Title

HPA-Axis Activation as a Key Moderator of Childhood Trauma Exposure and Adolescent Mental Health.

Journal

Research on Child and Adolescent Psychopathology, 46(1)

Authors

Geiss, Elisa
Vargas, Ivan
Lopez-Duran, Nestor
et al.

Publication Date

2018

DOI

10.1007/s10802-017-0282-9

Peer reviewed

HHS Public Access

Author manuscript

J Abnorm Child Psychol. Author manuscript; available in PMC 2023 October 20.

Published in final edited form as:

J Abnorm Child Psychol. 2018 January ; 46(1): 149–157. doi:10.1007/s10802-017-0282-9.

HPA-Axis Activation as a Key Moderator of Childhood Trauma Exposure and Adolescent Mental Health

Kate R. Kuhlman[1], **Elisa G. Geiss**[2], **Ivan Vargas**[3], **Nestor Lopez-Duran**[4]

[1]Department of Psychology, University of California Los Angeles, Los Angeles, CA 90095, USA

[2]Department of Social Science, Olivet College, Olivet, MI, USA

[3]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

[4]Department of Psychology, University of Michigan, Ann Arbor, MI, USA

Abstract

Individual differences in a child's sensitivity to stress may influence whether youth exposed to trauma develop symptoms of psychopathology. We examined the interaction between HPA-axis reactivity to an acute stressor and exposure to different types of childhood trauma as predictors of mental health symptoms in a sample of youth. Youth (n = 121, ages 9–16; 47% female) completed a standardized stress task, including 5 post-stress salivary cortisol samples. Parents also completed the Child Behavior Checklist as a measure of child internalizing and externalizing symptoms in the past month, and completed the Early Trauma Inventory (ETI) as a measure of their child's trauma exposure. More emotional abuse and non-intentional trauma were associated with greater internalizing symptoms. Youth exposed to physical abuse who demonstrated slower HPA-axis reactivity had elevated internalizing and externalizing symptoms. Youth exposed to emotional abuse or non-intentional traumatic events who demonstrated faster HPA-axis reactivity had elevated internalizing and externalizing symptoms. Profiles of exaggerated or attenuated HPA-axis reactivity to acute stress may be risk factors for psychopathology in children facing different stressful social environments.

Keywords

Physical abuse; Emotional abuse; Childhood trauma; HPA-axis; Stress; Internalizing; Externalizing

Trauma exposure during childhood is associated with increased risk for psychopathology across the lifespan (Chapman et al. 2007; MacMillan et al. 2001), higher comorbidity and

Kate R. Kuhlman krkuhlman@ucla.edu.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

recurrence of psychopathology, and poor treatment outcomes (Nanni et al. 2012). Yet, how different types of childhood adversity relate to psychopathology remains poorly understood. There is growing evidence that different types of childhood trauma and adversity may lead to psychopathology via structural and functional changes to the brain (McLaughlin et al. 2014; Teicher et al. 2016). Furthermore, there is significant variability in who will develop psychopathology following childhood trauma, and predictors of such variability are not well understood. Individual differences in reactivity of the body's physiological stress response system may provide an explanation for which youth show evidence of pathology in environments characterized by stress (Del Giudice et al. 2011; Ellis and Boyce 2008). For example, the hypothalamic-pituitary-adrenal axis (HPA-axis), can moderate the relationship between cumulative adversity during childhood and symptoms of psychopathology (Hagan et al. 2014; Steeger et al. 2016). In this study, we examined whether variability in the HPA-axis response to stress moderates the association between different types of childhood trauma and behavior problems in youth.

Both internalizing and externalizing problems during childhood have shown persistence and predictive validity for psychiatric disorders later in life (Hofstra et al. 2000; Sterba et al. 2007). Maltreatment and traumatic events during childhood are associated with increased risk for both internalizing and externalizing problems (Hussey et al. 2006; Lansford et al. 2002) that persist into adulthood (Bernet and Stein 1999; Chapman et al. 2007). Studies have begun to characterize how different types of adverse experiences in childhood predict diverging patterns of risk across disorders. For example, exposure to violence at home was related to depression, separation anxiety, posttraumatic stress, and conduct problems among preschool-aged youth, while non-interpersonal traumatic events were related to phobic anxiety (Briggs-Gowan et al. 2010). Among adolescents, exposure to physical abuse specifically contributes to elevated aggression, symptoms of depression, anxiety, and social problems (Lansford et al. 2002). Therefore, different types of trauma may predispose youth to different types of psychopathology. This is consistent with an emerging literature positing that different types of childhood trauma and adversity have differential effects on brain development and subsequent behavior (McLaughlin et al. 2014; Teicher et al. 2016). For example, McLaughlin et al. (2014) posit that the predominant approach to measuring adversity in childhood as cumulative has limited our understanding of the distinct consequences of adversity characterized by threat as opposed to deprivation. Adverse childhood experiences characterized by threat (e.g., physical abuse) are associated with alterations to fear learning and reduced activity in brain regions supporting emotional processing and control, whereas experiences characterized by deprivation (e.g., neglect) predict impairments in cognitive performance such as long-term memory, language ability, and overall academic achievement (McLaughlin et al. 2014). Exploring pathways from specific types of adversity to psychopathology warrants further investigation.

