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The differential calibration of the HPA axis as a function of trauma versus adversity: A systematic review and *p*-curve meta-analyses

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Abstract

Although there is an abundance of evidence linking the function of the hypothalamic-pituitary-adrenal (HPA) axis to adverse early-life experiences, the precise nature of the association remains unclear. Some evidence suggests early-life adversity leads to cortisol *hyper*-reactivity, while other evidence suggests adversity leads to cortisol *hypo*-reactivity. Here, we distinguish between trauma and adversity, and use *p*-curves to interrogate the conflicting literature. In Study 1, trauma was operationalized according to DSM-5 criteria; the *p*-curve analysis included 68 articles and revealed that the literature reporting associations between trauma and blunted cortisol reactivity contains evidential value. Study 2 examined the relationship between adversity and cortisol reactivity. Thirty articles were included in the analysis, and *p*-curve demonstrated that adversity is related to heightened cortisol reactivity. These results support an inverted U-shaped function relating severity of adversity and cortisol reactivity, and underscore the importance of distinguishing between “trauma” and “adversity”.

Keywords:

Review, p-curve, meta-analysis, HPA axis, cortisol, trauma, adversity

Highlights:

- We conducted *p*-curve meta-analyses of adverse life events and cortisol reactivity
- *Trauma* and cortisol *hypo*-reactivity literature contains evidential value
- *Adversity* and cortisol *hyper*-reactivity literature contains evidential value
- Inverted U-shaped function explains severity of adversity and cortisol reactivity
- Distinction between “*adversity*” vs “*trauma*” is important in probing the literature

1 Introduction

Adverse childhood experiences including child maltreatment, neglect, and community violence have been linked to increased risk of negative health outcomes later in life. In one seminal study, Felitti et al. (1998) obtained data from 13,494 adults who completed the adverse childhood experiences (ACE) questionnaire and a standardized medical evaluation. The authors found a strong dose response relationship between exposure to abuse or household dysfunction during childhood and risk of disease later in life, including ischemic heart disease, cancer, and chronic lung diseases (Felitti et al., 1998). The findings highlighted strong and cumulative negative impacts of adverse early life experiences on later health outcomes and led to detailed empirical inquiry into how life experiences become biologically embedded (Hertzman, 1999).

Of particular interest in this regard was understanding how adverse early life experiences impact “stress-sensitive” system of the brain such as the hippocampus and amygdala involved in learning, memory, and emotion regulation (Tottenham & Sheridan, 2010), as well as the prefrontal cortex (PFC), an area critical for decision-making, executive functioning, and top-down control of limbic regions (Arnsten, 2009; Berens et al., 2017). These regions are dense with glucocorticoid receptors, suggesting that their development and function might be altered as a consequence of environmentally-induced alterations in cortisol release. Indeed, rodent models have demonstrated that offspring of mothers that showed more licking and grooming had reduced levels of ACTH and corticosterone in response to acute stress (Liu et al., 1997). This plasticity of the HPA axis to early life programming is possible through epigenetic modification of glucocorticoid receptor genes (Meaney, 2010). Thus, rodent models have demonstrated that the HPA axis is a highly plastic biological system with demonstrated sensitivity to variation in the quality of the early-life environment (Liu et al., 1997; Meaney, 2010).

Although early-life adversity has consistently been shown to predict HPA dysregulation in humans, the nature of the association remains unclear (*See Tables 1-4 for summaries of the conflicting literature*). Several factors, including differences in how HPA axis reactivity is measured and differences in how adverse early life experiences are operationalized, potentially contribute to discrepant findings between studies. However, even when explicit criteria are used to define trauma versus adversity, and outcomes are confined to selected measures (e.g., cortisol reactivity to a stress induction), available evidence remains conflicting. For example, studies of the association between traumatic life experiences (as defined by DSM-V criteria) and cortisol reactivity to a laboratory stressor report conflicting findings, with some studies reporting cortisol hyper-reactivity and others reporting cortisol hypo-reactivity (*See Tables 1-2*). One powerful method for resolving such discrepancies is *p*-curve meta-analyses (Simonsohn et al., 2014a, 2015); therefore, we have conducted a comprehensive review and used *p*-curve meta-analytic techniques to examine associations between adversity and cortisol reactivity.

1.1 The stress response system

Environmental events that signal threat to an organism’s survival result in a set of neural and behavioural responses that regulate homeostasis within metabolic and physiological functions. When faced with an acute stressor, an elaborate network of neuroendocrine signals results in a shift of biological resources to enable the organism to adaptively face the acute stressor. This shift of biological resources involves increases in heart rate and blood pressure, and the metabolic release of glucose and nutrients thereby redirecting energy resources to allow the organism to overcome the acute stressor (Selye, 1950; Boyce & Ellis, 2005). The stress response system is composed of two anatomically separate

but functionally interconnected circuits – the corticotropin-releasing factor (CRF) system and the locus-coeruleus-norepinephrine (LC-NE) system (Boyce & Ellis, 2005; McEwen, 1998). The CRF system is involved in the regulation of the HPA axis as well as the corticolimbic circuitry of the amygdala. The LC-NE activation of the hypothalamus, on the other hand, results in the activation of the autonomic nervous system (ANS) and initiates fight or flight responses to stress. The simultaneous activation of the CRF and LC-NE systems, in addition to their projections to the amygdala, anterior cingulate cortex, and mesocorticolimbic dopaminergic systems allows for behavioural responses to stress (Boyce & Ellis, 2005). The sympathetic branch of the ANS reacts quickly to threat to optimize fight or flight responses through the release of catecholamines; the HPA axis, on the other hand, is comprised of a slower response of endocrine signals ultimately leading to the release of glucocorticoids (Ewing-Cobbs et al., 2017).

Evidence of plasticity within the HPA axis has been obtained from rodent studies reporting epigenetic modifications of glucocorticoid receptors as a function of variation in the quality of the early-life environment (Liu et al., 1997; Meaney, 2010). In humans, plasticity within the HPA-axis is demonstrated via observations that the reactivity threshold of the HPA-axis changes in response to chronic adversity (*See Tables 1-4*). Therefore, when considering the long-term biological embedding of adversity, the HPA-axis is an important physiological system to consider, not only because of its central role in responding to acute stressors, but also due to its high degree of plasticity. The HPA axis is comprised of a feedback loop between the hypothalamus, the pituitary gland, and the adrenal glands. In response to stress, CRF is released from the hypothalamus; CRF then stimulates the pituitary system to release adrenocorticotrophic hormone (ACTH) that ultimately results in the adrenal cortical secretion of glucocorticoids – cortisol in humans and corticosterone in animal species. Glucocorticoid secretion subsequently forms a negative feedback loop to the hypothalamus to inhibit the secretion of CRF (Berens et al 2017; Del Rey et al., 2008). The HPA axis is central to regulating a host of homeostatic systems in the body including the metabolic, cardiovascular, and immune systems, thereby allowing organisms to adapt to their changing environments. Furthermore, glucocorticoid production results in increased availability of glucose to facilitate “fight-or-flight” mechanisms in response to acute stress (Del Rey et al., 2008). Thus, in the face of a stressor, neuroendocrine signals redirect energy resources to allow the organism to overcome the stressor (Selye, 1950; Boyce and Ellis, 2005). Chronic exposure to adversity however, can disrupt the set-point of HPA activity, resulting in either hyper or hypo-reactivity (Yehuda et al., 2010). While HPA axis activation is adaptive under acutely stressful situations, chronic activation of the HPA axis, for example under conditions of long-term adversity or trauma, may lead to negative health outcomes and various pathologies (McEwen & Wingfield, 2003).

1.2 Theoretical frameworks for understanding the relationship between adversity and HPA axis function

Various theoretical frameworks have been proposed to understand the impact of adversities on HPA axis function. Broadly, there are two categories of theoretical perspectives: (1) “Toxic stress” models that view the consequences of chronic and extreme adversities as ultimately harmful to the body (Nelson, 2017; Selye, 1946; McEwen & Wingfield, 2003; Shonkoff & Garner, 2012); and (2) “Adaptationist” perspectives that view the calibration of the HPA axis in response to changing environmental conditions as evolutionarily adaptive (Del Giudice et al., 2011).

1.2.1 Allostatic load and overload: Wear and tear on the body

Allostatic load and overload explain how prolonged exposure to stressors can have potentially negative consequences on physiology. While allostasis has been defined as the *process* of maintaining homeostasis (Sterling & Eyer, 1988), allostatic load or overload is the wear and tear on the body associated with prolonged or dysregulated use of allostasis (McEwen & Stellar, 1993; McEwen, 1998; McEwen & Wingfield, 2003). The primary mediators of allostasis include the HPA axis, catecholamines, and cytokines, and the allostatic state of an organism refers to the sustained activity of these primary mediators (McEwen & Wingfield, 2003). Allostatic overload is further subdivided into Types I and II, where Type 1 overload is related to an emergency response to an acute stressor, and Type II overload is the stress response induced by chronic stressors that are not immediately dangerous (McEwen & Wingfield, 2003).

In the short term, allostasis has protective effects for an organism. For example, the release of glucocorticoids allows for the conversion of protein and lipids to carbohydrates allowing the organism enough energy resources to escape a potentially dangerous acute stressor (McEwen & Wingfield, 2003). If an allostatic state is sustained over a long period of time, however, the mediators of allostasis can become dysregulated leading to allostatic overload and can have damaging consequences for the body. For example, chronically elevated levels of glucocorticoids impede the function of insulin, and the combination of elevated insulin and glucocorticoids results in the storage of body fat and the formation of atherosclerotic plaques in coronary arteries (McEwen & Wingfield, 2003). Therefore, if allostatic load is not relieved and glucocorticoid secretion is chronically elevated, serious pathophysiological effects can occur (McEwen & Wingfield, 2003). According to this view then, stress reactivity is composed of a unidirectional, linear biological response to stressors, and chronically sustained stress responses are associated with stress-related pathophysiology. To illustrate, Danese and McEwen (2012) conducted a review and summarized the neural, endocrine, and immune correlates of childhood maltreatment; according to their summary, experiences of maltreatment are associated with blunted HPA axis reactivity in healthy individuals and heightened HPA axis reactivity in individuals with mental illnesses (*See Figure 1*). Moreover, the review summarizes the potentially negative consequences of adverse childhood experiences on allostasis, allostatic load, and age-related diseases (Danese & McEwen, 2012).

Figure 1: Graphical depiction of the relationship between severity of adversity and HPA axis reactivity as proposed by allostatic load/overload models (Danese & McEwen, 2012). In healthy individuals, exposure to trauma is associated with blunted HPA axis reactivity; in contrast, in individuals with comorbid mental illnesses, trauma is related to heightened HPA axis reactivity.

1.2.2 The General Adaptation Syndrome (G-A-S) Model

The first model to propose a curvilinear relationship between exposure to stress and stress reactivity was Hans Selye's *General Adaptation Syndrome* (G-A-S) model (Selye, 1946). According to the G-A-S there are three phases of the stress response: the alarm stage, the resistance stage, and the exhaustion stage. The alarm stage describes the organism's immediate response to an acute stressor and involves cortisol release by the HPA axis as well as ANS fight-or-flight reactions to the acute stressor. In the resistance stage, while the ANS response returns to normal, the body continues to produce elevated levels of cortisol and glucose to maintain arousal should a stressor reoccur. Eventually however, the body's resources are depleted, and the organism reaches the exhaustion stage marked by a drop in the release of cortisol and glucose (Guilliams & Edwards, 2010; Selye, 1946). Therefore, the G-A-S suggests that chronic stressors will result in the HPA axis moving from a hyper-reactive system to one that becomes under-responsive (Selye, 1946). The G-A-S model predicts that initial exposure to stressors result in a phase of hypercortisolism, reflective of the body's attempts to overcome the stressor. Critically, if the hypercortisolism phase is prolonged, it may ultimately result in modifications within the HPA axis resulting in reduced cortisol production, and ultimately hypocortisolism (Guilliams & Edwards, 2010; Selye, 1946). As depicted in Figure 2, the G-A-S model proposes an inverted U-shaped function to describe the stress response within individuals over time (Guilliams & Edwards, 2010; Selye, 1946). Like allostatic load/overload models, the G-A-S model considers the long-term impact of adversity on stress-reactivity as a contributing factor to the development of disease (Selye, 1946). For example, according to the G-A-S, various pathologies including hypertension, rheumatoid arthritis, allergies, and diabetes are by-products of these endocrine reactions (Selye, 1950).

Figure 2: Graphical depiction of relationship between duration of adversity and HPA axis reactivity as proposed by the G-A-S model (Selye, 1946). According to this model, acute stressors result in a phase of hypercortisolism; however, if exposure to adversity persists long-term, hypocortisolism will occur.

1.2.3 Adaptationist perspectives

The view that chronically elevated stress reactivity results in pathophysiology has been challenged by adaptationist perspectives suggesting that high reactivity phenotypes may be protective and beneficial under specific environmental conditions and may even result in normative or improved health outcomes (Boyce & Ellis, 2005). In a study of the effects of cardiovascular and immunologic reactivity on respiratory illness incidence, highly reactive children in high-stress families had significantly higher incidence of respiratory illness as compared to children with lower cardiovascular and immunologic reactivity. Importantly however, equally reactive children in low-stress families were the healthiest of all children (Boyce, Chesney, et al., 1995). According to this observation then, heightened reactivity does not always reflect a disadvantageous response that puts the organism at risk for developing pathophysiology. Based on the notion that stress-reactivity may reflect a conditional adaptation, the *Biological Sensitivity to Context (BSC)* model was developed (Boyce & Ellis, 2005). The *BSC* is an evolutionary-developmental theory with the hypothesis that there is a curvilinear, U-shaped relationship between exposure to adversity and the development of stress-reactivity profiles – with highly stress-reactive phenotypes emerging under both extremely stressful and highly protected environments (Boyce & Ellis, 2005). Highly reactive phenotypes are defined as individuals who demonstrate vigorous and/or persistent autonomic, adrenocortical, or other biological responses to stress. Critically, Boyce and Ellis (2005) argue that biological reactivity is an evolutionary adaptive response and is a result of heightened “biological sensitivity to context”. Under this model, the paradox of reactive phenotypes being present within two extreme environmental conditions is argued to be reflective of heightened “sensitivity to context” resulting in increased vigilance to threats under stressful environments, and increased susceptibility to resources in protected environments (Boyce & Ellis, 2005). According to this theoretical model, under both protected and extremely stressful environments, HPA axis reactivity is predicted to be heightened.

The *Adaptive Calibration Model* (ACM) of stress reactivity is an extension of the *BSC* and proposes that individual differences in stress reactivity reflect conditional adaptations –the evolved ability of organisms to modify their phenotypes and developmental trajectories to fit the conditions of the local environment (Del Giudice et al., 2011). Like the *BSC* perspective, according to this view, individual differences in stress reactivity are considered adaptive mechanisms rather than the result of pathological processes (Del Giudice et al., 2011). The central premise here is that across development, information is encoded into the stress response systems that feeds back on the long-term calibration of the system itself. This plasticity of the stress response systems allows for patterns of reactivity that are optimal for the developmental environment of that organism (Boyce & Ellis, 2005; Del Giudice et al., 2011). The *ACM* expands upon the *BSC* in that it also predicts a curvilinear U-shaped relationship between adversity and HPA axis reactivity; however, due to sex differences in life-history trade-offs, in environments characterized by traumatic stress, the *ACM* predicts blunted reactivity in males (Del Giudice et al., 2011). Therefore, both the *BSC* and *ACM* models predict a curvilinear relationship between exposure to adversity and stress reactivity; moreover, they challenge the notion that exposure to adversity results in dysregulation of biological functioning and derails normal development (Del Giudice et al., 2011).

Figure 3: Graphical depiction of the relationship between severity of adversity and HPA axis reactivity as proposed by the *BSC* model (Boyce & Ellis, 2005). According to this model, HPA hyper-reactivity emerges under both protected environments with low levels of adversity and extremely stressful environments.

1.3 Empirical findings on the association between life-experiences and HPA axis reactivity

Reports of the association between early-life adversity and HPA axis reactivity in humans are inconsistent (See Tables 1-4 for summaries of the conflicting literature). Both heightened cortisol reactivity (See Table 1), and blunted cortisol reactivity (See Table 2) to a social stress task have been reported in individuals exposed to traumatic life events. Likewise, in individuals exposed to moderate levels of adversity, some studies have reported heightened cortisol reactivity (See Table 3), while others have reported blunted cortisol reactivity (See Table 4). HPA axis hyper-reactivity would be suggestive of resistance or attenuated sensitivity to glucocorticoid negative feedback, while HPA axis hypo-reactivity

would be suggestive of exaggerated HPA axis suppression following chronic activation (Berens et al 2017). Whether exposure to adversities, however, result in the HPA-axis becoming hyper-reactive or hypo-reactive remains unclear with research supporting both hyper-reactive and hypo-reactive profiles.

Two meta-analyses have reviewed the relationship between adverse early-life experiences and cortisol reactivity to a laboratory stressor in humans. One found that early-life adversity was associated with blunted cortisol release in response to social stress (Bunea et al., 2017). A more recent meta-analysis of 54 studies investigated the association between early-life adversity and various measurements of cortisol including cortisol awakening response (CAR), baseline cortisol, non-stressed cortisol over time, and cortisol reactivity to a stressor. In this meta-analysis however, there was no significant relationship between early-life adversity and any of the cortisol measurements, including cortisol reactivity (Fogelman & Canli, 2018). Taken together then, it is uncertain whether there is any evidence supporting a link between early-life adversity and cortisol reactivity, and if there is an association, in what direction the HPA-system becomes dysregulated. Both meta-analyses reported a high degree of effect size heterogeneity across studies and suggested that inconsistent operationalizations of adversity and cortisol measurements contributed to the conflicting literature. Therefore, to accurately determine the association between adverse life-experiences and cortisol reactivity, methodological differences in cortisol measurements, as well as variation in defining the terms “adversity” and “trauma” have potentially contributed to the mixed findings in the literature.

1.4 Sources of variability and confounding factors

1.4.1 Cortisol measurements

One factor that may moderate the relationship between adversity and HPA axis reactivity is between-study differences in the type and timing of cortisol measurements. Cortisol is the end-product of the HPA axis; however, variation in cortisol measurements do not necessarily reflect dysregulation at other points within the HPA axis (Nicolson, 2008). The conclusion is often made that the HPA axis has become dysregulated based solely on results obtained from cortisol values; however, even when cortisol levels are within normal ranges, other probes within the HPA axis may reflect abnormalities. For example, elevated CRH or ACTH secretion may be coupled with decreased adrenal sensitivity; therefore, while CRH and ACTH levels may be elevated, cortisol values may be within normal ranges (Nicolson, 2008). Despite the observation that variation in cortisol levels do not reflect all changes within the HPA axis, cortisol measurements are the most common way to assess HPA axis function. This is largely due to the relatively non-invasive procedures involving the collection of salivary cortisol samples. That said, there is considerable variation in how cortisol data can be obtained, including measurements obtained from urine, serum, saliva, hair, and nails (Guilliams & Edwards, 2010; Nejad et al., 2016; Nicolson, 2008). One additional benefit of obtaining salivary cortisol measurements is that the cortisol obtained from saliva is in the unbound form (free fraction used to measure HPA axis status). In contrast, the cortisol obtained through serum is bound to corticosteroid binding globulin (CBG), and the free cortisol must be separated from the bound cortisol in serum samples making its analysis more complicated (Guilliams & Edwards, 2010).

In addition to the variability introduced from the type of cortisol sample collected, there are other sources of variability including whether the cortisol measure is a *basal* measure of cortisol or a *reactivity* measure to an acute stressor. Basal measures of cortisol are used to assess spontaneous cortisol secretions, including circadian patterns of HPA axis activity; they can be measured via 24-hour

urinary sampling or repeated salivary sampling (Nicolson, 2008). One measure of circadian rhythm often used is the cortisol awakening response (CAR). Cortisol levels increase sharply during the first 30-40 minutes of waking, and the CAR measures this increase in cortisol levels. The CAR may reflect an important individual difference measure of cortisol as it appears to be relatively stable within individuals and has a genetic component (Nicolson, 2008; Wust et al., 2000). Despite this relative intra-individual stability, it appears to have some degree of sensitivity to short-term environmental influences. For example, the CAR is sensitive to the impact of stress related to a workday versus a weekend and therefore, can vary depending on the day of the week (Kunz-Ebrecht et al., 2004; Nicolson, 2008).

In contrast to basal measures of cortisol, reactivity measures assess cortisol response to acute stressors. Reactivity measures can assess cortisol response to pharmacological stimulation (e.g., Dex/CRH tests), physical stress (e.g., physical exercise or cold pressor test), emotional induction stressors (e.g., watching an emotional film, or discussing past trauma), or psychosocial stressors (e.g., Trier Social Stress Test - TSST). The type of task used to assess cortisol reactivity can introduce variability in the results obtained from such studies; further variability is also introduced in the form of timing and number of saliva samples collected (Nicolson, 2008). Among psychosocial stressors however, those that involve social-evaluative threat and are uncontrollable produce the greatest and most consistent increases in cortisol (Nicolson, 2008). Despite the utility of psychosocial stressors in providing reliable measures of cortisol reactivity, empirical findings on associations between life-experiences and cortisol reactivity to the psychosocial stress remain mixed (*See Tables 1-4*).

1.4.2 Trauma versus adversity

One major source of variation when examining relations between early-life experiences and HPA axis function is the lack of a clear definition of trauma. More troublesome is the fact that there are no conceptual boundaries to determine what constitutes “adversity” versus “trauma”. (*See Krupnik, 2019 for an excellent summary*). In some cases, a narrow definition of trauma is used in accordance with Criterion A of trauma-related disorders as defined in the DSM-V. Whereas in other cases, trauma is defined broadly and can constitute virtually any negative life event that results in lasting changes (Krupnik, 2019). As a result of the unclear definitions and boundaries of trauma and adversity, the definition of an adverse event may range from extremely negative experiences (e.g., maltreatment or sexual violence), to more mild negative experiences (e.g., the loss of a family pet or changing residences). Still others have proposed that whether a negative event is traumatic or not could depend on subjective versus objective experiences; in other words, trauma could be defined as an individual’s *subjective experience* of an event rather than exposure to it (Krupnik, 2019).

While using a diagnostic manual, such as the DSM-V to operationalize trauma allows for a precise and narrow definition, one disadvantage is that it introduces the confound of psychopathology. Adversities experienced in early childhood are a risk factor for the development of stress-related psychopathology in adulthood (Fogelman & Canli 2018; Green et al., 2010; Heim et al 2008; Nemeroff, 2004). Therefore, the impact of traumatic life experiences on stress reactivity is often confounded with the presence of comorbid post-traumatic stress disorder (PTSD) or major depressive disorder (MDD). For instance, it becomes difficult to tease apart the relative effects of maltreatment versus PTSD status on HPA axis reactivity, as many studies compare maltreated individuals with PTSD to non-maltreated individuals without PTSD (Bremner et al., 2003; Danese & McEwen, 2012; Schalinski et al., 2015). One review reported that overall, maltreated individuals exhibit heightened basal cortisol levels and tend to

have blunted cortisol reactivity to laboratory psychosocial stress tasks. Interestingly however, the review suggests that psychopathology moderates the relationship between adversity and HPA axis reactivity. In particular, healthy participants with a history of adverse life experiences produce a blunted cortisol response to a laboratory stressor, while individuals with PTSD exhibit heightened cortisol reactivity (Danese & McEwen, 2012). This underscores the importance of delineating between trauma and adversity, while taking psychopathology into account when evaluating the impact of early-life adversities on HPA axis reactivity.

1.5 Current studies: *p*-curve meta-analyses

Different theoretical frameworks make distinct predictions about the relationship between adversity and HPA axis reactivity. For example, the *G-A-S* model (Selye, 1946) and the review by Danese and McEwen (2012), predict that chronic exposure to traumatic life events should be related to blunted HPA axis reactivity, at least in individuals without any comorbid mental illnesses. In contrast, the *BSC* (Boyce & Ellis, 2005) and *ACM* models (Del Giudice et al., 2011) make the opposite predictions – namely that exposure to traumatic experiences should be related to heightened HPA axis reactivity. Empirically, the literature to date has provided contradictory results, with many studies reporting associations between adverse life-experiences and cortisol *hyper*-reactivity (See *Tables 1 and 3*), and others reporting cortisol *hypo*-reactivity (See *Tables 2 and 4*). Recent meta-analyses have also reported conflicting results (Bunea et al., 2017; Fogelman & Canli, 2018); therefore, it is unclear whether the empirical data supports a link between adverse life-experiences and HPA-axis reactivity.

P-curve is the distribution of statistically significant *p* values ($< .05$) for a set of findings, and its shape (whether it is right or left-skewed) is diagnostic of evidential value (Simonsohn, Nelson, & Simmons, 2014a). A set of findings contains evidential value only when selective reporting can be ruled out as the sole explanation for those findings, and only right-skewed *p*-curves, that is, those with more small (e.g., .01s) than large (e.g., .04s) significant *p* values, reflect evidential value (Simonsohn et al., 2014a). Importantly, *p*-curves that are not right-skewed indicate that the findings lack evidential value, and those that are left-skewed (containing more studies with *p* values around .04) suggest manipulation of data to reach the desired significance threshold (Simonsohn et al., 2014a). Conducting a *p*-curve meta-analysis may have many uses, including determining which set of contradictory findings is more likely to be correct (Simonsohn et al., 2014b; 2015).

Here, we use *p*-curve to examine the conflicting findings regarding the association between early-life experiences and HPA axis reactivity. Critically, we make a clear distinction between traumatic life experiences and adverse life experiences, and we predict differential reactivity within the HPA-axis as a function of the severity of adverse life-experiences. Furthermore, we have only included studies in these analyses that assess salivary cortisol reactivity to a laboratory-based stressor (e.g., TSST), and thus we have reduced some of the variability introduced as a result of differences in cortisol data collection. As shown in *Figure 4*, Study 1 assesses the literature reporting associations between traumatic life experiences and salivary cortisol reactivity. In Study 2, we examine the literature reporting associations between moderately adverse life experiences and salivary cortisol reactivity. When assessing each subset of results, if a right-skewed distribution of *p*-values is found, the conclusion can be drawn that there is evidential value in the findings and the results of the experiments have not been subject to selective reporting. Finding a left-skewed distribution on the other hand, would indicate a lack of evidential value and be suggestive of selective reporting. For example, in Study 1, if we find that the

literature reporting associations between trauma and cortisol hypo-reactivity contains evidential value, while the literature reporting a relationship between trauma and cortisol hyper-reactivity does not contain evidential value, we can have more confidence in the first subset of findings. Therefore, using *p*-curve to conduct these analyses will help clarify the inconsistencies in the literature and will allow us to determine which set of findings is more likely to be correct.

Figure 4: Graphical depiction of Study 1 and Study 2 aims. The orange curvilinear function represents the predictions that can be made about the relationship between adversity and HPA axis reactivity based on the G-A-S model. The U-shaped function in black represents the predictions that can be made concerning the relationship between severity of adversity and HPA axis reactivity based on the BSC model. In Study 1 (outlined in red), we will use *p*-curve to determine whether the literature reporting that exposure to trauma is related to heightened cortisol reactivity or blunted cortisol reactivity contains evidential value. In Study 2 (outlined in yellow), we will use *p*-curve to assess whether exposure to moderate adversity is related to heightened or blunted cortisol reactivity.

2 Methods

2.1 Study 1: Data sources and study selection

We conducted a thorough search of all human studies investigating the association between traumatic life experiences and cortisol reactivity to a psychosocial stressor from 1999 to 2020. The terms “trauma”, “adversity”, “stress”, “maltreatment”, and “early-life stress” are often used interchangeably in the literature; similarly, the terms “HPA-reactivity”, “cortisol reactivity” and “stress reactivity” are also used interchangeably. Therefore, we conducted a PsycINFO database search using the following terms:

((trauma or stress or adversity or early-life stress or maltreatment) and (HPA-reactivity or cortisol reactivity or stress-reactivity or cortisol hyper-reactivity or cortisol hypo-reactivity)) [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh].

The results yielded 2673 articles, we excluded articles published prior to 1999, reducing the results to 2447 articles. We imposed a further limit to include only peer-reviewed journals and human literature, which reduced the results to 1663 articles. These 1663 articles went to abstract review from the PsycINFO database search. For the purposes of this study, we were interested in human studies of traumatic life experiences. In accordance with DSM-5, the experience must have included qualifying

events for post-traumatic stress disorder (PTSD). Furthermore, we were interested in salivary cortisol reactivity to a laboratory stressor, thus basal or diurnal cortisol measurements and plasma or urine cortisol measurements were excluded. Based on these inclusion criteria, we selected 51 articles from the PsycINFO search to include in the *p*-curve analyses (See Figure 5).

To be thorough, we also conducted a PubMed database search using the following terms:

(((((((((trauma[Title/Abstract]) OR stress[Title/Abstract]) OR early-life stress[Title/Abstract]) OR adversity[Title/Abstract]) OR maltreatment[Title/Abstract]) AND HPA-reactivity[Title/Abstract]) OR cortisol reactivity[Title/Abstract]) OR stress-reactivity[Title/Abstract]) OR cortisol hyper-reactivity[Title/Abstract]) OR cortisol hypo-reactivity[Title/Abstract] AND (Humans[Mesh])).

The search yielded 2645 results, we excluded studies that were not conducted with human participants, and 1827 articles remained. These 1827 articles were reviewed for relevance according to their title. Of the 1827 articles, 59 articles went to full abstract review. When duplicates of the PsycINFO search results were removed and inclusion criteria were applied, 12 additional articles were added to the *p*-curve analyses (See Figure 6). An additional 5 articles were included from the reference sections of other articles in the searches (See Figure 7).

The following inclusion criteria were applied:

- 1.) Must be an empirical study with human participants
- 2.) Must measure traumatic life experiences in accordance with DSM-5 criteria:
Exposure to: death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence, in the following way(s): direct exposure; witnessing the trauma; learning that a relative or close friend was exposed to a trauma; indirect exposure to aversive details of the trauma, usually in the course of professional duties (e.g., first responders, medics) (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM–5]; American Psychiatric Association, 2013).
- 3.) Must include salivary cortisol reactivity to a laboratory stressor

2.1.1 Study 1: Study sample

The final pool included 68 unique articles published from 1999-2020. Of these 68 articles, 2 articles were included in both the hyper and hypo-reactivity *p*-curve analyses, because one portion of the results showed hyper-reactivity profiles, while the other showed hypo-reactivity profiles. For instance, in one study, trauma experienced before age 11 resulted in cortisol hyper-reactivity, while trauma experienced after age 11 resulted in cortisol hypo-reactivity (Bosch et al., 2012), therefore, this study was included in both the hyper-reactivity and hypo-reactivity *p*-curve analyses. Thus, the hypo-reactivity *p*-curve analysis included 48 results and the hyper-reactivity *p*-curve analysis included 22 results.

Figure 5: Flowchart - PsycINFO database search (trauma and cortisol reactivity)

Figure 6: Flowchart - PubMed database search (trauma and cortisol reactivity)

Figure 7: Number of articles included from each database

2.2 Study 2: Data sources and study selection

We conducted a search of human studies investigating the association between moderately adverse life experiences and cortisol reactivity to a psychosocial stressor from 1999 to 2020. We conducted a PsycINFO database search using the following terms:

((((stress or adversity) and HPA-reactivity) or cortisol reactivity or stress-reactivity or cortisol hyper-reactivity or cortisol hypo-reactivity). ab.

The search yielded 2515 results, we excluded articles published prior to 1999, reducing the results to 2350 articles. We imposed a further limit to include only English-language, peer-reviewed articles with human participants, which reduced the results to 1597 articles. These 1597 articles went to abstract review from the PsycINFO database search. For the purposes of this study, we were interested in human studies of moderately adverse life experiences (e.g., low SES, daily hassles, parental conflict). To ensure that we included only articles with moderately adverse life experiences, articles that measured traumatic experiences were **excluded**. Trauma was defined in accordance with DSM-5 criteria for qualifying events for post-traumatic stress disorder (PTSD). Once again, we were interested in salivary cortisol reactivity to a laboratory stressor as the outcome measure. Based on these inclusion criteria, we selected 23 articles from the PsycINFO search to include in the *p*-curve analyses (See Figure 8).

We also conducted a PubMed database search using the following terms:

(((((Stress[Title/Abstract]) OR (Adversity[Title/Abstract])) AND (HPA-reactivity[Title/Abstract])) OR (cortisol-reactivity[Title/Abstract])) OR (stress-reactivity[Title/Abstract])) OR (cortisol hyper-reactivity[Title/Abstract])) OR (cortisol hypo-reactivity[Title/Abstract])

The search yielded 2800 results, we excluded studies that were published prior to 1999 resulting in 2681 remaining articles. Next, we excluded articles that were not written in the English language, were not peer-reviewed or were animal studies, resulting in 1784 articles. Of these 1784 articles, 1268 were duplicates of the PsycINFO search and were therefore excluded, resulting in 516 articles that went to abstract review. After the abstract review, based on the inclusion criteria, 3 additional articles were included in the *p*-curve analyses (See Figure 9). Finally, an additional 4 articles were included from the reference sections of other articles (See Figure 10).

The following inclusion criteria were applied:

1. Must include empirical studies with human participants
2. Must measure moderately adverse life experiences (excluding severe adversity/trauma)
3. Must include salivary cortisol reactivity to a laboratory stressor

2.2.1 Study 2: Study sample

The final pool included 30 unique articles published from 1999-2020. Of these 30 articles, one article was included in both the hyper and hypo-reactivity *p*-curve analyses, because for males, adverse life experiences resulted in blunted cortisol reactivity, whereas for females, adverse life experiences resulted in heightened cortisol reactivity (Fearon et al., 2017). Therefore, this study was included in both

the hyper-reactivity and hypo-reactivity p -curve analyses. In total, the hypo-reactivity p -curve analysis included 16 results, and the hyper-reactivity p -curve analysis included 15 results.

Figure 8: Flowchart - PsycINFO database search (adversity and cortisol reactivity)

Figure 9: Flowchart - PubMed database search (adversity and cortisol reactivity)

Figure 10: Number of articles included from each database

2.3 *P*-curve data abstraction

We separated the articles from both the PsycINFO and PubMed searches into the following four groups:

- (1) The group of articles reporting that traumatic experiences are related to subsequent cortisol hyper-reactivity;
- (2) The group of articles reporting that traumatic experiences are related to subsequent cortisol hypo-reactivity;
- (3) The group of articles reporting that adverse experiences are related to subsequent cortisol hyper-reactivity; and
- (4) The group of articles reporting that adverse experiences are related to subsequent cortisol hypo-reactivity

Following open-science guidelines, we created four *p*-curve disclosure tables—one for each set of results (See *Tables 1-4*). The disclosure tables include the study reference, hypothesis of interest to the researchers, sample characteristics, measure of trauma, stress induction task, cortisol measurement, data analysis plan, the actual result subjected to *p*-curve analysis, the exact *p*-value, and the conclusion drawn by the authors of the paper. We followed the methods provided by Simonsohn et al. 2014a to conduct the *p*-curve analysis. Whenever there were more than two relevant *p*-values, we selected the *p*-value reported first; and in ANOVAs if an attenuation was predicted, the interaction statistic was selected for *p*-curve analysis (Simonsohn et al., 2014a). After creating the disclosure tables and obtaining all relevant results, we conducted four separate *p*-curves for each set of results. Conducting these *p*-curve analyses would determine which set of results, if any, contains evidential value. All *p*-curves were calculated using an online tool (<http://www.p-curve.com/app4/>).

