Characterizing the role of different childhood trauma subtypes in the neuroendocrine functioning of youth: implications for adolescent depression

by

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ABSTRACT

Adolescent depression is a major public health concern because childhood onset depression is associated with significant functional impairment and recurrent, chronic depression across the lifespan. A substantial proportion of depressed youth have been exposed to severe childhood maltreatment, and are shown to be less responsive to standard depression treatments. In comparison, depressed individuals without a history of trauma exposure are more likely to be treated effectively with psychotherapy and pharmacological interventions. This suggests that the mechanisms which underlie the development and maintenance of depression in individuals with a history of childhood trauma may differ from those without. In order to develop more effective treatments for adolescent depression, a better understanding of these mechanisms is necessary. One of the neurobiological mechanisms associated with the onset, course, and recurrence of depression is functioning of the HPA-axis, the body's physiological stress response system. The purpose of this study was to characterize the interplay between exposure to childhood trauma and HPA-axis functioning, while also examining the role of childhood trauma in the HPA-axis dysregulation of depressed adolescents. METHODS: Participants in this study were a community sample of 138 youth (aged 9-16) and their parents. All parents completed a semi-structured diagnostic interview, the Early Trauma Inventory (ETI), and the Children's Depression Inventory (CDI), while all youth completed a semi-structured diagnostic interview, a standardized laboratory stress protocol, the Socially Evaluated Cold Pressor Task, and completed a CDI. Each participant contributed 2 pre-stress and 5 post-stress salivary cortisol samples.

Additionally, each participant provided 4 diurnal salivary cortisol samples at home across 2 consecutive weekdays. RESULTS: We found that high reported exposure to general trauma was associated with greater cortisol awakening response and elevated cortisol at bedtime, physical abuse exposure was associated with greater peak reactivity to acute stress, and emotional abuse was associated with delayed down-regulation of cortisol following acute stress compared with non-abused or traumatized youth. Additionally, we found that high reported emotional abuse beginning during the school-aged years was associated with elevated diurnal cortisol throughout the day, while moderate to high reported physical abuse exposure across childhood or even low exposure during early childhood was associated with steeper slopes and acceleration of cortisol to acute stress. Finally, youth with a history of exposure to general trauma who also have depression demonstrate elevated cortisol at bedtime, as well as adrenocortical hypersensitivity to the laboratory setting. Taken together, we found that childhood trauma has a heterogeneous relationship with later HPA-axis functioning, which can occur throughout childhood but may be stronger as these experiences begin later in childhood. With respect to youth with depression, we found evidence of hypersensitivity of the HPA-axis to daily stressors when they also reported a history of frequent non-intentional or accidental trauma during childhood. DISCUSSION: Our findings convey the importance of research incorporating multiple indices of HPA-axis functioning to inform our understanding of stress reactivity. Furthermore, these findings demonstrate that different forms of childhood stress may influence the neurobiological stress systems in different ways across development. Ultimately, depressed youth with a history of reported trauma exposure demonstrate unique patterns of neuroendocrine regulation compared with other depressed or traumatized youth. Overall, this dissertation presents a comprehensive examination of neuroendocrine functioning in youth in the context of childhood trauma exposure

and psychopathology. Findings from this dissertation enhance our understanding of the nature of HPA-axis functioning within the context of lifespan stress reactivity and developmental psychopathology and may help guide the search for novel intervention targets.

Chapter 1: Introduction

More than ten percent of children in America are exposed to severe physical, emotional, or sexual abuse (Finkelhor, Turner, Ormrod, & Hamby, 2009, 2010) and 66% of youth report exposure to a traumatic event by the end of adolescence (Read, Ouimette, White, Colder, & Farrow, 2011). Exposure to childhood abuse and trauma is associated with increased risk for depression during adolescence (Andersen & Teicher, 2008) and poor physical and mental health across the lifespan (Chapman et al., 2004; Chapman, Dube, & Anda, 2007). This is a significant public health concern because the development of depression during adolescence is associated with lifetime risk for poor physical health (Weissman et al., 1999), chronic recurrent psychopathology (Fombonne, Wostear, Cooper, Harrington, & Rutter, 2001), and disability (González, 2010; Mathers & Lancar, 2011). Yet, the mechanisms through which exposure to abuse and trauma during childhood are associated with depression are poorly understood. One possible mechanism may be the impact that abuse and trauma have on the body's physiological stress response system, the Hypothalamic-Pituitary-Adrenal-Axis (HPA-axis) (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008). Therefore, the focus of this dissertation will be to clarify the role of childhood exposure to abuse and trauma on the functioning of the HPA-axis in depressed and non-depressed adolescents.

Both pre-clinical (Ladd et al., 1999; Sanchez, Ladd, & Plotsky, 2001; Sanchez, 2006) and human subjects research (Gunnar & Quevedo, 2007; Heim et al., 2008) has shown that exposure to early trauma is associated with changes in the HPA-axis response to stress. However, individuals exposed to trauma display inconsistent HPA-axis anomalies, namely

hyperreactivity to acute stress (Saltzman, Holden, & Holahan, 2005), hyporeactivity to acute stress (MacMillan et al., 2009; Peckins, Dockray, Eckenrode, Heaton, & Susman, 2012), and hypercortisolemia across the day (Cicchetti & Rogosch, 2001). One potential source of this conflict is the possibility that different types of trauma may impact HPA-axis functioning differently. For example, neglect has been associated with elevated morning cortisol and a greater diurnal slope of decline throughout the day (Kertes, Gunnar, Madsen, & Long, 2008) while severe physical abuse has been linked to atypically low morning cortisol (Cicchetti & Rogosch, 2001). Furthermore, physical abuse exposure has been linked with both blunted reactivity to acute stress (Fisher, Kim, Bruce, & Pears, 2012) and hyper-reactivity to novel, neutral stimuli (Ivanov et al., 2011). However, our understanding of how different types of abuse impact aspects of HPA-axis functioning is limited due to the overrepresentation of studies looking broadly at maltreatment rather than abuse subtypes. In addition, there is a paucity of research examining both diurnal and acute reactivity simultaneously, as a more comprehensive representation of HPA-axis functioning. Therefore, the first aim of this study was to determine how different subtypes of childhood exposure to abuse and trauma impact different components of HPA-axis functioning.

Understanding the impact of different types of trauma exposure on aspects of HPA-axis functioning within a developmental framework is important to our understanding of the sensitivity of the HPA-axis to stressors in the environment across childhood. Age of traumatization may contribute to the association between childhood trauma exposure and HPA-axis functioning, such that exposure to different types of trauma during sensitive periods of psychosocial or neurobiological development may facilitate long-term changes in the physiology of the stress response. To date, much of our understanding has been contributed by animal

models suggesting that there are sensitive periods for HPA-axis development where exposure to early life stress can lead to lifelong adaptations (Gunnar & Quevedo, 2007; Levine, 2005; Sanchez et al., 2001). However, only one study of adults has examined age of trauma exposure as a factor in the long term associations between childhood trauma and HPA-axis functioning among humans (Yehuda, Golier, Yang, & Tischler, 2004). Therefore, it remains unclear how age of traumatization moderates the association between exposure to specific types of trauma exposure and HPA-axis functioning among adolescents. Therefore, the second aim of this study was to determine whether age of trauma onset contributed to the association between trauma exposure and HPA-axis functioning. This is important to our understanding of developmental psychopathology in that the HPA-axis may be more sensitive to forms of abuse and trauma during specific periods of development.

Finally, exposure to trauma during childhood and corresponding anomalies in HPA-axis functioning have been implicated in the development of depression. To date, there are inconsistent findings with regard to the HPA-axis dysregulation present among depressed youth (Birmaher et al., 1996; Lopez-Duran, Kovacs, & George, 2009). This inconsistency may be related to the distinct patterns of HPA-axis regulation and reactivity for depressed adults with and without a history of abuse (Heim, 2000; Heim, Mletzko, Purselle, Musselman, & Nemeroff, 2008). Given the high rate of child abuse and trauma exposure among depressed youth (Lewis et al., 2010), it is possible that previous inconsistent results may be explained by childhood exposure to trauma. Specifically, exposure to abuse may be an important factor in the association between depression and HPA-axis functioning. Therefore, the third aim of this study was to determine whether childhood trauma exposure moderates the association between depression and HPA-axis functioning.

The Hypothalamic-Pituitary-Adrenal-Axis: Physiology, Assessment & Development

Physiology. The HPA-axis is a stress response system that facilitates adaptive bio-behavioral responding to stress. The purpose of the HPA-axis is to maintain homeostasis and promote successful adaptation to stress within the environment through a complex hormonal cascade (Aguilera, 2012). When a stressor or threat is perceived (e.g., pain, extreme temperatures, or perception of threat) and recognized as such by the limbic system, the paraventricular nucleus (PVN) of the hypothalamus secretes corticotrophin releasing factor (CRF) and vasopressin (AVP) to the pituitary gland (Stratakis & Chrousos 1995). In response, the pituitary secretes adrenocorticotrophin hormone (ACTH) to the adrenal gland. ACTH stimulates the adrenal gland to increase production and release of glucocorticoids (cortisol in humans) as well as epinephrine (See Gunnar & Vazquez, 2006). The purpose of this is to initiate the physiological response to stress which, in collaboration with the sympathetic nervous system, redistributes energy to the brain and the muscles to promote survival and regulation in response to stress (Gunnar & Quevedo, 2007).

Glucocorticoids are essential to the maintenance, duration and down-regulation of the stress response, by regulating CRH secretion by the hypothalamus and ACTH secretion by the pituitary. Glucocorticoids are able to regulate the stress response through glucocorticoid (GR) and mineralcorticoid receptors (MRs)(De Kloet, 1991; Sapolsky, Romero, & Munck, 2000). GRs and MRs play complementary roles in HPA-axis regulation in that MRs have greater affinity for glucocorticoids than GRs (De Kloet, 1991; Gunnar & Quevedo, 2007). MRs are densely concentrated in the hippocampus and binding of glucocorticoids to MRs is associated with the regulation of tonic HPA-axis functioning. In contrast, GRs are found throughout the brain and binding of glucocorticoids to GRs is associated with regulation of the acute stress

response (Aguilera, 2012; De Kloet, 1991; Sapolsky et al., 2000; Smith & Vale, 2006). Due to the tonic regulatory role of MRs and their greater affinity for glucocorticoids, only when basal levels of glucocorticoids are exceeded, are GRs activated (De Kloet, 1991; Gunnar & Quevedo, 2007). MRs and GRs also have opposing effects on neural processes such that glucocorticoid reception by MRs promotes glucose in the brain while glucocorticoid reception by GRs inhibit the circulation of glucose in the brain which causes cell death (De Kloet, 1991; Gunnar & Quevedo, 2007). Thus, moderate levels of glucocorticoids are associated with optimal functioning because both excessively high exposure to glucocorticoids during stress and excessively low basal levels of glucocorticoids would be associated inhibition of glucose in the brain by GRs and MRs respectively (De Kloet, 1991; Gunnar & Quevedo, 2007).

Assessment. Due to the complexity of the stress response system, anomalies in a specific aspect of the axis may impact overall HPA-axis functioning differently. Varying methods have been developed to test subcomponents of the HPA-axis which allow us better understanding of the system, such as acute reactivity to stress and circadian regulation; however, variation in these methods increase the likelihood that conflicts in existing literature may be due to differences in what aspect of the axis was assessed.

For example, repeated activation of the stress response system could result in hyper- or hypo-sensitivity of the pituitary to CRH, therefore resulting in anomalies in ACTH production by the pituitary. Anomalies in pituitary response to CRH are typically assessed using the combined Dexamethasone Suppression Test (DST) /CRF test (Heuser, Yassouridis, & Holsboer, 1994). This is an elaboration of the commonly used dexamethasone suppression test (DST) (Nugent, Nichols, & Tyler, 1965), and is a systematic way of assessing tonic regulation of the HPA-axis through the administration of a low dose of dexamethasone at 23:00 and the measurement of

ACTH and/or cortisol the following afternoon. Dexamethasone acts on GRs in the pituitary in a similar way to cortisol and thus suppresses the secretion of ACTH and cortisol the following day. The suppression of ACTH and cortisol mimics the effects of a temporary adrenalectomy on the system. For the DST, some researchers measure plasma ACTH in order to assess functioning of the pituitary directly. Abnormally high ACTH in response to the DST, or failure to suppress, indicates that the pituitary gland is overactive and has dysregulated feedback inhibition. In the combined DST/CRF test, a low dose of dexamethasone is administered at 23:00 and then CRF is administered intravenously at 15:00 the following day. Either ACTH or cortisol is then assessed over the next few hours as a reflection of reactivity to CRF exposure. In contrast to the standard DST (which simulates an adrenalectomy), the administration of CRF is intended to stimulate the secretion of ACTH from the pituitary and thus lead to glucocorticoid production. In this test, abnormally low cortisol following the administration of CRF would indicate hyposecretion of ACTH to the adrenal gland. The advantages of using either the DST or the combined DST/CRF test are that the researcher is able to control for individual differences in the sensitivity of the hypothalamus to stress and threat in the environment.

While the DST or combined DST/CRF method allows the researcher to control for an important source of individual variability, it is limited in that only conclusions can be drawn about one subcomponent of the HPA-axis within a dynamic system. Any DST or DST/CRF test where the outcome is ACTH has only assessed the functioning and potential dysregulation of the pituitary gland, while any DST or combined test which assesses cortisol as an outcome will be unable to determine the source of observed anomalies (i.e. dysregulated pituitary, adrenal or feedback sensitivity through MR and GR receptors). Furthermore, because the combined DST/CRF test eliminates individual differences in limbic activation of the stress-response, the

observed reactivity of the HPA-axis may not reflect an individual's typical physiological response to acute stressors in the environment.

Glucocorticoid production can also be assessed by exposing participants to a standardized psychosocial stressor and measuring cortisol (either through blood or saliva) in close succession before and after exposure to this stressor. If taken frequently enough throughout the stress paradigm, these samples enable the assessment of individual differences in baseline, peak, and regulation of glucocorticoids after stress. Peak cortisol responses to the stressor could reflect the intensity of excitatory input into the axis, sensitivity of the axis at the hypothalamus, pituitary, or the adrenal, duration of activation, or efficiency of regulation onset, while cortisol regulation following peak are likely a reflection of the density of GRs, primarily in the hippocampus (Sapolsky, Meaney, & McEwen, 1985). A system which quickly returns to baseline cortisol levels after reaching peak is an adaptive response to a mild, acute stressor and likely reflects the sensitivity and density of GRs to shut down the stress response. In comparison, a sustained elevation in cortisol, or poor regulation, in response to the stressor likely reflects a lower density of GRs and thus a delay in the "shutting down" of the stress-response. Many studies assessing acute HPA-axis reactivity do not employ a dense sampling strategy following the stressor, and instead assess pre-stress and a single post-stress sample which is intended to reflect peak responses (See Clements, 2012 for a review of methodological concerns in salivary cortisol research). However, there is significant variability in peak HPA-axis reactivity to a psychosocial stressor (Lopez-Duran, et al., 2009). For this reason, previous studies that have not used a dense sampling approach have limited our understanding of the HPA-axis response because peak may not have been accurately captured and this method does not allow us to assess regulatory processes in the stress response. Instead, these studies only provide a rough and vague estimation

of hyper- or hypo- reactivity of the HPA-axis. Therefore, in this study we assessed acute HPA-axis reactivity to a psychosocial stressor using dense sampling of salivary cortisol to enable conclusions about adrenal sensitivity to HPA-axis activation as well as the regulation of that activation.

Glucocorticoids also circulate throughout the body according to a circadian pattern. A typically developing human should demonstrate their highest cortisol levels in the morning and their lowest cortisol levels in the evening (Clements, 2012). Circadian patterns of cortisol regulation can be assessed using an individual's urine, blood, or saliva. This method allows us to understand how the volume of glucocorticoids changes throughout the day to maintain homeostasis. Abnormally high diurnal cortisol can be an indicator of several dysregulations in the axis; namely, there could be chronic hypersecretion of CRH/AVP by the hypothalamus, or hypersecretion of ACTH by the pituitary (Aguilera, 2012). Abnormally low diurnal cortisol can be an indicator that the hypothalamus has down-regulated secretion of CRF/AVP to the pituitary (Aguilera, 2012), possibly following repeated activation to chronic environmental stress (Heim, Ehlert, & Hellhammer, 2000; Miller, Chen, & Zhou, 2007). In addition, MRs have high-affinity for glucocorticoids and their sensitivity to low concentrations of circulating glucocorticoid play an important role in maintaining basal levels throughout the day as well as before and after stress (Aguilera, 2012). Diurnal functioning of the HPA-axis is important to our understanding of the stress system because the HPA-axis reflects the body's ability to maintain homeostasis and conserve energy for daily survival. Dysregulations in diurnal functioning are often a reflection of exposure to chronic activation of the stress system and may result in long-term alterations in the acute stress response despite fluctuations in chronic stressors over time. Also, adaptive diurnal functioning of the HPA-axis has implications for other physiological processes such as

immune functioning (Heim et al., 2002; Watts-English, Fortson, Gibler, Hooper, & De Bellis, 2006), growth (Kertes et al., 2008), sleep (Buckley & Schatzberg, 2005) and therefore dysregulation may be related to disruptions in these systems as well.

In addition, there is a dramatic increase in cortisol as a response to waking up which is referred to as the cortisol awakening response (CAR) (Federenko et al., 2000). Currently, it is debated as to whether CAR is part of the circadian cortisol rhythm, or whether it is a form of HPA-axis reactivity to the process of transitioning from being asleep to being awake (Fries, Dettenborn, & Kirschbaum, 2009). Despite this debate, there is some consensus that CAR is a reliable approximation of the flexibility of the HPA-axis (Federenko et al., 2000) which is emerging as an important indicator of overall HPA-axis functioning.

Development. The development of the HPA-axis is highly influenced by social experiences in the child's early environment (Gunnar & Donzella, 2002; Gunnar, 1998). In an optimal rearing environment, there is growing evidence to support that the HPA-axis is more sensitive to stress during the first three months of life (Gunnar, 1998). This may also be influenced by the parent-child relationship such that infants demonstrate hyper-secretion of cortisol following separation from their mother, but only if the infant has an insecure attachment (Gunnar, 1998). During the early childhood years, there appears to be a shift in HPA-axis regulation to hypo-responsiveness (Tarullo & Gunnar, 2006). This period of hypo-responsiveness is also observed in rodent offspring and can be disrupted after extended and repeated separations from the mother (Colorado, Shumake, Conejo, Gonzalez-Pardo, & Gonzalez-Lima, 2006; Kuhn & Schanberg, 1998). These findings suggest that maternal care-giving buffers HPA-axis responses during much of childhood (Gunnar & Donzella, 2002). It appears that maternal buffering of glucocorticoid production to stress allows the offspring to

adapt to repeated stressors (e.g., new environments) and develop social behaviors to regulate the stress response to novel experiences (e.g., babysitters) (Gunnar, 1998; Tarullo & Gunnar, 2006). Maternal buffering of HPA-axis responses also likely promotes optimal neurobiological development by protecting the developing offspring's brain from exposure to high levels of glucocorticoids. Exposure to high levels of glucocorticoids facilitate cell death and inhibit the development of neuronal connections (Gunnar, 1998).

Early childhood is also a sensitive period for neurobiological development, specifically in the limbic system which initiate's the body's reaction to stress in the environment (Gunnar & Quevedo, 2007; Gunnar & Vazquez, 2006). During periods of neural development, the consequences of exposure to high levels of glucocorticoids can result in long-term neurobiological impairments. Therefore, children who have been exposed to abuse and maltreatment within the care-giving environment during early childhood are likely to develop chronically high and dysregulated diurnal cortisol as well as anomalies in neurobiological structures which were developing at the time of the abuse. This has been shown in non-human primates, such that monkey offspring who are in a disrupted care-giving environment fail to show diurnal variation in cortisol levels across the day (Sanchez et al., 2001; Sanchez, 2006), while monkey offspring who are maltreated by their mothers show HPA-axis hyper-reactivity to stressors (Sánchez et al., 2005). Children who were living in orphanages for extended periods typically demonstrate high cortisol throughout the day which remain similarly elevated from morning to night (Gunnar, Morison, Chisholm, & Schuder, 2001). Also, adults who were sexually abused between the ages of 3-5 were more likely to have reduced hippocampal volume in comparison with adults who were sexually abused during adolescence (Andersen et al., 2008; Andersen & Teicher, 2008). This indicates that exposure to early childhood trauma may be

associated with neurobiological consequences within the limbic system, which initiates and regulates the HPA-axis.

Puberty is associated with an increase in morning cortisol levels (Halligan et al., 2004; Netherton et al., 2004) as well as an increase in acute stress reactivity (Tarullo & Gunnar, 2006). These changes to HPA-axis functioning have been attributed to changes secondary to sexual maturation (Gunnar, Wewerka, Frenn, Long, & Griggs, 2009; Legro, 2003; Stroud, Papandonatos, Williamson, & Dahl, 2004). It is possible that laboratory stress tasks are also more effective in older youth due to the cognitive challenges involved however this appears unlikely given patterns of activation to commonly used stressors throughout childhood (Gunnar et al., 2009). Puberty also represents the achievement of reproductive capacity as well as a developmental increase in need and ability for autonomy (Lerner, Boyd, & Du, 2010). The co-occurrence of these changes in HPA-axis functioning and the development of autonomy has been considered an indication that social regulation of the HPA-axis ends at the transition to adolescence (Tarullo & Gunnar, 2006). Given the vulnerability of the stress response system during childhood, it is likely that disruptions in the care-giving environment before pubertal onset would facilitate dysregulated HPA-axis functioning, especially in diurnal cortisol.

Childhood trauma exposure and HPA-axis functioning

With this understanding of the physiology, assessment and development of the HPA-axis, we can now explore the existing literature on the association between early childhood trauma and HPA-axis functioning. Contrary to the large volume of research looking at diurnal cortisol in maltreated children, research looking specifically at the association between childhood traumatic experiences and acute HPA-axis reactivity to psychosocial stressors has been documented by only 11 studies.

Many previous studies of the association between childhood abuse and HPA-axis functioning have looked at cumulative trauma exposure or have conceptualized several types of abuse exposure as one construct (e.g., maltreatment). These studies have produced conflicting results. For example, one study found that healthy adults with exposure to severe maltreatment during childhood exhibit lower ACTH and HPA-axis reactivity to a psychosocial stressor compared with non-maltreated adults (Carpenter et al., 2007). In contrast, other studies of adult samples have found that exposure to childhood maltreatment is associated with hyperactivity of the HPA-axis to external stimulation, which is enhanced among individuals with depression (Heim, 2000; Heim et al., 2008). Most recently, a study comparing maltreated and non-maltreated youth found that maltreated youth demonstrated attenuated HPA-axis reactivity to the TSST-C, which was specific to youth exposed to physical and/or sexual abuse, and not youth exposed only to neglect (Trickett, Gordis, Peckins, & Susman, 2014). Maltreated youth also demonstrate hyper-reactivity to non-aversive stimuli compared with non-maltreated youth (Ivanov et al., 2011), which may indicate that, rather than facilitating hyperactivity to stress exposure, abuse may be associated with perceiving neutral environmental stimuli as threatening.

Furthermore, there have been many studies documenting associations between child maltreatment and either tonic or diurnal functioning. For example, two studies of youth who were exposed to maltreatment showed no differences from non-maltreated youth in baseline cortisol functioning (MacMillan et al., 2009; Ouellet-Morin et al., 2011) while one study found that baseline cortisol levels for maltreated youth were lower than their non-maltreated counterparts (Gordis, Granger, Susman, & Trickett, 2008). Some studies have found some forms of child trauma exposure to be associated with elevated cortisol in the morning (Cicchetti & Rogosch, 2001) while others have found some child trauma exposure to be associated with

attenuated cortisol throughout the day((described as a lack of significant decrease in cortisol across the day; Bevans, Cerbone, & Overstreet, 2008). Other studies have found that children who exhibit generally "atypical" diurnal cortisol patterns are more likely to have been maltreated (Linares et al., 2008). These relationships may also vary by severity of abuse. For example, in a sample of healthy children, exposure to moderate adversity was associated with elevated cortisol throughout the day while individuals with exposure to severe adversity demonstrated similar diurnal cortisol regulation to non-abused controls (Gustafsson, Nelson, & Gustafsson, 2010). Similarly, children with a moderate amount of cumulative adversity demonstrate greater CAR while severe adversity is associated with similar CAR to children with little to no adversity (Gustafsson, Anckarsäter, Lichtenstein, Nelson, & Gustafsson, 2010).

Inconsistencies in the association between abuse exposure and circadian HPA-axis functioning have been explained in part by trauma subtype (Bruce, Fisher, Pears, & Levine, 2009). This is likely because HPA-axis functioning in response to stress varies by the nature of the threat, the emotions elicited by the threat, the level of individual control during the stressful event, and individual differences in regulatory responses to that threat (Miller et al., 2007). Therefore, different types of childhood stress, including accidental trauma and emotional, physical, or sexual abuse, that vary in each of these domains may result in unique changes in HPA-axis functioning. A comprehensive examination of each type of abuse exposure and its association with the nuances of HPA-axis functioning is necessary to characterize these associations.

Emotional abuse is defined as "injury to the psychological capacity or emotional stability of the child as evidenced by an observable or substantial change in behavior, emotional response, or cognition" and injury as evidenced by "anxiety, depression, withdrawal, or aggressive

behavior" (Department of Health and Human Services, 2011). In one study, infants who were exposed to maternal withdrawal exhibited elevated baseline cortisol before a separation task (Bugental, Martorell, & Barraza, 2003). These findings suggest that maternal withdrawal influences the development of tonic maintenance of the HPA-axis. However, these consequences may result in impairments in acute reactivity during adulthood. For example, healthy adults with high reported exposure to emotional neglect in childhood exhibit lower and flatter cortisol in response to acute stress (Carpenter et al., 2007). Children who have been exposed to emotional abuse and neglect have been found to have atypical circadian cortisol patterns (Carlson and Earls, 1997; Gunnar et al., 2001), including low morning cortisol (Bruce et al., 2009), and little variation in cortisol throughout the day (Gilles et al., 2000). In summary, emotional abuse appears to be associated with significant impairments in the tonic and circadian functioning of the HPA-axis which in turn facilitates blunting of acute reactivity to stress. It is important to keep in mind however that these studies have examined both emotional abuse and emotional neglect which may represent two different, but overlapping, constructs.