Some individuals are more biologically sensitive to deleterious environments than others and therefore more susceptible to psychopathology in stressful social contexts (Ellis and Boyce 2008). More sensitive children living under conditions of stress or maltreatment would be more at risk for psychopathology via repeated physiological activation of the stress system and subsequent allostatic wear-and-tear on the brain and body. This has also been demonstrated in experimental studies where neuroendocrine stress reactivity in infant

macaques moderated the association between nurturing parenting and behavioral outcomes (Suomi 1997). That variability in stress sensitivity (either hyper- or hypo-sensitivity) can be risk-augmenting or risk-protective is the central hypothesis of biological sensitivity to context (BSC) theory (Ellis and Boyce 2008). In the context of childhood trauma exposure, BSC hypothesizes that the association between childhood trauma and behavioral symptoms would be greatest among youth demonstrating greater sensitivity of the stress response system. For example, childhood maltreatment was associated with internalizing symptoms among young adults with greater HPA-axis reactivity to conflict (Hagan et al. 2014). Likewise, more frequent family life events are associated with more internalizing and externalizing behaviors among adolescents with larger salivary cortisol responses to conflict (Steeger et al. 2016). However, the BSC also predicts that high reactivity may be protective in contexts of low stress and high parental care. Likewise, attenuated biological responses to stress can be a risk factor for some forms of stress-related psychopathology (e.g., PTSD; Yehuda et al. 1998, 2000). For example, medical trauma such as a motor vehicle accident is predictive of the development of PTSD among those with atypically low cortisol immediately after the event (Yehuda et al. 1998) Thus, variability in stress sensitivity can moderate the impact of stress on psychopathology but it is unclear whether the direction of this effect is determined by the type of trauma exposure and other contextual factors (e.g., parenting). The Adaptive Calibration Model (ACM), an extension of BSC, posits that experiences during development that are characterized by unpredictability, physical threat/danger, and supportive parental care all individually contribute to the calibration of activation thresholds within the stress response system (Del Giudice et al. 2011). Yet, no study to date has tested the association of these three distinct developmental contexts (unpredictable events, physical threat, parental support/care) in behavioral outcomes at varying degrees of stress sensitivity.

The purpose of the present study was to extend our understanding of biomarkers of vulnerability to psychopathology by testing the interaction between trauma exposure and HPA-axis response to an acute stress task as a predictor of internalizing and externalizing symptoms. The present study examines the role of individual differences in biological sensitivity, measured by the speed of HPA-axis activation to stress, in the associations between different types of childhood trauma and mental health symptoms in youth. We examined these hypotheses within three common but distinct subtypes of trauma exposure in childhood that correspond with environmental domains within the ACM: physical abuse, emotional abuse, and non-intentional trauma/unpredictable traumatic events. Research examining the HPA-axis as a moderator of the association between different types of trauma and behavioral symptoms is still rare and hypotheses for specific trauma subtypes are still somewhat exploratory. However, based on the BSC theory and the ACM, we hypothesized that trauma exposure would be associated with greater behavioral symptoms among individuals with greater HPA-axis sensitivity, but that the strength of this association would be different in the context of low parental support/care (e.g., emotional abuse), physical threat/danger, and unpredictable life events.

Method

Participants

Participants were 121 youth (47% female), ages 9–16 (M_{age}=12.77; SD_{age}=2.26) from a study aimed to characterize the mechanisms underlying adolescent anxiety and depression (Lopez-Duran et al. 2015), and therefore were oversampled for internalizing psychopathology. As determined via semi-structured clinical interview, 20% of participants met criteria for depression, 11% met criteria for an anxiety disorder, and 20% met criteria for an externalizing disorder according to the DSM-IV-TR. The sample was 70% Caucasian, 10% biracial, 6% African American, 3% Latino, 2% Asian, 6% other, and 3% did not respond. Youth in this sample predominantly lived with both biological parents (65%) and in educated families (75% of participants' mothers earned a bachelor's degree or higher). Participants were excluded from the larger study if they had a pervasive developmental disorder, were currently taking asthma medications, had psychotic symptoms, a current diagnosis of PTSD, or currently had a significant medical condition (e.g., cancer).

Procedures

Participants were recruited from the community via flyers, local advertisements, and referrals from clinicians and pediatricians. All eligible participants and their parents provided signed assent and consent to participate and youth were compensated for their time. All participant visits occurred in the afternoon. The stress task consisted of a 30-min baseline phase, 5-min stress task, and 60-min recovery period. After the baseline phase, a research assistant (RA) led the youth into the experiment room to complete the stress task. Immediately following the stress task, the participant watched a 60-min *National Geographic* documentary.

Stress Reactivity—The stress task used in this study was the Socially-Evaluated Cold Pressor Task designed for eliciting HPA-axis activation by combining thermal stress and social evaluation (Schwabe et al. 2008). The participant placed their hand in ice water (33–39 ° F) for up to 3 min while an RA recorded their facial expressions with a video camera. HPA-axis reactivity was estimated from cortisol extracted from six saliva samples obtained during the 90-min laboratory session. To obtain cortisol samples, the child provided passive drool directly into a salivette tube. No agents (e.g., chewing gum) were used to facilitate saliva production. Saliva samples were taken just before the stress task, and 25, 35, 45, 55, and 65 min after stress task initiation. All salivettes were stored in a freezer at −20° Celsius until assayed. Samples were assayed in duplicate at the university's core assay facility within six months of collection using a commercial enzyme immunoassay kit (Salimetrics, Inc.). The sensitivity of the assay was 0.01 lg/dl. To decrease interassay variability, all samples from the same child were assayed in the same batch.

Measures

Childhood Trauma Exposure—Parents (81% mothers) completed the Early Trauma Inventory about their child (Bremner et al. 2000). In this 50-item paper and pencil questionnaire, the parent marked *yes* or *no* to a series of potentially traumatic events including *physical abuse* (being hit to the point of bruising or injury), *sexual abuse* (being

forced to engage in sexual acts), *emotional abuse* (persistently being ridiculed or insulted by a caregiver), or *non-intentional traumatic events* (witnessing an accident, natural disaster). The non-intentional trauma subscale was designed to capture exposure to potentially traumatic events that were secondary to chance. This inventory produces a score for each subtype that reflects the total number of events to which each child was exposed.

Behavioral Symptoms—Child internalizing and externalizing symptoms were reported on the Achenbach Child Behavior Checklist (CBCL) by the participant's parent (Achenbach 1991). The CBCL is a 114-item caregiver-reported measure of internalizing (e.g., sadness, withdrawal, worry) and externalizing (e.g., aggression, hyperactivity) behaviors. Parents were asked to report on a scale of 0–2, whether the given behavior is *not true*, *sometimes true, often or very true* of their child. Some examples of internalizing items are "Would rather be alone than with others" (social withdrawal), and "Cries a lot" (depression). Some examples of externalizing items are "Argues a lot", and "Disobedient at home" (Aggressive behavior). Internalizing and externalizing symptoms were then converted to gender-normed T-scores which were used as the dependent variables in all analyses. The CBCL internalizing scale displays high internal consistency within this sample, Cronbach's α = .82, as did the CBCL externalizing scale, Cronbach's α = .85.

