support significantly moderated the relation between PTSD symptom severity and either cortisol or ACTH. Lifetime trauma load was the only significant predictors of cortisol in the Step 4 for both USS and PSS, $\beta = -.216$, t (117) = -2.321, $p = .022$; $\beta = -.224$, t (117) = -2.448, $p = .016$, respectively. No variables significantly predicted ACTH for either USS or PSS. Please refer to Tables 3-6 for detailed results.

Table 3.

Post-Deployment Social Support - Cortisol

	Cortisol				
Variable	β	SE	*t*	*p*	ΔR^2
PSS					
Step 1					.089
Lifetime Trauma Load	-.243	.005	-2.79	.006	
Marital Status	-.171	.019	-1.97	.052	
Step 2					.011
Lifetime Trauma Load	-.213	.005	-2.35	.020	
Marital Status	-.174	.019	-2.00	.048	
PTSD Severity	-.110	.001	-1.21	.229	
Step 3					.003
Lifetime Trauma Load	-.213	.005	-2.35	.021	
Marital Status	-.169	.020	-1.94	.055	
PTSD Severity	-.130	.001	-1.35	.178	
PSS	.061	.002	.653	.515	
Step 4					.006
Lifetime Trauma Load	-.224	.005	-2.45	.016	
Marital Status	-.168	.020	-1.92	.057	
PTSD Severity	-.105	.001	-1.05	.298	
PSS	.069	.002	.736	.463	
PSS*PTSD	-.085	.000	-.918	.361	

*p<.05;**p<.01;***p<.001

Note: PSS = Post-Deployment Social Support

Table 4.

Post-Deployment Social Support - ACTH

		ACTH				
Variable		β	SE	*t*	*p*	ΔR^2
PSS						
Step 1						.000
	PTSD Severity	-.003	.001	-.028	.977	
Step 2						.016
	PTSD Severity	-.050	.001	-.515	.607	
	PSS	.135	.003	1.40	.163	
Step 3						.004
	PTSD Severity	-.033	.001	-.328	.744	
	PSS	.140	.003	1.45	.150	
	PSS*PTSD	-.067	.000	-.711	.479	

*p<.05;**p<.01;***p<.001

Note: PSS = Post-Deployment Social Support

Table 5.

Unit Social Support – Cortisol

		Cortisol				
Variable		β	SE	*t*	*p*	ΔR^2
USS						
Step 1						.089
	Lifetime Trauma	-.243	.005	-2.79	.006	
	Marital Status	-.171	.019	-1.97	.052	
Step 2						.011
	Lifetime Trauma	-.213	.005	-2.35	.020	
	Marital Status	-.174	.019	-2.00	.048	
	PTSD Severity	-.110	.001	-1.21	.229	
Step 3						.000
	Lifetime Trauma	-.211	.005	-2.30	.023	
	Marital Status	-.172	.020	-1.95	.053	
	PTSD Severity	-.110	.001	-1.21	.231	
	USS	-.015	.002	-.167	.867	
Step 4						.001
	Lifetime Trauma	-.216	.005	-2.32	.022	
	Marital Status	-.173	.020	-1.96	.052	
	PTSD Severity	-.111	.001	-1.22	.226	
	USS	-.012	.002	-.131	.896	
	USS*PTSD	.035	.000	.390	.697	

*p<.05;**p<.01;***p<.001

Note: USS = Unit Social Support Scale

Table 6.

Unit Social Support - ACTH

	ACTH				
Variable	β	SE	*t*	*p*	ΔR^2
USS					
Step 1					.014
PSS	.118	.003	1.31	.193	
Step 2					.002
PSS	.135	.003	1.40	.163	
PTSD Severity	-.050	.001	-.515	.607	
Step 3					.000
PSS	.133	.003	1.28	.203	
PTSD Severity	-.049	.001	-.505	.614	
USS	.004	.003	.042	.966	
Step 4					.002
PSS	.135	.003	1.29	.200	
PTSD Severity	-.053	.001	-.540	.590	
USS	.007	.003	.074	.941	
USS*PTSD	.041	.000	.444	.658	

*p<.05;**p<.01;***p<.001

Note: PSS = Post-Deployment Social Support
USS = Unit Social Support Scale

Trauma load. Hierarchical regression analyses evaluated the hypothesized influence of lifetime trauma load and combat severity on the relation between PTSD symptom severity and both basal cortisol and ACTH. Neither lifetime trauma load nor combat severity significantly moderated the relation between PTSD symptom severity and either cortisol or ACTH. However, the main effect of lifetime trauma load (see Table 7) was significantly predictive of baseline cortisol in Step 3, β = -.213, t (119) = -2.349, p = .02, accounting for 4.2% incremental variance in the model, ΔR^2 = .042, ΔF (1, 119) = 5.518, p = .02. Lifetime trauma load and marital status were the only significant predictors of cortisol in the Step 4 for lifetime trauma load, β = -.212, t (118) = -2.327, p = .022; β = -.176, t (118) = -2.012, p = .047, respectively. Lifetime trauma load was the sole significant predictor of cortisol in Step 4 for combat severity, β = -.21, t (117) = -

2.287, $p = .024$. No variables significantly predicted ACTH for either lifetime trauma load or combat severity. Please refer to Tables 7-10 for detailed results.

Table 7.

Lifetime Trauma Load - Cortisol

	Cortisol				
Variable	β	SE	*t*	*p*	ΔR^2
Lifetime Trauma					
Step 1					.030
Marital Status	-.173	.020	-1.94	.000	
Step 2					.029
Marital Status	-.176	.020	-1.99	.049	
PTSD Severity	-.169	.001	-1.91	.059	
Step 3					.042
Marital Status	-.174	.019	-2.00	.048	
PTSD Severity	-.110	.001	-1.21	.229	
Lifetime Trauma	-.213	.005	-2.35	.020	
Step 4					.001
Marital Status	-.176	.020	-2.01	.047	
PTSD Severity	-.111	.001	-1.22	.224	
Lifetime Trauma	-.212	.005	-2.33	.022	
Lifetime Trauma*PTSD	.037	.000	.420	.675	

*p<.05;**p<.01;***p<.001

Table 8.

Lifetime Trauma Load - ACTH

	ACTH				
Variable	β	SE	*t*	*p*	ΔR^2
Lifetime trauma					
Step 1					.014
PSS	.118	.003	1.31	.193	
Step 2					.002
PSS	.135	.003	1.40	.163	
PTSD Severity	-.050	.001	-.52	.607	
Step 3					.002
PSS	.136	.003	1.41	.162	
PTSD Severity	-.036	.001	-.365	.716	
Lifetime Trauma	-.048	.008	-.505	.614	
Step 4					.007
PSS	.147	.003	1.51	.133	
PTSD Severity	-.044	.001	-.436	.663	
Lifetime Trauma	-.045	.008	-.480	.632	
Lifetime Trauma*PTSD	.084	.000	.923	.358	

*p<.05;**p<.01;***p<.001
Note: PSS= Post-deployment Social Support Scale

Table 9.

