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Linking plasma cortisol levels to phenotypic heterogeneity of posttraumatic stress symptomatology

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Summary
Introduction: Recent confirmatory factor analytic studies of the dimensional structure of posttraumatic stress disorder (PTSD) suggest that this disorder may be best characterized by five symptom dimensions—re-experiencing, avoidance, numbing, dysphoric arousal, and anxious arousal. Hypothalamic-pituitary-adrenal (HPA) axis dysregulation in PTSD and has been attributed to enhanced glucocorticoid responsiveness. However, little is known about how altered HPA-axis function is related to this contemporary phenotypic model of PTSD.
Methods: We compared morning plasma cortisol levels of drug-free civilian adults with PTSD ($N = 29$) to trauma-exposed (TC; $N = 12$) and non-trauma-exposed healthy controls (HC; $N = 23$). We then examined the relation between cortisol levels and a contemporary 5-factor 'dysphoric arousal' model of PTSD symptoms among individuals with PTSD.
Results: After adjustment for white race/ethnicity, education, lifetime alcohol use disorder, and current smoking status, the PTSD (Cohen's $d = 1.1$) and TC (Cohen's $d = 1.3$) groups had significantly lower cortisol levels than the HC group; cortisol levels did not differ between the TC and PTSD groups. Except for age ($r = -.46$), none of the other demographic, trauma-related, or clinical variables, including lifetime mood/anxiety disorder and severity of current depressive and anxiety symptoms, were associated with cortisol levels. In a stepwise linear regression analysis,

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age ($\beta = -.44$) and severity of emotional numbing symptoms ($\beta = -.35$) were independently associated with cortisol levels in the PTSD group; none of the other PTSD symptom clusters or depression symptoms were significant. Post hoc analyses revealed that severity of the emotional numbing symptom of restricted range of affect (i.e., unable to have loving feelings) was independently related to cortisol levels ($\beta = -.35$).
Conclusion: These results suggest that trauma-exposed civilian adults with and without PTSD have significantly lower cortisol levels compared to healthy, non-trauma-exposed adults. They further suggest that low cortisol levels among adults with PTSD may be specifically linked to emotional numbing symptomatology that is unique to the PTSD phenotype and unrelated to depressive symptoms.

1. Introduction

Exposure to traumatic events increases the risk for developing posttraumatic stress disorder (PTSD). Over the past two decades, a growing body of emerging confirmatory factor analytic (CFA) studies has begun to examine more refined models of PTSD symptom dimensionality that extend the 3-factor *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition* (DSM-IV) model to more refined, theory-based 4- or 5-factor models (Yufik and Simms, 2010). The most recent development in this literature is a novel 5-factor 'dysphoric arousal' model, which builds on theoretical work by Watson (Watson, 2005) to suggest that PTSD symptomatology comprised separate re-experiencing, avoidance, numbing, dysphoric arousal (e.g., sleep difficulties), and anxious arousal (e.g., exaggerated startle) symptom clusters (Elhai et al., 2011). To date, more than a dozen CFA studies conducted in a broad range of trauma-exposed samples, including nationally representative samples, have found that this model provides a significantly better representation of PTSD symptom dimensionality than the DSM-IV or alternative 4-factor models (Elhai et al., 2011; Pietrzak et al., 2012; Armour et al., 2013). Table 1 shows how PTSD symptoms are mapped in each of the models. Emerging work from our group has found preliminary evidence of potential neurobiological correlates for the 5-factor model in relation to serotonin 1b receptor (Pietrzak et al., 2013b) and norepinephrine transporter (Pietrzak et al., 2013a) systems in PTSD. However, to date, no study of which we are aware has examined how cortisol levels may relate to this newly proposed and empirically supported phenotypic model of PTSD symptomatology.

PTSD has been linked to altered glucocorticoid signaling based on the idea of enhanced glucocorticoid responsiveness on the one hand (Yehuda et al., 1993, 2004) and lower ambient cortisol on the other (Yehuda et al., 1995a). However, there is also increasing recognition of the complex interactive effects of the molecular mechanisms underlying PTSD risk after trauma; the neuroendocrine consequences of early life adversity; as well as findings of gene-by-environment interactions that explain, at least in part, how early in life trauma may increase risk for adult PTSD (Yehuda et al., 2010). A limitation of extant research, however, is that few studies have examined the relation between basal cortisol levels and heterogeneous symptom clusters that characterize

Table 1 Item mappings of DSM-IV, dysphoria, numbing, and dysphoric arousal structural models of PTSD symptom dimensionality.

DSM-IV PTSD symptom	Item mappings			
	DSM-IV	Dysphoria	Numbing	Dysphoric arousal
B1. Intrusive thoughts of trauma	R	R	R	R
B2. Recurrent dreams of trauma	R	R	R	R
B3. Flashbacks	R	R	R	R
B4. Emotional reactivity to trauma cues	R	R	R	R
B5. Physiological reactivity to trauma cues	R	R	R	R
C1. Avoiding thoughts of trauma	A	A	A	A
C2. Avoiding reminders of trauma	A	A	A	A
C3. Inability to recall aspects of trauma	A	D	N	N
C4. Loss of interest	A	D	N	N
C5. Detachment	A	D	N	N
C6. Restricted affect	A	D	N	N
C7. Sense of foreshortened future	A	D	N	N
D1. Sleep disturbance	H	D	H	DA
D2. Irritability	H	D	H	DA
D3. Difficulty concentrating	H	D	H	DA
D4. Hypervigilance	H	H	H	AA
D5. Exaggerated startle response	H	H	H	AA

Note: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; R, re-experiencing; A, avoidance; H, hyperarousal; D, dysphoria; N, numbing; DA, dysphoric arousal; AA, anxious arousal.