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Disentangling the Impact of Childhood Adversity:
Unique Effects of Deprivation and Threat

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Abstract

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By Allison N. Macdonald

It is well established that childhood adversity increases risk for multiple forms of psychopathology. However, less is known about the developmental mechanisms linking childhood adversity to psychopathology, and whether those mechanisms are specific to different types of adversity. Prevailing cumulative-risk models treat childhood adversity as a unitary construct, which implicitly assumes that very different experiences influence development similarly. However, emerging research suggests that specific types of adversity may have unique effects. Identifying dimensions of experience that cut across multiple types of adversity, based on neuroscience principles of experience-dependent plasticity, may be a more effective strategy for delineating the impact of adversity experiences on developmental processes. The current dissertation tested a novel conceptual model distinguishing childhood adversity along dimensions of threat and deprivation, and examined their specific associations with (1) corticolimbic structure and (2) stress processes. Results from the dimensions of adversity model were compared to prevailing cumulative-risk models to determine the relative merits of the two approaches. Participants were drawn from a large study of youth at risk for serious mental illness with variability in exposure to childhood adversities. Study 1 investigated whether threat and deprivation were differentially associated with corticolimbic structure. Results revealed deprivation-specific associations with smaller cortical and hippocampal volumes, and an interactive effect of threat and deprivation on superiorfrontal cortical thickness. Study 2 examined whether stress sensitivity mediates the association between childhood adversity and basal cortisol and whether these associations differ by adversity dimension and sex. Results indicated that both threat and deprivation were associated with increased stress sensitivity, which subsequently predicted higher basal cortisol levels; however threat effects were specific to females. Across both studies, the dimension-specific associations were masked in the prevailing cumulative-risk approaches. These results highlight the importance of assessing the specific nature of adversity and provide preliminary support for the differentiation of threat and deprivation dimensions.

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Disentangling the Impact of Childhood Adversity: Unique Effects of Deprivation and Threat

Speculation that adverse childhood experiences influence mental health has played a prominent role in etiologic theories of psychopathology for over a century (Breuer & Freud, 1893). Accumulating empirical evidence corroborates early theories and has shown that childhood adversity is one of the most robust determinants of psychopathology. In large epidemiological studies, childhood adversity consistently explains a substantial proportion of mental disorder onsets across development (Afifi et al., 2008; Green et al., 2010; Kessler et al., 2010; McLaughlin, Green, et al., 2012) and increases risk for internalizing, externalizing, and psychotic disorders (Evans, Li & Whipple, 2013; Edwards et al. 2003). Despite the strength of the evidence linking childhood adversity to the onset of psychopathology, the mechanisms that underlie these associations remain poorly understood. These gaps stem from problems related to the measurement of childhood adversity and the choice of outcomes measures.

Studying Childhood Adversity: Challenges to Current Approaches

The prevailing approach to studying childhood adversity – the cumulative-risk approach – treats childhood adversity as a unitary construct encompassing a wide range of different adversity experiences. Blanket terms like "maltreatment" and "adversity" are used to capture subjects with varied histories of sexual abuse, physical abuse, neglect, emotional abuse, parental psychopathology, and poverty. The cumulative-risk approach sums the number of adversities experienced to create a risk score, thus placing the emphasis on the *number* of distinct adverse experiences, rather than the severity or type (Evans, Li, & Whipple, 2013). While earlier work tended to focus on specific types of adversity, cumulative-risk models became the dominant approach in the field following the Adverse Childhood Experiences

Study (ACE; Felitti et al. 1998) and the introduction of the allostatic load model (McEwen, 2002). These seminal works emphasized a strong dose-response relationship between the number of adverse exposures and outcomes and viewed adversities from a stress perspective. Adverse experiences were stressors, and the more stressors experienced, the worse the impact. The cumulative-risk approach has been widely used and supported by a number of studies (e.g., Kraemer et al. 2005; Sameroff, 2006; Sameroff, Seifer, & McDonough, 2004; Chapman, Witfield, Felitti, Dube, Edwards, & Anda, 2004; Thurner, Finklehor & Ormrod, 2006).

There are, however, a number of conceptual and statistical challenges that arise with cumulative–risk models. First, the cumulative-risk model implicitly assumes that different adversity experiences, regardless of their nature, uniformly impact outcomes. For example, cumulative-risk scores assume that physical abuse and sexual abuse influence outcomes in exactly the same way as neglect and poverty. Second, the cumulative-risk model operationalizes childhood adversity as an additive composite of experiences. However, additive composite scores are only appropriate if their components – the adverse experiences – are truly equal and exchangeable. If they are not – and different experiences have distinct effects - then any relationship found between the cumulative score and outcome is likely to be inaccurate. Third, cumulative scores can act as a proxy risk factor for only one, or a subset of, adversity exposures constituting the cumulative score. That is, while the results may indicate that the level of adversity affects an outcome, the effect may actually be driven by one or two of the adversities included in the cumulative score. As a result, cumulative-risk models are unable to identify and quantify the distinct effects of different types of adversity.

A related challenge to the study of childhood adversity involves the focus on psychiatric diagnostic outcomes. Most studies on childhood adversity have looked at associations

between exposure and psychiatric diagnoses. These studies have consistently found the association between childhood adversity and different types of commonly occurring psychiatric illness to be largely non-specific, with little variation in the strength of associations across disorder classes (Green et al. 2010; Kessler et al. 1997; McLaughlin et al. 2012; Kessler et al. 2010). This is unsurprising, given increasing evidence that psychiatric disorders arise from a relatively few transdiagnostic processes (Macdonald et al. 2016). Studies that use diagnoses as outcome of interest offer little insight into the mechanisms and processes disrupted by childhood adversity, and are unlikely to advance our understanding of etiology or inform our intervention strategies.

Delineating Adversities

Challenges inherent to the cumulative-risk model highlight the need for an effective strategy for conceptualizing and distinguishing different types of adverse experiences. Previous studies have attempted to categorize adverse experiences into different subtypes (e.g., dependent vs. independent, social vs. nonsocial, physical abuse vs. emotional abuse). However, these categories often lack a strong theoretical rationale for why they should predict distinct outcomes. Classification is based on surface similarities and differences among the adversity types, without consideration of how and why these subtypes may have different effects.

Developmental neuroscience and principles of experience-dependent plasticity may be helpful in thinking about how and why the nature of different experiences may govern distinct consequences. There is now strong consensus that environmental inputs, in concert with genetic factors, shape the developing brain and calibrate a range of biological and neurocognitive systems to help meet the demands of the environment (Fox, Leavitt, & Nelson, 2010; McCrory & Viding, 2015). Animal models have shown that substantial

deviations from what is expected or needed from the environment (e.g., caregiving, enrichment, safety) can compromise neurodevelopment (Fox, Leavitt, & Nelson, 2010; Rutter et al. 2004; Greenberg, 1987). For example, decreases in environmental inputs with a single modality (e.g., vision, olfactory), as well as a general lack of stimulation (e.g., environmental enrichment) can lead to decreases in dendritic arborization, neuronal depth, and glia cells, in a number of brain regions (Kikusui, Ichikawa, & Mori, 2009; Sheridan & McLaughlin, 2014; Markham & Greenough, 2004). There is also growing evidence the different types of adversity experiences are associated with epigenetic changes in genes that govern neurodevelopment (Cecil et al. 2016). Taken together, these findings suggest that adversity experiences may lead to distinct biological changes that vary according to the nature and demands of the experience.

Drawing upon these principles of experience-dependent plasticity, investigators have recently proposed distinguishing between inadequate inputs (e.g., neglect/deprivation) and harmful inputs (e.g., threat/abuse) when conceptualizing different childhood adversities (Humphreys & Zeanah, 2015; McLaughlin, Sheridan, & Lambert, 2016). These two types of inputs represent different experiential deviations from the expected environment (Fox et al. 2010). Specifically, McLaughlin, Sheridan, and Lambert (2014) have proposed a novel conceptual model that distinguishes experiences along dimensions of threat (harmful input) and deprivation (inadequate input), which the researchers argue have distinct effects on neural and developmental processes. *Threat* refers to interpersonal exposures that involve harm or threat of harm, such as physical and sexual abuse. In contrast, *deprivation* refers to exposures that reflect an absence of expected environmental inputs such as poverty, neglect, and limited psychosocial support.

To date, two studies in humans have utilized the dimensions of adversity approach to examine the distinct effects of threat and deprivation. Lambert and colleagues (2016) found that threat experiences in youth (i.e., exposure to violence) were uniquely associated with automatic emotion regulation deficits (i.e. poor adaptation during emotional Stroop Task), whereas deprivation (i.e. poverty) was uniquely associated with poor cognitive control. Meanwhile, Busso and colleagues (2016) found that threat (i.e., interpersonal violence), but not deprivation (i.e., poverty), was associated with blunted sympathetic and cortisol reactivity. In interpreting their findings, the authors suggested that threat experiences may specifically disrupt emotion processing and stress physiology, while deprivation experiences may disrupt higher-order cognitive systems.