Combat Severity - Cortisol

		Cortisol				
Variable		β	SEB	*t*	*p*	ΔR^2
CES						
Step 1						.089
	Lifetime Trauma	-.243	.005	-2.79	.006	
	Marital Status	-.171	.019	-1.97	.052	
Step 2						.011
	Lifetime Trauma	-.213	.005	-2.35	.020	
	Marital Status	-.174	.019	-2.00	.048	
	PTSD Severity	-.110	.001	-1.21	.229	
Step 3						.000
	Lifetime Trauma	-.213	.005	-2.35	.021	
	Marital Status	-.176	.020	-2.00	.048	
	PTSD Severity	-.102	.001	-1.05	.295	
	CES	-.021	.005	-.218	.828	
Step 4						.001
	Lifetime Trauma	-.210	.005	-2.29	.024	
	Marital Status	-.174	.020	-1.98	.051	
	PTSD Severity	-.112	.001	-1.09	.278	
	CES	-.019	.005	-.205	.838	
	CES*PTSD	.028	.000	.299	.765	

*p<.05;**p<.01;***p<.001

Note: CES=Combat Experiences Scale

Table 10.

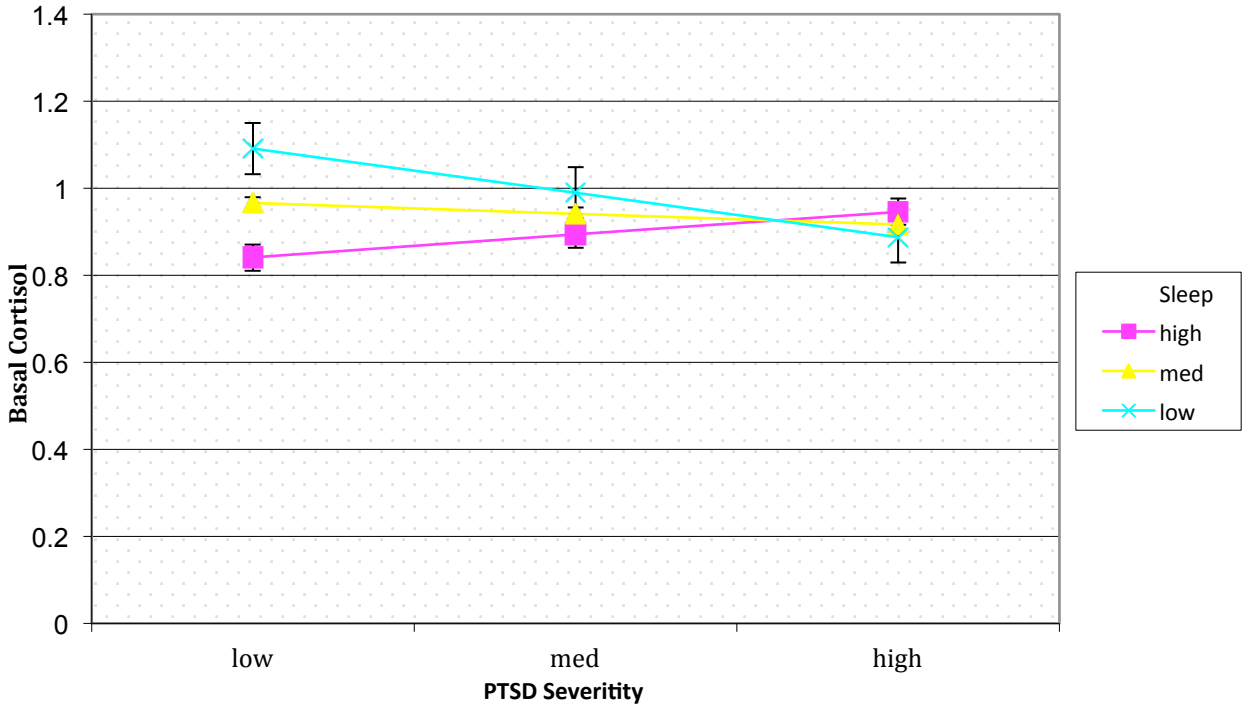
Combat Severity - ACTH

		ACTH				
Variable		β	SE	*t*	*p*	ΔR^2
CES						
Step 1						.014
	PSS	.118	.003	1.31	.193	
Step 2						.002
	PSS	.135	.003	1.40	.163	
	PTSD Severity	-.050	.001	-.52	.607	
Step 3						.005
	PSS	.143	.003	1.47	.144	
	PTSD Severity	-.027	.001	-.264	.792	
	CES	-.075	.008	-.773	.441	
Step 4						.000
	PSS	.141	.003	1.44	.153	
	PTSD Severity	-.030	.001	-.285	.776	
	CES	-.074	.008	-.759	.449	
	CES*PTSD	.011	.000	.116	.908	

*p<.05;**p<.01;***p<.001

Note: CES = Combat Experiences Scale

Sleep. Hierarchical regression analysis evaluated the hypothesized influence of sleep disturbance on the relation between PTSD symptom severity and both basal cortisol and ACTH. There was a nominally significant main effect of sleep disturbance on baseline cortisol in Step 3, β = -.197, t (115) = -1.902, p = .06, which became significant after including the moderation variable into the model in Step 4, β = -.218, t (114) = -2.146, p = .034. The association between PTSD symptom severity and baseline cortisol was significantly moderated by sleep disturbance, β = .242, t (113) = 2.541, p = .012, accounting for 4.7% incremental variance in the model, ΔR^2 = .047, ΔF (1, 114) = 6.455, p = .012. Thus, sleep disturbance, lifetime trauma load, and the interaction between PTSD symptom severity and sleep disturbance significantly predicted baseline cortisol in the Step 4. Interestingly, as illustrated in Figure 2, individuals with low sleep disturbance and low PTSD symptom severity had high levels of basal cortisol compared to individuals with medium and high sleep disturbances. Conversely, individuals with high sleep disturbance and high PTSD symptom severity had high levels of basal cortisol compared to individuals with medium and low sleep disturbance, demonstrating a crossover interaction. Thus, the direction of the relationship between PTSD symptom severity and cortisol changes depending on whether an individual has low or high levels of sleep disturbance. As with all previous examined moderators, no variables significantly predicted ACTH. Please refer to Tables 11 & 12 for detailed results.



Note: Moderation analyses included all participants for whom a CAPS score was available. A subset of participants in the NTC group (n=12) were administered the CAPS for assurance of group assignment.