3 Results

3.1 *Study 1.1: Traumatic experiences and cortisol hyper-reactivity p-curve*

We first aimed to determine whether a history of experiencing traumatic events was related to heightened cortisol reactivity. Based on our research results, 22 studies reported evidence of cortisol hyper-reactivity to a stressor after having experienced traumatic life events. To determine whether evidential value is present in this set of findings, we conducted a *p*-curve analysis of all 22 reported results. As outlined in Simonsohn et al. (2014a; 2015), a set of results contains evidential value if either the half *p*-curve (*p*-values below .025) is significantly right-skewed at $p < .05$, or if both the half *p*-curve and full *p*-curve are significantly right-skewed at $p < .10$. The *p*-curve for this set of results was not significantly right-skewed (half: $z = -1.12$, $p = .1321$; full: $z = -1.62$, $p = .0531$). Neither condition was met in this case (See *Figure 11*); therefore, the *p*-curve did not indicate evidential value. Moreover, as shown in *Figure 12*, these results do not hinge upon a few extreme observations of *p*-values. If we remove the smallest and largest *p*-values, the conclusion drawn from *p*-curve would not be much different from what we observed when we included all 22 *p*-values in the analysis. In other words, if we drop the largest *p*-values from this set of literature, the resultant *p*-curve would still not be significantly right-skewed

Figure 11: Trauma-Cortisol Hyper-reactivity *p*-curve. The blue line shows the distribution of *p*-values from the data (22 statistically significant results). For example, 41% of the significant *p* values were between .01 and .02. The red dotted line shows the expected distribution of *p* values if there were no effect. The green dashed line shows the distribution of *p* values if an effect existed with studies powered at 33%. $N = 22$ *p* values, *p*-curve is not significantly right-skewed.

Figure 12: Dropping the lowest and highest *p* values on the significance of right-skewness of the full *p*-curve (top row), half *p*-curve (middle row), and the test for flatness relative to 33% power (bottom row). The red solid line demonstrates the significance threshold of $p = .05$. The filled circle demonstrates the results reported in the text, the open circle demonstrates the results relative to the significance level if (*k*) number of *p*-values were dropped.

According to the guidelines provided by Simonsohn et al (2014a; 2015), a follow-up test should be conducted when p -curve is not significantly right-skewed, namely, testing whether it is flatter than one would expect if studies were powered at only 33%. Therefore, we compared the observed p -curve with the p -curve that would be expected if the studies had an average power of 33%. An absence of evidential value can be concluded if the full p -curve is significantly flatter than the p -curve of 33% power at $p < .05$, or if both the half p -curve and binomial tests are significant at $p < .10$. In this case, these conditions were not met (half: $z = -3.4$, $p = .9997$; full: $z = -1.16$, $p = .1236$; binomial: $p = .3051$). Thus, we could not conclusively reject the null that the set of studies contains a small, but detectable effect. In other words, while the p -curve was not significantly right-skewed and did not indicate evidential value; p -curve could not reject a very small effect and could not indicate that evidential value was totally absent. Therefore, the conclusion from this set of findings is inconclusive, the current p -curve is too noisy to reject the possibility of a small effect and at the same time, does not provide support for the existence of evidential value. In this case, more p -values are required to determine whether the studies contain evidential value for a small effect. We must, however, keep in mind that the average power for this set of studies was low. In the case of studies investigating a relationship between having had traumatic life experiences and cortisol hyper-reactivity to a laboratory stressor, the power is 16%, 90% CI [5,42]. Based on this, if the same studies were done again, only 16% of them would detect a significant result.

To be thorough and to follow the exact guidelines provided by Simonsohn et al. (2014a), we also conducted a robustness test for the above p -curve. In the robustness p -curve analysis, 3 alternative p -values were included in the analysis. The results remained unaltered with the robustness check; that is, the test for evidential value was nonsignificant (half: $z = -1.23$, $p = .1086$; full: $z = -1.2$, $p = .1147$). The follow-up analysis determined that the p -curve was not significantly flatter than if the studies were, on average, powered at 33% (half: $z = 3.26$, $p = .9994$; full: $z = -1.5$; $p = .0668$; binomial $p = .0817$), and the estimate of average power was 12%, 90% CI [5,36]. Finally, because the experience of traumatic events is related to the diagnosis of certain psychopathologies, we aimed to ensure that these results were not driven by comorbid psychopathology. Therefore, we removed 6 studies that included patients with PTSD/MDD from the original 22 studies. The results of the p -curve analysis did not change. Neither of the conditions of p -curve were met, and the p -curve was not significantly right-skewed (half: $z = -0.25$, $p = .3996$; full: $z = -1.48$, $p = .0692$; *See Supplementary Results for further details*).

3.2 Study 1.2: Traumatic experiences and cortisol hypo-reactivity p -curve

Next, we determined whether the literature reporting a relationship between the experience of traumatic events and cortisol hypo-reactivity to a laboratory stressor contained evidential value. Our literature search yielded 48 results that were included in the cortisol hypo-reactivity p -curve analysis. Again, a set of results contains evidential value if either the half p -curve is significantly right-skewed at $p < .05$, or if both the half and full p -curves are significantly right-skewed at $p < .10$. The p -curve for the 47 results was significantly right-skewed (half: $z = -5.37$, $p < .0001$; full: $z = -5.85$, $p < .0001$). In this case, both conditions were met, and the p -curve demonstrates that these results contain evidential value (*See Figure 13*). Once again, as illustrated in *Figure 14*, these results do not hinge upon extreme observations and were not altered by removing extreme observations of p -values from the original analysis. The studies investigating the association between traumatic life experiences and cortisol hypo-reactivity also have higher power than those of the hyper-cortisol reactivity set; in this case, the power is 46%, 90% CI [29,63].

Figure 13: Trauma-Cortisol Hypo-reactivity p-curve. The blue line shows the distribution of p-values from the data (48 statistically significant results). For example, 40% of the significant p values were below .01. The red dotted line shows the expected distribution of p values if there were no effect. The green dashed line shows the distribution of p values if an effect existed with studies powered at 33%. $N = 48$ p values, **p-curve is significantly right-skewed**

Figure 14: Dropping the lowest and highest p values on the significance of right-skewness of the full p-curve (top row), half p-curve (middle row), and the test for flatness relative to 33% power (bottom row). The red solid line demonstrates the significance threshold of $p = .05$. The filled circle demonstrates the results reported in the text, the open circle demonstrates the results relative to the significance level if (k) number of p-values were dropped.

We also conducted a robustness test for this p -curve in accordance with the guidelines provided by Simonsohn et al. (2014a; 2015). Six alternative p -values were included in the p -curve and the results remained unaltered with the robustness check; the test for evidential value remained significant (half: $z = -3.9$, $p < .0001$; full: $z = -4.63$, $p < .0001$), and the estimate of average power was 35%, CI 90% [19,53].

Once again, to ensure that these results were not driven by underlying psychopathology within the participants of the studies, we removed 4 studies that included participants with PTSD/MDD. Once again, the two conditions that determine whether a p -curve is significantly right-skewed were met; therefore, the p -curve for this set of results was significantly right-skewed (half: $z = -5.5$, $p < .00001$; full: $z = -6.53$, $p < .00001$; See *Supplementary Results for further details*).

3.3 Study 2.1: Adverse experiences and cortisol hyper-reactivity p -curve

To determine whether evidential value exists in the literature reporting associations between moderate adversity and heightened cortisol reactivity, we conducted a p -curve analysis of 15 results from our search. The p -curve for the 15 results was significantly right-skewed (half: $z = -2$, $p = .0227$; full: $z = -1.56$, $p = .0598$). The p -curve demonstrates that these results contain evidential value (See *Figure 15*). Once again, as demonstrated in *Figure 16*, these results do not hinge upon extreme observations and are not altered by removing extreme observations of p -values from the original analysis. However, the estimate of power for tests included in this p -curve was only 19%, 90% CI [5,50].

Figure 15: Adversity-Cortisol Hyper-reactivity p -curve. The blue line shows the distribution of p -values from the data (15 statistically significant results). For example, 53% of the significant p values were below .01. The red dotted line shows the expected distribution of p values if there were no effect. The green dashed line shows the distribution of p values if an effect existed with studies powered at 33%. $N = 15$ p values, p -curve is significantly right-skewed.

Figure 16: Dropping the lowest and highest p values on the significance of right-skewness of the full p -curve (top row), half p -curve (middle row), and the test for flatness relative to 33% power (bottom row). The red solid line demonstrates the significance threshold of $p = .05$. The filled circle demonstrates the results reported in the text, the open circle demonstrates the results relative to the significance level if (k) number of p -values were dropped.

For the robustness test for this p -curve, we entered six alternative p -values. The test for evidential value remained significant (half: $z = -3.31$, $p = .0005$; full: $z = -2.84$, $p = .0023$), and the estimate of average power was 39%, CI 90% [13,68].

3.4 Study 2.2: Adverse experiences and cortisol hypo-reactivity p -curve

Based on our literature search, we found 16 studies that reported results showing that a history of moderately adverse life experiences was related to cortisol hypo-reactivity. We entered these results into p -curve to determine whether this set of literature contains evidential value. In this case, the two conditions that determine whether a p -curve is significantly right-skewed were not met; that is, the half p -curve was not significantly right-skewed at $p < .05$, and both the half and full p -curves were not significantly right-skewed at $p < .10$. Therefore, as shown in Figure 17, the p -curve for this set of results was not significantly right-skewed (half: $z = -1.58$, $p = .0572$; full: $z = -0.4$, $p = .3453$). Figure 18 shows that these results do not change if we remove the largest p -values and the conclusion drawn from the p -curve would remain unaltered.

Figure 17: Cortisol hypo-reactivity p -curve. The blue line shows the distribution of p -values from the data (16 statistically significant results). For example, 31% of the significant p values were between .01 and .02. The red dotted line shows the expected distribution of p values if there were no effect. The green dashed line shows the distribution of p values if an effect existed with studies powered at 33%. $N = 16$ p values, p -curve is not significantly right-skewed

Figure 18: Dropping the lowest and highest p values on the significance of right-skewness of the full p -curve (top row), half p -curve (middle row), and the test for flatness relative to 33% power (bottom row). The red solid line demonstrates the significance threshold of $p = .05$. The filled circle demonstrates the results reported in the text, the open circle demonstrates the results relative to the significance level if (k) number of p -values were dropped.

Next, we conducted the follow-up test required when p -curve is not significantly right-skewed (Simonsohn et al., 2014a; 2015). That is, we tested whether the p -curve is flatter than one would expect if studies entered into the analysis were powered at 33%. An absence of evidential value can only be concluded if the full p -curve is significantly flatter than the p -curve of 33% power at $p < .05$. In this case, the full p -curve was significantly flatter than the p -curve of 33% (full: $z = -1.86$, $p = .0313$), indicating that evidential value is inadequate or absent. Here, we reject the null of a small effect against an alternative of an even smaller effect and we conclude that this set of studies lacks evidential value, meaning that either the effect does not exist or it is too small for us to rule out selective reporting as an alternative explanation. In other words, these results demonstrate that direct replications of the submitted studies are not expected to succeed; the estimated power of these studies was 7%, 90% CI [5,29].

In the robustness p -curve analysis, 4 alternative p -values were included in the analysis. The results remain unaltered, the test for evidential value was nonsignificant (half: $z = -1.6$, $p = .0548$; full: $z = -0.45$, $p = .3254$); the full p -curve was significantly flatter than if the studies were powered at 33% (full: $z = -1.8$; $p = .0358$), and the estimate of average power was 7%, 90% CI [5,30].

4 Discussion

Empirical reports of how life experiences are related to HPA axis reactivity remains contradictory, with some studies reporting that adverse experiences are related HPA axis hyper-reactivity and others reporting HPA axis hypo-reactivity (See *Tables 1-4*). Here, we have conducted a systematic review of the literature and used p -curve meta-analytic techniques to resolve some of the apparent inconsistencies in the reported findings. Critically, in the current meta-analyses, we operationalized our criteria for life experiences very carefully. In the literature, the term “adversity” is defined broadly with adverse events ranging from mild adversities (e.g., changing schools) to extreme trauma (e.g., sexual abuse); therefore, one factor in contributing to the mixed findings may be the lack of consensus on appropriate definitions of adverse life events versus a traumatic life events (Krupnik, 2019). One strength of the analyses conducted here is that the terms trauma and adversity were clearly delineated. Traumatic life events were defined in accordance with DSM-5 criteria for qualifying events for the development of PTSD. In contrast, adverse life events were defined as stressors experienced throughout development that were *not* traumatic (e.g., low SES, parental conflict). Therefore, by including studies that were comparable in each meta-analysis, we were able to test specific hypotheses about the relationship between the severity of adverse life experiences and HPA axis reactivity.

In Study 1, we used p -curve to examine the literature reporting a relationship between traumatic life experiences and HPA axis reactivity. The literature here was mixed in that some studies reported HPA axis hyper-reactivity after exposure to trauma, while others reported HPA axis hypo-reactivity. The p -curve analyses here provided support for the evidence linking trauma with blunted HPA-axis reactivity. The p -curve of the HPA hyper-reactivity literature was inconclusive in that while it did not show a significantly right-skewed p -curve, it also did not demonstrate a curve flatter than one would expect if the studies were powered at only 33%. Therefore, in this case, the p -curve was too noisy to determine whether a very small effect exists or not. This limitation of the current meta-analysis may be reflective of the lack of power in the studies that were included in the HPA hyper-reactivity p -curve analysis. Importantly, the studies that were entered into the p -curve analysis for the literature reporting blunted HPA reactivity had higher power than those in the literature reporting HPA hyper-reactivity. Overall then, we can be more confident in the literature linking traumatic life events to a blunting of cortisol

reactivity given that the p -curve of these studies was significantly right-skewed and the studies entered into the meta-analysis had greater statistical power.

In Study 2, we examined the literature reporting relations between moderately adverse life events and HPA axis reactivity. In contrast to Study 1, here we found that the literature reporting an association between adverse life events and HPA axis hyper-reactivity contained evidential value. Conversely, the literature reporting HPA axis hypo-reactivity after exposure to moderately adverse life events did not contain evidential value. In this case, because we were able to conclude that evidential value was lacking, we were able to demonstrate that the effect of HPA axis hypo-reactivity after exposure to moderately adverse life events either does not exist, or we cannot exclude selective reporting as an alternative explanation for the findings. Therefore, the p -curve analyses conducted in Study 2 demonstrate that we can have much more confidence in the literature reporting HPA axis hyper-reactivity after exposure to moderately adverse life events.

The p -curve results of the current analyses support the notion that under traumatic life conditions, the HPA-system becomes desensitized and exhibits a blunted reaction to laboratory stressors. In contrast, the results indicate that under moderately adverse conditions, the HPA axis becomes hyper-reactive. These results are consistent with the predictions made by Danese and McEwen (2012), in that they reveal that the literature reporting blunted cortisol reactivity after exposure to traumatic events contains evidential value. However, Danese and McEwen (2012) predicted that underlying psychopathology moderates the association between adversity and HPA axis reactivity. Specifically, they expected that after exposure to adversity, cortisol reactivity would be heightened in individuals with underlying psychopathology, and blunted in healthy individuals. While we could not completely control for the confound of underlying PTSD, when we removed studies that explicitly mentioned underlying mental illnesses in their study sample, the results remained unaltered. Consistent with the predictions of Danese and McEwen (2012), this demonstrates that in otherwise healthy individuals, exposure to trauma is related to blunted cortisol reactivity. Similarly, these findings are congruent with predictions that can be made using the G-A-S model; according to this model, if exposure to an acute stressor becomes chronic, the HPA axis will move from a hyper-responsive system to a hypo-responsive one. While the G-A-S model does not precisely describe associations between HPA axis reactivity and severity of adversity, the assumption can be made that the body only reaches the “exhaustion stage” reflected by blunted cortisol reactivity if stressors are either chronic or severe.

In contrast, the p -curve analyses conducted here do not provide direct support for the BSC model. According to this model, we would have expected HPA hyper-reactivity in individuals who had experienced traumatic life events, and HPA hypo-reactivity in individuals who had experienced moderately adverse life events. Our p -curve analyses, however, provides evidence for the opposite effect. The results lend support to an *inverted* U-shaped relationship between severity of adversity and cortisol reactivity, while the BSC model predicts a U-shaped function. One potential explanation is that HPA axis reactivity is only one aspect of “biological reactivity”, it could be the case that biological reactivity as measured by heart rate variability, respiratory sinus arrhythmia (RSA), or preejection period (PEP), could provide evidence in support of the BSC model. Furthermore, it could also be the case that the range of experiences that the BSC makes predictions about are all within “normative” experiences; that is, the BSC may be making predictions about variability in experiences ranging from highly protected environments to moderately stressful, but not traumatic environments. Careful examination of the empirical study used to provide evidence for the BSC model lends support to this idea, as the

measures of adversity used were moderately adverse (e.g., family discord, SES, and family stress; Ellis et al., 2005). Consistent with the findings of the *p*-curve analyses, the authors reported that adversity was associated with heightened cortisol reactivity (Ellis et al., 2005). According to the *BSC* paradigm, the paradox of biologically reactive phenotypes being present under both protected and stressful environmental conditions is reflective of a heightened “sensitivity to context”. This heightened sensitivity is said to be adaptive to organisms as it results in increased vigilance to threats under stressful environments, and increased susceptibility to resources under protected environments (Boyce & Ellis, 2005). While individual differences in genotype may result in differential sensitivity to the environment, this differential sensitivity does not translate to heightened cortisol reactivity under extremely stressful environments as defined by exposure to traumatic events. It could be the case that individuals who are highly sensitive to their environments experience a form of “helplessness” when faced with extremely traumatic situations and exhibit blunted HPA axis reactivity.

Based on the literature and the results of these *p*-curve meta-analyses, there appears to be an inverted-U shaped relationship between severity of adversity and cortisol reactivity. Exposure to traumatic life experiences is related to blunted HPA axis reactivity, while exposure to moderate adversities is related to heightened HPA axis reactivity. The role that glucocorticoid release plays in glucose metabolism and the body’s expenditure of resources may partially explain these relationships. When exposed to stressful experiences, glucocorticoids are produced and result in increased availability of energy resources to facilitate “fight or flight” responses (Del Rey et al, 2008). Under chronically stressful or traumatic conditions, “fight or flight” may not be feasible, and thus, the organism’s physiology may adapt in a manner that does not waste energy resources. If the organism perceives the situation as completely inescapable, there is little utility in releasing glucocorticoids and mobilizing energy resources unnecessarily. On the other hand, a history of exposure to moderate levels of adversity may signal that the likelihood of success in overcoming the stressors is high. In this case, the organism’s physiology may adjust in a manner to release energy resources in the face of acute stressors.

The inverted U-shaped relation between severity of adversity and stress reactivity corresponds closely to Hans Selye’s *G-A-S* model, which suggests that chronic stressors will result in the HPA axis moving from a hyper-reactive system to one that becomes under-responsive (Selye, 1946). The *G-A-S* model views hypocortisolism as a harmful response with significant clinical implications (Selye, 1946). However, it may be the case that the hypocortisolism in response to traumatic experiences reflects the body’s tendency to use biological resources only under appropriate environmental circumstances. The evidence obtained from the current *p*-curve analyses provides partial support for the inverted U-shaped function. Indeed, we found support for the hypotheses that after experiencing traumatic life events, the HPA axis exhibits blunted reactivity; while after experiencing moderate levels of adversity, the HPA axis exhibits heightened reactivity. What remains to be tested however, is how the HPA axis responds under conditions of little to no adverse experiences.

The finding that the HPA axis becomes differentially reactive according to the severity of adversity experienced highlights the importance of having clear definitions for traumatic versus adverse events. Indeed, the lack of consensus regarding definitions of adversity and trauma may have contributed to the mixed findings reported to date (Bunea et al., 2017; Fogelman & Canli, 2018; Krupnik, 2019). If clear boundaries are set for what is objectively considered traumatic versus adverse, we may be able to find more reliable patterns in the findings reported in the literature. That said, using DSM-5 criteria for determining traumatic life events is not the only method available. One limitation of using

DSM-5 criteria to define traumatic life events is that it introduces a confound of stress-related psychopathology into the analysis. In fact, many individuals that experience traumatic life events (as defined using DSM-5 criteria) will also fit the criteria for the development of PTSD and other stress-related disorders. We were able to partially control for this confound in our analyses by excluding studies that explicitly reported psychopathology in their study samples (*See Supplementary Analyses*). However, it is possible that other studies included in the analyses did not directly measure or report psychopathology within their samples; as such, we cannot be certain that the participants in those studies did not also have stress-related psychopathology. Nevertheless, not all individuals who experience traumatic life events will develop PTSD or other stress-related disorders. Therefore, using DSM-5 criteria to define traumatic events may differentiate trauma from adversity, but it may or may not introduce the confound of psychopathology into the analysis.

A recent model suggests that any stressor can be traumatic if its severity overwhelms self-regulatory processes. The model proposes that individuals with compromised or under-developed self-regulation (e.g., children) are most vulnerable to becoming traumatized; this view of trauma may help explain sensitive periods in HPA axis calibration. Future research should investigate whether there are age-related differences in the HPA axis reactivity as a function of exposure to traumatic versus adverse life events. If the hypothesis that individuals with under-developed self-regulation are more vulnerable to the effects of life-experiences is correct, children who have experienced moderate adversity may demonstrate blunted cortisol reactivity. In other words, only moderate levels of adversity may be sufficient to produce a biological profile in children akin to what adults demonstrate after traumatic events. Finally, the analyses here investigated literature reporting associations between traumatic versus adverse life experiences and HPA axis reactivity. Basal HPA axis function as measured by CAR, however, could provide different results. It could be the case, for example, that traumatic life experiences result in heightened basal cortisol levels, but blunted cortisol reactivity (Danese & McEwen, 2012). Future research should investigate the literature assessing associations between life experiences and basal cortisol measures as it may help further clarify the contradictory results in the field.

4.1 Conclusion

Understanding how life-experiences become biologically embedded is of great interest to researchers. The HPA axis is one biological system that exhibits plasticity to environmental conditions and has been shown to become differentially calibrated as a function of life experiences. Various theoretical models make different predictions about how life experiences are related to HPA axis reactivity. Empirical evidence investigating the relationship between life-experiences and HPA axis reactivity, however, is mixed. *P*-curve is the distribution of statistically significant *p*-values for a set of findings and can be used as a powerful tool when literature on a given topic provides mixed results. *P*-curve can determine which subset of contradictory results contains evidential value. Here, we used *p*-curve as a tool to determine how traumatic and adverse life experiences are related to HPA-axis function. We found that the literature reporting an association between traumatic experiences and cortisol hyper-reactivity was inconclusive, while the literature reporting an association between traumatic experiences and cortisol hypo-reactivity contained evidential value. Moreover, when we assessed the literature reporting associations between adverse life experiences and cortisol reactivity; we found the opposite pattern of results. That is, we found that the literature reporting an association between moderately adverse life experiences and cortisol hyper-reactivity contained evidential value, while the literature reporting cortisol hypo-reactivity did not. These results help clarify the mixed

findings in the literature and they provide support for an inverted U-shaped relationship between severity of adversity and HPA axis reactivity. Moreover, the results of these analyses highlight the importance of having clear definitions and conceptual boundaries for defining the terms “adversity” and “trauma”.

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Supplementary Results

Cortisol hypo-reactivity in healthy participants– removed PTSD/MDD Patients

From the original 48 studies included, 4 were removed because the sample included participants with PTSD/MDD. Therefore, 44 studies were entered that that reported results showing that a history of traumatic life experiences was related to cortisol hypo-reactivity in healthy patients. We entered these results into *p*-curve to determine whether this set of literature contains evidential value. In this case, the two conditions that determine whether a *p*-curve is significantly right-skewed were met; therefore, as shown in Figure x, the *p*-curve for this set of results was significantly right-skewed (half: $z = -5.5$, $p < .00001$; full: $z = -6.53$, $p < .00001$). As shown in Figure x, these results do not change if we remove the highest *p*-values and the conclusion drawn from the *p*-curve would remain unaltered.

Note: The observed *p*-curve includes 44 statistically significant ($p < .05$) results, of which 31 are $p < .025$. There were no non-significant results entered.

Figure 3. Cortisol hypo-reactivity *p*-curve. The blue line shows the distribution of *p*-values from the data (44 statistically significant results). For example, 43% of the significant *p* values were below .01. The red dotted line shows the expected distribution of *p* values if there were no effect. The green dashed line shows the distribution of *p* values if an effect existed with studies powered at 33%. $N = 44$ *p* values, *p*-curve is significantly right-skewed.

Figure 4. Dropping the lowest and highest p values on the significance of right-skewness of the full p -curve (top row), half p -curve (middle row), and the test for flatness relative to 33% power (bottom row). The red solid line demonstrates the significance threshold of $p = .05$. The filled circle demonstrates the results reported in the text, the open circle demonstrates the results relative to the significance level if (k) number of p -values were dropped.

An additional test was conducted to remove all studies that had used any patient samples (e.g., anorexia, chronic fatigue syndrome etc.), therefore, this analysis included studies with only healthy participants. Forty results were entered into p -curve and once again, this set of results contained evidential value as the p -curve was significantly right-skewed (half: $z = -6.19$, $p < .00001$; full: $z = -6.47$, $p < .00001$). As shown in Figure x, these results do not change if we remove the highest p -values and the conclusion drawn from the p -curve would remain unaltered.

Note: The observed p -curve includes 40 statistically significant ($p < .05$) results, of which 27 are $p < .025$. There were no non-significant results entered.

Cortisol hyper-reactivity p -curve in healthy participants

We removed 6 studies that included patients with PTSD/MDD from the original 22 studies. The results of the p -curve analysis did not change. Neither of the conditions of p -curve were met, and the p -curve was not significantly right-skewed (half: $z = -0.25$, $p = .3996$; full: $z = -1.48$, $p = .0692$). P -curve indicates that evidential value is inadequate or absent if the 33% power test is $p < .05$ for the full p -curve or if both the half p -curve and binomial 33% power test are $p < .1$. Here, neither condition was met, the test for 33% power was not significant (half: $z = -2.63$, $p = .9957$; full: $z = -0.93$, $p = .1766$; Binomial test $p = .5238$). Therefore, like the results obtained with all data entered, the p -curve for the subset of studies that were entered (excluding those with patients with PTSD/MDD) was inconclusive.

Note: The observed p -curve includes 16 statistically significant ($p < .05$) results, of which 11 are $p < .025$. There were no non-significant results entered.

Figure 5. Cortisol hyper-reactivity p -curve. The blue line shows the distribution of p -values from the data (16 statistically significant results). For example, 19% of the significant p values were below .01. The red dotted line shows the expected distribution of p values if there were no effect. The green dashed line shows the distribution of p values if an effect existed with studies powered at 33%. $N = 16$ p values, **p -curve is not significantly right-skewed.**

Figure 6. Dropping the lowest and highest p values on the significance of right-skewness of the full p -curve (top row), half p -curve (middle row), and the test for flatness relative to 33% power (bottom row). The red solid line demonstrates the significance threshold of $p = .05$. The filled circle demonstrates the results reported in the text, the open circle demonstrates the results relative to the significance level if (k) number of p -values were dropped.

An additional test was conducted to remove all studies that had used any patient samples (e.g., social anxiety disorder, fibromyalgia etc.), therefore, this analysis included studies with only healthy participants. Thirteen results were entered into p -curve and once again, the conclusions previously drawn were not altered. This set of results did not contain evidential value as the p -curve was not significantly right-skewed (half: $z = -0.33$, $p = .3713$; full: $z = -1.33$, $p = .091$). The test for 33% power was also not significant (half: $z = -2.43$, $p = .9924$; full: $z = -0.85$, $p = .1985$; Binomial test $p = .5239$). As shown in Figure x, these results do not change if we remove the highest p -values and the conclusion drawn from the p -curve would remain unaltered.

Note: The observed p -curve includes 13 statistically significant ($p < .05$) results, of which 9 are $p < .025$. There were no non-significant results entered.

Original Paper	Quoted text from original paper indicating prediction of interest	Sample Characteristics	Type of Trauma	Stress Induction Task	Cortisol Measurement	Data Analysis Plan	Quoted text from original paper with statistical results	Results	P-value	Conclusion quoted from original text
Kern & Laurent 2019	We expected that women's reported history of childhood maltreatment at 3 months postnatal would predict greater cortisol reactivity to mother-infant stress at 12 months postnatal, which would predict higher affective symptoms (controlling for 12-month symptoms) at 18 months postnatal.	Participants were the 47 women from a larger longitudinal study of mother-infant stress regulation who completed all measures involved in the current study.	CTQ: The CTQ uses 25 items scored on a 5-point Likert scale (from 1 = "never" to 5 = "very often") to assess the occurrence during childhood of five forms of maltreatment: physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect.	The Strange Situation (SS) involves seven 3-minute episodes in which the infant is twice separated from the mother—first with an unfamiliar female "stranger" in the room, then with no one in the room—before being reunited; during separations, women were able to watch their infant on a remote computer monitor. This task has been shown to elicit behavioral and physiological stress responses in infants and their mothers.	Salivary Cortisol: Each woman contributed four saliva samples via passive drool: the first soon after arrival, the second immediately following the completion of the SS procedure, the third 20 min after the start of the second separation from the mother, and the fourth 30 min after the preceding sample.	Childhood maltreatment reported at 3 months postnatal—the total score and, if a significant overall effect was detected, individual subtypes—was used to predict women's cortisol response trajectories during the mother infant stress task at 12 months postnatal using multilevel modeling in HLM.	Table 2 - CTQ total correlation with T3 Cortisol Sample 1	$r(45) = .31$	.034	As predicted, early life adversity appeared to contribute to ongoing symptom elevations via heightened HPA reactivity to stress
Shalev et al 2019	We hypothesize that bereavement and suicidal ideation will each, independently be related to baseline cortisol, total cortisol output, and cortisol reactivity in response to the TSST, and that cortisol measures will predict future suicidal ideation.	A total of 427 bereaved and non-bereaved youth were enrolled in the study, of whom 223 (52%) completed the acute laboratory social stress task and were available for follow-up. The 223 youths included 114 offspring from 79 parentally-bereaved families and 109 offspring from 65 nonbereaved families.	Bereavement: The deceased parents (probands) died within 24 h of either suicide ($n = 29$), accidental death ($n = 17$), or sudden natural death ($n = 33$).	TSST: Bereaved and nonbereaved offspring participated in a modified version of the Trier Social Stress Test (TSST), a procedure designed to induce a moderate stress response. The TSST was conducted on average 6 years ($SD = 1.3$, range: 2.8–9.2) after bereavement in bereaved youth.	Salivary Cortisol: Salivary cortisol samples were obtained immediately after the social stress task (15 min after baseline), and 5, 10, 20 min after the social stress task (20, 25, 35 min after baseline).	We examined the relationship of cortisol measures with demographic and clinical variables to identify significant covariates to include in our regression models (Table 1) and controlled for covariates known to potentially affect cortisol levels. We used Bonferroni correction to account for multiple comparisons.	Table 3 - t-test for Bereaved vs. Non-bereaved and Cortisol Reactivity	$t(221) = 3.05$	.003	As hypothesized, we found that parental bereavement was associated with greater cortisol reactivity.

Table 1: *P*-curve Disclosure Table of Trauma-Cortisol Hyper-reactivity Literature

Chen et al 2018	Our main goal was to examine whether cortisol levels during baseline, stressful, and recovery periods of the TSST differed for bullied and nonbullied youth, in a sample of Chinese children. We hypothesized finding a significant association between greater bullying victimization and stronger cortisol reactivity during the TSST, such that victims would have higher cortisol reactivity than non-victims during stressful and recovery periods.	Participants were 80 children (4-5th grades, 45% girls) with a mean age of 10.83 ($\pm$ 0.70 SD) years, selected from 970 students in 18 classes in two elementary schools. Sixty-five victims actively agreed to participate in the stress test; they were selected from 120 identified victims. Meanwhile, a nonbullied group of 25 children was randomly selected from the pool of nonbullied children who had no victimization in the previous semester; they matched the bullied group in age and gender distributions.	Olweus Bully/Victim Questionnaire: We used six items involving physical, verbal, and relational victimization from the Olweus Bully/Victim Questionnaire. Each of the three subscales consisted of two items. Sample items include: "being hit, kicked, or slapped by others" (physical), Being laughed at by others (verbal), and Being excluded by others (relational/social).	TSST: The TSST is an empirically-supported protocol to elicit psychosocial stress, developed by Kirschbaum et al. (1993). It involves public speaking and mental arithmetic, as stressors.	Salivary Cortisol: Six saliva samples were collected from each participant, to measure the cortisol response to the TSST across a 70 min period. The first sample (T1) was collected at 5 min after arrival in the room next to the experiment room, during the 10 min rest period. The second sample (T2) was collected when participants were about to finish the preparation of their speeches. The third sample (T3) was collected immediately at the end of the mental arithmetic task. The other three samples (T4, T5, and T6) were collected separately at 10 min, 25 min, and 40 min after the end of the arithmetic task.	Because there were no sub-type differences, and there were significant correlations in subtype membership ($r-s = 0.291 \sim 0.430$, $p < 0.001$), we combined them into one larger group of bullied youth, and in our final analysis we compared them to non-bullied youth. Repeated-measures analyses of variance (ANOVAs) was used with the six measurements of cortisol representing time as a within-subject factor, and bullying victimization status (bullied versus nonbullied) as a between-subject variable	A significant main effect of bullying victimization was found, $F(1, 78) = 7.07$, $p = 0.009$, $\eta^2 = 0.08$, $\Phi = 0.75$, which indicated that cortisol levels during TSST were higher for bullied than nonbullied children.	$F(1,78) = 7.07$	.009	The current study of Chinese children also provided evidence for a link between bullying victimization and cortisol levels, in the context of the TSST. Children with a history of victimization had higher cortisol than those without a history.
Coppens et al 2018	Studies on the association between ECA and HPA axis reactivity in FM are lacking, but in other FSS, an association was found between ECA and HPA axis responses during the TSST; however, both decreased and increased responses were found in individuals with ECA, again stressing the need for further research.	Twenty-seven female FM patients and 24 age-matched female controls were recruited in a tertiary care center and through advertisements, respectively.	CTQ: Participants completed the Childhood Trauma Questionnaire – short form (CTQ-SF), a well-validated 25-item self-report instrument, to measure exposure to ECA.	TSST: The TSST is the gold standard laboratory procedure to induce psychosocial stress; it consists of a public speech (5 minutes) and an arithmetic task (5 minutes) performed in front of an evaluating audience (two PhDs or MSc students wearing white laboratory coats).	Salivary Cortisol: Salivary cortisol was assessed at baseline (T0), immediately before the TSST (after a relaxation/waiting period of 30 minutes) (T1), immediately after the TSST (T2), and 10 (T3), 20 (T4), 30 (T5), and 75 minutes after the TSST (T6).	The group-by-time interaction effect in these models was followed up by a priori planned contrasts using independent samples Student's t-tests, with step-down Bonferroni correction for multiple testing.	Significant main effects of group [$F(1,43)=7.04$, $p=0.011$, lower in FM] and ECA [$F(1,43)=5.18$, $p=0.028$, higher in participants with ECA] were found for cortisol responses.	$F(1,43) = 5.18$	.028	Cortisol responses were higher in participants with ECA.