Physical abuse is generally defined as "any non-accidental physical injury to the child" and can include striking, kicking, burning, or biting the child, or any action that results in a physical impairment of the child (Department of Health and Human Services, 2011).
In one study, infants who were exposed to frequent spanking exhibited hyper-reactivity following a separation task compared with non-spanked children (Bugental et al., 2003). These findings suggest that harsh physical punishment facilitates hyper-reactivity to psychosocial stress early in life. However, among preadolescent youth (age 10-12), exposure to violence and physical abuse is associated with decreased cortisol in response to a stressor (Fisher, Kim, Bruce, & Pears, 2012; Peckins, Dockray, Eckenrode, Heaton, & Susman, 2012). These findings reflect

that exposure to trauma and violence contributes to hyper-responsiveness of the axis to stress during childhood and hypo-responsiveness of the axis to acute stress upon the transition to adolescence. Taken together, these findings likely indicate a shift in HPA-axis functioning from childhood to adulthood. Among healthy adults who had been exposed to maltreatment, moderate to severe physical abuse was associated with diminished ACTH and cortisol response to acute stress (Carpenter et al., 2007). However, no studies to date have documented the association of physical abuse, specifically, with circadian HPA-axis functioning. Many studies have relied heavily on previous findings related to "maltreatment" however. Therefore, physically abused children are thought to have flat diurnal cortisol with atypically low morning cortisol and atypically high evening cortisol levels (Hart, Gunnar, & Cicchetti, 1996; Kaplan, Pelcovitz, & Labruna, 1999)

Sexual Abuse is defined as the employment, use, persuasion, inducement, enticement, or coercion of any child to engage in, or assist any other person to engage in, any sexually explicit conduct or simulation of such conduct for the purpose of producing a visual depiction of such conduct (Department of Health and Human Services, 2011). Also included in the definition of sexual abuse are: rape, molestation, prostitution, or other form of sexual exploitation of children, or incest with children (Department of Health and Human Services, 2011). Sexual abuse exposure is associated with hyper-secretion of both ACTH and cortisol in response to acute stress among healthy adults (Carpenter et al., 2007). Adults who have a history of childhood sexual abuse also show enhanced suppression of cortisol in the DST, which indicates enhanced feedback inhibition of the HPA-axis (Stein, Yehuda, Koverola, & Hanna, 1997). In contrast, sexually abused girls (ages 7-15) demonstrate hypo-secretion of ACTH in response to CRH stimulation but no differences in cortisol response (De Bellis et al., 1994). Notably, the sexually

abused girls in this sample with high dysthymia demonstrated elevated tonic cortisol levels before the task which was interpreted as a dysregulation of their diurnal rhythm (De Bellis et al., 1994).

While these studies provide a foundation for understanding the association between childhood trauma and HPA-axis stress reactivity, there are significant methodological limitations to them. For example, many studies collect saliva samples aimed at assessing reactivity by way of cortisol response, but not necessarily regulation of that response (e.g., Bugental et al., 2003; Ivanov et al., 2011). Regulation of the HPA-axis reflects the process of returning cortisol levels back to baseline. Regulation is most likely a reflection of HPA-axis negative feedback sensitivity, which is determined largely by the density of GRs throughout the brain and MRs in the hippocampus (Aguilera, 2012; Liu et al., 1997; Sapolsky et al., 2000). High GR density, and corresponding efficient negative feedback of the HPA-axis, has long been associated with exposure to variations in maternal warmth in rodent models while low GR density, and corresponding poor negative feedback of the HPA-axis, has also be associated with exposure to stress during prenatal and early development (Liu et al., 1997). Therefore, the existing literature on children does not sufficiently characterize differences in the entire stress reactivity process as associated with childhood trauma.

Furthermore, each of these studies either examines the role of a specific childhood stressor (e.g., domestic violence) or a sum of cumulative stress and trauma exposure, which does not allow us to differentiate the roles of different childhood stressors on an individual's short- and long-term psychological and physiological response. This is a significant gap in the literature given that much of the research on the impact of early life stress on neurobiological development has been tested in animal models where early life stress is operationalized as lack

of maternal care or an insufficient environment for development. Trauma is defined as an event that involves actual or threatened death, serious injury, threat to one's physical integrity, witnessing an event that involves death, injury, or a threat to the physical integrity of another person, or learning about unexpected or violent death, serious harm, or threat of death or injury experienced by a family member or other close associate (American Psychological Association, 2000). According to this definition, some forms of child abuse such as emotional abuse and low levels of neglect may not be considered "traumatizing." It is likely that exposure to emotional abuse and neglect may be associated with different HPA-axis reactivity than exposure to something acutely traumatizing like a car accident, or something which chronically affects the child's physical safety, such as physical or sexual abuse. Furthermore, this is convincing evidence that chronic stress in the form of abuse may facilitate long-term changes in stress reactivity while acute trauma exposure may have a temporary impact on stress functioning that indicates risk for psychopathology. For example, among children exposed to acute injuries, the emergence of dysregulated production of cortisol prospectively predicted the development of PTSD symptoms at least 6 weeks later (Delahanty, Nugent, Christopher, & Walsh, 2005). However when comparing children exposed to a motor vehicle accident to children exposed to emotional stress, the motor vehicle accident was associated with elevated tonic cortisol, however these differences we no longer present 1 and 6 months following the accident (Pervanidou, 2008). Furthermore, healthy, non-maltreated children who were witnesses to violence within the past 12 months prospectively predicted lower HPA-axis reactivity to a psychosocial stress task (Peckins et al., 2012). Taken together, only recent acute trauma exposure during youth appears to be related to anomalies in HPA-axis functioning for most children while exposure to chronic stressors appears to have long-term effects.

To date, there is limited research documenting the association between childhood exposure to different types of trauma and HPA-axis functioning. Therefore, one aim of this study was to differentiate between emotional, physical, sexual abuse and accidental trauma in their associations with subcomponents of HPA-axis functioning, including the cortisol awakening response, diurnal regulation of cortisol, reactivity to an acute stressor, and regulation from acute stress.

Developmental context of childhood trauma exposure and HPA-axis reactivity

Age of traumatization has been identified as an important developmental contextual factor in the relationship between childhood trauma and the development of psychopathology (Cicchetti, Rogosch, Gunnar, & Toth, 2010; Davidson & Smith, 1990; Kaplow & Widom, 2007). For example, in an early study of the psychiatric consequences of childhood trauma exposure, patients who exhibited symptoms of post-traumatic stress were more likely to have been exposed to their first trauma before the age of 10 years, while individuals who reported no symptoms reported experiencing their first traumatic experience at around age 14 (Davidson & Smith, 1990). In another study of female adults with a history of sexual abuse, women who were sexually abused before the age of 12 were more likely to develop depression throughout the lifespan, while women who were sexually abused after age 12 were more likely to develop symptoms of PTSD (Maercker, Michael, Fehm, Becker, & Margraf, 2004). Further, another study of adults who were sexually and physically abused before the age of 12, children abused before the age of 5 were more likely to have significant anxiety and depression symptoms during adulthood than participants whose abuse occurred later in childhood (Kaplow & Widom, 2007). Each of these findings suggest that adult risk for developing depression may be more associated with abuse occurring earlier in childhood. This finding was extended recently such that children

who were severely maltreated during the first five years of life who also endorsed elevated depression and anxiety symptoms exhibit dysregulation of diurnal cortisol (Cicchetti et al., 2010). The association between age of traumatization and the development of depression also seems to remain salient across the lifespan in both community (Kraaij, Arensman, & Spinhoven, 2002) and severely abused samples (Kuhlman, Maercker, Bachem, Simmen, & Burri, 2013).

Age of traumatization is likely an important consideration in the relationship between childhood trauma exposure and HPA-axis functioning because early childhood is a sensitive period for neurobiological development, specifically in the limbic system which manages the body's regulation of stress in the environment (Gunnar & Quevedo, 2007; Gunnar & Vazquez, 2006). Very few studies have examined this association directly. In one study of adult males with and without PTSD, age of trauma was negatively correlated with the number of GRs, while age of trauma onset was positively correlated with HPA-axis response following dexamethasone suppression (Yehuda et al., 2004). This study offered the conclusion that, consistent with animal models, that there are sensitive periods of HPA-axis development that occur early in childhood. However, there are no other studies among children or adolescents addressing whether age of onset moderates the association between childhood trauma and HPA-axis functioning. Therefore, there is a paucity of research examining these associations for specific abuse and trauma. This is an important gap in the literature given that developmental sensitivity of neurobiological systems, such as the HPA-axis, is often implicated as a mechanism for the future predisposition to developing psychiatric disorders, such as depression (Andersen & Teicher, 2008). Therefore, the second aim of this study was to examine age of traumatization as a contributor to the association between childhood trauma exposure and functioning of the HPA-axis among depressed and non-depressed adolescents.

Childhood trauma exposure as an explanation of the association between depression and HPA-axis functioning

The overall goal of this dissertation will be to contribute to our understanding of adolescent depression within the context of exposure to childhood abuse. Among adults, the HPA-axis dysregulation observed in depressed patients was consistent with impairments in the negative feedback loop of the HPA-axis (Burke, Davis, Otte, & Mohr, 2005), which may be an indicative of reduced GR density or sensitivity to quickly regulate the acute stress response (Young, Haskett, Murphy-Weinberg, Watson, & Huda, 1991). There is growing evidence that there is HPA-axis dysregulation among depressed youth (Burke, Davis, Otte, & Mohr, 2005; Guerry & Hastings, 2011; Lopez-Duran, Kovacs, & George, 2009; Von Werne Baes, de Carvalho Tofoli, Martins, & Juruena, 2012), and that the dysregulation observed is similar to that of adult depressed samples (Kaufman, Martin, King, & Charney, 2001). Furthermore, depressed youth demonstrate chronically high diurnal cortisol, a dysregulated response to the DST, which also supports the claim that depression is associated with impairments in the negative feedback loop of the HPA-axis, but suggests that depression is not associated with increased pituitary sensitivity to CRF or adrenal sensitivity to ACTH (Lopez-Duran et al., 2009). Additionally, as children age the association between childhood depression and dysregulated diurnal rhythms increases, with the dysregulation preceding the onset of the depressive disorder (Guerry & Hastings, 2011). For example, elevated CAR prospectively predicted the onset of depression (Adam et al., 2010). This suggests that some of the HPA-axis functioning anomalies that are associated with this psychopathology precede the onset of clinically significant behavioral symptoms.

However, there have also been several studies concluding that the HPA-axis is not dysregulated in depressed samples of youth (Birmaher & Heydl, 2001; Birmaher et al., 1996). Some of the variability in findings related to HPA-axis dysregulation among depressed youth may be explained by childhood trauma exposure. These inconsistencies may be due to the high representation of abused youth among depressed samples (Lewis et al., 2010), and the HPA-axis dysregulation associated with those experiences during childhood. For example, in a sample of 7-13 year old children, depression with a history of abuse was associated with hypersecretion of ACTH in an exogenous CRH administration compared with depressed but not abused and control children (Kaufman et al., 1997). Furthermore, adult women with exposure to severe childhood sexual and physical abuse, regardless of depression status, demonstrate hypersecretion of ACTH while only those with both depression and childhood abuse exposure exhibited hypersecretion of cortisol (Heim, 2000). Both of these findings highlight the important contribution of childhood abuse exposure in components of HPA-axis functioning. However, these findings may be further elaborated by examining these associations by trauma subtype, which has yet to be presented in the literature to date.

Inconsistencies in the association between psychopathology and circadian HPA-axis functioning have also been better explained in relation to childhood abuse exposure (Cicchetti & Rogosch, 2001; Cicchetti et al., 2010; Weems & Carrion, 2007). Specifically, youth with high levels of internalizing symptoms (Cicchetti & Rogosch, 2001), depression (Hart et al., 1996) and PTSD (Weems & Carrion, 2007) who also have been exposed to trauma demonstrate elevated diurnal cortisol throughout the day. Another study clarified that only school aged children who had experienced sexual and physical abuse before the age of 5 who also had high depressive symptoms demonstrated a flat diurnal cortisol pattern (Cicchetti et al., 2010). Given these

findings, it is possible that reduced cortisol throughout the day is an adaptive and protective neurobehavioral response to exposure to repeated stressors in the environment. Thus, individuals who continue to demonstrate hyperreactivity of the HPA-axis are a subset whose neurobiological system is not adapting to the chronically stressful environment and are therefore more likely to develop and maintain stress-related psychopathology. Therefore, in this study we clarify the role of exposure to different types of childhood abuse in the association between depression and HPA-axis functioning among adolescent youth by testing the hypothesis that childhood trauma exposure moderates the relationship between depression and HPA-axis functioning.

It is also possible that the length or severity of specific psychopathology, such as depression, may influence the long-term adaptations to the HPA-axis in response to trauma exposure. For example, among adolescents with moderate depression symptoms, childhood maltreatment was associate with elevated cortisol response to a stressor while adolescents with severe depression symptoms demonstrated high and blunted cortisol throughout the task regardless of maltreatment background (Harkness, Stewart, & Wynne-Edwards, 2011). Therefore it is possible that childhood trauma exposure may be impacting HPA-axis reactivity, while chronic depression may be impacting the system's diurnal regulatory system. It is also possible that exposure to trauma during sensitive developmental periods result in a hyperactive HPA-axis. This hyperactivity serves as an adaptive response to novel stressors, but becomes down-regulated in response to recurring threats within the environment (Kant, Eggleston, & Landman-Roberts, 1985). Individuals who fail to develop this down-regulation of the HPA-axis in response to current stress may then be neurobiological predisposed to stress-related psychopathology, such as depression across the lifespan. Evidence of this has been shown in research with adults who have been exposed to childhood abuse. Specifically, adult males with a

history of child abuse and current MDD demonstrated HPA-axis hyper-reactivity to the Dexamethasone/CRF test, while depressed men without a history of child abuse did not (Heim et.al., 2008). This finding suggests that exposure to child abuse may facilitate impaired negative feedback inhibition of the pituitary which may be a risk factor for developing depression (Heim et al., 2008). This has also been replicated among adolescents, where depressed adolescents demonstrated significantly higher cortisol in response to a stress task which was accounted for entirely by adolescent exposure to early life adversity and recent stress (Rao, Hammen, Ortiz, Chen, & Poland, 2008). Therefore, while we hypothesized that exposure to different types of childhood abuse will moderate the association between depression and different components of HPA-axis functioning, it is likely that depression will be uniquely associated with tonic and circadian indices of HPA-axis regulation as an artifact of disease severity and duration.

Aims and Hypotheses

The goal of this dissertation was to explain the association between different types of exposure to childhood trauma and adolescent HPA-axis functioning within a developmental psychopathology framework. To do this, we cross-sectionally examined parent-reported childhood trauma exposure as a predictor of diurnal and acute HPA-axis functioning in a sample of depressed and non-depressed adolescents. Based upon the existing literature, we addressed three important aims:

Aim 1 Determined whether different subtypes of childhood exposure to abuse and trauma were associated with different components of HPA-axis functioning. To address this aim, we examined the association between three types of trauma exposure (emotional abuse, physical abuse, and general trauma) as well as a simultaneous model of all types and two different components of HPA-axis functioning: acute stress reactivity (a) and circadian cortisol (b). Given

the paucity of previous research examining specific components of HPA-axis functioning as explained by specific subtypes of abuse exposure, our hypotheses were general and somewhat exploratory. We hypothesized that: high reported emotional abuse would be associated with atypically flat circadian cortisol patterns and impairment in the regulation to acute stress, high reported physical abuse would be associated with hyperreactivity to acute stress as defined by peak cortisol, and that more accidental (general) trauma would be associated with blunted HPA-axis response to acute stress. See Figure 1.1 for a model of this aim.

Aim 2 Determined whether age of traumatization (onset) impacted the association between trauma exposure and HPA-axis functioning. We hypothesized that age of traumatization would moderate the association between types of trauma exposure and HPA-axis reactivity (physical, emotional, accidental trauma), such that exposure to subtypes of trauma at earlier ages would be associated with more profound pattern of neuroendocrine functioning. See Figure 1.2 for an example of this model for physical abuse, which is replicated for the other three types of trauma exposure.

Aim 3 Determined whether exposure to childhood abuse and trauma moderates the association between depression and HPA-axis functioning. We hypothesized that exposure to frequent subtypes of trauma would moderate the association between adolescent depression and HPA-axis functioning, specifically that regulation of the acute stress response would be impaired among depressed youth with greater exposure to trauma however this may vary by specific types of abuse or trauma exposure. See Figure 1.3 for a model of this aim.

Chapter 2: Methods

Participants

Participants in this study were taken from a larger research study conducted at the University of Michigan Psychoneuroendocrinology and Affective Laboratory (MichiganPAL): Project RAAD. Project RAAD (Research on Adolescents with Anxiety and Depression; HUM00034924) aimed to characterize the cognitive, affective, and neuroendocrine mechanisms that underlie adolescent anxiety and depression. Youth in this study participated in three laboratory visits across two weeks. Data collection from this study began in May of 2011 and concluded in January 2013. Participants for this study were 138 youth, ages 9-16. Participants were recruited from the Ann Arbor and surrounding communities via flyers, referrals from clinicians, referrals from primary care providers, and advertisements on websites targeting parents of adolescents who may have concerns about their child's mental health. Families who were interested in participating first completed a phone screen where their eligibility for the study was determined. Participants were excluded from the larger study if they had a pervasive developmental disorder, were currently taking medications for asthma, were experiencing psychotic symptoms, or currently had any significant medical conditions (e.g., cancer). Participants were further excluded from the present study if they currently had an anxiety disorder in the absence of a major depressive episode. All eligible participants and their participating parents provided signed assent and consent to participate in the study and all participants were compensated for their time at the completion of the study.

Non-depressed sample. This sample was composed of all participants who did not meet criteria for any current or past anxiety or depressive disorders but does include some youth with ADHD or other externalizing disorders.

Depressed sample. This sample was composed of all participants who met criteria for a current Major Depressive Episode according to the semi-structured clinical interview. This group also included some youth with comorbid anxiety, ADHD or ODD.

Measures

Childhood trauma exposure. Each child's parent completed the Early Trauma Inventory about their child as a paper and pencil questionnaire (Bremner, Bolus, & Mayer, 2007; Bremner, Vermetten, & Mazure, 2000). In this inventory, the parent was asked to mark "yes" or "no" to a series of potentially traumatic events. For items where the parent marked "yes," they were to indicate the age of the child at the time of the event, as well as the duration of the event in years. These potentially traumatic events include general traumatic events such as witnessing an accident or exposure to a natural disaster, physical abuse such as being hit to the point of bruising or injury, sexual abuse such as being forced to engage in sexual acts, or emotional abuse such as persistently being ridiculed or insulted by a caregiver. Compared with the abuse subscales, the general trauma subscale was "comprised of a range of stressful and potentially traumatic events that are mostly secondary to chance events, … as opposed to events in the abuse domains that typically involve perpetration by an individual known to the victim with a specific intent to harm the victim" (Bremner, Vermetten, & Mazure, 2000). This inventory produces a total score for each subtype of abuse that reflects the total number of abuse events multiplied by the duration of each of those events. Each subtype total score can be then summed to create a proxy for total abuse and trauma exposure.

Child Depression Inventory. Also during the laboratory visit, both the parent and child completed the Children's Depression Inventory (CDI-S for Self and CDI-P for parent informant) (Kovacs, 1983). The CDI is a self-report measure of general dysphoria with good reliability and validity for children ages 8–17 years that has demonstrated good reliability in previous research on depression in children and adolescents (Klein, Dougherty, & Olino, 2005). In this study, both the CDI-P and CDI-S demonstrated high reliability, $\alpha = .86$ and $\alpha = .91$, respectively.

Clinical interview. Following the completion of the consent process, each participating parent and their child completed a semi-structured diagnostic interview via the Interview Schedule for Children and Adolescents-Diagnostic Version (ISCA-D; Sherrill & Kovacs, 2000). These interviews were conducted by trained, advanced doctoral students who were directly supervised by a licensed clinical psychologist. In this diagnostic interview, the clinician spent 1-2 hours alone with the participant's parent assessing the child for developmental milestones as well as lifetime and current mood disorders, psychotic symptoms, anxiety disorders, eating disorders, ADHD, conduct disorders, and substance use disorders. During this time, the child completed the laboratory stress protocol. Once the parent interview and the laboratory stress protocol were completed, the clinician conducted a similar 1-hour interview with the youth. These interviews were then scored by the clinician, reviewed by the licensed clinical supervisor, and discussed with a team of clinicians to assure there was a clinical consensus on the diagnosis. All parents received a brief letter regarding the results of this clinical interview and, where appropriate, were referred to mental health professionals in the community for further evaluation and intervention.

Procedures

Diurnal HPA-axis reactivity. Each participant contributed two consecutive weekdays of home saliva samples to assess for diurnal HPA-axis functioning. On each of these days, participants were asked to provide passive drool into sterile salivette tubes immediately after waking, 45 minutes after waking, just before dinner, and immediately before bed. Participants were asked to refrain from eating or drinking for 1 hour before each saliva sample and store these saliva samples in a freezer until they were returned to the laboratory. Each participant also kept a log on the days of their home saliva sampling where they recorded the time each sample was taken, their sleep and wake times, and whether the day included any significant stressors.

Acute Stress Reactivity. Each child participated in a neuroendocrine reactivity task at MichiganPAL (michiganpal.org) located at a large, public university in the Midwest (See Figure 2.1 for stress task timeline). Children were not familiar with the laboratory, although it is possible that some youth had participated in research in the building before. All visits were conducted in the afternoon (1:00pm or 4:00pm) between May 2011 and January 2013. The stress task protocol consisted of a 30-minute baseline phase, a 5-minute stress task, and a 60-minute regulation/recovery period for a total of 95 minutes.

Baseline phase. A 30-minute baseline phase was used to allow for the regulation of the stress response to any stressors that occurred prior to arrival and because the laboratory was novel to the participant. During the baseline phase, each participant met a research assistant (RA) who accompanied them for the duration of the laboratory visit. The RA first directed the youth to a waiting room where he/she was given the option of playing with one of the lab's preselected activities for 30 minutes (a puzzle, an etch-a-sketch, building with manipulatives, or

reading a magazine). Participants were encouraged to keep physical activity to a minimum during this phase and were discouraged from using their mobile phones.

Stress task. After the baseline procedures, the child was led into the experiment room by the research assistant to complete the stress task. The stress task used in this study was the Socially-Evaluated Cold Pressor Task (Schwabe, Haddad, & Schachinger, 2008). In this task, the participant was escorted into a separate room, directed to sit on a stool beside a large bucket of ice water (33-39° F), and look directly into a video-camera placed approximately 12 inches from their face. At this time, the RA began recording with the video camera and read the following to the participant from a script:

"In a moment I will ask you to place your hand into this bucket of water. Please keep your hand in the water for as long as you can while continuing to look into the camera. I will hold this stop watch so that you may see how much time has passed. After 3 minutes, you may remove your hand from the water and dry off your hand. If at any point you experience pain or extreme discomfort, you should remove your hand from the bucket. Now, you may place your hand in the bucket when you are ready."

When the participant submerged their hand in the bucket of ice water, the RA began the stopwatch so that the participant could see how much time had passed. If the participant removed their hand before 10 seconds had passed, the RA asked the participant to replace their hand in their bucket until they had achieved at least 10 seconds. Once the participant exceeded 10 seconds, they were free to remove their hand from the bucket as soon as they began to feel "significant discomfort." However, they were instructed to continue looking into the camera until 3 minutes had passed. If the participant was able to keep their hand in the bucket for the full 3 minutes, the RA asked them to remove their hand from the bucket. For every participant,

once 3 minutes had passed, the RA turned off the camera and provided the participant with a dry towel for their arm.

Regulation phase. Immediately following the stress task, the participant was led into a new room with a couch and a television. The child was instructed to watch one of 4 60-minute *National Geographic* documentaries, "Appalachian Trail", "Ocean Drifters", "The Ballad of the Irish Horse", or "Rainforest". These videos were selected for their lack of significant emotionally arousing content.

HPA-axis stress reactivity. HPA-axis stress functioning was estimated from cortisol levels extracted from a total of 7 saliva samples obtained during the course of the 90-minute laboratory session. To obtain cortisol samples, the child spit directly into a salivette tube. No agents (such as chewing gum) were used to facilitate saliva production in the children. The first saliva sample was taken in the first minute of the baseline period. At this time, a stopwatch was started and all further samples were collected according to a strict schedule. The baseline saliva sample was taken just before the youth began the stress task. Saliva samples continued to be taken at 25, 35, 45, 55, and 65 minutes after the initiation of the stress task. Only the post-stress samples were used in the analysis of stress-reactivity (see analysis section below). All salivettes were stored in a freezer at -20^{o} Celsius until assayed. Samples were assayed at a University of Michigan Core Assay Facility within 6 months of collection in duplicate and averaged using a commercial enzyme immunoassay kit (Salimetrics). 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. Duplicates varying more than 15% were re-assayed.

Data Analysis

All data analyses were conducted in SPSS 20.0. Raw salivary cortisol values were transformed using the Box-Cox transformation to optimally address issues of skewness and kurtosis (Miller & Plessow, 2013). In each model, we first tested the association between sex and age on each index of HPA-axis functioning: cortisol awakening response, diurnal regulation, and acute reactivity. If age or sex were predictors of patterns of cortisol change where $p < .10$, the impact of age or sex on that pattern of cortisol regulation or reactivity was included in all further models. Age and sex were included as covariates where appropriate in these models because previous studies have shown evidence of significant differences in cortisol across the transition into adolescence (Gunnar, Wewerka, Frenn, Long, & Griggs, 2009), as well as between sexes (Kudielka & Kirschbaum, 2005). Therefore, including these as covariates in our models allowed us to account for the relationships between trauma exposure and HPA-axis functioning above what is accounted for by age and sex.

Aim 1 To determine the unique association between subtypes of childhood trauma and adolescent HPA-axis functioning, we conducted separate analyses for cortisol awakening response, diurnal cortisol regulation, and acute stress reactivity.

In the cortisol awakening response analyses, we conducted unadjusted and adjusted multiple, hierarchical linear regressions predicting change from waking to 45 minutes post-waking (cortisol awakening response) from trauma subtypes.

In the diurnal cortisol regulation analyses, we conducted unadjusted and adjusted growth curve models using linear mixed modeling predicting waking cortisol (intercept) and slope of diurnal cortisol regulation to dinner and then bedtime from each trauma subtype. In these models, each subtype of trauma exposure was log transformed and centered at the mean. For each of

these mixed models, we used an unstructured covariance matrix to allow for variation in the correlation between cortisol at different samples, account for the impact of waking cortisol levels on diurnal slope, and the random effects for every model were the intercept (waking) and the linear slope.

To determine the association between childhood trauma subtypes and acute stress reactivity we conducted separate growth curve models using linear mixed modeling for trajectories of HPA-axis reactivity across the entire stress protocol (reactivity from baseline), trajectories of cortisol increase to peak response (reactivity to peak), and trajectories of cortisol regulation from peak (regulation from peak). To do this, we used a modified version of Growth Curve Analysis using landmark registration and an unstructured covariance matrix, where three components of stress reactivity were tested in three separate models (See Lopez-Duran, Mayer, & Abelson, 2014). Landmark registration is a process of identifying each individual's peak in the stress reactivity curve and anchoring each individual's reactivity curve to that landmark as the intercept (Ramsay & Li, 1998). The use of landmark registration aided us in controlling for individual differences in peak time in response to the stress task (Lopez-Duran, Hajal, Olson, Felt, & Vazquez, 2009; Lopez-Duran et al., 2014). In the first model we estimated the influences of our predictors on baseline cortisol as well as the acceleration of cortisol from baseline towards peak reactivity. The second model estimated peak cortisol levels as the intercept, linear and quadratic slope towards that peak represented by minutes to peak. The random effects in this model were the intercept and the linear slope and the effects of age and sex were tested as covariates and included in the conditional models if they were associated with variations in cortisol regulation. The third model estimated HPA-axis regulation using landmark registration of peak cortisol as the intercept, linear and quadratic slope away from that peak represented by

minutes during regulation. The random effects in this model were the intercept and the linear slope, and the model included baseline cortisol as a covariate (See Figure 2.2 for representations of these HPA-axis reactivity models).Within each of these stress reactivity analyses, there were four separate linear mixed models: one model for each subtype of trauma exposure, and one adjusted model which included the impact of each subtype of abuse simultaneously. For each mixed model, we used an unstructured covariance matrix to allow for variation in the correlation between cortisol at different samples, account for the impact of baseline (Sample 2- 0 minutes to stress) cortisol levels on stress reactivity, and the random effects for every model were the intercept and the linear slope of that specific model.