Figure 2. Moderating Effect of Sleep Disturbance on Relation between PTSD Symptom Severity and Basal Cortisol

Table 11.

Sleep - Cortisol

		Cortisol				
Variable		β	SE	*t*	*p*	ΔR^2
PSQI						
Step 1						.082
	Lifetime Trauma	-.238	.005	-2.69	.008	
	Marital Status	-.163	.020	-1.84	.069	
Step 2						.011
	Lifetime Trauma	-.208	.005	-2.26	.026	
	Marital Status	-.166	.020	-1.88	.063	
	PTSD Severity	-.108	.001	-1.17	.245	
Step 3						.028
	Lifetime Trauma	-.213	.005	-2.34	.021	
	Marital Status	-.163	.020	-1.86	.066	
	PTSD Severity	-.001	.001	-.010	.992	
	PSQI	-.197	.006	-1.90	.060	
Step 4						.047
	Lifetime Trauma	-.179	.005	-1.98	.050	
	Marital Status	-.117	.020	-1.34	.183	
	PTSD Severity	-.087	.001	-.796	.428	
	PSQI	-.218	.006	-2.15	.034	
	PSQI *PTSD	.242	.000	2.54	.012	

*p<.05;**p<.01;***p<.001

Note: PSQI= Pittsburg Sleep Quality Index

Table 12.

Sleep - ACTH

		ACTH				
Variable		β	SE	*t*	*p*	ΔR^2
PSQI						
Step 1						.016
	PSS	.124	.003	1.36	.175	
Step 2						.002
	PSS	.141	.003	1.44	.152	
	PTSD Severity	-.048	.001	-.49	.627	
Step 3						.002
	PSS	.142	.003	1.45	.150	
	PTSD Severity	-.074	002	-.649	.518	
	PSQI	.049	.009	.453	.652	
Step 4						.000
	PSS	.142	.003	1.44	.151	
	PTSD Severity	-.068	.002	-.573	.568	
	PSQI	.050	.009	.461	.646	
	PSQI*PTSD	-.018	.000	-.182	.856	

*p<.05;**p<.01;***p<.001
Note: PSS= Post-deployment Social Support Scale
PSQI= Pittsburg Sleep Quality Index

Given the significant moderating effect of sleep disturbance on the relation between PTSD symptom severity and cortisol, further exploratory analyses were conducted to determine whether this moderating effect held uniform across the DSM-IV PTSD symptom clusters (i.e., re-experiencing, avoidance, arousal), or whether the effect was driven by certain symptom clusters. Therefore, three additional exploratory hierarchical regression analyses were conducted, one with each symptom cluster as the independent variable. First, the association between symptom severity in the re-experiencing cluster and baseline cortisol was significantly moderated by sleep disturbance, $\beta = .191$, $t\ (116) = 2.143$, $p = .034$, accounting for 3.3% incremental variance in the model, $\Delta R^2 = .033$, $\Delta F\ (1, 116) = 4.594$, $p = .034$. Second, the association between symptom severity in the avoidance cluster and baseline cortisol was significantly moderated by sleep disturbance, $\beta = .184$, $t\ (117) = 2.114$, $p = .037$, accounting for 3.2% incremental variance in the

model, $\Delta R^2 = .032$, ΔF (1, 117) = 4.468, $p = .037$. Third, the association between symptom severity in the arousal cluster and baseline cortisol was significantly moderated by sleep disturbance, $\beta = .192$, t (116) = 2.175, $p = .032$, accounting for 3.4% incremental variance in the model, $\Delta R^2 = .034$, ΔF (1, 116) = 4.732, $p = .032$. Thus, the moderating effect of sleep disturbance on the relation between PTSD and cortisol was demonstrated to be significant across the PTSD symptom clusters. Please refer to Tables 13-15 for detailed results.

Table 13.

Re-experiencing

	Cortisol				
Variable	β	SE	*t*	*p*	ΔR^2
PSQI					
Step 1					.084
Lifetime Trauma	-.242	.005	-2.75	.007	
Marital Status	-.167	.020	-1.90	.060	
Step 2					.004
Lifetime Trauma	-.230	.005	-2.57	.011	
Marital Status	-.171	.020	-1.94	.055	
Re-experiencing	-.067	.039	-.752	.453	
Step 3					.034
Lifetime Trauma	-.223	.005	-2.53	.013	
Marital Status	-.162	.019	-1.87	.065	
Re-experiencing	.007	.042	.072	.942	
PSQI	-.200	.005	-2.14	.035	
Step 4					.033
Lifetime Trauma	-.219	.005	-2.52	.013	
Marital Status	-.143	.019	-1.66	.099	
Re-experiencing	-.009	.041	-.091	.928	
PSQI	-.242	.005	-2.57	.011	
PSQI *Re-experiencing	.191	.010	2.14	.034	

*p<.05;**p<.01;***p<.001

Note: PSQI= Pittsburg Sleep Quality Index

Table 14.

Avoidance

		Cortisol				
Variable		β	SE	*t*	*p*	ΔR^2
PSQI						
Step 1						.086
	Lifetime Trauma	-.246	.005	-2.81	.006	
	Marital Status	-.168	.020	-1.92	.057	
Step 2						.016
	Lifetime Trauma	-.207	.005	-2.29	.024	
	Marital Status	-.169	.019	-1.95	.054	
	Avoidance	-.134	.034	-1.48	.143	
Step 3						.024
	Lifetime Trauma	-.205	.005	-2.28	.024	
	Marital Status	-.167	.019	-1.94	.055	
	Avoidance	-.061	.037	-.626	.533	
	PSQI	-.173	.006	-1.82	.071	
Step 4						.032
	LifetimeTrauma	-.189	.005	-2.13	.036	
	Marital Status	-.141	.019	-1.65	.102	
	Avoidance	-.058	.037	-.602	.548	
	PSQI	-.204	.006	-2.16	.033	
	PSQI * Avoidance	.184	.010	2.11	.037	

*p<.05;**p<.01;***p<.001

Note: PSQI= Pittsburg Sleep Quality Index

Table 15.