This dimensions of adversity approach has two key advantages. First, this approach to conceptualizing and measuring childhood adversities is rooted in neuroscience principles and findings. It focuses on how the nature and characteristics of the experiences may interact with and modify different processes. As such, dimensions of threat and deprivation are more likely to capture experiences that have similar effects and confer risk through shared mechanisms. Second, this approach allows us to examine whether different types of experiences have unique effects. This remains an outstanding, and critical question, that has significant implications for our understanding of etiology, but more importantly, for the design of our intervention approaches. Utilizing the dimensions of adversity model can help overcome some of the limitations posed by the cumulative-risk model and may uncover differential associations that were previously obscured by cumulative risk scores.

Identifying Mechanisms

Our cursory understanding of the links between childhood adversity and psychopathology also underscores a need for research designs that focus on biological mechanisms that cut

across traditional diagnostic boundaries. Consistent with the Research of Domain Criteria (RDoC) initiative, our studies should investigate transdiagnostic mechanisms that are disrupted by childhood adversity and confer risk for psychopathology more broadly. Corticolimbic neurodevelopment and stress processes are of particular interest in this regard.

Converging evidence from animal models, experimental designs, and clinical populations has shown that corticolimbic regions are uniquely sensitive to adversity (McEwen et al. 2016; Bogden et al. 2016; Lupien, 2009; Teicher et al. 2002). Long-term volumetric differences in corticolimbic regions have been documented in relation to a wide range of childhood adversities including abuse, neglect, poverty, community violence, poor parental care, and poverty (Teicher, 2016; McCrory, De Brito, & Viding, 2011; Edmiston et al. 2011; Teicher, Anderson, Polcari, 2012; Andersen et al. 2008; Chaney et al., 2014; Dannlowski et al., 2012; Frodl et al., 2010; Baker et al., 2013; Cohen et al., 2006; Korgaonkar et al., 2013; van Harmelen et al., 2010). However, these associations vary by region in magnitude, direction, and type of adversity. Notably, relationships between childhood adversity and corticolimbic structure have been observed in individuals with and without psychopathology (e.g., Eveared et al. 2016; Opel et al. 2014; Edmiston et al. 2011). This consistency suggests that childhood adversity may exert a "prepotent influence" on neurodevelopment that is independent of psychiatric status (Teicher et al. 2016). Thus, alterations in corticolimbic structure may precede, and contribute to, risk for psychopathology.

Childhood adversity is also proposed to impact stress pathophysiology, particularly through alterations of the HPA-axis. Decades of research suggest childhood adversity is associated long-term changes in the development and regulation of the HPA-axis (for review see Gunnar & Quevedo, 2007; Repetti, Robles, & Reynolds, 2011). However, the findings

are inconsistent in regards to the direction of this relationship, with evidence for both hyper- and hypo-active HPA functioning following adversity (Carrion et al. 2001; Cicchetti & Rogosch, 2001b; De Bellis et al. 1999; Delahanty et al. 2005; Pfeffer et al. 2007; Dozier et al. 2006; Carlson and Earls, 1997; Bruce et al. 2009a). Both increases and decreases in cortisol levels can lead to variation in gene activity and epigenetic patterns, as well as direct changes to brain structure and function in ways that may ultimately increase vulnerability for psychopathology (McEwen & Gianoros, 2011).

While there is ample evidence that childhood adversity is associated with changes in corticolimbic structure and stress processes, the direction and extent of these associations varies across studies. This is likely due to the fact that studies vary widely in the types of adversities measured, as well as whether co-occurring forms of adversity are taken into consideration. While certain forms of trauma and abuse tend to be well defined and investigated, that amount of deprivation in these same environment is usually unmeasured. Thus, it can be difficult to interpret the current findings in the literature and it remains unclear whether childhood adversities have general vs. specific effects on corticolimbic structure and stress processes. A more effective strategy for examining different types of childhood adversity and their mechanistic underpinning is needed.

Current Studies

Current approaches to studying childhood adversity limit our ability to identify whether different types of adversity have distinct effects on the processes that underlie risk for psychopathology. Identifying dimensions of experience that cut across multiple types of adversity (threat and deprivation; McLaughlin et al. 2014), based on neuroscience principles of experience-dependent plasticity, may be a more effective strategy for delineating the impact of childhood adversity and identifying relevant biological mechanisms. Accordingly,

we designed two studies that aimed to test the dimensions of adversity approach by 1.) determining whether threat and deprivation have distinct effects on corticolimbic structure and stress processes, and 2.) examining whether the inferences drawn from a model of childhood adversity change based on how adversity is conceptualized and modeled. In Study 1 we examined whether threat and deprivation have dimension-specific associations with corticolimbic structure. In Study 2 we examined whether stress sensitivity mediates the association between childhood adversity and basal cortisol and whether these associations differ by adversity dimension and sex. Each study is presented separately followed by general conclusions.

The following studies utilize participants from the North American Prodromal Longitudinal Study -2 (NAPLS-2), which includes individuals who are at clinical-high risk (CHR) for psychosis, as well as healthy controls. The clinical-high risk population is ideally suited to test the effects of childhood adversity as these samples are enriched for childhood adversity experiences and allow for a wider variation of adversity than what is typically afforded by community samples (Bendall, Jackson, Hulbert, & McGorry, 2008; Larsson, et al. 2013; Matheson, et al. 2013; Read, van Os, Morrison, & Ross, 2005, Ruby et al. 2014). Childhood adversity and trauma are also associated with psychotic-like experiences, such as low-grade delusion ideation, isolated auditory hallucinations, and perceptual aberrations even among individuals who do not have a psychotic disorder (Janssen et al. 2003; Kelleher et al. 2008). Additionally, CHR samples also provide an enriched range of psychiatric syndromes. In addition to putative prodromal symptoms (i.e., sub threshold positive symptoms), 80% of CHR individuals have comorbid diagnoses of mood, personality, and externalizing disorders that are independent of psychosis outcome (Addington et al., in press).

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Differential Associations of Deprivation and Threat with Corticolimbic Structure

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Abstract

Childhood adversity is a powerful predictor of psychopathology. Prevailing approaches treat childhood adversity as a unitary construct and assume that very different experiences influence development similarly. However, recent evidence indicates that different forms of childhood adversity may exert unique effects on the neural pathways mediating the association between childhood adversity and psychopathology. The current study utilized a conceptual framework that distinguishes adversity experiences along dimensions of threat and deprivation and examined whether threat and deprivation experiences have distinct effects on corticolimbic structure. Results from the dimensions of adversity model were compared to prevailing single-risk and cumulative-risk models to test the relative merits of the respective approaches. Participants (n=739, mean age = 19.2) were drawn from a large study of youth at risk for serious mental illness. Retrospective reports of childhood adversity and structural magnetic resonance imaging were completed at the baseline visit. Results revealed subtle dimension-specific associations with corticolimbic structure. Deprivation was uniquely associated with smaller hippocampal and cortical volumes. There was also a significant interaction between threat and deprivation; threat was associated with thicker superior frontal cortices at high levels of deprivation. Importantly, these specific associations were masked in the single-risk and cumulative-risk models. The findings highlight the importance of assessing specific types of childhood adversity.

Differential Associations of Deprivation and Threat with Corticolimbic Structure

Childhood adversity is among the strongest predictors of psychopathology. Youth exposed to adversity have higher rates of internalizing, externalizing, and psychotic disorders (Evans, Li & Whipple, 2013; Edwards et al. 2003; Kessler et al. 2010), diminished cognitive functioning (Gould et al. 2012), and poorer treatment responses (Teicher & Samson, 2013). In the case of serious mental illness, individuals exposed to childhood adversity are nearly three times more likely to exhibit psychotic symptoms than those without, even after controlling for common demographic and clinical confounds (Varese et al. 2012; Mathenson, Shepherd, Pinchbeck, Laurens, & Carr, 2013). Despite the consistency of evidence linking childhood adversity to psychiatric outcomes, the nature and specificity of the mechanisms that underlie these associations remain poorly understood.

Progress in the field of childhood adversity has been hampered, in part, by prevailing approaches to measuring and conceptualizing adversity. Current models treat childhood adversity as a unitary construct and are poorly suited to identifying consequences of specific adverse experiences. However, emerging research suggests that specific types of adversity may have unique effects on biological and developmental processes (Lambert et al. 2016; Busso et al. 2016; Humphreys & Zeneah, 2014; Cecil et al. 2016). Furthermore, existing studies have primarily focused on diagnostic outcomes, hindering identification of potential mechanisms. As a result, we lack a clear understanding of what biological and psychological processes are disrupted by childhood adversity, and whether these disruptions vary as a function of adversity type. However, if different types of adversity are associated with distinct mechanisms and sequelae such knowledge will be critical to developing effective interventions. To address these outstanding questions, we examined whether different dimensions of childhood adversity have distinct effects on neural structure.