Aim 2 To determine whether age of onset moderated the association between childhood trauma exposure and adolescent HPA-axis functioning, identified all participants in our study who were exposed to at least one traumatic event as reported on the ETI. We then used parent-reported information from the ETI to determine the youngest age a child was reported to experience each subtype of trauma. All continuous variables used as predictors were transformed as necessary to reduce skew and kurtosis, and centered at the mean. Therefore, in all models where age of onset was a predictor, 0 represents average age of exposure to their first trauma within that subtype. We then conducted models with the same methods reported for Aim 1 predicting cortisol awakening response, diurnal cortisol regulation, stress reactivity from baseline, reactivity to peak, and regulation from peak from the main effects of each trauma subtype, age of onset, and the interaction between age of onset and trauma subtype.

Aim 3 To determine whether childhood trauma exposure moderated the association between current depression and adolescent HPA-axis functioning, we conducted models with the same methods reported for Aim 1 predicting cortisol awakening response, diurnal cortisol

regulation, stress reactivity from baseline, reactivity to peak, and regulation from peak from the main effects of current depression, each trauma subtype, and the interaction between depression and trauma subtype. In these models, depression was a binary variable where 0 indicates no current depression and 1 indicates depression.

In order to conduct the proposed analyses, we needed a minimum of 75 youth. This participant number allowed us to test the largest proposed model (Aim 1 & 2 the adjusted Linear Mixed Models) with up to 15 fixed effects without concern for over-fitting the data.

Chapter 3: Results

Childhood Trauma Exposure and adolescent HPA-axis functioning

This dissertation represents data from 121 youth (51% male; M_{age} = 12.8; SD_{age} = 2.3), 85% of whom reported exposure to at least one traumatic event. The experiences reported ranged in subtype such that 71% of our sample reported experiencing at least one general trauma, 48% reported experiencing at least one incident of physical abuse, 31% reported at least one emotional abuse experience, and 6% of our sample reported at least one sexual abuse experience. Among the participants exposed to general trauma, the most frequently endorsed general traumatic events were: serious personal injury or illness (25%), serious illness or injury of a parent (13%), serious illness or injury of a sibling (13%), death of a friend (18%), separation or divorce of parents (20%), witnessing violence (14%), family mental illness (24%), and family substance abuse (11%). See Table 3.1 for descriptive information and correlations between all study variables. These youth represent a range of psychiatric disorders such that 29% met criteria for at least one current psychiatric disorder and 7% met criteria for comorbid psychiatric disorders (e.g., depression and ADHD, or Depression and any anxiety disorder). Specifically, 14% of our sample met criteria for a current depressive disorder, 6% met criteria for comorbid depression and anxiety disorders, and 18% met criteria for ADHD, ODD, or Conduct Disorder. No participants in this study met criteria for PTSD. The results of Aim 1 and Aim 3 of this dissertation included data provided from all of these participants, while the results of Aim 2 only included data from youth reporting exposure to at least one traumatic event (n = 102). See Table 3.1 for descriptive information and correlations between all study variables.

[Insert Table 3.1 here]

Trauma Exposure and Cortisol Awakening Response

To test the hypothesis that trauma subtypes would be associated with cortisol awakening response, we conducted unadjusted and adjusted multivariate regressions where abuse subtypes were included as predictors of change in cortisol from waking to 45 minutes later. In the unconditional model, as expected, greater cortisol upon waking was associated with greater cortisol 45 minutes later, $\beta = .64$, $t = 5.18$, $p < .001$. In conditional model including age and sex as predictors, age, $\beta = .131$, $t = 1.49$, $p = .14$, and sex, $\beta = .011$, $t = .125$, $p = .90$, were not significant predictors of change in cortisol from waking to 45 minutes later. Therefore age and sex were not included in any of the subsequent conditional abuse models predicting cortisol awakening response.

We then conducted separate unadjusted models for each subtype of trauma exposure (See Table 3.2). Physical and emotional abuse were not associated with the cortisol awakening response, $p = .23$ and $p = .09$, while more reported general trauma was associated with a greater cortisol awakening response, $\beta = .204$, $t = 2.24$, $p < .05$. However, in an adjusted model accounting for all three types of trauma simultaneously, the effect of general trauma exposure was no longer significant, $\beta = .16$, $t = 1.57$, $p = .12$, and neither physical abuse or emotional abuse were significant predictors of the cortisol awakening response.

[Insert Table 3.2 here]

Trauma Exposure and Diurnal Cortisol Regulation

To test the hypothesis that trauma subtypes would be associated with diurnal regulation of cortisol levels, we conducted traditional growth curve models with subtypes of trauma predicting changes in cortisol across the day measured at waking, dinnertime and bedtime. We first examined unconditional linear and quadratic growth models of diurnal cortisol using waking cortisol values as the intercept. The quadratic model was the best fit to the data (linear model AIC = 310.8 vs. quadratic model AIC = 309.7). For this quadratic unconditional model, there was a linear decrease of cortisol over time, time β = -.068, t(122.1) = -5.57, $p < .001$, but this decrease somewhat decelerated later in the day, time^2 β = .001, t(102.5) = 1.77, p = .08, suggesting that the decline in cortisol throughout the day became less pronounced between dinner and bedtime.

We then conducted separate conditional models for age and sex. In our unadjusted sex model, sex did not impact cortisol levels at wakening, sex β = .033, t(103.0) = .45, p = .66, or the linear decline of diurnal cortisol, sex x time β = .03, t(113.7) = 1.22, p = .22 respectively. However, there was a trend to suggest that males had a steeper linear decline in cortisol between dinner and bedtime than females, sex x time^2 β = -.003, t(97.5) = -2.09, p = .04. In our unadjusted age model, age was not associated with waking cortisol (intercept), or cortisol trajectory throughout the day, age β = -.02, t(105.1) = -1.21, p = .23, age x time β = .007, t(117.8) = 1.29, p = .20, and age x time^2 β = -.0005, t(99.9) = -1.35, p = .18. Therefore, in all further diurnal cortisol models, the effects of sex on the intercept and slopes of diurnal cortisol were included as covariates while the effects of age on the intercept and slopes of diurnal cortisol were not.

We then conducted separate conditional unadjusted models for each subtype of childhood trauma exposure (physical abuse, emotional abuse, and general trauma) as they influenced both

waking cortisol and slope of diurnal cortisol (See Table 3.3). Physical and emotional abuse did not impact cortisol upon waking (intercept) or cortisol trajectories during the day. In contrast, general trauma exposure was associated with a steeper linear decline during the day, GT x time β = -.037, t (103.3) = -2.36, p =.02, and a more intense deceleration of the decline as bedtime approached, GT x time^2 β = .002, t (88.0) = 2.16, p =.03, suggesting increasing levels of cortisol between dinner and bedtime (See Figure 3.1).

[Insert Table 3.3 here]

[Insert Figure 3.1 about here]

We then conducted an adjusted model of all three trauma exposure subtypes as predictors of waking cortisol and diurnal regulation. Consistent with the unadjusted models, there were no effects of physical or emotional abuse on waking cortisol or cortisol trajectories over time, while general trauma exposure continued to impact the linear decline, GT x time β = -.044, t(102.3) = -2.49, p = .015, and later deceleration over time, GT x time^2 β = .002, t(87.2) = 2.19, p = .03.

Trauma Exposure and Acute Stress Reactivity

To test the hypothesis that trauma subtypes would be associated with acute stress reactivity, we conducted three series of growth curve analyses which model acute stress reactivity from baseline, reactivity to peak, and regulation from peak.

HPA-reactivity from baseline. We first examined unconditional linear, quadratic and cubic growth models of acute stress using baseline cortisol values as the intercept. The cubic model was the best fit to the data (linear model AIC = -225.2 vs. quadratic model AIC = -247.5 vs. cubic model AIC = -253.4). In the unconditional model, from baseline, intercept β = -1.70, t(128.4) = -43.7, p < .001, cortisol values increased initially, time β = .006, t(505.4) = 2.92, p < .01, decelerated as participants approached their peak response, time^2 β = -.0003, t(480.0) = -

3.51, $p < .001$, after which the deceleration intensified, time^3 $\beta = -.000002$, $t(480.0) = 2.83$, $p < .01$.

We then conducted separate conditional models for age and sex. In our unadjusted sex model, sex did not impact baseline, sex $\beta = .056$, $t(120.8) = .685$, $p = .50$, linear, sex x time $\beta = .0001$, $t(475.7) = .017$, $p = .99$, quadratic, sex x time^2 $\beta = -.00003$, $t(452.0) = -.187$, $p = .85$, or cubic slope of HPA-axis reactivity to acute stress, sex x time^3 $\beta = .000$, $t(452.0) = .219$, $p = .83$. Older participants were more likely to have higher cortisol immediately before the stress task than younger participants, age $\beta = .044$, $t(123.0) = 2.51$, $p < .05$. However, age did not impact the linear, quadratic, or cubic slopes of stress reactivity, age x time $\beta = .0004$, $t(484.0) = .451$, $p = .65$, age x time^2 $\beta = -.00003$, $t(460) = -.739$, $p = .46$ and age x time^3 $\beta = .000$, $t(460) = .649$, $p = .52$ respectively. Therefore, sex was not included as a covariate in any further models of HPA-axis reactivity from baseline, while the impact of age on the intercept was included as a covariate.

[Insert Table 3.4 here]

We then conducted conditional unadjusted models for each subtype of childhood trauma exposure (physical abuse, emotional abuse, and general trauma) as they influenced cortisol at baseline and slope of acute stress reactivity. Physical abuse did not impact baseline pre-stress cortisol, PA $\beta = .021$, $t(118.9) = .40$, $p = .69$, while there were trends to suggest that physical abuse plays a dampening role in the initial linear increase in cortisol, PA x time $\beta = -.006$, $t(481.0) = -1.89$, $p = .059$, an emphasis on the acceleration towards peak, PA x time^2 $\beta = .0002$, $t(456.0) = 1.92$, $p = .055$, and a more rapid regulation, PA x time^3 $\beta = -.000002$, $t(456.0) = -1.80$, $p = .072$. Emotional abuse was not related to baseline cortisol, EA $\beta = -.002$, $t(120.6) = -.046$, $p = .96$, or the initial cortisol increase after the stressor, EA x time $\beta = -.004$, $t(481.0) = -1.52$, $p = .13$. However, there were trends suggesting that more emotional abuse was related to greater

acceleration to peak, EA x time^2 β = .0002, t(456.0) = 1.70, p = .09, and the regulation from that peak, EA x time^3 β = -.000002, t(456) = -1.76, p = .08. General trauma was not related to differences in baseline cortisol, GT β = .049, t(110.3) = .966, p = .34, the approach to peak, GT x time^2 β = .0002, t(408) = 1.38, p = .17, or regulation, GT x time^3 β = -.000001, t(408) = -1.11, p = .26, however there was a trend suggesting that more general trauma exposure was related to a dampening of the initial cortisol increase from baseline, GT x time β = -.005, t(428.7) = -1.73, p = .08. We then conducted an adjusted model of all three trauma exposure subtypes as predictors of acute stress reactivity from baseline. See Table 3.4 for results of adjusted model of HPA-axis response from baseline. When accounting for exposure to childhood trauma of all three types, physical abuse, emotional abuse and general trauma were not associated with differences in baseline cortisol, linear, quadratic, or cubic slope of acute stress reactivity from baseline.

Reactivity to Peak. To test whether subtypes of childhood trauma exposure were associated with peak (intercept) and reactivity to peak (slope), we first examined unconditional linear and quadratic growth models of post-stress cortisol using peak values as the intercept. The quadratic model was the best fit to the data (linear model AIC = 27.1 vs. quadratic model AIC = -16.2). For the unconditional quadratic model, cortisol values increased linearly from baseline, time β = .008, t(271.5) = 6.18, p < .001, and this increase accelerated, time^2 β = .0002, t(165.0) = 7.05, p < .001, as individuals approached their peak response, intercept β = -1.69, t(121.3) = -45.9, p < .001.

We then conducted conditional unadjusted models for age and sex. Sex was not associated with cortisol peak, sex β = .037, t(114.0) = .470, p = .64, sex x time β = -.0001, t(255.7) = -.018, p = .99, sex x time^2 β = .00002, t(152.1) = .315, p = .75. Older participants were more likely to have higher cortisol peaks than younger participants, age β = .034, t(116.5) = 2.03,

$p < .05$. However, age was unrelated to the trajectory of HPA-axis reactivity towards peak, age x time $\beta = -.001$, $t(259.6) = -1.20$, $p = .23$, or age x time^2 $\beta = -.00001$, $t(155.6) = -1.18$, $p = .24$. Therefore, in all further models, the effect of age on peak cortisol was included as a covariate.

We then conducted conditional unadjusted models for each of our trauma exposure subtypes (physical abuse, emotional abuse, general trauma) as they influenced both the slope and peak parameters of post-stress cortisol curves. More physical abuse was related to a greater initial increase in cortisol, PA x time $\beta = .004$, $t(258.4) = 2.03$, $p < .05$, and an increased acceleration as individuals approached their peaks, PA x time^2 $\beta = .0001$, $t(149.1) = 2.76$, $p < .01$, but physical abuse was not related to peak cortisol values, PA $\beta = .025$, $t(114.9) = .488$, $p = .63$. Given that in our reactivity from baseline models, physical abuse was not associated with variability in baseline cortisol, this model suggests that physical abuse is associated with hyper-sensitivity of the HPA-axis to acute stressors. Emotional abuse was not related to differences in the peak response to the task, EA $\beta = -.024$, $t(115.7) = -.546$, $p = .59$, or changes in cortisol approaching those peaks, EA x time $\beta = -.001$, $t(255.9) = -.396$, $p = .69$ and EA x time^2 $\beta = -.00001$, $t(150.3) = -.303$, $p = .76$. Similarly, general trauma was not related to differences in the peak response to the task, GT $\beta = .006$, $t(104.5) = .112$, $p = .91$, or the changes in cortisol approaching those peaks, GT x time $\beta = -.001$, $t(230.7) = -.379$, $p = .71$ and GT x time^2 $\beta = .00001$, $t(140.4) = .395$, $p = .69$.

We then conducted an adjusted model of all three childhood trauma exposure subtypes as predictors of peak cortisol and activation slopes. See Table 3.4 for results of adjusted model of peak activation of the HPA-axis response. Consistent with the unadjusted models, higher reported physical abuse continued to be associated with hypersensitivity to stress via steeper

accelerations of cortisol toward peak levels after accounting for exposure to emotional abuse and general trauma (See Figure 3.2).

[Insert Figure 3.2 about here]

Regulation from Peak. We then examined unconditional linear and quadratic growth models of post-peak cortisol regulation using peak values as the intercept. The quadratic model was the best fit to the data (linear model AIC = -174.5 vs. quadratic model AIC = -195.6). For this quadratic model, from the average predicted peak, intercept β = -1.69, $t(122.3)$ =-43.3, p < .001, cortisol values declined over time, time β = -.013, t(328.3) = -9.55, p < .001, and this decline decelerated throughout the regulation phase, time^2 β = .00004, t(294.5) = 5.12, p < .001.

We then conducted conditional unadjusted models for age and sex. Males demonstrated no differences in peak cortisol, sex β = -.012, t(116.6) = -.203, p = .84, or initial declines in cortisol following their peak, sex x time β = .004, t(316.6) = 1.48, p = .14, however male participants showed less deceleration of this decline in cortisol over time compared with female peers, sex x time^2 β = -.0001, t(281.1) = -1.82, p < .07. Age was not related to differences in peak cortisol values, age β = .006, t(121,9) = .512, p = .61, nor was it associated with differences in the regulation of cortisol away from that peak, age x time β = -.0004, t(321.9) = -.648, p = . 52, age x time^2 β = -.000003, t(295.2) = -.158, p = .87. Therefore, in all further cortisol regulation models, the effects of sex on the intercept and slopes of post-peak cortisol regulation were included as covariates, while age was not.

We then conducted conditional unadjusted models for each of our childhood trauma subtypes (physical abuse, emotional abuse, and general trauma) as they influenced both the peak and slopes of post-stress cortisol regulation. Physical abuse was not related to peak cortisol, PA β = .006, t(113.8) = .153, p = .88, or the regulation of peak cortisol over time, PA x time β =.002,

$t(309.5) = .957$, $p = .34$ and PA x time^2 $\beta = -.0001$, $t(287.2) = -1.02$, $p = .31$. Emotional abuse exposure was not related to peak cortisol values, EA $\beta = -.011$, $t(116.3) = -.338$, $p = .74$, or the linear regulation of cortisol from that peak, EA x time $\beta = .002$, $t(320.0) = 1.49$, $p = .14$. However, more emotional abuse was related to less accelerated decline in cortisol values throughout the regulation phase, EA x time^2 $\beta = -.0001$, $t(276.5) = -2.17$, $p < .03$. General trauma exposure was not related to peak cortisol, GT $\beta = -.021$, $t(104.2) = -.553$, $p = .56$, nor the slopes of cortisol regulation away from that peak, GT x time $\beta = .002$, $t(281.7) = .893$, $p = .37$ and GT x time^2 $\beta = -.00003$, $t(242.4) = -.585$, $p = .56$.

We then conducted an adjusted model of all three trauma exposure subtypes as predictors of peak cortisol and regulation slopes which did not represent an improvement in model fit from the unadjusted models of cortisol regulation. See Table 3.4 for results of adjusted model of HPA-axis regulation. When accounting for exposure to multiple subtypes of childhood trauma, physical abuse and general trauma were not related to peak cortisol response, nor the slopes of regulation away from that peak. However, more emotional abuse exposure continued to be associated with less deceleration of cortisol during the regulation phase. This suggests that youth who were exposed to more emotional abuse in this sample exhibited elevated cortisol for more of the regulation phase following the acute stressor compared with their peers (See Figure 3.3).

[Insert Figure 3.3 about here]

Age of trauma onset as a moderator between trauma exposure and HPA-axis functioning

In the second aim of this study, we sought to clarify whether age of trauma onset moderated the association between exposure to physical abuse, emotional abuse, general trauma and patterns of HPA-axis functioning. To do this, we entered age of first traumatic experience as a moderator in all models of HPA-axis functioning as predicted by childhood trauma subtypes

for all of our participants who reported at least one traumatic experience in childhood. See Table 3.5 for descriptive information and correlations between all study variables for youth with reported exposure to at least one traumatic incident.

[Insert Table 3.5 about here]

Age of Trauma Exposure and Cortisol Awakening Response

To examine whether age of onset for each trauma subtype would be associated with cortisol awakening response, we conducted multivariate regressions where abuse subtypes were included as predictors of change in cortisol from waking to 45 minutes post-wakening. As expected, cortisol at waking was highly predictive of cortisol 45 minutes later in the unconditional model, β = .458, t = 4.53, p < .001. Sex was not related to the cortisol awakening response, β = -.012, t = -.12, p = .91, however there was a non-significant trend to suggest that older youth demonstrated greater cortisol awakening responses, β = .176, t = 1.76, p = .08. Therefore age was included in the subsequent abuse models predicting cortisol awakening response, while sex was not.

We then conducted regression models for the main effect of each subtype of trauma and the age of onset for that subtype on the cortisol awaking response. In a second regression for each trauma subtype, we added the interaction between the duration of the trauma subtype and its age of onset as a predictor of cortisol awakening response. Age of physical abuse, emotional abuse, nor general trauma onset was not associated with cortisol awakening response. In these models, only high reported general trauma was associated with the greater cortisol awakening response, β = .37, $t(59)$ = 3.16, p = .003. However there was no interaction between general trauma exposure and the age of onset predicting cortisol awakening response, p = .78. See Table 3.6 for the results of these models

[Insert Table 3.6 about here]

Age of Trauma Exposure and Diurnal Cortisol Regulation

To examine whether age of trauma onset would be associated with diurnal regulation of cortisol, we conducted traditional growth curve models with subtypes of abuse and their age of onset predicting changes in cortisol across the day. We first examined unconditional linear and quadratic growth models of diurnal cortisol using waking cortisol values as the intercept. The quadratic model was the best fit to the data (linear model AIC = 238.9 vs. quadratic model AIC = 233.9). For this quadratic model, from waking, intercept β = -1.07, t(86.2) = -28.3, $p < .001$, cortisol values declined, time β = -.09, t(93.3) = -6.08, $p < .001$, and this decline decelerated during the evenings, time^2 β = .002, t(80.7) = 2.69, p = .009.

We then conducted conditional unadjusted models for age and sex. Sex was not related to cortisol at waking, sex β = -.188, t(107.5) = -.70, p = .49, or initial decline in cortisol across the day, sex x time β = .067, t(81.1) = 1.34, p = .19, however there was a non-significant trend to suggest that the deceleration of cortisol decline later in the day was more pronounced in females compared with males, sex x time^2 β = -.003, t(77.5) = -1.77, p = .08. Age was not related to differences in waking cortisol, age β = -.011, t(83.8) = -.62, p = .54, or the diurnal decline in cortisol, age x time β = .01, t(92.1) = 1.57, p = .12 and age x time^2 β = -.001, t(79.2) = -1.60, p = .11. Therefore, the effect of sex on the intercept and slope of diurnal cortisol was included as a covariate in all further diurnal cortisol models while age was not.

[Insert Table 3.7 here]

We then conducted conditional unadjusted models testing the main effects for each subtype of childhood trauma exposure and their age of onset (physical abuse, emotional abuse, and general trauma) as they influenced cortisol throughout the day. We then added the

interaction between childhood trauma subtype and age of onset for that subtype to these models to test whether the age of onset for a subtype of childhood trauma moderated the association between trauma exposure and adolescent diurnal cortisol regulation. See Table 3.7 for results of main effects and interaction models of diurnal cortisol by childhood trauma exposure subtype. While accounting for total exposure to physical abuse, a later age of onset of physical abuse was associated with higher cortisol at waking, PA β = .044, $t(40) = 2.69$, p = .01, but not the decline in cortisol across the day. When the interaction between physical abuse and age of onset was added to this model there was no improvement in model fit (no interactions AIC = 118.7 vs. interactions AIC = 121.4), and physical abuse, age of onset of physical abuse, and their interaction did not impact cortisol upon waking (Intercept), linear, or quadratic slopes. When accounting for total exposure to emotional abuse, earlier onset of emotional abuse was associated with lower cortisol upon waking, EA β = -.039, $t(22.4) = -2.35$, p = .03, and less decline in cortisol throughout the day, EA x time β = .015, $t(23) = 2.56$, p = .02 and EA x time^2 β = -.001, $t(21.1) = -2.31$, p = .03. When the interaction between emotional abuse and age of onset was added to this model, the model fit improved (no interactions AIC = 59.1 vs. interactions AIC = 55.4). In this model, as age of onset for emotional abuse increases from age 5, exposure to emotional abuse was associated with lower cortisol at waking, EA x onset β = -.044, $t(22.3) = -2.03$, p = .05, and less deceleration of the diurnal regulation across the day, EA x Onset x time^2 β = -.001, $t(21.1) = -1.73$, p = .03 (See Figure 3.6). When accounting for total exposure to general trauma, age of onset of general traumatic events were unrelated to diurnal cortisol. When the interaction between general trauma and age of onset were added to this model there was no improvement in model fit (no interactions AIC = 194.9 vs. interactions AIC = 200.6), and there were no significant interactions between general trauma and age of onset on diurnal cortisol.

[Insert Figure 3.6 about here]

Age of Trauma Exposure and Acute Stress Reactivity

To examine whether age of onset for trauma subtypes would be associated with acute stress reactivity, we conducted three series of growth curve analyses which model acute stress: reactivity from baseline, reactivity to peak, and regulation from peak. For each subtype of childhood trauma, we conducted a main effects model of trauma exposure and age of onset of trauma exposure as predictors of the intercept and slope of cortisol change over time. We then added the interaction between exposure and age of onset to the model for each subtype of trauma to test our hypothesis that age of onset for some subtypes of childhood trauma would moderate the impact of trauma on acute HPA-axis reactivity.

Reactivity from baseline. We first examined unconditional linear, quadratic and cubic growth models of acute stress response using baseline cortisol values as the intercept. The cubic model was the best fit to the data (linear model AIC = -139.8 vs. quadratic model AIC = -153.7 vs. cubic model AIC = -158.3). For this cubic model, from baseline, intercept β = -1.69, t(103.3) = -35.9, $p < .001$, cortisol increased over time, time β = .006, t(408.3) = 2.52, p = .01, began to decrease following their peak response to the stressor, time^2 β = -.00003, t(388) = -3.14, p = .002, and this decrease decelerated throughout the regulation phase, time^3 β = .000003, t(388) = 2.59, p = .01.

We then conducted conditional unadjusted models for age and sex. Sex was not related to baseline cortisol, intercept β = -.082, t(99) = .85, p = .40, or any of the slopes of the reactivity curve, sex x time β = -.003, t(391.4) = -.50, p = .62, sex x time^2 β = .0001, t(372) = .27, p = .79, sex x time^3 β = .000, t(372) = -.19, p = .85. Older participants were more likely to have higher baseline cortisol than younger participants, intercept β = .049, t(100.1) = 2.34, p = .022, however,

age was not associated with the slopes of the reactivity curve, age x time β = .00001, t(394.9) = .01, p = .99, age x time^2 β = -.00002, t(376) = -.40, p = .69 and age x time^3 β = .000, t(376) = .36, p = .72 respectively. Therefore, sex was not included in models of HPA-axis reactivity from baseline, while the impact of age on baseline was included as a covariate.

We then conducted conditional unadjusted models of HPA-axis reactivity from baseline for each subtype of abuse. When accounting for total exposure to physical abuse, age of onset of physical abuse was not associated with baseline or slope of HPA-axis reactivity to the stress task. When we included the interaction terms into this model there was no improvement in model fit (no interactions AIC = -126.8 vs. interactions AIC = -120.0), and there were no interactions between physical abuse and age of onset on baseline or slope of stress reactivity. See Table 3.8 for parameter estimates of both the main effects and interaction models for physical abuse and age of onset predicting stress reactivity. When accounting for total exposure to emotional abuse, age of onset of emotional abuse was not related to baseline cortisol or slope of reactivity. When we included the interaction between emotional abuse and age of onset resulted in no improvement in model fit (no interactions AIC = -134.8 vs. interactions AIC = -122.2). However, there was a significant interaction between emotional abuse and age of onset on the linear increase in cortisol from baseline, emotional abuse x onset x time β =-.002, t(95.9) = -2.10, p = .04. Given that in Aim 1 we found that emotional abuse was not associated with HPA-axis reactivity from baseline (See Table 3.4), this result suggests that among youth who were exposed to at least one trauma, emotional abuse is less related to reactivity if the abuse occurred at or before age of 5. However, the impact of emotional abuse increased leading to blunted reactivity to the stressor when the onset of abuse occurred later in childhood. See Table 3.9 for parameter estimates of both the main effects and interaction models for emotional abuse and age of onset

predicting stress reactivity. When accounting for total exposure to general trauma, age of onset was not related to baseline cortisol or the slopes of HPA-axis reactivity to stress. In the interactions model there was no improvement in model fit (no interactions AIC = -64.4 vs. interactions AIC = -58.1), and there were no significant interactions between general trauma exposure and age of onset as predictors of HPA-axis reactivity. See Table 3.10 for parameter estimates of both the main effects and interaction models for general trauma and age of onset predicting stress reactivity.