Data Analysis

All data analyses were conducted in SPSS 23.0. Raw salivary cortisol values were transformed using the Box-Cox transformation to address skewness and kurtosis (Miller and Plessow 2013). All other continuous predictor variables were log transformed to reduce skew and kurtosis, and centered at the mean. To compute total cortisol output to the stress task, we computed the Area Under the Curve Increase (AUCi) using trapezoidal aggregation from 6 samples including 0, 25, 35, 45, 55, 65 min post-stress (Pruessner et al. 2003). To identify the speed of HPA-axis activation to the task, we identified each individual's peak response to the task using the peak identification procedures described in Lopez-Duran et al. (2014). We computed a slope by dividing the difference between each participant's baseline cortisol concentration and peak cortisol value by the number of minutes between their baseline and peak. Gender normed T-scores for internalizing and externalizing symptoms were used as the dependent variables in all models. Given the high correlation between externalizing and internalizing, r = .76, p < 0.001, we covaried for clinically significant symptoms (T > 65) in each of these domains, Internalizing with Clinical Externalizing r = .23, p = 0.010 and Externalizing with Clinical Internalizing, r = .45, p < 0.001, so as to not overfit the variance in our models.

We conducted multiple hierarchical linear regressions predicting internalizing and externalizing symptoms with all continuous predictors centered at the mean. We first tested the main effects of speed of HPA-axis activation and trauma exposure, adjusting for child's age, sex, baseline cortisol, total cortisol response to the task (AUCi), and whether the child also demonstrated clinically meaningful symptoms in the alternate symptom domain (internalizing vs externalizing). Total cortisol output (AUCi) was included in all models to isolate the interaction of speed of HPA-axis activation and trauma exposure from HPA-axis recovery. We then added the interaction between trauma exposure and speed of HPA-axis

activation for each trauma subtype separately. Trauma subtypes included physical abuse, emotional abuse, and non-intentional trauma. Sexual abuse was not included as a predictor due to low endorsement of sexual abuse exposure.

Results

Youth in this study experienced a wide range of trauma exposures during childhood; 84.7% of youth were exposed to at least one traumatic event, including physical abuse (47%), emotional abuse (30%), and non-intentional trauma (71%), and 41.3% of youth were exposed to more than one trauma subtype. The average youth demonstrated a 66% increase in cortisol from baseline to their peak response to the stressor. Youth in this study also demonstrated a range of behavioral symptoms, per parent report, such that 15% and 6% of the sample exceeded the clinical threshold (T > 65) for internalizing or externalizing behaviors, respectively. See Table 1 for descriptive statistics and bivariate correlations between all study variables.

Childhood Trauma Exposure, Stress Reactivity, and Internalizing Behaviors

We conducted an adjusted hierarchical regression model predicting internalizing T-scores from childhood exposure to physical abuse, emotional abuse, and non-intentional trauma, as well as HPA-axis reactivity, while controlling for the child's age, sex, clinically significant externalizing behaviors, baseline cortisol, and total cortisol output in response to the task.[1] In the adjusted main effects model, $R^2 = .14$, $F(9, 92) = 1.67$, $p = .108$, there were no significant main effects of either trauma subtype or HPA-axis response to the task on internalizing symptoms, $p > .22$. We then added the interactions between each subtype of abuse and slope of cortisol increase to this model, $\Delta R^2 = .10$, $p = .012$ (See Table 2). In this model, with average HPA-axis reactivity, physical abuse was not associated with internalizing symptoms, more emotional abuse was associated with greater internalizing symptoms, $p = 0.027$, and more non-intentional trauma was associated with greater internalizing symptoms, $p = 0.021$. With increasing speed of HPA-axis reactivity, physical abuse was associated with fewer internalizing symptoms, $p = 0.007$, emotional abuse was associated with greater internalizing symptoms, $p = 0.001$, and non-intentional trauma was associated with greater internalizing symptoms, $p = 0.017$. See Fig. 1a–c for the effect of each subtype of childhood trauma on internalizing symptoms by HPA-axis reactivity.

Child Trauma Exposure, Stress Reactivity, and Externalizing Behaviors

We then conducted an adjusted hierarchical regression model predicting externalizing T-scores from childhood exposure to physical abuse, emotional abuse, and non-intentional trauma, as well as HPA-axis reactivity. In the main effects model, $R^2 = .31$, $F(9, 92) = 4.47$, $p < 0.001$, there were no significant main effects of either trauma subtype or HPA-axis response to the task on externalizing symptoms, $p > .178$. We then added the interactions between each subtype of abuse and slope of cortisol increase to this model, $\Delta R^2 = 0.06$, $p = 0.043$. In this model, when HPA-axis reactivity was average, none of the trauma

[1]Previous investigations using this sample found exposure to any trauma during infancy was related to patterns of within-subject change in HPA-axis reactivity, however the pattern of results in the adjusted models remain unchanged when accounting for exposure to any trauma during infancy (Kuhlman et al. 2015b).

subtypes were associated with externalizing symptoms. As HPA-axis reactivity increased, more physical abuse was associated with fewer externalizing symptoms, $p = 0.013$, more emotional abuse was associated with greater externalizing symptoms, $p = 0.005$, and more non-intentional trauma was associated with greater externalizing symptoms, $p = 0.027$. See Fig. 1d–f for the effect of each subtype of childhood trauma on externalizing symptoms by HPA-axis reactivity.