Hyperarousal

		Cortisol				
Variable		β	SE	*t*	*p*	ΔR^2
PSQI						
Step 1						.083
	Lifetime Trauma	-.244	.005	-2.77	.006	
	Marital Status	-.165	.020	-1.87	.063	
Step 2						.005
	Lifetime Trauma	-.221	.005	-2.40	.018	
	Marital Status	-.162	.020	-1.84	.068	
	Hyperarousal	-.077	.002	-.837	.404	
Step 3						.033
	LifetimeTrauma	-.226	.005	-2.49	.014	
	Marital Status	-.165	.019	-1.91	.059	
	Hyperarousal	.037	.003	.353	.725	
	PSQI	-.215	.006	-2.11	.037	
Step 4						.034
	Lifetime Trauma	-.217	.005	-2.42	.017	
	Marital Status	-.121	.020	-1.38	.170	
	Hyperarousal	.030	.003	.284	.777	
	PSQI	-.235	.006	-2.33	.021	
	PSQI * Hyperarousal	.192	.001	2.18	.032	

*p<.05;**p<.01;***p<.001

Note: PSQI= Pittsburg Sleep Quality Index

Discussion

The primary aim of this study was to compare baseline neuroendocrine levels by trauma group among a sample of OIF/OEF/OND veterans. Specifically, this study sought to examine basal cortisol and ACTH to test whether levels differed significantly by individuals in the NTC, TE, or PTSD groups. To further understand the relationship between trauma group and these biomarkers, an exploratory aim was to examine potential moderators of the relationship between PTSD symptom severity and basal neuroendocrine levels.

Trauma Group Differences on Cortisol and ACTH

The primary aim of the present study sought to determine whether basal cortisol and ACTH differed according to trauma group. The ANOVA examining group differences in cortisol was marginally significant (p=.054), suggesting that mean basal cortisol levels likely differ according to trauma group. Post-hoc tests revealed that mean basal cortisol levels differed significantly between NTC and PTSD groups, with the NTC group having significantly higher levels of cortisol than the PTSD group. Mean scores of baseline cortisol in the TE group did not differ from the NTC or PTSD groups, supporting the notion that aberrant patterns in physiology are unique to the psychopathological effects of trauma as opposed to exposure to trauma alone.

Notably, this is one of the first studies to examine cortisol and ACTH in the OEF/OIF/OND population, which tend to be younger in age compared to veterans of other conflicts. Much of the extant research examining basal effects of cortisol and ACTH have been conducted in civilian (e.g., Newport et al., 2004) or older military populations (e.g., Gulf War, Vietnam, etc.; Golier et al., 2007; Liberzon et al., 1999). Although this is one of the first studies to examine the neuroendocrine effects of combat exposure from the OEF/OIF/OND conflicts, these findings are consistent with much of the extant literature, which has demonstrated lower basal cortisol levels in PTSD patients compared to nonclinical samples (De Kloet et al., 2007; Klaassens et al., 2012; Neylan et al., 2005; Rohleder et al., 2004; Wessa et al., 2006; Yehuda et al., 2005; Yehuda et al., 2004; Yehuda et al., 2002; Yehuda, Southwick, & Krystal, 1993). Notably, however, unlike the present findings, several studies have demonstrated lower basal cortisol in both the PTSD and TE groups compared to the NTC group (De Kloet et al., 2007; Horn et al., 2014; Klaassens et al., 2012). However, consistent with findings from the present study, these studies have also failed to find any statistical differences between PTSD and TE basal cortisol levels.

As suggested by Morris et al. (2012), differential categorization of control groups (i.e., combined TE and NTC vs. NTC only) could contribute to the inconsistency of the literature, such that combining two groups with varied experiences (TE and NTC) into one conditional "non-clinical" group could lead to misrepresentation of control groups. Furthermore, differential findings could likely reflect differences in measurement methodology. In their systematic review and meta-analysis, Meewisse and colleagues (2007) pooled across studies using different types of measurement (i.e., urine, saliva, plasma, or serum) to conduct subgroup analyses. These subgroup analyses demonstrated that studies assessing cortisol via plasma or serum showed significantly lower levels in people with PTSD compared to NTC group, but did not differ between PTSD and TE individuals. Indeed, these and the present findings may suggest that differences in cortisol levels relate to being exposed to trauma general, rather than to the acquisition of PTSD.

In addition to inconsistent categorization of control groups in the extant literature, psychiatric comorbidity is an important consideration when discussing the mixed findings within the literature, with some studies excluding individuals with comorbid psychiatric disorders and others not. A meta-analysis examining basal neuroendocrine levels among individuals with comorbid PTSD and MDD found that daily cortisol output was significantly lower for the PTSD and comorbid PTSD and MDD groups, compared to the NTCs and, similar to the present findings, TE and NTC groups did not differ significantly (Morris et al., 2012). Similarly Newport and colleagues (2004) also considered comorbidity in their study investigating women with child abuse histories and diagnoses of either PTSD, MDD, or comorbid PTSD and MDD and found that, compared to healthy controls individuals with early childhood abuse and PTSD had significantly lower baseline plasma cortisol levels. Unlike the aforementioned studies, the

present study excluded individuals with psychiatric comorbidities. However, findings of lower basal cortisol among individuals with PTSD were consistent across studies that included co-occurring disorders (Morris et al., 2012; Newport et al., 2004), suggesting comorbidity may not influence the direction of basal cortisol among individuals with PTSD.

Although the present findings are consistent with the majority of studies in the extant literature which have demonstrated overall lower baseline cortisol levels among PTSD individuals (e.g., De Kloet et al., 2007; Klaassens et al., 2012; Neylan et al., 2005; Rohleder et al., 2004; Wessa et al., 2006; Yehuda et al., 2005; Yehuda et al., 2004; Yehuda et al., 2002; Yehuda, Southwick, & Krystal, 1993) and frequently TE individuals as well (De Kloet et al., 2007; Horn et al., 2014; Klaassens et al., 2012) , they are inconsistent with a number of studies that have reported higher basal cortisol levels in patients with PTSD (Baker et al., 2005; Golier et al., 2012; Inslicht et al., 2006; Klaassens et al., 2012; Liberzon et al., 1999; Lindley et al., 2004; Young & Breslau, 2004). There have been numerous postulates in the literature as to why findings are mixed for directionality in the cortisol PTSD literature. Once more, it is likely that variations in assessment methodology largely account for the discrepancies in the literature surrounding basal neuroendocrine activity. Although no patterns emerge between methodologies used in studies finding lower basal cortisol among individuals PTSD versus studies finding higher basal cortisol among individuals with PTSD, lack of conformity between and even within studies may account for the discrepant findings. For instance, Baker et al. (2005) compared CSF, plasma, and urinary cortisol measurements in individuals with combat-related PTSD to healthy controls. No group differences were detected in the plasma or urinary free cortisol. However, mean CSF cortisol concentrations were significantly higher in the PTSD positive individuals compared to the healthy controls. The authors explain this incongruence of findings by stating that CSF cortisol more

accurately illustrates brain glucocorticoid levels. Indeed, it is noteworthy to reiterate that various assessment mediums (e.g., blood, saliva, urine, etc.) reflect various concentrations of cortisol (Meewisse et al., 2007). For example, whereas salivary cortisol consists of completely free (i.e., biologically active, unbound) fraction, less than 10% of cortisol in plasma is free (Le Roux et al., 2002). The majority is bound to cortisol-binding globulin (CBG) or other proteins and is biologically inactive. Because the majority of cortisol in serum is bound to proteins, changes in binding proteins can alter measured serum/plasma cortisol concentrations without influencing free concentrations (Hamrahian, Oseni, & Arafah, 2004). Several conditions (e.g., pregnancy, hypothyroidism, obesity) and oral contraceptive use are known to influence CBG levels (Westermann, Demir, & Herbst, 2004). Although pregnancy and obesity are exclusionary criteria in the parent study, hypothyroidism and use of oral contraceptives are not screened out and may serve to influence the present results. Furthermore, results of other published studies may be affected by the failure to control for these factors.