[Insert Table 3.8 about here]

[Insert Table 3.9 about here]

[Insert Table 3.10 about here]

Reactivity to peak. To test whether subtypes of childhood trauma exposure were associated with peak cortisol (intercept) and reactivity to peak cortisol (slope), we first examined unconditional linear and quadratic growth models of post-stress cortisol using peak values as the intercept. The unconditional quadratic model was the best fit to the data (linear model AIC = 51.5 vs. quadratic model AIC = 18.1). For this quadratic model, cortisol increased over time, time β = .008, $t(218.9) = 5.34$, $p < .001$, and this increase accelerated, time^2 β = .0002, $t(130.4) = 6.21$, $p < .001$, approaching peak values, β = -1.68, $t(97.9) = -38.5$, $p < .001$.

We then conducted conditional unadjusted models for age and sex. Sex was not related to peak cortisol, sex β = .045, $t(93.8) = .50$, $p = .62$, or cortisol increase approaching this peak, sex x time β = -.0001, $t(211.5) = -.03$, $p = .98$ and sex x time^2, β = .00003, $t(125.4) = .48$, $p = .63$. There was a non-significant trend to suggest that older participants had higher cortisol peaks than younger participants, age β = .033, $t(94.7) = 1.68$, $p = .095$, however, age was not related to the slope of cortisol activation towards this peak, age x time β = -.001, $t(211.4) = -1.26$, $p = .21$ and

age x time^2 β = -.00001, t(123.6) = -.70, p = .48. Therefore, the effect of age on peak cortisol responses were included as a covariate in all further models of reactivity to peak, while the effects of age on slope and the effect of sex on peaks and slopes were not.

We then conducted conditional, unadjusted models for each of our subtypes of trauma exposure; first testing the main effect of age of onset for each type of abuse, and second testing the interaction between abuse exposure and age of onset. When accounting for total exposure to physical abuse, age of onset of physical abuse was not associated with peak cortisol or slopes of cortisol activation to the stress task. When we included the interaction terms into this model there was improvement in model fit (no interactions AIC = -47.7 vs. interactions AIC = -47.0). More physical abuse beginning at the average age of 4 was associated with a trend toward greater acceleration of cortisol approaching peak, PA x time^2 β =.0001, t(98.7) = 1.77, p < .10. We also found a significant interaction between physical abuse and age of onset such that as the age of onset of physical abuse occurs later in childhood, there is a greater association between more physical abuse on steeper slopes of cortisol increase, PA x onset x time β =.003, t(98.7) = 2.16, p = .03, and acceleration to peak, PA x onset x time^2 β =.0001, t(54.9) = 2.22, p = .03 (see Table 3.8). In previous models, we found that more physical abuse was associated with steeper and more accelerated approaches to peak among youth (See Table 3.4 and Figure 3.2). This model, among only trauma exposed youth, indicates that exposure to more physical abuse during childhood is associated with steeper and more accelerated profiles of cortisol increase in response to the stressor, which can be exaggerated when high reported physical abuse exposure begins later in childhood (See Figure 3.5). When accounting for total exposure to emotional abuse, age of onset was not associated with peak or slope of peak activation. In previous models, emotional abuse was not associated with reactivity to peak (See Table 3.4). In this model, more

emotional abuse was associated with flatter slopes of cortisol increase when the abuse began at the mean age of 5. In the interactions model there was no improvement in model fit (no interactions AIC = -52.3 vs. interactions AIC = -53.0). However, there was a significant interaction between emotional abuse and age of onset on increase in cortisol approaching peak, such that high reported emotional abuse was associated with flatter slopes of cortisol increase to acute stress as the age of onset occurred earlier during childhood, EA x onset x time β = -.001, t(52.7) = -2.34, p = .023 (see Figure 3.6). When accounting for total exposure to general trauma, age of onset was not associated with peak cortisol or the slope of HPA-axis reactivity. There was no improvement in model fit when including the interactions in this model (no interactions AIC = 57.4 vs. interactions AIC = 62.4) and there were no significant interactions between general trauma exposure and age of onset as predictors of HPA-axis reactivity (see Figure 3.7).

[Insert Figure 3.5 about here]

[Insert Figure 3.6 about here]

Regulation from peak. We first examined unconditional linear and quadratic growth models of post-peak cortisol regulation using peak values as the intercept. All of our models include pre-stress cortisol as a control. The quadratic model was the best fit to the data (linear model AIC = -102.6 vs. quadratic model AIC = -1191). For this quadratic model, from peak, intercept β = -1.68, t(99.6) = -36.6, p < .001, cortisol decreased over time, time β = -.013, t(266.3) = -8.33, p < .001 and this decrease decelerated as the distance from peak increased, time^2 β = .0002, t(237.8) = 4.62, p < .001.

We then conducted conditional unadjusted models for age and sex. Sex was not associated with peak cortisol or the change in cortisol from peak, sex β = .025, t(95.5) = .27, p = .79, sex x time β = .004, t(254.6) = 1.36, p = .18 and sex x time^2 β = -.0001, t(225.7) = -1.57, p

= .12. There was a trend to suggest that age was associated with greater peak cortisol, age β = .034, $t(96.5) = 1.67$, $p = .098$, but not the change in cortisol during regulation from peak, age x time β = -.0004, $t(256.7) = -.52$, $p = .60$ and age x time^2 β = -.000007, $t(238.5) = -.34$, $p = .74$. Therefore, the effect of age on peak cortisol was included as a covariate in these models, while the effect of age on regulation slope and sex on either peak or slope were not.

We then conducted conditional, unadjusted models for each of our subtypes of trauma exposure; first testing the main effect of age of onset for each type of abuse, and second testing the interaction between abuse exposure and age of onset. When accounting for total exposure to physical abuse, age of onset of physical abuse was not associated with peak cortisol or slopes of cortisol regulation from peak. When we included the interaction terms into this model there was improvement in the model fit (no interactions AIC = -107.1 vs. interactions AIC = -102.0), however there were no significant interactions between physical abuse and age of onset on cortisol regulation from peak. When accounting for total exposure to emotional abuse, age of onset was not associated with differences in peak cortisol or the regulation of cortisol from that peak. When the interaction between emotional abuse and age of onset were added to this model, there was no improvement in the model fit (no interactions AIC = -104 vs. AIC = -101.2), and there were no significant interactions between emotional abuse and age of onset on peak cortisol or the regulation of cortisol from peak. When accounting for total exposure to general trauma, age of first exposure to general trauma was not associated with peak cortisol or the slope of cortisol regulation. When the interaction between general trauma and age of onset were entered into the model, there was improvement in the model fit (interactions AIC = -68.6 vs. AIC = -69.3). In our previous model, general trauma was not associated with the regulation of cortisol from peak (See Table 3.4). Among only youth with some exposure to a traumatic event, there

were non-significant main effects suggesting that more general trauma exposure was associated with less steep declines in cortisol moving away from peak and greater acceleration of this decline later in the regulation phase when the onset of general trauma occurs at the average age 1.5 years. As the age of first general trauma exposure increased, general trauma was related to a less steep decline in cortisol during the regulation phase immediately following peak, GT x onset x time β =.002, t(188.1) = 2.07, p = .04, and less acceleration of this decline throughout the regulation phase, GT x onset x time^2 β = -.0001, t(150.2) = -2.61, p = .01 (see Figure 3.7).

[Insert Figure 3.7 here]

Childhood trauma as a moderator between depression and HPA-axis functioning

Finally, we were interested in whether childhood trauma exposure moderates the association between depression and HPA-axis functioning. In this sample, 24% of our sample met criteria for a depressive disorder at some point in their childhood and 14% of our sample met criteria for a current depressive episode. Within these depressed youth, 6% also met criteria for a comorbid anxiety disorder. Across the entire sample, 19% of participating youth met criteria for an externalizing disorder (e.g., ADHD or ODD). As expected, youth who met criteria for current depression had higher symptoms of depression according to both the parent- and self-report. In addition, youth who met criteria for current depression were significantly older and their parents reported more exposure to emotional abuse during childhood than their non-depressed peers. See Table 3.11 for comparisons between depressed and non-depressed youth for all study variables.

[Insert Table 3.11 here]

Childhood trauma exposure as a moderator between depression and CAR

To test the hypothesis that childhood trauma exposure would moderate the association between depression and CAR, we conducted unadjusted multivariate regressions where

depression, trauma subtypes, and the interaction between depression and trauma subtypes were included as predictors of change in cortisol from waking to 45 minutes later. Age and sex were not included as covariates in these models because they were previously shown to not be significant predictors of CAR (See page 35).

We then conducted separate unadjusted regression models to examine whether each subtype of trauma (physical abuse, emotional abuse, general trauma) interacted with current depression to impact the cortisol awaking response. There were no significant interactions between any of the trauma exposure subtypes and current depression on the magnitude of cortisol awakening response. Therefore, trauma exposure did not moderate the link between depression and CAR (See Table 3.12)

[Insert Table 3.12 here]

Childhood trauma exposure as a moderator between depression and diurnal cortisol regulation

To test the hypothesis that trauma exposure would moderate the association between depression and diurnal regulation of cortisol levels, we conducted traditional growth curve models with subtypes of abuse and current depression predicting changes in cortisol across the day. Given the findings from previous models (See page 36), sex was included as a covariate in all diurnal models, while age was not.

We conducted conditional unadjusted models testing the main effects for each subtype of childhood trauma exposure (physical abuse, emotional abuse, general trauma) and current depression as they influenced cortisol throughout the day. We then tested the interaction between childhood trauma subtype and current depression on diurnal cortisol regulation (see Table 3.13). First, we examined the potential moderating effect of physical abuse. The interaction model did

not improve the model fit (no interactions AIC = 290.5 vs. interactions AIC = 294.2), and there were no significant interactions between current depression and physical abuse exposure on cortisol change throughout the day. Next, we examined the potential moderating effect of emotional abuse. There was no improvement in model fit (no interactions AIC = 291.5 vs. interactions AIC = 294.6) and there were no significant interactions between emotional abuse and current depression on waking cortisol or cortisol regulation throughout the day. We then examined the possible moderating effect of general trauma. The interaction model improved the model fit (no interactions AIC = 275.2 vs. interactions AIC = 273.0). In this model, depression was not associated with any dysregulation of diurnal cortisol regulation with average general trauma exposure during childhood. As general trauma exposure during childhood increased, depression was associated with more intense reduction of cortisol from awakening and a more intense deceleration of this reduction towards bedtime, depression x GT x time β = -.118, t(103.9) = -1.96, p = .05 and depression x GT x time^2 β = .01, t(87.9) = 2.50, p = .01 (see Table 3.13 and Figure 3.8).

[Insert Table 3.13 here]

[Insert Figure 3.8 about here]

Childhood Trauma Exposure as a Moderator between Depression and Reactivity to Acute Stress

To test the hypothesis that childhood trauma would moderate the association between current depression and HPA-axis reactivity to acute stress, we conducted three series of growth curve analyses which model acute stress: reactivity from baseline, reactivity to peak cortisol, and regulation from peak cortisol. For each subtype of childhood trauma (physical abuse, emotional abuse, general trauma), we conducted a main effects model of trauma exposure and current

depression as predictors of the intercept and slope of cortisol change over time in response to an acute stress task. We then added the interaction between trauma exposure and current depression to the model for each subtype of trauma to test our moderation hypothesis.

Reactivity from baseline. As presented previously (See page 37), we conducted an unconditional, cubic growth curve model from baseline with the effect of age on baseline cortisol included as a covariate. Then, we conducted conditional unadjusted models for the main effects of trauma subtypes and depression, followed by models including the interaction between abuse exposure and current depression. First we examined the interaction between depression and physical abuse on HPA-axis reactivity from baseline. There was no improvement in model fit when the interaction between depression and physical abuse were added to this model (no interactions AIC = -240.6 vs. interactions AIC = -235.5), and there were no interactions between physical abuse and current depression on baseline or slope of stress reactivity from baseline (see Table 3.14). Next, we examined the interaction between depression and emotional abuse. There was no improvement in model fit (no interactions AIC = -240.6 vs. AIC = -235.8), and there were no significant interactions between emotional abuse and current depression as predictors of HPA-axis reactivity from baseline (see Table 3.15). Finally, we examined the interaction between depression and general trauma exposure on HPA-axis reactivity from baseline. When the interaction between general trauma and depression was added to this model, there was improvement in model fit (no interactions AIC = -212.3 vs. interactions AIC = -228.1). When an average amount of exposure to general trauma is reported (M_{GTE} = 2.6), there was a significant impact of depression on baseline cortisol. As exposure to GTE increases for these depressed youth, the impact of depression on baseline cortisol increased, depression x GT β = .604, $t(108.2) = 3.87$, $p < .001$ (see Figure 3.9 and Table 3.16).

[Insert Table 3.14 here]

[Insert Table 3.15 here]

[Insert Table 3.16 here]

[Insert Figure 3.9 here]

Reactivity to Peak. We then conducted unadjusted, quadratic growth models using landmark registration of stress reactivity to peak where the effect of age on the intercept was included as a covariate (39).

We then conducted conditional unadjusted models for each trauma subtype, depression and their interactions. First we examined physical abuse exposure as a moderator between depression and reactivity to peak. When we included the interaction between physical abuse and depression into this model there was no improvement in model fit (no interactions AIC = -20.9 vs. interactions AIC = -19.6), and there were no significant interactions between physical abuse and current depression on peak cortisol or the slopes of cortisol increase to peak (See Table 3.14). Next, we examined emotional abuse exposure as a moderator between depression and reactivity to peak. When the interaction between depression and emotional abuse were added to this model there was no improvement in model fit (no interactions AIC = -10.4 vs. interactions AIC = -7.47), and there were no significant interactions between emotional abuse exposure and depression on peak reactivity to acute stress (See Table 3.15). Finally, we examined general trauma exposure as a moderator between depression and reactivity to peak (see Table 3.16) .When the interaction between depression and general trauma exposure were added to this model there was improvement in the model fit (no interactions AIC = -5.56 vs. interactions AIC = -20.1). At average mean exposure to general trauma during childhood (M_{GTE} = 2.6), depression is not associated with variability in the slope of cortisol increase approaching peak. However, as

reported exposure to general trauma increased, peak cortisol values increased and the slope of cortisol increase approaching this peak is steeper, general trauma x depression β = .350, t(102.9) = 2.22, p = .029, and general trauma x depression x time^2 β = .0002, t(148.6) = 1.66, p = .099.

Regulation from Peak. We then conducted unadjusted, quadratic growth models using landmark registration of regulation from peak where the effect of age on the intercept was included as a covariate (See page 41).

We then conducted conditional models assessing each subtype of childhood trauma (physical abuse, emotional abuse, general trauma), depression, and their interactions as predictors of the slope of post-peak cortisol regulation. First, we examined physical abuse as a moderator between depression and regulation of cortisol from peak (see Table 3.14). When we included the interaction between depression and physical abuse into this model there was no improvement in model fit (no interactions AIC = -144.5 vs. AIC= -139.9), and there were no significant interactions between physical abuse and depression on peak cortisol values or cortisol regulation from peak. Next, we examined emotional abuse as a moderator between depression and regulation of cortisol from peak (See Table 3.15). When the interaction between depression and emotional abuse was included in this model there was no improvement in model fit (no interactions AIC= -160.1 vs. interactions AIC= -158.7) however there was a non-significant trend suggesting an interaction between emotional abuse and current depression on peak cortisol, β = -.199, t(114.8) = -1.81, p = .07. Finally, we examined reported exposure to general trauma as a moderator between depression and regulation of cortisol from peak (See Table 3.16). When the interaction between general trauma and depression was included in this model, there was improvement in model fit (no interactions AIC = -136.7 vs. interactions AIC = -142.7). At average mean exposure to general trauma during childhood (M_{GTE} = 2.6), depression was

associated with greater peak cortisol, depression β = .252, t(257.2) = 1.95, p = .06, but not with variability in the regulation of cortisol following peak. However, as exposure to general trauma increased, depression was associated with steeper initial regulation of cortisol and greater deceleration of this effect over time, general trauma x depression x time β = -.015, t(257.2) = -2.64, p = .009 and general trauma x depression x time^2 β = .0004, t(207.5) = 2.91, p = .004 (see Table 3.16 and Figure 3.10). Similar to our reactivity to peak model, high reported general trauma among depressed youth was associated with elevated peak cortisol which likely indicates that exposure to high general trauma is associated with HPA-axis reactivity, rather than impaired regulation of the acute HPA-axis response.

[Insert Figure 3.10 about here]

Post-hoc analysis

Given that we found that reported exposure to more general trauma moderated the association between depression and both diurnal and acute HPA-axis functioning, we conducted a post-hoc analysis to test the specificity of this finding. To do this, we calculated a total trauma exposure variable by summing the total duration values of physical, emotional, sexual abuse and general trauma for each individual. We then tested Total Trauma as a moderator of depression and cortisol awakening response, diurnal regulation, HPA-axis reactivity from baseline, reactivity to peak, and regulation from peak. We found that Total Trauma was not a moderator of the association between depression and HPA-axis functioning in any of these models. Therefore, this suggests that exposure to more general trauma may represent a specific type of childhood stress that facilitates anomalies in HPA-axis functioning among depressed youth**.**

Chapter 4: Discussion

Childhood trauma exposure and adolescent HPA-axis functioning

In this study, we aimed to characterize the association between exposure to physical abuse, emotional abuse, and general trauma during childhood in the HPA-axis functioning of adolescents. We found that exposure to any of the subtypes of childhood trauma were not associated with anomalies in the cortisol awakening response. Youth who reported exposure to more general traumatic events throughout their childhood demonstrated a steeper decline in cortisol from morning to evening, and deceleration of this decline approaching bedtime compared to youth with low exposure to general trauma. In response to acute stress, we found no associations between physical abuse, emotional abuse, or general trauma and acute stress reactivity from baseline. However, we found that youth who were exposed to more physical abuse had a steeper slope of HPA-axis activation to our stress task compared with youth reporting low physical abuse exposure. Additionally, youth with reported exposure to high emotional abuse displayed a higher and flatter regulation of cortisol following their peak response to the stress task compared with youth exposed to low emotional abuse.

Exposure to physical abuse, emotional abuse or general traumatic events were not related to the cortisol awakening response in our sample. This was true both when looking at each form of childhood trauma separately, and when considering them simultaneously. This suggests that high reported exposure to stress during childhood may not be associated with later dysregulation of the cortisol awakening response among adolescents. These findings were unexpected given

that, among adult samples, general life stress is generally associated with a greater cortisol awakening response, while fatigue, exhaustion, and PTSD are associated with a blunted cortisol awakening response (Chida & Steptoe, 2009). Also among adult samples, more childhood stress such as early trauma (Mangold, Wand, Javors, & Mintz, 2010), death of a close family member, or divorce/separation of parents has been linked to having a blunted cortisol awakening response (Meinlschmidt & Heim, 2005). To date there have been only two studies using youth samples examining the association between childhood trauma exposure with CAR. First, high reported exposure to physical abuse and neglect was related to blunted CAR among 12-13 year old post-institutionalized youth but only for those who were in the pre- or early stages of puberty compared with youth in the mid- to late stages (Quevedo, Johnson, Loman, LaFavor, & Gunnar, 2012). Additionally, a slightly younger group of children (aged 7-12) who were experiencing difficulty related to complicated grief were shown to exhibit blunted cortisol awakening responses (Kaplow et al., 2013). The failure to find an association between childhood trauma exposure and CAR in this study may suggest that elevated CAR is related to recent or ongoing stress, rather than distal stress; while blunted CAR may be related to the presence of poor psychological adjustment that is secondary to childhood trauma exposure. For example, getting insufficient sleep is associated with greater CAR magnitude (Vargas & Lopez-Duran, 2014) and therefore associations between childhood trauma exposure and adolescent CAR may be specific to those youth with ongoing sleep problems.

We found that reported exposure to more general traumatic events was associated with anomalies in diurnal regulation of cortisol, while physical and emotional abuse were not. Specifically, youth with high reported exposure to general traumatic events demonstrated no differences in cortisol at waking, more decline in cortisol from morning to evening, and elevated

cortisol at bedtime. These patterns were consistent in both the unadjusted models of general trauma exposure, and were more robust when accounting for the impact of physical and emotional abuse. Compared with abuse, the general trauma subscale was developed to comprise events that are non-intentionally harmful to the child, perpetrated by a stranger, and secondary to chance (Bremner et al., 2000). The most prevalent general traumatic events reported were serious personal injury or illness (25%; $M_{duration} = 1.20$; $SD_{duration} = .48$), family mental illness (24%; $M_{duration} = 5.24$; $SD_{duration} = 5.2$), parent separation or divorce (20%; $M_{duration} = .20$; $SD_{duration} = .40$), and death of a friend (18%; $M_{duration} = .20$; $SD_{duration} = .44$). Overall, the internal consistency of the general trauma subscale was low ($\alpha = .54$), suggesting that our sample reported general traumatic events that were widely distributed across the items. Thus, exposure to more general trauma during childhood is likely a proxy for predictability of security in the child's environment. These findings may better explain why some previous studies, only having assessed cortisol in the morning and at night, reported that childhood trauma is associated with flat diurnal patterns across the day (Bevans et al., 2008; Cicchetti & Rogosch, 2001). Our findings suggest that this flat curve is driven by elevated cortisol at night, but not chronically elevated cortisol throughout the day. Youth in this sample were exposed to an average of 3 general traumatic events. This, in conjunction with generally short durations for our most frequently endorsed general traumatic events, the association between high reported general trauma exposure and elevations in bedtime cortisol may have important implications for our understanding of the impact of living in an unpredictable environment during childhood, where youth may experience chronic anticipatory anxiety. In the absence of other indicators of diurnal dysregulation, cortisol elevation at bedtime among youth exposed to more general traumatic events may indicate cognitive or emotional difficulties falling or staying asleep, which over time

could lead to bedtime being a source of stress for these youth. Thus, elevated bedtime cortisol may be a consequence of chronic sleep problems, secondary to repeated trauma exposure. Alternatively, exposure to repeated, unpredictable stress during childhood may result in physiological alterations to the circadian regulation of the HPA-axis that lead to elevated cortisol at the end of the day. These elevations in cortisol may be interpreted by these youth as physiological arousal and lead to difficulty falling or staying asleep, as is characteristic to many stress-related disorders such as depression or post-traumatic stress disorder (American Psychological Association, 2000). Future studies are warranted to clarify the direction of this relationship.

Consistent with two previous studies of adolescent youth (MacMillan et al., 2009; Ouellet-Morin et al., 2011), we found no association between physical abuse or emotional abuse and diurnal regulation of cortisol. However, some studies have documented chronically low cortisol in the morning and elevated cortisol at bedtime among maltreated children (e.g., Hart et al., 1996; Kaplan et al., 1999). Furthermore, several studies on the association between early care giving and diurnal cortisol regulation have been conducted with foster children (Bruce et al., 2009) or institutionalized youth (Carlson & Earls, 1997; Gunnar, Bruce, & Grotevant, 2000). These studies have found that both youth in the foster care system or institutional care demonstrate flat profiles of diurnal cortisol throughout the day, driven largely by low morning cortisol (Bruce et al., 2009; Carlson & Earls, 1997; Gunnar et al., 2000). It is possible that the inconsistency between our results and these previous findings are a function of the older age of our sample. Previous studies have focused primarily on preschool or school-aged children with maltreatment exposure, where the physical and emotional abuse may be ongoing or recent. Thus our failure to replicate these findings may indicate that dysregulation in diurnal regulation of

cortisol among abused children does not persist into adolescence. It is also possible that these diurnal regulation profiles were not observed in our sample due to the potential protective nature of living with a family during childhood, as only a small subsample of our participants were formerly in foster-care.

In the reactivity task, we found that more exposure to physical abuse was associated with a steeper slope of increase in cortisol to peak, more emotional abuse was associated with maintaining elevated cortisol longer following the peak response to the task, while exposure to more general traumatic events was not associated with differences in the cortisol response to the stress task. These findings are consistent with previous studies showing that child maltreatment (Harkness et al., 2011), specifically physical abuse (Ivanov et al., 2011), were associated with HPA-axis hyperreactivity to acute stress. Physical abuse during childhood may lead to hypersensitivity of the HPA-axis to acute stress in two ways. First, exposure to repeated physical abuse may facilitate cognitive processing of threat in the environment, thus enabling the HPA-axis response more rapidly in the presence of stress. Alternatively, repeated activation of the HPA-axis during physical abuse may result in increased sensitivity throughout the hormonal cascade (e.g., pituitary sensitivity to CRH, or adrenal sensitivity to ACTH), resulting in faster secretion of cortisol early in the stress response. Future investigations may consider replicating these findings using the Dex/CRH test to clarify this potential mechanism. Taken together, these findings suggest that exposure to physical abuse during childhood may increase the sensitivity of the HPA-axis to stress in the environment well into adolescence. Increased sensitivity of the HPA-axis to environmental stressors may result in over-interpretation of non-threatening environmental stimuli as threatening, as was found by Ivanov and colleagues (2011).

We also found that emotional abuse was associated with a slower decline in cortisol following peak responses to acute stress. This indicates that when accounting for other forms of childhood trauma, exposure to emotional abuse is uniquely associated with less efficiency in shutting down the HPA-axis, or the negative feedback loop. This is consistent with previous studies showing that children whose mothers reported low maternal warmth at age 5, show later impairments in regulating the HPA-axis response following acute stress (Kuhlman, Olson, & Lopez-Duran, 2013). The negative feedback loop is the process through which the HPA-axis response to acute stress is regulated and is related to the density of GRs (Young, et. al., 1991). These findings suggest that exposure to low maternal warmth or emotional abuse during childhood may result in low GR density in the hippocampus, thus limiting the efficiency of the HPA-axis to shut-down the stress response. Pre-clinical animal models have shown that maternal care behaviors in rodents are related to increased density of GRs, while maternal separation leads to lower GR density (Heim & Nemeroff, 2001; Meaney, 2001). Similarly, maternal depression during pregnancy is associated with variability in the methylation of GR receptor genes and hypersecretion of cortisol during infancy (Oberlander et al., 2008), which may facilitate impaired regulation of the HPA-axis throughout the lifespan. These differences in GR density may have serious psychiatric implications. For example, in a postmortem study of adult suicide victims, individuals with a history of child abuse had lower GR density in the hippocampus than non-abused suicide completers (McGowan et al., 2009). Our findings suggest that emotionally abused children may have impairment in the HPA-axis negative-feedback loop, which may increase the intensity of the youth's experience of stress and prolong duration of exposure to high levels of cortisol following acute stress. Over time, this may create vulnerability for the development of internalizing symptoms as has previously been shown in a prospective, longitudinal study of the

association between maternal warmth, HPA-axis reactivity and preadolescent internalizing symptoms (Kuhlman et al., 2013).

To date, this is the first study to comprehensively examine HPA-axis functioning in a sample of adolescents in the context of exposure to multiple forms of childhood trauma. Furthermore, this is the first study to differentiate the association between HPA-axis dysregulation and subtypes of childhood trauma exposure in a youth sample. Our findings have several important implications. Methodologically, the findings of this study emphasize the importance of assessing multiple indices of HPA-axis functioning. Here we found that physical and emotional abuse were both associated with different anomalies in acute HPA-axis reactivity, while exposure to several general traumatic events during childhood may disrupt the diurnal regulation of cortisol, specifically at night. These findings suggest that different types of stress represent distinct deviations from the optimal developmental environment, and further highlight plasticity of the neurobiological system, and the limits to it, in adapting to multiple forms of stress throughout childhood. Furthermore, we found consistent associations between subtypes of abuse and HPA-axis functioning in our unadjusted models as well as when accounting for exposure to other forms of abuse. This is further evidence that exposure to different subtypes of abuse have unique associations with HPA-axis functioning and that stress during childhood is a heterogeneous construct. Along these lines, a large proportion of the previous studies examining the relationship between childhood trauma and HPA-axis dysregulation have collapsed across several forms of childhood stress (e.g., maltreatment). Our findings emphasize the importance for future studies to assess for multiple forms of childhood stress in order to differentiate which childhood trauma experiences play a role in the development of dysregulated HPA-axis functioning.