Discussion

The purpose of this study was to examine whether individual differences in HPA-axis responses to acute stress moderated the relationship between exposure to different types of trauma and behavior problems in youth. Consistent with our hypotheses and the BSC theory, exposure to emotional abuse and non-intentional traumatic events were associated with elevated internalizing and externalizing symptoms when youth demonstrated exaggerated HPA-axis reactivity. In contrast with BSC, physical abuse was associated with elevated internalizing and externalizing symptoms among youth demonstrating attenuated HPA-axis reactivity. These findings highlight that both biological sensitivity and insensitivity can be risk factors for psychopathology in youth and underscore the importance of continuing to examine how physiology interacts with different types of childhood adversity to either promote or impair health.

To our knowledge, two studies to date have examined HPA-axis reactivity to acute stress as a moderator of life stress exposure and mental health symptoms (Hagan et al. 2014; Steeger et al. 2016). In particular, greater stress reactivity strengthened the relationship between stressful family events and both internalizing and externalizing symptoms in a healthy sample of adolescents (Steeger et al. 2016). Our study extends this finding by examining the moderating role between family life stress and mental health in a sample of adolescents with a high rate of current psychopathology. Hagan et al. (2014) found that the association between childhood maltreatment and internalizing symptoms was strongest among youth with exaggerated HPA-axis reactivity to acute stress. In contrast, the association between childhood maltreatment and externalizing symptoms was strongest among youth with attenuated HPA-axis reactivity to acute stress. We also extend this finding by demonstrating that mixed results on the association between stressful experiences and HPA-axis reactivity may be clarified by examining stressful childhood experiences by subtypes, specifically differentiating between physical and emotional abuse. For youth with an attenuated HPA-axis activation slope, exposure to physical abuse was related to more symptoms of psychopathology, reliably exceeding the clinical significance threshold for internalizing symptoms (See Fig. 1). In a previous study with this sample, physical abuse exposure was related to steeper within-subject slopes of HPA-axis activation (Kuhlman et al. 2015a). This suggested that youth in this sample exposed to higher amounts of physical abuse were more likely to have a fast activating HPA-axis and potentially that sensitization of the HPA-axis stress response may be an adaptive response to living in a physically abusive environment. Taken together with the present analyses, a fast-activating HPA-axis may facilitate behavioral responses such as avoiding physically abusive caregivers, seeking social support, or other behaviors that may buffer the long term negative consequences of the abuse, including psychopathology. However, a recent study of adolescents showed that

among youth living in high conflict families, those with an attenuated HPA-axis response to a conflict task exhibited fewer symptoms of psychopathology (Saxbe et al. 2012). The inconsistencies between our results may be explained by their use of total cortisol output as their measure of HPA-axis reactivity, while we controlled for total cortisol production in order to examine the unique contribution of the slope or speed of HPA-axis *activation*. Our findings support the need for a nuanced treatment of HPA-axis function that does not assume that greater stress reactivity reflects vulnerability.

In particular, faster HPA-axis activation in response to stress was linked to lower internalizing and externalizing symptoms, whereas an attenuated slope of cortisol increase was related to more symptoms. Of note, this association was independent of total cortisol response to the stressor (AUCi), suggesting that the timing of HPA-axis activation is important to our understanding of the link between stress and psychopathology above and beyond total cortisol production. Robust activation of the HPA-axis to acute stress is adaptive and signals a flexible, intact system whereas maladaptive behaviors may be characterized by a less steep or *delayed* HPA-axis activation following acute stress. There are several reasons that a delayed activation of the HPA-axis may be related to psychopathology. For example, upon exposure to stress, the central nervous system activates processes that redistribute energy through the body allowing for escape and self-defense, enhance learning and memory for threat-related information, and circulate pro-inflammatory cytokines, all of which serve to promote survival from similar threats in the future (See Herman and Cullinan 1997; Silverman and Sternberg 2012). The HPA-axis is involved in the regulation of each of these processes and delayed activation may result in less efficient redistribution of energy, failure to attend to or retain information relevant to the context of the threat, and poor regulation of inflammation. Given that our approach to the temporal dynamics of HPA-axis activation is novel, these pathways have yet to be experimentally probed in humans.

In contrast with physical abuse, increasing speed of HPA-axis reactivity strengthened the association between both emotional abuse and non-intentional trauma and mental health symptoms. It is important to note, however, that these effects were not reliably associated with symptoms that exceed the clinical threshold (see Fig. 1). Exposure to a neglectful or emotionally abusive caregiver has been linked to atypical diurnal functioning of the HPA-axis (Gunnar and Quevedo 2007). These alterations to the functioning of the HPA-axis are most often observed to be transient and improve with improvements in the caregiving environment (McLaughlin et al. 2015; Slopen et al. 2014), yet even transient upregulation in circulating glucocorticoids can have long-standing implications for the development of the central nervous system. Emotional abuse is associated with attenuated cortisol responses to stress in adulthood, which increases with advancing age (Carpenter et al. 2009). Taken together with our findings, it is possible that down-regulation of the threat response system in an environment with more non-intentional stressors and/or deficits in protective caregiving may be protective against the damaging effects of elevated glucocorticoids on the brain, and less likely to promote behavioral symptoms. Yet, studies differentiating between physical abuse, emotional abuse, and other types of childhood life stress remain rare, thus limiting the ability to disentangle resilience and vulnerability to psychopathology in different childhood environments.

For youth with average HPA-axis reactivity to acute stress, exposure to more emotional abuse and non-intentional trauma were related to greater internalizing symptoms. This suggests that while subtypes of adversity during childhood tend to cooccur (Copeland et al. 2007), unpredictable traumatic events and exposure to emotional abuse convey unique risk for the development of internalizing behaviors despite intact physiological reactivity. Such stressors as emotional abuse and non-intentional traumatic events have been repeatedly linked to psychopathology, most commonly depression (Hammen 2015), however these associations have been explained by different mechanisms. For example, emotional abuse may be particularly detrimental to psychosocial development and subsequent depression given that the presence of emotional abuse likely also indicates less exposure to nurturing caregiving. Low exposure to parental warmth predicts the development of internalizing symptoms (Kuhlman et al. 2014), and the presence of a nurturing caregiver can be protective against psychopathology in the face of other adversities (Hagan et al. 2010). In comparison, non-intentional trauma, such as natural disasters (Goenjian et al. 1996) have been linked to the development of internalizing symptoms. Specifically, anxiety disorders may occur via down-regulation of basal cortisol and sensitization to future stressors (Yehuda 1997). The independent main effects of emotional abuse and non-intentional trauma exposure on internalizing symptoms suggest that each of these subtypes of childhood trauma exposure contribute to mental health, specifically internalizing symptoms, and further investigation is needed to determine whether this occurs via different pathways.