The present findings, indicating lower levels of basal cortisol among individuals with PTSD compared to NTCs, are in contrast to the few studies that have failed to find any significant differences in basal cortisol between PTSD, NTC, and TE groups (Hockings et al., 1993; Klaassens et al., 2012; Lindley et al., 2004; Meewisse et al., 2007; Miller et al., 2007; Savic et al., 2012). Interestingly, overall results from several meta-analyses indicated no significant differences in basal cortisol levels between PTSD and control groups. (Klaassens et al., 2012; Meewisse et al., 2007; Miller et al., 2007). However, subgroup analyses within these studies typically did reveal significant differences, depending on considered variables. Lack of standardization across the different studies examined in these meta-analyses likely accounts for the null findings, such that lack of uniformity across assessment mediums and methodology likely

results in non-comparable basal cortisol levels between studies. Regardless, results of the ANOVA (albeit nominally significant) and post-hoc tests were in line with the proposed hypothesis that mean basal cortisol levels would be significantly lower among individuals in the PTSD group.

No significant group differences were found for ACTH. Lack of significant findings for group differences on basal ACTH in the present study is consistent with the much of the current literature, which has failed to find significant differences in baseline ACTH between PTSD, TE, and NTC conditions (Baker et al., 2005; Golier et al., 2012; Liberzon et al., 1999; Savic et al., 2012). However, these findings are contradictory with results from two studies which demonstrated higher basal ACTH among individuals with PTSD when compared to their TE and NTC counterparts (de Kloet et al., 2012; Golier et al., 2007). Notably, however, the study by Golier and colleagues (2007) demonstrated significantly higher basal levels of ACTH in the PTSD group compared to the TE group only. Furthermore, ACTH levels were also significantly higher in the NTC group compared to the TE group, suggesting the effect was perhaps due to extraneous factors.

Regardless, lack of significant findings for group differences on basal ACTH in the present study could be accounted for by a number of explanations. First, fewer studies have examined ACTH than cortisol, both at baseline and in response to a stressor. To our knowledge, only six studies have examined basal ACTH (Baker et al., 2005; de Kloet et al., 2012; Golier et al., 2012; Golier et al., 2007; Liberzon et al., 1999; Savic et al., 2012). As previously discussed, this gap in the literature could be due to the fact that that ACTH is a serum-based biomarker. Because typically fewer studies use blood serum-based assessments, the lack of ACTH assessments in the literature could be due largely to logistical limitations. However, it is also

possible that far fewer findings on basal ACTH have been published because an effect for ACTH is infrequently demonstrated. Because null findings are less likely to be accepted for publication, this shortage of studies reporting on basal ACTH could be attributed to a consistent lack of effect found for ACTH. However, it is possible that ACTH plays a more critical role in stress reactivity rather than at resting state.

To that end, most of extant literature has examined ACTH as a baseline by which to compare reactivity. Using a baseline assessment as a comparison for a reactivity assessment does not necessarily require the stringent standardization that assessing baseline levels alone might. For instance, variations in basal assessments (e.g., time, place, medium, etc.) are less detrimental to the study design when the basal assessment is serving only as a comparison group for reactivity. Variations in basal assessments are more likely to be confounding, however, when the primary goal of the assessment is to examine basal functioning. Therefore, because the majority of studies examining basal ACTH have done so to compare ACTH at baseline to ACTH at reactivity, it is possible, in fact evident, that less standardization between studies took place. This same limitation can also be applied to the aforementioned cortisol studies.

Summary of Aim One

Group differences in cortisol were marginally significant, with post-hoc analyses revealing that the NTC group had significantly higher levels of cortisol than the PTSD group, supporting the hypothesis that cortisol would be lower in the PTSD group. Mean scores of baseline cortisol in the TE group did not differ from the NTC or PTSD groups. These findings are consistent with the majority of the extant literature, which has demonstrated lower basal cortisol levels in PTSD patients compared to nonclinical samples. No significant group

differences were found for ACTH. Lack of significant findings for group differences on basal ACTH in the present study is consistent with the majority of the current literature, which has failed to find significant differences in baseline ACTH between PTSD, TE, and NTC conditions. Notably, this is one of the first studies to examine cortisol and ACTH in the OEF/OIF/OND population.

Moderation Analyses

An exploratory aim was to examine potential moderators of the relationship between PTSD symptom severity and basal neuroendocrine levels. Sleep disturbance was the only significant moderator of the relation between PTSD symptom severity and basal cortisol. Individuals with low sleep disturbance and low PTSD symptom severity had high levels of basal cortisol compared to individuals with medium and high sleep disturbances. Interestingly, however, individuals with high sleep disturbance and high PTSD symptom severity also had high levels of basal cortisol compared to individuals with medium and low sleep disturbance, indicating a crossover interaction in which the direction of the relationship changes depending on whether an individual has low or high levels of sleep disturbance. This finding suggests that greater sleep disturbance may have more of an effect on basal cortisol in individuals with low levels of PTSD symptom severity, whereas the effects of sleep disturbance may not be as profound in individuals with medium or high PTSD symptomatology. In other words, PTSD severity likely has more of an effect on basal cortisol than does sleep disturbance when present at high levels in conjunction. This finding could suggest that the neuroendocrine system in individuals with high PTSD symptom severity is more reactive to the influences of sleep disturbance than individuals with lower levels of sleep disturbance. Research suggests that basal

cortisol levels among individuals with PTSD are lower in late night and early morning hours, and remain lower throughout the night, compared to healthy controls (Yehuda, 2002). This lack of diurnal modulation could perhaps explain why, unlike individuals with PTSD and low sleep disturbance (suggesting an adequately modulating cortisol pattern), individuals with PTSD and high sleep disturbance display higher basal cortisol.

To determine if the moderation effect of sleep disturbance was driven by any of the PTSD symptom clusters in particular, follow-up analyses were conducted. These exploratory analyses indicated that the moderating effect of sleep persisted across PTSD symptom clusters, significantly influencing the relationship between re-experiencing symptoms, avoidance symptoms, and arousal symptoms and basal cortisol. These findings suggest that sleep plays an influential role on basal cortisol levels across the three different PTSD symptom clusters, indicating that no one cluster was accounting for the significance of the moderator in the initial sleep moderation analysis.