Age of onset as a moderator of the association between childhood trauma exposure on adolescent HPA-axis functioning

The purpose of the second aim of this dissertation was to test whether age of onset for physical abuse, emotional abuse, and general trauma moderated the relationship between frequency and duration of trauma exposure and HPA-axis functioning. Among youth who have been exposed to at least one general traumatic experience, more general trauma incidents were associated with greater cortisol awakening response. This effect was not moderated by the age these experiences first occurred. We also found that exposure to more emotional abuse was associated with lower morning and more flat cortisol regulation throughout the day as the age of abuse onset occurred later in development. In relation to acute stress reactivity, we found that physical abuse was associated with a steeper increase in cortisol in response to the stress task, which was moderated by the age of physical abuse onset. Specifically, the impact of high reported exposure to physical abuse became stronger (steeper cortisol increase and acceleration to peak following acute stress) as the age of abuse onset occurred later in childhood. In comparison, exposure to high reported emotional abuse was associated with blunted reactivity to the acute stressor which was exaggerated as the age of abuse onset occurred later. Finally, we found that exposure to general trauma beginning earlier in childhood was associated with prolonged elevations in post-peak cortisol, or less efficiency in the post-peak regulatory slope of the acute stress response.

In this study, we found a main effect of total general trauma exposure such that more general trauma was associated with a greater cortisol awakening response. The age of onset for these general traumatic events was unrelated to the amplitude of the cortisol awakening response, suggesting that experiencing stressful events during specific phases of childhood may not result

in differences in the long term functioning of the initial surge of cortisol associated with waking. To date, there have been very few studies examining the role of age of trauma onset on HPA-axis functioning, and these studies have focused on the comparison between child and adult exposure to trauma (e.g., Santa Ana et al., 2006), not differences within childhood. Furthermore, no study to date has examined long term associations with the cortisol awakening response. However, given that in the first aim of this study there were no main effects of exposure to subtypes of trauma on the cortisol awakening response during adolescence, it is notable that when accounting for the age of onset of these experiences, more general trauma was associated with a greater cortisol awakening response. This suggests that more exposure to unpredictable stressful events during childhood has consequences for the functioning of circadian features of the HPA-axis over and beyond the contribution of age and experiences during key developmental phases.

With respect to diurnal regulation of cortisol, we found that later onset of emotional abuse was associated with lower cortisol upon waking, and less diurnal decline throughout the day. This effect remained when accounting for variations in participant age, frequency, and duration of emotional abuse exposure. This finding suggests that exposure to the same duration and amount of a specific stressful environment, in this case emotional abuse, at different stages of development can facilitate anomalies in the diurnal regulation of cortisol. Furthermore, we found that there was a significant interaction between amount of emotional abuse exposure and age of onset of emotional abuse exposure, such that this finding was stronger as the age of abuse onset was later in childhood. For this sample, later exposure is characterized by 3 or more emotional abuse experiences beginning after the age of 6. This subgroup of youth, compared with the other participants, showed lower cortisol at waking and slow decline in cortisol until bedtime, while the other participants showed higher waking cortisol, and rapid decline in cortisol

until the evening. This finding is consistent with the pattern of diurnal HPA-axis regulation observed in younger children within the foster care system and who have been institutionalized (Bruce et al., 2009; Carlson & Earls, 1997; Gunnar et al., 2000). Taken together, this finding expands upon previous contributions to the literature by demonstrating these relationships in an adolescent sample whose abuse experiences are no longer ongoing. This finding further highlights the potential detrimental impact of lacking a nurturing care giving environment during key developmental phases. These differences in diurnal regulation of cortisol may indicate physiological variations in the functioning of the HPA-axis, or psychological differences in the modulation of stress throughout the day. Physiologically, the slower decline in cortisol throughout the day may indicate poor regulation from the cortisol awakening response. Alternatively, these individuals may be hypersensitive to daily stressors, resulting in more frequent activation of the HPA-axis which impede diurnal decline in cortisol. Furthermore, given that we also found that emotionally abused youth show poorer regulation of post-peak cortisol to acute stressors; this sub-group may show elevated cortisol throughout the day due to extended elevations in cortisol following daily stressors.

The association between age of onset and diurnal regulation of cortisol was specific to emotional abuse, and did not apply to physical abuse or exposure to general traumatic events. Similar to our previously reported findings, the specificity to emotional abuse may indicate that exposure to emotional abuse during school-age development is a proxy for an insufficiently protective environment. For example, in the case of physical abuse and general trauma, both include the occurrence of real or potential physical threats to safety; however, emotional abuse may merely represent an environment that would be insufficiently protective in the presence of physical threats. Thus, adaptive neurobiological development within such an environment may

facilitate, or even necessitate, an altered physiological stress response system for survival. This is consistent with existing theories that neurobiological changes in development mediate the associations between emotional abuse in childhood and long-term behavioral problems (Yates, 2007). Further longitudinal research is necessary to explore why these effects are observed when the emotional abuse onset begins during school-age.

Finally, we tested age of onset as a moderator of physical abuse, emotional abuse, and general trauma on patterns of acute stress reactivity. We found that steeper slopes of cortisol increase in response to the stressor observed among our entire sample were exaggerated among those youth exposed to physical abuse, which became stronger as the abuse onset was later in childhood. Youth who were exposed to any physical abuse during early childhood (age 4 or younger) demonstrated reactivity slopes with increased intensity (steeper slopes), suggesting hypersensitivity of the HPA-axis to stressors. Further research is necessary to understand whether these patterns of reactivity are driven by cognitive processes of threat recognition, or whether there are physiological differences in the hormonal cascade of the axis. These findings are consistent with previous studies showing that youth who have been spanked or exposed to harsh physical punishment at young ages show hypersensitivity to acute stressors in later stages of development, such that exposure during early childhood may have a stronger association with later patterns of stress reactivity (Bugental et al., 2003; Kuhlman, Olson, et al., 2013; Roisman et al., 2009).

We also found that exposure to emotional abuse during childhood was associated with a flattened slope of cortisol increase in response to acute stress, which was exaggerated as the abuse began later in childhood (after age 6 in this sample). This finding is a significant contribution to emerging research on the potential neurobiological consequences of emotional

abuse (De Bellis et al., 1999; Yates, 2007), such that exposure to any amount of emotional abuse early in life may be associated with later hypo-reactivity of the HPA-axis to acute stress, while high reported emotional abuse at any time during child development may have the same impact. This finding is consistent with previous studies showing that childhood emotional abuse exposure is related to blunted HPA-axis responses to acute stress during adulthood (Carpenter et al., 2009), and may have long-term negative consequences throughout developmental stages.

While a few studies have linked age of trauma onset to patterns of symptom presentation (Dunn, McLaughlin, Slopen, Rosand, & Smoller, 2013; Kaplow & Widom, 2007; Maercker et al., 2004; Schoedl et al., 2010), almost no human studies to date have identified developmental mechanisms in these relationships. One study was able to demonstrate a link between age of trauma onset with hippocampal volume (Tupler & De Bellis, 2006), however there are no human studies examining the association between developmental timing of stress exposure and the later functioning of the stress response system. These findings demonstrate that long term associations exist between childhood exposure to different types of HPA-axis functioning, and this study is the first to examine the role of trauma exposure onset. Thus, longitudinal studies are needed to assess the interaction between human development and exposure to childhood stress as contributors to long-term anomalies in the functioning of the HPA-axis. Furthermore, this study demonstrates that these anomalies extend beyond dysregulated responses to acute stress, but relate to chronic diurnal dysregulation as well. For example, long term regulation of the HPA-axis appears to be uniformly vulnerable to emotional abuse exposure throughout childhood, while physical abuse during early childhood, in even small doses, is associated with long term sensitivity to acute stress. These findings highlight early childhood as a sensitive period for the development of the HPA-axis and how it will respond to stress across the lifespan. While there

are considerable methodological considerations to be made in a cross-sectional study with retrospectively reported trauma exposure, such as this one, these findings underscore the need for longitudinal investigations of the timing and severity of childhood trauma exposure as they relate to later functioning of key neurobiological systems.

Furthermore, these findings extend our findings from Aim 1, such that they demonstrate not only unique associations between subtypes of childhood trauma exposure and HPA-axis reactivity, but also overlapping periods of potential sensitivity. For example, in this study we found that physical abuse was associated with steeper increases and acceleration of cortisol following acute stress. This was true for youth with both low and high exposure to physical abuse before the age of 4, but also among youth for whom high physical abuse exposure began after age 4. In contrast, we found that emotional abuse exposure was associated with a slower increase in cortisol in response to acute stress, which was also prevalent among both high and low exposure to emotional abuse during early childhood, although increasingly true for youth with high exposure beginning after age 6. These findings suggest that the HPA-axis may be more sensitive to exposure to any type of abuse during early childhood (0-5 years) which may "program" the physiological response for later adaptive functioning in a similar environment. We found that different profiles of later functioning of the HPA-axis were associated with specific subtypes of child trauma exposure, however the HPA-axis appeared to have an overlapping period of sensitivity to both forms of abuse. The HPA-axis is largely conceptualized as an adaptive system that is designed to develop in a way that promotes survival in a given environment. Therefore, it may be the case that rapid HPA-axis activation to acute stress is adaptive in a physically threatening system, while suppressing acute stress reactivity is adaptive in an emotionally abusive environment. For example, in response to a physically abusive

caregiver, rapid HPA-axis activation may facilitate redistribution of resources to enable self-defense and escaping from the situation, and thus be adaptive for survival. In contrast, an emotionally abusive environment may include similarly distressing situations that are less effectively managed by behavioral responses that are facilitated by the HPA-axis. Specifically, emotional and physical abuse often occur together, and maladaptive behavioral responses to emotional abuse such as self-defense or running away from an abuser may facilitate episodes of physical abuse. Therefore hyper-sensitivity of the HPA-axis to acute stress among chronically emotionally abused youth would only be maladaptive for the developing neurobiological system. In sum, these findings are important preliminary evidence that different forms of early childhood abuse and trauma have distinct and long-term HPA-axis correlates. Future studies may benefit from more differentiation of what constitutes early life stress in order to more clearly quantify developmental processes within the neurobiological system.

Childhood trauma exposure as a moderator between depression and adolescent HPA-axis functioning

The purpose of the third aim of this dissertation was to test whether trauma exposure moderates the association between depression and HPA-axis functioning. In this study we found that youth with the most exposure to general trauma during childhood who also currently have depression demonstrated atypical cortisol regulation at bedtime compared to their peers. Anomalies in HPA-axis regulation were also reflected in their reactivity to an acute stress task where they exhibit a blunted response to the laboratory stressor but consistently higher cortisol compared with their peers at baseline, peak activation and regulation. To date, this is the first study to quantify the interplay between current depression and a history of different types of childhood trauma exposure on multiple indices of neuroendocrine functioning.

Specifically, depression was not associated with greater amplitude of cortisol awakening response in this sample. Furthermore, no forms of childhood trauma exposure moderate this finding. The lack of association between depression and CAR in this sample is inconsistent with previous studies suggesting that greater amplitude in cortisol awakening response is found in adolescents preceding a depressive episode (Adam et al., 2010; Vrshek-Schallhorn et al., 2013), or adults who are currently depressed (Pruessner, Hellhammer, Pruessner, & Lupien, 2003; Vreeburg, Hoogendijk, van Pelt, & et al, 2009). However, these previous studies don't account for exposure to childhood trauma in their findings, which were accounted for in our main effects models here. These findings may indicate the importance of assessing for childhood exposure to abuse and traumatic events in future studies aimed at characterizing the neuroendocrine dysregulation related to affective disorders. For example, exaggerated cortisol awakening response has been identified as a vulnerability factor of the onset of depression (Vreeburg et al., 2010), while both blunted and exaggerated CAR have been associated with depression to date (Chida & Steptoe, 2009). Among our sample, there was a main effect of general trauma exposure on the amplitude of CAR. Our study suggest that some of these anomalies in cortisol awakening response may be better accounted for by a history of living in an unpredictable, potentially unsafe, environment during childhood.

When examining regulation of diurnal cortisol in these youth, we found that as exposure to general trauma increased, depression was associated with a more intense slope of cortisol decline from waking and an extreme deceleration of this decline approaching the end of the day. However, this effect was moderated by current depression such that among depressed youth, as exposure to general trauma increased, decline in cortisol throughout the day was steeper and cortisol at bedtime increased. This finding may provide insight into why children with anxiety

disorders have higher peri-sleep cortisol compared with depressed or healthy children, while depressed adolescents show elevated peri-sleep cortisol compared with anxious or healthy peers (Forbes et al., 2006). Our results suggest that these elevations in peri-sleep cortisol may be driven by youth with a history of exposure to multiple unpredictable, and potentially unsafe, traumatic experiences which may be a proxy for the security of the developmental environment. This finding may suggest that there is a dysregulation in the physiology of the HPA-axis, such as the CRH gene transcription within the periventricular nucleus (PVN) of the hypothalamus which are responsible for modulating circadian dependent pulses of CRH secretion (Buckley & Schatzberg, 2005). This finding may also indicate a psychologically-driven activation of the HPA-axis in response to bedtime. Given the association between sleep difficulties and both trauma exposure (Sadeh, 1996) and depression (Dahl et al., 1996), and that this general trauma related pattern of elevated bedtime cortisol was strongest among depressed youth, further investigations are needed to determine whether, and in which direction, this observed dysregulation in diurnal cortisol is related to ongoing sleep difficulties. If so, depressed youth with a history of general trauma exposure may benefit from interventions targeting sleep hygiene to reduce the perpetuation of this anomaly in diurnal cortisol regulation or further vulnerabilities for impaired mood regulation.

Finally, we examined the interplay between current depression and trauma history in HPA-axis reactivity to an acute stressor. While controlling for the impact of depression, we found that abuse and trauma exposure were not associated with patterns of HPA-axis reactivity to an acute stressor. However, the association between depression and HPA-axis reactivity to acute stress was moderated by exposure to more general traumatic events. Specifically, elevated baseline cortisol preceding the stress task, and consequently a blunted response, was evident

among depressed youth as childhood exposure to general trauma increased. Given that these depressed youth with a history of general trauma exposure only demonstrated cortisol dysregulation at bedtime, elevations in cortisol at baseline are likely an indication of hypersensitivity of the HPA-axis to a novel environment. Furthermore, continued elevation in cortisol throughout the laboratory visit is likely indicative of a failure to regulate that activation in the same amount of time as their peers. The implications of this finding are two-fold. Methodologically, these data suggest that trauma-exposed and clinical samples of youth need a longer baseline adaptation period in laboratory stress protocols. Furthermore, this finding highlights the important role of pairing acute stress reactivity with diurnal regulation of cortisol in order to accurately describe HPA-axis reactivity. Yet, previous studies have been unable to disentangle anomalies in diurnal regulation of cortisol from a response to the laboratory environment. Clinically, this may provide insight into depressive symptoms as they differ for trauma-exposed and non-trauma-exposed depressed youth. Specifically, depressed youth with a history of general trauma exposure may endorse loss of pleasure or interest in activities that require travel to novel environments, which may be driven by increased physiological stress in those situations. In comparison, other depressed peers may endorse loss of pleasure or interest in activities due to cognitive distortions, low energy, or diminished capacity to experience pleasure.

In conclusion, we found that while depression is associated with specific anomalies in HPA-axis functioning, exposure to an unpredictable and potentially unsafe environment during childhood accounts for much of this association. Of note, reported history of physical or emotional abuse did not account for, or moderate, the association between depression and neuroendocrine functioning. This suggests that living in an unpredictable environment may be uniquely associated with maladaptive patterns of regulation across development. For youth in

this study, general trauma exposure was a better predictor than current depression of exaggerated CAR. We also found that some anomalies in neuroendocrine functioning were specific to the subgroup of youth with both a history of general trauma and current depression. Given that we examined multiple indices of HPA-axis functioning, this subgroup appears to demonstrate psychological hypersensitivity of the HPA-axis to approaching bedtime, and entering novel environments, which result in dysregulated diurnal and acute regulation of cortisol compared with their peers. Further research is necessary to understand what characterizes this subgroup of youth, such as genetic predisposition, which may aide in the development of improved assessments and interventions for their depressive illness.

Limitations

The contribution of these findings should be considered within the context of several strengths and limitations.

In this study, we did not collect data on the pubertal status of our sample and therefore cannot comment on how our findings are related to pubertal development. Given that the average age of our participants was 13 years, more than half of our sample had likely surpassed Tanner Stage III (See Table 3 of Euling et al., 2008). Therefore, a proportion of our sample likely reflected a transitional cohort of children ranging from pre- to early adolescence. Pubertal status has been identified as a critical contributor to HPA-axis functioning (Gunnar et al., 2009; Hankin et al., 2010), and may be a developmentally critical period for the reprogramming of the HPA-axis following early care experiences (Quevedo et al., 2012). Therefore, pubertal status may be contributing to the variability in cortisol across our sample due to the wide age range (9-16 years). In addition, there has been some evidence to suggest that pubertal development is associated with the development of internalizing problems (Marceau, Neiderhiser, Lichtenstein,

& Reiss, 2012), especially adolescent depression among females (Angold, Costello, & Worthman, 1998). While we will not be able to comment on the role that pubertal status plays in the association between trauma exposure and adolescent HPA-axis functioning among depressed and non-depressed adolescents, the findings would be more specific and reliable if we could account for this effect. One approach we have taken to address this limitation is testing age and sex as covariates in all of our models. Given that females demonstrate puberty related changes in HPA-axis functioning earlier than males (Gunnar et al., 2009), this approach allowed us to account for some of the variability in HPA-axis functioning that is accounted for by age as a function of sex, but future efforts at replication of these findings would benefit from assessment of pubertal status directly for any youth above age 9.

To activate the HPA-axis, participants completed the SE-CPT which includes a physiological stimulus and a social-evaluative component. We chose this task to minimize the cognitive resources engaged during the protocol, and to more closely approximate physiological stressors in the environment. Therefore, these findings may not reflect HPA-axis reactivity to stressors initiated by cognitive processes that are not captured by the SE-CPT and further studies should be conducted to replicate these findings with other psychosocial stress tasks.

Each participant in this study was asked to contribute 8 saliva samples at home. Participants recorded the time that each sample was completed during these 2 days, however no objective methods were used to assess the integrity of these data. Therefore, it is possible that HPA-axis indices such as the cortisol awakening response which are highly sensitive to timing in relation to waking are not accurate reflections of the cortisol awakening response for these individuals. Future studies should consider the use of MEMS caps, collecting these samples in a sleep lab, or other objective measures of insuring the validity of these data.

Childhood trauma exposure in this study was provided retrospectively by the parents of our participants. This occurred in order to ascertain potential abuse and trauma exposure for each child throughout their development, especially those occurring before the development of the child's ability to remember and report (e.g., during infancy or toddlerhood). This introduces two important considerations for our data. First, more than 80% of child abuse and neglect is perpetrated by primary caregivers (Famularo, Kinscherff, Fenton, & Bolduc, 1990; Sedlak et al., 2010). Therefore, it is possible that rates of abuse and neglect are under-reported in this study, as rates of abuse are considerably higher when self-reported by youth (Stoltenborgh, IJzendoorn, Euser, & Bakermans-Kranenburg, 2011). That being said, in our sample of 138 youth, 48% endorsed that their child was exposed to physical abuse, 31% endorsed that their child was exposed to emotional abuse, and 6% endorsed that their child was exposed to sexual abuse. In the United States, it is estimated that 33% of children are exposed to physical abuse, 33% are exposed to emotional/psychological abuse, and 15% are exposed to sexual abuse (Flaherty et al., 2009). Therefore only rates of sexual abuse appear to be under-reported compared with nationally representative studies. Second, the use of retrospective parent-report introduces the possibility that parents are not accurately reporting the age of onset for specific events. Future studies may benefit from corroborating parent reports of child abuse and neglect with multiple sources including other adults that are close to the youth and even government agencies such as Child Protective Services.

In addition to methodological limitations of the current study, there are also limitations to these findings related to sample characteristics. While youth and families assessed for this study were consistent with that of the local community, findings from this highly educated and predominantly Caucasian sample may not generalize to other geographic regions of the United

States. For example, African American youth are exposed to higher rates of child abuse and neglect than Caucasian and Latino youth (Sedlak et al., 2010). Additionally, families with lower socioeconomic status (defined by low parent education and household income) are more likely to have abused and neglected children than families with higher SES (Sedlak et al., 2010). Therefore efforts to replicate these findings in samples with more representation of non-Caucasian ethnicities and families with lower parent education are necessary to understand the generalizability of these findings.

Another potential limitation of this study is that trauma exposure is commonly associated with the development of anxiety disorders, specifically PTSD. Due to the overarching goal of this study to inform our understanding of adolescent depression, participants were excluded if their only internalizing diagnosis was an anxiety disorder. This means that our findings cannot speak to the associations between the exposure to early trauma and HPA-axis functioning among children with PTSD. However, several studies have found that exposure to severe abuse before the age of 12 is more likely to result in the development and maintenance of depression than anxiety (Maercker et al., 2004; Schoedl et al., 2010). Therefore, these findings are likely relevant to our understanding of the majority of children exposed to severe abuse. Despite this, the prevalence of PTSD within the population is approximately 8% (American Psychological Association, 2000), and among those exposed to trauma, 20-30% of children will develop PTSD (McCloskey & Walker, 2000). Despite the rates of exposure to abuse and trauma, no participants in this study met criteria for PTSD. This suggests that either these children recovered from sub-clinical post-traumatic symptoms following traumatic events, or our sample may be resilient to the impact of significant life stressors, and furthermore cannot confidently be

applied to our understanding of the diverse outcomes associated with exposure to early trauma, such as posttraumatic stress disorder.

Finally, in these studies we have examined the relationship between childhood trauma exposure and HPA-axis functioning in adolescence, however this study is cross-sectional and no causality may be inferred from these data. Furthermore, our theoretical model implies that exposure to childhood trauma influences later HPA-axis functioning, however it is also possible that individual differences in physiological stress reactivity may play a role in facilitating stressful experiences from the environment. The findings in this study would be enriched by longitudinal investigations of childhood trauma exposure with multiple assessments of HPA-axis functioning where transactional modeling approaches can begin to disentangle these associations.

Conclusions

Taken together, the results of this dissertation inform our working understanding of the relationship between childhood traumatic experiences, neuroendocrine dysregulation, and depressive disorders. To our knowledge, this is the first study to examine the role of different types of childhood trauma exposure in multiple neuroendocrine processes during adolescence. Specifically, we confirmed our hypotheses that different types of childhood stress would be related to specific disruptions in the regulation of the HPA-axis. Namely, physical abuse may influence the sensitivity of HPA-axis *activation* to stress in the environment, emotional abuse may impair the *regulation* of that acute stress response, and cumulative accidental stress may disrupt the ability to regulate the HPA-axis around specific stressors such as bedtime. Furthermore, this is among the first studies to examine the role of timing in the association between childhood stress and later HPA-axis functioning. For example, the HPA-axis may be hypersensitive to exposure to physical abuse during early childhood and vulnerable to the

development of chronically elevated diurnal cortisol when exposed to emotional abuse throughout the school-aged years. Finally, this study provides insight into the interplay between childhood trauma exposure and the neuroendocrine dysregulation associated with depressive disorders. Specifically, elevated cortisol at bedtime was unique to depressed youth with high reported general trauma exposure in childhood and these same youth demonstrate hypersensitivity to entering a novel environment, such as a research lab. These results are consistent with and extend a number of previous studies and make several important methodological and theoretical contributions to our field.

Methodologically, these findings demonstrate the need for studies integrating findings from multiple indices of HPA-axis functioning. For example, without our assessment of diurnal cortisol in this study, depressed youth with a history of general trauma exposure may have been interpreted as having chronically elevated cortisol. However, given that our diurnal assessments of these youth were no different from that of their peers (with the exception of bedtime), it is likely that the novel, laboratory environment was an acute trigger for the HPA-axis. This may be methodologically avoided in future research with the use of a longer baseline phase, home visits, or the use of a familiar setting. Furthermore, this study employed the use of landmark registration to model acute stress reactivity, which has only been used once before (Kuhlman et al., 2013). In an acute stress task with dense sampling of post-stress cortisol regulation, this data analysis method may allow better insight into the timing of cortisol change over time, and therefore the nature of HPA-axis dysregulation.

Theoretically, these findings contribute preliminary evidence that some forms of exposure to childhood stress play different roles in the development of HPA-axis dysregulation. This may explain why some forms of childhood stress occurring at different ages are associated

with different mental health outcomes across the lifespan (Kaplow & Widom, 2007; Kuhlman, Maercker, Bachem, Simmen, & Burri, 2013; Maercker et al., 2004). In this sample, hypersensitivity to stress was observed among adolescent youth with exposure to any amount of physical abuse during early childhood, while reduced activation of the stress response was associated with emotional abuse in any amount during early childhood. Furthermore, these associations were also seen among youth whose exposure to high amounts of abuse beginning at any point in childhood. Clinically, these findings highlight the importance of child welfare programs and mandated reporters in preventing child abuse that may result in long term changes to the functioning of the neurobiological stress system. Furthermore, this study emphasizes that exposure to childhood stress in the form of living in an unpredictable environment, as approximated here by general trauma, is associated with detriments to the long-term psychological and physiological response to stress. Finally, this study provides some evidence that the neuroendocrine dysregulation associated with depression, may be moderated, or at times, better accounted for by exposure to an unpredictable environment during childhood. This has both methodological and clinical implications. First, future studies investigating the prodromal processes in the development of depression would benefit from accounting for childhood trauma history. Second, there may be specific subtypes of youth depression which can be differentiated by the presence or absence of childhood trauma exposure; however further studies are required to disentangle whether there are additional genetic, neurobiological, or behavioral markers that would enable this clinical distinction.

Future directions

This dissertation provides preliminary evidence for the development of a program of research dedicated to understanding the role of childhood trauma exposure in the development of

psychiatric disorders across the lifespan. Here we have examined the role of specific childhood trauma subtypes, physical abuse, emotional abuse and accidental trauma, while neglecting other forms of childhood stress. Furthermore we have taken only a cross-sectional view of associations between childhood stress and neuroendocrine functioning during adolescence. These data provide evidence to support longitudinal investigations of these relationships; including multiple assessments of changes in HPA-axis functioning across childhood and adolescence, as well as repeated assessments of childhood trauma exposure and psychiatric symptoms. These longitudinal assessments would provide more insight into the processes through which childhood trauma facilitates adaptations in HPA-axis functioning, elucidating the role of family relationships, sociodemographics, community resources, and interventions. Additionally, this study limited its investigation to adolescence (ages 9-16), while childhood trauma has been associated with HPA-axis dysregulation as well as negative health outcomes across the lifespan (Anda et al., 2006; Chapman et al., 2007; Kuhlman et al., 2013). Conducting this longitudinal research into adulthood may also generate important findings on the neurobiological underpinnings of disease and resilience.

Table 3.1. Means, standard deviations and correlations between demographic, trauma exposure, and HPA-axis functioning indicators.

