PREDICTING POSTTRAUMATIC STRESS DISORDER SYMPTOMS DURING ADOLESCENCE: A LONGITUDINAL STUDY OF THE ROLE OF HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS DYSFUNCTION

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Posttraumatic stress disorder (PTSD) is a trauma-related disorder that may develop in response to traumatic or stressful events. Dysfunction of the Hypothalamic-Pituitary-Adrenal (HPA) axis has been implicated in the disorder. Studies support such dysfunction as being a consequence of PTSD, rather than a precursor. However, most studies of the HPA are either cross-sectional or have been carried out in adults. The aim of the present study was to identify whether HPA dysregulation interacts with stressful experiences to increase the likelihood of developing PTSD symptoms in a community-recruited sample of healthy adolescent girls. Adolescent girls (N = 550) and one of their parents participated. Adolescents' clinical symptoms were assessed at baseline and at a nine month follow-up. Saliva samples were collected from all adolescent participants at waking, 30 minutes after waking, and 8 pm on 3 consecutive days. Flattened diurnal slope of cortisol at baseline was associated with increased PTSD symptoms nine months later. Baseline cortisol awakening response (CAR) per se was not prospectively related to developing PTSD symptoms, but its interactions with stressful experience was associated with elevated PTSD symptoms at follow-up. Effects were small and need to be replicated in samples with more severe stressors, as well as more clinical levels of PTSD. Nevertheless, findings suggest that dysregulated basal HPA functioning may be involved in the development of PTSD symptoms.

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CHAPTER 1

INTRODUCTION

Trauma and PTSD in Adolescence

A traumatic event is characterized as one experienced first-hand or witnessed and involves actual or threatened death, serious injury, or violence to oneself or others (American Psychiatric Association, 2013). Although estimates vary widely, a significant number of children and adolescents are exposed to traumatic life events. In the 2008 report by the Presidential Task Force on Posttraumatic Stress Disorder and Trauma in Children and Adolescents, 39% to 85% of children witnessed community violence, and 25% to 43% of the youth were exposed to sexual abuse (APA, 2008). In a longitudinal population based study in North Carolina, 1,420 children and adolescents were interviewed about extreme stressors, traumatic events and background vulnerability factors through adolescence (Costello, Erkanli, Fairbank, & Angold, 2002); of the 25% who reported extreme stressors in their lives, the majority (72%) reported at least one significant traumatic event over the period of adolescence (Costello et al., 2002). In the continuation of the North Carolina study, more than two thirds of 1420 children and adolescents had experienced a potentially traumatic event by the age of 16. Of those, more than 20% had some evidence of having been traumatized, suffering school problems, emotional difficulties or physical problems (e.g., heart disease) (Copeland, Keeler, Angold, & Costello, 2007).

The occurrence of a traumatic event is necessary but not sufficient for the diagnosis of Post-Traumatic Stress Disorder (PTSD; APA, 2013). The diagnosis of PTSD was first introduced into the third edition of the Diagnostic and Statistical Manual of

Mental Disorder (*DSM-III*; American Psychiatric Association, 1980). The most recent criteria for PTSD, in the *DSM-5* (APA, 2013), include a history of exposure to traumatic event(s) that meets specific criteria and symptoms from each of four symptom clusters: intrusion, avoidance, negative alterations in cognitions and mood, as well as alterations in arousal and reactivity. Moreover, symptoms must persist for more than a month and cause clinically significant impairment or distress (APA, 2013).

In the US, the lifetime prevalence of PTSD in adults is 6.8% (Kessler et al., 2005); the twelve-month prevalence of PTSD in adult population is about 3.5% (DSM-5; APA, 2013). Several population-based epidemiological studies have examined the prevalence of PTSD in children, particularly in high-risk children who experienced specific traumatic events (Fitzpatrick & Boldizar, 1993; Hoven et al., 2005; Qouta, Punamäki, & Sarraj, 2003). For example, Qouta and colleagues (2003) investigated the prevalence of PTSD among children who have been exposed to military violence (e.g., shooting, fighting or explosion) in Palestine; the results showed that 87.5% of the children suffered from moderate to severe levels of PTSD (Qouta et al., 2003). Hoven and colleagues (2005) examined the prevalence of PTSD in school children six months after 9/11. The study conducted in 8236 students in from grades 4 through 12 in New York public schools, and it reported that 10.6% of the children had PTSD symptoms (Hoven et al., 2005).

The prevalence has also been studied in adolescent samples. Kilpatrick and colleagues (2003) assessed the prevalence of PTSD among adolescents based on data from the National Survey of Adolescents, which contained a national household probability sample of 4,023 telephone-interviewed adolescents with ages from 12 to17

years. The findings indicated that the six-month PTSD prevalence was 3.7% for boys and 6.3% for girls (Kilpatrick et al., 2003). Similar results were reported in the National Comorbidity Survey - Adolescents Supplement (NCS-A) (Merikangas et al., 2010). The NCS-A was conducted to estimate the lifetime prevalence of *DSM-IV* (APA, 2000) disorders in 10,123 adolescents aged 13-18 in the US. The lifetime prevalence rates of PTSD were 8.0% for females and 2.3% for males (Merikangas et al., 2010). Moreover, the prevalence of PTSD showed consistent increases with age, with nearly twofold increase from 13- to 14- year age group to 17- to 18-year age group (3.7% and 7.0%, respectively) (Merikangas et al., 2010).

As reviewed above, traumatic events are much more common than PTSD itself, supporting the diagnostic specification that trauma by itself is necessary but not sufficient for youth to develop PTSD. Rather, certain individuals may be at increased risk of developing the disorder in the face of trauma. The following sections review biological models of the stress response in general, and then focuses on detailed dysfunctional mechanisms related to the stress response system that may explain why some individuals develop PTSD while others do not.

Biological Model of Stress Response

General Stress Response

Traumatic events and an individual's reactions to those events have the potential to initiate an individual's biological stress response systems. The latter refers to the initial and long-term response of the body to a physical or psychological stressor that endangers homeostasis (De Kloet et al, 2006). The term "homeostasis" was first used by Canon

(1935) to describe the coordinated physiological process that maintains the steady states in an organism. Appropriate activation of physiological stress responses is necessary and crucial for individuals to survive in an emergency or intense environment. Inappropriate, repeated exaggerated or prolonged responsiveness of the stress system, however, may impair growth and development, and therefore may account for a number of endocrine, metabolic, autoimmune, and psychiatric disorders (Charmandari, Tsigos, & Chrousos, 2005).

In order to cope with psychological and physiological stressors, a cascade of hormones is initially released that assist an organism in reacting to internal and external demands imposed by stressors (McEwen, 2007). Typically, two key systems are involved in an initial stress response: the Sympathetic Nervous System (SNS) and the Hypothalamic-Pituitary-Adrenal (HPA) axis.

The Sympathetic Nervous System (SNS)

The SNS is a part of the Autonomic Nervous System (ANS), which is a system of sensory and motor nerves, providing autonomous regulation to organs without the need for voluntary intervention (Lovallo, 2005). The role of the SNS is to mobilize and restore the body's resources under stress (Lipov & Kelzenberg, 2012). The SNS influences individuals' physiological changes, such as heart rate and blood pressure, in the presence of threatening or stressful stimuli (Cacioppo & Berntson, 2011; Kamarck & Lovallo, 2003).

The SNS is the primary response system to stressful stimuli. It is always active and becomes more active during times of stress (Lovallo, 2005). It potentially plays a significant role in the body's adjustment to the demands imposed by stress stimuli

(Lovallo, 2005; 2007). Adjustments in the SNS system activity accompany every human action and reaction. Particularly, it is the main means for acute regulation of cardiovascular function (Goldstein, 2000).

The SNS is essential for the integration and expression of the so–called "Fight or Flight" response towards stressors. The "Fight or Flight" response is an integrated set of cardiovascular and endocrine changes designed to allow an organism to survive in a threatening environment (Lovallo, 2005). Once the SNS is activated, it forces blood flow to muscles, increases blood pressure, increases heart rate, and induces pupil dilation, allowing individuals to quickly respond to stressful stimuli. For example, the sympathetic activation of the cardiovascular system leads to an adaptive responding by adjusting the circulation of blood to walking or running (Pace & Heim, 2011). However, the duration of the initial SNS activation is short, lasting only a couple of minutes.

The Hypothalamic-Pituitary-Adrenal (HPA) axis

The SNS system represents an immediate reaction to stressors. Beside the SNS response towards stress, a series of neuroendocrine changes occur in the HPA-axis in response to stress. The HPA-axis is a neuroendocrine system and one of the most fundamental physiological systems involved in responding to and coping with internal and external challenges. The system typically contributes to a constellation of physiological, emotional and behavioral responses that serve to adapt the organism to change in demand and thereby maintains stability and health (McEwen, 2004). In addition to the initial stress response, the HPA axis can also be programmed for future coping.

The hypothalamus, pituitary and adrenal cortex are the three major structures in the HPA-axis. The hypothalamus provides inputs to the brain, modifying the autonomic regulation and controlling endocrine function (Lovallo, 2005). In addition to its own endocrine functions, it also connects to and communicates with higher brain centers, such as the frontal cortex; accordingly, the hypothalamus assists in decision-making and planning (Lovallo, 2005). The pituitary is a gland connected to the base of the brain by the pituitary stalk (Rhodes, 2000). During times of stress, the pituitary secretes several hormones into the bloodstream that stimulate the adrenal cortex and other tissues of the body (Rhodes, 2000). The adrenal cortex is located along with the adrenal gland, close to the frontal part of the kidney (Rhodes, 2000). The adrenal cortex mediates the stress response through the production of several steroid hormones (e.g., glucocorticoids); (Rhodes, 2000)

HPA Axis in The Stress Response

The stress-induced hormone response is principally regulated by the HPA-axis (see Figure 1); (Ehlert, Gaab, & Heinrichs, 2001; Flinn, Nepomnaschy, Muehlenbein, & Ponzi, 2011; Tsigos & Chrousos, 2002). There are two basic functions of the HPA axis in the stress response. First, the HPA axis is involved in the process of mobilizing energy resources within the body, which helps achieve the proper stress response (Klimes-Dougan, Hastings, Granger, Usher, & Zahn-Waxler, 2001). Second, the HPA axis serves a homeostasis function to regulate other stress response systems, therefore mitigating the stress response (Klimes-Dougan et al., 2001).

More specifically, when individuals encounter a stressor, the hypothalamus, pituitary and adrenal cortex will be activated systematically to serve functions of the

HPA axis. The primary hypothalamic nucleus that regulates endocrine function during stress is the paraventricular nucleus of the hypothalamus (PVN; Whitnall, 1993). The PVN is located within the hypothalamus and contains several large, complex subnuclei (Swanson & Kuypers, 1980), which help modify autonomic regulation during the stress response. When human or animals encounter a stressor, the PVN is activated; meanwhile, the activation of the PVN triggers two stress-related hormones released by the hypothalamus: the corticotrophin-releasing factor (CRF) and arginine vasopressin (AVP). CRF and AVP together play a well-documented role in regulating body response in both resting (or *basal*) levels, and stress conditions (Rivier & Vale, 1983; Sztainberg & Chen, 2012). In stress conditions, the CRF has been identified as a key neuropeptide responsible for initiating the endocrine and autonomic response towards stress (Shekhar, Truitt, Rainnie, & Sajdyk, 2005). The administration of CRF integrates both autonomic and behavioral responses, such as increased anxiety, decreased sexual behaviors and food consumption (Dunn & Berridge, 1990; Lowry & Moore, 2006; Steckler & Holsboer, 1999).