One possible explanation as to why sleep disturbance was the only significant moderator of all of the other hypothesized moderators is the proximal nature of its assessment. Whereas the other examined moderators are more distal in nature (e.g., social support, lifetime and combat trauma load), sleep is a more proximal variable. For instance, whereas the social support and trauma load measures assess events that may have occurred years prior the assessment (i.e., unit social support, social support following deployment, trauma during combat, lifetime trauma load), the sleep measure used in the present study assessed past month sleep disturbances.

In addition to sleep being the only significant moderator, lifetime trauma load was the only variable of interest that demonstrated a significant main effect on basal cortisol. Greater lifetime trauma load was negatively associated with basal cortisol, such that individuals with

higher lifetime trauma loads had lower basal cortisol. These findings are consistent with prior research, which demonstrates that basal cortisol is lower among individuals with current PTSD who report a history of childhood abuse (Newport et al., 2004). Although some research has been done examining baseline cortisol and ACTH among survivors of childhood abuse (Morris et al., 2012; Savic et al., 2012), studies controlling for the effects of lifetime trauma load in analyses examining basal neuroendocrine indices are scarce (Golier et al., 2012).

The present findings may suggest a cumulative effect of lifetime trauma on the HPA-axis system, wherein chronic stress or trauma leads to the perpetuation or failure of the stress system activation. This disruption to the stress system activation prompts the development of an allostatic load, inevitably making the neuroendocrine system more vulnerable to stress (De Kloet et al., 2005). Animal studies have suggested that sustained exposure to trauma leads to elevated cortisol signaling capacity, which in turn results in lower levels of cortisol efficiently suppressing HPA axis functioning (De Kloet et al., 2005). This relationship between trauma load and suppressed cortisol output is further supported by animal models, which have found reinstating appropriate HPA signaling to be an effective treatment approach for PTSD (Cohen et al., 2006; De Kloet et al., 2005). Based on the rationale that endogenous cortisol provides an inadequate signal to contain the stress reactions of PTSD patients, pilot studies have shown that cortisol administration ameliorated PTSD symptoms (Aerni et al., 2014; Schelling et al., 2004).

Integrating these findings in the context of the present study's main hypotheses (i.e., PTSD will result in lower basal cortisol) could suggest that individuals with higher lifetime trauma load may be more likely to have PTSD, which in turn is affecting the HPA-axis. Conversely, it could be that greater exposure to trauma affects the HPA-axis, which in turn, gives rise to PTSD. This positive association between cumulative effects of trauma and PTSD

likelihood is vastly reported in the literature, which suggests that greater exposure to multiple traumatic events is predictive of greater PTSD symptomatology (Breslau, 2009; Cloitre et al., 2009; Messman-Moore et al., 2000). Indeed, investigation into the direction and causality of the effects of trauma exposure on HPA-axis functioning and development of PTSD is a promising future direction, such that risk factors may be identified and thus targeted through early intervention.

Although lifetime trauma load was the only significant main effect predicting basal cortisol across all five cortisol models, the main effect of sleep did become significant when the interaction term for sleep and PTSD symptom severity was added into the final step of the sleep model for cortisol. Additionally, several control variables were significantly predictive of basal cortisol in the final step of several of the models. For instance, lifetime trauma load significantly predicted baseline cortisol across the cortisol models. Surprisingly, given the relation between trauma load and PTSD symptom severity (Dohrenwend et al., 2006; McNally, 2006), lifetime trauma load has been infrequently controlled for in studies examining basal cortisol (e.g., Golier et al., 2012), and thus, it is difficult to say whether this finding is consistent with previous research. However, these findings, coupled with existing evidence for the inverse relationship between cumulative effects of early trauma and basal cortisol e.g., (Newport et al., 2004), highlight the need for future studies to account for lifetime trauma load in analyses when examining the effects of certain factors on basal cortisol. Also, marital status was significantly negatively associated with basal cortisol in the final step of the model examining the moderating effects of lifetime trauma load.

Notably, no variables (control or otherwise) significantly predicted basal ACTH in any of the five ACTH models. The same explanations for the lack of effect seen in the ANOVA

examining group differences in basal ACTH may be relevant in the explanation of the null moderation results. The lack of variables significantly predicting basal ACTH could be simply due to the fact that basal ACTH is not as indicative a biomarker of trauma and trauma-related psychopathology (i.e., PTSD) as its neuroendocrine counterpart, cortisol. It could be that ACTH is not as affected by trauma more generally, or possibly that trauma-related effects on ACTH are more adequately demonstrated in reactivity, rather than basal, states.

Summary of Aim Two

Sleep disturbance was the only significant moderator of the relation between PTSD symptom severity and basal cortisol, such that the effect of greater sleep disturbance on basal cortisol was more profound in individuals with low levels of PTSD symptom severity, but not in individuals with medium or high levels of PTSD symptom severity. That is to say there was a demonstrated greater effect of PTSD on basal cortisol than sleep disturbance when both sleep and PTSD symptoms were high. The moderating effect of sleep remained consistent in analyses across PTSD symptom clusters, suggesting no one cluster was accounting for the significance of the moderator in the initial sleep moderation analysis. Furthermore, lifetime trauma load was persistently predictive of basal cortisol. Across all five cortisol models, lifetime trauma load was negatively associated with basal cortisol, such that individuals with higher lifetime trauma loads had lower basal cortisol. No predictive or moderating effects were demonstrated for ACTH.

Limitations

Limitations of the present study include a modest sample size and unequal sample sizes between the trauma groups. Because tests of ANOVA assume equal variance across groups and

are robust against small deviations from heterogeneity of variance (i.e., homoscedasticity), the unequal sample sizes between groups proves a limitation. However, a hypothesis test was performed to validate the assumption, (i.e., Levene's Test) and showed that the assumption of homoegenity of variance was met for each group for both cortisol and ACTH. Notably, these tests are not powerful to detect small deviations; however, they are able to detect larger deviations. Additionally, deviation from heterogeneity of variance was checked by inspecting residual plots, which showed that all group variances were near to equal. Moreover, despite the fact that the ANOVA examining group differences on cortisol demonstrated a nominally significant effect, the present study is limited in that post-hoc tests were conducted in the absence of a true significant finding ($p<.05$). Although results of the post-hoc tests demonstrated significant differences in basal cortisol between the NTC and PTSD groups, post-hoc analyses are typically not conducted in the absence of a significant ANOVA result and thus should be interpreted with caution.

Additionally, the present study was largely underpowered to examine gender differences, as the vast majority of the total study sample was composed of males (89.9%). Considering disparate rates of PTSD among men and women (Breslau et al., 1998; Kessler et al., 1995; Kilpatrick et al., 2003), as well as the varied likelihood of experiencing certain types of combat trauma according to gender (Street et al., 2013; Vogt et al., 2011; Vogt et al., 2005), future studies should account for gender differences when investigating the potential influence of combat trauma exposure on neuroendocrine activity.