Table 1: *P*-curve Disclosure Table of Trauma-Cortisol Hyper-reactivity Literature

Mielock et al 2017	We hypothesized that cortisol responses would be higher in maltreated women with current MDD and blunted in maltreated women without current MDD compared to non-maltreated women.	The sample included 26 women with a history of maltreatment before the age of 10 (15 with current MDD) and 26 women with no history of maltreatment (17 with current MDD).	The Childhood Adversity Interview (CAI): is a semi-structured interview that was administered by trained raters. Seven subtypes of childhood adversity occurring before age 10 were assessed: separation/loss; life-threatening illness or injury; physical neglect; emotional abuse; physical abuse or assault; witnessing domestic violence; and sexual abuse or assault.	TSST: involved a 2-hour pre-stress period, a 5-minute public-speaking task (following a 5-minute preparation period) followed by a 5-minute mental arithmetic task performed in front of an audience, and a 60-minute post-stress period.	Salivary Cortisol: Pre-stress saliva samples were collected at 30-minute intervals for 2 hours prior to the stress task, with the final sample provided immediately prior to the stress tasks (five samples). Post-stress saliva samples were collected immediately after the tasks and at 10-minute intervals for 60 minutes (seven samples).	To examine within- and between-individual changes simultaneously, we specified a multilevel model (MLM) using Hierarchical Linear Models (HLM v. 6) consisting of a within-person (i.e., level 1) sub-model describing cortisol and alpha-amylase responses to each TSST and between-person (i.e., level 2) sub-model describing how cortisol/alpha-amylase responses to each TSST varied between maltreated/non-maltreated and current MDD/non-MDD groups.	The maltreatment X MDD X time interaction (i.e., anticipatory reactivity) was significant ($b = -.017$, $SE = .009$, $p = .046$). Simple slope analyses revealed stronger anticipatory cortisol reactivity for maltreated women without current MDD ($b = .020$, $SE = .006$, $p < .001$) compared to those with current MDD ($b = .014$, $SE = .005$, $p = .005$). In contrast, non-maltreated women with ($b = .003$, $SE = .005$, $p = .513$) and without current MDD ($b = -.008$, $SE = .005$, $p = .110$) did not exhibit anticipatory cortisol reactivity.	$t(24) = 3.33$	.003	Maltreated women showed greater anticipatory cortisol reactivity during the TSST protocol compared to non-maltreated women. Maltreated women also showed rapid deceleration in cortisol levels. Whereas non-maltreated women showed initial declines in alpha-amylase levels but rapidly increasing alpha-amylase levels during the TSST protocol, maltreated women did not exhibit changes in alpha-amylase levels during the TSST protocol. Contrary to expectation, MDD did not impact cortisol or alpha-amylase responses.
Flanagan et al 2015	This exploratory study addressed this gap in the literature by examining whether ACE severity influenced the effects of intranasal oxytocin on measures of HPA axis function (e.g. salivary cortisol and Dehydroepiandrosterone [DHEA]) to a social stress laboratory paradigm among cocaine-dependent individuals.	Our sample was comprised of 31 cocaine-dependent individuals who responded to local media advertisements. Inclusion criteria included current cocaine dependence consistent with DSM-IV diagnostic criteria.	The Adverse Childhood Experiences (ACE) Survey: is a 10-item self-report survey used to assess 10 domains including childhood abuse (emotional, sexual and physical), neglect (emotional and physical) and household dysfunction (domestic violence, substance abuse, mental illness, criminal house- hold member and parental divorce/separation).	TSST: Participants performed the Trier Social Stress Task (TSST) and were told that at 2:00 (s)he would soon perform to an audience a speech and arithmetic task.	Salivary Cortisol: Enzyme-linked immunosorbent assays were used to measure salivary cortisol and DHEA levels.	To estimate the effect of administration of oxytocin or placebo on the response to the social stress task; linear mixed effects models that use all serially measured time points following administration of the study drug tested the neuroendocrine responses to intranasal oxytocin compared to placebo as well as the modification of the oxytocin effect by increased ACE scores (treatment ACE interaction).	Results indicate that there is a significant positive association between baseline ACE scores and cortisol response levels in the untreated placebo group ($\beta = 0.247$, 0.09 , $t(115) = 2.5$, $p = 0.014$).	$t(115) = 2.5$	.0138	Results indicate that ACE scores and cortisol reactivity to the TSST were positively correlated in our sample.

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Jaffee et al 2015	We hypothesized that with consistent exposure to harsh, rejecting, or dangerous relationships and environments across early and middle childhood, the cortisol response to experimentally induced stressors would be relatively low. In contrast, we hypothesized that in the absence of an early childhood history of harsh, nonresponsive parenting, recent exposure to traumatic events would be associated with increased cortisol reactivity.	The sample included 400 children (51% male) who participated in the Children's Experiences and Development Study (CEDS), which was conducted from 2009 through 2011 in England. Participants ranged from 8 to 11 years ($M = 9.99$, $SD = 0.74$). We sampled a 'higher risk' group that included children who had experienced relatively high levels of harsh, nonresponsive parenting at age 3 years. A 'lower risk' group included children who had experienced relatively low levels of harsh, nonresponsive parenting at age 3 years.	Recent Traumatic Events: Recent traumatic events (at follow-up) were measured with the Traumatic Events Screening Inventory. Events were coded as having happened only if both the child and caregiver reported the event ($M = 0.61$, $SD = 0.85$). In the past year, 58% of children experienced no traumatic events, 27% one event, and 15% 2–4 events.	Social Provocation Task (SP): The social provocation (SP) task was designed to elicit feelings of frustration and anger in children and was modified from a task developed by van Goozen et al. (1998).	Salivary Cortisol: Saliva was collected at 20 and 10 min prior to the start of the SP task, at the end of the SP task, and at approximately 20, 45, and 65 min following the conclusion of the SP task. Because cortisol concentrations at time t reflect cortisol activity $t - 15$ to $t - 30$ min earlier, cortisol reactivity to the SP task was assessed by subtracting the lowest cortisol value collected by the end of the SP task (which reflected cortisol activity prior to or in the very early stages of the SP task) from the cortisol value collected 20 min following the SP task (which reflected cortisol activity at the conclusion of the SP task).	An ordinary least squares regression analysis was conducted in which cortisol reactivity values were regressed on harsh, nonresponsive parenting, traumatic events, and covariates (medication status, the previous night's bedtime, and time of initial saliva sampling) at the first step and on the interaction between harsh, nonresponsive parenting and traumatic events at the second step.	Tests revealed the predicted effect of recent trauma in the group that experienced lower levels of harsh, nonresponsive parenting at age 3 ($\theta = .13$, $SE = .05$, $p < .01$); the more traumatic events youth had recently experienced, the higher their cortisol reactivity.	$t(53) = 2.6$	.01205	The more traumatic events children had recently experienced, the greater their cortisol reactivity to the social provocation task, but only if children had experienced lower levels of harsh, nonresponsive parenting in early childhood.
Kuhlman et al 2015	Here, we aimed to identify the contribution of physical abuse, emotional abuse, and non-intentional trauma to multiple indices of neuroendocrine functioning (CAR, diurnal regulation, acute reactivity) hypothesizing that each trauma subtype would be associated with distinct anomalies in neuroendocrine functioning.	Participants were 121 youth (51% male), ages 9–16 (M age = 12.8; SD age = 2.3) from a study aimed to characterize the mechanisms that underlie adolescent anxiety and depression.	Early Trauma Inventory: The parent indicated whether their child had been exposed to 50 potentially traumatic events. Four subtypes: non-intentional traumatic events (witnessing an accident); physical abuse (being hit to the point of bruising or injury); sexual abuse (being forced to engage in sexual acts); or emotional abuse such as persistently being ridiculed or insulted by a caregiver).	Socially -Evaluated Cold Pressor Task: The stress task used in this study was the Socially-Evaluated Cold Pressor Task, which was specifically designed and validated for the activation of the HPA-axis in laboratory settings by combining thermal stress and social evaluation.	Salivary Cortisol: Seven samples were collected via passive drool at 30 min before the task (–30), immediately before the task (0) and at 25, 35, 45, 55, and 65 min after the start of the task.	4 x (adversity subgroup) x 7 (time). To determine the association between childhood trauma subtypes and acute stress reactivity, we used a modified version of Growth Curve Analysis using landmark registration (Lopez-Duran et al., 2014), where we modeled slope of cortisol activation to the stress task, peak cortisol (intercept), and the slope of recovery from the stress task simultaneously.	In unadjusted models, more physical abuse was related to greater acceleration as individuals approached their peaks, $PA \times Time2b = .0001$, $t(439.5) = 2.41$, $p = .02$.	$t(439.5) = 2.41$	.01636	In the reactivity task, more exposure to physical abuse was associated with a steeper activation slope, which is consistent with previous studies showing that childhood exposure to violence is associated with hyperreactivity to acute stress.

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Dietz et al 2013	It was hypothesized that parentally bereaved children would evidence a significantly different trajectory of cortisol response compared with nonbereaved controls, marked by greater reactivity to acute stress. In this article, psychiatric disorders associated with cortisol response in offspring were considered possible confounds and were controlled to isolate the influence of bereavement on the acute stress responses of participants.	The participants were 181 youth, aged 10 to 29, from 62 parentally bereaved families and 53 nonbereaved families; 66.3% of participants had at least 1 sibling in the study.	Parental Loss: The deceased parents (probands) died within 24 hours of definite verdicts of suicide (n = 21), accidental death (n = 13), or sudden natural death (n = 28). Nonbereaved offspring had two living biological parents, lived in the home of at least one of them, and had no first-degree relatives who had died within the 2 years before recruitment.	TSST: Offspring watched a 10-minute travel video during which baseline cortisol sample was obtained (0 minutes). For the next 15 minutes, participants were asked to prepare and deliver a brief speech and then perform a mental arithmetic task while being observed by research staff.	Salivary Cortisol: Salivary cortisol samples were obtained immediately after the social stress task (15 minutes after baseline), and 5, 10, and 20 minutes after the social stress task (20, 25, 35 minutes after baseline). Cortisol response was operationalized as changes in cortisol levels across the five time points during the laboratory procedure.	Group (2) x Time (4) ANOVA. ANOVA was used to assess group differences in total cortisol output.	The total cortisol secretion, as measured by AUC, was higher in the bereaved than in the nonbereaved groups [$F(1,179) = 6.15$, $p = .01$].	$F(1,179) = 6.15$; Robustness $t(40) = 2.32$	.01407	Bereaved youth showed overall higher total cortisol output but showed no significant increase in cortisol levels over time in response to social stress. Within the bereaved group, offspring bereaved due to sudden natural death showed a significant increase in cortisol relative to baseline.
Bosch et al 2012	We examined adversities during five age periods (pre/postnatal, 0—5 years, 6—11 years, 12—13 years, 14—15 years), to investigate their specific effects on the HPA-axis. We anticipated that effects of adversities on the cortisol responses would depend on their timing, and that pre/postnatal adversity would render individuals more sensitive to persistent effects of later adversities on the HPA-axis.	Complete HPA-axis and adversity measurements were available for 640 participants. Adolescents were excluded if stressful life events were assessed more than 3 months before (n=60) or after the experiment (n = 60). We excluded adolescents with cortisol outliers (>3 SD, n = 11), and who used corticosteroids (n = 38), leaving a total of 471 (32.3% low- risk) participants for analysis.	Pre/postnatal adversity, adversities during ages 0—5 (early childhood) and 6—11 (middle childhood), adversities during ages 12—13 (early adolescence), and adversities during ages 14—15 (middle adolescence) were measured via semi-structured interviews. Duration of the adversities was measured in months.	Social Stress Test: The experimental session during T3 consisted of a number of different challenges (orthostatic stress, spatial-orienting task, gambling task, startle-reflex task, and social stress test). The social stress test (Groninger Social Stress Test) involved a standardized protocol inspired by the Trier Social Stress Test (Kirschbaum et al., 1993).	Salivary Cortisol: HPA-axis responses towards the social stress test were assessed by four cortisol samples, before the introduction of the social stress test ('pretest'), directly after the test ('during test'), 20 min after the test ('end of test'), and 40 min after the test ('post test').	Repeated-measures general linear models (GLM, Greenhouse—Geisser corrected) were used to examine (1) the main effects of adversities per period and (2) the interaction of pre/postnatal risk with each later adversities on the HPA-axis.	Figure 1 Subjects with the highest number of late childhood adversities (ages 6—11) displayed the highest cortisol overall level (mean level of cortisol across the four cortisol measurements, $F(1,441) = 8.08$, $p = .005$).	$F(1,441) = 8.08$	.0046	The transition in cortisol activity from hypersecretion after adversities before age 11 and hyposecretion afterwards emphasizes puberty as a major developmental period of the HPA-axis. Puberty may be marked by a transition in how adversities affect the HPA-axis, with cortisol hypersecretion before age 11 and hyposecretion after age 11.

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Gola et al 2012	Here we investigate whether the type of trauma (rape vs. other trauma types) is associated with differential stress responses when confronted with trauma-related material, using cortisol as a physiological stress marker.	Cortisol reactivity was assessed in 30 individuals with current PTSD according to DSM-IV. All PTSD patients were refugees (4 from Africa, 5 Balkan, 21 Middle East and Afghanistan) with multiple highly stressful war and torture experiences, including or not including rape. To compare basal cortisol levels of the PTSD group with a non-PTSD group, we further examined a third healthy control group (n = 28; 17 female, 11 male; mean age = 26.9 years, SD = 7.0).	War and rape trauma: To investigate the influence of trauma type on cortisol reactivity, patients were divided into two groups: raped (n = 10; 6 female, 4 male; mean age = 34.0 years, SD = 10.2) vs. non-raped (n = 20; 8 female, 12 male, mean age = 33.7 years, SD = 8.7). Rape was defined as any traumatic stressor involving unwanted vaginal or anal penetration obtained by the use of force or threat of force.	Traumatic Reminders: Participants were interviewed in a standardized manner about their individual child and adulthood traumatic experiences using the event checklist of the CAPS and the vivo checklist of war, detention and torture event which assesses common traumatic experiences in conflict regions and during torture.	Plasma and Salivary Cortisol: Plasma and salivary cortisol levels of PTSD patients were measured at three time points during a detailed and standardized clinical interview, starting at 10:00 a.m., once before and twice after assessing individual rape, war and torture experiences.	Salivary and plasma cortisol reactivity were analyzed using mixed model ANOVAs with trauma type (raped vs. non-raped) or trauma type and gender or current depression as fixed effect and time (t1, t2, and t3) as repeated measure factor.	Differential cortisol responses were observed in PTSD patients who had been raped compared to those who had not been raped [t2, t(27) = 2.35, p < .05]. PTSD patients who had been raped showed a significant cortisol increase when reminded of their traumatic events (t1 vs. t2, p < .001), and returned to baseline levels at t3 (t2 vs. t3, p = .11; t1 vs. t3, p = .92).	t(27) = 2.35 .02634	Trauma groups had comparable basal salivary or plasma cortisol levels, however, our results demonstrate differential salivary cortisol responses in PTSD patients who had been raped compared to those who had not been raped. Consistent with a typical diurnal decline, salivary cortisol levels decreased in the course of the interview for the group with no past experience of rape, whereas those PTSD patients who had been raped showed a significant salivary cortisol increase when reminded of their traumatic events.
Harkness et al 2011	This study examined the hypothesis that depressed adolescents with a history of childhood maltreatment will show greater cortisol reactivity to psychological stress challenge than those without, and this relation will be moderated by level of depression severity.	Participants were 71 individuals (48 females) ages 12—21 years (M = 15.39, SD = 2.11). The depressed adolescents all met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for a current non-bipolar, non- psychotic mood disorder.	CECA: Participants were interviewed using the Childhood Experience of Care and Abuse contextual semi-structured interview and rating system (CECA).	TSST: We followed precisely the procedure outlined by Krischbaum, Pirke, and Hellhammer (1993) in defining the time points for salivary sample collection during the TSST.	Salivary Cortisol: Participants were asked to refrain from eating and drinking for 1 h prior to their arrival at the lab. All saliva was collected in previously labeled 5 ml polypropylene vials by passive drool between the hours of 3 pm and 5 pm because this is a period of low cortisol relative to the morning.	5 (time) x 3 (depression group: minimal depression, mild/moderate depression, moderate/severe depression) x 2 (childhood maltreatment: presence versus absence) repeated measures analysis of covariance (RMANCOVA) controlling for age and parental occupation status.	A significant 3-way interaction of time by depressed group by childhood maltreatment in the quadratic trend, F(2, 63) = 3.39, p < .05, h2 = .10.	F(2, 63) = 3.39; Robustness F(2,63) = 3.41 .03997	Consistent with hypotheses, a history of childhood maltreatment was associated with significantly higher cortisol reactivity and total cortisol exposure (i.e., AUC) to a psychosocial stress challenge.

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Hibel et al 2011	Here we extend the previous analyses by examining the influence of IPV on cortisol levels, reactivity, and regulation across early infancy, later infancy, and toddlerhood. We determine if children exposed to IPV exhibit divergent patterns of cortisol reactivity and recovery across early childhood.	Data for this analysis came from the larger project's home interview and assessments at three time points across early childhood: when the child was approximately 7 months, 15 months, and 24 months of age. From the total of 1,292 dyads eligible, 1,102 participated in all three home visits and are thus included in the analyses.	IPV: To assess violence between partners, the Conflict Tactics Scale—Couple Form Revised (CTS-CF-R) was administered. The CTS-CF-R consists of 19 items exploring conflict and violence between the partner and the mother in the past 12 months. The CTS-CF-R contains three subscales: verbal discussion, verbal aggression, and physical aggression.	Challenge Task: Lab-TAB- Challenge tasks designed to elicit emotional reactivity were administered to the child. At the early infancy visit, three tasks were presented to the child: the barrier task, the mask task, and the arm restraint task. At the later infancy and toddlerhood visits, two tasks were presented to the child: the toy removal task and then the mask task.	Salivary Cortisol: To assess changes in cortisol indicative of the child's adrenocortical response to the emotion challenge tasks, three saliva samples were collected: a pretask sample collected prior to administration of the challenge tasks, a sample 20 min after the final task was completed (or prior, if the child reached "peak emotional arousal"), and then a final sample 20 min later. The child was considered to have reached peak arousal if he or she produce.	The main analyses employ a series of mixed-model repeated-measures ANCOVAs determining the relationship between violence exposure and physiology across early infancy, later infancy, and toddlerhood.	Children that were exposed to IPV exhibited a significantly different response to the tasks than those not exposed, $F(2, 1,089) = 4.45$, $p < .01$. Children exposed to higher levels of physical violence at 24 months had higher cortisol reactivity from pretask to posttask.	$F(2, 1089) = 4.45$ Robustness $F(1, 99) = 4.45$	.00119	The analyses presented examined the contributions of IPV on adrenocortical levels, reactivity, and recovery to a set of emotion eliciting challenge tasks when the child was 7, 15, and 24 months of age. Adrenocortical dysregulations first appeared at 24 months, revealing toddlers exposed to high accumulated levels of IPV across their first 2 years had higher cortisol reactivity than those with little to no violence exposure.
Ivanov et al 2011	This protocol tested the hypothesis that traumatized and aggressive youths will exhibit higher levels of responsiveness to the active psychological challenge (Violent film) than aggressive youth with no trauma whereas the responsiveness to the neutral psychological challenge (Non-Violent film) will not differ between the two groups	We identified 30 children ages 8–12, who have exhibited patterns of aggressive behavior, indicated by school suspension due to engaging in physical fighting. Of these 25 children completed the experimental protocol and provided data included in the analyses.	To assess traumatic stress exposure, the caretaker filled out: i) the Codington Life Events Scale for the purpose of inquiring about the occurrence of traumatic experiences within the past 12 months; and ii) the Posttraumatic Stress Reaction Index (PTSRI) Parent version, which queries the parent about the occurrence of traumatic experiences in the child and the nature of the reactions to them, following the DSM criteria for PTSD. Children also completed the PTSRI, Child version.	Violent film: Since TSST presents stressful stimuli unrelated to personal trauma history we introduced emotionally laden stimuli that we considered relevant to some aspects of these children's experiences (e.g. physical aggression) and used two types of films as psychological probes. The Violent film (VF) involved scenes depicting preparation for and enactment of a boxing match. The Non-Violent film (NVF) depicted everyday family interactions in a situational comedy format.	Salivary Cortisol: Cortisol samples, pulse and blood pressure were collected at baseline just before the start of each film (T1), 15 min into the viewing (T2), at the end of the viewing (T3), and 15 min post viewing (T4).	2 (group: adversity vs no adversity) x 2 (film type: violent vs. non-violent) x 4 (time) ANOVA.	The main effect for group was registered during the Violent film at T3 ($F = 4.556$, $d.f. = 1/23$, $p = 0.044$), indicating significantly heightened cortisol response in Trauma youth compared to Non-Trauma counterparts.	$F(1,23) = 4.556$	.04368	The main effect of group (Trauma vs. Non-Trauma) showed a significantly heightened HPA response pattern for the Trauma children that was most pronounced during the Non-Violent film. Although the Violent film elicited higher cortisol response than the Non-Violent film in the Non-Trauma aggressive children, these responses were overall lower than the responses to either film in the Trauma group, pointing to an overall heightened HPA responsiveness in the Trauma children.

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Elzinga et al 2010	The aim of the present retrospective study is to investigate HPA reactivity to a psychosocial stressor (TSST) in patients with SAD who report a history of (emotional, physical, or sexual) childhood abuse vs patients with SAD who do not report experiences of abuse during childhood.	Four groups: (1) Social Anxiety Disorder + Childhood Abuse [n=9]; (2) Social Anxiety Disorder - Childhood Abuse [n=9]; (3) PTSD [n=16]; (4) Healthy controls [n=16].	Traumatic Experiences Checklist (TEC): A reliable and valid self-report inventory that assesses emotional abuse and neglect, physical abuse, sexual harassment, and sexual abuse, as well as general traumatic events, including loss of significant others, life threat by disease, parental divorce, and psychopathology of parents (i.e., alcohol or drug abuse).	TSST: The psychological challenge test consisted of a free speech (5 min) and a mental arithmetic task (5 min), performed in front of an audience of three individuals, which was preceded by an anticipation phase (5 min) in which participants prepared the speech.	Salivary Cortisol: measures were obtained at 10 assessment points over a 130-min period, at -65, -35, -25, -10, 0, +15, +25, +40, +50, and +65 min with reference to the start of the stressor. All assessments were performed between 1 PM to 4 PM.	4 x 10 repeated measures ANOVA. To compare the four groups on cortisol reactivity to the TSST, ANOVA for repeated measures were conducted with Group as between-subject factor and Time as within subjects factor. 4 (Group: SAD + CA vs SAD - CA vs PTSD vs Controls) x 10 (Time: 10 assessment points) repeated measures ANOVA	A main effect of Group was found ($F(3,46) = 4.03$, $p < 0.05$, $\eta^2 = 0.21$), which was specified by a significant Group x Time interaction ($F(27,414) = 2.62$, $p < 0.05$, $\eta^2 = 0.15$).	$F(3,46) = 4.03$.01258	We found that a history of childhood abuse (CA) was associated with greatly enhanced cortisol reactivity to a psychosocial stress task in patients with social anxiety disorder (SAD) compared to patients with SAD who did not report childhood abuse, and compared to patients with PTSD related to CA and healthy controls without a history of CA.
Pesonen et al 2010	Aims: The Finnish experience in World War II created a natural experiment to test whether separation from a father serving in the armed forces or from both parents due to war evacuation are associated with alterations in HPA axis response to psychosocial stress in late adulthood. Our primary hypothesis was that individuals who have undergone separation as child evacuees have different HPA axis responses as adults to psychosocial stress.	The participants came from the Helsinki Birth Cohort Study (N = 8760). In years 2001—2004, 2003 randomly selected participants attended a clinical examination. From the subset who attended the 2001—2004 examination, we invited 407 participants selected by random-number tables to participate in the Trier Social Stress Test (TSST), performed during 2004—2005. Of these, 287 (144 men and 143 women) agreed to participate, corresponding to 70.5% of those invited. We had separation data available for 282 of those participants.	Childhood Separation Experiences: In the current sample, 68 participants were in the “separated from both parents” group. The “father-separated” group included 129 non-evacuated participants who reported that their fathers served in the Finnish armed forces during these wars. The “non-separated” group included 85 participants who did not experience separation from their parents because of either war.	TSST: Briefly, after standing for 5 min to register the cardiovascular baseline, subjects were given 3 min to prepare a 5-min speech. After the speech, they were asked to perform a series of serial subtractions for another 5 min. The committee, blind to participants’ separation experiences, minimized all verbal and non-verbal communication with the subject.	Salivary and Blood Cortisol: We obtained saliva (by Salivette1) and blood at baseline (prior to entering the laboratory, approximately 18 min before the TSST stressor ended and at 0, 10, 20, 30, 45, 60, and 90 min after the end of the stressor).	To illustrate HPA axis response with conventional summary measures, we used baseline, post-stress peak value, increment (post-stress peak minus baseline value, an indicator of HPA axis responsiveness), time-weighted AUCg, and time-weighted AUC increment (time-weighted AUCg minus the baseline value, an indicator of excess HPA axis output because of stress). We tested whether these indicators are associated with separation experiences by multiple linear regression.	Analyses using the mixed model (Table 2) show that, compared with the non-separated, those who were separated from both parents had higher salivary cortisol and plasma ACTH concentrations across all time points during the TSST. In addition, participants separated from both parents had greater salivary cortisol reactivity to the TSST.	$t(152) = 2.2$.029	We have shown that ELS is associated with altered responsiveness of the HPA axis more than 60 years after childhood separation. In comparison to non-separated participants, individuals separated from both parents at a mean of 3 years of age displayed 20—25% higher salivary cortisol and plasma ACTH levels across the time points during the TSST, and higher salivary cortisol reactivity in response to the TSST, more than 60 years later.

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Rao et al 2008	The current study extends findings by systematic evaluation of early-life and recent stress on HPA response to a psychosocial stressor in depressed and non-depressed adolescents.	30 adolescents with depression and 25 controls were recruited. The depressed adolescents met criteria for major depressive disorder (MDD), with a minimum duration of four weeks and a score of ≥ 15 on the first 17-items of the Hamilton Depression Rating Scale (HDRS).	The Child Adversity Interview: Seven types of adversity including separation/loss, life-threatening illness/injury, physical neglect, emotional abuse/assault, physical abuse/assault, witnessing violence, and sexual abuse/assault were assessed.	TSST: A modified version of a standard psychosocial stressor used in adults, the Trier Social Stress Test (TSST) was administered to 30 adolescents with major depressive disorder and 25 healthy adolescent volunteers.	Salivary Cortisol: Baseline saliva samples were collected at 30-minute intervals for two hours (5 samples). Saliva samples were obtained immediately after the task and at 10-minute intervals for 60 minutes (7 samples). The time of HPA assessment was in the late afternoon/early evening, and was based on prior data suggesting a delayed circadian phase in adolescents.	2 (group) x 7 (time) Repeated measures ANOVA.	Among experiential factors, early-life adversity and chronic stress during adolescence were significant predictors. Table 2 - Predictors of net peak salivary cortisol concentration in response to the TSST - early-life adversity	$t(53) = 3.8$.00038	HPA response to the stressor was highest in those who had a combination of early-life adversity and high levels of chronic stress during adolescence.
van der Hal-Van Raalte et al. 2008	We expected the youngest Holocaust child survivors, who lacked the prewar experience of a relatively protected family life, to show the most elevated cortisol responses to a stressful challenge, with men showing stronger responses than women.	Participants were 203 child Holocaust survivors, who were born between 1935 and 1944 in countries occupied by the Nazi regime, and immigrated to Israel after 1945. or the purpose of analysis, the sample was divided into three age groups: born between 1935 and 1937 ($n = 43$), between 1938 and 1940 ($n = 43$) and between 1941 and 1944 ($n = 47$).	Child Survivors of the Holocaust and PTSD Functional Impairment: PTSD functional impairment was assessed by means of the Post-traumatic stress diagnostic scale (PDS). The 49-item self-report scale assesses DMS-IV symptoms of PTSD. It provides a categorical diagnosis of PTSD, as well as an overall measurement of symptom severity.	Stressful Task: Through the questionnaire participants were confronted with questions about their Holocaust survival experiences and exposure to other shocking life events, e.g. sexual, physical or emotional abuse, traumatic experiences during the wars and the terrorist attacks in Israel, combat trauma, death of close relatives after the Holocaust, life-threatening illnesses and traffic accidents.	Salivary Cortisol: Three saliva samples were collected at 20 min intervals during the procedure, with the first sample taken 20 min after the start. After a resting period of 40min, a fourth sample was taken to assess the post-stress cortisol level.	Analysis of covariance between the two PTSD groups with gender as a second factor and loss of parents, depression and physical health as covariates	The interaction between PTSD functional impairment and gender was significant for reactivity at 20 min from the beginning of the session, $F(1, 97) = 3.97$, $p = 0.049$, see Figure 3. Males with functional PTSD impairment showed the strongest reactivity	$F(1,97) = 3.97$.049	We noticed neuroendocrine effects in stress reactivity through elevated cortisol levels in the youngest male age group, and in male respondents suffering from PTSD-related functional impairment even when controlling for differences in loss of parents, depression and physical health.

Table 1: *P*-curve Disclosure Table of Trauma-Cortisol Hyper-reactivity Literature

Luecken & Appelhans 2006	The current study evaluates cortisol responses to a stressful speech task in young adults from bereaved and maritally intact, control families. We expected that parental loss in the context of higher reports of abuse or conflict would be associated with elevated cortisol across the task and greater cortisol reactivity to the task relative to those from intact families.	Participants included 88 undergraduate students (ages 18–28 years, mean age = 19.6 years). The sample included 55 females and 33 males, representing a variety of ethnic backgrounds.	CTQ: The Childhood Trauma Questionnaire Q assesses five dimensions, including emotional abuse, emotional neglect, physical abuse, physical neglect, and sexual abuse. A total abuse score was calculated by summing scores on the five subscales. The conflict subscale (nine items) from the Moos Family Environment Scale provided a self report of the amount of conflict within the family.	Speech task: Participants were given 4 min to prepare and 4 min to deliver a speech to defend themselves from a false accusation of shoplifting. The speech was videotaped and was given in front of an “audience”. Participants were told that speeches would be evaluated for clarity and the strength of their arguments, and would be rated in comparison to speeches given by other participants.	Salivary Cortisol: Five saliva samples were collected for determination of cortisol before, during, and after a moderately stressful speech task. Samples were collected at pretask, immediately following the task, and at 15, 30, and 45 min following the task.	Evaluation of differences between the two groups in the pattern of cortisol responses to the speech task were conducted with repeated-measures general linear models, with five repeated measures of cortisol as dependent variables, and family group, abuse, and the group by abuse interaction as independent variables.	A significant between-subjects interaction of family group and reported abuse on cortisol across all time periods, $F(1, 79) = 4.7$, $p = .02$.	$F(1, 79) = 4.7$	.03317	Overall, parental loss was associated with elevated cortisol in response to a novel stressor relative to participants from intact families. As hypothesized, the combination of early parental loss and reports of abusive treatment was associated with elevated cortisol relative to those who experienced parental loss in the absence of abusive treatment, and relative to those from intact early family environments.
Bremner et al 2003	The purpose of this study was to assess cortisol responsivity to a stressful cognitive challenge in patients with PTSD related to childhood abuse. Based on findings in animal studies, we hypothesized an increased cortisol and sympathetic response to stressful cognitive challenge in PTSD patients relative to controls.	Subjects included 41 men and women, 18 years of age or older who underwent a stressful cognitive challenge in conjunction with measurement of cortisol, heart rate and blood pressure, and behavioral responses. Subjects included men and women with civilian PTSD ($N = 23$) and healthy men and women without trauma or PTSD ($N = 18$).	Early Trauma Inventory: PTSD patients were included with a history of childhood physical or sexual abuse, defined as rape, attempted rape, molestation, physical assault or attack with injury, before the age of 18, as measured by the Early Trauma Inventory (ETI), and the diagnosis of PTSD based on the Structured Clinical Interview for DSMIV (SCID).	Cognitive Challenge Test: The cognitive tests were based on a protocol previously used in studies of aging and included challenging arithmetic (multiplication, division, addition and subtraction), cognitive tasks (stroop task, e.g. looking at the word red spelled in the color green and naming the color green), problem solving, matching figures to numbers and memory for figure-number pairings, and unscrambling words.	Salivary Cortisol: There was a baseline cortisol measure before the cognitive challenge. Salivary cortisol was measured at 0, 10, 15, 20, 30, 35, 45, 60, 75, and 90 min after the initiation of the challenge.	2 (group: PTSD vs healthy controls) x 10 (time) repeated measures ANOVA.	Salivary cortisol levels were elevated in PTSD patients relative to controls during the hour preceding the cognitive stressor and during the course of the stress challenge (i.e. from -60 to +20 min) ($F = 6.79$; $df = 1,38$; $p < 0.0001$).	$F(1,38) = 6.79$	.01302	PTSD patients in this study had increased cortisol levels in anticipation of and during a stressful cognitive challenge compared to healthy subjects. Both PTSD patients and controls showed a similar 1.5-fold increase in cortisol levels during the stressor relative to their own baseline.