The secretion of CRF and AVP causes the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary (Rivier & Plotsky 1986). ACTH is a peptide hormone produced by the cells in anterior pituitary and is carried by the peripheral circulation of its effects to organs (Rhodes, 2000). ACTH then acts on the adrenal cortex to initiate the release of glucocorticoids (GCs) (e.g., cortisol in primates and corticosterone in rodent species) (Herman et al., 2003; Romeo, 2010; Sapolsky, Krey, & McEwen, 1984; Vinson, Whitehouse, & Hinson, 2000). During periods of stress, the activation of ACTH and

glucocorticoids vary according to the intensity of stress, as well as to individuals' ability to cope with the stress (Romeo, 2010).

Glucocorticoids, the body's primary stress response, are hormones produced by the adrenal cortex that increase glucose production in the body and promote lipid breakdown in fat tissue (Rhodes, 2000). Over the course of stress, GCs establish two major functions. First, as the primary stress reaction, GCs act on all the cells in the body to maximize individuals' abilities to protect organs from stress (Handwerger, 2009; Munck, 2000). Second, in addition to assisting the body's defense mechanism to stress, the release of glucocorticoids also has wide-ranging effects on the body's metabolism, including increasing muscular efficiency, energy resources, cellular metabolism and brain functions (Cacioppo & Berntson, 2011). In humans, cortisol is the primary type of glucocorticoids.

Cortisol is one of the major hormones synthesized and secreted from the human adrenal cortex in response to stress (Meijer, Kloet, & McEwen, 2000), and it can be activated in both stressful and non-stressful situations (Lovallo, 2005). The presence of cortisol is necessary for regular autonomic function, as well as for all forms of physiological regulation. The absence of cortisol in stress response can lead to damaging effects in an individual's body, such as threatening individual's homeostasis (Munck, Guyre, & Holbrook, 1984) and immune system. During a period of stress, the psychological perception of stress and associated negative affect can release cortisol into circulation. Therefore, it may facilitate regulatory and management functions in bodily systems in stressful circumstances (Kellner, Yehuda, Arlt, & Wiedemann, 2002; Munck et al., 1984; Munck, 2000).

Similar to other neuroendocrine axes, the output of the HPA-axis is controlled by a negative feedback loop (Romeo, 2010), exemplified by the glucocorticoids feedback on the PVN and elevated glucocorticoids suppression, AVP and ACTH release (Herman & Cullinan, 1997). Cortisol levels are generally detected by the negative feedback mechanism, in which glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs) in the hippocampal region of the brain inhibit further HPA activity (De Kloet & Reul, 1987; De Kloet, Vreugdenhil, Oitzl, & Joels, 1998). These two receptors are important targets of cortisol activity (McEwen, DeKloet, & Rostene, 1986; De Kloet, 2013); however, their functions in relation to cortisol are slightly different. The MRs are sensitive to low levels of cortisol and generally respond to normal and daily glucose demands. The GRs are sensitive to high levels of cortisol, indicating that they can only detect cortisol when it reaches high levels (Lovallo, 2005), and they are expressed in many important tissues and organs (Meijer et al., 2000), such as the liver and lungs. Overall, both MRs and GRs are found in high concentrations all over the neural-pituitary network that controls the negative feedback on the HPA-axis (De Kloet, Joëls , & Holsboer, 2005). When cortisol levels go up in a stressful environment, the effects in the brain will be mediated by the receptors (De Kloet et al., 1998). When individuals are no longer in a stressful environment or the amygdala no longer detects a threat, negative feedback inhibition of the HPA axis is activated by the hippocampus, reducing individuals' hormone levels back to the basal rate (Lovallo, 2005).

HPA Axis Functioning in Adolescents

Adolescence is defined as the gradual transformation from childhood to adulthood (Spear, 2003), and it is a significant transition period that is qualitatively different from

both childhood and adulthood. However, since there is no preset onset or termination of adolescence, the boundaries of the period are hard to determine (Spear, 2003). In humans, an age range from 12 to 18 years is commonly considered adolescence.

The developmental stage involves numerous biological changes, including increased volumes of cortical grey matter (Giedd et al., 1999) and decreased white matter (Pfefferbaum et al., 1994) in the brain. Changes in social behaviors, emotion regulation and cognitive skills also occur during this phase of development (Steinberg, 2007; Tottenham, Hare, & Casey, 2011). This transition period also is associated with moderate emotional upheaval and increases in negative life events (Caspi & Moffitt, 1991; Graber & Brooks-Gunn, 1996). Furthermore, developmental demands, including being independent from parents, establishing interaction with peers, forming social interactions with others and developing identities, are challenges faced during adolescence. All of these changes and transitions may result in a sensitive response towards stressors and play a role in increasing risk for developing PTSD (Deykin & Buka, 1997; Paus, Keshavan, & Giedd, 2008; Yule et al., 2000).

Hormone changes are another significant modification during the adolescence. Specifically, the HPA axis functioning is distinct in adolescence from adulthood in its responses to stress and regulation by hormones (Van den Bergh, Van Calster, Smits, Van Huffel, & Lagae, 2008). During adolescence, the HPA axis is characterized by a prolonged activation towards acute stress compared to adulthood (McCormick & Mathews, 2007; 2010; McCormick, Mathews, Thomas, & Waters, 2010; Paus et al., 2008) and stress-related hormone release decreases with progression through adolescence

(DiLuigi et al., 2006; Goel & Bale, 2007; Romeo et al., 2006; Romeo, Karatsoreos, Jasnow, & McEwen, 2007; Romeo, Lee, Chhua, McPherson, & McEwen, 2004).

Animal studies have demonstrated that stress experience and pubertal development interact to modulate the HPA axis reactivity (Romero et al., 2006). There is also emerging evidence indicating increased release of stress-related hormone, cortisol, during the adolescence (Spear, 2003). Furthermore, chronic exposure to stress during the adolescence changes hormone secretion dramatically (Romero et al., 2006), which may further influence stress responses in late adolescence or early adulthood.

Over the years, the links between stress exposure in adolescence and psychological dysfunctions have been demonstrated. In humans, the enduring effects of stress exposure in adolescence alter the physiological responses and contribute to psychological disorders in young adulthood (McCormick & Mathews, 2007). Evidence also was indicated that increased stress burdens over adolescence are associated with greater incidence of anxiety or depressive disorders in later adolescence or early adulthood (Goodyer, 2002; Turner & Lloyd, 2004).

Measuring HPA Axis Functioning via Cortisol

Given that glucocorticoids (e.g., cortisol in primates) are the end product of the HPA cascade released in response to stress, their assessment has become a common approach to measuring HPA axis functioning (Handwerger, 2009). Generally, cortisol exhibits a diurnal pattern (Bair-Merritt, Johnson, Okelo, & Page, 2012), reaching a peak in 20-45 minutes after waking, steeply declining in the few hours afterwards, then fluctuating over the day corresponding to daily activities, and eventually decreasing to its lowest at night before sleep (Figure 2). In the majority of individuals who follow a day-

night schedule, cortisol production peaks 20-45 minutes after awakening (Chida, & Steptoe, 2009). However, in 20% of individuals, cortisol concentration reach their peak during the last few hours during sleep (Klimes-Dougan et al., 2001; Kudielka & Kirschbaum, 2003). The purpose of the peak cortisol concentration is to prepare the body for action and stimulate the appetite upon awakening (Klimes-Dougan et al., 2001). Furthermore, gender differences in the diurnal pattern of cortisol have also been documented in adolescents and children (Klimes-Dougan et al., 2001). In adolescents, females display higher midday and late afternoon cortisol levels than males (Klimes-Dougan et al., 2001).

Cortisol levels under basal conditions reflect an adrenal function, and can be assessed in urine, saliva or plasma (Klaassens, Giltay, Cuijpers, van Veen, & Zitman, 2012).[1] Saliva and plasma cortisol are commonly used to assess cortisol levels reflecting the past 1-hour (Kirschbaum & Hellhammer, 1989; Linkowski et al., 1994). However, plasma cortisol, especially single blood draw collection, cannot provide reliable estimates (Yehuda, 1997). Any stressors or stress-related cues in the environment before blood withdrawal may potentially increase the cortisol levels in blood (Yehuda, 1997). Therefore, the plasma cortisol may not be able to represent individuals' basal cortisol levels. Unlike plasma cortisol, salivary cortisol is typically measured as free cortisol, indicating that the cortisol levels in saliva are not affected by saliva flow rate, proteins and protein-bound molecules (Kirschbaum & Hellhammer, 1994). Additionally, saliva

[1] Urinary cortisol reflects individuals' activity over a 15-24 hour period (Baum & Grunberg, 1995), and it is often used in longitudinal studies to evaluate interpersonal differences in HPA axis function over three major periods: peri-trauma physiological activity, the HPA reactions in the time of traumatic events (Delahanty, Raimonde, & Spoonster, 2000), and posttraumatic neuroendocrine responses. Urine samples are often collected over a 24-hour period to assess levels of urinary free cortisol (UFC). However, if the collection periods are shorter than 24-hour (e.g., 10–15 hours), the comparability of studies is limited due to the cortisol diurnal pattern and corresponding variation (Handwerger, 2009).

collection is noninvasive and expedient (Hibel, Granger, Cicchetti, & Rogosch, 2007), which can be accomplished in a natural environment with minimal interruption of the daily flow of activities and routines.

Cortisol Awakening Response (CAR)

Based on the observation that cortisol levels reach their peak upon awakening (Späth-Schwalbe, Schöller, Kern, Fehm, & Born, 1992; Späth-Schwalbe et al., 1993; Weibel, Follenius, Spiegel, Ehrhart, & Brandenberger, 1995), the *Cortisol Awakening Response* (CAR; Pruessner et al., 1997) was first termed in the late 1990's. CAR indicated that within the first 30-45 minutes after awakening, free cortisol levels showed approximately 50-75% increase. During the past two decades, the CAR has been found to be a reliable biological marker and index for individuals' adrenocortical activity (Schmidt-Reinwald et al., 1999). Additionally, it has been used in various populations, both healthy and clinical samples (Chida & Steptoe, 2009; Clow, Thorn, Evans, & Hucklebridge, 2004; Roberts, Wessely, Chalder, Papadopoulos, & Cleare, 2004). Typically, two parameters have been assessed: the overall volume of cortisol released over the waking period, and the change of cortisol from the level recorded following waking (CAR) (Chida & Steptoe, 2009).

The CAR can be influenced by a number of factors, such as waking up in darkness versus light (Fries, Dettenborn, & Kirschbaum, 2009) or the events that happened the day before. Nevertheless, it has gained attention in developmental science as a consistent, recurring and powerful indicator of HPA axis activity (Wilhelm, Born, Kudielka, Schlotz, & Wüst, 2007). Rather than self-report questionnaires and clinic interviews, CAR can provide relatively objective information about biological

mechanisms related to the stress response. In most studies of CAR (Bicanic et al., 2013; Inslicht et al, 2011; Keeshin, Strawn, Out, Granger, & Putnam, 2013), saliva samples for the repeated assessment of cortisol after awakening were collected in individuals' natural environment (e.g., home). This approach has provided a number of advantages (Shirtcliff, Granger, Schwartz, & Curran, 2001), such as controlling for laboratory setting and disturbance of natural routine.