Furthermore, although the aims of the study were to compare basal cortisol and ACTH between trauma groups, the samples assessed were likely not the purest baseline measure of these neuroendocrine markers. For instance, although participants were given approximately an hour to

acclimate to the testing environment and the insertion of the indwelling catheter, it is possible that the anticipation of the upcoming blood draws and/or lab procedures could have resulted in manipulated "basal" states. However, this possibility is small, considering the information provided to participants during the consenting process is worded in an accurate, yet non-threatening way:

> "On the day of your appointment, you will meet a member of the research team at the VIPBG where you are today and they will walk with you to the CRSU at 4:00 pm…If urine tests are clean, you will be fitted with a blood pressure cuff and a catheter in your arm through which small samples of blood will be drawn. No more than 75 mls (about 5 tablespoons) of blood will be taken from your arm over the course of the testing session. Your blood pressure, heart rate, and breath alcohol levels will also be assessed several times during the testing session. The time spent in the CRSU will be used to further collect data regarding personality and alcohol preferences. For example, you will be asked to complete more questionnaires; you may be asked to participate in a mock job interview (to assess extraversion, which is a personality trait), and to complete a mental math test (to assess short term memory); you may also be asked to stand on a balance board (to assess you balance). Your activities during the testing will be recorded on videotape for later scoring. The videotape is erased within one month of your testing session…"

Indeed, even the description of the stress paradigm is described in a manner that that informs the participant of their potential to participate in the task, while at the same time using non-threatening language that likely would not induce enough anticipatory stress to affect the participants' basal neuroendocrine activity. Moreover, given that the informed consent is administered during the initial office visit, it is typically administered approximately a week (or more) prior to the laboratory visit, making anticipatory stress less acute.

Another potential limitation of the study involves the diurnal fluctuation of cortisol and ACTH in basal assessment. However, the schedule for the lab procedures was designed to accommodate this fluctuation, assessing for both neuroendocrine markers at a standardized timepoint in which cortisol and ACTH have been shown to modulate over the course of their 24

hour pattern by metabolic inputs relating to blood glucose levels, around 5PM (See Figure 3; Lovallo, 2006; Van Cauter et al., 1992). Moreover, assessing basal cortisol and ACTH in a highly standardized manner, wherein baseline samples were obtained at the same time for each participant, will likely reduce the likelihood of diurnal variation. To that end, assessing basal cortisol and ACTH via serum likely produces a more temporally accurate baseline measure, unlike the use of other, more distal mediums through which cortisol can be assessed (e.g., urinary cortisol; Handwerger, 2009).

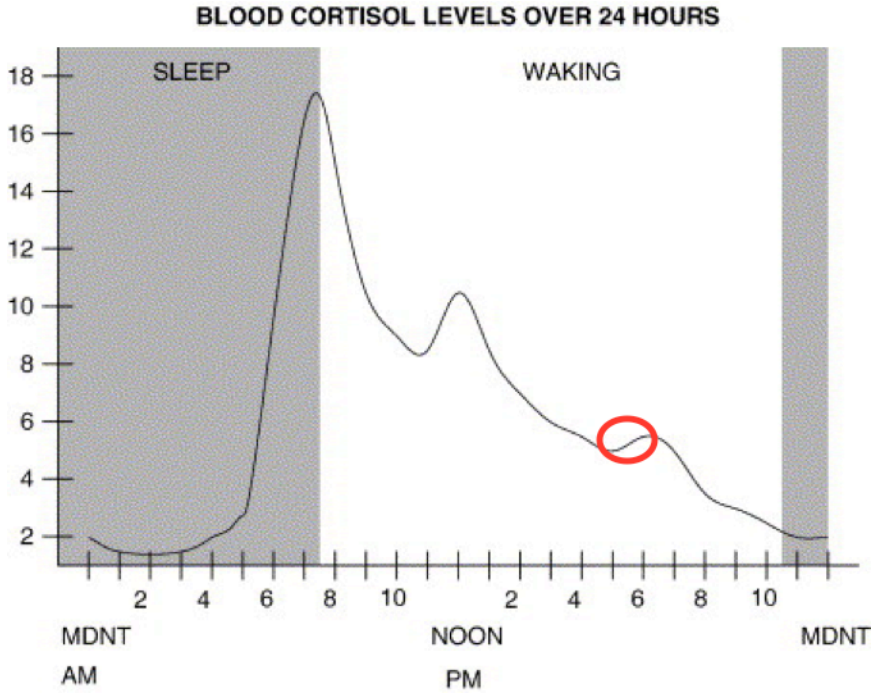


Figure 3. Standardized assessment of cortisol. Adapted from "Cortisol secretion patterns in addiction and addiction risk.," by W.R. Lovallo, 2006, *International Journal of Psychophysiology, 59*(3), p. 195-202.

Implications

The findings from the present study indicate an effect of PTSD on basal neuroendocrine functioning, particularly on cortisol. It is noteworthy, however, that although differences in basal cortisol were marginally significant in the ANOVA, and there were significant differences revealed in post-hoc comparisons, the present findings do not necessarily support the use of cortisol as a diagnostic biomarker for PTSD. A biomarker is defined as a unique identifier of a condition that can be measured in a laboratory that occurs as a result of the disease process (Katz, 2004). A more inclusive definition suggests that a biomarker is defined by any reliable measure associated with the presence and severity of a specific disease state (Naylor, 2003). Working from these definitions, Yehuda and colleagues (2013) emphasize the reliable standards by which a biomarker must be determined. They state that, in order for a biomarker to be effective clinically or empirically, it must perform consistently across laboratories and population samples, with established reference ranges for normative populations against which it can be compared. Because cortisol has not been demonstrated to perform consistently across—and occasionally within—samples, and because there are no established reference ranges by which abnormal cortisol levels can be compared, extensive and more sophisticated investigation of cortisol in relation to trauma and trauma-related phenotypes is warranted before it may be implicated as a biomarker. To that end, replications in larger and varied samples are necessary before inferences can be made regarding the predictive utility of cortisol as a biomarker for PTSD.

Although inferences cannot be made from these findings to implicate cortisol as a diagnostic biomarker, research in this area may still yield important clues into the etiology of PTSD. The findings of the present study fit with current theories of PTSD relating to aberrant stress responses. Furthermore, applying this area of research to target potentially modifiable risk factors (e.g., sleep) that cushion the effects of environmental and biologic vulnerability to

negative mental health outcomes following trauma will have significant clinical implications (Amstadter et al., 2009). To that end, the finding that sleep disturbance significantly moderated the relation between PTSD symptom severity and basal cortisol, such that sleep disturbance had a greater effect on cortisol among individuals with low PTSD symptom severity than among individuals with medium or high PTSD symptom severity, suggests that perhaps sleep should be a primary focus of treatment only after PTSD symptom severity has been managed. For instance, therapeutic attempts to target sleep among individuals with high levels of PTSD symptomatology may prove less effective until PTSD symptom severity is decreased.