Table 1: *P*-curve Disclosure Table of Trauma-Cortisol Hyper-reactivity Literature

Luecken 2000	A three-way interaction was hypothesized, in which participants who lost a parent and reported low levels of parental caring from their surviving parent would show increased cortisol reactivity to a stressful task relative to other participants.	Participants included 61 Duke University and North Carolina University students, age 18-27. Participants were divided between loss (n=30) and no-loss (n=31) groups. Criteria for participation were either: (1) prior to age 16, the participant experienced the death of one biological parent, or (2) the participant was raised by both biological parents, and both parents were still living and had never divorced.	Parental Loss: Prior to age 16, experiencing the death of one biological parent, versus controls who had not experienced parental loss.	Speech Task: For the speech task, participants were seated in front of a video camera. They were given instructions by a lab assistant reading a script, and were told to give a 3-minute speech that would be videotaped and evaluated.	Salivary Cortisol: Saliva samples were collected from each subject for use in the determination of baseline cortisol levels and cortisol reactivity to a stressful speech task; one immediately prior to the task, one 5 minutes following the completion of the task, and one 20 minutes after the completion of the task.	2 (adversity: parental loss vs no loss) x 2 (parental care: high caring vs low caring) x 3 (time) repeated measures ANCOVA with participant sex and time of day as covariates.	A significant three-way interaction of Loss by Care by Period was found ($F(2,54) = 4.45$, $p = .01$).	$F(2,54) = 4.47$	.01598	Specifically, the current results suggest that participants who lost a parent and reported low caring from the surviving parent had higher cortisol levels following a stressful task relative to other participants, who showed stable cortisol levels during and after the task.
Luecken 1998	This study proposes to test the hypothesis that early loss of a parent, coupled with poor quality family relationships, would result in long-term increased cardiovascular and cortisol reactivity to stress.	Subjects included 30 university students who lost one parent before age 16, and 31 control subjects. Criteria for participation were either: 1) before age 16, the subject experienced the death of one biological parent, or 2) the subject was raised by both biological parents, both parents were still living and had never divorced. Subjects could not be experiencing significant health problems or taking medications that could affect cardiovascular or cortisol measures.	Parental Loss: Before age 16, the subject experienced the death of one biological parent.	Speech stressor and Movie stressor: For the speech stressor, subjects were seated in front of a video camera. They were instructed to give a 3-minute speech, which would be recorded and evaluated. The video stressor, viewed in the same room, was taken from the movie "Terms of Endearment." The 7-minute clip depicts two young boys experiencing the death of their mother.	Salivary Cortisol: Six saliva samples were collected from each subject for use in the determination of baseline cortisol levels and cortisol reactivity to both tasks; one immediately before each task, one 5 minutes after the completion of each task, and one 20 minutes after the completion of each task.	Statistical analyses involved repeated-measures analysis of covariance with BP, heart rate HR, and cortisol levels as the dependent variables, parental loss group and FR as between-subjects factors, and period (baseline, task, or recovery) as within-subjects factors. 2(group) x 6(time) ANOVA.	A loss by period interaction was found for cortisol reactivity to the speech, ($F(2,52) = 4.3$, $p < .03$), such that subjects in the loss group showed an average increase in cortisol levels (from baseline to recovery) as a result of the speech, whereas no-loss subjects showed an average decrease	$F(2,52) = 4.3$	.01870	Cortisol elevation was associated with parental loss during the speech task only, and with family relationships only during the movie.

Table 1: *P*-curve Disclosure Table of Trauma-Cortisol Hyper-reactivity Literature

Original Paper	Quoted text from original paper indicating prediction of interest	Sample Characteristics	Type of Trauma	Stress Induction Task	Cortisol Measurement	Data Analysis Plan	Quoted text from original paper with statistical results	Results	P-value	Conclusion quoted from original text
Peckins et al 2020	Given that past research found an association between hypo-reactivity of the HPA-axis and interpersonal violence exposure, but not poverty, we hypothesized exposure to violence would be associated with a blunted cortisol response over and above the effects of social deprivation.	The final sample resulted in 222 adolescents (n= 117 girls) who identified as Black or African American/non Hispanic (n= 167), Caucasian/non-Hispanic (n= 29), Hispanic (n= 9), biracial (n= 14), and other (n= 3).	Violence Exposure: Violence exposure was conceptualized as: (1) violence directed at the child by a primary caregiver (physical and emotional abuse), (2) intimate partner violence exposure, and (3) exposure to community violence.	Socially Evaluated Cold-Pressor Task (SECPT): The SECPT is a laboratory stress paradigm that contains both physiological and social-evaluative components. During the SECPT, subjects immerse their hand in ice water while being watched by a research assistant and videotaped.	Salivary Cortisol: Adolescents provided a total of 9 saliva samples via passive drool throughout the SECPT protocol: immediately prior to the onset of the SECPT (Sample 1) and at 3 min, 15 min, 25 min, 30 min, 35 min, 40 min, 45 min, and 60 min post-SECPT onset (Samples 2–9).	We performed GCM-LR's to test whether violence exposure (with and without controlling for social deprivation) and social deprivation (with and without controlling for violence exposure) were associated with the cortisol response to the SECPT.	Violence exposure was associated with a less steep reactivity slope, $b = -0.01$, $SE = 0.001$, $p < .001$, decreased peak activation, $b = -0.28$, $SE = 0.07$, $p < .001$, and less steep recovery slope, $b = 0.003$, $SE = 0.001$, $p < .01$. Violence exposure was associated with a blunted cortisol response to the SECPT even when controlling for the effects of social deprivation and all covariates.	$t(218) = -3.73$	.00024	We found that violence exposure experienced during childhood was associated with overall blunting of the HPA-axis, above and beyond the effects of social deprivation and a myriad of relevant covariates.
DePasquale et al 2019	The present study investigated whether (a) at earlier stages of puberty, PI children show a smaller cortisol stress response compared to nonadopted children earlier in puberty while (b) at later stages of puberty, there would be no difference between PI and nonadopted children's cortisol responses, suggesting pubertal recalibration of the stress response.	280 children ages 7 through 14 years; 122 children were adopted from institutions in 14 countries between the ages of 6 months and 5 years, after spending an average of 95% of their lives in institutional care, and 158 children of similarly high socioeconomic status in their biological families served as the nonadopted comparison group.	Adoption from orphanages: Inclusion criteria for the PI youth - international adoption after having spent 50% of preadoption life in institutional care.	TSST-C: Participants engaged in a modified version of the TSST-C, involving a socially evaluative public speaking task and verbal math performance.	Salivary Cortisol: Saliva samples were collected seven times during the session (20, 0, +5, +20, +40, +60, and +80 min, where 0 represents the beginning of 5-min preparatory period before the TSST-C.	Group differences (PI vs. NA) in family environment were tested via a t-test.	Adoption status significantly predicted cortisol levels such that PI children exhibited lower cortisol levels than NA children ($t = 2.56$, $p = .01$).	$t(278) = 2.56$	.011	In sum, early-pubertal post institutionalized children show blunted HPA axis reactivity compared to nonadopted peers. At later pubertal stages, this pattern seems to normalize, providing support for the pubertal recalibration hypothesis following early institutionalization.

Table 2: P-curve Disclosure Table of Trauma-Cortisol Hypo-reactivity Literature

Joos et al 2019	We also hypothesized that adolescents who reported experiencing greater number of stressors would be more likely to present with blunted reactivity	Data were collected for a study of early adolescents from urban low-income households (N = 101; 59% female; 10–12 years old; 59% female).	Community Violence: Community stress ($\alpha = .83$) included 13 items reflecting witnessing or experiencing community violence or crime (e.g., “You saw someone threatened with a knife or gun”). Adolescents indicated whether each event happened or not in the last six months.	TSST-M: a standardized protocol previously demonstrated to elicit a cortisol response in typically developing early adolescents. Youth were instructed by a two-person panel of “experts” to prepare and deliver a 5-minute speech introducing themselves to a new class, then completed oral serial subtraction for 5 min.	Salivary Cortisol: Cortisol reactivity was measured in response to the TSST-M via saliva, collected by passive drool into a 5-milliliter tube. Immediately prior to beginning the TSST-M, participants provided the first saliva samples (S1). The second saliva sample (S2) was taken immediately following completion of the TSST-M, and four additional samples were taken at 10-minute intervals (S3-S6) thereafter.	Data analysis was completed in two steps. First, latent profiles of cortisol reactivity were identified and described using latent profile analysis (LPA). After the optimal profile solution was selected based on theoretical rationale and fit indices, we examined whether profile membership was associated with proposed variables of interest, expressing these as pairwise differences.	Table 4: Chi-squared value for community stress row.	Chi2(2) = 8.26	.016	In accordance with the toxic stress model, exposure to more community violence and less family support were associated with blunted cortisol reactivity, and Reactive profile membership was associated with fewer trauma symptoms.
Lovallo et al 2019	The contribution of ELA to blunted reactivity and risk for alcoholism gains significance in light of disrupted family relationships often occurring in alcoholic households. We examined cortisol and heart rate responses to mental stress in healthy FH+ and FH– young adults and predicted that exposure to ELA would have a greater impact on stress reactivity in FH+ persons.	The present sample includes 709 persons (398 females) recruited through community advertisement.	ELA: ELA was assessed as follows: Physical or Sexual Adversity (“Have you ever been mugged or threatened with a weapon or ever experienced a break-in or robbery?” “Have you ever been raped or sexually assaulted by a relative?” yielding a possible 3 points) and Separation from Parents (“Before you were 15, was there a time when you did not live with your biological mother for at least 6 months?” “Before you were 15, was there a time when you did not live with your biological father for at least 6 months?” for a possible 2 points).	Stress Protocol: The protocol (75 min) included a prestress baseline (30 min), during which the subject sat quietly and read general interest magazines, followed by mental stress (45 min) consisting of simulated public speaking (30 min) and mental arithmetic (15 min).	Salivary Cortisol: Saliva samples were collected using the Salivette device and were taken at 9 periods across both days: awakening, arrival at the lab, min 10 and 20 of the baseline period, min 15, 30, and 45 of the stress protocol or continued rest, and at 30 min post stress or rest, and at bedtime.	Dependent variables were cortisol and heart rate responses to stress along with self-reports. Cortisol data were log transformed to normalize the distribution. Cortisol reactivity was measured as the average change from rest day to stress day in saliva samples taken at minutes 30 and 45 of the stress period and at the same two times during the extended rest protocol. The analysis used a general linear model including ELA (scaled as 0, 1, or >1 adverse experiences), FH (FH+, FH–), and the ELA x FH interaction.	Cortisol responses are shown in the top panels of Figure 1. FH+ subjects had smaller responses than FH–, $F(1, 707) = 4.15$, $p < .043$, and ELA led to progressively diminished cortisol responses to stress, $F(1, 689) = 4.57$, $p < .011$, in agreement with our previous report on a smaller sample	$F(1, 689) = 4.57$	.03289	We previously reported that exposure to ELA during childhood and adolescence contributes in a dose-response manner to blunting of stress axis reactivity in early adulthood. The present findings are based on an expanded study sample and show that FH+ persons are vulnerable to ELA while their FH– counterparts appear to be resilient.

Table 2: *P*-curve Disclosure Table of Trauma-Cortisol Hypo-reactivity Literature

Timothy et al 2019	We wanted to evaluate the effect of early adversity on the HPA axis function (Cortisol reactivity to acute stress), and its association with DNA methylation in the SLC6A4 gene (5-HTTLPR). It was hypothesized that early adversity would influence both DNA methylation and HPA axis reactivity and possibly affect behaviour.	The Children of alcoholics (COA) group, comprised 50 male children and adolescents, (age 8–16 years), ascertained from offspring of treatment seeking alcohol-dependent patients (from multiplex alcoholism families) at the Centre for Addiction Medicine, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India. Fifty healthy children and adolescents, matched for age, socio-economic status and ethnicity, were recruited from the community to form the control group.	Childhood adversity, collected from the subjects using a modified version of WHO Adverse Childhood Experiences Scale (International Questionnaire) (ACE (IQ)). The domains of the adverse experiences were physical, emotional and sexual abuse along with neglect, peer violence and collective violence. The severity of abuse was graded on a Likert Scale and all the scores were summed up to give an ACE score.	TSST-C: The Trier Social Stress Test for children (TSST-C) (public speaking an arithmetic) and modified for Indian children was administered to each child, and saliva samples collected (once before the test, and at 0, 10, 20, 30, 45 and 60 min after the test) and stored at –80 °C until analysis.	Salivary Cortisol: Cortisol estimation in the saliva samples was done by ELISA according to the protocol provided (kits from IBL Int GMBH). The cortisol indices generated were cortisol concentrations at each time point (t_B at baseline and t0, t10, t20, t30, t45 t60 at subsequent time points).	Data was tested for normality. Differences between the demographic variables, adversity and cortisol indices between the COA and control groups were tested using the Student's t-test. Repeated measures ANOVA was used to test the change in cortisol concentration with time.	Table 4: Pearson correlation between ACE score in the COA group and AUCG.	$r(49) = -0.32$	02	In our study, the cortisol curve after the Trier stress test was found to be flatter in the COA compared to controls. The relative blunting of cortisol response to stress (AUCG and AUCI) was associated with higher externalizing symptom scores, especially in the COA, who had experienced higher ELS.
Hengesch et al 2018	The aim of the current study was to compare neuroendocrine, cardiovascular/autonomous, and subjective stress reactivity of ELA vs. control participants, and in addition, to address potential gender differences.	The ELA group -- 22 adults (14 females; age ranging from 19 to 30 yrs.) who were adopted by Luxembourgish families after being institutionalized in the 1990s in international orphanages during their early childhood. The mean age at adoption was 6.4 months. Twenty-two healthy participants (11 females; age ranging from 19 to 28 yrs.) without institutionalization/adoption history served as control group.	Institutional Rearing: Adopted by Luxembourgish families after being institutionalized in the 1990s in international orphanages during their early childhood.	Two previously validated stressful elements (bilateral feet CPT and the Paced Auditory Serial Addition Task (PASAT)) were combined in an extended Cold Pressor Test (CPT).	Salivary Cortisol: Saliva samples were taken at minutes –30, –20, –5, +3, +15, +25, +40, and +55.	Group differences were explored by two factorial ANOVA examining the influence of two independent variables (ELA and GENDER) on one dependent variable (MAP; HR; cortisol responses; subjective ratings; performance measures).	Peak salivary cortisol responses were different between ELA groups ($p = .03$), with lower cortisol reactivity in ELA participants compared to controls, but no main effect of GENDER, and no significant interaction effect of ELA x GENDER (see Fig. 1 and Table 2).	$F(1,43) = 4.85$	.033	Although ELA participants showed higher stress-induced changes in arousal and anxiety ratings, as well as similar cardiovascular stress reactivity, their HPA stress axis responsiveness was blunted as compared to controls.

Table 2: *P*-curve Disclosure Table of Trauma-Cortisol Hypo-reactivity Literature

O'Connor et al 2018	Therefore, using data from the recent O'Connor et al. (2017) study, the primary aim of the current paper was to investigate whether childhood trauma was associated with low levels of cortisol reactivity to a laboratory stressor and lower resting cortisol levels (not previously reported) in individuals vulnerable to suicide.	One hundred and sixty participants (100 females) were recruited to a previous attempt (n = 49), a suicidal ideation but no attempt (n = 55) and a control group (n = 48) based upon established measures of suicidal behavior (see below). Participants were aged between 18 and 62 years (M = 26.84 years, SD = 9.32) with 73.8% identified as Caucasian.	Childhood Trauma Questionnaire: A brief 28-item self-report inventory was used to assess for a history of abuse or neglect in childhood or adolescence. The CTQ has five subscales relating to types of maltreatment: emotional, physical and sexual abuse and emotional and physical neglect, with five items for each subscale (1 = never true, 5 = very often true). In the current study, we were interested in exposure to any type of childhood trauma, therefore, we created a total childhood trauma score.	Maastricht acute stress test (MAST): The MAST is a recently developed stress protocol designed to be both physiologically and psychologically challenging by combining an uncontrollable physical stressor (i.e., a cold pressor challenge) with a social-evaluative (i.e., mental arithmetic) component. In addition, it has been shown to yield similar subjective and cortisol stress responses to the Trier Social Stress Test, however, it does not require the presence of a panel.	Salivary Cortisol: To measure cortisol reactivity to stress, saliva samples were taken using Salivettes (Sarstedt, Germany) during the resting cortisol phase and then at the beginning of the stress task (T00), at +10, +20, +30 and +40 min post-task.	Hierarchical linear regression was utilised, following the procedures outlined by Kenny et al. (1998), to test whether childhood trauma was associated with lower levels of cortisol reactivity to a laboratory stressor (AUCg and AUCi) and lower resting cortisol levels in suicide attempters and ideators.	At step 2, again as predicted, childhood trauma ($\beta = -0.23$, $p = 0.02$) significantly entered the equation, $F(1, 92) = 5.32$, $p = 0.02$, and explained an additional 5% in the variability in AUCg levels, indicating higher levels of trauma were associated with lower cortisol levels.	$F(1,92) = 5.32$	.02	Second, higher levels of childhood trauma were found to be associated with lower resting cortisol and blunted cortisol reactivity to stress in adulthood (while controlling for age, gender, BMI, medication usage, time of day and smoking status).
Monteleone et al 2018	On the basis of our previous findings, we hypothesize that AN patients with early traumatic experiences display a reduced cortisol response to TSST together with an altered negative emotional response.	Twenty-four AN women and 17 healthy women were enrolled in the study. Patients were classified as maltreated (Mal) or non-maltreated (noMal) according to their Childhood Trauma Questionnaire scores.	Childhood Trauma Questionnaire: The CTQ asks respondents to report on childhood experience across five types of childhood maltreatment: emotional neglect (EN), emotional abuse (EA), sexual abuse (SA), physical neglect (PN) and physical abuse (PA). Scoring of the CTQ produces 5 subscale scores for each subtype of maltreatment and a composite CTQ total score.	TSST: The TSST was performed in the afternoon, between 2.30 p.m. and 4.30 p.m., when the HPA axis activity is relatively stable and at a low level, so changes induced by experimental challenges are clearly evident.	Salivary Cortisol: Saliva sample were collected in Salivette tubes (Sarstedt; Rommelsdorf, Germany) at the end of the resting period (T=-20); immediately before starting the TSST (T = 0), at the end of the TSST (T=10) and 10 (T=20), 30 (T=40) and 50min (T=60) after the end of the test. Saliva was separated by centrifugation and stored at -20 °C until assayed for cortisol levels.	A two-way analyses of variance (ANOVA) and covariance with repeated measures were employed to test differences in saliva cortisol levels and anxiety scores among the groups. Between- group differences at each time point were evaluated by the post-hoc Tukey's test.	Two-way ANOVA with repeated measure yielded a significant main effect for time ($F(5,16) = 4.08$, $p = 0.001$) and a significant group $\times$ time interaction ($F(10,190) = 2.82$, $p = 0.002$), indicating that saliva cortisol levels changed significantly after the TSST and that significant differences among the groups emerged in the timing of cortisol changes.	$F(10,190) = 2.82$	.002	The first finding of our study was a significantly decreased saliva cortisol response to TSST in AN women reporting childhood maltreatment compared to both AN women and healthy women without history of childhood trauma exposure. Indeed, Mal AN women exhibited a flattened cortisol response to TSST whereas noMal AN patients had a TSST-induced clear-cut increase in saliva cortisol levels that did not differ statistically from healthy controls.

Table 2: *P*-curve Disclosure Table of Trauma-Cortisol Hypo-reactivity Literature

Trautmann et al 2018	We hypothesized that (a) acute trauma exposure would lead to an increase in reported alcohol craving compared to a neutral condition, (b) trauma-related increase in craving would be positively related to experienced childhood traumas, and (c) the association between childhood traumas and trauma-induced craving could be explained by increased peri-traumatic stress reactivity, indicated by (c1) an association between childhood traumas and stress reactivity and (c2) an association between stress reactivity and craving.	96 subjects agreed to participate and were randomized to either the trauma or a neutral condition (also see description of the trauma film paradigm subsequently) with an equal group size (n = 48). One participant in the trauma condition dropped out during the study resulting in a group size of n = 47 for this condition.	Trauma History Questionnaire: Other than the broader construct of childhood maltreatment, which has been the predominant construct in previous studies on effects of early adversities, the THQ measures the history of exposure to actual traumatic events according to the DSM-IV A1 criterion of posttraumatic stress disorder (American Psychiatric Association 2000). The THQ consists of questions on 24 traumatic events including information about the age of trauma exposure. All reported traumatic events experienced until the age of 18 were summarized.	The Trauma Film Paradigm: We used the trauma film paradigm (TFP) as a laboratory trauma-analogue stressor. In the TFP, non-clinical participants watch films containing scenes showing traumatic events such as accidents, physical assault, or rape.	Salivary Cortisol: As a marker of endocrine stress reactivity, we assessed salivary cortisol levels. Saliva samples were collected 1 min before the film as well as 1, 10, 20, and 30 min after the film using Salivettes devices.	To test for differences between participants of the trauma and the neutral film condition in demographics and baseline variables, F tests from robust regression models (see following text) for dimensional and chi-square tests for categorical outcomes are reported.	(Fig. 2) with a significant three-way interaction sex × childhood traumas × film condition (b = 8.3 [4.4– 12.1], p < 0.001). In males, but not in females (p's > .459), the number of childhood traumas was positively associated with increase in HRR (b = 3.0 [1.2–4.7], p = 0.001) and SCR (b = 0.3 [0.0– 0.7], p = 0.050), whereas CortR in the trauma condition decreased with increasing numbers of childhood traumas (b = – 62.4 [–107.9 to – 16.9], p = 0.008) (Fig. 3a–c).	F(2,95) = 8.3 .00048	Although ELA participants showed higher stress-induced changes in arousal and anxiety ratings, as well as similar cardiovascular stress reactivity, their HPA stress axis responsiveness was blunted as compared to controls.
Cordero et al 2017	Based on the literature reviewed above, we expected that IPV-PTSD mothers and their toddlers would have a low diurnal cortisol release pattern, and blunted cortisol reactivity to stress.	For the current study, 45 mothers (HC, n=18; IPV-PTSD, n=27) and their young children (12-42 months of age) were included in the analyses.	PTSD: Participant-mothers were interviewed using the Clinician Administered PTSD Scale to assess PTSD with confirmation of the severity of the current PTSD symptoms via the Posttraumatic Symptom Checklist - short version.	Modified Crowell Procedure: A 30-min mother-child interaction procedure known as the “Modified Crowell Procedure”, which consisted of free and structured play, separation-reunion, clean-up and exposure to novelty.	Salivary Cortisol: The “laboratory stressor” consisted of two 3-min separations from the mother with 8 min interval between them, and exposure to two novel stimuli. Four salivary samples for the assessment of cortisol were collected from the mother and the child: baseline (before the procedure begin), immediately after the end of the stress situation (T0), and at 30 (T30) and 60 (T60) min	Effect of IPV-PTSD on cortisol levels during the laboratory session and diurnal release were analyzed using ANOVAs with repeated measurements. In case of a significant group by condition interaction effect, post-hoc t tests were performed.	ANOVA repeated measures of mothers' cortisol levels during the laboratory stressor showed a significant effect for time (F(3,129)=29.03, p<0.001, η^2 =0.41) and group x time interaction (F(3,129)=3.63, p<0.015, η^2 =0.08)	F(3,129) = 3.63 .015	The current findings showed that mothers with IPV-PTSD as compared to HC had lower cortisol levels in response to the laboratory stressor, which included child-parent separation; this being the case even though distress behavior of the children and mothers' rating of toddler's anxiety was similar between groups.

Table 2: *P*-curve Disclosure Table of Trauma-Cortisol Hypo-reactivity Literature

England-Mason et al 2017	The purpose of the current study was to investigate cortisol reactivity and difficulties with emotion regulation in postpartum women with a history of childhood maltreatment.	Participants included a community sample of 140 new mothers who were recruited from the maternity ward at St. Joseph's Healthcare Hamilton, Ontario.	CTQ: The CTQ is a 28-item self-report questionnaire that evaluates types and frequency of abuse and neglect using a 5-point Likert scale (1 = never; 5 = very often). In the present sample using moderate-severe cutoffs, 15.7% of women reported experiencing emotional abuse, 12.9% reported sexual abuse, 7.9% reported physical abuse, 4.3% reported physical neglect, and 0.7% reported emotional neglect. Overall, 22.1% of women reported experiencing at least one form of moderate-severe childhood trauma, and 11.4% of women reported experiencing two or more forms of moderate-severe childhood trauma.	The Emotional Stroop: At the 7-month visit, participants completed a 17-min computerized Emotional Stroop task involving emotional and neutral stimuli. The Emotional Stroop paradigm is a clinically-relevant adaptation of the original Stroop procedure, where the emotional significance of word stimuli is varied so as to study the interference of emotionally salient words on colour naming. The Emotional Stroop has been previously used to investigate the relationship between selective attention to cues of social and emotional threat and engagement of the HPA axis.	Salivary Cortisol: All visits commenced between 1000 h and 1430 h (M = 1138 h, SD = 0135.7 h), and immediately following consent procedures the first salivary sample was collected. The start time of salivary sample collection was included in analyses as a covariate. Immediately following the baseline sample collection, participants completed the computerized Emotional Stroop task. Then two more samples were collected at 20- and 40- min following completion of the task.	The main analytical approach was to determine whether and how latent difficulties with emotion regulation would interact with maternal exposure to childhood maltreatment to predict cortisol reactivity.	Of all of the entered predictor variables, only maternal history of maltreatment ($\beta = -0.18$, $t = -2.13$, $p = 0.03$), bedtime ($\beta = 0.16$, $t = 1.98$, $p = 0.048$), and visible minority status ($\beta = 0.21$, $t = 2.71$, $p = 0.01$) significantly contributed to the variance in cortisol reactivity.	$t(134) = -2.13$.035	The significant interaction effect revealed that only women who reported higher levels of child maltreatment and greater difficulties with emotion regulation exhibited decreased cortisol reactivity to psychosocial challenge.
Ewing-Cobbs et al 2017	The primary aim of the study was to characterize salivary cortisol and sAA stress-related reactivity and regulation in children and adolescents sustaining traumatic injury in comparison to a healthy non-injury control group.	Participants were 8-15 years of age and hospitalized for traumatic brain injury (TBI; $n=55$; M age =13.9 yrs; 40 males) or extracranial injury (EI; $n=29$; M age 12.3 yrs, 20 males) following vehicular accidents, and a healthy non-injured comparison group ($n=33$; M age =12.5 yrs, 16 males).	Injury: The external cause of injury in a vehicle accident was selected to meet the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013) criterion A for a PTSD diagnosis that specifies exposure to a potentially life-threatening situation.	TSST-C: All participants completed The Trier Social Stress Test for Children (TSST-C), an established laboratory procedure involving public speaking (social evaluative stress) and mental subtraction (cognitive stress).	Salivary Cortisol: Saliva samples were collected using 1×4 CM polyolefin swabs placed under the participants tongue for 2 mins at 20 minutes before and right before the TSST-C. Post-stressor samples were collected immediately after (sAA only), as well as 20 and 40 (cortisol only) minutes after to capture the distinct profiles of the analytes.	Variable distributions, comparability of demographic and psychosocial variables for the TBI, EI, and healthy comparison groups were examined using ANOVA or chi square. GLM examined the effects of group, saliva collection time, age, and their interactions on salivary analytes	The healthy comparison group showed significantly greater reactivity than the injured groups, $X^2(1)=5.86$, $p=.015$; no differences in post-stressor regulation of cortisol were obtained	$\chi^2(1)=5.86$.015	Compared to a healthy non-injured group, injured children (8 to 12 years), but not adolescents (13 to 15 years), had elevated cortisol, and injured participants (regardless of age) showed dampened cortisol reactivity to social evaluative threat.

Table 2: *P*-curve Disclosure Table of Trauma-Cortisol Hypo-reactivity Literature

Lovallo et al 2017	In the Oklahoma Family Health Patterns cohort, exposure to ELA leads to progressively diminished cortisol and heart rate reactivity to psychological stress in adulthood. In the present analysis, we examined whether the impact of ELA on cortisol and heart rate reactivity would differ as a function of COMT Val158Met genotypes.	Participants were 252 healthy young adults participating in the Oklahoma Family Health Patterns (OFHP) project who had been genotyped for the COMT Val158Met polymorphism along with ancestry informative markers (AIMS) and had sufficient background data to compute ELA scores	Early Life Adversity: ELA was derived from C-DIS-IV items as follows: Physical or Sexual Adversity (“Have you ever been mugged or threatened with a weapon or experienced a break-in or robbery?” “Have you ever been raped or sexually assaulted by a relative?” and Emotional Adversity (“Before you were 15, was there a time when you did not live with your biological mother for at least 6 months?” Each person was assigned to an ELA group based on 0, 1, or ≥ 2 reported adverse events.	Stress Procedure: Stress testing lasted 105 min, including a resting baseline in a seated position (30 min) followed by simulated public speaking (30 min) and mental arithmetic (15 min) and a 30-min resting recovery period as described elsewhere. The resting control day involved sitting for 105 min during the same time of day while reading general interest magazines and watching nature videos.	Salivary Cortisol: Saliva samples for cortisol determination were collected using Salivettes at 9 times across each day including: 2 at home (upon awakening and at bedtime) and 7 in the lab (3 prestress, 3 during the stress protocol, and 1 during recovery). Cortisol responses to the stressor were computed as the difference between the mean of the 3 values obtained during the stress protocol and the corresponding values on the resting control day	Cortisol responses to stress were then calculated as the average of the three samples taken during the stress period on the stress day (STR1, STR2, STR3) minus the same three samples taken on the rest day. Cortisol data were analyzed by a general linear model including: Genotype (Met/Met, Val/Met, Val/Val), ELA (0, 1, ≥ 2), and the G × ELA interaction term.	In contrast, persons with greater ELA exposure had progressively smaller cortisol responses, $F(df = 2,244) = 4.56, p = .011$, partial $\eta^2 = .037$ and we observed a significant $G \times ELA$ interaction, $F(df = 4, 244) = 2.78, p = .028$, partial $\eta^2 = .045$, suggesting that effect of ELA on adult cortisol responses depends in part on the person’s genotype.	$F(4, 244) = 2.78$	.028	Exposure to ELA may lead to diminished stress responses in otherwise healthy young adults, although carriers of specific genotypes may respond differently to ELA history.
Troller-Renfree et al 2017	We predicted that at age 12 positive biases would predict less blunted (similar to never institutionalized children's reactivity) physiological reactivity to stress in children who received the foster care intervention	The sample included 136 children, abandoned in infancy and placed into institutions in Bucharest, Romania, and who were part of the Bucharest Early Intervention Project. Children were randomized to either receive care as usual (CAUG) or a high quality foster care intervention (FCG). A sample of 48 (26 female) age-matched community-reared children who had never been institutionalized (NIG), were recruited for comparison	Institutional Care: Children raised in institutions that experienced psychosocial deprivation	Peer Evaluation Stress Paradigm (details available in original article) .	Salivary Cortisol: Participants provided a saliva sample during a baseline resting period prior to beginning the peer evaluation task and a second sample approximately 15 minutes after the task was finished	First, following an “intent to treat approach” analyses were conducted with the two randomized groups (CAUG, FCG) examining the size and direction of attention biases at 12 years of age. Attention biases at 12 were related to social outcomes. Third, attention biases were related to physiological reactivity. Regressions were conducted for the entire previously institutionalized sample and separately for each group.	Table 1: Cortisol levels following peer task (difference between CAUG and NIG)	$t(95) = -2.94$	.004	At age 12, among children who received the foster care intervention, positive biases were related to less blunted (or more reactive) cortisol reactivity during a social stressor, which may indicate stress responses more similar to the NIG.

Table 2: *P*-curve Disclosure Table of Trauma-Cortisol Hypo-reactivity Literature

Kliewer et al 2016	It was expected that as youth's victimization experiences increased their cortisol responses would decrease, and their salivary alpha amylase responses would increase.	Youth and their maternal caregivers (N= 358 families) were recruited for a 4-wave longitudinal study of the consequences of exposure to violence. The analytic sample for the present study included 242 urban adolescents who had biological data at Wave 4. Youth were either in the 5th or 8th grade at baseline (M= 11.98 years, SD= 1.56, range = 9–16 years)	Victimization: Survey of Children's Exposure to Violence. Youth indicated on a scale from 0 (never) to 4 (almost every day) how often they had experienced 10 types of victimization ranging from being slapped, hit, or punched by someone to being shot. Items began with the stem, "How many times in the past year have you yourself been ...". All items used in the study are listed on Table 2.	The Social Competence Interview (SCI): During the hot phase, the interviewer asks the adolescent to re-experience a stressful event and asks questions about the participant's thoughts/feelings during the event. The cool phase asks the participant to describe how the situation would have ideally ended.	Salivary Cortisol: Saliva samples were collected from the adolescents directly before the start of the SCI (2 samples), at the end of the "hot" phase, and 10, 10, and 20 min later, yielding 6 samples.	Descriptive information on and correlations among the study variables is presented first. Next, structural equation modeling was utilized to test the primary study hypotheses using Mplus version 7.31, which allowed missing data to be handled with full information maximum likelihood (FIML).	As hypothesized, victimization was negatively associated with total cortisol output ($b = -.15$, $p < .05$), after accounting for time of day of data collection, adolescent sex, and pubertal status at baseline, each of which were significant, and adolescent age, which was not significant.	$r(235) = -.15$	.02088	Structural equation modeling revealed that youth's victimization experiences were negatively associated with total cortisol output in response to a stress task. However, no such association was observed between victimization and salivary alpha amylase. Our findings contribute to a growing literature supporting the attenuation hypothesis, which is particularly applicable for youth experiencing chronic stress.
Koss et al 2016	We sought to examine differences in children's cortisol reactivity to a laboratory setting among children with varying degrees of early life experiences. This included investigations of the impact of early life adversity on cortisol reactivity as well as examinations of longitudinal change, indicative of recovery of the HPA axis, in children's cortisol reactivity following adoption. We examined the extent to which indices of diurnal cortisol and stress reactivity together reflect hypocortisolism in the context of chronic stress.	Participants included 167 children taking part in a larger longitudinal study of the transition to family care following international adoption. Sixty-five children (38 female, 27 male) were adopted from orphanages or institutions (post-institutionalized; PI), 49 children (19 female, 30 male) were adopted from international foster care (post-foster care; PFC) and 53 non-adopted (NA) same-aged children (27 female, 26 male) who were born and raised in similar types of families (education/income) that adopt internationally-born children.	International Adoption: Children adopted internationally from institutions or orphanages	Each laboratory session was approximately 2 hours and consisted of a number of challenging tasks, including brief separations, exposure to novel, arousing stimuli, interactions with strangers, transitions between tasks and rooms, and electrophysiological assessments (see supplemental materials for a detailed description of tasks and timing of cortisol sampling).	Salivary Cortisol: Three saliva samples were collected throughout the laboratory session at each of the four assessments (12 total laboratory samples). The samples were not collected in response to any one task but rather reflect children's reactivity to the demands of the laboratory session as a whole.	Analyses were conducted in four parts. First, descriptive statistics were examined and ANOVAs were conducted to examine group differences in children's kindergarten behavior problems. Second, latent growth models were fit examining cortisol reactivity in the laboratory using multilevel structural equation modeling (MSEM) in MPLUS. Next, regression analyses were conducted to examine whether home diurnal hypoactivity predicted laboratory hypoactivity.	Figure 3: Association between early adversity and hypocortisolism	$r(167) = -.56$	<.0000 1	Blunted cortisol reactivity to laboratory stressors was observed among post-institutionalized and post-foster care children compared to non-adopted peers.