Studies have demonstrated that CAR has high intra-individual reliability (Hucklebridge, Hussain, Evans, & Clow, 2005). The cortisol rise pattern after awakening has been observed in most healthy adults (Wüst et al., 2000), children and adolescents, and older individuals (Pruessner et al., 1997). Furthermore, CAR has found to be independent of the effects of awakening time, sleep duration and quality, physical activity and alcohol consumption (Hibel, Mercado, & Trumbell, 2012; Pruessner et al., 1997; Pruessner, Hellhammer, &Kirschbaum, 1999; Schmidt-Reinwald et al., 1999; Wüst, Federenko, Hellhammer, & Kirschbaum, 2000).

HPA Axis Functioning in PTSD

HPA Axis Dysregulation in PTSD

Dysregulation of the HPA axis has been proposed to be an important biological mechanism underlying stress-related psychological disease in adults (Mehta & Binder, 2012). Traditional research on the role of the HPA-axis in stress indicated that chronic stress disorders (e.g., PTSD) were thought to be characterized by elevated cortisol levels compared to normal (Pitman, 1997). However, the neuroendocrine changes in PTSD involving the HPA axis are distinct from the stress responses based on early observations

that compared individuals with PTSD to either other mental health disorders or healthy individuals (Duval et al., 2004; Kellner & Yehuda, 1999; Meewisse, Reitsma, De Vries, Gersons, & Olff, 2007; Morris et al., 2012; Yehuda, 2001; 2006; Yehuda & LeDoux, 2007).

In PTSD, the HPA-axis is characterized by reduced cortisol levels and increased sensitivity of the negative feedback loop, which suggest alterations in the number and sensitivity of glucocorticoid receptors (Pitman, 1997; Yehuda, 2002a; Yehuda & Seckl, 2011). Typically, dysregulation is reflected with diminished baseline cortisol levels (Bicanic et al., 2013; Boscarino, 1996; 2004; Delahanty, Raimonde, & Spoonster, 2000; Keeshin et al., 2014; Mason, Giller, Kosten, Ostroff, & Podd, 1986; Rohleder, Joksimovic, Wolf, & Kirschbaum, 2004; Wessa, Rohleder, Kirschbaum, & Flor, 2006; Yehuda et al., 1990; Yehuda et al., 1995; Yehuda, Teicher, Trestman, Levengood, & Siever, 1996), the exaggerated suppression of cortisol in response to dexamethasone (de Kloet et al., 2007; Duval et al., 2004; Goenjian et al., 1996; Grossman et al., 2003; Kosen, Wahby, & Giller, & Mason, 1990) and the increased number and sensitivity of GRs (Rohleder et al., 2004; Stein, Yehuda, Koverola, & Hanna, 1997).

Evidence of Abnormal Cortisol Responses in PTSD during Adulthood

Cortisol Responses in PTSD and MDD

With a high comorbidity and overlapping symptoms between PTSD and Major Depressive Disorder (MDD; Davidson, Swartz, Storck, Krishnan, & Hammett, 1985; Kellner & Yehuda, 1999), initial hypotheses suggested that the two disorders would likely share a similar neuroendocrine profile (Yehuda, 2001). However, the evidence indicated divergent HPA-axis patterns between two conditions (Figure 3).

In most neuroendocrinology studies, MDD has been consistently associated with *elevated* HPA-axis activity, characterized by increased resting cortisol levels (Oquendo et al., 2003; Pruessner, Hellhammer, Pruessner, & Lupien, 2003), reduced cortisol suppression in response to dexamethasone (Nelson & Davis, 1997) and insensitivity to glucocorticoid feedback activity (Pariante & Miller, 2001). In contrast to MDD, PTSD has been associated with *diminished* HPA activity (Ehlert et al., 2001). Overall, PTSD appeared to be the reverse of the corresponding dysregulation described in MDD and other stress responses (Mason et al., 1986; Pitman, 1997; Yehuda, 2002a). The distinctive HPA activity observed in PTSD has been termed as the *HPA paradox* (Mason et al., 1986; Yehuda, 2002a).

Compared to MDD, the paradoxically diminished cortisol levels in PTSD have been observed in a variety of samples and the finding has been replicated over the years (Kosen et al., 1990; Mason et al., 1986; Yehuda, Halligan, Golier, Grossman, & Bierer, 2004). However, studies comparing PTSD to PTSD with comorbid MDD reported inconsistent findings. Studies have reported no difference between the two groups (Pinna, Johnson, & Delahanty, 2014; Savic, Knezevic, Damjanovic, Spiric, & Matic, 2012; Yehuda et al., 1990) or lower afternoon and evening cortisol levels in the PTSD-only group (Morris, Compas, & Garber, 2012)

Cortisol Response in PTSD and non-MDD Mental Disorders

The most comprehensive studies investigating the relationship of cortisol and PTSD have been conducted in adult populations. Single-point estimation (Boscarino, 1996; Goenjian et al., 1996; Yehuda et al., 1996), circadian release of cortisol (e.g., 24-hour cortisol) and repeated measurements (Yehuda et al., 2009) have been utilized in

investigating 24-hour diurnal cycle of cortisol. Most of the psychophysiological studies in PTSD were performed cross-sectional, comparing PTSD to non-PTSD individuals (e.g., healthy controls or other mental disorders) (Pitman et al., 2012). The first published research in PTSD and cortisol evaluated 24-hour urinary free-cortisol levels in male hospitalized patients (Mason et al., 1986). The study reported that cortisol levels were significantly lower in PTSD hospitalized patients than those with other mental health disorders (e.g., MDD, bipolar disorder and schizophrenia) (Mason et al., 1986). The finding was unexpected at the time, especially in the light of a large number of findings in enhanced cortisol levels with chronic stress and depression.

Since then, the association between PTSD and diminished cortisol levels has been studied thoroughly in adults; however, the evidence is not uniform. Over the past decades, the majority of literature supports the view that PTSD is associated with *reduced* cortisol levels. Yehuda and colleagues (1990) replicated the previous findings in a study comparing PTSD patients to healthy individuals by assessing 24-hour urinary cortisol levels. The results further indicated that 24-hour urinary cortisol execration was significantly lower in the PTSD group than the control group (non-PTSD, healthy people) (Yehuda et al., 1990). The finding was supported in another study compared cortisol levels in PTSD to that in psychiatric diagnosed patients (Yehuda, Boisoneau, Mason, & Giller, 1993).

Other than 24-hour free urinary cortisol levels, plasma and saliva cortisol have also been used to assess HPA-axis. Boscarino (1996) compared plasma cortisol levels in PTSD to non-PTSD using a sample of 2000 Vietnam veterans. The study indicated that plasma cortisol levels were significantly lower in individuals with PTSD than those

without PTSD (Boscarino, 1996). Additionally, by evaluating the magnitude of cortisol, the study reported only 4% difference was observed in the morning cortisol levels (Boscarino, 1996). Furthermore, the lower morning plasma cortisol levels were observed in diagnosed PTSD patients (Gill, Vythilingam, & Page, 2008; Horn, Pietrzak, Corsi-travali, & Neumeister, 2014; Stoppelbein, Greening, & Fite, 2012; Vythilingam et al., 2010), partners of prostate cancer patients (Thomas et al., 2012) and women with breast cancer suffering PTSD (Luecken, Dausch, Gulla, Hong, & Compas, 2004). In addition to the results from plasma cortisol discussed above, results from saliva cortisol have also supported the finding of decreased cortisol levels in PTSD (Gill, Vythilingam, & Page, 2008; Glover & Poland, 2002; Neylan et al., 2005; Rohlerder et al., 2004; Wessa et al., 2006; Yehuda, Golier, & Kaufman, 2005).

However, other studies have not found this pattern. For example, two studies (Bonne et al., 2003; Shalev et al., 2008) reported no difference in cortisol levels comparing individuals with and without PTSD. Whereas, other studies have reported *higher*, not lower, cortisol levels in PTSD. An earlier study of Vietnam veterans reported that veterans with chronic PTSD had higher 24-hour urinary cortisol levels compared to veterans without PTSD (Pitman & Orr, 1990). Later, the same results were replicated in samples of sexually abused women suffered PTSD (Lemieux & Coe, 1995) and trauma survivors developed PTSD (Maes et al., 1998). As with studies in urinary cortisol, research on plasma and salivary cortisol supported the elevated cortisol levels in PTSD. By assessing plasma cortisol in veterans with PTSD, veteran without PTSD, and nonveteran controls, Liberazon and colleagues (1999) observed elevated cortisol levels in PTSD patients but not in the other two groups (Liberzon, Abelson, Flagel, Raz, & Young,

1999). Furthermore, studies (Lindley, Carlson, & Benoit, 2004; Young & Breslau, 2004) in salivary cortisol also reported supportive evidence.

In summary, most studies of PTSD have demonstrated that PTSD is associated with distinct endocrine modifications; primarily involving a highly sensitized HPA axis characterized by decreased basal cortisol levels and increased negative feedback regulation (Yehuda, 2002b). However, several factors may contribute to the inconsistent findings in the literature. Individual differences, such as gender, body weight, and mood status, instead of PTSD itself, may have impacts on cortisol levels. Thus, they may further contribute to the cortisol differences observed in PTSD and non-PTSD group rather than the disorder itself. Furthermore, the individual difference brings more variability in cortisol levels; essentially, it may lead to inconsistent findings in cross-sectional group comparison (Yehuda, 2006). In addition to individual difference, studies have examined cortisol levels in diverse populations; trauma type may potentially lead to the mixed findings. Alternatively, low cortisol may be present in only specific subtypes of PTSD. Furthermore, methodology issues have often been ignored. Biological specimens requires specific room temperature and conditions to store, so even the slightest variation to these conditions can affect cortisol concentrations and may have contributed mixed findings.

Evidence of Abnormal Cortisol Responses in PTSD during Adolescence

Prior work looking at PTSD in adolescents focused on the neurobiological impact of traumatic events. Specifically, acute stress contributes to an increased activation of noradrenergic system that may in part be reflected in a number of behaviors related to PTSD (Compas, 1987; Schwarz & Perry, 1994; Spear, 2003). Initially, the cortisol

pattern of PTSD in children and adolescents was assumed to be similar to that of adults (Pynoos & Eth, 1985). However, several studies (De Bellis et al., 1994; Carrion et al., 2002; Lipschitz et al., 2005; Reynolds et al., 2013) of cortisol patterns comparing children with and without PTSD provided a different picture from the initial assumption and the results were not consistent in the literature.

Studies have reported no relationship between cortisol levels and the occurrence of PTSD in this age group. For example, a prospective longitudinal study found no difference in either plasma or 24-hour urinary free cortisol in 13 girls who experienced childhood sexual abuse compared to match healthy controls (De Bellis et al., 1994). As with the studies in plasma and urinary cortisol, studies in salivary cortisol also provided similar findings. For example, salivary cortisol levels were found to be no different in 28 adolescents who developed PTSD after traumatic events compared to those who did not (Lipschitz et al., 2005). The same results were supported in another study with a community sample of 501 school pupils (Young, Sweeting, & West, 2012).