		Correlations														
	M (SD)	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.
1. Age	12.8 (2.3)	1.0														
2. Sex (female = 1)	--	-.056	1.0													
3. Physical Abuse[1]	1.53 (3.4)	-.002	.127	1.0												
4. Emotional Abuse [1]	1.90 (4.5)	.160†	-.037	.403**	1.0											
5. General Trauma[1]	2.55 (3.9)	.250*	-.059	.272**	.425**	1.0										
6. Current Depression	--	.236*	-.033	-.038	.297**	-.042	1.0									
7. CDI-Parent[1]	12.3 (6.7)	.289**	-.013	.044	.340**	.181	.459**	1.0								
8. CDI-Self	8.71 (9.3)	.364**	-.274**	-.019	.275**	.241*	.527**	.488**	1.0							
9. Baseline cortisol[2,3]	.146 (.27)	.152†	.020	.046	.059	.058	.087	.121	.124	1.0						
10. AUCg2,3	9.07 (17.6)	.082	-.018	.042	.069	-.009	.076	.130	.119	.892**	1.0					
11. Peak cortisol[2,3]	.189 (.56)	.037	-.040	.049	.071	-.037	.053	.111	.112	.760**	.961**	1.0				
12. AUCi[2,3]	1.55 (8.4)	-.096	-.032	.058	.009	-.119	.015	.040	-.050	-.010	.399**	.559**	1.0			
13. Waking Cortisol[2,3]	.297 (.15)	-.119	.044	.074	-.007	.125	-.070	-.057	-.084	.065	.074	.043	.085	1.0		
14. CAR[2,3]	.096 (.24)	.128	-.016	.104	.168	.163	.037	-.024	.035	-.149	-.101	-.059	.005	-.299**	1.0	
15. Dinner Cortisol[2,3.]	.123 (.149)	-.014	-.100	.026	.030	-.149	.012	-.095	.027	.269**	.429**	.464**	.219*	.033	.161†	1.0
16. Bedtime cortisol[2,3]	.114 (.144)	-.136	-.351**	.054	.041	.055	.025	-.125	.113	.128	.265**	.306**	.151	.037	.016	.559**

Note: † $p < .10$; * $p < .05$; ** $p < .01$; [1] log transformed for multivariate analyses;[2] box transformed for multivariate analyses; [3] µg/dl

Table 3.2. Results of unadjusted and adjusted regression models predicting cortisol awakening response from trauma subtypes.

	Predictor	R^2	F	β	t
Unadjusted Physical Abuse Model		.23	15.8**		
	Waking Cortisol			.473	5.39**
	Physical Abuse			.106	1.21
Unadjusted Emotional Abuse Model		.25	16.6**		
	Waking Cortisol			.483	5.53**
	Emotional Abuse			.147	1.68†
Unadjusted General Trauma Model		.27	16.5**		
	Waking Cortisol			.454	4.98**
	General Trauma			.204	2.24*
Adjusted Trauma Model		.28	8.29**		
	Waking Cortisol			.455	4.90**
	Physical Abuse			.043	.428
	Emotional Abuse			.069	.639
	General Trauma			.164	1.57

Note: ** $p < .01$, * $p < .05$, $^{\dagger}p < .10$

Table 3.3. Unadjusted and adjusted growth curve models of diurnal cortisol regulation predicted by childhood trauma exposure by subtypes.

	Unadjusted Physical Abuse Model (AIC=285.5)		Unadjusted Emotional Abuse Model (AIC = 287.0)		Unadjusted General Trauma Model (AIC = 269.8)		Adjusted Model (AIC=278.8)	
	β	*t*	*β*	*t*	*β*	*t*	*β*	*t*
Intercept	-1.12	-20.6**	-1.13	-20.8**	-1.14	-19.4**	-1.14	-19.3**
Hours	-.09	-4.75**	-.09	-4.70**	-.08	-4.15**	-.08	-4.11**
Hours^2	.003	2.85**	.003	2.78**	.003	2.37*	.003	2.36*
Physical Abuse	.023	.43					.019	.31
Physical Abuse x Hours	-.011	-.64					-.012	-.58
Physical Abuse x Hours^2	.001	.79					.001	.69
Emotional Abuse			-.006	-.14			-.046	-.87
Emotional Abuse x Hours			.001	.05			.021	1.22
Emotional Abuse x Hours^2			.0001	.09			-.001	-1.03
General Trauma					.058	1.23	.081	1.51
General Trauma x Hours					-.037	-2.36*	-.044	-2.49*
General Trauma x Hours^2					.002	2.16*	.002	2.19*

Note: *$p < .05$; **$p < .01$ † $p < .10$

Table 3.4. Estimates of fixed effects for adjusted growth curve models of acute HPA-axis reactivity predicted by childhood trauma exposure by subtypes.

	HPA-axis reactivity from Baseline Adjusted Model (AIC = 197.2)		Reactivity to Peak Adjusted Model (AIC = -3.04)		Regulation from Peak Adjusted Model (AIC = -226.6)	
	β	*t*	*B*	*t*	*β*	*t*
Intercept	-1.71	-41.2**	-1.69	-42.0**	-.61	-5.95**
Minutes	.007	2.85**	.008	5.87**	-.016	-6.92**
Minutes^2	-.0003	-3.35**	.0002	6.83**	.0003	5.12**
Minutes^3	.000003	2.70**	--	--	--	--
Physical Abuse	.037	.58	.050	.81	.026	.54
Physical Abuse x Minutes	-.005	-1.36	.005	2.38*	-.001	-.29
Physical Abuse x Minutes^2	.0002	1.36	.0001	3.11**	.00002	.25
Physical Abuse x Minutes^3	-.000002	-1.30	--	--	--	--
Emotional Abuse	-.016	-.30	-.018	-.35	.004	.09
Emotional Abuse x Minutes	-.0006	-.19	-.00078	-.45	.003	1.40
Emotional Abuse x Minutes^2	.0001	.52	-.00002	-.76	-.0001	-2.41*
Emotional Abuse x Minutes^3	-.000001	-.71	--	--	--	--
General Trauma	.053	.92	.005	.10	-.027	-.63
General Trauma x Minutes	-.004	-1.13	-.002	-1.00	.0004	.22
General Trauma x Minutes^2	.0001	.67	-.00003	-.66	.00003	.54
General Trauma x Minutes^3	.000000	-.36	--	--	--	--

Note: **$p < .01$; *$p < .05$; † $p < .10$

Table 3.5. Means, Standard Deviations and Correlations between demographic, age of trauma exposure, and HPA-axis functioning indicators among participants exposed to at least 1 traumatic experience on the ETI.

		Correlations														
	M (SD)	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.
1. Age	12.9 (2.3)	1.0														
2. Physical Abuse[1]	1.53 (2.6)	-.058	1.0													
3. Physical Abuse Age	4.5 (3.2)	.014	-.261†	1.0												
4. Emotional Abuse [1]	2.25 (4.9)	.171	.356**	.156	1.0											
5. Emotional Abuse Age	5.43 (5.0)	.370	-.292	.019	-.552**	1.0										
6. General Trauma[1]	2.93 (4.1)	.248*	.085	.109	.394**	-.167	1.0									
7. General Trauma Age[1]	1.46 (3.2)	.019	.004	.167	.265**	.048	.172	1.0								
8. Baseline cortisol[2,3]	.148 (.28)	.237*	.015	-.055	-.006	.334	.089	-.100	1.0							
9. AUCg[2,3]	8.26 (11.7)	.191	.012	-.071	-.016	.322	.052	-.079	.898**	1.0						
10. Peak cortisol[2,3]	.151 (.24)	.164	.027	-.112	-.023	.232	.032	-.072	.744**	.948**	1.0					
11. AUCi[2,3]	.898 (3.9)	-.076	.118	.019	-.042	.011	-.059	.013	-.188†	.206*	.404**	1.0				
12. Waking Cortisol[2,3]	.309 (.16)	-.069	-.043	.322	-.081	-.468*	.017	.103	.051	.069	.044	.105	1.0			
13. CAR[2,3]	.079 (.24)	.173	.160	-.122	.207	-.310	.255*	-.020	-.129	-.078	-.048	-.009	-.335**	1.0		
14. Afternoon Cortisol[2,3.]	.119 (.15)	.088	.070	.123	.059	-.061	-.124	-.069	.300**	.502**	.535**	.287**	.033	.075	1.0	
15. Bedtime cortisol[2,3]	.115 (.13)	-.089	.032	.011	.011	-.281	.010	-.027	.132	.297**	.332**	.189	.039	-.074	.482**	1.0

Note: † $p < .10$; * $p < .05$; ** $p < .01$; [1] log transformed for multivariate analyses;[2] box transformed for multivariate analyses; [3] μg/dl

Table 3.6. Results of unadjusted and adjusted regression models predicting cortisol awakening response from trauma subtypes.

		Main Effects Model			Interactions Model		
Model	Predictor	R^2	F	β	R^2	F	β
Physical Abuse		.39	5.33**		.39	4.16**	
	Waking Cortisol			.59**			.60**
	Age			-.014			-.02
	Physical Abuse			.13			.10
	Age of Physical Abuse Onset			-.03			.01
	Physical Abuse X Age of Onset			--			-.06
Emotional Abuse		.48	3.85*		.49	3.02*	
	Waking Cortisol			.46*			.40
	Age			-.20			-.24
	Emotional Abuse			.04			.002
	Age of Emotional Abuse Onset			-.21			-.01
	Emotional Abuse X Age of Onset						-.26
General Trauma		.34	7.18**		.34	5.66**	
	Waking Cortisol			.49**			.48**
	Age			-.02			-.02
	General Trauma			.37**			.37**
	Age of General Trauma Onset			-.09			-.07
	General Trauma X Age of Onset			--			-.04

Note: ** $p < .01$, * $p < .05$, $^{\dagger}p < .10$

Table 3.7. Estimates of unadjusted, fixed effects for childhood trauma exposure by subtypes, age of onset and interactions predicting diurnal cortisol regulation.

		Main Effects Model			Interaction Models		
		AIC	*β*	*t*	AIC	*β*	*t*
Physical Abuse Model	Intercept	118.7	-1.26	12.8**	121.4	-1.28	-13.2**
	Hours		-.08	-2.07*		-.08	-1.94
	Hours^2		.003	1.31		.003	1.20
	Physical Abuse (PA)		.126	1.37		.186	1.92†
	PA x Hours		-.027	-.71		-.049	-1.23
	PA x Hours^2		.002	.69		.003	1.09
	PA Onset		.044	2.69**		.010	.39
	PA Onset x Hours		-.002	-.22		.011	1.01
	PA Onset x Hours ^{2}		-.002	-.19		-.001	-1.02
	PA x Onset		--	--		.053	1.60
	PA x Onset x Hours		--	--		-.020	-1.43
	PA x Onset x Hours ^{2}		--	--		.001	1.13
Emotional Abuse Model	Intercept	59.1	-1.01	-5.99**	55.4	-.99	-6.31**
	Hours		-.22	-3.60**		-.23	-3.90**
	Hours^2		.01	2.67*		.01	2.92**
	Emotional Abuse (EA)		-.119	-1.28		-.178	-1.94†
	EA x Hours		.067	1.97†		.085	-2.51*
	EA x Hours ^{2}		-.003	-1.56		-.005	-2.13*
	EA Onset		-.039	-2.35*		.004	.14
	EA Onset x Hours		.015	2.56*		.003	.29
	EA Onset x Hours ^{2}		-.001	-2.31*		-.001	-.071
	EA x Onset		--	--		-.044	-2.03*
	EA x Onset x Hours		--	--		.013	1.65
	EA x Onset x Hours ^{2}		--	--		-.001	-1.73†
General Trauma Model	Intercept	194.9	-1.09	-15.66**	200.6	-1.09	-15.66**
	Hours		-.12	-4.45**		-.12	-4.47**
	Hours^2		.01	2.97**		.01	2.99
	General Trauma (GT)		-.055	-.84		-.057	-.87
	GT x Hours		.006	.26		.007	.28
	GT x Hours ^{2}		-.0002	-.10		-.0002	-.13
	GT Onset		.004	.27		-.0004	-.03
	GT Onset x Hours		-.002	-.26		.0001	-.001
	GT Onset x Hours ^{2}		.0001	.15		-.0001	-.07
	GT x Onset		--	--		.013	.52
	GT x Onset x Hours		--	--		-.004	-.45
	GT x Onset x Hours ^{2}		--	--		.0002	.40

Note: ** $p < .01$, * $p < .05$, $^{\dagger}p < .10$

Table 3.8. Unadjusted growth curve models of stress reactivity predicted by exposure to physical abuse, age of onset, and the interaction between physical abuse exposure and age of onset.

	Reactivity from baseline				Reactivity to Peak				Regulation from Peak			
	Main Effects		Interactions		Main Effects		Interactions		Main Effects		Interactions	
	B	*t*	*β*	*t*	*β*	*t*	*β*	*t*	*β*	*t*	*β*	*t*
Intercept	-2.09	-8.25**	-1.76	-25.2**	-1.75	-26.3**	-1.76	-25.7**	-2.05	-7.35**	-1.76	-24.1**
Minutes	.007	1.53	.007	1.40	.008	3.02**	.006	2.45*	-.02	-5.84**	-.018	-5.75**
Minutes^2	-.0003	-1.86†	-.0003	-1.79†	.0002	3.75**	.0001	3.06**	.0003	4.23**	.0004	4.23**
Minutes^3	.00003	1.55	.00003	1.51	--	--	--	--	--	--	--	--
Physical Abuse (PA)	.025	.71	.035	.39	.033	.45	.061	.72	.030	.38	.052	.57
PA x Minutes	-.002	-.46	-.001	-.20	.0002	.05	.005	1.39	.009	2.74**	.010	2.62**
PA x Minutes^2	.0001	.45	.0001	.35	.00002	.31	.0001	1.77†	-.0003	-3.07**	-.003	-3.05**
PA x Minutes^3	-.000001	-.42	-.000001	-.39	--	--	--	--	--	--	--	--
PA Age of Onset	.0003	.02	.007	.34	-.010	-.70	-.019	-.01	-.006	-.44	-.014	-.64
PA Age of Onset x Minutes	.001	.91	.0005	.33	-.001	-1.35	-.002	-2.37*	-.001	-1.25	-.001	-1.23
PA Age of Onset x Minutes^2	-.00005	-1.18	-.0001	-.74	-.00002	-1.42	-.000004	-2.57*	.00003	1.65†	.00004	1.51
PA Age of Onset x Minutes^3	.0001	1.20	.000001	.84	--	--	--	--	--	--	--	--
PA x Age of Onset	--	--	-.013	-.44	--	--	.017	.63	--	--	.014	.47
PA x Age of Onset x Minutes	--	--	.001	.38	--	--	.003	2.16*	--	--	.001	.57
PA x Age of Onset x Minutes^2	--	--	-.00001	-.07	--	--	.00005	2.16*	--	--	-.00003	-.70
PA x Age of Onset x Minutes^3	--	--	.000	-.04	--	--	--	--	--	--	--	--

Note: ** $p < .01$, * $p < .05$, $^{\dagger}p < .10$

Table 3.9. Unadjusted growth curve models of acute HPA-axis reactivity predicted by exposure to emotional abuse, age of onset of exposure, and the interaction between emotional abuse exposure duration and age of onset.

	Reactivity from baseline				Reactivity to Peak				Regulation from Peak			
	Main Effects		Interactions		Main Effects		Interactions		Main Effects		Interactions	
	β	*t*	*β*	*t*	*β*	*t*	*β*	*t*	*β*	*t*	*β*	*t*
Intercept	-2.20	-5.76**	-1.89	-14.8**	-1.87	-18.5**	-2.10	-5.41**	-1.87	-17.9**	-1.69	-23.5**
Minutes	-.003	-.45	-.005	-.77	.01	3.0**	.01	3.07**	-.01	-2.54**	-.02	-6.49**
Minutes^2	.00007	.26	.0001	.52	.00003	3.95**	.0003	4.20**	.0001	.77	.0003	3.95**
Minutes^3	.00001	-.38	-.000002	-.60	--	--	--	--	--	--	--	--
Emotional Abuse (EA)	.100	1.12	.109	1.18	.051	.67	.028	.38	.031	.38	.010	.13
EA x Minutes	.003	.58	.0004	.08	-.01	-2.13*	-.008	-2.90**	.003	1.08	.004	1.45
EA x Minutes^2	-.0001	-.71	-.0001	-.32	-.0001	-2.43*	-.0001	-3.06**	-.00004	-.50	-.0001	-.87
EA x Minutes^3	.000001	.69	.000001	.36	--	--	--	--	--	--	--	--
EA Age of Onset	.025	1.55	.027	.96	.015	1.08	.044	1.94†	.015	.98	.040	1.66
EA Age of Onset x Minutes	.001	1.37	.003	2.48*	-.001	-1.26	.001	1.18	-.0002	-.34	-.001	-1.34
EA Age of Onset x Minutes^2	-.0001	-1.70†	-.0001	-2.37*	-.00001	-.98	.00002	1.06	.00001	.56	.00003	1.35
EA Age of Onset x Minutes^3	.000001	1.66†	.000001	2.12*	--	--	--	--	--	--	--	--
EA x Age of Onset	--	--	-.001	-.05	--	--	-.026	-1.65	--	--	-.023	-1.38
EA x Age of Onset x Minutes	--	--	-.002	-2.10*	--	--	-.001	-2.34*	--	--	.001	1.43
EA x Age of Onset x Minutes^2	--	--	.0001	1.74†	--	--	-.00002	-1.93†	--	--	-.00003	-1.13
EA x Age of Onset x Minutes^3	--	--	-.000001	-1.46	--	--	--	--	--	--	--	--

Note: ** $p < .01$, * $p < .05$, $^\dagger p < .10$

Table 3.10. Growth curve models of acute HPA-axis reactivity predicted by exposure to general trauma, age of onset of exposure, and the interaction between general trauma exposure duration and age of onset.

	Reactivity from baseline				Reactivity to Peak				Regulation from Peak			
	Main Effects		Interactions		Main Effects		Interactions		Main Effects		Interactions	
	β	*t*	*β*	*t*	*β*	*t*	*β*	*t*	*β*	*t*	*β*	*t*
Intercept	-1.71	-23.8**	-1.71	-23.8**	-1.68	-24.5**	-1.67	-24.4**	-1.69	-23.5**	-1.69	-23.5**
Minutes	.007	1.89†	.007	1.89	.009	3.86**	.008	3.85**	-.01	-6.49**	-.01	-6.47**
Minutes^2	-.0003	-2.21*	-.0003	-2.21*	.00002	4.29**	.0002	4.27**	.0003	3.95**	.0002	3.79**
Minutes^3	.000003	1.83†	.000003	1.83†	--	--	--	--	--	--	--	--
General Trauma (GT)	.065	.72	.066	.73	-.011	-.12	-.013	-.15	.011	.12	.014	.16
GT x Minutes	-.007	-1.58	-.007	-1.58	-.002	-.66	-.002	-.53	.005	1.82†	.003	1.24
GT x Minutes^2	.0002	1.37	.0002	1.36	.000002	.03	-.00001	.22	-.0001	-2.00*	-.0001	-1.00
GT x Minutes^3	-.000002	-1.25	-.000002	-1.25	--	--	--	--	--	--	--	--
GT Age of Onset	-.016	-.80	-.017	-.71	-.010	-.52	-.011	-.49	-.008	-.39	-.006	-.28
GT Age of Onset x Minutes	.002	1.73†	.002	2.00*	.00001	.02	.0003	.35	-.001	-.91	-.001	-1.97*
GT Age of Onset x Minutes^2	-.00007	-1.77†	-.0001	-2.07*	-.000004	-.36	-.000004	-.28	.00003	1.59	-.00001	2.79**
GT Age of Onset x Minutes^3	.000001	1.83†	.000001	2.15*	--	--	--	--	--	--	--	--
GT x Age of Onset	--	--	.002	.07	--	--	.003	.10	--	--	-.003	-.09
GT x Age of Onset x Minutes	--	--	-.002	-1.00	--	--	-.0005	-.39	--	--	.002	2.07*
GT x Age of Onset x Minutes^2	--	--	.0001	1.07	--	--	.000005	.14	--	--	.002	-2.61**
GT x Age of Onset x Minutes^3	--	--	-.000001	-1.13	--	--	--	--	--	--	--	--

Note: ** $p < .01$, * $p < .05$, $^{\dagger}p < .10$

Table 3.11. Between group comparison of demographic, trauma exposure, and cortisol variables for depressed and non-depressed youth.

	Depressed M (SD)	Non-depressed M (SD)	*t*
Age	14.1 (2.0)	12.5 (2.3)	-2.59*
Physical Abuse[1]	1.0 (1.6)	1.62 (3.6)	.41
Emotional Abuse[1]	4.9 (7.1)	1.44 (3.9)	-2.59*
General Trauma[1]	2.0 (2.7)	2.63 (4.1)	.43
CDI-Parent[1]	21.5 (9.3)	10.9 (5.0)	-5.50**
CDI-Self	21.4 (11.5)	6.8 (7.3)	-4.59**
Baseline cortisol[2,3]	.26 (.63)	.13 (.15)	-.60
AUCg[2,3]	11.9 (22.2)	8.6 (16.8)	-.83
Peak cortisol[2,3]	.21 (.38)	.19 (.58)	-.58
AUCi[2,3]	.65 (1.1)	1.69 (9.03)	-.17
Waking Cortisol[2,3]	.27 (.11)	.30 (.16)	.70
CAR[2,3]	.13 (.32)	.09 (.23)	-.37
Dinner Cortisol[2,3.]	.15 (.19)	.12 (.14)	-.089
Bedtime cortisol[2,3]	.14 (.21)	.11 (.13)	-.25

Note: ** $p < .01$, * $p < .05$, $^{\dagger}p < .10$; [1] log transformed for multivariate analyses;[2] box transformed for multivariate analyses; [3]µg/dl

Table 3.12. Results of regression models predicting cortisol awakening response from trauma subtypes, current depression, and the interaction between trauma subtypes and current depression.

		Step 1			Step 2		
Model	Predictor	R^2	F	β	R^2	F	β
Physical Abuse		.244	10.46**		.253	8.12**	
	Waking Cortisol			.473**			.476**
	Physical Abuse			.105			.133
	Depression			-.022			-.041
	Physical Abuse X Depression			--			-.098
Emotional Abuse		.261	11.41**		.269	8.84**	
	Waking Cortisol			.478			.486**
	Emotional Abuse			.179†			.234*
	Depression			-.092			-.041
	Emotional Abuse X Depression			--			-.126
General Trauma		.271	10.90**		.282	8.56**	
	Waking Cortisol			.454**			.449**
	General Trauma			.205*			.236*
	Depression			.010			-.043
	General Trauma X Depression						-.124

Note: ** $p < .01$, * $p < .05$, $^{\dagger}p < .10$

Table 3.13. Estimates of fixed effects for childhood trauma exposure by subtypes, Depression and interactions predicting diurnal cortisol regulation.

		Main Effects Models			Interaction Models		
		AIC	*β*	*t*	AIC	*β*	*t*
Physical Abuse Model	Intercept	290.5	-1.11	-19.7**	294.2	-1.11	-19.7**
	Hours		-.09	-4.61**		-.09	-4.64**
	Hours^2		.003	2.77**		.003	2.79**
	Physical Abuse (PA)		.021	.39		.010	.18
	PA x Hours		-.011	-.63		-.005	-.28
	PA x Hours^2		.001	.78		.0004	.38
	Depression		-.094	-.88		-.082	-.73
	Depression x Hours		.003	.09		-.003	-.08
	Depression x Hours ^{2}		-.0001	-.05		.0003	.14
	PA x Depression		--	--		.108	.62
	PA x Depression x Hours		--	--		-.060	-1.02
	PA x Depression x Hours ^{2}		--	--		.004	1.16
Emotional Abuse Model	Intercept	291.5	-1.11	-19.6	294.6	-1.12	-19.8**
	Hours		-.09	-4.51**		-.09	-4.40**
	Hours^2		.003	2.69**		.003	2.60*
	Emotional Abuse (EA)		.010	.22		-.028	-.51
	EA x Hours		-.00003	-.002		.005	.30
	EA x Hours ^{2}		.0001	.14		-.0002	-.16
	Depression		-.104	-.85		-.200	1.44
	Depression x Hours		.005	.11		.019	.40
	Depression x Hours ^{2}		-.0004	-.14		-.001	-.40
	EA x Depression		--	--		.154	1.42
	EA x Depression x Hours		--	--		-.022	-.60
	EA x Depression x Hours ^{2}		--	--		.001	.57
General Trauma Model	Intercept	275.2	-1.13	-18.6**	273.0	-1.13	-18.7**
	Hours		-.08	-3.94**		-.08	-3.96**
	Hours^2		.003	2.23*		.003	2.17*
	General Trauma (GT)		.056	1.17		.062	1.26
	GTx Hours		-.037	-2.37*		-.029	-1.85†
	GTx Hours ^{2}		.002	2.18*		.002	1.52
	Depression		-.049	-.39		-.077	-.56
	Depression x Hours		-.011	-.27		-.050	-1.11
	Depression x Hours ^{2}		.001	.23		.004	1.30
	GTx Depression		--	--		-.089	-.48
	GTx Depression x Hours		--	--		-.118	-1.96*
	GTx Depression x Hours ^{2}		--	--		.010	2.50**

Note: ** $p < .01$, * $p < .05$, $^\dagger p < .10$

Table 3.14. Unadjusted growth curve models of stress reactivity predicted by exposure to physical abuse, current depression, and the interaction between physical abuse exposure and current depressive status.

	Reactivity from baseline				Reactivity to Peak				Regulation from Peak			
	Main Effects		Interactions		Main Effects		Interactions		Main Effects		Interactions	
	B	*t*	*β*	*t*	*β*	*t*	*β*	*t*	*β*	*t*	*β*	*t*
Intercept	-1.93	-10.6**	-1.92	-10.5**	-2.17	-10.7**	-2.15	-10.7**	-1.70	-28.5**	-2.05	-8.94**
Minutes	.01	2.88**	.007	2.89**	.008	6.23**	.008	6.25**	-.02	-7.43**	-.02	-7.46**
Minutes^2	-.0003	-3.34**	-.0003	-3.35**	.0002	7.03**	.0002	7.04**	.0002	4.02**	.0002	4.06**
Minutes^3	.000002	2.65**	.000002	2.66**	--	--	--	--	--	--	--	--
Physical Abuse (PA)	.024	.45	.001	.03	.023	.50	.008	.15	.018	.32	.001	.01
PA x Minutes	-.006	-1.89†	-.006	-1.96†	.003	1.92†	.003	1.78†	.003	1.28	.003	1.16
PA x Minutes^2	.0002	1.93†	.0003	2.07*	.0001	2.61**	.0001	2.31*	-.0001	-1.32	-.0001	-1.09
PA x Minutes^3	-.000002	-1.80†	-.000002	-.95†	--	--	--	--	--	--	--	--
Depression	.123	1.02	.143	1.19	.026	.23	.045	.40	.089	.75	.101	.84
Depression x Minutes	-.001	-.14	-.0005	-.08	-.005	-1.30	-.002	-.63	-.001	-.17	-.002	-.41
Depression x Minutes^2	.00002	.08	-.000004	-.02	-.0001	-1.18	.0001	.15	.0001	.54	.0001	.84
Depression x Minutes^3	.000	-.03	.00000	.07	--	--	--	--	--	--	--	--
PA x Depression	--	--	.263	1.38	--	--	.204	1.23	--	--	.180	.96
PA x Depression x Minutes	--	--	.005	.50	--	--	.005	.80	--	--	.001	.87
PA x Depression x Minutes^2	--	--	-.0003	-.76	--	--	.0002	1.53	--	--	-.0001	-.50
PA x Depression x Minutes^3	--	--	.0000003	.77	--	--	--	--	--	--	--	--

Note: ** $p < .01$, * $p < .05$, $^\dagger p < .10$

Table 3.15. Unadjusted growth curve models of acute HPA-axis reactivity predicted by exposure to emotional abuse, depression, and the interaction between emotional abuse exposure duration and current depressive status.

