Predicting PTSD Prospectively Based on Prior Trauma History and Immediate Biological Responses

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ABSTRACT: Studies examining the biopsychology of posttraumatic stress disorder (PTSD) have suggested that PTSD is characterized by alterations of the primary stress pathways: the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). More recent investigations point to the presence of these alterations soon after a traumatic event, leading researchers to suggest that acute biological responses may serve as risk or resilience factors for the development of PTSD. The present article reviews the evidence for early biological predictors of PTSD, with a focus on the role of prior trauma as a contributor to both hormonal abnormalities and increased risk for the development of PTSD following a subsequent trauma.

KEYWORDS: PTSD; cortisol; predictors; catecholamines; heart rate; trauma history

The majority of studies examining the biopsychology of posttraumatic stress disorder (PTSD) have focused on elucidating biological abnormalities present in adult trauma victims with chronic PTSD. These studies have suggested that PTSD is characterized by alterations of the primary stress pathways: the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS: see Ref.[1] for a review). More recent investigations point to the presence of these alterations soon after a traumatic event, leading researchers to suggest that acute biological responses may serve as risk or resilience factors for the development of PTSD.[2,3] The present article reviews the evidence for early biological predictors of PTSD, with a focus on the role of prior trauma as a contributor to both hormonal abnormalities and increased risk for the development of PTSD following a subsequent trauma.

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Biological Alterations in Chronic PTSD

Early biological studies revealed that PTSD was characterized by SNS hyperreactivity to both trauma-reminiscent and nontrauma-reminiscent stimuli (i.e., exaggerated startle responses: see Ref. 4). The finding that PTSD patients reacted to stress in an exaggerated manner led researchers to examine whether PTSD was associated with alterations in basal SNS activity. Results of these studies have been mixed. Although most research has found no difference in plasma catecholamine levels between PTSD patients and controls,[5−7] for an exception see Ref. 8, studies collecting 24-h urine samples have generally found greater catecholamine levels in adults with chronic PTSD than either nontraumatized controls or similarly exposed persons who did not develop PTSD (see Ref. 9 for a review). These discrepant findings are likely attributable to methodological differences in the assessment of catecholamine levels. Specifically, as plasma samples provide an approximation of catecholamine levels over the last few minutes, 10 the acute time frame encompassed in a single blood draw may not be sufficient to examine general systemic alterations in SNS hormones. Urine samples average hormone levels across a longer time frame (the duration of the collection period) than do plasma samples and suggest a persistent elevation of sympathetic hormones in PTSD.

In contrast to the relatively consistent finding of elevated 24-h urinary catecholamine excretion in PTSD, studies examining alterations in HPA axis activity have produced variable findings. Initial studies were relatively consistent, reporting lower 24-h urinary cortisol excretion in victims with PTSD relative to victims without PTSD and normal controls (see Ref. 1 for a review), suggesting a downregulation of the HPA axis in PTSD. Findings of greater numbers of lymphocyte glucocorticoid receptors[11] in PTSD patients further suggested hypofunctioning of the HPA axis in PTSD.

However, more recently, a number of studies have produced contradictory findings (see Ref. 12 for a review), with some studies finding higher 24-h urinary cortisol levels in PTSD,[13−16] and some finding no differences in cortisol output between patients with PTSD and controls.[17,18] A number of possible explanations for these discrepant findings have been posited including whether sampling was conducted in a clinical research center or while participants were in their natural environment and/or failure to control for smoking and other pharmacologic agents.[12] Of note, studies reporting higher levels of cortisol in PTSD have also typically included samples consisting primarily of premenopausal women, suggesting that inconsistent findings may be due to differences in gender and/or menopausal status between studies.[12] Finally, failure to consider the presence of diagnoses comorbid with PTSD may also contribute to the discrepant findings. Despite high comorbidity rates (35–50%),[19,20] relatively little research has examined the impact of comorbid depression on the

biology of PTSD. This is a large limitation, as depression and PTSD have often been associated with opposite abnormalities of HPA axis functioning. For instance, cortisol levels of patients with major depressive disorder (MDD) often are resistant to suppression following treatment with dexamethasone,[21,22] suggestive of a hyposensitive HPA axis negative feedback loop. In contrast, PTSD patients have been found to hypersuppress the release of cortisol in response to low-dose dexamethasone treatment,[23,24] suggesting the opposite: that the HPA axis negative feedback loop is hypersensitive in PTSD.