However, other studies found *increased* cortisol levels in the presence of PTSD in children and adolescents. Carrion and colleagues (2002) compared the physiologic response in 51 children with a history of trauma exposure and PTSD symptoms to 31 matched healthy controls by evaluating diurnal salivary cortisol over the course of three days. Their findings were inconsistent with De Bellis et al. (1994)'s, indicating that children who were experiencing PTSD showed elevated diurnal cortisol secretion (Carrion et al., 2002). Furthermore, an investigation reported sex difference in cortisol levels, indicating that girls with PTSD symptoms had significantly increased cortisol levels compared to boys with PTSD symptoms (Carrion et al., 2002). Similar to the

previous study, Pervanidou (2008) reported elevated evening cortisol levels in 60 children in the aftermath of trauma.

In contrast to the studies mentioned above, other studies suggested *decreased* cortisol levels in children and adolescents with PTSD. Five years after the 1988 earthquake in Armenia, Goenjian and colleagues (1996) investigated basal cortisol levels and cortisol suppression following dexamethasone administration in 37 adolescents with PTSD (Goenjian et al., 1996). In this study, the saliva samples were obtained three times a day, in addition to before and after dexamethasone administration. The results suggested that diminished basal salivary cortisol levels and enhanced suppression by dexamethasone were associated with more PTSD symptoms (Goenjian et al., 1996). In a second study, lower morning saliva cortisol levels were observed in 10 girls aged from 5-7 years who had a history of sexual abuse when compared to a control group (King, Mandansky, King, Fletcher, & Brewer, 2001). Similar results were found in two studies using different samples: 52 female adolescent rape victims with PTSD showed reduced CAR (Bicanic et al., 2013) and a flattening morning CAR correspondence with PTSD severity was found in 24 adolescent girls with a history of sexual abuse (Keeshin et al., 2014).

In summary, altered cortisol concentrations have been associated with PTSD in youth, but findings are mixed and inconsistent. Diverse findings may be the results of several methodological differences across the studies. First, the cortisol pattern evaluated varied widely across the studies. Diurnal cortisol levels, CAR, morning cortisol levels and evening cortisol levels have all been used in studies of PTSD in adolescents. The less

consistency in cortisol methods used in research highlights the need for validation of cortisol measures appropriate for use with adolescents.

Second, different trauma types were evaluated in the studies. Studies of PTSD and cortisol among children and adolescents have focused on a number of trauma types, such as natural disaster (e.g., Goenjian et al., 1996), significant incidents (e.g., Bicanic et al., 2013), or a history of trauma exposure (e.g., Carrion et al., 2002). There has not been a trauma type that has served to unify the studies in PTSD in adolescents. Furthermore, in contrast to these types of events that do not occur frequently in adolescents, stressful life events are relatively common in youth and have profound impacts on psychopathology in adolescents (Tennant, 2002). Finally, the discrepancy in the literature may reflect differences in which developmental stage characterized the samples. All these factors may have contributed to the mixed findings.

In addition to the mixed findings in studies on cortisol and PTSD in children and adolescence, explaining discrepancies between the cortisol profiles of children versus adult PTSD was also unclear. There are two potential explanations. First, brain development and developmental-related hormone changes together modify stress regulation in adolescence. During the adolescence, individuals are still in the process of hormone maturation, and the hormone release levels within the body are different from adults (Romero et al., 2006). Therefore, the hormone reactions to stress may differ in adults and adolescents. Second, in addition to development, chronic and acute stress exposure can also alter the stress-related hormone regulation in the development period (Romero et al., 2006).

The HPA Axis Model in Developing PTSD

Since not all individuals who are exposed to trauma will develop PTSD, different models have been proposed to explain why some individuals develop PTSD after a trauma whereas others do not. Many of these have implicated potential biological differences, particularly in the HPA-axis, which exist before, during or after exposure to a trauma. Four hypotheses in particular speak to the questions of when and how HPA-dysregulation becomes associated with PTSD.

The first hypothesis suggests that the occurrence and development of PTSD is associated with a pre-existing, dysregulated HPA-axis and that diminished basal cortisol activity is already present before trauma exposure (Galatzer-Levy et al., 2014; Pitman, 1989; van Zuiden, Kavelaars, Geuze, Olff, & Heijnen, 2013). The second hypothesis proposes that PTSD occurs because of the dysregulation of the HPA axis at the time of trauma (Pitman et al., 2006; Yehuda, 2002b). A third hypothesis is that HPA dysregulation associated with PTSD occurs after the trauma and acute response, but during the period of recovery (Pitman et al., 2006). A final fourth hypothesis is that HPA dysregulation is a distal consequence of PTSD itself, not of the trauma (Pitman et al., 2006). Given the nature of the study, the first three hypotheses will be discussed fully in the following sessions.

Dysregulated Cortisol as A Pre-trauma Vulnerability for PTSD Development

The first hypothesis posits that PTSD is the result of an interaction between a pre-existing dysregulated HPA and exposure to a trauma. A pre-existing dysregualated HPA might be the consequence of two developmental events. First, exposure to life adversity in early childhood may shape the biological responses to stress in adulthood and lead to a

dyregulated HPA axis system (McGowan, 2013; Watamura, Donzella, Kertes, & Gunnar, 2004; Yehuda et al., 2010). Second, chronic stress exposure during adolescence may influence the development of the HPA axis (Romero et al., 2006; Romero, 2009). Experiencing chronic stress in adolescence damages the hippocampus development (McEwen, 2012; Pitman et al., 2012), and it also interferes with stress-related hormone development. As a consequence, chronic stress disrupts the HPA maturation and regulation, reducing the capability of HPA axis during stress response.

In this model, pre-existing HPA dysregulation then interacts with trauma to lead to PTSD. Reduced cortisol levels before trauma exposure result in inadequate cortisol signaling, which will essentially influence individuals' fear response and inhibition (Pitman et al., 2012). As a result, individuals will develop an increased sensitization to the environment (Pitman et al., 2012). When a traumatic event occurs, individuals are overwhelmed by a series of negative emotion, such as fear and horror. Generally, under these circumstances, cortisol is activated, breaking down fat and circulating energy within the body in response to the trauma-induced emotion arousal. Once the brain is no longer signaling threatening cues in the environment, the acquired fear response will extinguish (Pitman et al., 2012) and the cortisol levels will return back to basal levels. However, for individuals with pre-existing diminished cortisol levels, they are not able to properly contain the stress response and signal safety once threats no longer exist. Furthermore, individuals with this vulnerability may fail to inhibit negative emotional response and fear, as well as adapt to safety environment (Foa & Kozak, 1986; Pitman et al., 2012; Wingenfeld et al., 2012). Over time, the lasting impacts of acquired fear

response may lead to an increased sensitivity and exaggerated response towards trauma-related cues in the environment, contributing to the subsequent PTSD symptoms.

Dysregulated Cortisol as A During-trauma Factor for PTSD Development

An alternative model posits that HPA-dysregulation is not a pre-existing vulnerability, but rather emerges at the time of trauma exposure and that this predicts PTSD later (Shalev & Freedman, 2005; Shalev et al., 2000; Yehuda, 2002b). Cortisol plays a major role in responding to and coping with demands of physical and psychological stressors (Zohar et al., 2011). It also promotes recovery within the body through rapidly restoring homeostasis (Zohar et al., 2011). Alternations in cortisol release during trauma exposure, both too high and too low, prolong trauma-induced emotion arousal and distress (Yehuda, 2009), delay the recovery from the traumatic event (De Quervain, 2006) and influence the memory function in the hippocampus (Pitman et al., 2012).

The modified cortisol release during the trauma exposure not only reduces individuals' capacity to distinguish and inhibit trauma-related memory; it also leads to more strongly encoded and more subjectively distressing memories of the event (Yehuda & LeDoux, 2007). In particular, the cortisol alternations contribute to the formation of durable traumatic memory (Pitman et al., 2012), interfere in working memory (Pitman et al., 2012), impact on the processing and interpretation of trauma-related information (Zohar et al., 2011), eventually, the dysregulated cortisol levels lead to long-term memory disruptions (Zohar et al., 2011). The cortisol-induced exacerbation in the consolidation of the traumatic memory (Mouthaan et al., 2014) could mediate the

hyperarousal symptom and further lead to the elaboration of avoidance symptom that commonly occurs in the PTSD.

What might lead to altered acute HPA dysregulation at the time of the trauma exposure? A number of factors have been proposed. First, the HPA-axis function may change at the time of trauma exposure depending on specific genotype and previous trauma history (Mehta et al., 2011). The sensitization of HPA-axis is regulated by three major factors: glucocorticoids signaling, glucocorticoids receptors and GR sensitivity. All three factors are coded in a few certain genes, such as GR target genes FKBP5 (Mehta & Binder, 2012; Mehta et al., 2011). During the trauma exposure, the environmental challenges induced increases in cortisol circulating and releasing result to an increased introduction of FKBP5 messenger, leading to the alternations in HPA-axis (Mehta et al., 2011). Furthermore, in addition to the trauma exposure, the interaction between gene expression and previous trauma history is important in determining the HPA-axis regulation during the trauma exposure later (Binder et al., 2008; Mehta et al., 2011). The epigenetic changes may originally be induced by previous trauma experience, and in response to subsequent trauma, the changes progress over time (Zuiden et al., 2011). Prior trauma experience may desensitize the HPA-axis response to trauma, leading to insufficient glucocorticoids signaling (Yehuda et al., 2013) during the trauma exposure later.

A second factor may be the developmental stage of when the traumatic events occur. Adolescence is a critical transition period, and it appears to be an unusually stressful life stage. Trauma exposure during the period may alter HPA-axis regulation in adulthood (Di Luigi et al., 2006; Dorn & Chrousos, 1997). During adolescence, the HPA

axis is still being developed and this ongoing development may lead to several costs (Spear, 2003). One potential cost associated with the HPA axis development is that the HPA axis may not become functionally mature until it is sufficiently developed. As a consequence, adolescents may experience a decrease in their ability to adapt to environmental challenges and stressors. With the environmental and development demands, adolescents are required to maintain an increase activity of the HPA axis, especially adequate and appropriate cortisol release and circulation. Thus, when the traumatic events occur, adolescents are not able to facilitate proper cortisol activity to stress as the HPA axis functions are still emerging.

Dysregulated Cortisol as An After Trauma Factor for PTSD Development

The third model indicates that after trauma and during the recovery period, the dysregulation in the HPA-axis may influence the PTSD development later (Zoladz & Diamond, 2013). In particular, the dysregulated HPA axis is a result from the enhanced negative feedback inhibition of the HPA axis, which is due to the increased GR sensitivity (Sorrells & Sapolsky, 2007). Given the important function of GRs in the homeostatic mechanism in regulating stress response, the key role of GRs during the recovery period is to prevent cortisol from overshooting organs and brain regions (Yehuda, 2009). However, the elevated negative feedback inhibition of the HPA-axis would contribute to subsequent rapidly decline and suppression in cortisol levels (Hill & Tasker, 2012), even lower than basal levels before trauma exposure. Consequently, hyperactivated and excess GR sensitivity facilitates pro-longed fear conditioning and a failure in fear extinction (Yehuda, 2002b), leading to severely disrupted cortisol levels, emotional dysregulation and subsequent PTSD symptoms (Yehuda, 2002b).

One possible explanation to the enhanced sensitivity of GRs after trauma is the external post-trauma environmental circumstances (Yehuda et al., 2013). During the recovery period of trauma, external environment (e.g., social support, a safety physical environment) is critical. Subsequent challenges in the environment may further induce more burden and distress to individuals. As a result, HPA axis continues to be active. The ongoing cortisol releasing and signaling would interfere with the function of GR, leading to an elevated suppression to cortisol and over sensitized GRs.