	Reactivity from baseline				Reactivity to Peak				Regulation from Peak			
	Main Effects		Interactions		Main Effects		Interactions		Main Effects		Interactions	
	B	*t*	*β*	*t*	*β*	*t*	*β*	*t*	*β*	*t*	*B*	*t*
Intercept	-1.95	-10.6**	-1.92	-10.4**	-1.69	-41.7**	-1.69	-41.9**	-1.71	-28.7**	-1.70	-28.8**
Minutes	.006	2.69**	.006	2.63**	.008	6.00**	.008	6.01**	-.02	-7.63**	-.02	-7.77**
Minutes^2	-.0003	-3.14**	-.00003	-3.09**	.0002	6.75**	.0002	6.79**	.0002	4.15**	.0002	4.28**
Minutes^3	.00002	2.43*	.000002	2.39*	--	--	--	--	--	--	--	--
Emotional Abuse (EA)	-.014	-.30	.026	.48	-.027	-.60	.008	.16	-.037	-.78	.012	.23
EA x Minutes	-.004	-1.57	-.005	-1.78†	.0002	.11	.001	.36	.004	2.24*	.003	1.28
EA x Minutes^2	.0002	1.77†	.0002	1.89†	.00001	.25	.00002	.65	-.0002	-3.09**	-.0001	-1.99*
EA x Minutes^3	-.000002	-1.84†	-.0000002	-1.92†	--	--	--	--	--	--	--	--
Depression	.130	2.05	.210	1.57	.043	.37	.114	.90	.121	.97	.231	1.68†
Depression x Minutes	.003	.38	.0002	.03	-.005	-1.42	-.004	-.98	-.0005	-1.07	-.009	-1.62
Depression x Minutes^2	-.0001	-.49	-.0001	-.18	-.0001	-1.51	-.001	-.84	.0002	1.76†	.0004	2.14*
Depression x Minutes^3	.000001	.56	.000001	.27	--	--	--	--	--	--	--	--
EA x Depression	--	--	-.167	-1.50	--	--	-.143	-1.37	--	--	-.199	-1.81†
EA x Depression x Minutes	--	--	.005	.83	--	--	-.002	-.55	--	--	.006	1.42
EA x Depression x Minutes^2	--	--	-.0002	-.71	--	--	-.0001	-.95	--	--	-.0001	-1.33
EA x Depression x Minutes^3	--	--	.000002	.64	--	--	--	--	--	--	--	--

Note: ** $p < .01$, * $p < .05$, $^{\dagger}p < .10$

Table 3.16. Growth curve models of acute HPA-axis reactivity predicted by exposure to general trauma, current depression, and the interaction between general trauma exposure duration and current depressive status.

	Reactivity from baseline				Reactivity to Peak				Regulation from Peak			
	Main Effects		Interactions		Main Effects		Interactions		Main Effects		Interactions	
	B	*t*	*β*	*t*	*β*	*t*	*β*	*t*	*β*	*t*	*β*	*t*
Intercept	-1.77	-9.06**	-1.83	-9.49**	-1.71	-39.9**	-1.71	-40.62**	-1.73	-26.7**	-1.73	-27.2**
Minutes	.007	2.64**	.007	2.67**	.009	5.86**	.009	5.93**	-.02	-7.28**	-.02	-7.26**
Minutes^2	-.0003	-3.03**	-.0003	-3.08**	.0002	6.50**	.0002	6.54**	.0003	4.35**	.0003	4.19**
Minutes^3	.000002	2.38*	.000002	2.42**	--	--	--	--	--	--	--	--
General Trauma (GT)	.063	1.24	-.002	-.02	.015	.29	-.023	-.44	.015	.30	-.023	-.44
GT x Minutes	-.005	-1.73†	-.005	-1.56	-.001	-.48	-.0004	-.22	.002	1.14	.003	1.93†
GT x Minutes^2	.0002	1.37	.0002	1.60	.00001	.32	.000001	.02	-.00003	-.60	-.000001	-1.50
GT x Minutes^3	-.000001	-1.09	-.000002	-1.47	--	--	--	--	--	--	--	--
Depression	.243	1.94†	.329	2.73**	.123	1.01	.168	1.38	.204	1.58	.252	1.95†
Depression x Minutes	-.0003	-.04	-.001	-.10	-.007	-1.68†	-.007	-1.63†	.0004	.08	-.001	-.17
Depression x Minutes^2	-.00005	-.18	-.00001	-.36	-.0001	-1.58	-.0001	-.84	.000004	.26	.0001	.38
Depression x Minutes^3	.000001	.29	.000002	.57	--	--	--	--	--	--	--	--
GT x Depression	--	--	.604	3.87**	--	--	.350	2.22*	--	--	.358	2.26*
GT x Depression x Minutes	--	--	-.003	-.32	--	--	.0004	.06	--	--	-.015	-2.64**
GT x Depression x Minutes^2	--	--	-.0003	-.92	--	--	.0002	1.66†	--	--	.0004	2.91**
GT x Depression x Minutes^3	--	--	.00001	1.35	--	--	--	--	--	--	--	--

Note: ** $p < .01$, * $p < .05$, $^\dagger p < .10$

Figure 1.1

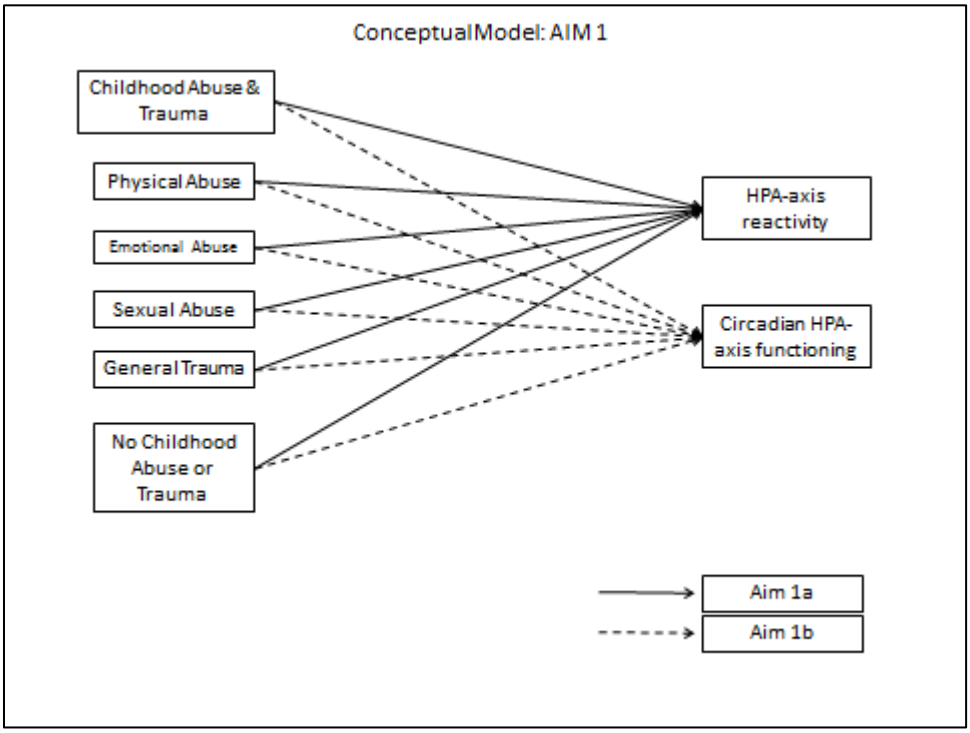

ConceptualModel: AIM 1
Childhood Abuse & Trauma
Physical Abuse
Emotional Abuse
Sexual Abuse
General Trauma
No Childhood Abuse or Trauma
HPA-axis reactivity
Circadian HPA-axis functioning
Aim 1a
Aim 1b

Figure 1.2

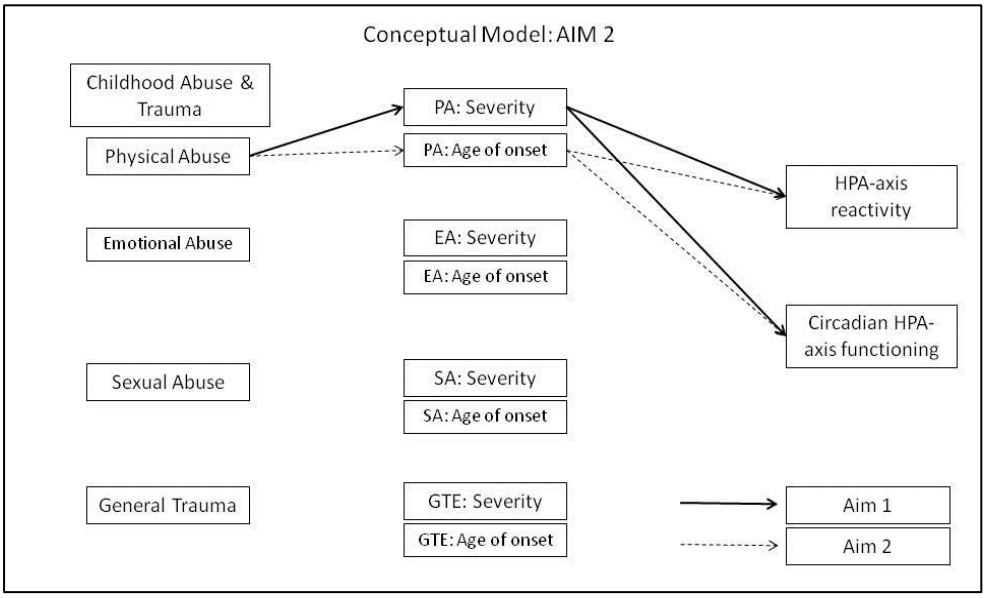

Conceptual Model: AIM 2
Childhood Abuse & Trauma
Physical Abuse
Emotional Abuse
Sexual Abuse
General Trauma
PA: Severity
PA: Age of onset
EA: Severity
EA: Age of onset
SA: Severity
SA: Age of onset
GTE: Severity
GTE: Age of onset
HPA-axis reactivity
Circadian HPA-axis functioning
Aim 1
Aim 2

Figure 1.3

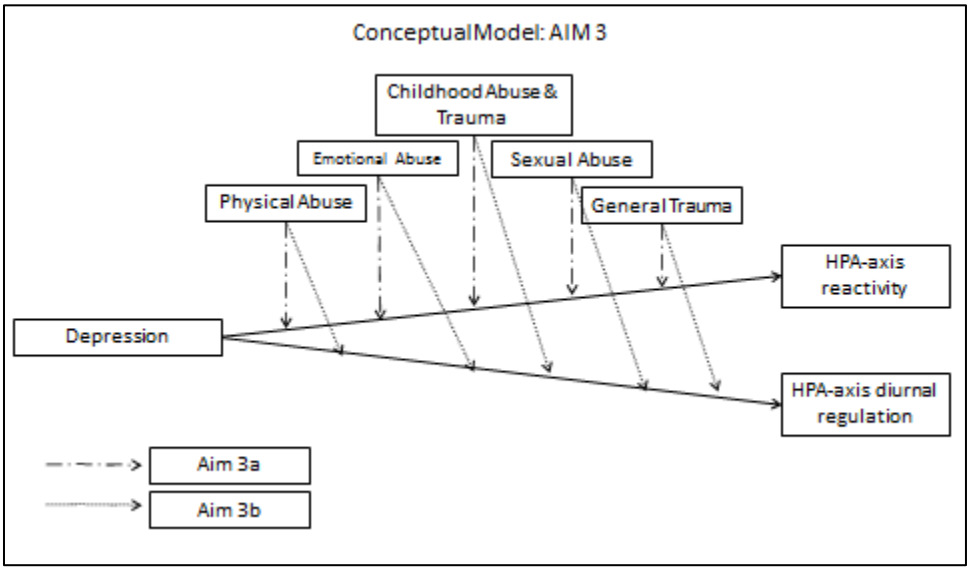

ConceptualModel: AIM 3
Childhood Abuse & Trauma
Emotional Abuse
Sexual Abuse
Physical Abuse
General Trauma
HPA-axis reactivity
Depression
HPA-axis diurnal regulation
Aim 3a
Aim 3b

Figure 2.1

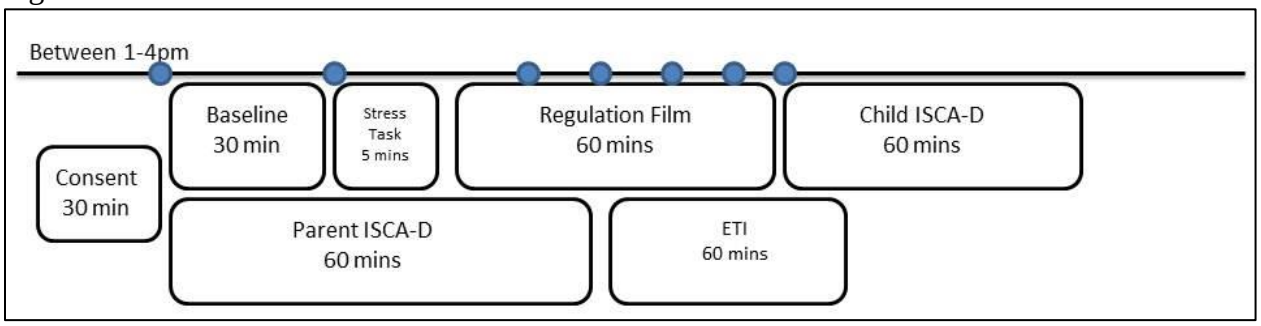

Between 1-4pm
Consent
30 min
Baseline
30 min
Stress
Task
5 mins
Regulation Film
60 mins
Child ISCA-D
60 mins
Parent ISCA-D
60 mins
ETI
60 mins

Figure 2.2 Cortisol Reactivity Models

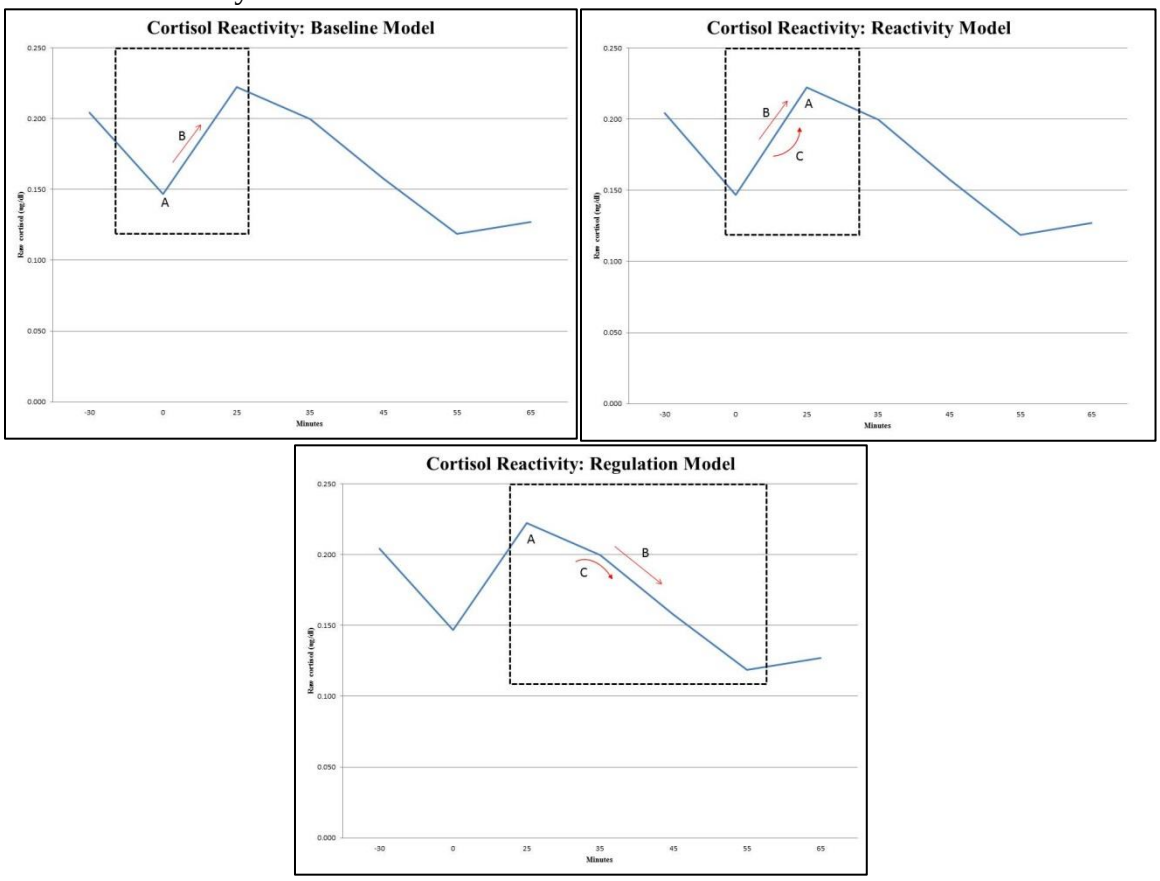


Figure 3.1. Diurnal cortisol regulation comparing youth with high and low exposure to general trauma during childhood.

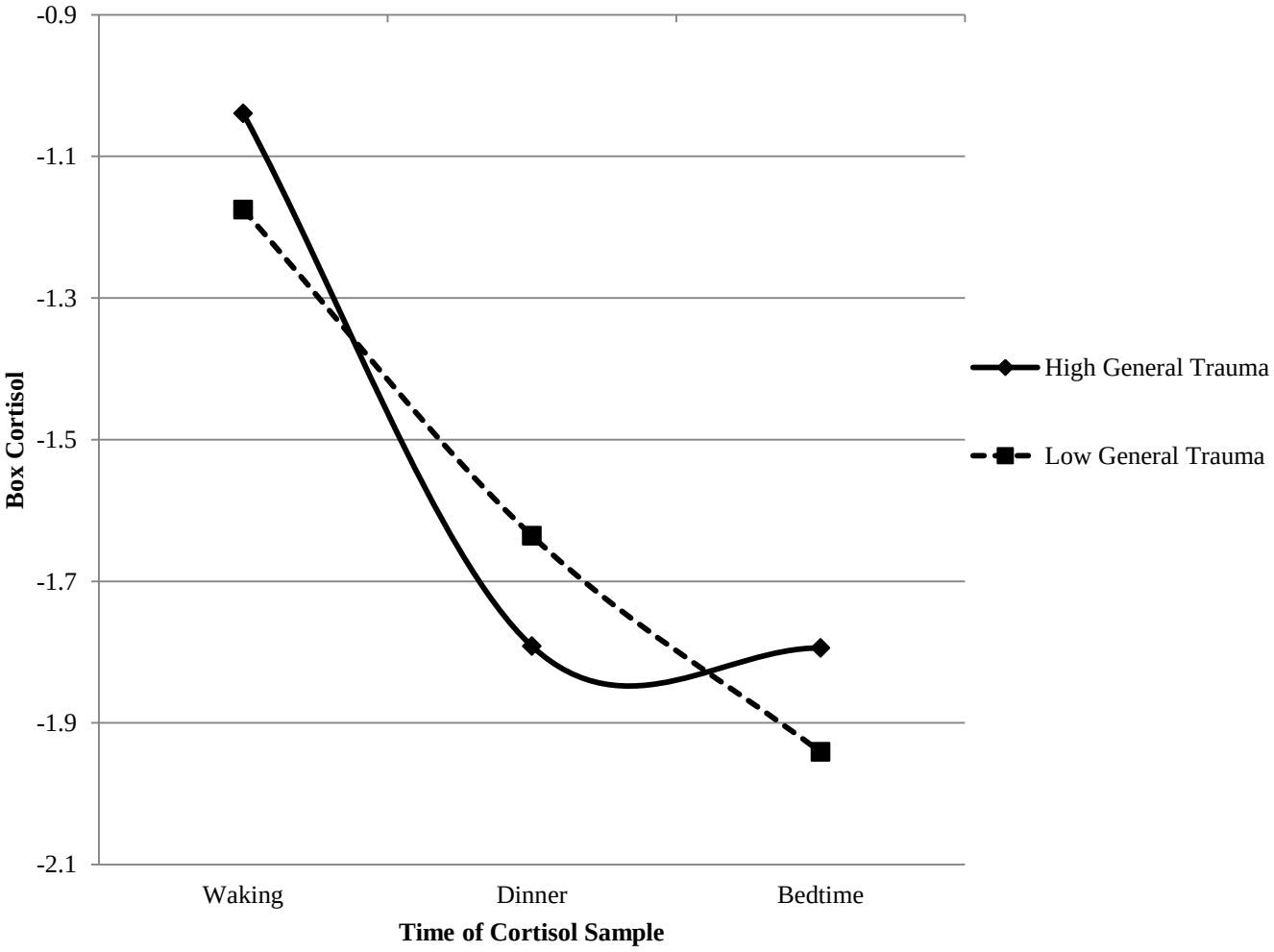


Figure 3.2. Adjusted growth curve model for HPA-axis activation to peak cortisol by childhood physical abuse exposure.

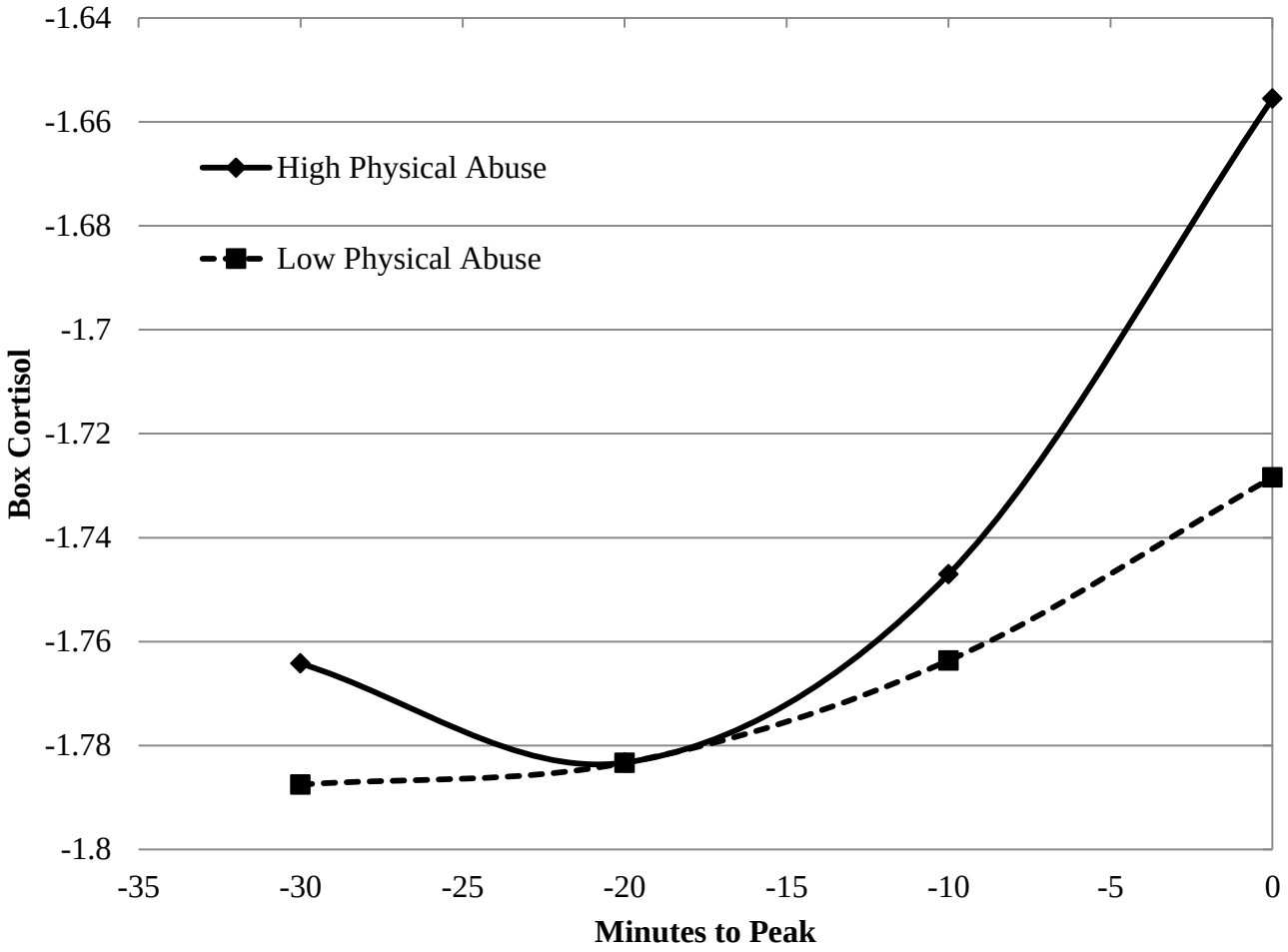


Figure 3.3. Adjusted growth curve model of regulation of acute HPA-axis response by childhood emotional abuse exposure.

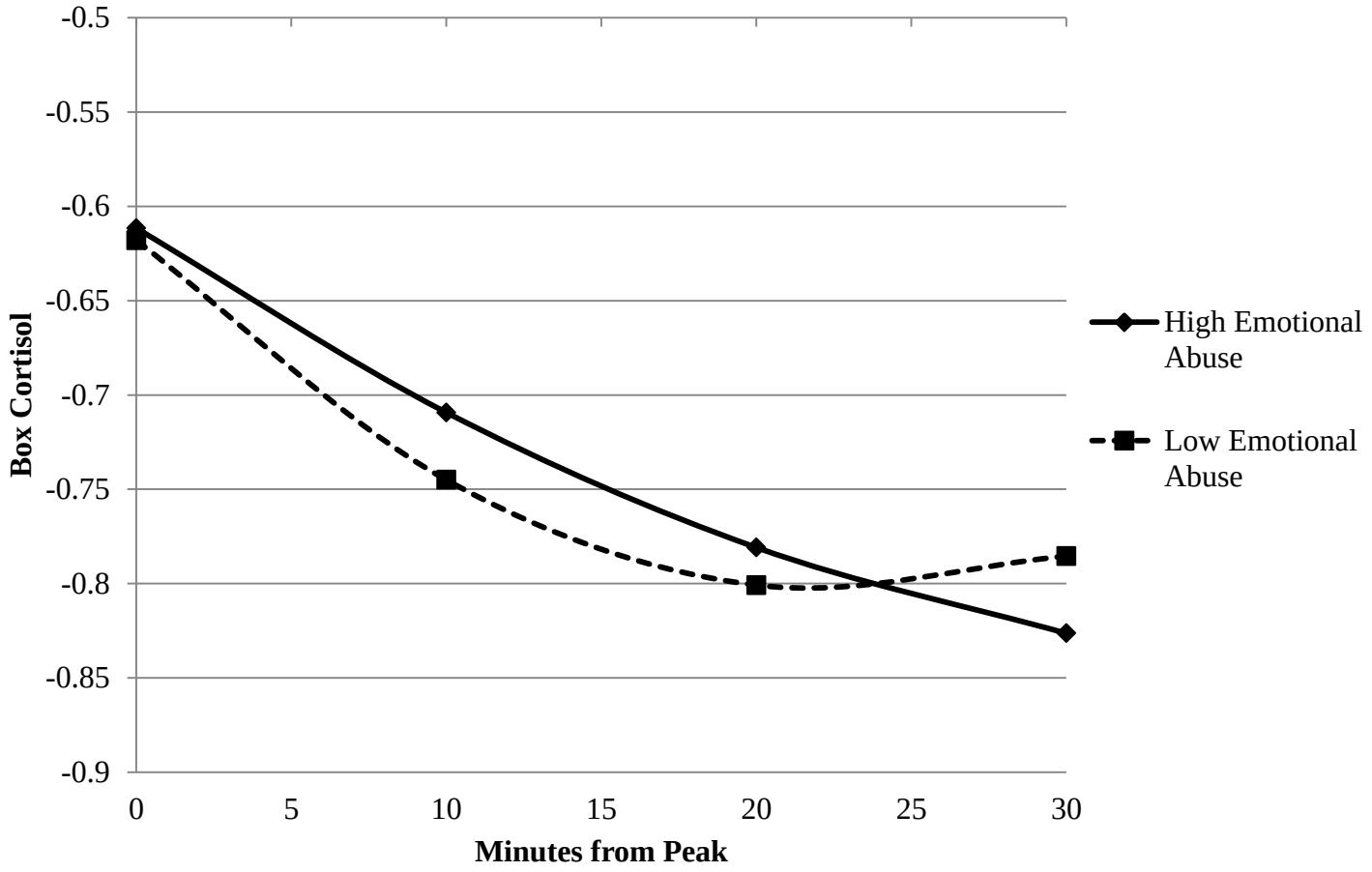


Figure 3.4. Diurnal cortisol regulation comparing youth with early exposure to emotional abuse during childhood.