Table 2: *P*-curve Disclosure Table of Trauma-Cortisol Hypo-reactivity Literature

Martinson et al 2016	HPA axis (i.e., cortisol) reactivity to an emotional closeness induction task is expected to be suppressed (i.e., blunted) in women with a history of sexual trauma compared to women without such histories. PTSD symptom severity is expected to be inversely correlated with cortisol reactivity.	Participants were 50 women, 18 years of age or older (MAge = 19.70, SD = 4.19), who were enrolled in undergraduate psychology courses at a large public university in Maine. The majority of women were single (43.1%) and Caucasian (88.2%).	Sexual Trauma and PTSD: a list of 16 behaviorally-specific sexual trauma questions was used as a pre- screening measure to evaluate potential eligibility for this study. PTSD checklist—civilian version (PCL-C) is a 17-item self-report measure for civilians reflecting the 17 DSM-IV symptoms of PTSD. A total severity score was obtained by summing the scores from each of the 17 items	Participants came into the lab and participated in a 45 min emotional closeness exercise with a male confederate and completed self-report questionnaires of closeness, state anxiety/depression, and cortisol assays at the aforementioned time points.	Salivary Cortisol: Salivary cortisol samples were collected using the Salivette® Cortisol with a synthetic swab from Sarstedt, Inc. (Newton, NC).	A 2 (group: sexual trauma, controls) × 5 (time: baseline, 15 min into task, 30 min, 45 min into task, after 15 min post-task relaxation period) mixed factorial design. The primary dependent variables were cortisol levels and psychological reactivity. Post-hoc analyses for ANOVA analyses were conducted with follow up tests of simple main effects.	Results of this analysis revealed a significant effect for Time, $F(2.26,108.3) = 2.95$, $p < .001$. There was also a main effect for Group, $F(1,48) = 5.31$, $p = .03$. These results were qualified by a significant time × group interaction, $F(2.26,108.3) = 3.09$, $p = .04$	$F(2.26,108.3) = 3.09$	.04	As hypothesized, the primary finding of this study was that women with a history of sexual trauma exhibited a blunted cortisol response and greater anxious mood in reaction to the intimacy induction task compared to women in the control group.
Hostinar et al 2015	We aimed to test whether parent support would be more effective than stranger support in lowering cortisol stress responses for NA children, but not PI children, as a reflection of the enduring effects of severe early social deprivation.	We recruited 81 children aged approximately 9–10 years ($M = 9.85$, $SD = .55$, range: 8.87 – 11.09), half of whom were internationally adopted PI children ($N = 41$, M age = 9.7 years, $SD = .56$, range 8.87 – 10.99; 51.2% females) and half who were non-adopted – i.e., born and raised by their birth families in a large urban Midwestern area ($N = 40$, M age = 9.97 years, $SD = .52$, range 9.09 – 11.09; 50% females).	Institutional Rearing: Children raised in institutions that experienced psychosocial deprivation.	TSST-C: This paradigm consisted of a public speaking oneself to a hypothetical new classroom of students) and a mental arithmetic task (subtracting out loud by 3s from 307).	Salivary Cortisol: Participants expelled saliva through a straw into pre-labeled vials. Time was coded as 0, 1, 2, and 3 given that the samples were equally spaced at 20-minute intervals.	Hierarchical Linear Modeling was used to analyze the cortisol data because it is ideal for auto-correlated samples collected from the same individual and it allows for greater statistical power than traditional RM ANOVA models	Results (Table 3) indicated a significant interaction of Group × Condition on cortisol reactivity (linear term: $F(1, 194) = 5.08$, $p = .025$; quadratic term: $F(1, 147) = 3.76$, $p = .055$), with no main effects of Group or Condition on reactivity (p 's > .09).	$F(1, 194) = 5.08$	.025	Cortisol reactivity for PI children in both conditions was lower than that of non-adopted children in the stranger support condition.

Table 2: *P*-curve Disclosure Table of Trauma-Cortisol Hypo-reactivity Literature

Jaffee et al 2015	We hypothesized that with consistent exposure to harsh, rejecting, or dangerous relationships and environments across early and middle childhood, the cortisol response to experimentally induced stressors would be relatively low. In contrast, we hypothesized that in the absence of an early childhood history of harsh, nonresponsive parenting, recent exposure to traumatic events would be associated with increased cortisol reactivity.	The sample included 400 children (51% male) who participated in the Children's Experiences and Development Study (CEDS). Participants ranged from 8 to 11 years (M = 9.99, SD = 0.74). We sampled a 'higher risk' group that included children who had experienced relatively high levels of harsh, nonresponsive parenting at age 3 years. A 'lower risk' group included children who had experienced relatively low levels of harsh, nonresponsive parenting at age 3 years.	Recent Traumatic Events: Recent traumatic events (at follow-up) were measured with the Traumatic Events Screening Inventory. Because agreement between caregiver and child reports was modest (kappas ranged from 0 for low base rate events like 'child was kidnapped' to .51 for 'family member was in trouble with the police or in prison'), events were coded as having happened only if both the child and caregiver reported the event (M = 0.61, SD = 0.85).	Social Provocation Task (SP): The social provocation (SP) task was designed to elicit feelings of frustration and anger in children and was modified from a task developed by van Goozen et al. (1998).	Salivary Cortisol: Saliva was collected at 20 and 10 min prior to the start of the SP task, at the end of the SP task, and at approximately 20, 45, and 65 min following the conclusion of the SP task. Nineteen percent of children refused to participate in round 2 of the SP task (often because they were very distressed). Because cortisol concentrations at time t reflect cortisol activity t – 15 to t – 30 min earlier, cortisol reactivity to the SP task was assessed by subtracting the lowest cortisol value collected by the end of the SP task (which reflected cortisol activity prior to or in the very early stages of the SP task) from the cortisol value collected 20 min following the SP task (which reflected cortisol activity at the conclusion of the SP task).	An ordinary least squares regression analysis was conducted in which cortisol reactivity values were regressed on harsh, nonresponsive parenting, traumatic events, and covariates at the first step and on the interaction between harsh, nonresponsive parenting and traumatic events at the second step. All variables were mean-centered prior to analysis. The main effect of recent traumatic events on cortisol reactivity was qualified by a significant interaction involving harsh, nonresponsive parenting	The main effect of recent traumatic events on cortisol reactivity was qualified by a significant interaction involving harsh, nonresponsive parenting (Table 1 and Figure 1). Results were unchanged, controlling for participation in round 2 of the SP task (interaction: b = .26, SE = .10, p < .05) or baseline cortisol values (inter- action: b = .21, SE = .09, p < .05).	t(54) = -2.8	.007	The lowest levels of cortisol reactivity were observed among children who had experienced higher levels of harsh, nonresponsive parenting in early childhood and two or more recent traumatic events.
Kempke et al 2015	We expected, in line with extant theories and findings concerning the long-term effects of early childhood trauma on the HPA axis, that higher levels of self-reported early childhood trauma would be negatively associated with both cortisol activity and cortisol responses to experimentally-induced psychosocial stress.	Participants were 43 consecutively admitted female patients diagnosed with CFS according to the Center for Disease Control and Prevention criteria for CFS. Among the 43 enrolled patients, two patients did not complete the study for personal reasons, and one patient refused to be exposed to experimental stress. Thus, the final study sample consisted of 40 patients.	Childhood Trauma (CTQ): The Childhood Trauma Questionnaire — Short Form (CTQ-SF) was used to measure exposure to early childhood maltreatment. The CTQ-SF measures five dimensions of childhood trauma: emotional abuse (EA), sexual abuse (SA), physical abuse (PA), emotional neglect (EN), and physical neglect (PN). The CTQ scores range from 5 to 25.	TSST: he TSST is a widely used standardized psychosocial stress test consisting of a role-play (5 min) and mental arithmetic (5 min) task in front of an evaluative audience instructed to maintain a neutral facial expression.	Salivary Cortisol: Salivary cortisol samples ere collected at arrival, after a 30-min rest period/2 min before the onset of the TSST (baseline), immediately after the TSST (0), and at +10, +20, +30, +45 and +90 min relative to the end of the TSST. The stress test was performed between 2:45pm and 3:15pm in a lab specifically set up for the TSST, with a separate waiting and testing room.	Hierarchical regression analyses were performed with stress indices (AUC) as dependent variables and the different trauma domains as independent variables to evaluate the association between cortisol reactivity and early childhood trauma.	Results of the TSST showed that emotional neglect (EN) was inversely associated with measures of increase in cortisol. Specifically, emotional neglect (EN) was strongly significantly negatively related to AUCI ($\beta = -.535, p < .05$) and delta cortisol ($\beta = -.508, p < .05$).	t(38) = -2.41	.02090	Results revealed that emotional neglect was clearly negatively related to cortisol reactivity in the TSST. Taken together, our findings seem to suggest that childhood emotional neglect is associated with a reduced ability to activate the neuroendocrine stress system when confronted with acute psychosocial stress, but not with a fundamental impairment in daily cortisol activity.

Table 2: P-curve Disclosure Table of Trauma-Cortisol Hypo-reactivity Literature

McLaughlin et al 2015	We present comprehensive data on autonomic nervous system (ANS) and HPA axis reactivity from the Bucharest Early Intervention Project (BEIP), the only randomized controlled trial of foster care as an alternative to institutional rearing for abandoned children. We provide evidence for a causal link between the early caregiving environment and stress response system reactivity in humans with effects that differ markedly from those observed in rodent models.	A sample of 136 children (aged 6–30 months) was recruited from Bucharest. An age-matched sample of 72 community-reared children was recruited from pediatric clinics in Bucharest and comprised the NIG. Half of children in the institutionalized group were randomized to a foster care intervention, resulting in two groups: the foster care group (FCG) and the group who received care as usual (prolonged institutional care (CAUG)). A total of 138 children participated in the 12-y physiological reactivity assessment (CAUG, n = 43; FCG, n = 48; NIG, n = 47).	Institutional rearing: children raised from early infancy in institutions in Bucharest, Romania versus a randomized controlled trial of foster care as an alternative to institutional rearing for abandoned children.	TSST: Participants completed three laboratory-based procedures designed to elicit a physiological response: (i) a peer-evaluation task that was passive in nature (ii) an evaluated social performance task requiring instrumental cognitive responses—the TSST, a widely used stress induction procedure that has been used with children and adolescents; and (iii) a nonsocial task designed to elicit frustration that required active responses.	Salivary Cortisol: Participants expectorated ~1.5 mL of saliva into a cryovial with a plastic straw. Saliva samples were stored immediately at –20 °C until they were shipped on dry ice to a laboratory in Boston. Samples were assayed for cortisol and DHEA-S by using commercially available luminescence immunoassay kits (CLIA; IBL)	3 (Group: FCG, CAUG, NIG) x 6 (Time: Peer evaluation, Speech preparation, Speech, Math, Frustration) ANCOVA controlling for sex.	From Table S2: Trier social stress task $F(2, 137) = 5.07, p = .008$	$F(2, 137) = 5.07$; Robustness $F(2, 137) = 4.54$	.00751	Children who remained in institutional care exhibited significantly blunted SNS and HPA axis responses to psychosocial stress compared with children randomized to foster care, whose stress responses approximated those of typically developing children.
Negriff et al 2015	We hypothesized that maltreatment would be linked with dampened cortisol, which in turn predicts accelerated pubertal development, which then predicts riskier psychosocial functioning (higher rates of depressive symptoms, delinquency, and substance use).	At Time 1 (T1), the sample was composed of 454 adolescents aged 9–13 years (241 males and 213 females). Time 2 (T2), Time 3 (T3), and Time 4 (T4) occurred on average 1, 2.7, and 7.2 years after baseline. The retention rate between T1 and T2 was 86.1% ($n = 391$), between T1 and T3 was 70.9% ($n = 322$), and between T1 and T4 was 77.5% ($n = 352$).	Maltreatment: The maltreatment group was recruited from active cases in the Children and Family Services (CFS) of a large west coast city. The comparison group was recruited using names from school lists of children aged 9–12 years residing in the same 10 zip codes as the maltreated sample.	TSST-C: Participants were read the beginning of a story, given 5 min to develop the next part of the story, and then spent 4 min presenting that story to an interviewer and a panel of two judges who maintained neutral facial expressions throughout the task. Next, the youth performed a challenging 4-min serial subtraction task before the judges.	Salivary Cortisol: Six saliva samples were obtained over 90 min: the first two were collected 45 min before the stressor and 10 min before the stressor (immediately after a 5-min relaxation protocol that included soft music and a still slide of a beach scene). The third saliva sample was obtained immediately after the stressor was complete, and the fourth, fifth, and sixth samples occurred 10, 20, and 30 min after the end of the stressor, respectively.	Structural equation models were tested using Mplus with the MLR estimator. Latent variables were constructed for delinquency (three manifest indicators) and substance use (two manifest indicators). Maltreatment status, cortisol excretion (AUCg), pubertal stage, and depressive symptoms were included as manifest variables.	For boys, maltreatment was associated with attenuated cortisol, and more pubertal change predicted subsequent delinquency. Table 2: Maltreatment → T1 cortisol ($b = -.25$, $S.E. = .06, p < .01$).	$t(240) = -4.16$	.00004	For boys, maltreatment was associated with attenuated cortisol patterns, supporting the attenuation hypothesis. For girls, maltreatment did not predict attenuated cortisol. This is inconsistent with other literature showing the effects of maltreatment on cortisol response for girls.

Table 2: *P*-curve Disclosure Table of Trauma-Cortisol Hypo-reactivity Literature

Peckins et al 2015	Based on previous research, it was hypothesized that maltreated youth would be more likely than nonmaltreated youth to present with the unemotional (i.e., blunted) pattern of stress reactivity at each occasion of measurement. A blunted pattern was expected to be present in maltreated youth regardless of maltreatment type.	The present study used data from the second, third, and fourth time points of a longitudinal study of the effects of maltreatment on the health and well-being of adolescents. At Time 1 (T1), the sample was composed of 454 adolescents ($n = 212$ females) ages 9–12 years ($M = 10.95$ years). Time 2 (T2), Time 3 (T3), and Time 4 (T4) occurred approximately 1, 2.5, and 4.5 years after baseline, respectively. The mean age of youth at T2, T3, and T4 was 12.11, 13.69, and 18.23 years.	Maltreatment: Neglect, physical abuse, or sexual abuse.	TSST-C: The TSST-C is a social and cognitive stressor consisting of two tasks: a story completion task and a mental, serial subtraction task, each lasting 4 min. Participants were told prior to the story completion task that their performance would be compared to the performances of their peers.	Salivary Cortisol: At each wave of data collection, participants provided six saliva samples by spitting into a 5-ml tube to measure cortisol reactivity in response to the TSST-C. Two baseline samples of saliva were collected, the first immediately upon arrival after consent/assent forms had been signed (at T –45 min TSST-C) and the second immediately following a 5-min relaxation period (at T –10 min TSST-C). Four poststressor saliva samples were collected; one sample immediately following the stressor (+0 TSST-C) and three samples at 10-min increments (+10 min, +20 min, and +30 min TSST-C).	Only data from T2, T3, and T4 were used in the analyses in order to be able to control for the effects of recent adversity (e.g., recent exposure to violence) on HPA axis activity. Descriptive analyses were performed for all variables. Independent t tests were performed to test for mean differences between maltreated and nonmaltreated youth in recent exposure to violence, recent exposure to trauma, and cortisol concentrations.	Frequencies and percentages for all categorical variables are provided in Table 1. Descriptive analyses were performed and are presented in Table 2. Maltreated adolescents presented with lower levels of cortisol than their nonmaltreated peers across all samples at T2 and T3. Refer to Table 2 for Cortisol Time 2 t-test.	$t(388) = -3.66$	.00029	A history of maltreatment was associated with an increased likelihood of exhibiting the blunted cortisol profile in comparison to the moderate and elevated profiles, and this pattern was consistent for both sexually/physically abused youth and emotionally abused/neglected youth, but only at T2 and T3
Schalinski et al 2015	To allow a differentiation of phasic and tonic levels of cortisol, the current study measured acute cortisol stress reactivity and long-term hair cortisol levels. Specifically, we investigated the impact of childhood sexual abuse (and other adverse experiences) on saliva cortisol reactivity and autonomic parameters towards an idiographic assessment of traumatic experiences in female patients with stress-related psychopathology.	Patients with stress-related disorders ($N = 43$) were recruited through the outpatient clinic for refugees at University of Konstanz. To compare results of hair cortisol levels, we further recruited 12 healthy control subjects from the general community. Forty-three female survivors of violence participated in the study. The age of the participants ranged from 16 to 56 years ($M = 34.9$, $SD = 10.5$).	Early Trauma Inventory (ETI): The Childhood adversities up to age 18 were recorded using the Early Trauma Inventory (ETI); German version. In an interview 55 items that score on four domains of maltreatment and abuse were assessed (general traumatic experiences, emotional abuse and neglect, physical maltreatment and sexual abuse).	Idiographic Trauma Interview: he interview about traumatic experiences included (1) the event checklist, (2) followed by the interview of childhood adversities.	Salivary Cortisol: Salivary cortisol, heart rate, systolic and diastolic blood pressure were recorded at 4 different time points during a standardized interview.	2 (Group: with and without sexual abuse) $\times$ 4 (time) repeated measures ANOVA.	Salivary cortisol levels differed for the group with and without childhood sexual abuse ($F(1, 31) = 6.25$, $p = .018$, $\eta^2 = .17$). Interestingly, the ANOVA showed a significant time $\times$ group interaction ($F(2.29, 71) = 3.08$, $p = .045$, $\eta^2 = .09$). Whereas the group with childhood sexual abuse responded with a down regulation of cortisol, the group without childhood sexual abuse did not differ from baseline.	$F(2.29, 71) = 3.08$	.045	In addition to previous reports, we found distinct activity patterns of cortisol (measured by responder rates facing the trauma assessment, mean salivary cortisol and cortisol accumulated in hair) among patients displaying hints of neurobiological subtypes.

Table 2: *P*-curve Disclosure Table of Trauma-Cortisol Hypo-reactivity Literature

Voellmin et al 2015	Therefore, the aim of the present study was to replicate the findings of attenuated endocrine and cardiovascular stress reactivity in association with a history of ACEs in a young, healthy, female adult sample.	The sample included 104 young and healthy females in the age of 18 to 25 years.	Adverse Childhood Experiences: ACEs before the age of 18 years were assessed retrospectively using a German translation of the "Early Trauma Inventory-Self Report" (ETI-SR), which includes general trauma, physical, emotional, and sexual abuse items.	The MIST was used to induce a psychosocial stress response. The MIST is a standardized psychosocial stress test during which participants have to solve arithmetic tasks displayed on a computer screen under time pressure and social evaluation.	Salivary Cortisol: Saliva was collected at seven measurement points, whereof two took place before the stress test (-10 and -1 min) and five after the stress test (+1, +10, +25, +40, and +55 min) using salivettes.	4 x 6 repeated measures ANOVA. GLM for repeated measures served to determine the effects of ACEs on endocrine and cardiovascular responses. In these models, the ACE total sum core as well as the different scores for duration and age of occurrence were used as continuous variables to examine effects of time, ACE scores, and the interaction of time by ACE scores.	Repeated measures analysis of cortisol response to stress showed a significant interaction of time x ACE total sum score [F(2.33, 221.60) = 5.89, $p < .001$; $\eta p^2 = .06$] as well as a significant main effect of ACE total sum score [F(1,95) = 7.52, $p < .01$; $\eta p^2 = .07$]	$F(2.33, 221.60) = 5.89$	.00192	Our results are in line with previous reports of attenuated endocrine (as well as cardiovascular (stress responses to a psychosocial stress test in healthy adults with a history of adverse childhood experiences. Importantly, blunted cortisol and heart rate responses were independent of emotional responses, suggesting that the diminished endocrine and cardiovascular stress reactivity cannot be explained by a reduced emotional reaction to stress.
Aiyer et al 2014	Based on previous findings, we hypothesized that cumulative exposure to violence during adolescence would be associated with a hyporesponsive cortisol pattern in early adulthood. Specifically, participants exposed to violence were predicted to exhibit signs of an attenuated stress response.	The present study included 266 participants who had cortisol data and data on our study variables across waves 1–7. The cortisol collection procedure is described in detail below. Participants were between ages 13.9 and 16.9 years at wave 1 (mean = 14.9; SD = .64) and between ages 21.9 and 24.3 years at wave 7 (mean = 22.1; SD = .66). The analytic sample was 80 % African American, 17 % Caucasian, and 3 % Mixed Race. The analytic sample was 43 % Male and 57 % Female.	Cumulative Exposure to Violence (ETV): Cumulative ETV was calculated by standardizing each subscale (witnessing violence and violence victimization) across each wave (waves 1–7), and adding scores to represent cumulative exposure to violence across adolescence and early adulthood.	Interview with sensitive information: The saliva was collected during wave 7 at three points during an in-person paper-and-pencil interview concerning sensitive information (e.g., substance use, sexual risk behavior, violent behavior, and discrimination). Such questions were thought to be somewhat stressful for participants, based on their sensitive nature.	Salivary Cortisol: We utilized salivary cortisol as our measure of the stress response, as it reflects the free portion of cortisol in plasma recommended by many researchers. The saliva was collected during wave 7 at three points during an in-person paper-and-pencil interview concerning sensitive information. Cortisol values were log transformed to reduce the skewness of the distribution. To make the repeated measurements of salivary cortisol more useful, we assessed the cortisol response by calculating area under the curve with respect to increase [AUC (I)]. This allowed us to assess changes in cortisol secretion over time.	We conducted a hierarchical regression analysis to examine the unique contributions of cumulative exposure to violence, mother support and father support to cumulative exposure to violence. At each step in the analysis, we also examined the contribution of participant race, sex, and interview start time to reduce potential confounding.	Introducing cumulative exposure to violence in step 2 resulted in improved model fit. Further, cumulative exposure to violence was negatively associated with cortisol area under the curve with respect to increase (See Table 3).	$r(246) = -.13$	.03407	We found evidence for the influence of cumulative exposure to violence during adolescence and early adulthood on cortisol responsivity in early adulthood. Focusing on a uniquely high-risk sample, we found that participants exposed to chronic violence demonstrate signs of an attenuated stress response.

Table 2: *P*-curve Disclosure Table of Trauma-Cortisol Hypo-reactivity Literature

Grimm et al 2014	In the present study, we sought to clarify the impact of ELS on stress responsivity and associated neural activity as well as to determine OXT effects on these parameters in healthy subjects with and without a history of ELS. We therefore, firstly, aimed to investigate the effects of OXT on deactivation of limbic regions implicated in psychosocial stress response. Secondly, we aimed to examine whether these OXT effects might differ in subjects with/without ELS.	Thirty-two healthy male subjects (age 28.4 +/- 4.5; range 21–37 years; IQ 112 +/- 15) were recruited out of a preexisting psychologically and somatically healthy community-dwelling sample (N = 541).	Childhood Trauma Questionnaire (CTQ): The CTQ consists of 28 items that are assigned to the following 5 subscales: emotional neglect, emotional abuse, physical neglect, physical abuse and sexual abuse. Participants were recruited for the ELS group, if their CTQ-score was no lower than 3 points below the 90th percentile, whereas control subjects had scores no higher than 3 points above the 50th percentile.	Montreal Imaging Stress Task (MIST): Psychological stress was induced using the Montreal Imaging Stress Task (MIST). The MIST uses a block design, and consists of mental arithmetic challenges that must be answered under time pressure.	Salivary Cortisol: Nine saliva samples were collected with the Salivette sampling device (Sarstedt Inc.) throughout the experiment at the following time-points: Baseline (saliva 1= T0), 45 min after OXT/placebo administration (saliva 2 / 6 = T1), immediately before (saliva 3 / 7 = T2 (20min after T1)) and after the MIST (saliva 4 / 8 = T3 (20min after T2)) as well as 20min after the completion of the MIST (saliva 5 / 9 = T4).	Behavioral data were analysed using t-tests for independent samples. Physiological data were analysed using repeated measures analyses of variance (ANOVAs) with the within-subjects factor substance (OXT, placebo) and the between-subjects factor ELS. Greenhouse–Geisser corrections were applied where appropriate. Further statistical analysis was conducted using t-test comparisons. All tests were two-tailed and the significant threshold was set at $P < 0.05$.	There was a main effect of ELS ($F(1,27) = 6.24$, $P = 0.021$) on cortisol concentrations at T3 (immediately after the MIST) and of substance on cortisol concentrations at T2 (immediately before the MIST; ($F(1,27) = 4.89$, $P = 0.039$) with lower concentrations in the ELS group and the placebo condition, respectively.	$F(1,27) = 6.24$	.018	Subjects who experienced ELS showed both blunted stress reactivity and limbic deactivation during stress. Our findings demonstrate that healthy subjects who experienced moderate to severe emotional neglect and abuse in their childhood not only show attenuated hormonal and limbic reactivity during psychosocial stress, but might also have an altered OXT sensitivity, since the previously reported stress-buffering effect of OXT was only found in subjects who did not experience ELS.
Pagliaccio et al 2014	We tested the hypotheses that genetic profile scores and early life stress exposure would predict increased cortisol responses to laboratory stressors in preschool-age children.	Data were analyzed from 120 children (58 females; 57.5% White, 30.0% African-American, and 12.5% of other or mixed race) enrolled in the Preschool Depression Study (PDS), a prospective longitudinal study of preschool-age children (N = 306) conducted at the Washington University School of Medicine Early Emotional Development Program (WUSM EEDP) in St Louis.	Stressful and Traumatic Life Events: Analyses examined stressors experienced from birth through the baseline assessment when participants were 3–5 years old (current subsample mean age at baseline assessment = 4.45 years, SD 1/4 0.77), at which time cortisol was collected. We summed the instances of stressful and traumatic life events reported by parents during the PAPA.	Behavioural Tasks: The second saliva collection occurred approximately 30min after separation from the parent, during which time the child performed a variety of behavioral tasks. Following this collection, the child performed more behavioral tasks and several stress-/frustration-inducing episodes from the Laboratory Temperament Assessment Battery.	Salivary Cortisol: Salivary cortisol was collected three times.	We used hierarchical linear regressions in SPSS to predict cortisol and regional brain volumes. Predictors were added in steps to understand their effects alone and controlling for covariates. Regressions first controlled for ethnicity and sex. Next, centered, continuous variables for genetic profile scores and life events were entered. Interactions between these factors and interactions with sex were then entered.	AUC cortisol levels were positively predicted by genetic profile scores ($b = 0.32$, $t = 3.04$, $p = 0.003$) and negatively predicted by life events ($b = -0.28$, $t = -3.00$, $p = 0.003$), even when controlling for all covariates. Together these factors accounted for 8% of the variance in cortisol beyond ethnicity and sex.	$t(118) = -3.00$	.003	Congruous with the literature suggesting that life adversity results in blunted HPA axis responses to acute stress (Carpenter et al, 2007; Lovallo et al, 2012; Ouellet- Morin et al, 2011), we found that the number of stressful and traumatic life events experienced by preschool age negatively predicted cortisol levels.

Table 2: *P*-curve Disclosure Table of Trauma-Cortisol Hypo-reactivity Literature

Shenk et al 2014	Adopting a multiple levels of analysis approach, the current study simultaneously tested the indirect effects of experiential avoidance, RSA, and cortisol in mediating the relationship between child maltreatment and subsequent PTSD symptoms using a sample of maltreated and non-maltreated adolescents.	One hundred ten adolescent females between the ages of 14–19 years of age participated in this study. wo distinct groups of adolescent females participated. A child maltreatment group (n= 51) was recruited from Child Protective Service (CPS) agencies investigating allegations of physical neglect or contact physical or sexual abuse..A non-maltreated, comparison group (n= 59) was recruited using posted flyers in a primary care outpatient clinic servicing the general medical complaints of at-risk, adolescent females.	Child Maltreatment: Child maltreatment was determined by a CPS investigation that resulted in a substantiated/indicated designation of child maltreatment. Of the 51 participants in the maltreatment group, 49% experienced sexual abuse, 45% experienced physical abuse, and 16% experienced physical neglect with 10% experiencing more than one form of abuse. Comparison females were screened and excluded if they had a substantiated case of child maltreatment within the twelve months prior to study participation.	Stressor Paradigm: The performance aspect of the stressor paradigm involved each participant completing a series of affect recognition tasks. Participant responses were timed and each participant was asked to identify the emotion as quickly as they could while not making any mistakes before the time elapsed. The interpersonal stressor involved participants viewing a series of video-clips of parent-adolescent conflict.	Salivary Cortisol: The first sample, Cortisol-Rest, was collected approximately 25 minutes (M= 25.30, SD= .24) after participants began their study appointment to give them time to acclimate to the research environment and procedures. Samples two through five were collected 5-, 10-, 20- and 30-minutes post stressor to detect the maximum cortisol response to the combined stressor, Cortisol-Stress. Saliva was obtained through passive drooling into 20 mL polypropylene vials and stored at –80°C until assayed.	A multiple mediator model was employed to identify the total and specific indirect effects of RSA-Stress, Cortisol-Stress and AAQ scores when explaining the relationship between child maltreatment and subsequent PTSD symptoms. The multiple mediator model was performed with Mplus v.6 using the maximum likelihood estimator to account for missing data.	$r(104) = -.21$ (Table 2)	$r(104) = -.21$	.03073	The maltreated group did display a hypocortisol reaction during the stressor condition once relevant demographic variables and health-related behaviors were controlled. This finding is consistent with previous research showing a relationship between child maltreatment and hypocortisol reactions during stress paradigms.
Sumner et al 2014	We hypothesized that child maltreatment would be associated with blunted cortisol reactivity to psychosocial stress as a function of rs110402 genotype (i.e., primarily among G allele carriers).	A community-based sample of 168 adolescents aged 13–17 was recruited for participation at schools, after-school programs, medical clinics, and the general community in Boston and Cambridge, MA.	Childhood Trauma Questionnaire: The CTQ is a 28-item scale that assesses the frequency of maltreatment exposure during childhood and adolescence. Three types of abuse are assessed: physical, sexual, and emotional. Childhood Experiences of Care and Abuse (CECA) Interview: The CECA assesses multiple aspects of caregiving experiences, including physical and sexual abuse.	TSST: Participants completed the Trier Social Stress Test (TSST; Kirschbaum et al., 1993), a widely-used stress induction procedure that has been used with children and adolescents (Buske-Kirschbaum et al., 1997; Stroud et al., 2009).	Salivary Cortisol: Saliva samples were taken after the initial baseline period, 15 min following the beginning of the speech portion of the TSST (reactivity period), and 15 min following completion of the recovery period.	3(time) x 2(childhood maltreatment) ANOVA.	There was a significant Time x Child Maltreatment interaction, $F(1.36, 205.90) = 5.05$, $p = .02$, $h^2 = .03$. As shown in Fig. 2, adolescents with a history of child maltreatment exhibited lower cortisol levels at the second [$t(156) = 1.83$, $p = .07$] and third [$t(146.23) = 2.69$, $p = .01$] cortisol assessments compared to those without a history of maltreatment.	$F(1.36, 205.90) = 5.05$	.016	In this community sample of adolescents, a history of child maltreatment was associated with blunted cortisol reactivity to a psychosocial stressor.

Table 2: *P*-curve Disclosure Table of Trauma-Cortisol Hypo-reactivity Literature

Suzuki et al 2014	The current study aimed to examine stress reactivity in individuals with and without a history of childhood trauma by measuring cortisol responses to the passive viewing of stressful images, specifically including images relevant to childhood trauma. In addition, participants with and without a diagnosis of current depression were studied to investigate whether cortisol stress reactivity may underlie resilience or vulnerability to depression.	A total of 80 participants (28 males and 52 females) were recruited into four groups comprising: 17 healthy participants with a history of childhood trauma (Healthy Abused: H/A) and 24 without (Healthy Non-abused: H/NA); and 21 depressed patients with a history of childhood trauma (Depressed Abused: D/A) and 18 without (Depressed Nonabused: D/NA).	Childhood Trauma Questionnaire (CTQ) was used to assess experiences of childhood trauma. . Those who scored at or above 'moderate-severe' level in at least one of the five subscales (emotional abuse (EA), physical abuse (PA), sexual abuse (SA), emotional neglect (EN) and physical neglect (PN)) of the CTQ were then assigned to the relevant experimental groups (H/A or D/A). Those who scored below the same level were assigned to non-abused groups (H/NA or D/NA).	Stress inducing images from International Affective Picture System (IAPS): Each participant viewed 48 stress-inducing images as well as 48 non-stress inducing images. Stress inducing images comprised 24 negative affect images chosen from IAP) and 24 images chosen from a public photo archive to represent each of four types of childhood trauma (emotional abuse, physical abuse, sexual abuse and emotional neglect.	Salivary Cortisol: Salivary cortisol was measured to investigate the effects of image exposure on HPA axis reactivity. Saliva samples were obtained by passive drool into sterile plastic tubes. Over the course of the sessions, two saliva samples were collected 5 min apart on three occasions: before session 1 (S1 and S2), between session 1 and 2 (S3 and S4), and after session 2 (S5 and S6).	2 (depression) x 2 (trauma) x 3 (time) ANOVA.	A two-way ANCOVA (childhood trauma x depression) showed a significant interaction of depression and childhood trauma ($F(68, 1) = 4.4, p < .05$). The main finding is that stress reactivity was higher in non-abused depressed patients than in all of the other groups. Another two-way ANCOVA (childhood trauma x depression severity) showed a main effect of childhood trauma with overall larger reactivity in non-abused group than abused group ($F(66, 1) = 4.6, p < .05$).	$F(1,68) = 4.4$; Robustness $F(1,66) = 4.6$	.039	We found a significant interactive effect of depression and childhood trauma on stress reactivity. The first main finding is that, irrespective of individuals' depressive states, those with a history of childhood trauma showed a reduced cortisol reactivity to stress. Although there were no differences in relation to admission status, childhood trauma was related to overall lower cortisol responses.
Trickett et al 2014	Because maltreated youth tend to have repeated and chronic exposures to maltreatment, we expected the maltreated youth to exhibit an attenuated cortisol response to the laboratory stressor as compared with the non-maltreated group.	The maltreatment group (N = 303) were recruited from active cases in a county Department of Children and Family Services (DCFS) of a large western U.S. city. The inclusion criteria were (1) a new substantiated referral to DCFS in the preceding month for any type of maltreatment; (2) child age of 9–12 years; The comparison group (N = 151) was recruited via mail using names from school lists of children aged 9–12 years residing in the same 10 zip codes.	Maltreatment: The nature of each maltreated adolescent's experience of abuse and neglect was obtained by examining the DCFS case record for each individual and entering this information into the Maltreatment Case Record Abstraction Instrument (MCRAI).	TSST-C: This modification of a common method used to elicit an HPA stress response in a laboratory context includes a social challenge (composing and performing a story in front of a panel of judges) and a cognitive challenge (oral serial subtraction).	Salivary Cortisol: We collected six saliva samples, two before and four after the TSST-C. The rationale for the number of samples and the timing of intervals was based on the importance of accurately assessing both baseline levels of cortisol and reactivity to the stressor. samples involved measures selected for content unrelated to trauma and stress. Data collection occurred primarily in the afternoon, with 96% of participants providing the baseline saliva sample between 1200 and 1700 hr. The earliest baseline sample was collected at 1223 hr, and the latest was collected at 1735 hr. We control for time of day in all analyses.	6 (time) x 2 (group: maltreatment vs. control) repeated measures ANOVA	A significant maltreatment group x sampling time interaction effect, $F(5, 426) = 5.78, p < .001$, was found, suggesting the cortisol response curve differed between maltreated and non-maltreated adolescents.	$F(5, 426) = 5.78$; Robustness $F(2, 424) = 3.89$	.00004	Findings indicated that for these young adolescents, maltreatment was associated with attenuated cortisol reactivity overall and that this result was pronounced in those youth who experienced more severe maltreatment as indicated by maltreatment that included physical and/or sexual abuse as well as, frequently, other forms of maltreatment, and as noted in the description of the sample, by more reports to DCFS.