In sum, chronic PTSD has been associated with alterations of the two primary stress pathways, although the direction of these alterations has not been consistent. The majority of these studies have examined hormone levels in chronic PTSD patients who have presented with PTSD and comorbid disorders for over 20 years, making conclusions concerning onset of alterations difficult. However, based on findings in chronic PTSD patients, researchers hypothesized mechanisms through which acute physiological responses to trauma could contribute to chronic distress and psychopathology. It is important to consider these theories in a historical context, as they were proposed when the majority of studies were reporting hyperactivity of SNS functioning and hypofunctioning of the HPA axis in PTSD. Pitman was the first to hypothesize that the pattern of hormone levels commonly observed in chronic PTSD patients could, if present during the acute phase of responding to a traumatic event, lead to the development of "overconsolidated" memories, and subsequent symptoms of PTSD.[25,26] Yehuda and colleagues supported and expanded this theory to suggest that, during traumatic stress, exaggerated catecholamine increases without the regulatory influence of accompanying cortisol increases could lead to inappropriate memory formation (either over-salient or fragmented memories) and result in the intrusion symptoms that characterize PTSD.[27,28] In other words, lower cortisol levels at the time of the trauma may fail to contain the sympathetic stress response leading to consequent prolonged availability of norepinephrine in the brain,[29] and altered consolidation and retrieval of memory of the traumatic incident.[1]

Initial support for these theories was provided by animal research, which has consistently shown that arousal (often operationalized as increased catecholamine levels) is associated with better retention of stress-related memories.[30−32] Low levels of cortisol have been shown to increase the memory-enhancing effects of catecholamines,[30,33] and high doses of glucocorticoids decrease these effects.[34] Human research has demonstrated that blocking β-adrenergic receptors with propranolol abolishes the enhancement of memories of slides presented along with an emotionally arousing narrative but does not impact memory of neutral slides,[35] suggesting that the adrenergic system is integrally involved in facilitating the consolidation of material learned under emotionally arousing conditions. In sum, arousal and accompanying physiological changes have been shown to be important factors in modulating memory consolidation of emotional events, and altered catecholamine or cortisol

activity during arousing situations may moderate memory consolidation and subsequent risk for PTSD symptoms.

Acute Biological Predictors of PTSD in Adults

Research examining whether initial physiological responses to trauma are associated with subsequent PTSD symptoms has typically been conducted in emergency department (ED) settings, as this environment affords the ability to assess physiological responses relatively soon after a traumatic event. In addition, vital signs and variables that may impact vital signs (i.e., type and extent of injury, medications, chronic diseases, substance use, etc.) are routinely recorded in medical charts. A number of studies have taken advantage of these data by examining the extent to which heart rate (HR) levels routinely assessed at varying times following hospital admission were associated with increased risk for subsequent PTSD. Although contradictory findings have been reported in a study of self-selected participants[36] and results may not generalize to seriously injured trauma patients,[37] prospective studies of consecutive ED patients have found that patients with higher HRs during their hospital stay are more likely to develop PTSD.[3,38,39]

Few studies have directly tested whether altered cortisol levels soon after trauma would increase one's risk for developing PTSD. Resnick and colleagues[40] measured plasma cortisol in 39 female rape victims within 51 h of the rape and found that those victims with prior assault histories had lower cortisol levels and were more likely to develop PTSD than were women without similar trauma histories. Plasma cortisol levels were not significantly related to subsequent PTSD; however, this may have been due to limited power afforded by the small sample size. Similarly, motor vehicle accident (MVA) victims who were subsequently diagnosed with PTSD had lower plasma cortisol levels 30 min after their accident than victims who subsequently met criteria for major depression.[41] Neither diagnostic group differed significantly from individuals who did not receive a diagnosis, but this may again have been due to the small sample size.

More recently, we examined initial urinary hormone levels in the immediate aftermath of an MVA in 99 accident victims.[2] As part of standard hospital protocol, MVA victims were catheterized upon arrival to the trauma unit, and urine was collected for the next 15 h. Although a 24-h sample would have allowed measurement of hormone levels across the diurnal cycle, catheters are typically removed after 15 h to reduce patient discomfort. Time of day of hospital admission was not significantly related to urinary hormone levels. Six weeks after the MVA, we met with participants in their homes to conduct the follow-up assessment. Victims who met acute PTSD diagnostic criteria had significantly lower urinary cortisol levels in the immediate aftermath of the accident than victims who did not meet diagnostic criteria. In addition,