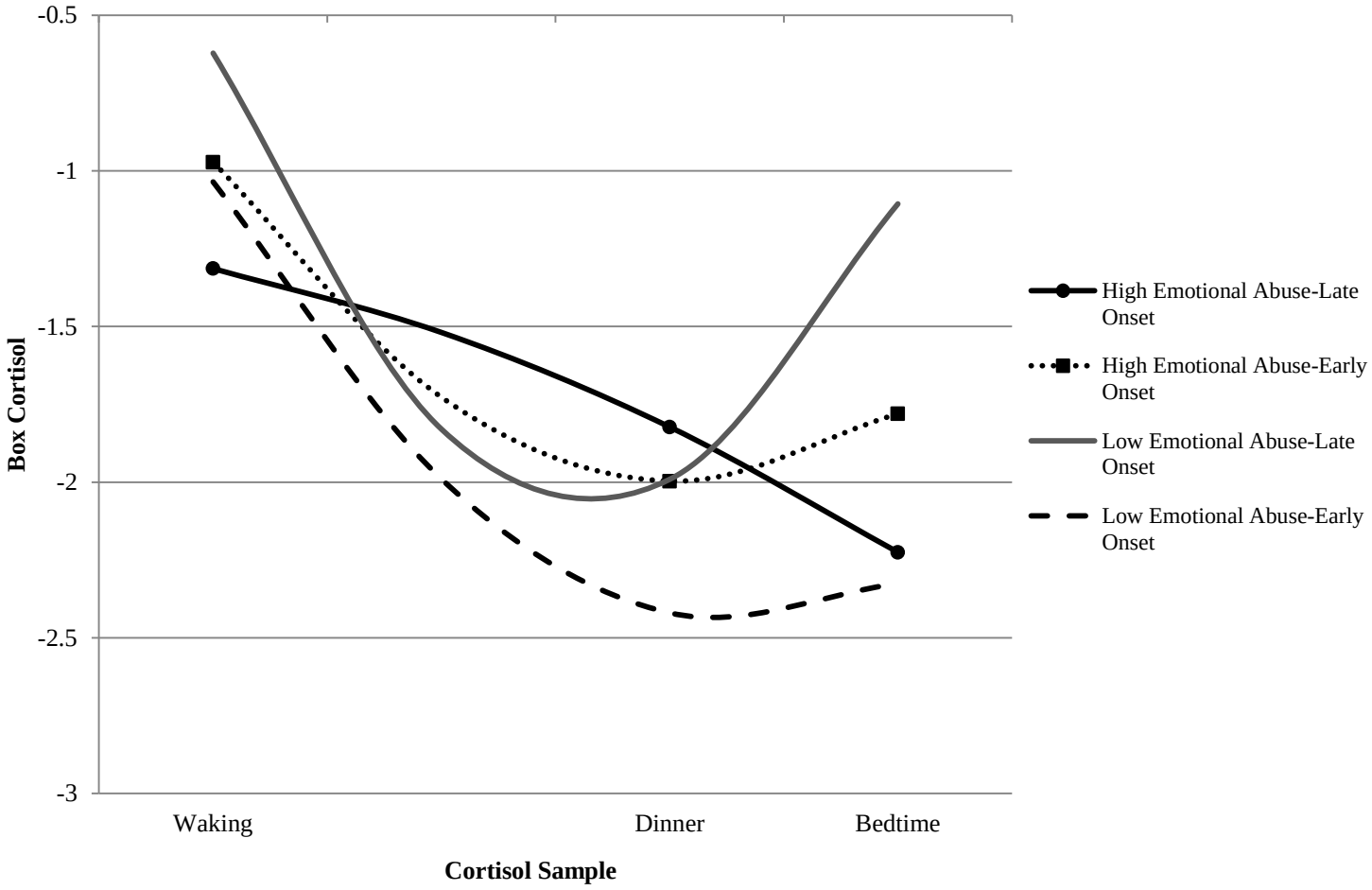


Figure 3.5. HPA-axis reactivity to peak by age of onset of exposure to physical abuse.

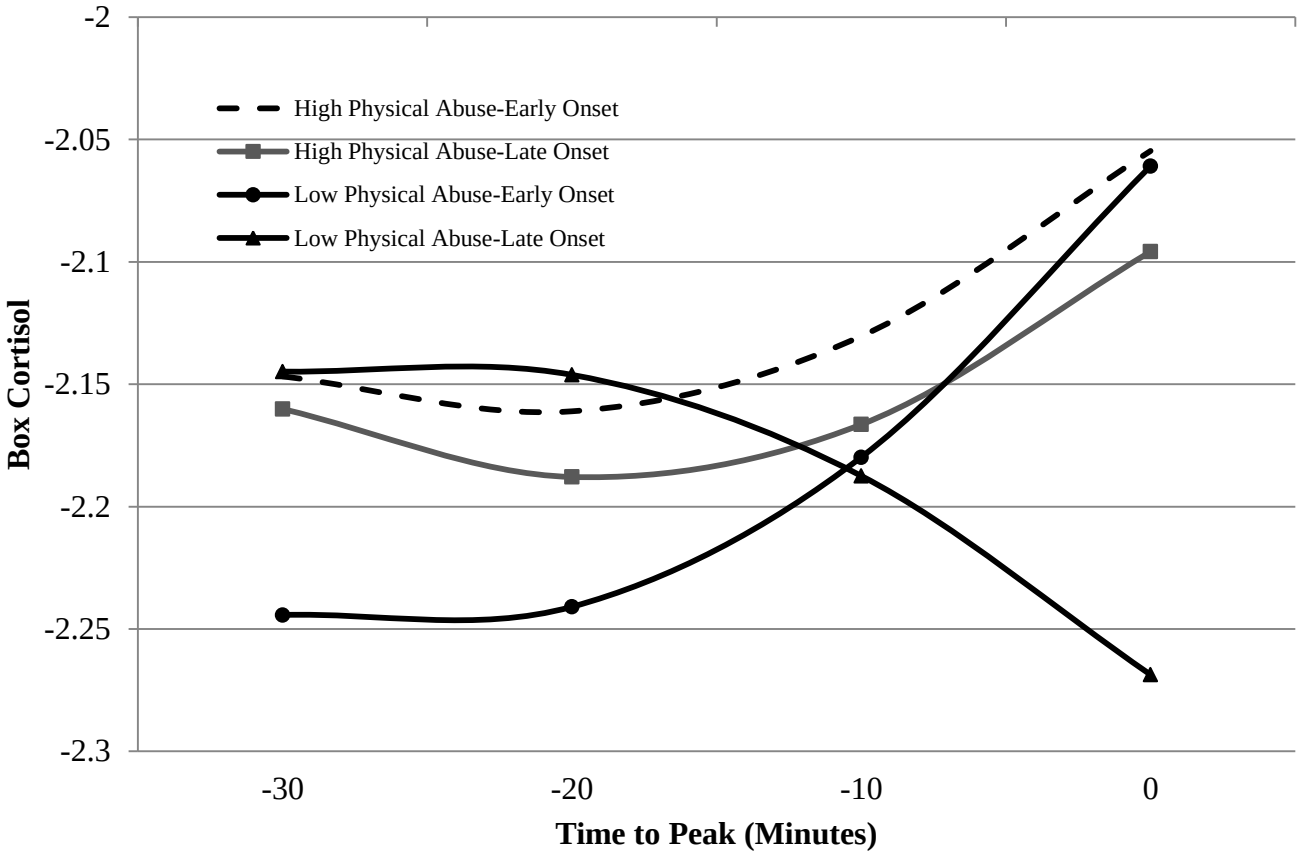


Figure 3.6. Acute stress peak activation by age of onset of exposure to emotional abuse.

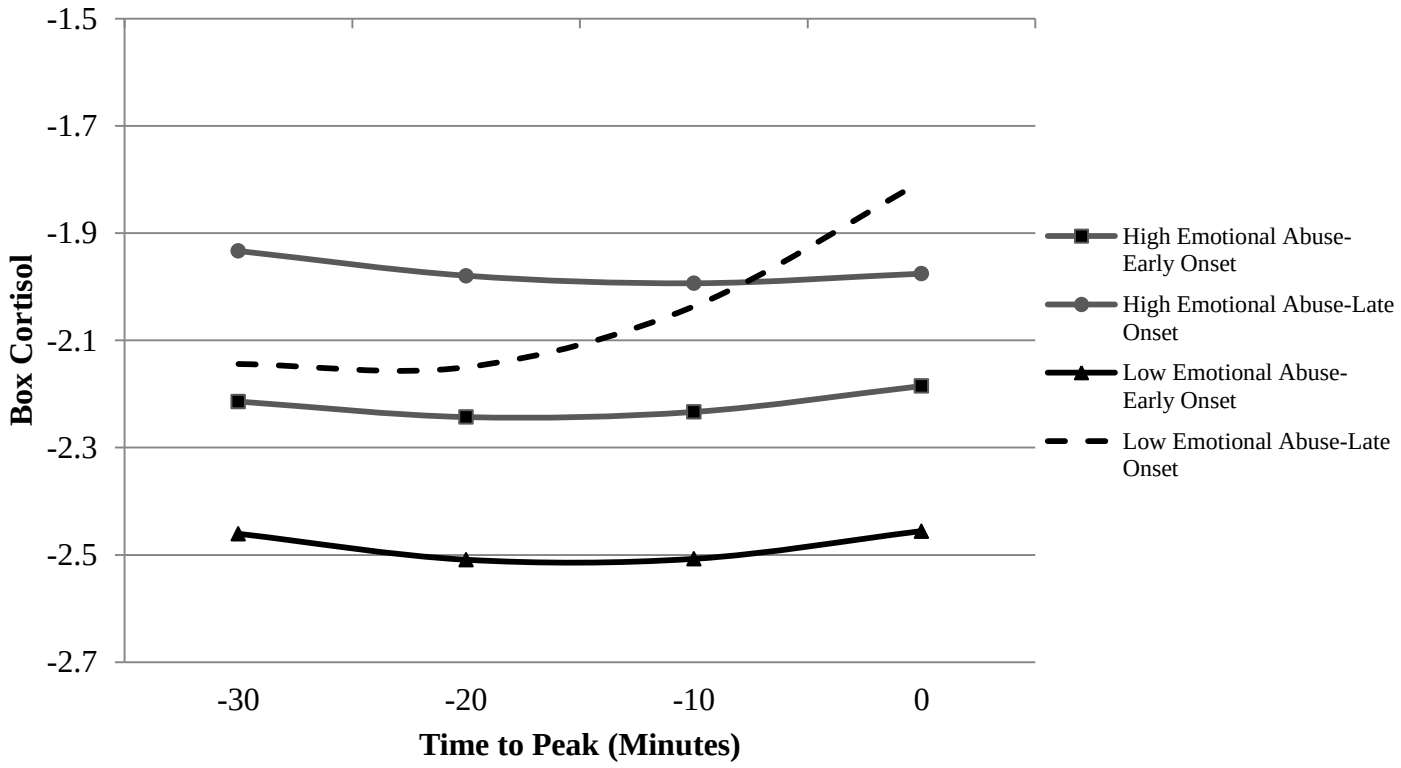


Figure 3.7. Acute stress regulation from peak by age of onset of general trauma exposure.

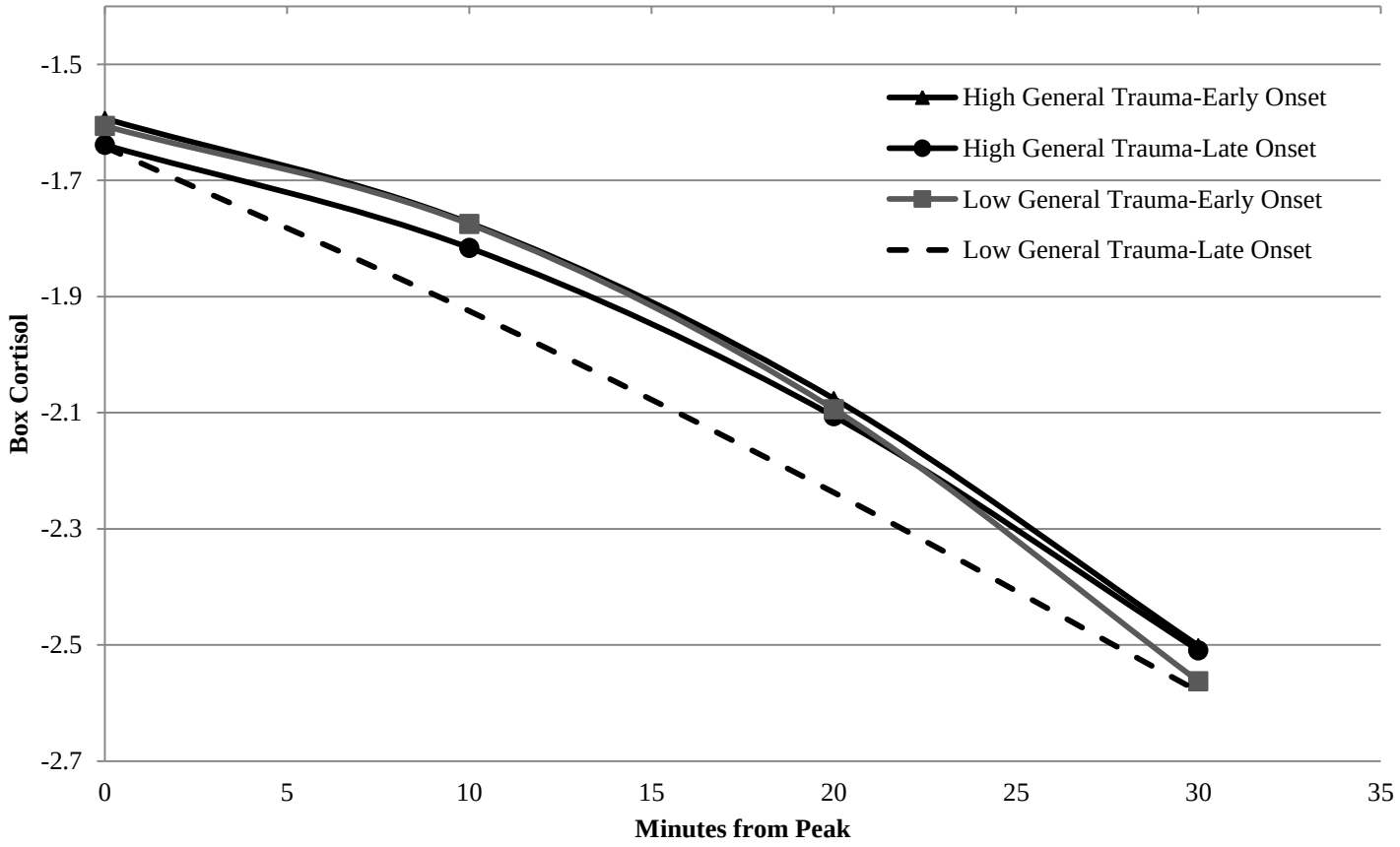


Figure 3.8. Diurnal cortisol regulation by general trauma exposure and current depression.

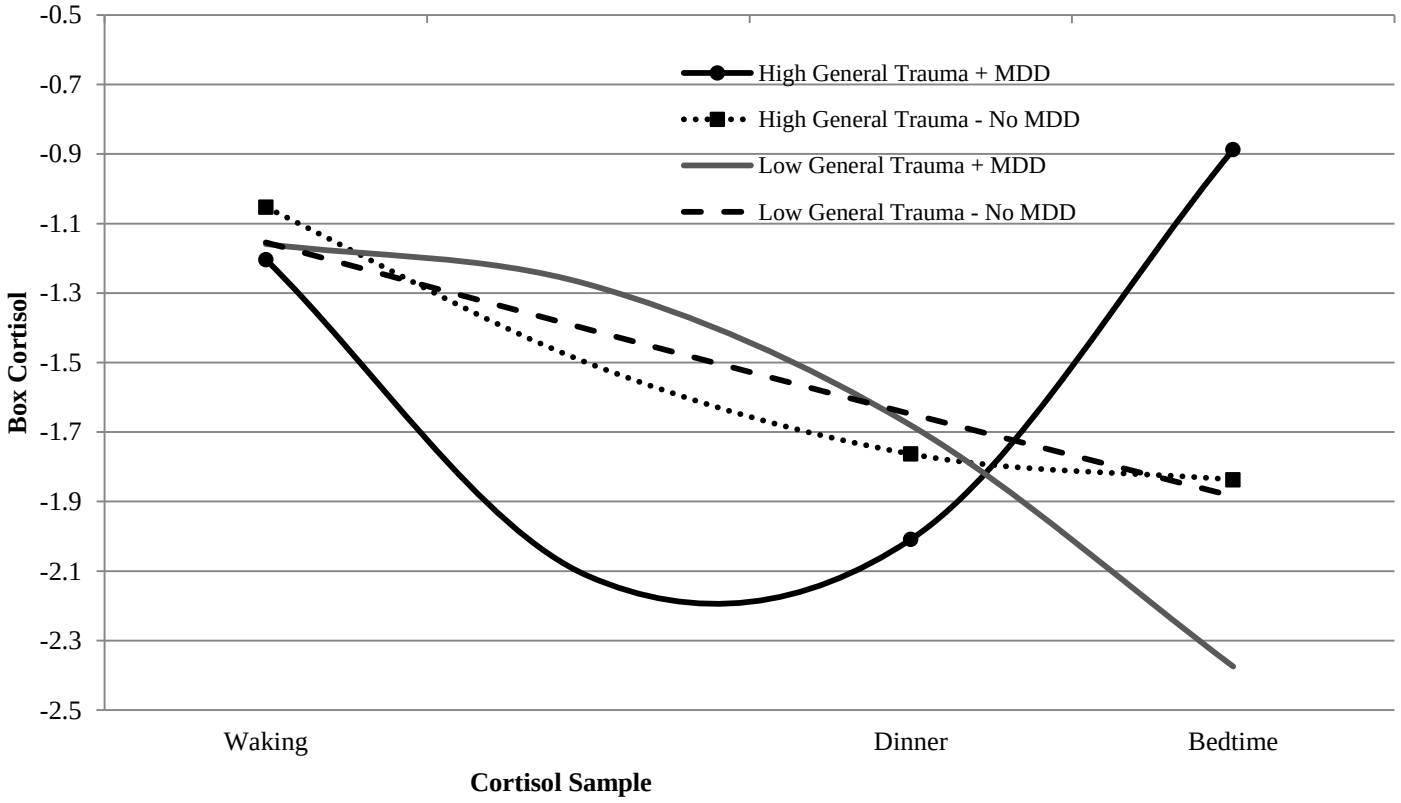


Figure 3.9. HPA-axis reactivity from baseline to acute stress by general trauma exposure and depression.

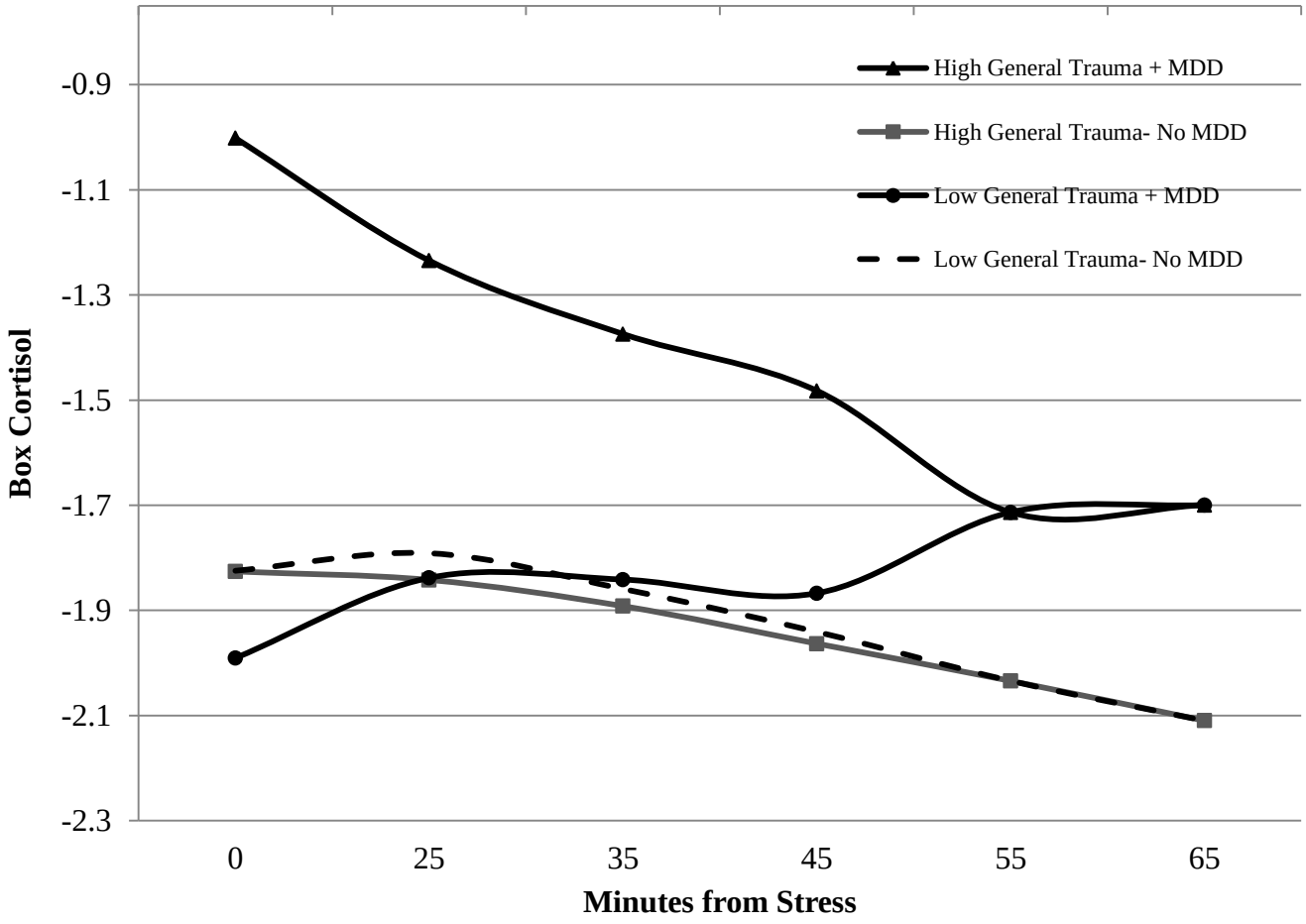
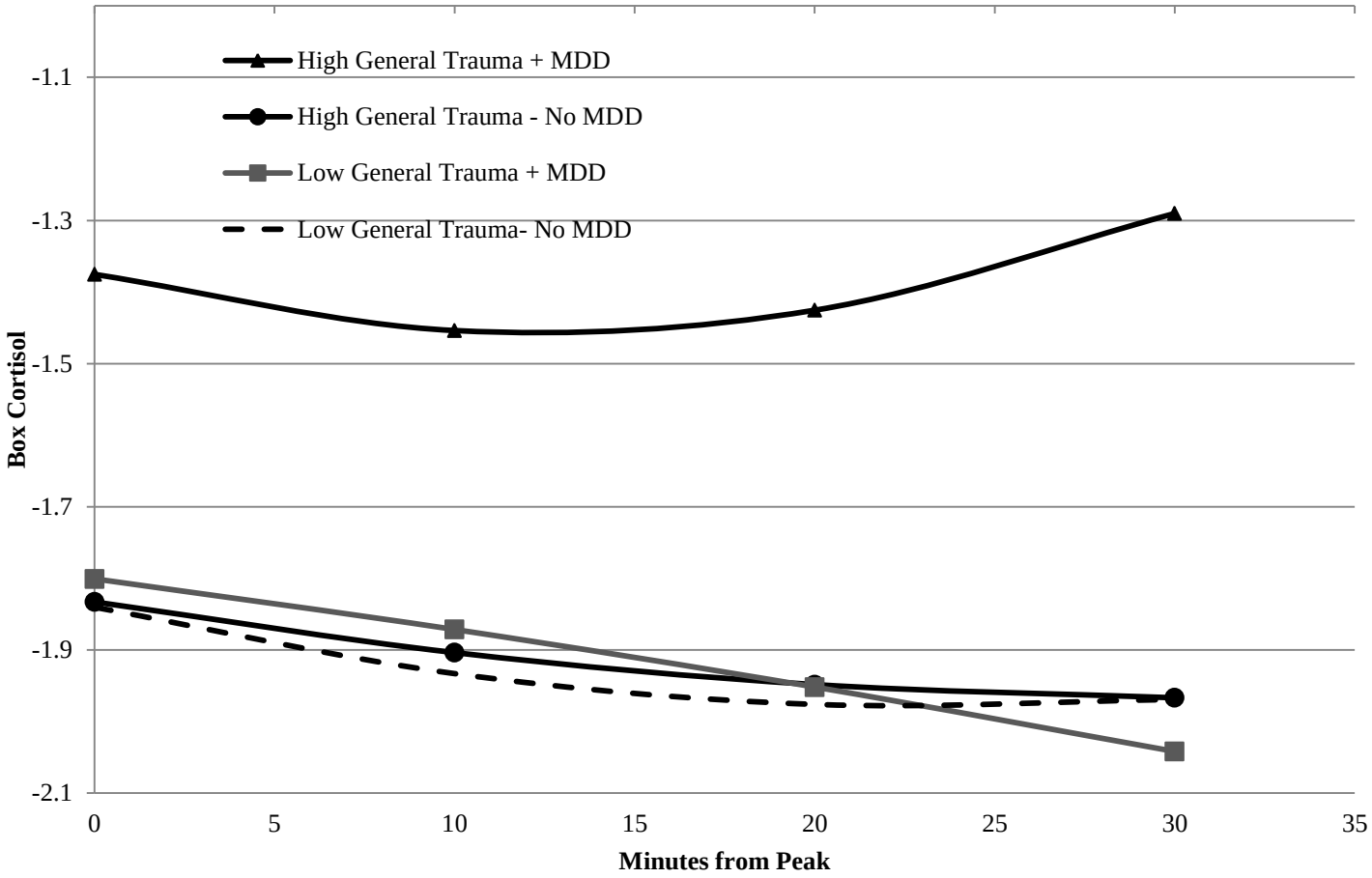


Figure 3.10. Acute stress regulation from peak by general trauma exposure and depression.



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