The contribution of these findings should be considered in the context of several limitations. These data are cross-sectional, and do not allow causal inferences. A more rigorous test of biological sensitivity to context would have included assessment of HPA-axis reactivity before and after exposure to different types of trauma and maltreatment, and would have also examined positive environmental factors in addition to trauma. This study was designed to characterize psychobiological processes underlying depression and anxiety in youth, and therefore oversampled for youth with internalizing disorders. As such, results pertaining to externalizing symptoms were less common than internalizing symptoms; only 6% of the sample exceeded the clinical threshold. Further, elevated externalizing behaviors are likely to be comorbid with internalizing symptoms within individuals in this sample rather than reflective of externalizing behavior disorders. Childhood trauma exposure was reported by the parents of our participants, and thus vulnerable to all of the limitations of retrospective reporting of events. While parent reports of youth life events are valid (Johnston et al. 2003), we have limited these analyses to whether an event occurred which is considered to be a measure of exposure that is less vulnerable to reporting error (Brewin et al. 1993; Hardt and Rutter 2004). Rates of maltreatment exposure in this sample are higher than what would be expected based on confirmed maltreatment cases through Child Protective Services (Finkelhor et al. 2014), however that is to be expected given that this study oversampled for youth with psychopathology. Pubertal status has been identified as important to the association between HPA-axis functioning and psychopathology (Colich et al. 2015). Information on pubertal status was not collected on all participants in this sample and therefore could not be examined here. This limitation is mitigated by our inclusion of sex and age in all of our models, however future investigations are necessary to understand the role of pubertal development in the observations made in this study. Finally, individual

differences in slope to peak may have been in response to a particular element (e.g., cold sensitivity) of this stressor and only relevant to how the child would respond to a similar stressor in the environment. Different stress paradigms elicit different profiles of HPA-axis response (Kuhlman et al. 2014), therefore replication of these findings using HPA-axis responses to different laboratory stressors and in larger and diverse samples are needed.

Conclusions and Future Directions

In this study, we demonstrated that individual differences in the speed of HPA-axis activation moderate the association between childhood trauma exposure and mental health in adolescents. Among youth with a quickly activating HPA-axis, exposure to emotional abuse and non-intentional trauma was associated with more internalizing and externalizing symptoms. However, the inverse association was found for youth exposed to physical abuse. Given that abuse subtypes tend to co-occur, one important contribution of these findings is to demonstrate that different types of trauma represent distinct social contexts where variability in functioning of physiological systems can be both a risk and protective factor for the development of psychopathology. For example, rapid HPA-axis activation may be protective for youth exposed to physical abuse and a risk factor for youth exposed to emotional abuse or non-intentional trauma. HPA-axis reactivity to pharmacological and psychological challenge is modifiable in adults using existing cognitive strategies and interventions (Abelson et al. 2010; Hammerfald et al. 2006). Thus, more careful characterization of the distinct role developing physiology plays among youth exposed to different types of stress is necessary to our understanding of developmental psychopathology and mitigating the lifelong mental health sequelae of child adversity.

Acknowledgements

This research would not be possible if not for the support of several individuals and organizations. Among them are the team at MichiganPAL for collecting this data 7 days a week for two years, the families who gave their time to improve our understanding of anxiety and depression, the faculty and fellows of the International Max Planck Research School on the Life Course who have provided valuable insight on the development of this project, and the following organizations for their financial support of this research: Blue Cross Blue Shield of Michigan Foundation, Barbara A. Oleshansky Memorial Award, American Psychological Foundation, and Rackham Graduate School at University of Michigan. The composition of this manuscript was made possible by the National Institute of Mental Health (15750) awarded to Dr. Kuhlman.

References

Abelson JL, Khan S, Young EA, & Liberzon I. (2010). Cognitive modulation of endocrine responses to CRH stimulation in healthy subjects. Psychoneuroendocrinology, 35, 451–459. doi:10.1016/j.psyneuen.2009.08.007. [PubMed: 19758763]

Achenbach TM (1991). Child behavior checklist/4–18. Burlington: University of Vermont, Department of Psychiatry.

Bernet CZ, & Stein MB (1999). Relationship of childhood maltreatment to the onset and course of major depression in adulthood. Depression and Anxiety, 9, 169–174. doi:10.1002/(SICI)1520-6394(1999)9:4<169::AID-DA4>3.0.CO;2-2. [PubMed: 10431682]

Bremner JD, Vermetten E, & Mazure CM (2000). Development and preliminary psychometric properties of an instrument for the measurement of childhood trauma: the early trauma inventory. Depression and Anxiety, 12, 1–12. doi:10.1002/1520-6394(2000)12. [PubMed: 10999240]

Brewin CR, Andrews B, & Gotlib IH (1993). Psychopathology and early experience: a reappraisal of retrospective reports. Psychological Bulletin, 113, 82–98. doi:10.1037/0033-2909.113.1.82. [PubMed: 8426875]

Briggs-Gowan MJ, Carter AS, Clark R, Augustyn M, McCarthy KJ, & Ford JD (2010). Exposure to potentially traumatic events in early childhood: differential links to emergent psychopathology. Journal of Child Psychology and Psychiatry, 51, 1132–1140. doi:10.1111/j.1469-7610.2010.02256.x. [PubMed: 20840502]

Carpenter LL, Tyrka AR, Ross NS, Khoury L, Anderson GM, & Price LH (2009). Effect of childhood emotional abuse and age on cortisol responsivity in adulthood. Biological Psychiatry, 66, 69–75. doi:10.1016/j.biopsych.2009.02.030. [PubMed: 19375070]

Chapman DP, Dube SR, & Anda RF (2007). Adverse childhood events as risk factors for negative mental health outcomes. Psychiatric Annals, 37, 359–364.