in-hospital levels of cortisol were negatively correlated with subsequent in-trusive and avoidant symptoms of PTSD ($r = -0.46$, $P < 0.01$). PTSD and non-PTSD patients did not differ in catecholamine levels. We have since repli-cated these findings in a study of over 400 MVA victims from whom we collected two in-hospital urine samples: from 0 to 5 h posttrauma and from 5 to 10 h posttrauma. Preliminary results suggested that lower urinary cortisol levels were associated with higher subsequent PTSD symptoms, but that the relationship was stronger for the second (5–10 h) sample and was stronger when using self-reported PTSD symptoms versus symptoms reported during a structured interview (Delahanty, unpublished data). These results were con-sistent with Yehuda's theory,[27] lending support to the hypothesis that increased adrenergic activity without the regulatory control of cortisol elevations would be associated with increased risk for the development of subsequent symptoms of PTSD.

However, the question remains as to why some individuals display an al-tered hormonal response following trauma and increased risk for PTSD while the majority of trauma victims do not. One possible explanation is that prior traumatic experiences may result in altered physiological reactivity to a sub-sequent trauma and increased risk for PTSD. Prior trauma history is one of the most consistent predictors of PTSD following a subsequent trauma,[42] and trauma history has been shown to alter HPA axis responses to subsequent stressors.[43,44] Resnick and colleagues[40] found that female rape victims with a previous history of assault were 6.7 times more likely to develop PTSD and had lower plasma cortisol levels following the rape than victims without such history. These findings led Yehuda and colleagues[45] to hypothesize that expo-sure to previous traumatic events may result in persistent biological changes in the relationship between SNS and HPA axis hormones, thereby increasing one's risk of developing PTSD upon exposure to a subsequent trauma. In our sample of MVA victims, 15-h urinary cortisol levels mediated the relationship between prior trauma history and PTSD symptoms, supporting this hypothesis and highlighting the importance of considering trauma history in studies of bi-ological predictors of PTSD.[46] To further examine the role that trauma history and initial physiological responses had in increasing risk for PTSD, we began studying first-time child trauma victims in an attempt to determine whether the relationship between early physiological responses to trauma and risk for PTSD existed in a group with no prior trauma history.

Biology of PTSD in Children

Similar to findings in the adult literature, research examining the biopsychology of PTSD in children has produced mixed results. In per-haps the most comprehensive study of stress hormone levels in children with PTSD to date, De Bellis and colleagues[47] investigated 24-h urinary

catecholamine and cortisol levels in children with chronic PTSD stemming from maltreatment experiences, children with overanxious disorder (OAD), and nontraumatized healthy controls. Children in the PTSD group were examined, on average, 2 years posttrauma. Most of the PTSD patients met criteria for at least one comorbid disorder including depressive disorders, oppositional defiant disorder, and attention-deficit hyperactivity disorder. Findings indicated that children with PTSD had higher cortisol levels than normal controls, higher urinary epinephrine than OAD children, and higher levels of dopamine and norepinephrine than both OAD children and controls. Further, urinary cortisol levels were positively correlated with duration of trauma and severity of PTSD symptoms. A follow-up study revealed that maltreated children with PTSD also had smaller cerebral volumes and exhibited a number of neurological deficits in comparison to matched controls, suggesting that persistent elevations in cortisol may be associated with neurological consequences in children.[48]

In contrast to De Bellis's findings,[47] other studies have found lower cortisol levels in children with chronic PTSD.[49,50] However, these studies differed greatly with respect to the manner in which PTSD symptoms/diagnosis were assessed, the length of time since trauma, the age range and gender ratio of children assessed, the manner in which cortisol was assessed (urine versus saliva), and the timing of physiological assessments. Accordingly, contradictory findings may have been due to these methodological differences across studies.

Few studies have explored acute biological predictors of PTSD in children. Consistent with the adult literature, elevated HR soon after trauma is associated with increased risk for the development of PTSD in child trauma victims.[51,52] Specifically, in an investigation of 190 children aged 8–17,[27] found that HR assessed upon admission to the ED significantly predicted PTSD severity and diagnostic status (subthreshold and full PTSD versus no PTSD) at follow-up after controlling for age, sex, and injury severity. In a similar study, we examined the extent to which HR levels assessed at varying times following admission to the ED were related to subsequent PTSD symptoms. HR was measured during emergency medical services (EMS) transport, upon admission to the ED, for the first 20 min following admission, and upon discharge. PTSD symptoms were assessed 6 weeks and 6 months later in patient's homes.[52] Findings revealed that HR recorded during EMS transport showed the strongest relationship with subsequent symptoms of PTSD at 6 weeks and 6 months. EMS HR reflected the measure most proximal to the traumatic event, and was not confounded by medications received during admission, suggesting that, as in adults, initial physiological hyperarousal is associated with increased risk for the development of PTSD symptoms.