Conceptualizing and Measuring Childhood Adversity

The prevailing approaches used to study childhood adversity are limited in their ability to delineate the consequences of specific adverse experiences. 'Single-risk' approaches examining the effect of single types of adversity (e.g., sexual abuse, neglect parental death) on outcomes have been utilized by a number of studies (e.g., Anda et al. 2006; Dubowtiz, Papas, Black, & Starr, 2002). While this approach attempts to isolate the effects of specific adversity types, it fails to take into account the high co-occurrence among adversities (Green et al., 2010; Finkelhor et al. 2007b). Consequently, it is impossible to determine whether an observed relationship is driven by the adversity under investigation (e.g., physical abuse), or by co-occurring adversities (e.g., neglect, poverty) that have not been accounted for. Additionally, if co-occurring adversities are differentially associated with outcomes of interest, effects may be suppressed (Evans et al. 2013).

More recently, the field has shifted to a 'cumulative risk' approach, which emphasizes the number, *r*ather than the type, of adverse exposures in relation to outcomes (Zeanah & Sonuga-Bark, 2016). The core assumption is that the total number of exposures is a better predictor of negative outcomes. The cumulative approach has been supported by many studies (e.g., Arata et a. 2007; Finkelhor, Ormord & Turner, 2009; Lauterbach & Armour, 2016) and has a number of advantages. For example, cumulative models reduce measurement error and collinearity (Ghiselli et al.1981), index co-occurring adversities, and fit well with theoretical stress models (e.g., allostatic stress model; McEwen, 2002). However, the additive nature of cumulative-risk models implicitly assumes that diverse experiences operate through similar mechanisms and that the associations between adversity exposures and outcomes are nonspecific. Per the cumulative approach, physical abuse and sexual abuse (cumulative risk score =2) are assumed to have the same impact as poverty and neglect (cumulative risk score

=2). This seems unlikely, given the differences in the nature of these experiences as well as recent findings suggesting that exposure to threat and deprivation may have distinct neurobiological signatures.

Principles of neurodevelopment suggest there is reason to believe that the nature of experiences matter. For example, developmental neuroscience has shown that the developing brain is shaped by certain kinds of environmental input, and that deviations from what is needed or anticipated can lead to distinct biological and functional consequences (Fox, Leavitt, & Nelson, 2010). Thus, emphasizing the number of adversity exposures, without attention to the nature of those exposures, may oversimplify the boundaries among distinct types of adversity that differentially interact with and modify the structure of the developing brain. In line with these principles, investigators have recently proposed an alternate approach to conceptualizing childhood adversity that distinguishing between inadequate inputs (e.g., deprivation) and harmful inputs (e.g., threat/trauma). Humphreys and Zeanah (2014) argue that deprivation and trauma represent distinct deviations from the expectable environment, which likely manifest in different biological and behavioral consequences. Similarly, McLaughlin, Sheridan, and Lambert (2014) have proposed a novel conceptual model that distinguishes between dimensions of deprivation and threat, which are posited to confer vulnerability to psychopathology through at least partially distinct neural, neuroendocrine, cognitive and emotional processes (McLaughlin, Sheridan & Lambert, 2014; Sheridan & McLaughlin, 2014). Specially, threat is proposed to alter development of the circuits that support emotional processing and fear learning, while deprivation is posited to alter neural regions that support cognitive performance and higher-order learning (McLaughlin & Sheridan, & Lambert, 2014). Characterizing childhood adversities along

dimensions of threat and deprivation aims to both address the oversimplification of cumulative models and bolster the identification of potential underlying mechanisms.

While animal models provide some evidence to suggest threat and deprivation may have distinct effects on neural development (Diamond, Rosenzewig, Bennett, Linder, 1972; Eiland, Ramroop, Hill, Manley, & McEwen, 2012; Markham & Greenough, 2004), few human studies have directly compared these dimensions. In one of the only studies to date utilizing the dimensions of adversity approach, Lambert and colleagues (2016) found that threat experience in youth (i.e., exposure to violence) was associated with automatic emotion regulation deficits (i.e. poor adaptation during emotional Stroop Task), but not cognitive control deficits in adolescents. In contrast, experience of deprivation (i.e. poverty) was associated with poor cognitive control, but not impairment in automatic emotion regulation. In interpreting their findings, the authors suggest that threat and deprivation disrupt different neural systems and processes. Specifically, threat experiences specifically disrupt emotion regulation and processing, while deprivation experiences disrupt higher-order cognitive processes.

An important next step in this line of investigation is to determine whether threat and deprivation differ in their associations with underlying neurobiology. Corticolimbic regions (i.e., hippocampus, amygdala, PFC) are of particular interest given their role in emotion processing, fear learning, executive function, and cognitive control processes, which are consistently implicated across multiple forms of psychopathology (Macdonald et al. 2016). A rapidly growing body of research suggests that childhood experiences can alter the trajectory of brain development, particularly in corticolimbic regions (i.e., hippocampus, amygdala, PFC), given their unique vulnerability to stress and experiential effects (Teicher, 2016; Lupien, McEwen, Gummar & Heim, 2009; Bogden 2016; Swartz & Monk, 2014).

Importantly, there is increasing evidence that individual differences in corticolimbic structure may mediate associations between adversity and later psychopathology (Burghy et al. 2012; Gorka et al. 2014; Tottenham et al. 2011; Swartz et al. 2015). For example, smaller hippocampal and medial prefrontal gray matter volumes have been found to partially mediate the association between reported childhood maltreatment and anxiety in adulthood (Gorka et al. 2014), as well as the association between early life adversity and vulnerability to depression in adolescents (Rao et al. 2010). These results suggest the structural changes may represent a neural embedding of childhood adversity, which may confer risk for future psychopathology. Whether these structural differences are uniquely associated with threat and deprivation remains an empirical question to be tested.

Threat. Threat involves experiences that denote harm or threat of harm to an individual. For humans, this dimension includes experiences of physical, sexual, and emotional abuse, as well as other types of interpersonal aggression (e.g., bullying). While it is difficult to fully disentangle the specific effects of threat on corticolimbic regions in the human literature, as few studies control for co-occurring deprivation experiences (e.g., SES), there is indirect behavioral and neural evidence to suggest threat experiences specifically impact frontoamygdalar development and functioning. It is well established that frontoamygdalar regions play critical roles in emotional and fear-related processing, both of which have been found to be atypical in individuals who have experienced childhood abuse. For example, experiences of childhood abuse are associated with enhanced sensitivity and attention to angry facial expressions (Pollak & Sinha, 2002), potential threats (Van Marle, Hermans, Qin, & Fernandez, 2009), and negative emotional cues (Van et al. 2009). Notably, there is evidence that these processing biases are specific to children who have experienced violence, and are not observed in children who have been neglected (Pollack et al. 2005).

Emotional functioning and fear-related processing deficits have been linked with larger amygdalar volumes in some studies (Mehta et al. 2009; Tottenham et al. 2010), although findings regarding the association between childhood maltreatment and amygdalar volume has been mixed (McCrory, De Brito, & Viding, 2011; Edmiston et al. 2011). Amygdalar hyperactivity in response to negative emotional stimuli, however, is consistently reported among abused youth (McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015; Maheu et al. 2010; Tottenham et al. 2011). This altered pattern of activity is hypothesized to reflect a neurobiological adaptation to promote rapid identification of potential threats and heightened reactivity to emotional information (Van Marle, Hermans, Qin & Fernandez, 2009). Additionally, smaller prefrontal cortical volumes and thinner frontal cortices are also observed among abused youth (Gold et al. 2016; Heim et al. 2013; Edmiston et al. 2011). Notably, these reductions are generally localized to frontal cortices, as opposed to global cortical reductions, suggesting potential specificity of threat experiences on frontal regions (Gold et al. 2016; Everared et al. 2016).

Deprivation. In contrast to threat, deprivation is characterized by the absence of cognitive and social inputs, as well as learning opportunities, during periods of development when such experiences are expected (Lambert et al. 2016, Fox et al. 2010). In humans, this dimension of adversity can encompass a range of experiences characterized by material, cognitive, and/or psychosocial deprivation, including poverty, emotional neglect, parental absence, and limited peer relationships during childhood. Together these experiences result in deprivation of important material and social-cognitive inputs that are hypothesized to scaffold healthy neurodevelopment.

Behavioral, neurocognitive, and neural evidence suggest deprivation exposures may specifically influence the development of cortical and hippocampal regions. Relative to

children who have been abused, children exposed to neglect are at greater risk for a wide range of cognitive deficits (Hildyard & Wolfe, 2002). In humans, deprivation-related experiences are consistently associated with disruptions in higher-order cognitive functions supported by cortical and hippocampal regions. For example, childhood poverty, institutionalization, and neglect have all been associated with poor performance on cognitive tasks involving working memory, long-term memory, inhibition, association learning, and/or set shifting (Bos, Fox, Zeanah, & Nelson, 2009; Farah et al. 2006; Mueller et al. 2010; Noble, McCandliss, & Farah, 2007; Dubowitz et al. 2002; Spratt et al. 2012; Farah et al. 2008, Rao et al. 2010). Consistent with these findings, Lambert et al. (2016) found that, deprivation, but not threat, was associated with poorer cognitive control – a higher-order cognitive processes that relies on working memory and set-shifting abilities (Miyake & Friedman, 2012).