Colich NL, Kircanski K, Foland-Ross LC, & Gotlib IH (2015). HPA-axis reactivity interacts with stage of pubertal development to predict the onset of depression. Psychoneuroendocrinology, 55, 94–101. doi:10.1016/j.psyneuen.2015.02.004. [PubMed: 25745954]

Copeland WE, Keeler G, Angold A, & Costello E. (2007). Traumatic events and posttraumatic stress in childhood. Archives of General Psychiatry, 64, 577–584. doi:10.1001/archpsyc.64.5.577. [PubMed: 17485609]

Del Giudice M, Ellis B, & Shirtcliff EA (2011). The adaptive calibration model of stress responsivity. Neuroscience & Biobehavioral Reviews, 35, 1562–1592. doi:10.1016/j.neubiorev.2010.1.007. [PubMed: 21145350]

Ellis BJ, & Boyce WT (2008). Biological sensitivity to context. Current Directions in Psychological Science, 17, 183–187. doi:10.1111/j.1467-8721.2008.00571.x.

Finkelhor D, Vanderminden J, Turner H, Hamby S, & Shattuck A. (2014). Child maltreatment rates assessed in a national household survey of caregivers and youth. Child Abuse & Neglect, 38, 1421–1435. doi:10.1016/j.chiabu.2014.05.005. [PubMed: 24953383]

Goenjian AK, Yehuda R, Pynoos RS, Steinberg AM, Tashjian M, Yang RK, et al. (1996). Basal cortisol, dexamethasone suppression of cortisol, and MHPG in adolescents after the 1988 earthquake in Armenia. The American Journal of Psychiatry, 153, 929–934. doi:10.1176/ajp.153.7.929. [PubMed: 8659616]

Gunnar MR, & Quevedo KM (2007). Early care experiences and HPA axis regulation in children: a mechanism for later trauma vulnerability. In De Kloet R, Oitzl MS, & Vermetten E. (Eds.), Progress in brain research (Vol. 167, pp. 137–149). Amsterdam, The Netherlands: Elsevier B.V.

Hagan MJ, Roubinov DS, Gress-Smith J, Luecken LJ, Sandler IN, & Wolchik S. (2010). Positive parenting during childhood moderates the impact of recent negative events on cortisol activity in parentally bereaved youth. Psychopharmacology, 214, 231–238. doi:10.1007/s00213-010-1889-5. [PubMed: 20521029]

Hagan MJ, Roubinov DS, Mistler AK, & Luecken LJ (2014). Mental health outcomes in emerging adults exposed to childhood maltreatment the moderating role of stress reactivity. Child Maltreatment, 19, 156–167. doi:10.1177/1077559514539753. [PubMed: 24920249]

Hammen CL (2015). Stress and depression: old questions, new approaches. Current Opinion in Psychology, 4, 80–85. doi:10.1016/j.copsyc.2014.12.024.

Hammerfald K, Eberle C, Grau M, Kinsperger A, Zimmermann A, Ehlert U, & Gaab J. (2006). Persistent effects of cognitive-behavioral stress management on cortisol responses to acute stress in healthy subjects—a randomized controlled trial. Psychoneuroendocrinology, 31, 333–339. doi:10.1016/j.psyneuen.2005.08.007. [PubMed: 16183205]

Hardt J, & Rutter M. (2004). Validity of adult retrospective reports of adverse childhood experiences: review of the evidence. Journal of Child Psychology and Psychiatry, 45, 260–273. doi:10.1111/j.1469-7610.2004.00218.x. [PubMed: 14982240]

Herman JP, & Cullinan WE (1997). Neurocircuitry of stress: central control of the hypothalamo–pituitary–adrenocortical axis. Trends in Neurosciences, 20, 78–84. doi:10.1016/S0166-2236(96)10069-2. [PubMed: 9023876]

Hofstra MB, Van der Ende J, & Verhulst FC (2000). Continuity and change of psychopathology from childhood into adulthood: a 14-year follow-up study. Journal of the American Academy of

Child and Adolescent Psychiatry, 39, 850. doi:10.1097/00004583-200007000-00013. [PubMed: 10892226]

Hussey JM, Chang JJ, & Kotch JB (2006). Child maltreatment in the United States: prevalence, risk factors, and adolescent health consequences. Pediatrics, 118, 933–942. doi:10.1542/peds.2005-2452. [PubMed: 16950983]

Johnston CA, Steele RG, Herrera EA, & Phipps S. (2003). Parent and child reporting of negative life events: discrepancy and agreement across pediatric samples. Journal of Pediatric Psychology, 28, 579. [PubMed: 14602848]

Kuhlman KR, Olson SL, & Lopez-Duran NL (2014). Predicting developmental changes in internalizing symptoms: examining the interplay between parenting and neuroendocrine stress reactivity. Developmental Psychobiology, 56, 908–923. doi:10.1002/dev.21166. [PubMed: 24009085]

Kuhlman KR, Geiss EG, Vargas I, & Lopez-Duran NL (2015a). Differential associations between childhood trauma subtypes and adolescent HPA-axis functioning. Psychoneuroendocrinology, 54, 103–114. doi:10.1016/j.psyneuen.2015.01.020. [PubMed: 25704913]

Kuhlman KR, Vargas I, Geiss EG, & Lopez-Duran NL (2015). Age of trauma onset and HPA Axis dysregulation among trauma-exposed youth. Journal of Traumatic Stress, 28. doi:10.1002/jts.22054/full.