These data were collected as part of a study paralleling our adult work, in which we examined initial urinary hormone predictors of PTSD in child trauma victims.[53] We collected 12-h urine samples initiated upon admission

to the trauma unit in 82 children (56 boys, 26 girls) aged 8–18. Follow-up assessment of PTSD symptoms occurred 6 weeks posttrauma. In contrast with the results of our adult study, in children with first-time traumas, *higher* levels of 12-h urinary cortisol and epinephrine predicted higher PTSD symptoms 6 weeks posttrauma. However, these findings seemed to be driven by significant findings in boys ($rs = 0.52$ for cortisol, 0.46 for epinephrine), as the relationships were not significant in girls ($rs = 0.01$ for cortisol, -0.17 for epinephrine). We have since replicated these findings in a small sample with a more equal gender distribution (33 boys, 28 girls).[54] Using identical methods, 12-h urinary cortisol was again significantly correlated with PTSD symptoms in boys ($r = 0.52$, $P < 0.05$) but not girls ($r = 0.27$, NS). However, it is important to remember that our age range of 8–18 includes girls who differ dramatically in hormone levels (due to pubertal status and menstrual phase), coping abilities, and a score of other variables that are known to impact both urinary hormones and risk for PTSD. Future research examining a much larger sample of girls is necessary to examine the influence of these variables on the relationship between initial biological risk factors and PTSD in trauma victims.

In our initial child study,[53] we excluded children with a prior trauma history in order to test the relationship between initial biological responses to trauma and subsequent PTSD in a sample that was not confounded by differing trauma histories. However, due to difficulties inherent in the enforcement of recruitment criteria during triage, eight children with a prior trauma history (typically abuse or maltreatment) were recruited into the study. Although the small number of subjects precluded our ability to conduct statistical analyses, inspection of the data for these children suggested an interesting pattern. Children with a prior trauma history tended toward higher levels of PTSD symptoms and lower urinary cortisol levels (Delahanty, unpublished data). In other words, children with a prior trauma history looked more like our adult trauma victims. Replication of these findings in larger and more diverse samples are necessary to determine with confidence whether traumatic events (especially those experienced in childhood) may result in altered SNS and HPA axis functioning in some children, and whether these children would be at increased risk of developing PTSD upon exposure to a subsequent trauma.

However, these findings are in line with De Bellis's[55] developmental traumatology model of PTSD. According to this model, the experience of childhood trauma can result in alterations of biological stress systems in some vulnerable child trauma victims. These individuals may respond to the traumatic event with elevated central corticotrophin-releasing hormone (CRH) and subsequent hypersecretion of cortisol. Over time (probably a number of years), elevated central cortisol levels could exert neurotoxic effects in the developing brain, possibly explaining decreased hippocampal volumes and other neurological alterations observed in PTSD (i.e., Ref. 56). Similarly, prolonged elevations of central CRH and hypersecretion of cortisol levels could disrupt normal

HPA axis functioning, ultimately resulting in enhanced negative feedback inhibition of the pituitary and eventually leading to lower basal cortisol levels. Research in child trauma victims has supported this timeline, suggesting that initially and within 2 years posttrauma, trauma experience and PTSD are associated with high levels of cortisol.[47,53,57] However, 5 years after exposure to an earthquake, children who were near the epicenter and had the highest PTSD symptoms exhibited *lower* baseline salivary cortisol levels and greater suppression of cortisol by dexamethasone.[49]