Table 2: *P*-curve Disclosure Table of Trauma-Cortisol Hypo-reactivity Literature

Feldman et al 2013	We hypothesized that children with PTSD would exhibit hypocortisolism, expressed in low baseline CT and minimal reactivity, and would select withdrawal strategies to regulate fear as compared to exposed children without PTSD.	Participants included 232 children from 232 families aged 1.5 to 5 years (M = 33.08 months, SD = 10.89) and their mothers (M = 31.27 years, SD = 5.55, range = 22.3–47.4). The sample included 47.6% males and 47.1% firstborns.	War Exposure: Citizens of Sderot were exposed repeatedly to rocket attacks from Gaza over a period of several years, had only 15 s to enter protected spaces after hearing the alert sirens, and were exposed to frequent mortar shelling.	To elicit the stress response, we used a detailed evocation of traumatic memories, combined with a fear paradigm that involved the presentation of increasingly fearful novel objects adapted from the Lab-TAB.	Salivary Cortisol: Baseline, following challenge, and recovery.	A repeated-measure multivariate analysis of covariance (MANCOVA) with group (controls, exposed children with PTSD, and exposed-no-PTSD) and child gender as the between-subject factors and child age as a covariate was computed for three measurements of CT.	The results indicated significantly greater stress reactivity among controls as compared to the exposed children, $F(2, 197) = 6.37, p < .01$.	$F(2, 197) = 6.37$; Robustness $F(2, 197) = 5.82$	.00209	Children with PTSD exhibited consistently low CT and sAA, exposed-no-PTSD displayed consistently high CT and sAA, and controls showed increase in CT following challenge and decrease at recovery and low sAA.
Bosch et al 2012	This study extends previous findings by exploring the effects of adversities from the prenatal period up to adolescence on adolescents' cortisol stress responses. We examined adversities during five age periods (pre/postnatal, 0–5 years, 6–11 years, 12–13 years, 14–15 years), to investigate their specific effects on the HPA-axis. We anticipated that effects of adversities on the cortisol responses would depend on their timing, and that pre/postnatal adversity would render individuals more sensitive to persistent effects of later adversities on the HPA-axis.	The data were collected in a focus sample of TRAILS (Tracking Adolescents' Individual Lives Survey), a large prospective population study of Dutch adolescents from age 11 to 21. Complete HPA-axis and adversity measurements were available for 640 participants. Adolescents were excluded if stressful life events were assessed more than 3 months before (n=60) or more than six months after the experiment (n = 60). In addition, we excluded adolescents with cortisol outliers (>3 SD, n = 11), as well as adolescents who used corticosteroids (n = 38), leaving a total of 471 (32.3% low- risk) participants for analysis.	Life Adversities: Including traumatic experiences measured via interview and self-report.	Social Stress Test: The experimental session during T3 consisted of a number of different challenges (orthostatic stress, spatial-orienting task, gambling task, startle-reflex task, and social stress test). The social stress test (Groninger Social Stress Test) involved a standardized protocol inspired by the Trier Social Stress Test (Kirschbaum et al., 1993).	Salivary Cortisol: HPA-axis responses towards the social stress test were assessed by four cortisol samples, before the introduction of the social stress test ('pretest'), directly after the test ('during test'), 20 min after the test ('end of test'), and 40 min after the test ('post test').	Repeated-measures general linear models (GLM, Greenhouse—Geisser corrected) were used to examine (1) the main effects of adversities per period and (2) the inter- action of pre/postnatal risk with each later adversities on the HPA-axis. Adversity variables were tested simultaneously and hence their effects were adjusted for each other. Investigated outcome variables were cortisol reactivity and cortisol overall level. Cortisol reactivity reflects the pattern of response, while cortisol overall level represents the average level across all four samples	Figure 1: Subjects with the highest number of adversities during early adolescence (ages 12– 13) had the lowest cortisol overall level ($F(1,441) = 4.80, p = .03$).	$F(1,441) = 4.8$	.028	The transition in cortisol activity from hypersecretion after adversities before age 11 and hyposcretion afterwards emphasizes puberty as a major developmental period of the HPA-axis. Results highlight the importance to take the timing of stress exposure into account. In addition to programming effects, pre/postnatal adversity interacts with childhood adversity in producing deviant cortisol levels. Puberty may be marked by a transition in how adversities affect the HPA-axis, with cortisol hypersecretion before age 11 and hyposcretion after age 11.

Table 2: *P*-curve Disclosure Table of Trauma-Cortisol Hypo-reactivity Literature

Fisher et al 2012	We aimed to follow-up Lester et al.'s findings, focusing on whether foster children in a similar age range to the children in the prior study (with varying profiles of prenatal substance exposure and maltreatment) would show a pattern of blunted cortisol responsivity to a laboratory psychosocial stressor.	Our participants included 57 children placed in foster care during the preschool period. (Results with 53 children)	Early Adversity: Early adversity (i.e., abuse and neglect experienced prior to placement in foster care during the preschool period) was coded from child welfare system records using the Maltreatment Classification System (MCS).	TSST-C: This standardized protocol is designed to induce moderate psychosocial stress in laboratory settings and has been shown to produce elevations in cortisol in adults and children.	Salivary Cortisol: Five salivary cortisol samples were collected at 15-min intervals beginning immediately prior to the TSST-C.	The children's AUCI scores were then dichotomized to compare children with increases and decreases in cortisol levels over time. Pearson's chi-square tests were conducted to examine the relations between early adversity, prenatal substance exposure, and salivary cortisol response over time.	There was a significant main effect of early adversity, physical abuse in particular, Pearson $\chi^2(1, N = 53) = 4.49, p = .03$. Among the children who experienced physical abuse, 77% ($n = 17$) showed a decreased cortisol response over time.	$\chi^2(1) = 4.49$	.034	Area under the curve with respect to increase (AUCI) analyses revealed that prenatal substance exposure or physical abuse significantly increased the likelihood of a negative AUCI (i.e., little or no HPA reactivity). Among children with prenatal substance exposure and physical abuse, 85% exhibited a negative AUCI.
Lovallo et al 2012	The present study examines cortisol and heart rate responses to a standardized psychological stress protocol incorporating simulated public speaking and mental arithmetic challenges. The study population included healthy young adults free of psychiatric comorbidities but who had experienced a range of physical and psychological adverse events in childhood and early adolescence.	Sample includes 354 participants (158 m; 196 f). The study population included healthy young adults free of psychiatric comorbidities but who had experienced a range of physical and psychological adverse events in childhood and early adolescence	Adversity: Lifetime adversity was based on C-DIS-IV items: Physical or Sexual Adversity (Have you ever been mugged or threatened with a weapon. Have you ever been raped or sexually assaulted?) and Emotional Adversity (Before you were 15, was there a time when you did not live with your biological mother for at least 6 months? Each person was assigned an adversity score ranging from 0 (no adverse events) to a maximum of 5.	TSST: 30 minute prestress baseline, when subjects sat quietly and read general interest magazines, followed by 45 min of behavioral stress. Stress included simulated public speaking followed by mental arithmetic.	Salivary Cortisol: Saliva samples were collected and taken at: awakening, arrival at the lab, min 10 and 20 of baseline period, at min 15, 30, and 45 of the stress protocol or continued resting protocol, and 15 and 30 min poststress or rest, and at bedtime. Stress reactivity as reported here was measured at min 10 and 20 of the baseline period and at min 30 and 45 of the stress period contrasted with samples taken at the same time during the extended resting protocol.	3 (adverse events: 0 vs 1 vs 2 or more) x 2 (gender: male versus female) ANOVA	The size of the cortisol response diminished as the number of lifetime adverse events increased [$F(2,348) = 5.79, p < .004$].	$F(2,348) = 5.79$	.00336	The present study shows that men and women who experience more adverse life events before age 15 also have smaller cortisol and heart rate responses to psychological stress. These findings seem to illustrate an impact of stress exposure in childhood and adolescence on the regulation of the stress axis in adulthood.

Table 2: *P*-curve Disclosure Table of Trauma-Cortisol Hypo-reactivity Literature

Peckins et al 2012	Cortisol reactivity (CR) was hypothesized to be attenuated in children exposed to violence.	Participants were 124 (n = 64 females) adolescents from a small city and rural communities. In the first wave of measurement at Time 1, girls were ages 8 (n = 21), 10 (n = 20) or 12 (n = 23) years and boys were ages 9 (n = 19), 11 (n = 21) or 13 (n = 20) years.	Exposure to violence: My Exposure to Violence (MyETV) is a self-report measure of ETV occurring within the past 12 months and over the child's lifetime. The MyETV is a well-validated measure consisting of six scales (Lifetime and past year exposure to: witnessed violence, victimization, and total exposure).	TSST-C: The TSST-C consisted of a story completion task followed by mental, serial subtraction while being monitored by two confederate judges. Different story completion tasks and judges were used at Time 1 and Time 2. Participants were told their performance would be compared to others of the same age.	Salivary Cortisol: Children passively drooled into a 5-mL tube until 4-mL of saliva was collected or 5 minutes passed. The samples were collected 20 min and 5 min pre-TSST-C, and 0 min, 10 min, and 20 min post-TSST-C.	Two multiple linear regression models were developed and Time 2 CR was regressed on age, Time 1 lifetime ETV, Time 1 CR, and symptoms of psychopathology (Model 1), and Time 1 covariates and ETV occurring in the 12 months before Time 2 (Model 2). Symptoms of MDD, GAD, and PTSD were included to examine the association between ETV and depression and anxiety, and to rule out the effect of symptoms of psychopathology on CR.	Refer to Table 2: $r(60) = 0.311$, $p = .01388$.	$r(60) = 0.311$	.01388	The hypothesis that adolescents with greater recent ETV would have significantly lower CR was supported for males. The findings held even after controlling for symptoms of psychiatric disorders, age, and CR and lifetime ETV at Time 1. Symptoms of MDD and GAD were positively associated with lifetime ETV at Time 1, indicating that adolescents with greater lifetime ETV report more symptoms of MDD and GAD.
Sturge-Apple et al 2012	In accordance with EST conceptualizations of differentiation in children's emotional security in family systems, we hypothesized that interparental violence would be primarily associated with children's cortisol reactivity to a standardized laboratory paradigm in which children were exposed to a simulated interparental conflict.	Participants included 201 two-year-old children and their mothers in a moderately-sized metropolitan area in the northeastern United States. We administered the abbreviated version of the Physical Assault Scale of the Conflict Tactics Scale 2 (CTS2) to insure that roughly equal proportions of participating mothers experienced (a) no violence (40%), (b) mild/moderate physical violence (24%), and (c) severe physical violence (36%) in the last year.	Interparental Violence: First, mothers self-report of inter-partner violence were assessed using subscales from the Revised Conflict Tactics Scale (CTS2). The CTS2 Physical Assault subscale contains 24 items designed to assess maternal and partner acts of physical violence toward each other in the inter-partner relationship.	Simulated Phone Argument Task: Children and their mothers participated in the Simulated Phone Argument Task (SPAT) to assess children's reactivity to interparental conflict. During this procedure, children witnessed live simulations of their parents engaging in a conflict and a subsequent resolution over the telephone. Each exchange lasted approximately 1 minute and was interspersed by a three-minute free period.	Salivary Cortisol: Baseline samples were collected on average within the first 15 minutes upon arrival to the laboratory, after maternal consent had been obtained. Cortisol – SPAT—Two post-task saliva samples were also obtained to assess trajectories of cortisol change across three assessments. The two post-task saliva samples were obtained approximately 25 and 37 minutes after the end of the simulated disagreement, the period in the SPAT to correspond roughly with the midpoints of the two peak periods of cortisol reactivity to stressors.	We examined unconditional latent growth curve models (LGC) for children's cortisol reactivity using MPlus 6.0 statistical software. Given the presence of significant individual differences in cortisol trajectories in both the SS and the SPAT paradigms, our next set of analyses examined interparental violence and maternal emotional unavailability as predictors of children's cortisol functioning.	Analyses revealed that interparental violence was a significant predictor of children's cortisol reactivity in the SPAT paradigm ($\beta = -.21$, $p = .039$). This pathway accounted for 8% of the variability in cortisol reactivity in the SPAT paradigm. The beta for this effect was negative which indicates that as interparental violence increased, children's cortisol reactivity was lower on average. This finding supports the hypocortisolism hypothesis for the interparental context.	$r(199) = .146$	.03863	Consistent with the hypocortisolism hypothesis, greater levels of adversity in family relationships were associated with children's lower cortisol reactivity to the family stressors

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Carpenter et al 2011	In contrast to our prior study, cortisol concentrations were measured in saliva rather than in plasma. We approached this study by examining the effect of each of five different subtypes of maltreatment independently and hypothesized that exposure to early life adversity would be associated with diminished cortisol response to acute psychosocial stress challenge.	One hundred and ten women, ages 18 to 61 years, were enrolled and completed all assessments in the study protocol.	The 28-item version of the Childhood Trauma Questionnaire (CTQ) -generates a total score and subscale scores for five types of maltreatment (emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect). CTQ subscale scores reaching the threshold for the "moderate to severe" range were considered positive for maltreatment. Subjects scoring "none or minimal" for each subscale were considered controls.	TSST: protocol involves public speaking role-playing, and mental arithmetic tasks in front of a panel of confederate judges. distress.	Salivary Cortisol: To minimize the effects of diurnal variation in cortisol response, the TSST was administered at the same time each test day. Subjects were instructed not to eat or exercise for 1h before the test. Saliva samples were collected at time points 0 (1:45 PM; immediately before meeting the judges and being told about the public speech and arithmetic recitation), 15 min (2:00 PM; the end of the anticipation period during which the subject prepared his or her speech), 30 min (2:15 PM; several minutes after completing the speaking/arithmetic test), 45 min, 60 min, 75 min, and 90 min	Repeated measures General Linear Model (GLM) was used to determine the effects of maltreatment on cortisol reactivity to TSST in models that included CTQ data (summarized as total score for 28-item scale, dichotomized scores for each of five subscales, or as the total number of subscales scored positive for maltreatment), estrogen use (dichotomized), and subject age. Huynh-Feldt adjustment was made for violations of sphericity assumptions.	Individual models assessing the effects of moderate– severe maltreatment according to maltreatment type revealed that physical abuse (PA) was a significant predictor of lower cortisol response to the TSST (effect of PA group— $F = 4.95$, $p < 0.005$).	$F(4,109) = 4.95$	.00105	In the present study involving a sample of 110 women from the community, we found a significantly lowered salivary cortisol response to a psychosocial stress task among subjects who reported a history of childhood physical abuse.
Ouellet-Morin et al 2011	Based on previous findings suggesting that early-life stress is associated with abnormal cortisol secretion, we hypothesized that bullied twins would have impaired cortisol responses to the PST whereas their nonbullied MZ co-twins will show an increase in cortisol secretion after exposure to this experimental stress task.	This study sample comprised 30 12-year-old MZ twin pairs (mean [SD] = 12.53 [0.52]) discordant on bullying victimization and with valid cortisol data (43.3% males). Hence, this substudy sample included one twin who had been the victim of bullying (n = 30 children) while their co-twin had not (n = 30).	Bullying Victimization: We derived a cumulative index of frequent, chronic, and severe bullying victimization by summing the scores to the three questions asked to mothers described above across age 7, 10, and 12 assessments. The victims of frequent bullying who experienced frequent psychological and physical harm had a maximum score of 6 at each time point (7, 10, and 12 years).	TSST: One hour after arrival, twins took part in an adapted version of the TSST for children, which includes a social stressor (speaking in front of judges) and a cognitive stressor (mental arithmetic).	Salivary Cortisol: We collected five samples of saliva to measure the cortisol response to the PST. Saliva was collected by asking children to use a straw to pass through 1 ml of saliva into the cryovials. The first samples were collected 20 and 2 minutes before the PST. A third sample was collected immediately at the end. A fourth and a fifth samples were collected 25 and 35 minutes after the start of the tasks.	5 (time) x 2 (bullying) repeated-measures ANOVA.	Repeated-measures ANOVA showed distinct patterns of cortisol secretion over time between bullied and nonbullied MZ twins (time x bullying: $F(2.2,122.9) = 3.82$, $P = .02$).	$F(2.2, 122.9) = 3.82$	.02113	This study provides evidence for a causal effect of early-life stress on cortisol reactivity in human beings. Our psychosocial stress test elicited a cortisol response in nonbullied children compared with a blunted response in bullied children.

Table 2: *P*-curve Disclosure Table of Trauma-Cortisol Hypo-reactivity Literature

Ouellet-Morin et al 2011b	We examined whether 12-year-old maltreated/bullied children had lower cortisol responses to psychosocial stress than same-aged children.	From the total E-Risk sample, we identified 190 12-year-old children (50.5% males) eligible to participate in a substudy of cortisol. Children were selected if they were identical twins and only one twin within the pair was bullied. Most twins were Caucasian (91.6%) and one third of the families came from a low socioeconomic background (33.7%). Children had an IQ within the normal range when they were 5 years of age (from 64 to 142; mean [SD] = 101.38 [14.32]).	Childhood Harm: Childhood harm consisted of either a history of childhood maltreatment or frequent bullying victimization. A total of 64 children from this substudy sample of 190 participants were harmed (33.7%); 23 were maltreated by an adult (12.1%), 27 were frequently bullied by their peers (14.2%), excluding those who were only occasionally bullied; and 14 were both maltreated and frequently bullied (7.4%).	The Psychosocial Stress Test (PST) took place at the research laboratory in the early afternoon (mean [SD] = 1:45 pm [22 minutes]). A video camera was installed in a room to record the cognitive and public speaking tasks adapted from the Trier Social Stress Test for Children.	Salivary Cortisol: Cortisol was measured through the collection of five saliva samples. We asked children to use a straw to pass through 1 mL of saliva into the cryovials. The first two samples were collected 20 minutes and 2 minutes before the PST. A third sample was collected 2 minutes after the task. The fourth and fifth samples were collected 25 minutes and 35 minutes after the start of the task.	We examined cortisol response using a piecewise latent growth curve model. We then tested whether maltreated/bullied and comparison children showed distinct patterns of cortisol response to stress. We extracted the intercept, baseline, and response slope estimates derived in Mplus to test, using linear regression models, whether cortisol responses were associated with social, emotional, and behavioral problems.	Comparison children exhibited the expected increase in cortisol after the PST, whereas maltreated/bullied children did not (Table 2).	$t(188) = -2.875$	.00451	This study provides support for the hypothesis that early exposure to adverse life conditions could result in lower HPA axis reactivity to stress in childhood. Our laboratory stress paradigm elicited a significant cortisol response in comparison children but not in maltreated/bullied children for whom measures of harm were collected prospectively and repeatedly in childhood.
Brand et al 2010	The primary goal of this study is to take this line of research one step further and investigate the association between maternal history of child abuse and maternal cortisol levels in a clinical sample of postpartum women, and to explore whether depressive symptoms and stressful life events, as well as comorbid PTSD moderated this relationship.	A total of 126 mother / infant dyads qualified for the present study. The infant sample contained 62 boys and 64 girls, with a mean age of 187±17 days at the time of the laboratory study. Most (94%) of the mother/infant dyads were Caucasian, the median maternal education level was college graduate, mean maternal age was 34 ± 4 years, and 95% of the mothers were married or cohabitating at the time of the infant follow-up.	Abuse history (CTQ): Mothers completed the CTQ, a validated measure assessing childhood exposure to emotional, physical, and sexual abuse. Child trauma was operationalized as mild or higher levels of sexual abuse or moderate or higher levels of physical abuse. We excluded emotional abuse in order to maintain consistency with the previous ELS literature.	Noise/arm stressor: The infant was placed in a car seat behind an occlusion screen, and the mother was permitted to view her infant on a TV monitor during a noise burst and an arm restraint stressor task. Saliva samples were taken from the mother and the infant immediately after the lab stressor tasks were completed (T2 - post-noise/arm stressor I), and again 20 minutes later (T3 - post-noise/arm stressor II).	Salivary Cortisol: Mother and infant salivary cortisol measures were: 1) baseline cortisol (T0 – study entry); and 2) cortisol change calculated as the area under the curve (AUC; linear trapezoid method) for T1, T2, and T3 cortisol samples, as measured from baseline (T0).	2 (Group: high vs low abuse) x 4 (time) ANCOVA. Hypothesis testing utilized analyses of covariance (ANCOVA) with maternal baseline cortisol, maternal cortisol change, infant baseline cortisol, and infant cortisol change as dependent variables.). Covariates included demographic and clinical characteristics that were significantly associated with the dependent variables. All tests were two-tailed, and an alpha of 0.05 was used throughout.	ANCOVAs revealed a statistically significant association between maternal abuse history and mother cortisol change ($F(1,111)=4.82$, $\eta^2=.04$, $p=.03$) but not maternal cortisol at baseline ($F(1,119)=1.37$, $\eta^2=.01$, $p=.24$). The maternal post-stressor cortisol concentrations were lower for mothers with a history of childhood abuse compared to mothers with no such history.	$F(1,111) = 4.82$	.03021	No differences in baseline cortisol were found for mothers with a history of child abuse; however, these women demonstrated greater decreases in cortisol in the context of the infant stressor paradigm. Our finding that maternal cortisol decreases in response to stress is consistent with those seen in healthy women with a history of childhood maltreatment (Carpenter et al., 2007).

Table 2: *P*-curve Disclosure Table of Trauma-Cortisol Hypo-reactivity Literature

Cutuli et al 2010	We expected a positive relationship between lifetime event scores and cortisol response to the session tasks, given past evidence suggesting that family difficulties that are more common in low income contexts (e.g., child maltreatment, exposure to domestic violence) are linked with differences in the stress response to psychosocial challenge.	This resulted in a sample of 66 children (25 females). An effort was made to include only families who had stayed in the shelter for at least three nights to allow for some time to adjust to the context; yet two (3%) families participated prior to their third night in shelter. Nearly all participants had ethnic minority backgrounds [n = 64; 97%: 53 (80.3%) African American; 10 (15.2%) multiracial; and 1 (1.5%) Native American]. Two (3.0%) children were Caucasian.	Negative Lifetime Events: Lifetime Events Questionnaire completed by the primary caregiver. This questionnaire elicits the number of stressful events that the child experienced during his or her lifetime, including events and situations that threaten the child directly as well as those experienced by the child that threaten a parent, a family member, or the integrity of the family (see Table 2). *Note: items included traumatic events	Cognitive Tasks: These tasks served as the challenge to elicit a cortisol response. First, children completed three subscales of the Wechsler Preschool and Primary Scale of Intelligence – Third Edition. Then a set of widely used tasks were employed to assess executive function skills, including Simon Says, Peg Tapping, the Computerized Pointing Stroop task, and the Dimensional Change Card Sort.	Salivary Cortisol: Children's salivary cortisol was collected in two contexts: 1) during the assessment session as a measure of HPA reactivity to the tasks, and 2) in the morning prior to breakfast to assess diurnal cortisol levels following wake up. During the assessment session, three samples were taken at roughly 30 minute intervals following a 15 minute consent process and an initial 5 minute rapport building period.	The relationships between negative lifetime events, cumulative socioeconomic risk, and cortisol response to cognitive tasks over the session were tested using a linear mixed model (LMM), controlling for age, sex, and time of day the session occurred. Again, additional models were run to inform the impact of lifetime events without socioeconomic risk considered, and of socioeconomic risk without lifetime events.	Those with the highest lifetime event scores have higher cortisol levels at the start of the session and, on average, decline over the course of the session. In contrast, those with the lowest number of lifetime events not only have lower intercept values at the start of the session, but also tend to show either no response or a rising pattern of cortisol response over the course of the session (See Table 6 Fixed Effects, Slope Estimates).	t(63) = -2.25	.02795	A history of many negative life experiences in this sample of young homeless children was linked to higher cortisol levels in the morning, higher levels at the start of an assessment session, and falling levels across a session of challenging cognitive tasks.
Gunnar et al 2009	Early life stress (ELS) is expected to increase reactivity of the hypothalamic–pituitary–adrenocortical (HPA) axis; however, several recent studies have shown diminished cortisol reactivity among adults and children with ELS exposure. The goal of this study was to examine cortisol activity in 10–12-year-old internationally adopted children to determine if moderate and severe ELS have different impacts on the HPA axis.	The participants were 124 children ages 10.02–12.21 years Children in the LA/PI group (23 girls, 19 boys) were adopted at 12 months or older (range 12–64 months) having spent at least 75% of their pre-adoption lives in institutional care. Children in the EA/FC group (20 girls, 24 boys) had been adopted before 8 months (range 0.5–8 months) and had spent less than 2 months in institutional care. Children in the NA group (17 girls, 21 boys) were raised continuously by their birth parents in the United States.	Adoption from orphanages or other institutions: The types of adversity to which these children were exposed likely varied, but nearly all institutions included the lack of a consistent, responsive, adult caregiver. Exposure to pathogens is also greater in group care settings such as orphanages. While many institutions make adequate nutrition available, problems in delivery (propped bottles) and health issues (parasites) may reduce the nutrition the child actually receives.	TSST-C: The TSST-C was then administered (Buske-Kirschbaum et al., 1997). This task involved providing the child with a story scenario and then giving him/her 6 min to develop a story (Speech Preparation Period), followed by 5 min of mental arithmetic (Speech/Math Period).	Salivary Cortisol: Eight samples were taken in the laboratory. Three were collected over the initial baseline period [after consent/assent (0 min), after electrode placement (+15 min) and after completion of baseline autonomic assessment (+30 min)]. Five were collected during the stress and recovery periods [immediately after the speech preparation (+40 min), after the speech/math period (+55 min), and then at 10 min intervals until +75 min].	Covariates with missing data were used, so the sample size varied slightly by analysis. N's are reported for each analysis. The statistical tests we used enable analyses with unbalanced designs. In all analyses, covariates were examined and, if non-significant, were removed from the models. Thus, only significant covariates appear in the results.	Because the lowest 3 and highest 2 trajectories appeared to differ in cortisol intercept, we examined the percentages of children who were assigned to these levels. Of the EA/FC children, 85% were on the lowest three trajectories, compared to 53% of the NA children, $\chi^2(1) = 9.53$, $p < .001$.	chi2(1) = 9.53	.002	Diminished cortisol activity was noted for the EA/FC group (moderate ELS), while the LA/PI group (severe ELS) did not differ from the NA group. These results suggest that moderate ELS is associated with diminished cortisol activity; however, marked individual differences in cortisol activity among the LA/PI children suggest that child factors modify the impact of severe ELS.

Table 2: *P*-curve Disclosure Table of Trauma-Cortisol Hypo-reactivity Literature

MacMillan et al 2009	The purpose of the present study was to examine whether resting levels of cortisol, heart rate, and pattern of stress response to a psychosocial stressor differed between youth exposed to maltreatment and a control group.	Female youths between the ages of 12 and 16 from three local child protection agencies (CPA) qualified for eligibility review. We recruited 67 female youths aged 12 to 16 with no prior history of depression from child protection agencies and a control group of 25 youths matched on age and postal code.	Childhood maltreatment was assessed using the Childhood Experiences of Violence Questionnaire (CEVQ), and the Childhood Trauma Questionnaire (CTQ)	TSST: The stress protocol for children and youth has a brief stress anticipation period, a public speaking task (5 minutes), and mental arithmetic (5 minutes) in front of a panel of two judges. Peak cortisol concentrations are reliably found 10 minutes after stress termination in this protocol.	Salivary Cortisol: Over the course of the first visit, both HR and saliva samples were recorded at -45, -25, -5, +20, +40, and +60 minutes, with the TSST at 0 minutes. During the preliminary phase of the study, a baseline salivary sample at -25 minutes was obtained (n = 16 of 67 participants), but initial analyses showed that participants had elevated cortisol in this first sample, so a sample was added at -45 minutes to have two possible true resting (basal) samples before the stress test.	To examine group differences independent t tests for continuous variables and chi-square analyses for categorical variables were conducted. Piecewise multilevel growth curve modeling examined differences between maltreated and control youth in resting and post-TSST levels of cortisol and HR.	Differences in slopes between the maltreated and control group are evident during the reactivity phase. Youth in the control group show an increase in levels of cortisol following the TSST and a gradual flattening over time, while maltreated youth do not show an increase in levels of cortisol, nor do they have a gradual flattening of response (Table 3).	t(90) = -3.51	.0007	We found a blunted cortisol response (but no difference in heart rate response) to a psychosocial stressor among maltreated female youth even after controlling for SES and Tanner pubertal staging, as well as current symptoms of MDD and PTSD.
Pierrehumbert et al 2009	We expected abused women (i.e. with CSA) to present more psychopathological troubles, to be more often categorized as Unresolved at the AAI, and to show more altered cortisol stress reactions than controls.	Two groups of adult female subjects were included in the study: a clinical group (women with an experience of CSA) and a control group. Inclusion criteria were to be over 18 years old (civil majority) and to report at least one episode of CSA (such as provocative touching, having been forced to touch another person's intimate parts, having been touched in intimate parts, having experienced attempted or completed genital rape) during childhood and/or adolescence (up to the age of 18 years).	Childhood Sexual Abuse/ The Early Trauma Inventory: Childhood sexual abuse such as provocative touching, having been forced to touch another person's intimate parts, having been touched in intimate parts, having experienced attempted or completed genital rape) during childhood and/or adolescence (up to the age of 18 years). The Early Trauma Inventory (ETI) is a structured interview concerning traumatic experiences in childhood and/or adolescence.	TSST: Consists of a public speaking task and mental arithmetic performed in front of an audience. This standardized procedure was developed so that to induce a moderate psychosocial stress under laboratory conditions.	Salivary Cortisol: Saliva samples were collected for the measurement of the stress hormone at 15, 44, 60, 65 min (i.e. before the stress procedure), 75, 85, 100, and 115 min (i.e. after the stress procedure).	3 (Group: Abused Organized, Abused Unresolved and Controls) x 8 time) ANOVA and a separate regression analysis.	We conducted a regression analysis to examine the possible contribution of psychopathology in the association between cortisol responses and the unresolved classification. Only the variable Unresolved remained in the model (Beta = 0.35; t = 2.14, p = 0.04).	t(34) = 2.14	.03961	The group of abused subjects with the Unresolved classification of trauma expressed the highest perceived stress, they also showed the most suppressed endocrine reactions, when compared to control subjects.

Table 2: *P*-curve Disclosure Table of Trauma-Cortisol Hypo-reactivity Literature

Elzinga et al 2008	The purpose of the present study was to investigate cortisol reactivity to a psychosocial stress task (TSST) in a sample of healthy men and women who had experienced either very few or relatively many adverse life events.	Eighty college students participated for financial or course credit (52 men and 28 women, age: mean +/- S.D.: 21.6 +/- 3.61 years). Participants between 18 and 37 years old were recruited from the University of Leiden through announcements.	Traumatic Experiences Checklist (TEC): The TEC is a reliable and valid self-report inventory that assesses emotional abuse and neglect, physical abuse, sexual harassment, and sexual abuse, as well as general traumatic events.	TSST: This psychosocial stress test, which mainly consists of a free speech and mental arithmetic task of 15min duration has repeatedly been found to induce significant endocrine and cardiovascular responses.	Salivary Cortisol: Salivary cortisol was measured to investigate the effects of exposure to early adverse events on the reactivity of the HPA axis. All physiological assessments and the subjective measure of distress were obtained at five assessment points over a 75-min period, at approximately -20, -1, +15, +40, +55 min with reference to the start of the stressor.	2 (low adversity group vs. high adversity group) x 5 (time) repeated measures ANOVA, gender was included as a covariate.	Using ANOVA rm with Group (high versus low AE group) as between subjects factor and Gender as covariate and (log transformed) cortisol as dependent variable, a significant Group x Time interaction was found ($F(4,296) = 3.36, p < 0.01$).	$F(4, 296) = 3.36$; Robustness $F(1,78) = 6.42$	.01039	In the present study, we found that non-clinical individuals that have been exposed to a relatively high number of adverse events had a significantly lower cortisol reactivity to a psychosocial stress task compared to individuals who had experienced none or one adverse event, while the two groups did not differ at baseline cortisol levels.
Matheson et al 2008	The present study evaluated the trauma experiences of Somali refugees to Canada and their capacity to cope effectively with acculturation stressors. It was expected that coping difficulties would mediate the relations between trauma experiences and poorer health outcomes that may be evident years after the traumatic events.	Participants (N = 90) were recruited from the Somali community (Ottawa, Canada) over the course of 2003, through bulletins posted at community centers and the university, in flyers, local and community newspapers, and through referrals from social service workers.	Traumatic Life Events Questionnaire (TLEQ): A modified version of the Traumatic Life Events Questionnaire (TLEQ) was administered to assess exposure to a range of traumatic events. These were presented in behaviorally descriptive terms (consistent with the DSM-IV stressor criterion A1). When participants reported experiencing an event, they then indicated whether it had caused them to experience intense fear, helplessness, or horror (PTSD stressor criterion A2 in the DSM-IV), and when the event occurred. Whether participants had encountered each of five clusters of trauma types was then evaluated.	Reminders of stressful experiences: Participants also provided saliva samples to assess cortisol reactivity to reminders of their stressor experiences.	Salivary Cortisol: To evaluate salivary cortisol levels in response to reminders of their stressor experiences, participants completed the survey during the 1st afternoon (i.e., when basal cortisol levels are relatively low). The timing of the questionnaire was paced to allow for the collection of saliva at four time points, 15 min apart, following (1) instructions and the completion of the informed consent and demographic questions (baseline); (2) completion of the TLEQ (excluding familial assault), IES-R, and BDI (along with questions regarding acculturation hassles and adaptation that were not analyzed in the present study) (30 min); (3) the description of a stressful event and how they coped (45 min); (4) self-reported physical health and trauma events involving familial assault (60 min).	3 (Group: no trauma, single trauma, multiple traumas) x 4 (time) ANOVA	Contrary to expectation, as seen in Table 4, the number of traumatic events encountered was negatively related to cortisol levels in response to reminder cues. In effect, as seen in Fig. 2, those who had not experienced any traumatic events, $F < 1$, or only one event, $F(3,66) = 1.27, ns$, did not show a cortisol decline over the course of the questionnaire session, whereas cortisol levels dropped steadily throughout the session among those who had encountered multiple traumatic events, $F(3,123) = 10.27, P < .01, \eta^2 = .200$.	$F(3,123) = 10.27$; Robustness $r(82) = -0.22$	.00001	Among those individuals that had experienced multiple traumatic events, salivary cortisol levels declined over the course of the questionnaire session. This was contrary to expectation, but there are several possible processes that might operate to promote such a decline. Trauma symptoms and multiple traumatic experiences were associated with an exaggerated morning cortisol rise, but with a blunted response to stressor reminder cues.