Evidence of Dysregulated Cortisol Before, During and After Trauma

In order to evaluate the first hypothesis described above, Heinrichs and colleagues (2005) examined salivary cortisol wakening response before exposure to traumatic stress in 43 professional firefighters to see if it predicted PTSD symptoms two years later. Results failed to find a prospective association (Heinrichs et al., 2005). A second study of 470 soldiers (van Zuiden et al., 2011) prospectively investigated whether pre-deployment cortisol awakening response (CAR) predicted subsequent development of PTSD after deployment; however, results again failed to find a prospective association. Additionally, van Zuiden and colleagues investigated morning plasma cortisol in military personnel before their deployment to Afghanistan and their PTSD symptoms six months afterwards (van Zuiden et al., 2012a; van Zuiden et al., 2012b) and again did not find an effect. Another longitudinal study examined whether the magnitude of the CAR before trauma exposure would predict PTSD symptoms 3 years later in a sample of 400 police officers (Inslicht et al., 2011). Results did not support a predictive relationship.

Over the past decades, research has documented that cortisol circulation and response at the time or in the aftermath of traumatic events was associated with PTSD

symptomology later (Delahanty et al., 2000; McFarlane, Barton, Yehuda, & Wittert, 2011; Resnick, Yehuda, & Acierno, 1997; Resnick, Yehuda, Pitman, & Foy, 1995; Yehuda, McFarlane, & Shalev, 1998). Initial results suggested that *decreased* cortisol levels in the peri-trauma period contributed to subsequent PTSD development; however, the findings were not conclusive. Most recently, Ehring and colleagues (2008) measured individuals' salivary cortisol levels 12 hours after motor vehicle accidents then assessed PTSD symptoms six months later. The findings indicated that diminished cortisol levels shortly after the events predicted PTSD symptoms at six month (Ehring, Ehlers, Cleare, & Glucksman, 2008). Over the years, the lower cortisol levels during the traumatic event and shortly afterwards predicted subsequent PTSD symptoms have been reported in a variety of samples (Delahanty et al., 2000; Resnick et al., 1995; McFarlane, Atchison, & Yehuda, 1997; Walsh et al., 2013; Yehuda et al., 1998).

However, other studies (Aardal-Eriksson, Eriksson, & Thorell, 2001; McFarlane et al., 2011) have reported the predictive value of increased cortisol levels during the trauma. One study reported that elevated cortisol levels in the afternoon a few days after trauma predicted PTSD symptoms later (McFarlane et al. 2011). Furthermore, there is evidence that high cortisol collected in the evening during the acute phrase predicted subsequent development of PTSD symptoms (Aardal-Eriksson et al., 2011; Pervanidou et al., 2007). In contrast to the findings above, other studies reported no relationship between acute cortisol response and subsequent PTSD development (Bonne et al., 2003; Shalev et al., 2008).

Several cross sectional studies have examined the GR sensitivity between PTSD and non-PTSD patients (De Kloet et al., 2007; Klaassens et al., 2012; Morris et al., 2012;

Yehuda, Lowy, Southwick, Shaffer, & Giller Jr, 1991), but only one study (Shalev et al., 2008) has evaluated the whether GR sensitivity predicts subsequent PTSD symptoms. Shalev and colleagues (2008) assessed the GR numbers within a mix-gender sample ten days, one month and five months after admission to an ER and PTSD symptoms were assessed at each follow-up session. The study reported that GR numbers after trauma did not predict the presence of PTSD symptoms later (Shalev et al., 2008). However, other studies (van Zuiden et al., 2011; 2012) investigated the predictive relationship of the GR numbers before trauma exposure and the development of PTSD symptoms after trauma exposure. The findings demonstrated the predictive value of GR numbers prior to trauma exposure for the development of PTSD symptoms later (van Zuiden et al., 2011; 2012).

Collectively, findings of the summarized prospective longitudinal studies did not support the predictive value of cortisol levels before trauma exposure for the development of PTSD in adult samples. However, the acute cortisol levels in response to trauma (e.g., in an emergency room) have been previously found to be a predictor of subsequent PTSD development (Delahanty et al., 2000; McFarlane et al., 1997; Resnick et al., 1997). Furthermore, a high-dose cortisol administration in the first few hours after traumatic events was associated with reduced risk of subsequent PTSD development (Schelling et al., 2004; Zohar et al., 2011). The discrepancy in the literature may reflect the differences in when cortisol levels were measured. A previous study has demonstrated that lower morning and higher evening cortisol levels shortly after traumatic events predicted PTSD symptoms following the events (Aardal-Eriksson, Eriksson, & Thorell, 2001).

Given the evidence described above, it was hypothesized that instead of basal HPA dysfunction, the HPA reactivity shortly after traumatic events might be involved in the pathophysiology of PTSD (van Zuiden et al., 2011). Taken together, the acute cortisol responses to traumatic events rather than pre-trauma cortisol levels were thought to relate to an increased risk for later PTSD development (Delahanty et al., 2000). Due to the methodological limitations and assessment time variation across studies, evidence for increased susceptibility to PTSD as a result of cortisol dysregualtion in the acute aftermath of traumatic events should be interpreted with caution (Zoladz & Diamond, 2013), especially considering the difficulties in measuring cortisol levels during the traumatic event.

Problems and Remaining Questions

The evidence of pre-traumatic cortisol levels in relation to subsequent development of PTSD is not conclusive, and the process involved in HPA axis alternations are not fully understood. Evidence to date has suggested that altered cortisol is a biological vulnerability factor in developing PTSD, but the exact mechanism still remains unknown at this time, especially in adolescents. There are several major issues that may not be well addressed in the literature.

First, cross-sectional studies in adolescents failed to untangle whether the dysregulation of cortisol precedes trauma-induced PTSD symptoms, or it is a consequence of the PTSD itself. Additionally, given the significant role of stress and its interaction with the HPA development during adolescence, it is important to take in account the interaction in PTSD development. The stress occurrence during the adolescence may result in subsequent alterations in the HPA function and further

mediates predisposition to the development of PTSD in early adulthood. Ultimately, the interaction of the HPA axis and stress experience in adolescence may provide evidence regarding the developmental pathways for risks and resilience to PTSD in adulthood.

Second, work on the predictive value of cortisol with respect to developing PTSD in adults developed around the studies of fire fighters or police officers, but significant gaps still remain in our knowledge of the predictive relationship in youth. From a methodological standpoint, assessing pre-traumatic factors in high-risk populations may not generalize or be the same as in other groups due to the fact that these individuals are frequently exposed to traumatic events. In other words, findings from these studies may not generalize to adolescents due to the unique natures of those samples.

Finally, studies in depression have demonstrated the key role of stressful or negative life events in the development of depression, but limited research on underlying mechanisms in trauma-related outcomes (e.g., PTSD) exist for a particularly high risk group, namely adolescent girls. Stressful events are more prominent in adolescent girls, so it would be of interest to study PTSD development in this population after the occurrence of stressful events. Adolescent girls have reported to be especially vulnerable to experience certain trauma-related symptoms after the events (Zona & Milan, 2011). Understanding interactions between pre-existing biological vulnerabilities and stressful life events can further our understanding of PTSD in youth.

Study Aims and Hypotheses

Based on the four models discussed above, the present study aimed to assess the prospective relationship between PTSD symptoms, cortisol levels, primarily CAR, and stressful life events in a large adolescent female sample who were assessed for PTSD

symptoms and daily cortisol patterns at a baseline assessment, and then who were re-assessed for PTSD symptoms and intervening stressful life events at a follow-up assessment nine months later. The study had four aims:

First, the present study examined the cross-sectional relationship between cortisol levels and PTSD symptoms at all time points.

Hypothesis 1: At baseline, CAR was predicted to be correlated with PTSD symptoms, but the magnitude of this correlation would be small. At follow-up assessment, baseline CAR was predicted to be negatively correlated with PTSD symptoms.

Second, the study examined the predictive relationship between baseline CAR and PTSD symptoms nine months later in adolescence girls.

Hypothesis 2: It was predicted that baseline CAR would predict PTSD symptoms assessed at nine month.

Third, adolescence is a period marked by major changes in hormone levels, especially stress-related hormone (Young & Altemus, 2004). During this period, the activation of the HPA-axis is altered by the occurrence of stress (e.g., acute or chronic stress) (Romeo et al., 2006). The current study sought to investigate the interaction of baseline cortisol levels and stressful life events in the development of PTSD symptoms nine months later.

Hypothesis 3: The relationship between baseline CAR and the development of PTSD symptoms at nine months would be moderated by self-reported stressful life events during the interval.

Fourth, the study sought to understand which daily cortisol profile of the several that can be computed would interact with stressful event to be most predictive of the development of PTSD symptoms in adolescence.

Hypothesis 4: Diurnal cortisol patterns, indicating the individual difference in the diurnal changes occurring from awakening to the evening, rather than CAR would have a larger interaction effect with stressful life events in predicting the development of PTSD symptoms at nine month.

CHAPTER 2

METHODS

Participants

A total of 550 adolescent girls between the ages of 13.5 and 15.5 (M_{age}= 14.39, *SD* = .63) and one of their parents participated in an ongoing study, the Adolescent Development of Emotions and Personality Traits (ADEPT) project. The ethnic and racial composition of the sample was 80.5% non-Hispanic Caucasian, and 57.8% of the adolescents' participating parents had a bachelor's degree or greater. Participants were recruited from the community through school events, online classifieds, word-of-mouth referral, and a commercial mailing list of homes with a daughter age 13-15 years. Families were financially compensated for their participation. Inclusion criteria were ability to read and understand questionnaires and participation of at least one biological parent. To ensure a healthy sample, exclusion criteria were adolescent medication use or disease that may impact HPA axis activities, lifetime history of major depressive disorder (MDD), dysthymia, or intellectual disabilities. Given the intensive reading required for adolescents when administrated assessment battery, intellectual disabilities was included as an exclusion criterion. Lifetime history of MDD or dysthymia was determined using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (KSADS-PL; Kaufman et al., 1997). This clinical interview was administered by trained diagnostic interviewers who were under close supervision of clinical psychologists. The study was approved by the participating university's Institutional Review Board.

Saliva Sample Collection and Assay

Saliva samples were collected from all adolescent participants. Participants were sampled on three consecutive days in their natural environment upon awakening, 30 minutes after awakening and in the evening around 8 p.m. Participants were free to decide when to wake up and follow their normal routine after awakening. Medication Event Mointoring System (MEMS) caps were utilized to record the time and date of saliva sample collection.

Saliva samples were collected by Salivette sampling device. Participants were asked to keep a diary of the awakening time, the time of each saliva sample collection, and discomfort occurring during any given sample collection day. Participants collected salivary cortisol samples by themselves or with parents' assistance. They were asked not to eat, drink, or brush their teeth during the first hour after awakening in order to minimize unnecessary sources of variation in saliva. They were also asked to inform the experimenter about any vigorous physical activity, the presence of oral diseases or injury before saliva collection to avoid the possibility of contamination. Participants were instructed not to touch the samples with their hands after each collection. They stored and kept their saliva samples in the freezer before returning them to the lab.