If enhanced negative feedback inhibition and lower levels of circulating cortisol are a long-term consequence of childhood exposure, then adults with a prior childhood trauma may have attenuated basal cortisol or may show reduced HPA axis reactivity relative to nontraumatized individuals. Upon exposure to a subsequent trauma in adulthood, lower peri- and initial posttraumatic cortisol levels may be associated with increased risk for the development of PTSD. However, the extent to which observed lower levels of cortisol during and after trauma in adults are *causally* associated with increased risk for developing PTSD symptoms is unclear and questionable. As mentioned previously, empirical and theoretical evidence has suggested mechanisms through which cortisol abnormalities could directly lead to the development of PTSD symptoms. For instance, animal and human research has suggested that low levels of cortisol may fail to contain sympathetic responses to trauma resulting in prolonged noradrenergic availability in the brain. This may result in overconsolidated traumatic memories, which could be manifest in the intrusive and avoidant symptoms of PTSD. However, and more parsimoniously, low cortisol levels may also simply reflect risk afforded by prior childhood trauma, and not be involved in any way causally with the development of PTSD. It will be difficult to tease apart which of these explanations is most likely, but pharmacologically altering cortisol levels soon after trauma exposure may suggest whether altered cortisol levels are causally related to PTSD symptom development. That is, if exogenously elevating cortisol levels soon after a traumatic event does not result in decreased symptom development, this would argue against a causal relationship of low cortisol to increased risk for PTSD.

De Bellis's model was not designed to clarify the relationship between initial cortisol levels and PTSD, but rather was intended to offer possible explanations for the differences in findings between child and adult studies of initial cortisol levels predicting PTSD. Current research has provided support for many parts of the model, but a longitudinal study following child trauma victims soon after trauma exposure into young adulthood and subsequent trauma exposure is necessary to truly test this model.

In addition, a number of other factors that have not been included in the developmental model may alter the relationship between initial biological responses and risk for PTSD in children. Most notably, gender is likely to play a major role. Girls consistently report more symptoms of PTSD than boys following exposure to a variety of traumas[58,59]; girls may be as much as six

times more likely than boys to develop PTSD following exposure to serious trauma.[60] In our preliminary work, the relationship between initial urinary stress hormone levels and PTSD symptoms was only significant in boys,[53] although initial elevated HR was significantly related to PTSD symptoms in both boys and girls.[52] It is likely that age/pubertal status will interact with gender to impact the relationship between initial physiological responses to trauma and subsequent PTSD symptoms, and future research should be sufficiently powered to examine the impact of these variables.

Notably, one variable that has been understudied in our conceptualization of the biology of developmental traumatology in children and adults is comorbidity. More than half of the adolescents with a current diagnosis of PTSD also meet criteria for a comorbid major depressive episode,[61] and research in adults has suggested that, in patients with comorbid depression and PTSD, each disorder may alter the biological expression of the other. In a community epidemiologic investigation, participants with comorbid PTSD and depression demonstrated evening cortisol elevations whereas those with "pure" PTSD or depression had normal salivary cortisol levels.[62] Depressed patients with comorbid anxiety disorders also had heightened physiological reactivity to social stressors than subjects with "pure" mood or anxiety disorders.[63] Finally, comorbid patients have higher norepinephrine levels than PTSD patients without comorbid depression or normal controls.[45] Given the high prevalence rates of comorbid depression and PTSD, and the oftentimes opposite impact that these disorders have on the HPA axis, it is necessary to consider the impact that symptoms of depression may have on physiological functioning and clinical symptoms.

An additional variable that must be taken into account when examining the relationship between initial physiological responses to trauma and PTSD in children is the family/parental environment. Child trauma victims are not just affected by their own responses to trauma; parental response to the child's trauma has been shown to consistently have an impact on child adjustment. Higher levels of general distress may result in a parent being less available to their child during the posttraumatic period.[64] However, parental posttraumatic stress symptoms stemming from the child's trauma has been more strongly related to the development of PTSD in children,[65,66] than general parental distress, suggesting specific risk afforded by parental posttraumatic stress symptoms and underscoring the importance of examining familial influences and responses to the child's trauma as moderators of adjustment in child trauma victims.

Conclusions and Summary

In sum, although findings have been mixed with respect to direction of physiological alterations observed in chronic PTSD, the few studies that have examined early biological predictors of PTSD have been relatively consistent,

suggesting that initial sympathetic hyperarousal appears to be associated with increased risk for PTSD in adults and children. On the other hand, the relationship between initial cortisol levels and PTSD symptoms has differed in adults and children. Viewing these findings from the perspective of a developmental model of biology and PTSD has helped to clarify the discrepant results and integrate them into a testable format. Given that childhood trauma is a risk factor for future traumatic experiences, a sufficiently powered, large-scale examination of this model in child trauma victims who are followed into young adulthood (and subsequent traumatic experiences in some participants), would shed light on contradictory findings in the literature and advance the theoretical understanding of the development of PTSD.

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