Table 2: *P*-curve Disclosure Table of Trauma-Cortisol Hypo-reactivity Literature

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Original Paper	Quoted text from original paper indicating prediction of interest	Sample Characteristics	Type of Adversity	Stress Induction Task	Cortisol Measurement	Data Analysis Plan	Quoted text from original paper with statistical results	Results	P-value	Conclusion quoted from original text
Blankenship et al 2019	It was hypothesized that greater early maladaptive parenting behaviors (low positive or high negative) would predict increased cortisol reactivity and reduced hippocampal sub-region volumes and that the association between parenting and off-spring hippocampal volume would be mediated by offspring cortisol reactivity	The present analyses were performed on a subset of children (n = 63) from a longitudinal study (N = 175) of high-risk offspring of depressed mothers and a nondepressed community comparison group.	Observed Parenting Behavior: At both Time 1 and Time 2, parents and their children completed parent-child interaction tasks modified from the Teaching Tasks Battery. Each task was coded on the following: maternal hostility, maternal intrusiveness, maternal support, maternal positive affect, and maternal negative affect.	Stressor Task and TSST: The stressor task required children to match colored chips to an animal as quickly as possible while being evaluated. The experimenter manipulated the timer so that the child failed to complete the task three times before the child was informed that the timer was broken and received their prize. At Time 2, the stressor included a modified version of the Trier Social Stress Task during which children were instructed to tell a 4.5 min story after 30 s of preparation followed by an unsolvable puzzle.	Salivary Cortisol: At Time 1 and Time 2, salivary cortisol samples were collected at baseline (after 30 min of quiet play preceding the stressor), and 20-, 30-, 40-, and 50-min post-stressor using a cotton roll dipped in Kool-Aid (~0.025 mg) and chewed until saturated (~ 1 min).	There were three primary aims of the present analyses: (a) to assess associations between early (Time 1) and concurrent (Time 2) parenting and cortisol reactivity on Time 2 hippocampal subregion volume in separate models, (b) determine whether these associations were timing-dependent, and (c) evaluate whether cortisol reactivity mediated associations between parenting and hippocampal subregion volume.	See Table 2 - Bivariate correlations of Time 2 negative with time 2 cortisol.	$r(61) = .28$	.02624	Critically, a significant indirect effect was observed, with greater negative parenting during early childhood predicting greater cortisol reactivity three years later, which, in turn, predicted reduced left hippocampal tail volume.
Doom et al 2018	As there are few data examining cortisol reactivity in low-income children in middle childhood, we tentatively predict that greater current negative life events will be associated with heightened cortisol reactivity, while greater preschool family conflict will be associated with blunted cortisol reactivity.	A total of 242 children who participated in the middle childhood follow-up of a longitudinal study are included in analyses (see Table 1 for participant demographics).	Negative Life Events — The 30-item Life Events Checklist (LEC) was completed by the parent to report what negative events happened to the family in the past year. Family Conflict — Conflict in the family was assessed using the 12-item conflict scale of the Self Report Family Inventory. Items of the conflict scale measure overt conflict, such as openly fighting, blaming, arguing, negative tone, and unresolved conflicts.	TSST- C: The stress reactivity protocol consisted of approximately 10 min of academic testing with a strict teacher and 10 min of the modified Trier Social Stress Test for Children (TSST-C).	Salivary Cortisol: The cortisol AUCi was calculated using the trapezoidal rule and reflected the child's total free cortisol output increase from the first sample (prior to starting the stressor) to the fourth sample (40 min after conclusion of challenging tasks).	Three regression models were calculated with cortisol intercept, diurnal cortisol slope, and cortisol AUCi (area under the curve with respect to increase) in response to stress as dependent variables. The final models were created by first including preschool and middle childhood negative life events, chaos, family conflict as independent variables.	The overall model significantly predicted T2 cortisol AUCi, $F(11, 140) = 2.32$, $p = .01$. Greater T2 family conflict, $t(140) = 2.75$, $p < 0.01$, and greater negative life events at T1, $t(140) = 2.17$, $p = .03$, were associated with an increased T2 cortisol AUCi.	$t(140) = 2.75$ Robustness $t(140) = 2.17$	.00675	Greater negative life events during preschool and greater concurrent family conflict were associated with increased free cortisol reactivity in middle childhood.

Table 3: *P*-curve Disclosure Table of Adversity-Cortisol Hyper-reactivity Literature

Busse et al 2017	We hypothesized first, that being of Latino ethnicity and scoring high on experiences of discrimination would be independently associated with blunted cortisol reactivity; and second, that the association between Latino ethnicity and blunted cortisol reactivity would be mediated by experiences of discrimination.	The complete study sample consisted of 158 individuals. Fifteen individuals were excluded, four because they reported being half Latino and half non-Latino, and 11 because of missing or insufficient cortisol data. The remaining 143 participants (80 female, 63 male) were between 18 and 29 years old (M = 20.49, SD = 2.08).	Discrimination: Assessed with the Experiences of Discrimination Scale (EOD). The EOD contains 9 items about past incidences of discrimination in specific settings, including finding housing, a job, and medical care. Each item is rated based on the frequency of these occurrences over the lifetime (0=never, 1=once, 2.5=two or three times, 5=four or more times). Individuals are also asked to indicate what category (e.g., race, sex) they consider to be the major reason for the experience of discrimination.	TSST: The TSST consists of a 5-min mock job interview and a 5-min mental arithmetic task in front of two neutral, non-supportive expert evaluators of diverse ethnicities (e.g., Latino, European, East Asian, mixed background) and both sexes. Including the instruction and preparation period, the TSST lasted 15 min.	Salivary Cortisol: After a 15-min rest period, a first saliva sample (–2 min) was collected, and participants were escorted to an adjacent room to complete the laboratory stressor. Upon completion of the TSST, a second saliva sample was collected (+1 min). Participants then returned to the waiting room where additional saliva samples were collected at +10, 20, 30, 45, 60 and 90 min. (nmol/L).	Pearson Product Moment Correlations were conducted to obtain an initial impression of associations between variables of interest. Univariate ANOVAs and basic regression models were then conducted to test the ethnicity, discrimination, sex variables and their interactions as predictors of the maximum cortisol increase and recovery.	Higher levels of discrimination were associated with a steeper maximum cortisol increase ($r = 0.17$, $p < 0.05$) and a more pronounced maximum cortisol recovery ($r = -0.19$, $p < 0.05$) in the overall sample.	$r(141) = .17$	.0423	Latinos experience more discrimination throughout their lifetime than non-Latinos, and that more discrimination experiences are associated with heightened cortisol reactivity.
Fearon et al 2017	We explored the role of cumulative contextual adversity on the stress response, testing whether this might account for any observed effects of attachment security or sensitivity, and whether higher quality of early care might moderate the impact of cumulative contextual adversity on HPA reactivity.	In total, 316 adolescents provided cortisol samples, 15 of whom were excluded due to asthma steroid pump use, which can interfere with cortisol measurements. A further 14 cases were lost due to problems with the labelling and storage of the samples. Of these, 232 had been observed in the Strange Situation at 12 months, 217 had completed assessments of general sensitivity and 212 completed the assessment of sensitivity during feeding	Cumulative Contextual Adversity: Using data completed by the child's carer and the child at the age 13 assessment, we dichotomized the following indices, scored as present versus absent (zero versus one): overcrowding, community violence exposure, house has no running water, house has no toilet, house has no electricity, the parent endorsed that members of the family had gone for whole day without eating because of a lack of food, primary caregiver is unemployed, caregiver has only primary-level education, relationship breakup with partner or husband, partner has been violent towards mother/caregiver.	TSST: Participants were told that they would be given 3 minutes to prepare a 5-minute speech on anything about themselves. After the speech, one of the 'examiners' administered a serial sevens subtraction task. This was maintained for 4 minutes without any intervention or responses from the 'examiners' irrespective of how well the participant was performing.	Salivary Cortisol: Before TSST procedure, participants (who had not eaten or drunk anything in the last hour) were first asked to provide a saliva sample by directly filling a 2 milliliter plastic sampling device (SaliCap) or using a short plastic straw to do so. After the TSST stressors research assistant entered the room and led the participant to the next room where a second saliva sample was collected. After the TSST, an unrelated interview was interrupted every 10 minutes to collect a saliva sample.	We modelled the cortisol response profile using polynomial functions to describe the change in cortisol over time, including terms for the intercept (the baseline level), linear, quadratic and cubic trends. The effects were then modelled as a function of level 2 variables (across individuals), such as attachment and parental sensitivity.	As Figure 4 shows, for females there was a stronger (linear) increase in cortisol response for those with high levels of adversity, compared to those with lower adversity (Linear $B = .053$, 95% CI [.005, .100], $p = .030$; Quadratic $B = -.006$, 95% CI [–.013, .001], $p = .106$).	$t(143) = 2.18$	.03089	The results of our study, though in need of replication, provide further evidence that early caregiving may indeed be implicated in HPA axis development into adolescence and in buffering the HPA axis from the effects of chronic and extreme adversity.

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McFayden-Ketchum et al 2016	We examined whether economic stress predicted physiological reactivity (cortisol levels) across a challenge task in the preschool classroom, hypothesizing that higher levels of economic stress would predict greater physiological reactivity, as measured by cortisol reactivity patterns.	The analyzed sample was 165 preschool-age children (M age = 4 years, 2 months, SD = 7 months; n = 85 [52%] female) enrolled full time in high-quality child care centers (as indexed by the Early Childhood Environment Rating Scale-Revised; M = 5.52, SD = 0.58) in a midwestern city and recruited by a bilingual and bicultural project manager.	Economic Stress: Primary caregivers reported on their family's level of economic stress via the 54-item Multicultural Events Schedule for Adolescents for Preschoolers (MESA). The MESA used in the current study was modified from the original for use with a younger age group by removing questions only appropriate for adolescents. We used the Economic Hassles subscale in the current analyses as an index of economic stress rather than income, which was confounded by group and also is difficult to assess accurately with immigrant samples because of unstable income, income from multiple sources, and shared income with family not in the United States.	Challenge Task: The teacher and child were presented with a standardized set of materials for four successive 5-min intervals beginning with two books as a warm-up, followed by novel and interesting puppets, followed by the pair being approached by a robotic toy, and concluding with a difficult-to-open Plexiglas® box containing an attractive toy. The items were chosen to mimic the types of challenges children face at child care as viewed from the child's perspective (e.g., academic content, novelty, unpredictability, and frustration)	Salivary Cortisol: — Children's cortisol was collected three times across a challenge task presented to the child and his or her primary teacher. Samples were collected just before the 20-min challenge (baseline), immediately after the 20-min challenge (reactivity), and 20 min after completion of the challenge (recovery). The area under the curve with respect to ground (AUCg) was calculated for the reactivity data.	All analyses were conducted with path analysis in Mplus in order to take advantage of full information maximum likelihood (FIML) estimation—a theory driven direct estimation approach that allows for modeling with partially missing cases. All analyses involving cortisol as an outcome controlled for cortisol collection times.	For Aim 2, to examine whether economic stress was associated with physiological reactivity across a challenging task, we tested the model estimating the effects of economic stress on cortisol reactivity (as measured by AUCg), again controlling for child age and sex. The model had excellent fit, $\chi^2(1, N=165) = 0.04$, ns, CFI = 1, RMSEA = .00. Economic stress was associated with greater reactivity ($\beta = .24$, CR = 2.89, $p < .01$).	$t(163) = 2.8$	.00573	Greater economic stress was associated with poorer child self-regulation and heightened physiological reactivity across a challenging classroom task for the sample as a whole
Mrug et al 2016	We hypothesized that shorter sleep duration and more sleep problems will predict higher cortisol levels and reactivity to stress (i.e., a social evaluative threat). We also examined gender differences in the effects of sleep on stress-related cortisol regulation and reactivity. *Note: The authors did not have any hypotheses regarding the relationship between economic stress and cortisol reactivity.	Participants were 84 adolescents (M age 13.36 years, SD = 0.95; 50% male; 95% African American, 4% Caucasian and 1% Hispanic) who took part in the Coping with Violence Study. The sample was socioeconomically heterogeneous, but comprised primarily low-income families; average annual family income was \$20,000-\$25,000 (range <\$5000 to \$70,000-\$90,000) and average parental education was some college but no degree.	Low Family Income: Reported on a 13-point scale from 1(<\$5000/year) to 13 (>\$90,000/year).	TSST-C: Adolescents were given five minutes to prepare the ending to a story and then five minutes to tell that story in front of two judges. Next, the judges asked the participants to perform serial subtraction for 5 min (subtracting 7 starting at 758). However, if the adolescent made five mistakes in a row, they were given an easier task (subtracting 3 starting at 307).	Salivary Cortisol: Whole saliva samples were collected by passive drool immediately before the TSST began (pre-test), 30 min after the 15-min test began (15 min post-test), and 70 min after the test began (55 min post-test).	Bivariate correlations among all variables were examined. Parent and child reports of wake and bed times, sleep quantity, and sleep problems were compared with paired samples t-tests, as were cortisol levels across the three time points. Total cortisol secretion and its increase during the studied period were also analyzed with area under the curve with respect to ground and increase (AUCg and AUCi).	Family income was associated with lower AUCi (See Table 3 correlation between family income and AUCi).	$r(82) = -.30$	.0056	Interestingly, family SES also was related to cortisol levels, with higher pre-test cortisol levels among adolescents with more highly educated parents, and lower stress reactivity in those with higher family incomes.

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Andreotti et al 2015	We predicted that chronic stress exposure during childhood would be related to reduced cortisol reactivity to an acute laboratory stressor. Further, we predicted that cortisol reactivity would account for variability in attentional bias to threat observed after acute laboratory stress exposure.	Participants for this study include 116 female undergraduate students currently enrolled at a selective university in the southeastern U.S. The mean age of the sample was 18.96 years (SD = 1.13), with a range of 18 to 22 years. The sample was 78.6% Caucasian, 8.5% African American, 6.8% Asian American, 4.3% Hispanic/Latina, and 0.9% endorsed more than one ethnicity.	Family Conflict: All participants completed the frequency (6 items) and intensity (7 items) subscales of the Children's Perception of Interparental Conflict Scale. This scale is designed to measure various aspects of conflict occurring in the home from a child's perspective. Each item is rated on a 3-point scale (true/sort of true/ false). In order to quantify family conflict exposure prior to 16 years of age in the current study, the items from the Frequency (6 items) and Intensity (7 items) subscales of the CPIC were summed to create a CPIC total score.	The Noisy Neighbor Task: Was used as an acute laboratory stressor and as a measure of physiological and psychological stress reactivity. During the task, each participant engaged in a conversation role-play with a gender-matched research assistant in which the participant was prompted to present an argument to convince a neighbor to lower the volume of her music. Participants were told they would be evaluated on the persuasiveness of their argument and were videotaped during the conversation.	Salivary Cortisol: The five data points allow for analyses of both reactivity to stress (as reflected in increases from pre- to post-stress task) and total concentration over the assessment period (as reflected in area under the curve of the five time points).	Descriptive statistics were first calculated for attentional bias, cortisol, and questionnaire variables for the whole sample as well as by randomization group. ANCOVA procedures were then used in this analysis to test study hypotheses for differences in attentional bias index scores between groups (i.e., randomization and conflict exposure), accounting for potentially confounding factors (i.e., DSM Depression and Anxiety scores).	As shown in Table 2, exposure to family conflict during development as measured by the CPIC scale was significantly positively correlated with cortisol AUC in the sample as a whole ($r = .26$, $p < .01$) and in the group that performed the dot probe first ($r = .28$, $p < .05$).	$r(114) = .26$ Robustness $r(100) = .28$	.00482	As hypothesized, individuals in the current study reporting a history of higher levels of family conflict tended to have increased AUC.
Hagan et al 2014	The current study tested a curvilinear relation between childhood exposure to IPC and the cortisol stress response in young adulthood. We hypothesized that higher and lower self-reported childhood exposure to IPC, relative to the mean, would be associated with a greater cortisol response to and across a stressful interpersonal task	One hundred six young adults were invited to a lab session 1–3 months after completing the screening survey, at which time they again completed the FES-C in reference to their family relationships prior to 16. Demographic characteristics of the final sample ($n=91$) are displayed in Table 1.	Childhood Exposure to Interparental Conflict (IPC): Young adults' perceptions of childhood (prior to age 16) exposure to IPC were measured with the Children's Perception of Interparental Conflict Scale (CPIC). Scores on the six-item Frequency (e.g., "I never saw my parents argue or disagreeing." $a=.92$) and seven-item Intensity (e.g., "My parents got really mad when they argued." $a=.91$) subscales were summed, with higher scores reflecting higher exposure to IPC.	Role-Play Task: Participants role-played a situation in which they were trying to study for an important exam but their neighbor was playing his/her music too loud. The participant was instructed to ask his/her "neighbor" to turn down the music. The neighbor was played by a gender-matched undergraduate research assistant who maintained a neutral facial expression and followed a scripted series of responses indicating refusal to cooperate.	Salivary Cortisol: After a 20-min resting period, the first saliva sample (T1) was collected. Participants then completed a 10-min roleplay task. Immediately after the task, participants provided a second sample (T2). Twenty minutes after the end of the task, participants gave a third sample (T3). Participants then responded to all self-report questionnaires. The fourth sample (T4) was collected 40min after the end of the task.	For the evaluation of reactivity, raw cortisol values were log-transformed, and residualized change scores were computed by regressing the 20min post-task (T3) cortisol sample on the baseline cortisol sample (T1) and identified covariates. Because the cortisol response peaks approximately 20min after exposure to stress, the T3 sample was used to best capture reactivity (change from baseline).	Whereas IPC frequency exhibited a curvilinear relation with cortisol reactivity, $B=.02$, $SE=.01$, $x^2=3.88$, $p<.049$, $R^2=.04$ similar to the pattern observed with AUCg (see Fig. 1), IPC intensity did not exhibit a linear ($p=.84$) or curvilinear ($p=.48$) association with reactivity.	Chi2(1) = 3.88 Robustness Chi2(1) = 8.65	.04886	We hypothesized that perceived exposure to childhood IPC would be related to cortisol reactivity in young adulthood in a curvilinear manner. In line with this hypothesis, we found that young adults who reported lower and higher exposure to childhood IPC exhibited greater cortisol output during a stressful interpersonal task compared to youth who reported moderate levels of IPC.

Table 3: *P*-curve Disclosure Table of Adversity-Cortisol Hyper-reactivity Literature

Aschbacher et al 2013	1) anticipatory cortisol reactivity will mediate associations between perceived stress and oxidative damage markers, and 2) the indirect path from perceived stress to oxidative damage via cortisol reactivity will be significant among chronically stressed caregivers, but not among age-matched low-stress controls.	This study was conducted as part of a larger study of caregiving stress and biological aging. A subset of 48 participants from the larger study participated in an acute laboratory stress task and had data available for analysis in the current study. Twenty-five participants were caregivers of a relative with dementia and twenty-three were age-matched controls with healthy spouses. Caregivers had provided care for 4.7 years on average (range: 8 months-11.42 years).	Caregivers: Twenty-five participants were caregivers of a relative with dementia and twenty-three were age-matched controls with healthy spouses. Caregivers had provided care for 4.7 years on average (range: 8 months-11.42 years). Perceived Stress Scale (PSS): The Perceived Stress Scale-10 (Cohen et al., 1983) is a standard 10-item questionnaire that assesses subjective perceptions of stress over the previous month. Items reflect uncontrollability, unpredictability and feeling that demands outweigh coping resources. Response options form a 5-point Likert scale ranging from 0=never to 4=very often.	TSST: The Trier Social Stress Task (TSST) is a gold-standard laboratory stress task used to evoke stress-arousal responses. In this study, because many participants were retired, they did not do a mock job interview, but instead discussed their strengths and weaknesses and completed a math task in front of an evaluative audience. All participants completed the TSST between 1400h and 1500h to control for diurnal rhythm variation.	Salivary Cortisol: Salivary samples were collected via the passive drool method in 2 mL SaliCaps tubes (IBL Hamburg, Germany) at multiple time-points during the acute stress task, which permitted quantification of anticipatory and peak cortisol reactivity: 0 (baseline), 15 (after 5 min instructions, 5 min preparation, 5 min speech) and 30 (to capture peak cortisol).	All hypotheses were tested at the same time using a bootstrapped moderated mediation model with the aid of the "Process" macro for SPSS. All variables were normalized prior to model entry to facilitate centering and interpretation of coefficients. Regression analyses were used to identify coefficients for individual paths	CG had significantly greater anticipatory (15-min) but not peak (30-min) cortisol reactivity than NC (p 's=.003 and .16 respectively; Figure 2), even when controlling for demographic, health behavior and medical factors, as reported in a previous analysis. As hypothesized, among chronically stressed CGs, higher perceived stress was significantly associated with greater anticipatory and peak cortisol reactivity (p 's $\leq .01$).	$t(46) = 3.15$ Robustness $r(25) = .565$	.00287	A consistent pattern emerged whereby chronically stressed caregivers who reported greater perceived stress, negative affect and threat had significantly greater cortisol increases while anticipating a stressful event.
Koss et al 2013	Consistent with the distressing nature of conflict, higher levels of children's perceived threat and child-related conflict were expected to be related to an elevated pattern of cortisol reactivity.	Data for the current study were drawn from participants taking part in a larger longitudinal project examining the effects of family functioning on child adjustment. The original sample consisted of 235 (129 girls, 106 boys) families including, mother, father, and their kindergarten-aged child; 193 families were included in the current study.	Child-Rearing Disagreements: Mothers completed an 8-item abbreviated version of the Child-Rearing Disagreements scale assessing the frequency of marital conflict about child-rearing issues; Perceived Threat: Children completed the six-item perceived threat subscale of the Children's Perception of Interparental Conflict scale for younger children assessing the degree to which children feel threatened by marital conflict. Sample items included "When my parents argue, I'm afraid that something bad will happen".	Simulated Phone Anger Task: Children and mothers were asked to engage in a play activity when the mother received a phone call believed to be from the child's father. Mothers were provided a scripted interaction by an experimenter to stage a marital dispute over the phone.	Salivary Cortisol: Children provided baseline cortisol levels collected after arrival in the laboratory setting. Cortisol levels were assessed prior to the simulated phone anger task to assess a baseline indication of physiological functioning. Two saliva samples were collected after the simulated phone anger task; the first was collected approximately 25 minutes after the peak of the simulated phone anger task. The second poststressor sample was collected 10 minutes later.	A growth mixture modeling approach was utilized to model different patterns of cortisol reactivity.	Higher levels of children's perceived threat were associated with a higher probability of being in the rising cortisol group compared to the falling group. Similarly, more frequent child-related conflict was associated with a higher probability of being in the rising group compared to both the falling group and the flat group. (See Table 1 Correlation between Child-Related Conflict and Post Conflict Cortisol).	$r(193) = .21$	.00321	The rising pattern, reflecting the sensitization hypothesis, was associated with histories of child-related conflict, perceived threat, and children's emotional insecurity.

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Wirtz et al 2013	Hypothesis 1: Cortisol responsivity to the Trier Social Stress Test will be stronger for participants high in role uncertainty compared with participants low in role uncertainty.	The study sample comprised 43 men (mean age +/- SEM: 44.5 +/- 2.0 years, mean body mass index +/- SEM: 25.7 +/- .4) who completed the measure of role uncertainty (see below). Our participants reported a great variety of different jobs including technicians, engineers, teachers, or craftsmen, and most (61.4%) worked for a private employer.	Role Uncertainty: Role uncertainty was measured by three Likert-scaled items of the scale "uncertainty" from the Instrument for Stress-oriented Task Analysis (ISTA), a well-established instrument in German-speaking countries. The uncertainty scale assesses role ambiguity and role conflict: (a) "How often do you get unclear instructions?"; (b) "How often do you get conflicting instructions from different supervisors?"; (c) "From how many people do you receive instructions on a regular basis?". Items had a 5-point Likert format, ranging from 1 (very seldom/ never) to 5 (very often), with higher scores reflecting higher uncertainty.	TSST: Participants were exposed to the Trier Social Stress Test (TSST), which combines a 5-min preparation phase followed by a 5-min mock job-interview, and 5-min mental arithmetic in front of a jury that displayed a stern attitude. The TSST has been used frequently and it reliably induces increases in biochemical parameters, most notably cortisol.	Salivary Cortisol: For determination of salivary cortisol levels, saliva samples were taken immediately before as well as every 10 minutes, at 0, 10, 20, 30, 40, 50, and 60 minutes after completion of the TSST.	Following previous methods we assessed associations between uncertainty and the cortisol/blood pressure stress response by calculating general linear models with repeated measures of cortisol/blood pressure as dependent variables and role uncertainty as continuous independent variable while controlling for age, BMI, and MAP as covariates in the main analysis.	As depicted in Table 3, general linear models with repeated cortisol measures and role uncertainty as continuous independent variable, and age, BMI, and MAP as covariates, revealed that higher role uncertainty scores were associated with higher cortisol stress reactivity (interaction uncertainty-by-TSST: $F(2.5, 89.4) = 3.94$, $p = .016$, partial $\eta^2 = .10$, $f = .33$). Further controlling for the second set of confounders (overcommitment, stress appraisal, perfectionism, time pressure) did not change the results; (interaction uncertainty-by-TSST: $F(3.9, 105.7) = 6.57$, $p < .001$, partial $\eta^2 = .20$, $f = .49$).	$F(2.5, 89.4) = 3.94$ Robustness $F(3.9, 105.7) = 6.57$	.01569	Our study investigated for the first time whether role uncertainty at work as a background stressor related to altered physiological reactivity to acute psychosocial stress in working men. The main finding of our study was that higher role uncertainty was associated with higher cortisol stress reactivity even when controlling for a broad set of potential confounders including cardiovascular risk factors and potentially confounding psychological constructs.
Hackman et al 2012	To date, studies of cortisol reactivity and SES have largely omitted investigation of neighborhood components of disadvantage. This study is uniquely positioned to determine if parental education and neighborhood disadvantage, as moderated by gender, are associated with cortisol reactivity to stress.	Analyses included a total of 77 participants (37 female, 48.1%) between the ages of 13 and 18 ($M = 16.4$, $SD = 1.2$).	Neighborhood Disadvantage: We employed a measure of concentrated neighborhood disadvantage based on the 2000 United States (U.S.) census tract for the participant's home address when the stress reactivity protocol was completed. The 77 participants lived in 59 census tracts. Six measures were employed: percentage of individuals below the poverty line, unemployed, and receiving public assistance, as well as the density of African-Americans, children under the age of 18, and female-headed households.	TSST-G: Participants completed the Trier Social Stress Test for Groups (TSST-G) a modified version of the TSST that induces a moderate level of stress. In order to increase social evaluation participants underwent the protocol in groups of 2 ($n = 27$, 35.1%) or 3 ($n = 50$, 64.9%), matched for gender.	Salivary Cortisol: Salivary cortisol was the primary outcome of interest, and saliva samples were collected at nine different times: at baseline, after speech preparation, at the end of the stressor tasks, and 10, 20, 30, 45, 60, and 75 min after the stressor.	Piecewise hierarchical linear modeling (HLM) was the primary analysis strategy 1. Piecewise HLM is a strategy based on longitudinal growth modeling that allows distinct modeling of the different phases of change over time, permits the separate modeling of reactivity and recovery phases following administration of a stressor, and offers advantages over the use of ANOVA or change scores.	With male coded as 0, and coefficients for disadvantage thus reflecting the effect for males, higher concentrated disadvantage predicted increased cortisol reactivity ($B = 0.006$, $p = 0.004$, $r^2_{effect} = 0.33$) and a steeper decline during recovery ($B = -0.003$, $r^2_{effect} = 0.34$).	$r(77) = .33$	.00298	In this analysis we found that concentrated neighborhood disadvantage, but not parental education, was associated with cortisol reactivity and recovery. However, this relationship was moderated by gender, such that higher concentrated disadvantage was associated with higher cortisol reactivity and steeper recovery in boys alone.

Table 3: *P*-curve Disclosure Table of Adversity-Cortisol Hyper-reactivity Literature

Ouellet-Morin et al 2008	The main goals of the present study were to analyze the genetic and environmental contributions to cortisol reactivity to an unfamiliar context in 19-month-old twins and to examine variations in genetic and environmental contributions to cortisol reactivity according to early FA.	Participants were families of twins from the Quebec Newborn Twin Study recruited between April 1, 1995, and December 31, 1998, in the greater Montreal area. A total of 989 families were contacted, of which 672 agreed to participate (68.0%).	Familial Adversity: Familial adversity was assessed to reflect the putative cumulative adverse effects of environmental risk factors on children's adjustment. In the present study, an FA index was created by combining information about 7 risk factors: maternal smoking during pregnancy, low birth weight, low family income, low maternal educational level, single parenthood, young motherhood, and maternal hostile or reactive behaviors.	Exposure to unfamiliar situations: Each twin was exposed to 2 unfamiliar situations known to be moderately stressful at that age. In the first situation, 1 twin and the mother were alone when a woman dressed as a clown entered the room and invited the child to approach by offering a set of familiar toys. In the second situation, a noisy, odd-looking, moving toy robot was placed on a platform in the opposite corner of the room.	Salivary Cortisol: Saliva was collected before and after the unfamiliar situations and stored at -80°C until analysis. The posttest sample was obtained 20 minutes after the end of the procedure to capture the peak cortisol response.	Differences in mean cortisol values according to zygosity and sex were investigated through analyses of variance. The association between FA and cortisol reactivity was tested using a 2-tailed χ^2 test, and multinomial logistic regressions were performed on the discrete patterns of cortisol reactivity. All statistical tests, except for the genetic modeling, were conducted on a subsample composed of only 1 twin, selected at random, per family.	Adverse environments have been associated with both lower and higher cortisol reactivity. We partitioned the sample into quartiles of cortisol reactivity, allowing for different associations to emerge at the lower (first quartile) and higher (fourth quartile) ends of the distribution. Figure 1 presents the distribution in quartiles of cortisol reactivity for high and low FA (χ^2 2,211=9.86; $P=.007$).	Chi2(2) = 9.86 Robustness Chi2(2) = 11.01	.00723	Familial adversity was associated with higher cortisol reactivity to stress.
Zwolinski et al 2008	The ultimate goal of this study was to examine whether stress reactivity was heightened following social exclusion for relationally victimized females in their luteal phase. Because of their interpersonal sensitivity, relationally victimized women are expected to be at greatest risk for cortisol reactivity to social evaluative stressors, namely peer exclusion.	A total of 33 female undergraduate students were recruited to participate in the current study. Initial recruitment was based on two factors. Three participants did not meet all of the eligibility criteria noted above, resulting in a participant pool of 30 females.	Relational Victimization: The Revised Self-Report of Aggression and Social Behavior Measure was used to assess history of relational victimization by peers at the current time and in the previous year (e.g., "A friend of mine has gone 'behind my back' and shared private information about me with other people"). Participants rated each item on a seven-point scale, "not at all true" to "very true". Using the same cutoff score in prior research to determine victimization group, individuals who received an average score or above (e.g., > 16) on the four-item Relational Victimization subscale were considered to be targets of relational aggression.	The Yale Interpersonal Stressor Task: Used to induce the experience of social exclusion. A number of tactics were used to exclude the participant. Exclusion began slowly and gradually included verbal (e.g., disagreeing, ignoring, criticizing participant's comments) and non-verbal tactics (e.g., confederates shift their bodies and chairs away from the participants and lack of eye contact or smiling).	Salivary Cortisol: Stress reactivity was measured using salivary cortisol. Two salivary samples (1.0 ml each) were taken from each participant using a screw tap container for the collection of sputum: once at the end of the baseline adjustment period and another following the second stressor session.	2 (relational victimization group: high, low) by 2 (menstrual phase: follicular, luteal) by 2 (time: baseline, post-stressor) repeated measures ANCOVA, controlling for state anxiety was conducted.	To examine changes in cortisol over two time points, a 2 (relational victimization group: high, low) by 2 (menstrual cycle phase: follicular, luteal) by 2 (time: baseline, post-stressor) repeated measures ANCOVA, controlling for state anxiety, was conducted which revealed a significant three-way interaction(1, 23) = 4.32, $p<.05$, partial η^2 = .16, power = .51. To investigate the	$F(1, 23) = 4.32$	.04901	This study found some support for the tend-befriend model as indicated by biological reactivity as well as distinct psychological responses to social exclusion in women. This biobehavioral response was influenced by history of relational victimization; low victimization tended to be associated with unique psychological response whereas high victimization predicted neuroendocrine reactivity to peer rejection.

Table 3: *P*-curve Disclosure Table of Adversity-Cortisol Hyper-reactivity Literature

Ellis et al 2005	High stress reactivity in the context of acute, severe childhood stressors may function to increase the overall readiness and capacity of individuals to deal with the very real dangers in their environment (even as it also results in chronic overarousal and associated sequelae). We thus anticipated that children who experience very stressful early home and or school environments would tend to develop high BSC.	A sample of 122 children and their parents and teachers was recruited from one of two cohorts (total N=500) in the longitudinal WFSW. The resulting sample included 73 girls and 49 boys from middle class families, representing 109 White, 4 African American, 4 Asian, 2 Hispanic, and 3 other race or biracial family units. Of the 122 families who were identified and agreed to participate, 120 completed all components of the study.	Family Stress: Family stress scores were computed separately for mothers and fathers based on their self-reports of five domains: (a) depression symptoms, (b) family expressed anger, (c) parenting stress, (d) role overload, and (e) financial stress. Total stress: To create an overall measure of stress in early childhood, the four composite family stress measures and the SES measure, which were already standardized, were combined in a unit-weighted composite (M=0.03, SD=0.65).	Challenge Tasks: An unfamiliar female researcher administered the challenges utilized in the reactivity protocol. They included (a) a structured child interview modified from the Gesell School Readiness Screening Test, (b) digit span recitation modified from the Kaufman Assessment Battery for Children, (c) 2–3 drops of lemon juice placed on the child's tongue, and (d) two emotion-evoking videotapes that were chosen to elicit fear and sadness.	Salivary Cortisol: There were four collection times: one immediately following the arrival of the study team, a second and third prior to and following the reactivity protocol, and a fourth at the termination of the assessment procedures.	In the present analyses, scores reflecting children's social environments, along with their respective ranges of values and interval cut points, were entered into the signal detection algorithm. The algorithm then selected the variable and cut point that maximized the efficiency with which children at risk for high reactivity profiles were identified.	High anticipatory adrenocortical activation to the in-home laboratory procedures was associated with mother-reported composite family stress in the infancy period (N=115; $\chi^2=5.76$; $p<.05$). Half of the children from families in which the mother reported very high family stress in infancy showed evidence of heightened hypothalamic–pituitary–adrenocortical (HPA) responses, while only 23% of children from lower stress families (mean level of Total Stress 5= -0.07) were similarly responsive.	Chi2(1) = 5.76	.0164	In Study 2, a relatively high proportion of children in very stressful environments showed evidence of heightened sympathetic and adrenocortical reactivity.
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Table 3: *P*-curve Disclosure Table of Adversity-Cortisol Hyper-reactivity Literature

Original Paper	Quoted text from original paper indicating prediction of interest	Sample Characteristics	Type of Adversity	Stress Induction Task	Cortisol Measurement	Data Analysis Plan	Quoted text from original paper with statistical results	Results	P-value	Conclusion quoted from original text
Mezuk et al 2020	Individuals residing in lower-SES neighborhoods will have blunted stress reactivity relative to those living in higher SES.	In total, 125 participants completed the baseline assessment: 40 high-SES NHWs, 33 high-SES AAs, 18 low-SES NHWs, and 27 low-SES AAs. In addition, three high-SES and four low-SES persons who identified as Asian or Hispanic race/ethnicity participated.	SES: Neighborhood SES was measured using a composite of the following five census tract variables: per capita income, percent owner-occupied housing units, median home value, percent not vacant housing units, and percent households not in poverty (<\$25,000). Individuals in the lowest and highest tertiles for all five SES variables were considered to reside in "low-" and "high-" SES neighborhoods, respectively.	TSST: Stress reactivity was assessed using the TSST, one of the most robust and well-validated paradigms for evoking an HPA-axis response.	Salivary Cortisol: Eight salivary cortisol (SC) samples (two prestress and six poststress) were taken to characterize the HPA-axis response.	We conducted a series of cross-sectional analyses of variance (ANOVAs) to explore how race and neighborhood SES relate to various features of HPA-axis reactivity. We used multilevel modeling (MLM) to estimate the association between race, neighborhood SES, and their interaction on HPA reactivity.	Living in a lower SES neighborhood was associated with 16% higher baseline (SC1) cortisol ($p = .05$), 8.4% shallower increase in response to the TSST ($p = .004$), and 1.0% steeper decline post-TSST ($p = .005$) than living in the higher neighborhood SES (Table 3, model 4).	$t(785) = -3.0$	0.0028	In sum, our findings are broadly consistent with prior work showing that social disadvantage is associated with HPA-axis alterations, here indicated by both higher initial cortisol levels and blunted TSST reactivity.
Chiang et al 2019	We hypothesized that all three types of stress would be associated with sub-optimal biological profiles, as evidenced by dampened cortisol and heightened IL-6 responses to acute stress.	Participants were 18 to 20-year-old adolescents ($n = 91$; $Mage = 18.37$, $SD = .51$; 57% female) drawn from a larger sample of 248 adolescents ($Mage = 18.31$, $SD = .77$) partaking in the second wave of a three-wave longitudinal study on the psychosocial contributions to the development of early health risk from mid-adolescence to early adulthood.	Major Life Events: Participants completed a major life event checklist. Example items included parents divorced or separated, family member became seriously ill, a close friend moved quite far away, you had a serious falling out or ended a friendship with a close friend, you were suspended or expelled in school, and your grades in school went down a lot.	TSST: Trier Social Stress Task (TSST), a well-established acute laboratory-based social stressor that activates the HPA axis and increases inflammation.	Salivary Cortisol: Six saliva samples were collected using oral swabs (Salimetrics) throughout the laboratory visit. They were collected immediately after the neutral-content video (baseline) and TSST, and 30, 45, 60, and 75 minutes after TSST onset. Cortisol values were then natural log-transformed to correct for their skewed distributions.	We first tested the main effects of stress and psychological resources on cortisol and IL-6 response trajectories by examining the cross-level interactions between stress and time and between psychological resources and time.	Major Life Events: Adolescents who experienced more major life events exhibited smaller cortisol responses (linear: $b(SE) = .07(.06)$, $p = .195$; quadratic: $b(SE) = -.03(.01)$, $p = .006$) relative to those who experienced fewer major life events (linear: $b(SE) = .21(.05)$, $p < .001$; quadratic: $b(SE) = -.05(.01)$, $p < .001$).	$t(89) = -3.0$	0.0035	We found that experiences of various stressors, including major life events, daily interpersonal stress, and early adversity, were associated with smaller cortisol responses to an acute laboratory-based stressor.