Specific forms of deprivation such as institutionalization (McLaughlin et al. 2015; Mehta et al. 2009) and poverty (Noble, Houston, Kan, & Sowell, 2012; Sheridan et al. 2012; Hair et al. 2015) are associated with smaller cortical volumes. Interestingly, a recent study by Everaerd et al. (2015) of brain morphology in psychiatrically healthy individuals exposed specifically to abuse, deprivation, or neither, found that individuals with a history of deprivation showed reduced cortical gray matter compared to subjects with a history of abuse. Additionally, poverty has been with associated with smaller hippocampal volumes in healthy individuals (Hanson et al. 2011; Hair et al. 2015). This relationship was specific to the hippocampus, and was not observed in the amygdala. In independent yet intersecting work, a number of animal models have shown that decreases in environmental enrichment and complexity lead to neuronal changes and morphological plasticity, such as decreases in dendritic arborization, neuronal depth, and glia cells, in cortical and hippocampal regions

(Markham & Greenough, 2004; Fiala, Joyce, & Greenough, 1987; Soffie, Han, Terao, & Eclancher, 1999; Greenough, Vokmar, & Juraska, 1973).

In summary, there is preliminary, though indirect, evidence that threat and deprivation may have distinct influences on specific corticolimbic regions. Disruptions in the neurodevelopment of these regions may underlie a number of the emotional processing and cognitive deficits that characterize adversity-exposed youth and confer risk for psychopathology. However, to date, no studies have examined whether dimensions of threat and deprivation have differential associations on corticolimbic structure.

Current Study

The aims of the current study are to 1.) test a novel conceptual model that distinguishes adversity experiences along dimensions of threat and deprivation to determine whether these dimensions have differential associations with corticolimbic structure, and 2.) compare these results to prevailing single-risk and cumulative-risk models. Given that threat and deprivation are hypothesized to have both unique and common neurobiological effects, this approach provides the opportunity to test the relative merits of the single-risk factor and cumulative approach versus the differentiation of adversity dimensions.

In order to test these models measures of corticolimbic structure, including cortical thickness, and self-reported childhood adversity were obtained from a large sample of individuals at risk for serious mental illness. Based on the current literature, we predicted threat would be specifically associated with larger amygdalar volume and smaller superiorfrontal volume/thickness, and that deprivation would be specifically associated with smaller hippocampal volume and cortical volume/thickness. Given the high rates of co-occurrence across adversity types, we also included an exploratory analysis to see if there was an interaction between threat and deprivation on any of the corticolimbic measures.

Finally, we hypothesized that both the single-risk the cumulative-risk approach would obscure the specificity of the associations revealed using the dimensions of adversity approach.

Method

Sample

The sample included 736 individuals between 12-30 years of age (mean=19.2, SD=4.3). All participants were recruited as part of the North American Prodome Longitudinal Study (NAPLS-2). Specific details about ascertainment, inclusion, and exclusion criteria have been described in detail elsewhere (Addington et al. 2012). Participants were included in the current study if they completed childhood adversity measures and MRI scans during the baseline visit. Of the 736 participants, 524 (70%) met clinical-high risk (CHR) criteria for serious mental illness; 212 (30%) did not meet the criteria for CHR status. Consistent with the literature, individuals who met criteria for CHR status reported higher levels of threat [(F (1,734)=99.89, p<. 01)] and deprivation [(F (1,734)=75.25, p<. 01)] exposures. There were no group differences in any of the corticolimbic brain measures. All analyses were conducted combining across the groups in order to include variation in exposure to adversity, ethnicity, and psychopathology.

Measures

Threat Exposure. Threat was operationalized to denote adverse experiences involving harm or threat of harm to an individual. Specific types of threat exposures were assessed using the *Documentation of Trauma Form*, a semi-structured interview that retrospectively assesses six types of negative childhood experiences before the age of 16. Participants where asked whether they had experienced the following: emotional abuse (e.g., “unjustified

punishment" "being sworn at"), neglect (e.g., "not able to find any attention or support from people at home"), physical abuse (e.g., "being kicked or punched"), psychological bullying (e.g. "taunted or sworn at by peers"), physical bullying ("physical assaulted at school"), and sexual abuse (e.g., "touched sexually against will", "sexual contact against will"). Responses were rated on a categorical 'present' or 'absent' scale. A threat composite score was created by summing responses to the physical abuse, sexual abuse, emotional abuse, physical bullying, and psychological bullying items. The threat composite score ranged from 0 (no endorsement of threat exposures) to 5 (endorsement of all threat exposures), and was used in all statistical analyses to capture variation in threat exposures.

Deprivation Exposure. Deprivation was operationalized to denote experiences involving the absence of expected cognitive and social inputs. In the current study, deprivation items included indices of childhood poverty, emotional neglect, parental absence, and restricted peer relationships during childhood. Poverty was determined by the ratio of income to needs, which was computed by dividing reported family of origins income by US census 2014 poverty line for a family of that size, with a value of <1 indication that a family was living below the poverty line. A dichotomous measure of poverty was used rather than the linear income to needs ratio because it is unlikely that deprivation of inputs exist at the higher end of income distribution. Neglect was assessed via the *Documentation of Trauma Form* described above. Restricted peer interactions (a proxy of psychosocial deprivation) was determined using the social subscales of *The Premorbid Adjustment Scale* (PAS; Cannon-Spoor et al. 1982), a widely used semi-structured interview designed to retrospectively assess social and academic functioning across development. Interviewers rated participants on a 0-6 scale for peer relationships during childhood (age 5-11 years). Scores falling between 4-6, which indicates social isolation and lack of same-aged peer relationships, were used to

indicate restricted peer relationships. Finally, absence of a biological parental figure (e.g., no/minimal contact) was determined from a demographic information interview. A deprivation composite score was created by summing items of childhood poverty, childhood peer relations, parental absence, and neglect. This deprivation composite ranged from 0 (no endorsement of deprivation exposures) to 4 (endorsement of all deprivation exposures), and was used in all statistical analyses to capture variation in deprivation exposures.

Neuroanatomical Volume and Thickness. The brain regions of interest included twelve lateralized measurements; cortical volume, cortical thickness, superiorfrontal volume, superiorfrontal thickness, hippocampal volume and amygdalar volume. Cortical volume measurements include a composite of thickness, surface area, and folding (Mechelli, Price, Friston, & Ashburner, 2005). However, cortical thickness and surface areas are distinct measures, show unique developmental trajectories, and may be driven by different underlying mechanisms (Raznahan et al. 2011; Wierenga et al. 2014). Thus, considering cortical thickness may provide independent information about brain development than considering volume alone (Hutton et al. 2009; Wallace et al. 2015). Additionally, twin studies suggest that environmental and genetic factors may differentially influence right and left brain regions (Yoon et al. 2010) and some studies in the maltreatment literature have showed only significant left-sided findings, while others have found only significant right-sided (see Teicher et al. 2016).

MRI scanning was performed at eight sites. Five sites (UCLA, Emory, Harvard, UNC, and Yale) used Siemens-Trio 3T scanners, two sites (Zucker-Hillside Hospital and UCSD) used GE HDx scanners, and one site (Calgary) used a GE Discovery scanners. All Siemens sites used a 12-channel head coil and all GE sites used an 8-channel head coil. Sequence parameters were optimized for each scanner manufacturer, software version and coil

configuration according to the ADNI protocol (http://adni.oni.usc.edu/methods/documents/mri-protocols/). Scans were acquired in the sagittal plane with a 1mm*1mm in-plan resolution and 1.2mm slice thickness. Siemens scans used a MPRAGE sequence with a 256(axial) x 240(sagittal) x 176 (coronal) mm field of view, TR/TE/TI=2300/2.91/900 ms and a 9 degree flip angle, while GE scanners used an IR-SPGR sequence with a 26 cm field of view, TR/TE/TI = 7.0/minimum full/400 and an 8 degree flip angle.

*Image processing***.** Subcortical volumetric segmentation of the hippocampus and amygdala was processed using FreeSurfer version 5.2 at Yale University by investigators who had participated in the FreeSurfer training course at the Martinos Center for Biomedical Imaging. The subcortical segmentation procedure assigns a neuroanatomical label to each voxel of the MRI volume, using a probabilistic atlas and Bayesian classification rule (Fischl et al..2002). Surface-based cortical reconstruction was performed to extract thickness measures by calculating the shorted distance from each point on the gray/white boundary to the pial surface at each vertex (Fischl & Dale, 2000). See Cannon et al. (2014) for details on the quality assurance procedure.

Data Analyses

Path analysis in Mplus version 5.21 (Muthen & Muthen, 2010) was used to model the associations between adversity dimensions (threat, deprivation), total adversity, and corticolimbic structure. Preliminary data analyses reveled a significant effect of MRI scanner site on brain measures, which may have resulted from differences in MRI scanner types (GE vs. Siemens). Site was dummy coded and included into all models to control for any site differences. Based on prior research, age, sex, and total intracranial volume were also

controlled for in all models. All brain volume and thickness measures were standardized prior to analyses.