After their return to the lab, saliva samples were placed in a -20 C freezer. Experimenter followed standard laboratory safety procedures for handling saliva samples. Salivary cortisol levels were determined by a time-resolved immuno-assay with fluorescence detection (DELFIA). An average coefficient of variation (CV) of duplicate assays of each sample was calculated. Any CV values greater than 12% for cortisol

values greater than 5 nmol/L were reanalyzed, as were any values ≥ 100 nmol/L. The average of the two assay values was used for analysis.

Measures

Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997) was used to evaluate and diagnose MDD at baseline and 9 month, respectively. The K-SADS-PL was adapted from the Present Episode version of the K-SADS-P (Chambers et al., 1985), which has been used in a large number of clinical, psychobiological and epidemiological studies of affective and child related psychiatric disorders. The K-SADS-PL is diagnostic instrument for the semistructured assessment of ongoing and past episodes of psychiatric disorders in children and adolescents according to DSM-III-R and DSM-IV criteria (Kaufman et al., 1997). The interview contains improved probes and anchor points, and surveys additional disorders that not included in K-SADS-P. The primary diagnoses assessed with the K-SADS-PL include MDD, Bipolar Disorders, Schizophrenia, Anorexia Nervosa, PTSD, and Adjustment Disorders (Kaufman et al., 1997). The K-SADS-PL is administrated by interviewing parents and child to gather all the sources of the information and the final summary ratings will be provided (Kaufman et al., 1997). The K-SADS-PL includes an introductory interview, which is used to establish rapport (Rutter & Graham, 1968), a screen interview, which helps streamline the assessment and improve administration efficacy, a diagnostic supplement, the Summary Lifetime Diagnoses Checklist and the Children's Global Assessment Scale (C-GAS) ratings. Five diagnostic supplements were included in the K-SADS-PL: Affective Disorders, Psychotic Disorders, Anxiety Disorders, Behavioral Disorders and Substance Abuse and Other

disorders (Kaufman et al., 1997). Once the interview has completed, symptoms were coded using current diagnoses, disorders targeted with medication, past diagnoses and time line.

Inventory of Depression and Anxiety Symptoms (IDAS-II; Watson et al., 2012) was used to measure PTSD severity and symptoms. The IDAS-II is a 99-item self-report measure that organized into 18 specific scales plus General Depression (Watson et al., 2012). Participants were asked to rate their experience with each symptom on a 5-point likert scale from "not at all" to "extremely." The 20-item General Depression scale was used to assess depressive symptoms in the present study. Among the 18 specific scales, the 4-item measures of traumatic intrusions, 4-item measures of traumatic avoidance, 10-item measures of dysphoria, and 8-item measures of panic were used to evaluate PTSD symptoms. The panic subscale was used to correspond with the hypervigilance symptom in PTSD (Watson et al., 2008). The scales showed strong convergent validity and high internal consistency in college, clinic and community samples (Watson et al., 2007; Watson et al., 2008; Watson et al., 2012). Scales had excellent internal consistency in the present study (α's > .79).

Stressful Life Events Schedule (SLES; Williamson et al, 2003) for children and adolescents was used to assess the intervening stressful life events. The SLES is an interview instrument, which was created to examine the relationship between stress and depression in children and adolescents (Williamson et al, 2003). In SLES administration participants were asked about the occurrence of a stressful life event; for the event, they were asked to use memory aid to date the occurrence of the event (Williamson et al., 2003). The duration of the event was recorded in order to differentiate between acute and

ongoing events; the subjective and objective threat of each event was evaluated, as well as the behavior-dependence/independence of the event. Objective threat ratings from the interviewers for all events adolescent participants reported during this nine month interval were used to calculate the severity of stressful life events. For each participant, the stressful life events severity score was calculated by squaring objective threat rating for each event and summing the squared ratings. In this calculation, an event with higher objective threat rating would be more heavily weighted in comparison to an event with lower objective threat rating. In addition, the number of stressful life events was also implemented in this calculation.

Procedure

Informed parental consent and adolescent assent were obtained during a lab visit. Adolescent participants completed the KSADS, IDAS-II, as well as the measurements of BMI and pubertal status. Parents provided demographic information and completed the SCID during this lab visit. Demographic information was obtained. Before the visit a cortisol collection kit was shipped to the family, and they received detailed instructions (verbal, written, and video) on how to collect three saliva samples a day for three consecutive days, keep a diary, and freeze samples prior to their first lab visit. Adherence to instructions was checked during the visit (diary, MEMS data) and generally was very high, but if significant problems or non-adherence were present, participants were given additional training and asked to retake samples in days after the visit. Both adolescents and their parents were compensated for participation in the study, including a bonus for documented adherence to cortisol collection instructions.

Statistical Analysis and Power Analysis

Prior to testing hypotheses, data were prepared, scored and screened for outliers. Outliers were defined as standardized scores > 3 standard deviations from the mean in all psychological and biological assessments. Other exclusion criteria for cortisol assessment were non-adherence to saliva sampling procedures and samples from ill adolescent participants.

In order to capture cortisol changes over a day and summarize the information obtained from repeated measurements, each day's raw cortisol data were used to create four cortisol parameters: the area under the curve (AUC; Pruessner et al., 2003) reflecting total volume of cortisol circulation over the day, AUC ground for the two morning samples only, the cortisol diurnal slope (Adam & Kumari, 2009), and the CAR (Pruessner et al., 1997). The CAR is defined as the increase in cortisol that occurs during the period between waking and 30-45 minutes after awakening (Pruessner et al., 1997). Cortisol values at each of the three sampling collection times (waking, 30 minute after waking, and evening) were also analyzed. Thus, a total of seven cortisol parameters were included in analyses. Prior to analysis, all seven cortisol parameters were adjusted for any time difference between the corresponding sample collection times and target times. We estimated a regression model of cortisol level at a given collection point as a function of collection time, and adjusted cortisol levels at the target time for each participant by entering their observed cortisol level and collection time in the model. Values for adjusted cortisol parameters were then averaged across three days to obtain more reliable indices (Hellhammer et al., 2007).

Twenty-three adolescent participants' salivary cortisol samples were identified as outliers or non-adherent even after additional training, and all 3 days of their cortisol samples were removed from the final analysis. A final sample of 527 participants was included in the final analysis. To test the first hypothesis, a Pearson bivariate correlation was used to evaluate the correlation between baseline CAR and PTSD symptoms at baseline and at nine month. To test the second hypothesis and to ensure that any effects observed were independent of adolescents' baseline clinical symptoms, four hieratical multiple regressions were conducted separately with baseline CAR entered as the predictor and each PTSD symptom cluster as the dependent variable, after first controlling for the adolescents' general depression and PTSD symptoms at baseline. In order to assess the third and fourth hypotheses, two path models were conducted separately with CAR and cortisol diurnal slope.

CHAPTER 3

RESULTS

Predictive Value of CAR for PTSD Symptoms at Nine Month Follow-up

Adolescent participants' characteristics and clinical symptoms at baseline and nine months are described in Tables 1 and 2. None of the adolescent participants met diagnostic criteria for PTSD based on KSADS at baseline. Table 3 summarizes the results of bivariate correlations used to assess the relationship between baseline cortisol parameters and PTSD symptoms (at both baseline and nine month follow-up). These correlations demonstrated that baseline CAR was not correlated with adolescents' PTSD symptoms at either time point (ps = .14 - .93). However, two PTSD symptoms at nine month follow-up, traumatic intrusions and traumatic avoidance, were positively correlated with the baseline cortisol diurnal slope (r = .09, ps < .05). As such, only diurnal slope was used as a diurnal cortisol profile in the path analysis to test the fourth hypothesis (see analytic plan).

Tables 4 and 5 show the results of four separate hierarchical multiple regressions used in testing the second hypothesis using two cortisol parameters separately: CAR and diurnal slope of cortisol (i.e., the predictive value of CAR at baseline to predict PTSD symptoms at nine month follow-up). In the first model of the analysis, general depression symptoms at both time points and corresponding PTSD symptoms at baseline in each regression positively predicted PTSD symptoms at nine months (ps < .01). However, after controlling for the above-mentioned variables (the second model of the analysis), baseline CAR was not associated with the development of any PTSD symptoms at nine

months (*p*s = .29 - .60). Similar results were revealed when the four hierarchical multiple regressions were reran by entering diurnal slope into the second model (*p*s = .33 - .52).

Interaction of Baseline Cortisol and Stressful Life Events for PTSD Symptoms at Nine Months

Figures 1 and 2 show the interaction of baseline CAR and diurnal slope with intervening stressful life events for the development of PTSD symptoms at nine months, respectively. Baseline PTSD symptoms were included in both path models and showed a positive significant association with the symptoms assessed at nine months (*p*s < .01). As seen in the figures, the severity of stressful life events positively predicted PTSD symptoms at nine months (*p*s < .01). However, the interaction between baseline CAR and intervening stressful life events only negatively predicted dysphoria symptoms at nine months ($p < .05$), but did not predict the development of panic, traumatic intrusions, and traumatic avoidance symptoms at nine month (*p*s = .13- .97) (see Figure 1). Similar results were revealed when testing the interaction effect between baseline diurnal slope and stressful life events. The interaction between diurnal slope of cortisol at baseline and stressful life events did not predict any PTSD symptoms at nine month follow-up (*p*s = .18 - .84) (see Figure 2).

Exploratory analyses were carried out to determine whether specific types of stressful events (as opposed to a global index of stressors) were more likely to interact with baseline cortisol profiles to predict symptoms. These analyses revealed that the interaction between baseline CAR and stressful events related to romantic relationships was a significant negative predictor of panic, intrusions, and avoidance symptoms at the

nine month follow-up (ps < .05). That is, the most severe symptoms occurred in adolescents with blunted CAR but experiencing high levels of stress (see Figure 3).

CHAPTER 4

DISCUSSION

To our knowledge, this is the first study to prospectively investigate the predictive value of CAR in the development of subsequent PTSD symptoms in adolescents. In addition to CAR, the study further examined the interaction effect of CAR and intervening stressful events for the development of PTSD symptoms. Three major findings emerged from the study. First, CAR did not predict PTSD symptoms, but diurnal slope of cortisol was prospectively related to PTSD symptoms. Second, stressful life events on their own were robust predictors of symptoms at nine months. Third and finally, the global index of stressful life events did not interact with HPA markers to predict PTSD symptoms, but it did predict associations with dysphoria. Moreover, stressful life events related to romantic relationships interacted with underactivation of the HPA axis to predict increases in PTSD symptoms. Each of these findings is reviewed in more details below.

Contrary to hypotheses, the results did not suggest a significant predictive association between CAR and the development of PTSD symptoms, consistent with the findings in adult samples (Heinrichs et al., 2005; Inslicht et al., 2011; van Zuiden et al., 2012). One possible explanation for the non-significant finding in the relationship of CAR and the development of PTSD symptoms was the relatively small changes in the severity of symptoms unique to PTSD, resulting in flooring effects (i.e., traumatic intrusions and traumatic avoidance symptoms both decreased from baseline to nine months decreased. On average, $M_{\text{difference}}$ = -.03 and -.57, respectively). In contrast, nonspecific distress-related symptoms increased (i.e. dysphoria and panic increased from

baseline to nine months. On average, $M_{difference}$ = .20 and .34, respectively). As a result, flooring effects may have reduced power for PTSD specific symptoms, but was less of an issue for nonspecific stress-related symptoms (Gootzeit, Markon, & Watson, 2015).