The demonstrated effect of lifetime trauma load on basal cortisol, evidenced consistently across all cortisol models, also has important clinical and empirical relevance. This relationship between cumulative trauma and negative mental health outcomes later in life holds meaningful developmental and clinical implications, suggesting that early experiences have lasting effects and may even serve as latent factors which predispose an individual to psychopathological development following an adverse event later in life (Messman-Moore & Long, 2000; Wolfe & Kimerling, 1997). Effects of cumulative trauma on development of PTSD may be of particular relevance among female veterans, seeing as rates of military sexual trauma (MST) are devastatingly high (approximately 20-40%; Surís & Lind, 2008). Thus, these findings could be applied to inform veteran- and MST-based treatment programs, calling for thorough assessment of pre-deployment history. The mechanisms underlying the relationship between early trauma and PTSD following trauma later in life require more understanding; this research would most likely benefit from an interdisciplinary approach, that accounts for multiple variables, such as psychosocial, cultural, biological and epigenetic factors. Although further interdisciplinary research is needed to elucidate underlying mechanisms of PTSD etiology, these findings offer

invaluable insight into the complex and interactive nature of differential responses to trauma, as well as underscore the importance of considering the influential and lasting effects that early childhood events have on later functioning, as triggered by the experience of a traumatic event in adulthood.

Future Directions

Findings from the present study may inform future investigations into neuroendocrine associations with trauma and trauma-related psychopathology. For instance, the sample used in the present study was from a larger parent study, which is currently mid-way through data collection. Because results of the present study were only marginally significant, with relative small effect sizes and large standard errors, re-running the analyses in the larger final sample may increase power, thus increasing the precision by which the effects are estimated (i.e., decreasing standard error). Another interesting future direction with which to expand these findings would be to examine cortisol and ACTH reactivity within the sample. Investigating trauma group differences on, as well as potential moderators influencing, neuroendocrine reactivity would likely provide a more comprehensive picture of the hypothesized effects of PTSD on the HPA-axis negative feedback loop. Furthermore, in light of the null effects of ACTH in present findings, follow-up analyses would allow for the potential differentiating effect of ACTH reactivity to be demonstrated. In other words, investigating the effect of trauma group on ACTH reactivity, as well as potential moderators of the relation between PTSD symptom severity and ACTH reactivity, would help distinguish whether no effects were seen for basal ACTH due to a lack of influence of PTSD on ACTH, or whether PTSD influences ACTH reactivity only.

Furthermore, seeing as the present study was restricted to combat trauma only, examination of the effect of other types of trauma on neuroendocrine activity may be a useful future direction. The differential effects of various trauma types on PTSD (e.g., interpersonal vs. accidental; Breslau et al., 1991; Kessler & Üstün, 2004) may also be seen at a biological level. Similarly, examination of other potential moderators of the relationship between PTSD and basal cortisol and ACTH is warranted, particularly because only one of the examined variables significantly moderated the relationship in the present study.

In addition to replication of analyses within larger and varied samples, clinical considerations provide several promising future directions to extend this research. For instance, because sleep disturbance significantly moderated the relation between PTSD symptom severity and basal cortisol, a crucial next step may be to investigate whether cortisol changes with sleep manipulation. Investigation of basal cortisol levels pre- and post- treatment for insomnia (e.g., Cognitive Behavior Therapy for Insomnia [CBT-I]; Perlis, Jungquist, Smith, & Posner, 2006) may implicate clinical pathways in which to target the physiological effects of PTSD. Similarly, investigation of basal cortisol levels pre-and post- treatment for PTSD may elucidate directionality of the relationship between PTSD and neuroendocrine reactivity. Moreover, cortisol levels should be compared between individuals with current PTSD to individuals with past, but not current PTSD to see if the physiological effects of PTSD remain following remittance.

Lastly, a promising next step in this research would be to examine how basal neuroendocrine levels across diagnostic groups are influenced by genomic factors. Seeing as basal stress levels and reactivity are moderately heritable (Steptoe, van Jaarsveld, Semmler, Plomin, & Wardle, 2009), examination of shared genetic risk factors seems like an informative

future direction for this literature. The ability to identify individuals with higher biological risk for PTSD would allow for targeted prevention and tailored intervention strategies, particularly among individuals knowingly entering environments that increase risk for trauma exposure (i.e., pre-deployment interventions for veterans). Although the current literature on the genetics of PTSD is not as vastly explored compared to that of other psychiatric phenotypes, examination of genetic influences on PTSD has meaningful implications. The ability to identify genetically at-risk individuals would allow for targeted prevention and tailored intervention strategies, particularly among individuals knowingly entering environments that increase risk for trauma exposure (i.e., pre-deployment interventions for veterans). Additionally, appropriating already limited treatment support to those most at risk would better enable effective use of resources (Amstadter et al., 2009). Applying this area of research to target modifiable risk factors (e.g., sleep) that cushion the effects of environmental and biologic vulnerability to negative mental health outcomes following trauma will have significant clinical implications (Amstadter et al., 2009). Examining the biological factors that influence PTSD has meaningful implications.

Conclusions

The present study aimed to compare baseline neuroendocrine levels by trauma group (PTSD, TE, NTC) among a sample of OIF/OEF/OND veterans. Consistent with the hypotheses, basal cortisol levels were marginally significantly different by trauma group, with basal cortisol levels in the PTSD being significantly lower than those in the NTC group. Basal cortisol in the TE group did not differ significantly from either the NTC or PTSD groups. Contrary to the hypotheses, no significant effect of trauma group was found for ACTH. A second, exploratory aim was to examine factors that may moderate the relation between PTSD symptom severity and

basal neuroendocrine levels. Sleep disturbance was the only significant moderator of this relationship in cortisol, with a greater effect of sleep disturbance on basal cortisol in individuals with low levels of PTSD symptom severity, but not in individuals with medium or high levels of PTSD symptom severity. Additionally, lifetime trauma load significantly predicted basal cortisol across all models. No predictive or moderating effects were demonstrated for ACTH. This study enhances the contradictory extant literature by reporting results from a highly standardized study, which eliminates methodological confounds that may contribute to inconsistent findings in the extant literature. Differential responses to trauma nod to the complexity of etiological and maintaining processes that occur between trauma exposure and the development of subsequent psychopathology. Examining the effects of trauma on basal physiology provides a critical stepping ground for future investigations that may inform targeted prevention and intervention efforts.

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