Four models were estimated for each corticolimbic region of interest: a differentiated dimensions of adversity model, an interaction model, a single- risk model, and a cumulative-risk model. To test the differentiated dimensions of adversity model, both adversity dimensions (threat and deprivation) were entered into the model for each outcome variable (lateralized corticolimbic measure). Entering both threat and deprivation into the model simultaneously allowed us to examine the effect of each adversity dimensions (e.g. threat), while controlling for the effect of the other (e.g., deprivation). To test the interaction model, threat, deprivation, and the interaction term were all entered as predictors for each corticolimbic region of interest. Simple slopes were examined at high (one standard deviation above the mean) and low (one standard deviation below the mean) levels of deprivation for significant interactions. To test the single-risk model, threat was entered as the predictor for each corticolimbic measure, without controlling for deprivation. Next, deprivation was entered as the predictor of each corticolimbic measure, without controlling for co-occurring threat. To test the cumulative model, a total adversity score (sum of threat and deprivation) was entered as the predictor for each corticolimbic region. Given that we are comparing models that are not nested, but based on the same manifest variables, Akaike information criteria (AIC) and Bayesian information criteria (BIC) were used to compare model fit (Akaike, 1974; Schartz, 1978; smaller values indicate better model fit). Standardized betas are presented in results and are used as a measure of effect size. Statistical significant level set at .05.

Results

Childhood Adversity Characteristics

Demographic and adversity characteristics are shown in Table 1. The majority of individuals in the current study reported at least one adversity exposure (74%; n=546). Across the entire sample, 58% (n=427) endorsed at least one threat exposure and 53.6% (n=398) endorsed at least one deprivation exposure during childhood. Females endorsed higher levels of threat compared to males [(F (1,734)=5.09, p=. 02)], and older individual endorsed higher levels of deprivation compared to younger individuals (t=3.63, p<. 01). Co-occurring adversities were common, with 48% of individuals reporting two or more adversity exposures. There was variability in exposure to the different dimensions of adversity; 20% (n=150) of the sample endorsed only threat exposures, 16% (n=119) endorsed only deprivation exposures, 37% endorsed co-occurring threat and deprivation exposures, and 25% reported no adversity exposure.

Point-biserial correlations between the specific adversity exposures comprising the threat and deprivation dimensions are shown in Table 3. The direction of the correlations between corticolimbic measures and the specific adversity exposures comprising the threat and deprivation dimensions were generally consistent with those observed using the dimension composite scores (Table 4). A moderate correlation was observed between threat and deprivation (r=. 48, p<. 01), which is consistent with the literature on the co-occurrence rates among different types of adversity (Green et al., 2010). However, this modest correlation also suggests a degree of independence of the two adversity dimensions. See Table 5 for zero-order correlations between adversity dimensions and corticolimbic structure measures.

Dimensions of adversity model

We first tested the association between deprivation and corticolimbic structure, controlling for threat. In support of our hypotheses, deprivation was associated with smaller left cortical volume (β= -.06, *p*<. 01), right cortical volume (β= -.06, *p*<. 01), left hippocampal volume (β= -.06, *p*<. 01) and right hippocampal volume (β= -.06, *p*<. 01). Next, we tested the association between threat and corticolimbic structure, controlling for deprivation. Contrary to our hypothesis, threat was not associated with amygdalar volume or superiorfrontal volume/thickness (Table 6). Although not significant, the direction of the associations between threat and superiorfrontal volume/thickness was in the opposite direction than predicted.

Interaction of threat and deprivation. We then conducted an exploratory analysis to test whether threat and deprivation interact to predict corticolimbic structure. A significant interaction between threat and deprivation emerged in predicting left superiorfrontal thickness (β= .07, *p*=. 04) and right superiorfrontal thickness (β= .10, *p*<. 01). Specifically, threat was associated with thicker bilateral superiorfrontal regions in individuals with high levels of deprivation (left superior frontal: B=0.11, z= 2.79, *p*< .01; right superior frontal: B=0.12, z=2.87, *p*< .01), but not in individuals with low levels of deprivation (Figures 1 and 2)

Prevailing Models

Single-risk model. Consistent with previous work utilizing single-risk models, we tested the association between each dimension of adversity and corticolimbic measure separately, without controlling for the other dimension. In the single-risk model, threat (not controlling for deprivation) was associated with thicker left superiorfrontal cortices (β= .07, *p*=. 03).

Deprivation (not controlling for threat) was associated with smaller left cortical (β= -.04, *p*<. 01) and right cortical volumes (β= -.05, *p*<. 01) (Table 6).

Cumulative-risk model. Finally, we estimated a cumulative-risk model using an aggregated total adversity score. Total adversity was associated with thicker left superiorfrontal cortices (β= .07, *p*=. 04), and larger left amygdalar volume (β= .06, *p*=. 05) (Table 6). Model fit comparisons for the dimensions of adversity and cumulative models are presented in Table 7.

Discussion

We tested a novel conceptual model that distinguishes between threat and deprivation exposures to determine whether these adversity dimensions have unique effects on corticolimbic structure. We found subtle dimension-specific associations with corticolimbic structure, which were masked in the single-risk or cumulative risk models. Specifically, we found that deprivation was uniquely associated with smaller hippocampal and cortical volumes. There was also a significant interaction, whereby threat was associated with larger superiorfrontal thickness at high levels of deprivation. Notably, we found a different pattern of results when estimating single-risk and cumulative-risk models. In the single-risk model, threat was associated with thicker left superiorfrontal cortices, while deprivation was associated with smaller cortical volumes. In the cumulative risk model, total adversity was also associated with thicker left superiorfrontal cortices and larger left amygdalar volumes.

Conceptualizing and Measuring Childhood Adversity

The notable differences in the pattern of associations observed across the dimensions of adversity, single-risk, and cumulative-risk models highlight the importance of assessing the nature of childhood adversities. Comparing these different models demonstrates how disparate findings can occur depending on how childhood adversity is conceptualized and

measured. This is most clearly illustrated in the cumulative-risk model findings, in which the deprivation-specific associations with hippocampal and cortical volumes were not observed. This masking effect results from combining adversity types that differ not just in relative magnitude of effect, but more significantly, in the direction. In this study, the effects were canceled out when deprivation (significantly and negatively associated with hippocampal and cortical volumes) was aggregated with threat (non-significantly and positively associated) into a cumulative score. The cumulative-risk results support the inaccurate conclusion that childhood adversity is not associated with structural alterations in these regions.

The single-risk approach revealed a different pattern of findings, but highlights similar challenges to interpretation. While the single-risk model did reveal associations between deprivation and cortical volumes (though not hippocampal volumes), it is unknown whether this association is driven by deprivation, co-occurring threat, or a combination of the two. It is only by referencing the dimensions of adversity model that we can confirm these associations are deprivation-specific. Relatedly, in the single-risk model, threat was associated with greater superiorfrontal thickness, consistent with findings in the cumulative model, but not the dimensions of adversity model. Interestingly, greater left superiorfrontal thickness was observed in the interaction model, suggesting that individuals who experience both high levels of threat and deprivation drive this association. The relationship is not simply one of cumulative additive effects, as might be extrapolated from the cumulative model findings - or driven by threat as indicated by the single-risk model - but rather a consequence of an interaction between the two adversity dimensions.

Taken together, these model comparisons highlight how different conceptualizations of childhood adversity can result in disparate conclusions that are at risk of being incomplete or inaccurate. These findings support the utility of the dimensions of adversity approach and

underscore the importance of assessing and controlling for co-occurring forms of adversity to disentangle their specific associations.

Dimensions of Threat and Deprivation

Our findings also provide evidence for subtle deprivation-specific associations with cortical and hippocampal volume in a large sample of psychiatrically diverse individuals. These deprivation-specific associations are consistent with previous studies that have found smaller cortical and hippocampal volumes in individuals who have been exposed to poverty (Hanson et al. 2011, Hair et al. 2015, Nobel, 2015), neglect (Dannlowski et al. 2012), and low parental involvement (Rao et al. 2010, Luby et al. 2012; Farah et al. 2008). However, given the most studies of deprivation-related exposures (e.g., neglect, poverty) do not control for co-occurring threat experiences, our results extend this line of research and provide evidence for specificity of these associations. Additionally, our measure of deprivation includes multiple indices of deprivation, rather than a single indicator (e.g., poverty as index of deprivation; Lambert et al. 2016, Busso et al. 2016). Thus, our findings also suggest that deprivation-specific associations can be detected even when a broader approach to conceptualizing deprivation exposure is utilized. It is important to note that our effect size is small, although in line with the effect magnitudes observed in similar studies of adversity experiences and brain structure (e.g., Noble et al. 2015; Luby et al. 2013).