However, we did find a positive association between diurnal slope of cortisol at baseline and the development of PTSD symptoms, even though the magnitude of this correlation was small. That is, a flattened decrease in cortisol across the day was associated with increased PTSD symptoms, particularly traumatic intrusions and traumatic avoidance symptoms. Flattened diurnal slope may be the result of an underactive HPA (i.e., less peak during the day resulting in a flatter slope across the day). Overall, adolescents with more severe PTSD symptoms have less cortisol secretion across the day. CAR per se was not a significant predictor, so it may be that diurnal slope is more sensitive to fluctuations in HPA activity given that it indexes cortisol across the day rather than during the early morning rising. This finding supports and extends previous evidence regarding the diurnal cortisol secretion in individuals with PTSD. For example, positive associations between flatter diurnal slope and PTSD symptoms, including intrusions, avoidance, and hyperarousal, were reported in a cross-sectional study using adolescent females with a history of sexual abuse (Keeshin et al., 2014). A similar pattern was also observed in adults with PTSD (Brummett et al., 2008; Thomas et al., 2012). Nevertheless, the above-mentioned studies were cross-sectional and investigated individuals who had already developed PTSD, so it is not possible to say whether the flattened diurnal slope of cortisol was a risk factor or a consequence of PTSD symptoms. This study provided prospective evidence that such a profile is a risk factor rather than a consequence. Moreover, this relationship was unique to traumatic intrusions

and traumatic avoidance symptoms of PTSD, but not other symptom nonspecific symptoms of the disorder.

In addition, the current findings demonstrated that stressful life events were a strong predictor of subsequent PTSD symptoms during adolescence, even during this relatively short nine-month assessment window. This predictive effect may be specific and clinically significant to adolescents, given that adolescence represents a transition period for both psychological and biological development. It is noteworthy that exposure to stressful life events during adolescence may have significant effects on the development of PTSD symptoms. Importantly, these effects are independent of pre-existing PTSD symptoms. Aside from PTSD symptoms, stressful life events have previously been linked to other mental health problems longitudinally, including substance use and depression symptoms, in adolescence (Doane et al., 2013; Low et al., 2012). As such, screening for stressful life events in adolescence may help with early detection and prevention of mental health problems, such as PTSD, substance use, and depression.

Despite the negative implications of stressful life events on the development of PTSD symptoms in adolescence, there was no evidence that HPA dysregulation, indexed by both CAR and diurnal slope of cortisol, interacted with stressful life events in general to predict or potentiate unique PTSD symptoms. However, the interaction between CAR and the global index of stressful life events was associated with increases in dysphoria symptom at nine months. Moreover, there was an interaction between CAR and stress related to romantic relationships to the subsequent development of PTSD symptoms (i.e., traumatic intrusions and traumatic avoidance) in adolescence. In these two interaction

findings, regardless of the source of stressful life events, when stress levels are high, adolescents with blunted CAR are experiencing greater PTSD symptoms. These findings suggest that individuals with blunted basal cortisol levels may have insufficient cortisol release in response to stress, which in turn, leads to behavioral dysregulation and consequently stress-related symptoms (Raison & Miller, 2003). This interpretation is supported by previous studies indicating individuals with low cortisol levels during the acute period of trauma exposure experienced elevated risk of developing subsequent PTSD symptoms (Delahanty et al., 2000; Schelling et al., 1999). Importantly, after receiving low doses of cortisol as a part of intensive care unit (ICU) treatments, individuals had lower rates of PTSD symptoms later on in comparison to those who did not receive cortisol in treatments (Schelling et al., 1999). As such, CAR alone was not a candidate pre-existing risk factor to develop PTSD symptoms. However, when individuals encounter stress, an adequate amount of cortisol release may protect against developing stress-related symptoms.

The findings of the current study should be interpreted in light of several limitations. First, rates of trauma exposure and PTSD were low in the present sample, meaning that the present study was only able to detect subsydromal symptoms, not syndromal levels of PTSD symptoms. Only a small portion of the adolescents experienced major, life-threatening trauma. Hence null effects may be due to health of the sample. Second, the sample in this study was healthy female adolescents. Future studies are needed for assessing adolescent males. In particular, it is not clear whether the biological mechanisms for developing PTSD symptoms in adolescent boys are different from those observed in adolescent girls. In addition, further research with a more

clinically severe adolescent sample is needed to investigate whether different mechanisms may be involved in the development of PTSD symptoms versus the onset of the syndrome as a whole. Third, the longitudinal assessment window in the present study, nine months, was short. Future research is needed to evaluate prospective biological mechanisms in developing PTSD symptoms in a longer time frame (i.e., years). Finally, the current study focused on a broad spectrum of stressful life events experienced by adolescents, rather than a specific type of stressor or trauma. Thus, it remains unclear whether different types of stressor or trauma may account for a different interaction effect with adolescents' stress response system, which may in turn, result in the differences in the symptoms onset.

Despite the above limitations, the present study provides important information on the prospective relationship between HPA functioning and subsequent PTSD symptoms during a critical developmental period. Diurnal slope of cortisol exhibits a prospective positive association with symptoms that are unique to PTSD, indicating adolescents with flattened diurnal slope are more likely to develop PTSD symptoms. CAR alone is not a biological vulnerability for the development of PTSD symptoms. However, the interaction between CAR and the global index of stressful life events, as well as the interaction between CAR and stress related to romantic relationships are important factors in developing PTSD symptoms. That is, when they encounter stress, adolescents with an underactivated HPA axis may have greater risk for broad stress-related symptoms. Identification of pre-existed vulnerability factors for PTSD symptoms provides early preventions to adolescents at risk. Given adolescence is a developmental

period full of challenges and stress, early screening and detection for underactivated HPA axis might be important to prevent adverse effects of stress.

CHAPTER 5

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Table 1
Descriptions of Adolescents' Characteristics and Baseline Cortisol Parameters

	M	*SD*
Adolescents' characteristics		
BMI	21.79	4.14
Age	14.39	.62
Puberty status	.00	1.79
Cortisol parameters		
Waking sample	7.44	3.58
30 minutes sample	15.44	6.25
Evening sample	1.76	1.68
CAR	7.99	5.76
AUC morning	5.79	2.15
AUC daily	120.18	46.47
Diurnal slope	-.41	.28

Note. *N* = 511-538. BMI = body mass index; PTSD = posttraumatic stress disorder; CAR = cortisol awakening response; AUC = the area under the curve

Table 2

Descriptions of Adolescents' Clinical Symptoms at Baseline and Nine Month Follow-up

Clinical symptoms	Baseline		Nine month follow-up	
	M	*SD*	*M*	*SD*
General depression	32.30	11.20	33.39	12.02
Dysphoria	16.03	6.35	16.23	6.69
Panic	10.25	3.20	10.59	3.90
Traumatic intrusions	5.28	2.03	5.25	2.11
Traumatic avoidance	7.16	3.65	6.57	3.33

Note. N = 439-538.

Table 3

Bivariate Correlations Between Baseline Cortisol Parameters and PTSD Symptoms Assessed at Both Baseline and Nine Month Follow-up

Cortisol Parameters	Baseline				Nine month follow-up			
	Dysphoria	Panic	Traumatic Intrusions	Traumatic Avoidance	Dysphoria	Panic	Traumatic Intrusions	Traumatic Avoidance
CAR	.03	.05	.07	.04	-.02	-.06	.00	.03
AUC morning	.00	.00	-.01	-.01	-.07	-.05	-.06	-.06
AUC daily	.04	.04	.03	.04	-.04	-.05	-.04	-.03
Diurnal slope	.06	.06	.07	.10*	.07	.02	.09*	.09*

Note. PTSD = posttraumatic stress disorder; CAR = cortisol awakening response; AUC = the area under the curve.
*$p < .05$

Table 4

Hierarchical Multiple Regression Analyses Predicting PTSD Symptoms at Nine Month From Clinical Symptoms and CAR at Baseline

		Nine month PTSD symptoms											
		Dysphoria			Panic			Traumatic Intrusion			Traumatic Avoidance		
		β	R^2	*p*	β	R^2	*p*	β	R^2	*p*	β	R^2	*p*
Model 1			.92			.53			.36			.25	
	Baseline general depression	-.32		.00	-.11		.03	-.13		.01	-.01		.90
	Nine-month general depression	.94		.00	.67		.00	.57		.00	.33		.00
	Baseline Corresponding PTSD symptom [a]	.36		.00	.25		.00	.23		.00	.33		.00
Model 2			.92	.34		.53	.29		.36	.60		.26	.36
	Baseline general depression	-.32		.00	-.11		.03	-.13		.01	-.01		.89
	Nine-month general depression	.94		.00	.67		.00	.57		.00	.33		.00
	Baseline Corresponding PTSD symptom	.36		.00	.25		.00	.23		.00	.33		.00
	CAR	.01		.34	-.03		.29	.02		.60	.04		.36

Note. PTSD = posttraumatic stress disorder; CAR = cortisol awakening response.

[a] The same PTSD symptom used as the dependent variable in the model, but assessed at baseline was entered.

Table 5

Hierarchical Multiple Regression Analyses Predicting PTSD Symptoms at Nine Month from Clinical Symptoms and Diurnal Slope of Cortisol at Baseline

		Nine month PTSD symptoms											
		Dysphoria			Panic			Traumatic Intrusion			Traumatic Avoidance		
		β	R^2	*p*	β	R^2	*p*	β	R^2	*p*	β	R^2	*p*
Model 1			.92			.53			.36			.25	
	Baseline general depression	-.32		.00	-.11		.03	-.13		.01	-.01		.90
	Nine-month general depression	.94		.00	.67		.00	.57		.00	.33		.00
	Baseline Corresponding PTSD symptom [a]	.36		.00	.25		.00	.23		.00	.33		.00
Model 2			.92	.52		.53	.33		.36	.49		.26	.50
	Baseline general depression	-.32		.00	-.11		.03	-.13		.01	-.01		.89
	Nine-month general depression	.94		.00	.67		.00	.57		.00	.33		.00
	Baseline Corresponding PTSD symptom	.36		.00	.25		.00	.23		.00	.33		.00
	Diurnal Slope	-.01		.52	-.03		.33	.03		.49	.03		.50

Note. PTSD = posttraumatic stress disorder.

[a] The same PTSD symptom used as the dependent variable in the model, but assessed at baseline was entered.

