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Hair cortisol concentrations and cortisol stress reactivity predict PTSD symptom increase after trauma exposure during military deployment

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Summary
Background: Previous evidence on endocrine risk markers for posttraumatic stress disorder (PTSD) has been inconclusive. Here, we report results of the first prospective study to investigate whether long-term hair cortisol levels and experimentally-induced cortisol stress reactivity are predictive of the development of PTSD symptomatology in response to trauma during military deployment.
Methods: Male soldiers were examined before deployment to Afghanistan and at a 12-month post-deployment follow-up using dimensional measures for psychopathological symptoms. The predictive value of baseline (i) hair cortisol concentrations (HCC, $N = 90$) and (ii) salivary cortisol stress reactivity (measured by the Trier Social Stress Test, $N = 80$) for the development of PTSD symptomatology after being exposed to new-onset traumatic events was analyzed.
Results: Baseline cortisol activity significantly predicted PTSD symptom change from baseline to follow-up upon trauma exposure. Specifically, our results consistently revealed that lower HCC and lower cortisol stress reactivity were predictive of a greater increase in PTSD symptomatology in soldiers who had experienced new-onset traumatic events (explaining 5% and 10.3%

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of variance, respectively). Longitudinal analyses revealed an increase in HCC from baseline to follow-up and a trend for a negative relationship between HCC changes and the number of new-onset traumatic events. Additional pre-deployment analyses revealed that trauma history was reflected in lower HCC (at trend level) and that HCC were negatively related to stressful load.
Conclusions: Our data indicate that attenuated cortisol secretion is a risk marker for subsequent development of PTSD symptomatology upon trauma exposure. Future studies are needed to confirm our findings in other samples.

1. Introduction

While epidemiological studies suggest that 41—86% of all people experience at least one traumatic event during their lifetime, only a relative minority (<10%) of these individuals actually develops posttraumatic stress disorder (PTSD; e.g., Breslau, 2009; Lukaschek et al., 2013; Wittchen et al., 2012a, 2013). This fact has prompted a substantial effort to identify biological vulnerability factors for PTSD with a particular focus on the regulation of neuroendocrine stress systems (reviewed in Bomyea et al., 2012; Zoladz and Diamond, 2013).

Previous *cross-sectional* research suggests that PTSD is related to a complex dysregulation of the hypothalamic—pituitary—adrenal (HPA) axis and its end product cortisol. Regarding basal cortisol secretion, most but not all studies have indicated general hypocortisolism in PTSD patients (for meta-analyses see Meewisse et al., 2007; Morris et al., 2012). Research on cortisol stress reactivity has also revealed mixed results: while some studies found PTSD patients to exhibit an exaggerated cortisol response to a variety of acute stressors (e.g., Bremner et al., 2003; Elzinga et al., 2003), others have failed to replicate this association (e.g., Simeon et al., 2007). In addition to studies suggesting cortisol dysfunctions specifically related to PTSD, growing evidence indicates that trauma exposure per se might be related to altered cortisol secretion. Specifically, it has been shown that traumatized healthy individuals also exhibit lower basal cortisol levels (for a meta-analysis see Morris et al., 2012) and diminished cortisol stress reactivity to psychosocial stress (e.g., Elzinga et al., 2008; Lovallo et al., 2012).

So far it remains unclear whether a dysregulation of cortisol production in PTSD patients either represent a premorbid vulnerability factor or reflect a response to trauma exposure. Interestingly, prospective research suggests that lower basal cortisol levels immediately after a traumatic event predict a higher risk for developing PTSD symptoms (e.g., Delahanty et al., 2000; Mouthaan et al., 2014) and that prior traumatization may underlie this association (e.g., Delahanty et al., 2003; Walsh et al., 2013). However, as these studies measured cortisol levels immediately after trauma exposure, it is unclear whether observed effects can be attributed to peri-traumatic conditions (cortisol response to the traumatic event) or result from pre-traumatic differences in cortisol secretion. The few truly prospective studies which have investigated basal cortisol levels *before* trauma exposure among high-risk groups have failed to demonstrate a predictive value of cortisol levels for PTSD symptomatology at follow-up (e.g., Heinrichs et al., 2005; van Zuiden et al., 2011b, 2012a). However, some studies found that a higher pre-traumatic number of glucocorticoid receptors (GRs; van Zuiden et al., 2011a, 2012a) and increased glucocorticoid (GC) sensitivity (van Zuiden et al., 2012b) predicted PTSD symptom development after military deployment. As it has been proposed that these vulnerabilities in glucocorticoid-signaling are associated with hypocortisolism (e.g., Rohleder et al., 2004; Yehuda et al., 1991), these studies provide indirect evidence for the notion of a predictive value of lower cortisol activity for PTSD symptom development.

An important limitation of the above studies is that previous cortisol assessment strategies in blood, saliva, or urine particularly only provide a reflection of short-term hormone levels (reviewed in Stalder and Kirschbaum, 2012). Hair cortisol analysis is likely to fill this methodological gap as it serves as a valid and reliable index of *long-term integrated* cortisol secretion (Stalder and Kirschbaum, 2012; Staufenbiel et al., 2013). Importantly, growing evidence highlights the potential of hair cortisol concentrations (HCC) as a correlate of long-term PTSD and trauma-related cortisol aberrations (Luo et al., 2012; Steudte et al., 2013; Steudte et al., 2011). Moreover, recent work by our laboratory showed that temporally distant trauma exposure is reflected in lower HCC in both PTSD patients *and* healthy controls, and that a large number and frequency of traumatization is related to lower HCC (Steudte et al., 2013). While this finding matches well with the above studies suggesting that prior traumatization is related to lower cortisol levels immediately after a subsequent traumatic event and a higher risk for developing PTSD, the cross-sectional nature of this study prevented direct testing of this hypothesis.

Given the unique potential of HCC to reflect *retrospective* information, Luo et al. (2012) obtained hair strands of adolescent survivors of the Wenchuan earthquake in China seven months after the disaster. Their findings revealed increased HCC in trauma-exposed individuals (with and without PTSD) in hair segments reflecting the period immediately after trauma exposure which were found to decline in PTSD patients in hair segments reflecting later time periods after trauma exposure (two to seven months). Importantly, no group differences in cortisol levels in the hair segment grown *before* the earthquake were detected. In this context, however, it is important to note that previous research suggests a declining pattern of HCC from proximal to more distal hair segments (''wash-out'' effect, reviewed in Stalder and Kirschbaum, 2012). Considering that Luo et al. (2012) took hair samples seven months after trauma exposure, it is conceivable that this may have weakened the possibility to detect existing associations. Thus, the current