While these findings should be considered preliminary, and are in need of replication, they provide a basis for speculating what may underlie these volumetric differences. One possible explanation is that limited cognitive and psychosocial stimulation fails to trigger the neurodevelopmental processes in cortical and hippocampal regions required for functioning in more complex environments (Sheridan et al. 2012; McLaughlin, Sheridan, & Lambert, 2014). The lack, or lower complexity, of environmental demands and opportunities may not

initiate the morphological plasticity that accompanies adaptation to increased environmental complexity. This is consistent with findings from animal models utilizing enriched environment paradigms, which have demonstrated experience-induced morphological plasticity via synaptogenesis, dendritic reorganization, neurogenesis and other non-neural components such as myelination, cerebrovasculature, astrocytic hyptertrophy in response to environmental enrichment, (Greenough et al. 1973; Fiala et al. 1978; Rampon et al. 2000, Greenough et al. 1986). There is evidence that while of some of the non-neural experience-induced changes are transient, others are more stable, and possibly permanent (Markham & Greenough, 2006). While the exact mechanisms driving these cellular changes are unknown, epigenetic processes are strong candidates. For example, rodent models of postnatal neglect that show decreases in brain-derived neurotrophic factor expression and neurogenesis in hippocampal and prefrontal regions (Lippmann et al. 2007; Kikusui & Mori, 2007; Macri, Laviola, Leussis, & Andersen, 2010; Roth et al. 2009).

Alternatively, smaller volumes may result from prolonged stress exposure, which has been shown to produce dendritic atrophy in cortical and hippocampal regions (Sousa & Almedia, 2012; Khourey et al. 2015; Cerqueira et al. 2005). Although threat and deprivation experiences both involve stress, the more enduring vs. acute nature of deprivation experiences may result in a more prolonged exposure to glucocorticoids and subsequent reductions in cell complexity and/or atrophy. However, it is worth noting that in humans, the association between childhood maltreatment and hippocampal volume is not present in pediatric populations, but is consistently observed in adolescent and adult samples (Edmiston et al. 2011). This developmental lag suggests that cellular atrophy in response to elevated cortisol is not solely responsible for the smaller volume, as we would expect to see these effects concurrently. Instead, deprivation exposures may alter epigenetic regulation of

neuromaturational processes that emerge post-puberty when the brain undergoes dramatic re-organization and maturation.

Another possibility is that the more enduring nature of deprivation experiences increases the chances that exposures overlap with sensitive periods during which specific regions are maximally susceptible to structural change following adversity. For example, a cross-sectional study of childhood sexual abuse found that the developmental timing of the exposure determined what specific regions were impacted, such that the hippocampus was maximally affected at ages 3-5 and the frontal cortex was maximally affected at ages 14-16 (see Anderson et al. 2008). Future research designs that include information about the timing, duration, and intensity of threat and deprivation exposures are needed to help tease apart whether the deprivation-specific associations with cortical and hippocampal structure are driven by the experience-dependent plasticity, cortisol effects, overlap with sensitive periods, or a combination of these factors.

In contrast to our predications, threat was not specifically associated with amygdalar volume. Given the mixed findings in the literature our results are consistent with several other studies that have failed to detect volumetric changes in the amygdala (DeBellis et al. 2002; Bremner et al. 1997; Stein 1997). However, larger left amygdalar volume was associated with threat in the single-risk model, and with total adversity in the cumulative model. This pattern suggests that left amygdalar volume may be influenced by both threat and deprivation exposures, and depend on the severity of adversity exposure more broadly. Consistent with this, a recent study found that amygdalar volumetric differences in physically and sexually abused adolescence disappeared when controlling for SES (Gold et al. 2016). These findings suggest that associations with amygdalar volume attributed to threat or trauma in some studies may be a consequence of variation with deprivation experiences. The

amygdala may be a region in which effects of adversity experiences are non-specific and function through similar stress mechanisms. Alternatively, longitudinal studies have found that childhood maltreatment is associated with larger amygdalar volumes at baseline, but smaller volumes during adulthood relative to healthy controls (Whittle et al. 2013; McEwen et al. 2016). Given the age range of this sample, and variability in the distance from time of documented threat exposure, it is possible that the impact of adversity on amygdala volume differs in magnitude or direction across development and is washed out in the current sample.

We also found an interaction between threat and deprivation on superiorfrontal thickness that was in the opposite direction than predicted. Although highly speculative, thicker superiorfrontal cortices may indicate disruptions and/or delays in normative neuromaturational processes. Normative age-related decreases in frontocortical thickness occur throughout adolescence and young adulthood and are associated with improved neuropsychological performance (Squeglia et al. 2013), cognitive control (Tamnes et al. 2010, 2013), and emotion regulation (Vijakakumar et al. 2014). These maturational changes are hypothesized to result from synaptic pruning, which helps increase neural efficiency by removing redundant synapses (Lenroot & Giedd, 2006). Thus, thicker frontal cortices may actually indicate poorer efficiency of these regions. This is consistent with findings that maltreated youth have greater difficulty, and demonstrate abnormal patterns of activation, on tasks that require regulation by the PFC (McLaughlin et al. 2015; Carrion et al. 2008; Muller et al. 2010). Of course, we cannot draw these inferences from the current data and further investigation with prospective longitudinal designs and functional measures of performance are needed.

The interaction between threat and deprivation also highlights potential buffering effects provided by an enriched and socially responsive environment (Gee, 2016). Social

enrichment, such as parental involvement and supportive peer relationships, are consistently identified as protective factors in the literature (Afifi & MacMillan, 2011; Collinshaw et al. 2007). When high levels of threat are experienced in the context of high deprivation – where less social support and resources are available – the consequences may be amplified. Given that threat and deprivation exposure tend to co-occur, it will be important to continue to understand how threat and deprivation experiences interact with on each other and whether there have synergistic effects.

Implications & Limitations

Delineating dimension-specific effects on neural development has the potential to inform preventative intervention efforts. Current interventions are employed in response to psychiatric symptoms, and few preventative options exist, despite the well-documented risk for psychopathology following adversity. As this line of research accumulates, it may be possible to tailor interventions to adversity histories and target the specific, and potentially modifiable, processes disrupted before the onset of illness. For example, youth who have experienced deprivation may benefit from interventions that seek to improve basic cognitive abilities, such as working memory, inhibition, and cognitive flexibility, as well as increase environmental enrichment, stimulation, and psychosocial support. If these interventions are developed and employed early, the long-term consequences of deprivation-related adversity may be mitigated. Although we did not find threat-specific effects, findings from other studies suggest that brief behavioral interventions the help target fear learning and improve emotion regulation may be particularly helpful for threat-exposed youth. This type of tailored and mechanism-informed approach could mitigate vulnerability for psychopathology conferred by childhood adversity.

There are several limitations to the current study that should be noted. First, our measures of self-reported childhood adversity and brain morphology were assessed concurrently, and as such, they are correlational and cannot provide evidence of a cause-effect relationship. Additionally, as is common in human studies, we do not have pre-exposure measures of brain characteristics and thus, cannot rule out the possibility that observed differences are congenital. Second, our adversity measurement relied on subjective retrospective reporting, which is vulnerable to errors in recall and/or biases in reporting. Adversity measures were also categorical (i.e., yes or no) and did not include information regarding the frequency, intensity, or timing of specific exposure types (e.g., times of sexual abuse, intensity of physical abuse). Future studies utilizing more extensive measures of such adversity characteristics will be needed to replicate these findings. Third, the poverty variable may index multiple components of environmental risk that can affect brain development such as family stress, maternal drug use, negative parenting, nutrition deficiencies, and environmental toxins. As such, it possible that poverty factors not specific to social-cognitive deprivation may have influenced the results. This issue may extend to a number of the adversity variables, which may be correlated with factors relevant to brain development that we were not able to assess in this study. Fourth, the adversity experiences included in this study do not encompass all forms of threat (e.g., community violence, witnessing domestic abuse) or deprivation, nor do they include parental psychopathology or non-interpersonal forms of trauma (e.g., car accidents, injuries, natural disasters). Finally, we did not control for psychiatric diagnoses and cannot rule out that volumetric differences are a consequence of disease processes, rather than adversity exposures. However, there were no structural differences between the CHR and healthy controls included in our sample, and there is

increasing evidence that structural abnormalities initially attributed to psychiatric illness may be a more direct consequence of childhood adversity (Teicher, 2016).