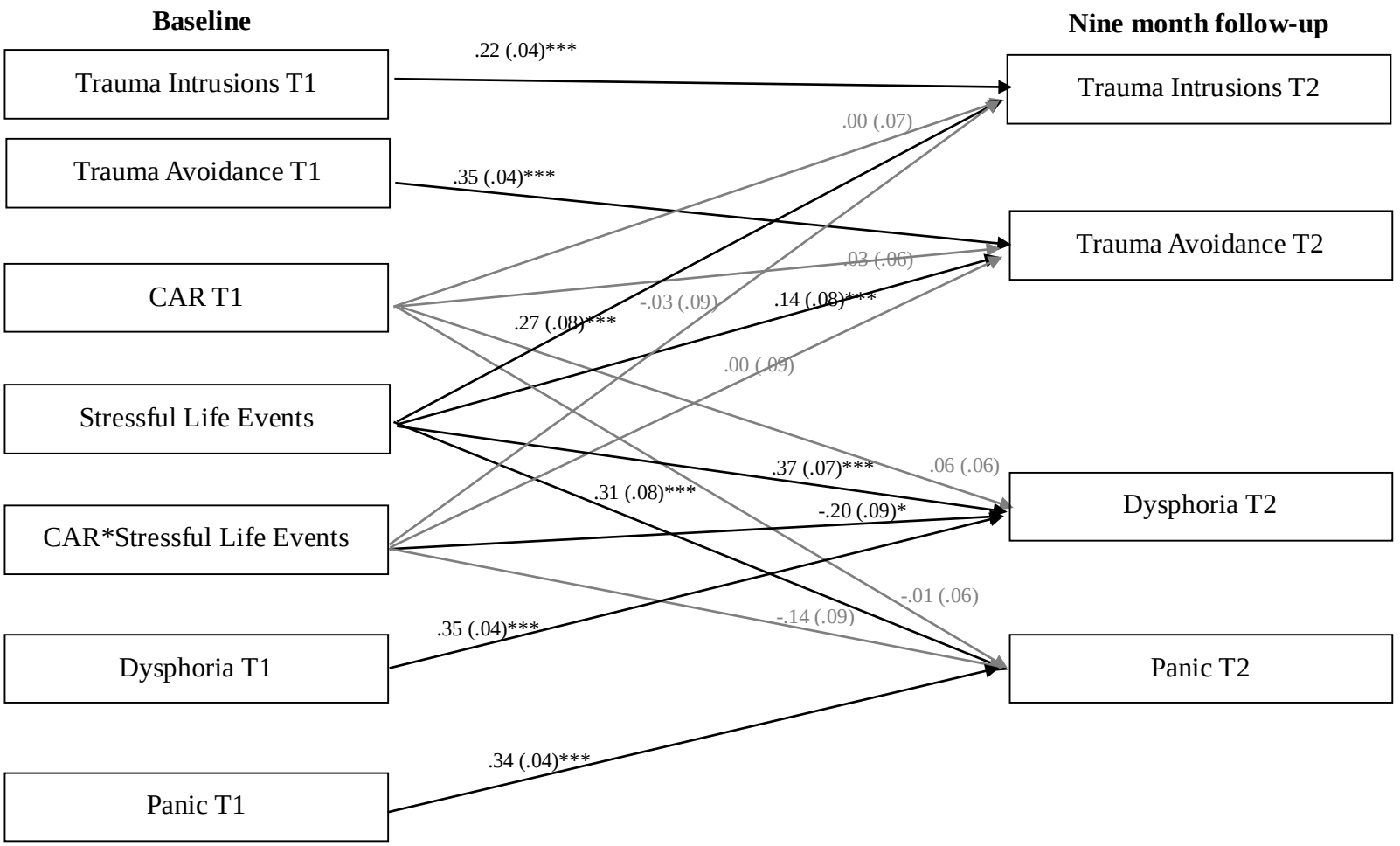

Figure 1. Path analysis model of baseline PTSD symptoms, CAR, and stressful life events predicting PTSD symptoms at nine month follow-up. The standard errors are in the parentheses. PTSD = posttraumatic stress disorder; CAR = cortisol awakening response. *p < .05. **p < .01. ***p < .001.

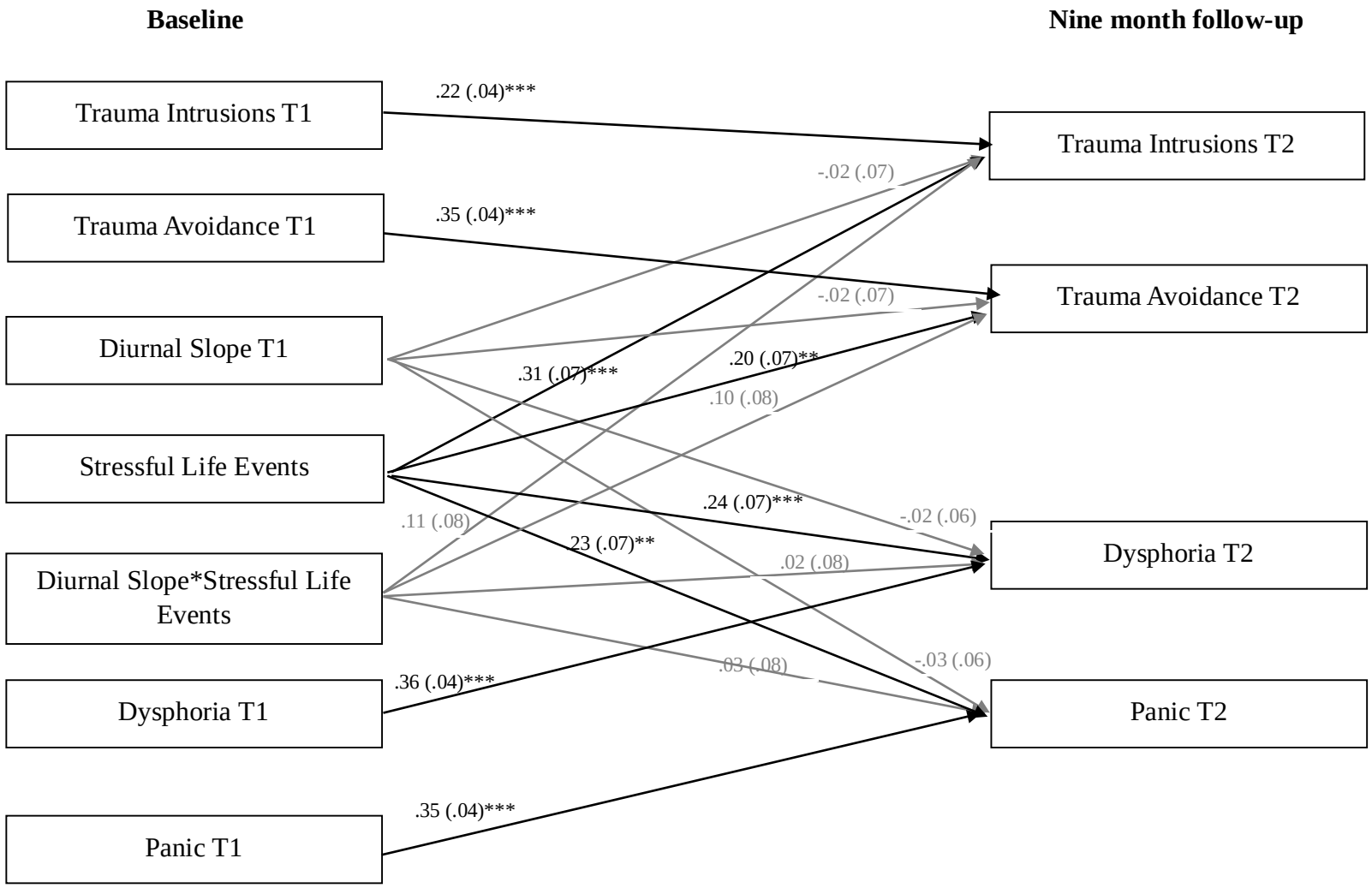

Figure 2. Path analysis model of baseline PTSD symptoms, diurnal slope, and stressful life events predicting PTSD symptoms at nine month follow-up. The standard errors are in the parentheses. PTSD = posttraumatic stress disorder. *$p < .05$. **$p < .01$. ***$p < .001$.

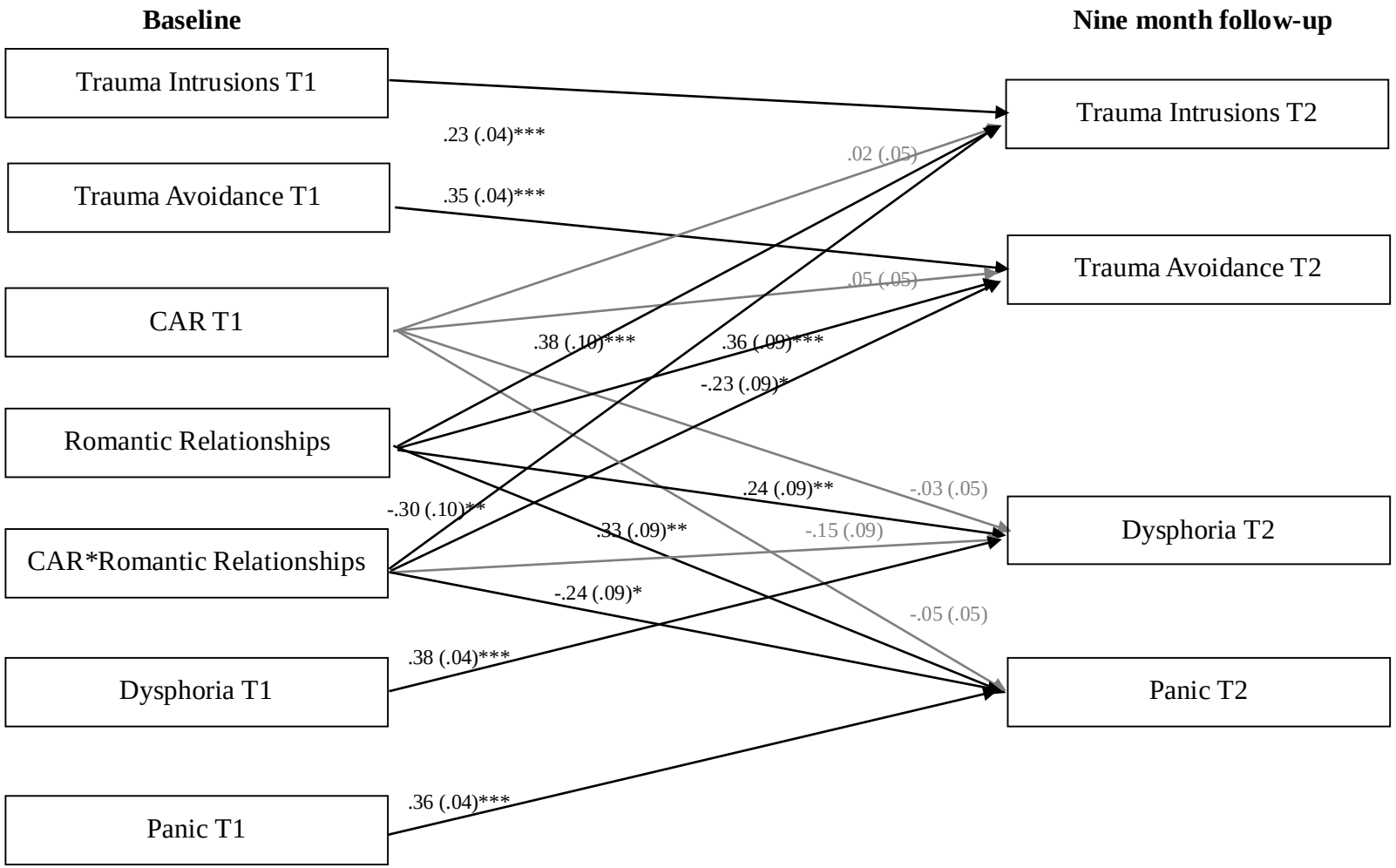

Figure 3. Path analysis model of baseline PTSD symptoms, CAR, and romantic relationships predicting PTSD symptoms at nine month follow-up. The standard errors are in the parentheses. PTSD = posttraumatic stress disorder; CAR = cortisol awakening response. *$p < .05$. **$p < .01$. ***$p < .001$.