Lansford JE, Dodge KA, Pettit GS, Bates JE, Crozier J, & Kaplow J. (2002). A 12-year prospective study of the long-term effects of early child physical maltreatment on psychological, behavioral, and academic problems in adolescence. Archives of Pediatrics and Adolescent Medicine, 156, 824–830. [PubMed: 12144375]

Lopez-Duran NL, Mayer SE, & Abelson JL (2014). Modeling neuroendocrine stress reactivity in salivary cortisol: adjusting for peak latency variability. Stress, 17, 285–295. doi:10.3109/10253890.2014.915517. [PubMed: 24754834]

Lopez-Duran NL, McGinnis EG, Kuhlman KR, Geiss EG, Vargas I, & Mayer SE (2015). HPA-axis stress reactivity in youth depression: evidence of impaired regulatory processes in depressed boys. Stress, 18, 545–553. doi:10.3109/10253890.2015.1053455. [PubMed: 26115161]

MacMillan HL, Fleming JE, Streiner DL, Lin E, Boyle MH, Jamieson E, et al. (2001). Childhood abuse and lifetime psychopathology in a community sample. American Journal of Psychiatry, 158, 1878–1883. doi:10.1176/appi.ajp.158.11.1878. [PubMed: 11691695]

McLaughlin KA, Sheridan MA, & Lambert HK (2014). Childhood adversity and neural development: deprivation and threat as distinct dimensions of early experience. Neuroscience and Biobehavioral Reviews, 47, 578. doi:10.1016/j.neubiorev.2014.10.012. [PubMed: 25454359]

McLaughlin KA, Sheridan MA, Tibu F, Fox NA, Zeanah CH, & Nelson CA (2015). Causal effects of the early caregiving environment on development of stress response systems in children. Proceedings of the National Academy of Sciences, 112, 5637–5642. doi:10.1073/pnas.1423363112.

Miller R, & Plessow F. (2013). Transformation techniques for cross-sectional and longitudinal endocrine data: application to salivary cortisol concentrations. Psychoneuroendocrinology, 38, 941–946. doi:10.1016/j.psyneuen.2012.09.013. [PubMed: 23063878]

Nanni V, Uher R, & Danese A. (2012). Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. American Journal of Psychiatry, 169, 141–151. doi:10.1176/appi.ajp.2011.11020335. [PubMed: 22420036]

Pruessner JC, Kirschbaum C, Meinlschmid G, & Hellhammer DH (2003). Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology, 28, 916–931. doi:10.1016/S0306-4530(02)00108-7. [PubMed: 12892658]

Saxbe DE, Margolin G, Spies Shapiro LA, & Baucom BR (2012). Does dampened physiological reactivity protect youth in aggressive family environments? Child Development, 83, 821–830. doi:10.1111/j.1467-8624.2012.01752.x. [PubMed: 22548351]

Schwabe L, Haddad L, & Schachinger H. (2008). HPA axis activation by a socially evaluated cold-pressor test. Psychoneuroendocrinology, 33, 890–895. doi:10.1016/j.psyneuen.2008.03.001. [PubMed: 18403130]

Silverman MN, & Sternberg EM (2012). Glucocorticoid regulation of inflammation and its functional correlates: from HPA axis to glucocorticoid receptor dysfunction. Annals of the New York Academy of Sciences, 1261, 55–63. doi:10.1111/j.1749-6632.2012.06633.x. [PubMed: 22823394]

Slopen N, McLaughlin KA, & Shonkoff JP (2014). Interventions to improve cortisol regulation in children: a systematic review. Pediatrics, 133, 312–326. doi:10.1542/peds.2013-1632. [PubMed: 24420810]

Steeger CM, Cook EC, & Connell CM (2016). The interactive effects of stressful family life events and cortisol reactivity on adolescent externalizing and internalizing behaviors. Child Psychiatry and Human Development. doi:10.1007/s10578-016-0635-6.

Sterba SK, Prinstein MJ, & Cox MJ (2007). Trajectories of internalizing problems across childhood: heterogeneity, external validity, and gender differences. Development and Psychopathology, 19, 345–366. doi:10.1017/S0954579407070174. [PubMed: 17459174]

Suomi SJ (1997). Early determinants of behaviour: evidence from primate studies. British Medical Bulletin, 53, 170–184. [PubMed: 9158292]

Teicher MH, Samson JA, Anderson CM, & Ohashi K. (2016). The effects of childhood maltreatment on brain structure, function and connectivity. Nature Reviews Neuroscience, 17, 652–666. doi:10.1038/nrn.2016.111. [PubMed: 27640984]

Yehuda R. (1997). Sensitization of the hypothalamic-pituitary-adrenal axis in posttraumatic stress disorder. Annals of the New York Academy of Sciences, 821, 57–75. doi:10.1111/j.1749-6632.1997.tb48269.x. [PubMed: 9238194]

Yehuda R, McFarlane A, & Shalev A. (1998). Predicting the development of posttraumatic stress disorder from the acute response to a traumatic event. Biological Psychiatry, 44, 1305–1313. doi:10.1016/S0006-3223(98)00276-5. [PubMed: 9861473]

Yehuda R, Bierer LM, Schmeidler J, Aferiat DH, Breslau I, & Dolan S. (2000). Low cortisol and risk for PTSD in adult offspring of holocaust survivors. The American Journal of Psychiatry, 157, 1252. doi:10.1176/appi.ajp.157.8.1252. [PubMed: 10910787]