Conclusion

Our findings contribute to an emerging line of research that suggests dimensions of threat and deprivation may have unique effects. These findings also challenge the implicit assumptions of the cumulative-risk approach and highlight the importance of assessing the specific nature of adversity experiences. Future work should continue to characterize and establish the validity of threat and deprivation dimensions, particularly in relation to bio-behavioral indices such as emotion regulation, reward sensitivity, executive functioning, and associative learning. This work is likely to identify mechanisms that can be targeted by preventative interventions to help mitigate the life-course risk for psychopathology following childhood adversity

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Appendix A: Manuscript 1 Tables

Table 1. Sample Characteristics (n=736)

Age, years (mean ± SD)	19.2 ± 4.3
*Sex, n (%)***	
Males	421 (57%)
Females	315 (43%)
*Race, n (%)***	
First Nations	10 (1.4%)
East Asian	22 (3.1%)
Southeast Asian	17 (2.4%)
South Asian	20 (2.8%)
Black	125 (17.5%)
Central/South American	29 (4.1%)
Middle Eastern	5 (0.7%)
White	417 (58.4%)
Native Hawaiian/Pacific Islander	2 (0.3%)
Interracial	68 (9.5%)
Threat Exposure n (%)[a]	
Sexual Abuse	76 (10.6%)
Physical Abuse	120 (16.8%)
Psychological Abuse	177 (24.8%)
Physical Bullying	158 (22.1%)
Psychological Bullying	358 (50.1%)
Deprivation Exposure n (%)[a]	
Emotional Neglect	212 (29.6%)
Restricted Peer Relations	123 (17.2%)
Parental Absence	41 (5.7%)
Poverty	195 (27.3%)
Threat only exposure	150 (20.4%)
Deprivation only exposure	119 (16.2%)
Threat & deprivation exposure	277 (37.6%)
No adversity exposure	190 (25.8%)

[a] Percentages add up to > 100% because one participant can score multiple items.
* $p < .05$ ** $p < .01$

Table 2. Descriptive Statistics of Childhood Adversity and Corticolimbic Structure Variables (n=736)

Variable	Mean	SD	Range
Threat[a]	1.2	1.37	0 - 5
Deprivation[a]	.77	.84	0 - 4
Total Adversity[a]	1.96	1.93	0 - 8
Total Brain Volume[b]	1548014.70	164857.17	1058178 - 2104659
Left Cortical Volume[b]	299213.70	32629.80	211585 - 404718
Right Cortical Volume[b]	298210.52	33016.61	191644 - 411674
Left Cortical Thickness[c]	3.16	.12	3 - 4
Right Cortical Thickness[c]	3.14	.12	3 - 4
Left Superiorfrontal Volume[b]	29017.77	3610.33	19977 - 40774
Right Superiorfrontal Volume[b]	27597.41	3716.26	17084 - 43573
Left Superiorfrontal Thickness[c]	3.51	.19	3 - 4
Right Superiorfrontal Thickness[c]	3.44	.22	3 - 4
Left Hippocampus Volume[b]	4217.65	468.26	2502 - 5625
Right Hippocampus Volume[b]	4264.59	464.16	2603 - 6221
Left Amygdala Volume[b]	1699.04	233.42	877 - 2745
Right Amygdala Volume[b]	1778.47	259.88	948 - 2759

Note. Raw brain volumes and thickness measurements not adjusted for total brain volume.
[a] Number of adversity exposures reported
[b] Volume measurement in mm^3
[c] Thickness measurement in mm

Table 3. Tetrachoric Correlations Between Specific Adversity Types (n=736)

Specific Adversity Types	1	2	3	4	5	6	7	8	9
1. Sexual Abuse[a]	-								
2. Physical Abuse[a]	.40**	-							
3. Psychological Abuse[a]	.35**	.57**	-						
4. Physical Bullying[a]	.20**	.23**	.30**	-					
5. Psychological Bullying[a]	.21**	.29**	.28**	.45**	-				
6. Emotional Neglect[b]	.35**	.45**	.57**	.20**	.31**	-			
7. Restricted Peer Relations[b]	.13**	.16**	.13**	.14**	.14**	.13**	-		
8. Parental Absence[b]	.06	.02	.06	.07	.03	.02	.10*	-	
9. Poverty[b]	.13**	.18**	.17**	.14**	.02	.02	.06	.08*	-

Note. The adversity exposures in the table make up the threat and deprivation composite scores.
[a] *Threat dimension items*
[b] *Deprivation dimension items*
* $p < .05$ ** $p < .010$

Table 4. Point-biserial Correlations Between Specific Adversity Types and Corticolimbic Structure (n=736)

	Cortical Volume r_{pb}		Cortical Thickness r_{pb}		Superiorfrontal Volume r_{pb}		Superiorfrontal Thickness r_{pb}		Hippocampus Volume r_{pb}		Amygdala Volume r_{pb}	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Threat[a]	.03	.04	.03	.06	.04	.09**	.08*	.12**	.01	.03	.01	.05
Sexual Abuse	.00	.01	-.04	-.02	.05	.03	.02	.00	-.04	-.05	-.05	-.03
Physical Abuse	.00	.00	-.02	-.01	.06	.04	.05	.05	-.03	-.01	.01	.00
Psych Abuse	.04	.06	.05	.07*	.04	.09*	.10**	.12**	.04	.05	.02	.02
Physical Bullying	.02	.03	.03	.04	.01	.06	.05	.08*	.01	.01	.03	.07
Psych Bullying	.03	.04	.05	.07	.00	.06	.05	.10**	.03	.04	.04	.10**
Deprivation[a]	-.16**	-.17**	-.09*	-.11**	-.05	-.09*	-.06	-.07*	-.07*	-.08*	.03	-.01
Neglect	-.12**	-.11**	-.03	-.03	-.02	-.03	-.02	.01	-.02	-.05	.02	-.04
Poverty	-.12**	-.12**	-.10**	-.12**	-.05	-.07*	-.06	-.07	.00	.01	.03	.00
Parental Absence	-.08*	-.10**	-.04	-.08*	-.07	-.09*	-.04	-.10**	-.14**	-.12**	.00	.01
Restricted Peers	-.02	-.03	-.01	-.02	-.01	-.02	-.02	-.02	-.07*	-.08*	.01	.01

Note. Partial correlations for threat items control for deprivation and total brain volume. Partial correlations for deprivation items control for threat and total brain volume. Left and right denote hemisphere lateralization. [a] Composite scores for each dimension of adversity.
* $p < .05$ ** $p < .01$

Table 5. *Zero-order Correlations Between Adversity Dimensions and Corticolimbic Structure (n=736*

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Threat	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
2. Deprivation	.46**	--	--	--	--	--	--	--	--	--	--	--	--	--	--
3. Total Adversity	.91**	.75**	--	--	--	--	--	--	--	--	--	--	--	--	--
4. Left Cortical Volume	.03	-.16**	-.14**	--	--	--	--	--	--	--	--	--	--	--	--
5. Right Cortical Volume	.04	-.17**	-.13**	.96**	--	--	--	--	--	--	--	--	--	--	--
6. Left Cortical Thickness	.03	-.09*	-.07	.57**	.54**	--	--	--	--	--	--	--	--	--	--
7. Right Cortical Thickness	.06	-.11*	-.06	.52**	.57**	.92**	--	--	--	--	--	--	--	--	--
8. Left SF Volume	.04	-.05	-.02	.67**	.65**	.48**	.45**	--	--	--	--	--	--	--	--
9. Right SF Volume	.09**	-.09*	-.01	.61**	.67**	.45**	.52**	.65**	--	--	--	--	--	--	--
10. Left SF Thickness	.08*	-.06	.02	.47**	.47**	.85**	.83**	.52**	.50**	--	--	--	--	--	--
11. Right SF Thickness	.12**	-.07*	.05	.37**	.46**	.71**	.84**	.43**	.55**	.84**	--	--	--	--	--
12. Left Hippocampus	.01	-.07*	-.06	.21**	.24**	.13**	.15**	.12**	.10**	.12**	.15**	--	--	--	--
13. Right Hippocampus	.03	-.08*	-.05	.16**	.29**	.07	.09*	.06	.05	.05	.11**	.74**	--	--	--
14. Left Amygdala	.01	.03	.04	.16**	.12**	.03	-.06	.12**	-.01	-.00	-.12**	.26**	.22**	--	--
15. Right Amygdala	.05	-.01	.03	.16**	.17**	.02	.04	.10**	.04	.01	.06	.26**	.32**	.53**	--

Note. All correlations control for total brain volume. Correlations for threat control for deprivation; correlations for deprivation control for threat.
* p <.05 ** p<.01

Table 6. Dimensions of Adversity, Single-risk, and Cumulative-risk Comparisons: Associations Between Adversity Dimensions and Corticolimbic Structure (n=736)

	Dimensions of Adversity						Single-Risk				Cumulative-Risk	
	Threat		Deprivation		Interaction		Threat		Deprivation		Total #	
Brain Measures	β	SE	β	SE	β	SE	β	SE	β	SE	β	SE
Left cortical volume	.02	.02	-.06**	.02	.02	.02	.01	.02	-.04**	.02	-.02	.02
Right cortical volume	.01	.02	-.06**	.02	.02	.02	-.01	.02	-.05**	.02	-.03	.02
Left cortical thickness	.01	.04	-.02	.03	.06	.03	-.00	.03	-.02	.03	-.01	.03
Right cortical thickness	.00	.03	-.03	.03	.04	.03	-.02	.03	-.04	.03	-.03	.03
Left SF volume	.04	.03	-.01	.03	.04	.03	.04	.02	.01	.02	.03	.02
Right SF volume	.04	.03	-.03	.03	.04	.03	.03	.02	-.01	.02	.01	.02
Left SF thickness	.05	.04	-.00	.04	.07*	.04	.07*	.03	.04	.03	.07*	.03
Right SF thickness	.02	.03	.00	.03	.10**	.04	.03	.03	.01	.03	.02	.03
Left hippocampus	.02	.03	-.06*	.03	-.01	.03	.00	.03	-.05	.03	-.03	.03
Right hippocampus	.03	.03	-.06*	.03	-.00	.03	-.01	.03	-.05	.03	-.02	.03
Left amygdala	.05	.04	.02	.04	-.05	.04	.06	.03	.04	.03	.06*	.03
Right amygdala	.02	.04	.01	.04	-.03	.04	.01	.03	-.00	.03	.01	.03