Table 4: *P*-curve Disclosure Table of Adversity-Cortisol Hypo-reactivity Literature

Raffington et al 2018	We first hypothesized that lower SES would be associated with lower memory functioning, lower CARs and stress hyporeactivity. Second, we predicted that cortisol dysregulation would associate with lower memory performance. Third, we hypothesized that lower SES would be related with smaller hippocampal volume that predicts lower memory performance.	A total of 147 children and parents participated in the baseline measurement of an ongoing longitudinal study, of which 5 children chose to discontinue their participation during the first session (final sample n = 142). 102 children (M = 7.16 years, SD = 0.46, range = 6.08 – 7.98, 46% female) were randomly assigned to the TSST–C. The other children functioned as a control group for an experimental task (not reported here) exploring effects of acute stress.	SES: Parents self–reported their total combined monthly household income after taxes and education degree from 1 = none to 13 = PhD with 9 or more indicating higher education. Occupational status was self–reported from 1 = never employed to 15 = high civil service. We chose to focus on maternal, not paternal, education and occupation to reduce the number of SES predictors. An SES composite score was computed based on a single factor analysis of family income, maternal education and occupational status	TSST–C: The TSST–C consisted of a story preparation, story telling, and mental calculation part (5 min each) and was performed in front of 2 live female judges and a video camera.	Salivary Cortisol: Salivary cortisol values were collected at 8 times: 10 min and immediately preceding the stress task and at 0, 10, 20, 30, 40, and 50 min after the stress task. All raw cortisol values were log transformed to correct for significant skew and standardized to sample 1 (the first pre-stress sample).	We tested whether cortisol reactivity was associated with SES and memory. Cortisol intercept and slope were regressed on SES to test for main effects of SES.	Lower income was associated with a lower CSR slope, representing both reactivity and recovery (see Table 3 for parameter estimates and Figure 1).	$r(85) = 0.25$	0.0195	We found that lower income children have both a blunted CAR and blunted reactivity and recovery to acute stress. Interestingly, the main effect indicating hyporeactivity in CAR and CSR was specific to using income as the predictor and did not replicate with education, occupation or an SES composite. We hypothesize that income may have specific effects because it is the most variable SES indicator and may be more closely associated with different levels of family stress related to financial strain.
Allwood et al 2017	We hypothesized that the associations between stress (perceived or objective) and cortisol and cardiovascular activity would be positive, such that high stress would be associated with higher cortisol, heart rate and blood pressure.	Participants were 51 healthy children/adolescents (52.9% boys) and their mothers. Participants ranged in age from 7–16 (M=12.41, SD=2.30), and the racial composition in this sample was 80.4% Caucasian, 7.8% African American, 7.8% Multi-racial, 2.0% Hispanic, and 2.0% Other.	The Perceived Stress Scale is a 14-item measure designed to assess one’s perception of stress over the past month. Each item is rated on a 5-point Likert scale with higher ratings indicating higher perceived stress (0 = “never,” 2 = “sometimes,” 4 = “very often”). Both child and parent completed the PSS, with parent ratings reflecting their perception of their child’s stress.	TSST–C: The stressor tasks included speech (5 minutes preparation, 5-minute speech), mental arithmetic (5 minutes) and mirror tracing (5 minutes) tasks. The speech and mental arithmetic tasks were modified from the TSST for Children; the mirror-tracing task was adapted from Allen and Matthews (1997).	Salivary Cortisol: Over the course of each stress session, seven to nine saliva samples were collected from each participant. The range of sensitivity was .007–3.0 ug/dL, and intra and inter- assay coefficients of variation less than 5 and 10%, respectively. Salivary cortisol data is expressed in micrograms per deciliter (ug/dL).	Pearson correlations were conducted to examine the bivariate associations between anxiety symptoms, perceived stress, SLEs, cortisol and cardiovascular measures. Lastly, a series of hierarchical regression analyses were planned to examine whether perceived stress mediated or moderated the association between SLEs and biological measures of stress.	Subjective stress (child-reported perceived stress) was significantly negatively associated with baseline and peak cortisol, as well as with cortisol change. In other words, as compared to children and adolescents with lower levels of perceived stress, those with higher levels of perceived stress had lower baseline and peak cortisol, and lower changes in cortisol (see Figure 1; Table 4)	$r(39) = -.42$	0.006	Contrary to hypotheses, findings revealed that compared to actual experiences of stress, perceived stress has greater associations with both cortisol and cardiovascular activity. Perhaps the normative stressors assessed in this study (e.g., moving to a new school, parental divorce) do not meet threshold to generate the types of biological alterations and stress responses found in studies that assess trauma and severe adversities.

Table 4: *P*-curve Disclosure Table of Adversity-Cortisol Hypo-reactivity Literature

Fearon et al 2017	We explored the role of cumulative contextual adversity on the stress response, testing whether this might account for any observed effects of attachment security or sensitivity, and whether higher quality of early care might moderate the impact of cumulative contextual adversity on HPA reactivity.	In total, 316 adolescents provided cortisol samples, 15 of whom were excluded due to asthma steroid pump use, which can interfere with cortisol measurements. A further 14 cases were lost due to problems with the labelling and storage of the samples. Of these, 232 had been observed in the Strange Situation at 12 months, 217 had completed assessments of general sensitivity and 212 completed the assessment of sensitivity during feeding	Cumulative Contextual Adversity: Using data completed by the child's carer and the child at the age 13 assessment, we dichotomized the following indices, scored as present versus absent (zero versus one): overcrowding, community violence exposure, house has no running water, house has no toilet, house has no electricity, the parent endorsed that members of the family had gone for whole day without eating because of a lack of food, primary caregiver is unemployed, caregiver has only primary-level education, relationship breakup with partner or husband, partner has been violent towards mother/caregiver.	TSST: Participants were told that they would be given 3 minutes to prepare a 5-minute speech on anything about themselves. After the speech, one of the 'examiners' administered a serial sevens subtraction task. This was maintained for 4 minutes without any intervention or responses from the 'examiners' irrespective of how well the participant was performing.	Salivary Cortisol: Before TSST procedure, participants (who had not eaten or drunk anything in the last hour) were first asked to provide a saliva sample by directly filling a 2 milliliter plastic sampling device (SaliCap) or using a short plastic straw to do so. After the TSST stressors research assistant entered the room and led the participant to the next room where a second saliva sample was collected. After the TSST, an unrelated interview was interrupted every 10 minutes to collect a saliva sample.	We modelled the cortisol response profile using polynomial functions to describe the change in cortisol over time, including terms for the intercept (the baseline level), linear, quadratic and cubic trends. The effects were then modelled as a function of level 2 variables (across individuals), such as attachment and parental sensitivity.	As Figure 4 shows, for females there was a stronger (linear) increase in cortisol response for those with high levels of adversity, compared to those with lower adversity (Linear B = .053, 95% CI [.005, .100], p = .030; Quadratic B = -.006, 95% CI [-.013, .001], p = .106). In contrast, for males, the effects of adversity on the linear (B = -.048, 95% CI [-.090, -.005], p = .029) and quadratic (B = .007, 95% CI [.0002, .013], p = .044) slopes were in the opposite direction.	$t(143) = 2.21$ Robustness Quad: $t(143) = 2.03$	.02869	The results of our study, though in need of replication, provide further evidence that early caregiving may indeed be implicated in HPA axis development into adolescence and in buffering the HPA axis from the effects of chronic and extreme adversity.
Laceulle et al 2017	It is hypothesized that adversity is related to changes in HPA-axis functioning. Based on the existing literature, effects are expected to be larger for social defeat than for loss/illness. Whether the HPA-axis will respond to adversity with hyper-reactivity or hypo-reactivity will be explored.	In total, 178 adolescents participated in the behavioural experiments both at age 16 and 19 and in the LSI at age 19 (no stress = 68; social defeat = 32 and loss/illness = 61, 17 participants experienced both social defeat and loss/illness and were included in both adversity groups). For one participant from the loss/defeat and social defeat group we did not have any data, resulting in a sample of 177 adolescents for the current study (46.3% girls).	Social Loss or Social Defeat: Participants were assessed with the Life Stress Interview LSI - social defeat group (i.e., if they had been a victim of bullying, sexual intimidation or violence or were dumped after a serious relationship), or comparison group (i.e., randomly selected from the pool of participants that experienced no loss or defeat, or a loss or defeat that was rated 1 or 2 on the severity and/or person-in-dependency scale).	Social Stress Task: This test was the last challenge of the experimental sessions at age 16 and 19. It involved a standardized protocol including public speaking and mental arithmetic, inspired by the Trier Social Stress Task , for the induction of moderate performance-related social stress.	Salivary Cortisol: We assessed HPA-axis responses towards the GSST using four cortisol samples (referred to as CE1, CE2, CE3, CE4).	Associations between adversity and HPA-axis functioning were examined using Univariate ANOVA's, one for each of the cortisol measures. Dependent variables were the HPA-axis functioning measures at T4. Independent variables were the HPA-axis functioning measures at T3 and the two adversity dummies (i.e., social defeat (1) vs the rest (0) and social loss (1) vs the rest (0)).	With regard to the effect of adversity, social defeat was related to changes in both basal cortisol and reaction to stress during adolescence. Specifically, adolescents who reported being exposed to social defeat showed higher basal cortisol (B = -0.39, SE = 0.19, p = 0.040, $\eta^2 = 0.029$) and lower reaction to the stress task (B = 0.33, SE = 0.17, p = 0.048, $\eta^2 = 0.030$).	$t(177) = 1.99$	.04813	Adolescents who reported being exposed to social defeat (but not loss/illness) showed increases in basal cortisol and decreases in reaction to the stress task from age 16 to 19, compared to their peers.

Table 4: *P*-curve Disclosure Table of Adversity-Cortisol Hypo-reactivity Literature

Lucas-Thompson et al 2017	In line with past research, we hypothesized that marital conflict and conflict appraisals have unique effects on physiological reactivity.	Two-parent families with at least one child between 10 and 17 years of age were recruited from the community through advertisements; 153 youth from 98 families (52% female; Mage = 12.92, SD = 2.16) and both of their parents participated in the current study.	Parent Conflict: Parents reported the frequency, intensity, and resolution of their marital conflict using two questionnaires. Parents reported the frequency and intensity of conflict using the five-item Conflict subscale of the Braiker–Kelley Partnership Questionnaire; the mean of each participant’s responses was calculated. Observed Conflict Behaviour: each parent was rated based on the degree to which specific destructive conflict behaviors were displayed (0 = absent to 2 = very strong display).	TSST: In the modified TSST, participants give a speech about personal characteristics (imagining that they are in front of a new classroom; approximately 5 min) and then engage in out-loud mental arithmetic (approximately 5 min).	Salivary Cortisol: Saliva was collected using the Salivette device (Sarstedt, Nußbrecht, Germany). We examined stress physiology via cortisol and sAA production in response to the TSST as captured by area under the curve (AUC).	Primary analyses were conducted separately on cortisol and sAA AUCi reactivity, as well as total amounts of cortisol and sAA produced across the TSST (AUCg). Generalized estimating equation (GEE) models (regression-based, nonparametric) were used to adjust for clustering of youth within families. Main effects were tested first; then, interactions were tested separately by creating multiplicative interaction terms (after centering) and controlling for lower order terms	Fathers who were observed to behave more negatively had adolescents who produced marginally less cortisol across the TSST. Adolescents of these fathers also displayed significantly less cortisol reactivity to the TSST. In terms of conflict appraisals, adolescents who appraised the properties of their parents’ conflict more negatively produced significantly lower levels of sAA across the TSST. Adolescent conflict property and threat appraisals were also significantly (and negatively) associated with cortisol AUCi reactivity (Table 1).	$r(139) = -.21$	.01244	More-negative behavior as displayed by fathers during marital conflict predicted lower levels of adolescent cortisol and sAA produced during the TSST
Obasi et al 2017	Based on previous research findings, the following hypotheses were made: (1) Rural African American emerging adults will exhibit blunted cortisol levels when experiencing higher levels of perceived stress; and (2) HPA-axis reactivity to acute stress will be lower among participants with low family resources.	Participants (N = 60) consisted of rural African Americans between the ages of 18 and 22 (X = 20.0, SD = 1.1). The majority of the participants were female (n = 39, 63.9%), unmarried (n = 58, 95.1%), and self-identified as 5th generation in response to immigrant status (n = 54, 88.5%).	Family Resources: Family resources was measured by the Family Resource Scale. The FRS is a 30-item self-report measure that assesses an individual’s perceived adequacy of concrete resources in the household. Resources include physical necessities and shelter (8 items), growth and support (9 items), necessities and health (7 items), interfamily support (2 items), child care (2 items), and personal resources (2 items).	TSST: Participants were to introduce themselves to the “committee” in a free speech (5 min) and convince them why they should be hired for a job vacancy. During the arithmetic component, participants were asked to serially subtract the number 13 from 1,022 as quickly and as accurately as possible (5 min).	Salivary Cortisol: Four samples of salivary cortisol were collected during the TSST. Peak cortisol levels are found in saliva 20–30 minutes after the experience of an acute stressor so sample #4 was designed to represent the peak cortisol response (PCR) to the TSST.	Individual difference predictors were modeled as cross-level interactions between these cortisol parameters and variables of interest (i.e., perceived stress or family resources). We tested whether some of the variability in PCR could be accounted for by family resources after controlling for age, sex, perceived stress, and family resources at baseline.	Family resources had a significant positive relationship with PCR ($\eta^2 = .001$, $t(56) = 2.30$, $p = .025$). More specifically, coming from a family with diminished levels of basic resources was associated with a blunted peak cortisol response to acute stress	$t(56) = 2.30$	.0252	Participants who reported lower consistency of having access to adequate family resources in the household had a blunted peak cortisol reactivity to acute stress.

Table 4: *P*-curve Disclosure Table of Adversity-Cortisol Hypo-reactivity Literature

Tackett et al 2017	Hypothesis 1: We predicted that low socioeconomic status (low summed education/income and neighborhood affluence) would predict lower cortisol reactivity and recovery, above and beyond prediction by race/ethnic group membership, in hierarchical regression models.	Of an initial sample of 350 participants, all Black, White, and Hispanic participants were selected for the present study (excluding smaller categories reflecting Asian, Multiracial, and Other groups), resulting in a sample of 296 children and their primary female caregivers (98% mothers). Children were primarily ages 9–10 years (M = 9.82, SD = 0.66; 140 males [47%], full age range 8–11).	SES: We also examined sociocontextual stress using different indices: an index of SES reflecting both mother's highest level of education and overall family income (referred to in this paper as summed education/ income), which is a commonly used approach to indexing SES in the literature and an index of SES reflecting overall neighborhood affluence (or, conversely, deprivation) coded from census data, which is another measure that has been used in previous research.	TSST- C: Participants engaged in an adapted version of the TSST-C, a laboratory paradigm consisting of a storytelling and math task designed to elicit a stress response to a psychosocial stressor.	Salivary Cortisol: Once the child had given assent, they rinsed their mouth out with water and were instructed to drink a small cup of water. After 30 min of sedentary activity (questionnaire and computer task completion), the baseline saliva sample was collected. Saliva samples were then collected 20 min after the start of the TSST (excluding speech preparation time, so from the beginning of the speech delivery; T2), 40 min after the start of the TSST (T3), and 60 min after the start of the TSST (T4). nmol/L	Hierarchical regression models were estimated to examine the incremental variance in cortisol reactivity and recovery predicted by summed education/income, neighborhood affluence, or FAM over and above race/ethnicity. Dependent variables were cortisol reactivity and cortisol recovery at T4.	Cortisol reactivity and EI (summed z-score of education and income) correlation in Table 3 - $r(257) = .20$	$r(257) = .20$ Robustness: $r(257) = .22$	.00121	These findings suggest that cumulative effects of stress and disadvantage may result in differences in stress response physiology as early as middle childhood, and that race-specific mechanisms account for additional variance in cortisol reactivity and recovery. These findings support the “wear-and-tear” theory regarding the effects of socioeconomic status and contextual stress on physiological functioning (McEwen, 2004), even as early as preadolescence.
Wan et al 2017	We were interested in exploring the role of stressful life events and their perceived impact on the blunted reactive cortisol stress response noted in the same group of breast cancer survivors. We evaluated whether the number of stressful life events and the individual's subjective appraisal of its impact, as measured by the LES, would influence physiological cortisol profiles.	Research participants comprised a group of breast cancer survivors and a group of women without a history of breast cancer. Breast cancer survivors (n = 19) and control group (n = 17)	Life Experiences Survey (LES): The LES is a questionnaire designed to measure life changes (also labelled as stressors) and their subjective impact. It comprises 47 items that list various common stressors. We calculated the following: (1) the total number of stressful life events, (2) the total number of positive events, (3) the total number of negative events, (4) the sum of the Impact score given to positive events (Positive Impact Score), (5) the sum of the Impact score given to negative events (Negative Impact Score) and (6) the sum of both positive and negative impact scores (Total Impact Score).	TSST: The TSST is a standardised laboratory protocol designed to induce a moderate stress response. The participant is asked to prepare a speech that is then delivered in front of a panel of judges who have been instructed to deliver no verbal or non-verbal feedback; this is followed by a challenging verbal arithmetic task in front of the same panel.	Salivary Cortisol: Saliva samples were collected on oral swabs. Participants were instructed to place the oral swabs under the tongue for three minutes. A total of seven saliva samples were collected: Arrival, after a 10-min acclimatisation period; Anticipation, immediately after the speech preparation; Arithmetic, immediately after the completion of both speech and arithmetic tasks; and 10-, 20-, 40-, 60-min afterwards, during which they completed the LES.	Using simple regression analyses, we assessed the following: (1) Whether the number of stressful life events experienced impacted the cortisol concentrations of both groups of participants; and (2) whether subjective appraisal of the stressful life event, affected participants' cortisol concentration.	In breast cancer survivors, there was a significant negative correlation between the number of stressful life events and the peak cortisol concentration ($r = -.464$, $p = .035$), indicating that a higher frequency of stressful events predicted lower levels of cortisol. The perceived impact of total stressful life events and peak cortisol concentrations was negatively correlated ($r = -.552$, $p = .013$).	$r(17) = -.464$ Robustness: $r(17) = -.552$	.04537	Overall, breast cancer survivors who experienced a higher number of stressful life events and perceived higher levels of disturbance associated with these events had lower levels of cortisol during the peak, lowest point (or trough) and the AUC in the reactive profile. The frequency and impact of positive stressful life events, in particular, were negatively correlated with the peak cortisol response and AUC, whereas the trough was negatively correlated with the number and impact of negative stressful life events.

Table 4: *P*-curve Disclosure Table of Adversity-Cortisol Hypo-reactivity Literature

Afifi et al 2015	<p>H1: Couples' communal coping and community support will contribute to their (a) lower baseline levels of cortisol and sAA and (b) less reactance and (c) greater recovery in their cortisol and sAA from a stressful discussion about economic uncertainty.</p> <p>H2: Couples' corumination and interparental conflict will contribute to their (a) higher baseline levels of cortisol and sAA and (b) greater reactance and (c) slower recovery from a stressful discussion about economic uncertainty.</p>	<p>The sample included 82 married (M=16.61years), heterosexual parents and one of their adolescent children (ages 12–18; M=14.7) from Southern California. The families included 44 Caucasian couples, 25 Latino couples, and 13 mixed-race couples where one partner was Caucasian and the other was Latino</p>	<p>Economic Uncertainty: Sixteen items were created by the authors to measure parents' economic uncertainty in the preinteraction survey. e EUS asked parents how uncertain or unsure they were that in the next year (time frame can be adjusted) that they will lose their job, no longer be able to pay their mortgage or rent, le for bankruptcy, and not be able to provide for their child's needs, among other issues (see Table 1 for scale items and factor loadings). e scale ranged from 1 to 5 with "1" being very unsure and "5" being very sure (items were then reverse coded so that higher scores equal greater economic uncertainty). Every item also had a "not applicable" option (these items were then omitted from the scale).</p>	<p>Stressful Discussion: Couples were asked to talk with each other for as long as they could up to 20 minutes about their uncertainties regarding their family's finances, or things they were unsure about regarding their family's financial future, that made them stressed and that tended to produce conflict between the two of them.</p>	<p>Salivary Cortisol: The parents and adolescent child provided baseline saliva samples and then took a survey. Immediately upon completing the discussion task, the couple provided a second set of saliva samples. A third saliva sample was collected 15 minutes after the end of the discussion and a fourth saliva sample was collected 40 minutes after the end of the discussion.</p>	<p>Dyadic growth curve modeling (using the SPSS Mixed Procedure) was used to examine the influence of husbands' and wives' communication skills on their cortisol and sAA response and recovery patterns to the discussion task (H1 and H2). The models represented two levels of analysis with the multivariate repeated measures (i.e., four cortisol scores and four sAA scores for the husband and a corresponding set of cortisol scores and sAA scores for the wife) at Level 1 and the couple (with the couples' score</p>	<p>Wives with higher economic uncertainty evidenced a blunted cortisol response, or an inhibited/diminished stress response, which was indicative of a sharp, immediate drop in cortisol in response to the stress task (rather than the expected increase) (See Table 4 - Mother x Economic Uncertainty).</p>	<p>$t(80) = -2.12$</p>	<p>.0372</p>	<p>Wives with lower economic uncertainty experienced a much greater cortisol increase to the discussion task compared to everyone else, whereas wives with higher economic uncertainty experienced a blunted cortisol response.</p>
Wieke de Vente et al 2015	<p>Since Kudielka et al. stated that ongoing chronic stress is generally associated with a hyperactive HPA axis and our sample was recruited within weeks to a few months after having called themselves sick (burnout), we expected to find support for a hyperactive rather than a hypoactive HPA axis.</p>	<p>Eighty- five patients were recruited through occupational physicians, general practitioners, and by self- referral to participate in a RCT about treatment efficacy of stress-management training. Twenty-seven patients did not fulfill the inclusion criteria (e.g., having major depression as a primary diagnosis) or refused to take part in the study. As a reference group, forty healthy individuals were recruited.</p>	<p>Burnout: Burnout complaints were measured with the Maslach Burnout Inventory-General Survey (MBI-GS), which consists of three subscales: emotional exhaustion (5 items), depersonalisation (4 items), and professional competence (6 items). Items were scored on 7-point Likert scales (0 = never to 6 = always/daily) and mean subscale scores were calculated. Higher scores reflect higher levels of emotional exhaustion, distant/cynical attitudes towards work, and professional competence.</p>	<p>Psychological Stressor: To study physiological reactivity and recovery, participants were exposed to an acute psychosocial stressor consisting of a speech preparation task, a mental arithmetic task, and a speech task.</p>	<p>Salivary Cortisol: Alpha-amylase and cortisol were determined in saliva. Means of the first (–4 min. in relation to the start of the stressor) and second (+5 min.) saliva samples were used as resting values, indicative of basal functioning (see Figure 1). For cortisol, the third (+20 min.) and fourth (+35 min.) saliva samples indicated reactivity, and the fifth (+50 min.) indicated sample recovery.</p>	<p>To test between-group differences in reactivity-recovery and in overall mean activity during the psychosocial stress procedure, mood, cardiovascular, and neuroendocrine reactivity and recovery during the psychosocial stress procedure were examined with ANOVA for repeated measures, using a one within- (time), one between- (group) subject factor design.</p>	<p>For cortisol, healthy males showed earlier and stronger cortisol reactivity immediately after cessation of the stressor than male patients. Mean reactivity immediately after the stressor of healthy males was 0.91 ng/mL, which is almost equal to the operational guideline for cortisol reactivity of 1 ng/mL. A cortisol reaction could not be observed in male patients (See Table 2).</p>	<p>$F(2,89.5) = 3.32$</p>	<p>.04066</p>	<p>This study assessed whether burnout is characterised by dysregulation of the sympathetic vagal balance and the HPA axis. In contrast to prediction, reduced cortisol reactivity to an acute psychosocial stressor was observed in male patients, which suggests hyporeactivity of the HPA axis, rather than hyperactivity.</p>

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Calhoun et al 2014	Given that relational victimization is a significant source of stress during adolescence, it was hypothesized that relational victimization would be associated with dysregulated HPA stress responses, as indicated by hypo- or hyperreactivity to the social stressor task.	Participants included 62 youth (73% female) at the adolescent transition, between the ages of 12 and 16 years ($M = 14.70$, $SD = 1.33$).	The victimization subscales of the Revised Peer Experiences Questionnaire were used to assess overt and relational forms of victimization. The relational victimization subscale assessed being the recipient of direct or indirect social aggression (e.g., “A teen left me out of an activity or conversation that I really wanted to be included in”).	TSST: Adolescents participated in the TSST during the laboratory assessment.	Salivary Cortisol: Adolescents provided salivary cortisol samples using a passive drool procedure on three occasions throughout the baseline laboratory assessment described above: immediately prior to the speech task (following a 20-min relaxation period), 20 min postspeech, and 40 min postspeech. Changes in cortisol levels from baseline to stressor represent cortisol “reactivity,” while comparisons of baseline and poststressor levels of cortisol are indicative of poststressor cortisol “recovery” (i.e., return to baseline).	Descriptive statistics and correlations (or t values, for gender and medication usage) were computed for all study variables. Primary study analyses consisted of latent difference structural equation models for pre–post–post study designs. A logarithmic transformation was applied to cortisol values prior to model identification.	Results indicated that higher levels of relational victimization were associated with a more hyporeactive cortisol response to the social stressor task (See table 2; Relational victimization and cortisol reactivity).	$t(60) = 2.25$	.028	Relational victimization was associated with blunted HPA reactivity in this study. Some evidence suggests that individuals with histories of chronic stress (characteristic of the adolescents in this study) may be more prone toward blunted HPA responses. Similar to other chronic stressors, relational victimization during adolescence may serve as a stable source of stress that frequently engages HPA stress responses, increasing allostatic load to the point that HPA responses become dysregulated.
Quas et al 2014	A small set of children, it was hypothesized, would exhibit heightened reactivity across all systems (i.e., high activation of the SNS and the HPA axis, and high deactivation of the PNS), a pattern suggested by studies in which reactivity in multiple systems have each independently been linked to early childhood stress and suggested by Del Giudice et al. (2011) among children exposed to chronic threats.	A total of 324 4- to 6-year-olds involved in a longitudinal study of family social status, biological responses to adversity, and health served as participants. Children were recruited from kindergarten classrooms in public schools in an urban area in Northern California. Subsample: This sample included 111 11- and 12-year-olds in an urban public school in northwestern Canada whose parents consented to a science study on stress regulation.	Chronic Stress: From the measures of income and education, a composite index of socioeconomic status (SES) was created. Parents also completed measures of their mental health, financial stress, parental stress, and marital/relationship functioning, both in the fall of children’s participation in the larger study and again in the spring. An overall index of chronic stress was created by averaging parents’ standardized scores on the four measures in the fall and spring. This created a single cross-time marker of chronic family adversity that could be included as a predictor of subgroup reactivity differences.	TSST—Child (TSST-C), which required they finish a story and complete mental arithmetic in front of one observer.	Salivary Cortisol: Saliva samples were collected using a dental role before the TSST-C began (baseline) and 10 and 25 min after the TSST-C ended.	Scores in each sample were entered into latent profile analysis (LPA), a form of finite mixture modeling that identifies potential unobserved subgroups among a set of indicators. Models were fitted within a structural equation framework, and missing data were estimated using full information maximum likelihood using Mplus 6.11	The subgroups differed in SES, calculated as the mean of standardized scores based on parents’ highest education level and annual income, $F(5, 284) = 2.56$, $p = .027$. Children in the underaroused subgroup came from substantially lower SES families ($M = -1.31$) than children in the other subgroups. A one-way group ANOVA conducted predicting the adversity index also revealed group differences, $F(4, 223) = 2.48$, $p = .05$.	$F(5, 284) = 2.56$ Robustness $F(4, 223) = 2.48$	.02795	In PAWS, the underaroused children had significantly lower family SES than did the other subgroups. Perhaps these children had encountered a larger range of other potentially stressful experiences, rendering the laboratory assessment innocuous or unchallenging by comparison. Alternatively, exposure to mild chronic stress, which often accompanies low SES, may already be compromising these children’s general response tendencies.

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Badanes et al 2011	In study 1, we worked with a sample of high risk preschoolers and examined whether known significant stressors impacting the family system (maternal depression and serious financial strain) predicted which children exhibited attenuated cortisol across the day in two normal environments (home and child care) and across a stress paradigm presented to the child in the presence of the mother or lead teacher.	Participants— Participants were 110 preschoolers (53% female) enrolled in one of 14 full- day child care classrooms. The children were 2 to 6 years of age (M = 4.03, SEM = .07). Seventy-five percent of children were identified by parents as white and 25% as non-white.	Stressful Home Environment: Financial Strain: assessed with the Family Finances questionnaire consisted of one item addressing family size, 2 items assessing sources of income, 1 question asking about amount of income earned, and 5 items asking about insecurity of critical resources. Items asked whether in the past 12 months the following was true or false for the family: 1) Your family went without a telephone, 2) You didn't pay all or part of the rent/ mortgage because you did not have enough money, 3) Your family was evicted for failure to pay, 4) You didn't pay all or part of the gas/electric/oil bill, 5) You had your oil/gas/electricity turned off for failure to pay.	Stress Paradigm: Children participated in a 20-minute semi-structured mild stressor with the support of their lead teacher at child care and of a parent at home.	Salivary Cortisol: Three saliva samples were collected across both the classroom and the home interactions in 20-min intervals; at baseline before the task began; at the end of the interaction assumed to reflect cortisol reactivity to the task, and 20-minutes after the task ended assumed to reflect recovery to the task.	A series of hierarchical binary logistic regression models were computed first predicting internalizing problems (0, 1 above the clinical cutoff for internalizing symptoms as rated by mother, teacher, or both) from all of the available demographic control variables, the family risk variables, and the potential allostatic load marker of hypocortisolemia	Although stress (in this case only financial strain) predicted attenuated cortisol, $\chi^2(1) = 4.01$, $p = .04$, both financial strain and maternal depression predicted internalizing symptoms (see results above), and attenuated cortisol predicted internalizing symptoms (see results above), the effect of stress on internalizing symptoms was not reduced with the inclusion of attenuated cortisol in the model.	Chi2(1) = 4.01	.04523	The results from study 1 support our hypothesis that stress within a high risk sample early in development is associated with HPA-axis attenuation. Specifically, the data illustrate that serious financial strain is related to both blunted basal cortisol and attenuated stress reactivity in preschoolers.
Neuport et al 2006	The main goal of the present study was to examine potential age and SES differences in physiological reactivity to cognitive stressors. We also sought to examine the role of SES in reactivity. Specifically, we expected higher SES would be associated with greater physiological reactivity to cognitive tasks.	Participants in the present study were from the Boston oversample of the Midlife in the United States (MIDUS) Survey. The Boston In-Depth Study of Management Processes in Midlife included 302 adults (aged 25-74 years) from a probability sample of the Greater Boston area. Eighty-eight (29%) individuals provided salivary cortisol readings during the cognitive tests.	SES: Socioeconomic status was operationalized as years of education. This strategy was chosen because it captures the well-established gradient of socioeconomic disadvantage, and it captures the primary educational benchmarks that provide the foundation for subsequent stratification processes by occupation and earnings. Moreover, educational attainment has been the primary proxy for socioeconomic status in previous investigations, thereby allowing comparability with other studies.	Cognitive Challenge: Cognitively challenging tests in four domains (vocabulary, short-term working memory, speed, and reasoning) were given to participants. Similar cognitive tests have elicited stress reactions in past studies.	Salivary Cortisol: Physiological stress was assessed by salivary cortisol levels which were collected via Sarstedt Salivettes; the participants inserted a cotton-like swab into their mouths for 30 seconds and then placed it into a glass container. Each participant completed between five and seven Salivette trials, depending on how much time they required to complete the interview after the cognitive tests.	Multilevel modeling was used to examine age and education differences in cortisol trajectories. At Level 1, each person's variability (e.g., change in cortisol levels over time) is represented by an intercept and slope that become the outcome variables in a Level 2 model in which they may depend on person-level characteristics (e.g., age and education).	An additional model testing for education differences (i.e., replacing age with the continuous education variable in the previous model) indicated that those with higher education were more reactive than those with less education (see Model 2 of Table 3).	$r(72) = .3$	.00094	The main purpose of this study was to investigate age and SES differences in physiological reactivity to cognitive stressors. Consistent with past work and in line with our hypotheses, older adults were more reactive compared to younger adults. Higher SES (in this case, education) was also associated with heightened reactivity.

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