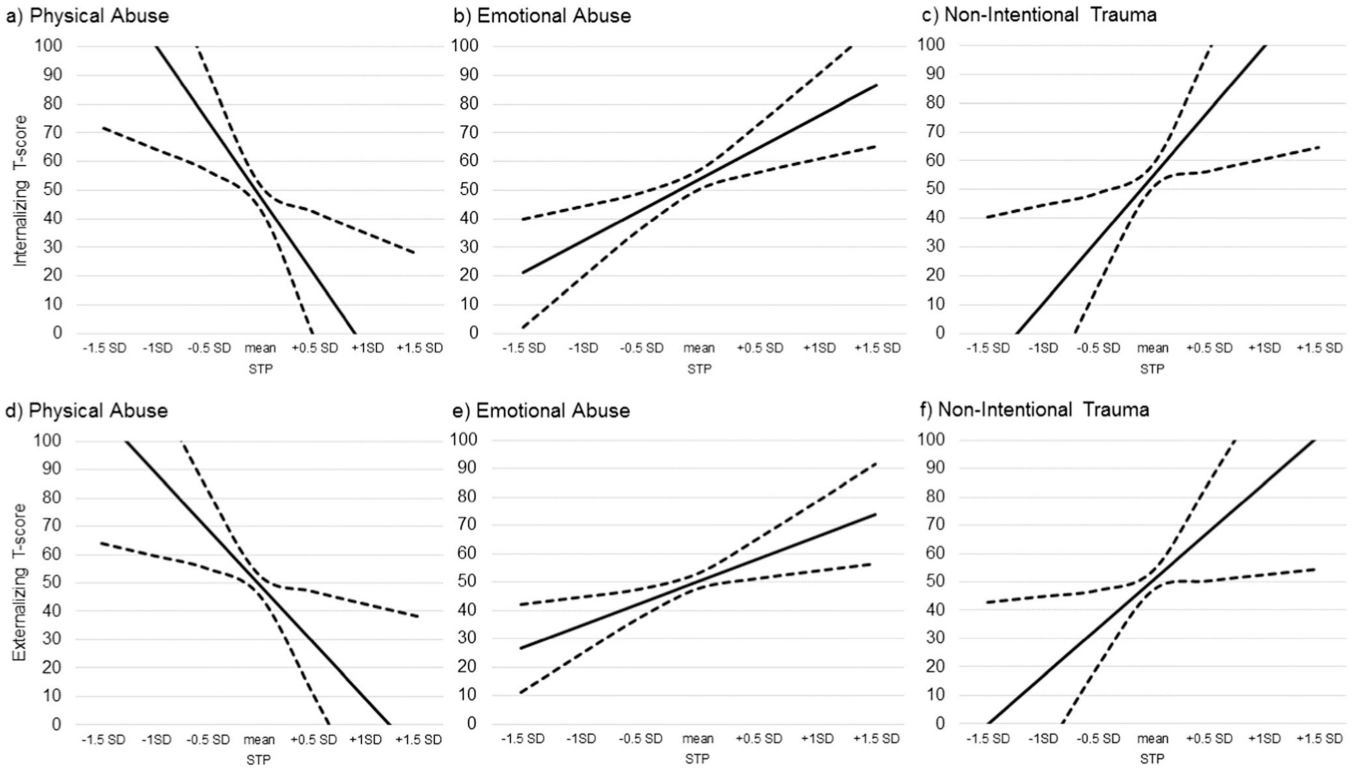

Fig. 1.

Unstandardized effect of physical abuse, emotional abuse, and non-intentional trauma on internalizing and externalizing T-scores by HPA-axis reactivity (STP=Slope to peak) following acute stress exposure. Note: *Solid black lines* represent unstandardized parameter estimates, while *dotted black lines* represent 95% confidence intervals. T-scores > 70 are considered clinically significant

J Abnorm Child Psychol. Author manuscript; available in PMC 2023 October 20.

Table 1

Raw means, standard deviations, and correlations for all study variables

	Mean[a] (SD)	**1.**	**2.**	**3.**	**4.**	**5.**	**6.**	**7.**	**8.**	**9.**	**10.**
1. Age	12.77 (2.26)	1.0									
2. Sex (% female)	47	−0.074	1.0								
3. Physical Abuse[b]	.84 (1.26)	0.041	0.098	1.0							
4. Emotional Abuse[b]	.64 (1.33)	.186†	0.005	.380**	1.0						
5. Non-intentional Trauma[b]	1.60 (1.70)	.240*	−0.057	.302**	.437**	1.0					
HPA-axis reactivity											
6. Baseline Cortisol[c]	.15 (.27)	.152	0.087	0.078	.114	.163†	1.0				
7. Slope to peak[b]	0.004 (0.032)	−.109	0.055	−0.003	.200*	−0.044	.297**	1.0			
8. Peak Cortisol[c]	.25 (.92)	0.045	0.057	0.044	.163†	.057	.716**	.754**	1.0		
9. AUCi[c]	1.67 (26.89)	−0.069	0.027	0.066	.108	−0.069	0.066	.660**	.678**	1.0	
Behavioral symptoms											
10. CBCL Internalizing t-scores	53.10 (11.60)	0.064	−0.033	.123	.147	.161†	0.061	−0.037	−0.007	−0.033	1.0
11. CBCL Externalizing t-scores	48.24 (10.65)	.153	0.053	0.079	0.028	0.001	0.072	0.078	0.085	0.094	.786**

HPA-axis hypothalamic pituitary adrenal axis

[a] Raw means and SD are reported

[b] log transformed for multivariate analyses

[c] Box Cox transformed for multivariate analyses

$^{*}p < 0.05$

$^{**}p < 0.01$

$^{\dagger}p < .10$

Table 2

Unstandardized estimates predicting internalizing and externalizing symptoms from childhood trauma subtypes, HPA-axis reactivity to laboratory stress, and their interactions

	Internalizing symptoms		Externalizing symptoms	
	***b* (*SE*)**	***t***	***b* (*SE*)**	***t***
Physical abuse	−2.78 (2.13)	−1.30	−0.63 (1.78)	−0.35
Emotional abuse	3.76 (1.67)	2.25*	0.41 (1.39)	0.29
Non-intentional trauma	4.72 (2.00)	2.36*	0.58 (1.68)	0.35
Slope to peak	−960.73 (280.57)	−3.42**	−622.0 (232.46)	−2.68**
Physical abuse × slope to peak	−1852.89 (671.8)	−2.76**	−1401.94 (553.06)	−2.54*
Emotional abuse × slope to peak	765.52 (232.2)	3.30**	552.38 (191.72)	2.88**
Non-intentional trauma × slope to peak	1559.46 (641.0)	2.43*	1190.54 (527.54)	2.26*

Model covaries for age, sex, baseline cortisol, total cortisol output (AUCi), and clinically significant symptoms in opposite domain

* $p < 0.05$

** $p < 0.01$