Note. All models control for total brain volume, sex, age, and scanner site. SF= superiorfrontal. * p <.05 ** p<.01

Table 7. Fit Statistics of Cumulative-risk and Dimensions of Adversity Models

	AIC	BIC
Cortical Volume		
Cumulative-risk	-123.39	-84.89
Dimensions of Adversity	*-130.68*	*-89.33*
Cortical Thickness		
Cumulative-risk	*2385.50*	*2424.00*
Dimensions of Adversity	2388.825	2430.17
Superiorfrontal Volume		
Cumulative-risk	*2536.05*	*2574.56*
Dimensions of Adversity	2538.10	2579.45
Superiorfrontal Thickness		
Cumulative-risk	*2638.54*	*2677.04*
Dimensions of Adversity	2641.79	2683.15
Hippocampal Volume		
Cumulative-risk	2871.55	2918.05
Dimensions of Adversity	*2871.33*	*2913.68*
Amygdalar Volume		
Cumulative-risk	*3302.87*	*3341.37*
Dimensions of Adversity	3306.72	3348.07

Note. Italicized model is best fitting model for each brain regions of interest. AIC = Aikaike Information Criteria. BIC = Bayesian Information Criterion.

Appendix B: Manuscript 1 Figures

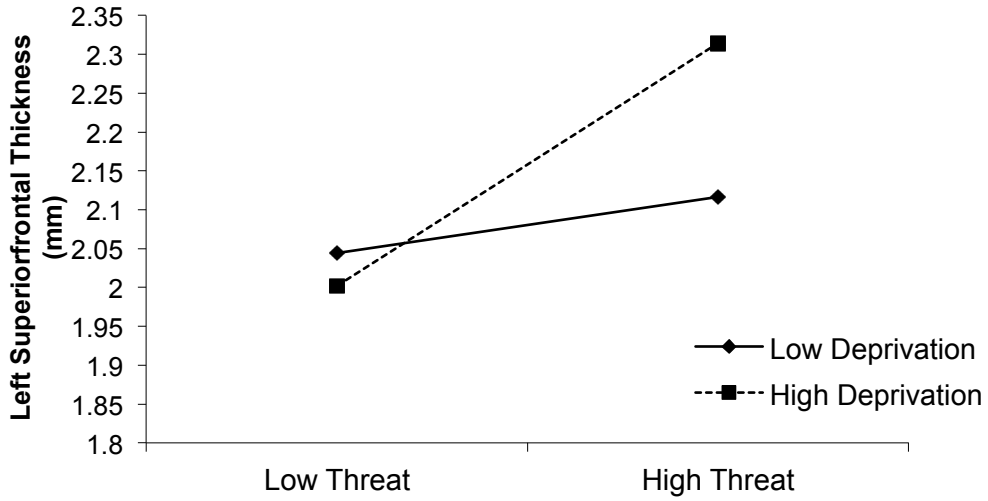

Figure 1. Simple slopes of threat on left superiorfrontal thickness at one standard deviation above and below mean deprivation (Simple Slope: B=0.11, z= 2.79, $p < .01$).

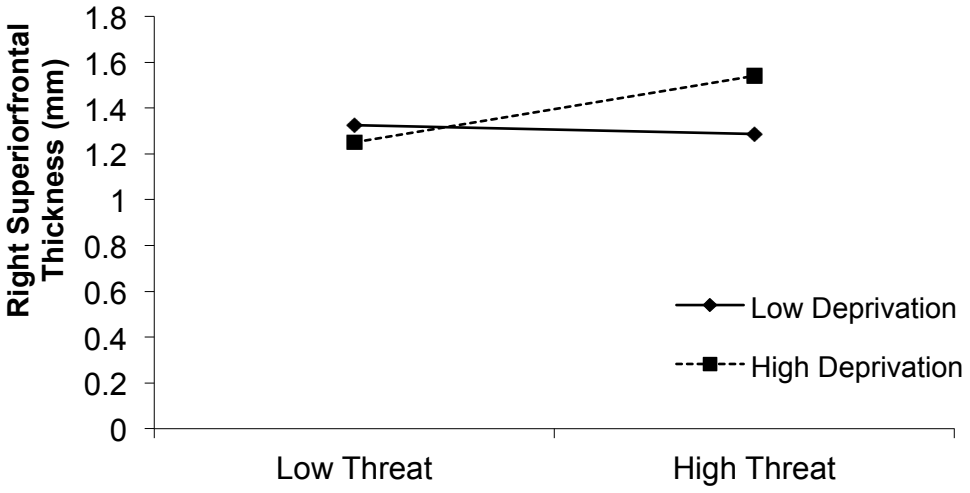

Figure 2. Simple slopes of threat on right superiorfrontal thickness at one standard deviation above and below mean deprivation (Simple Slope: B=0.12, z=2.87, $p < .01$)

The Conditional Effects of Childhood Adversity on Stress Processes

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Abstract

Childhood adversity is associated with poor mental and physical health outcomes across the life span. Alterations in the HPA-axis are considered a key mechanism underlying these associations, although findings have been mixed. These inconsistencies suggest that mediating factors may underlie variations in this these associations, and that differences in adversity type, and sex, may be relevant. The current study examined whether stress sensitivity mediates the association between childhood adversity and basal cortisol, and whether distinct dimensions of adversity (threat and deprivation) and sex have differential associations with these proposed pathways. Salivary cortisol samples, daily hassle stress ratings, and retrospective measures of childhood adversity were collected from a large sample of youth at risk for serious mental illness (n=605, mean age = 19.3). Results indicated that childhood adversity was associated with increased stress sensitivity, which subsequently predicts higher basal cortisol levels; however, these associations varied by adversity dimension and sex. Specifically, deprivation had an indirect effect on basal cortisol through stress sensitivity in both sexes; however the indirect effect of threat on basal cortisol was specific to females. These findings highlight the role of stress sensitivity in stress vulnerability following childhood adversity and highlight potential sex differences in sensitivity to threat exposures.

The Conditional Effects of Childhood Adversity on Stress Processes

Childhood adversity is associated with poor mental and physical health outcomes across the life span (Collinshaw et al. 2007; Danese et al. 2009; Price et al. 2013). Alterations in the HPA-axis are considered a key mechanism underlying these associations, although findings vary widely across studies (Lupien et al. 2009; Gunnar & Quevedo, 2007; Repetti, Robles, & Reynolds, 2011; Evans, 2007; Tyrka et al. 2008). Both elevated and blunted patterns of basal cortisol levels and reactivity are reported in individuals exposed to a wide range of childhood adversities (see Hunter, Minnis, & Wilson, 2011 for review). These mixed findings suggest that mediating factors, such as stress sensitivity, may underlie variations in this these associations, and that differences in adversity type and sex, may be relevant in understanding the diverse effects of childhood adversity and stress processes. Accordingly, the current study examined whether stress sensitivity mediates the association between childhood adversity and basal cortisol, and whether different types of adversity and sex have differential associations with these proposed paths.

Stress Sensitivity

Over the past decade stress sensitivity has been identified as a key endophenotype for a range of psychiatric disorders (Harkness et al. 2015). While stress sensitivity is currently a broad construct in the literature, and lacks a consistent operationalization, implicit consensus converges on the idea that individual differences in stress sensitivity are reflected in the threshold of stress required to elicit responses (Monroe & Harkness, 2005; Hankin, Badanes, Smolen, & Young, 2015; Harkness et al. 2015). There is also growing support and theorizing that childhood adversity may confer vulnerability to psychopathology, in part, by increasing stress sensitivity. Specifically, experiences of adversity in childhood may reduce an

individual's tolerance to subsequent, even minor stressors, later in life (Hammen, Henry & Daley, 2000; Harkness, Hayden, & Lopez-Duran, 2015).

Stress sensitivity, in the form of heightened stress perception, may be a particularly relevant aspect of the sequale following childhood adversity. Transactional perspectives of stress posit a dynamic interplay between stressful experiences, subjective perceptions of stress, and the biological stress response (Gunnar & Quevedo, 2007). Yet the intermediary appraisal processes that intervene between the experience and the biological response have received less attention in the childhood adversity literature. Instead, most studies have focused on biological measures of stress reactivity. However, experiences with adversity in childhood are likely to influence both cognitive and biological processes that shape future subjective perceptions of stress. For example, childhood adversity may shape the development of locus of control, coping strategies, and schemas that may lower their tolerance to subsequent stressors (Chorpita & Barlow, 1998). Additionally, early experiences with adversity may calibrate the developing corticolimbic circuit, such that it becomes more attuned, and responsive, to detecting potential stressors and threats (Chen & Baram, 2016).

Growing evidence supports the notion that early experiences impacts future perceptions and responses to stress (Chen & Baram, 2015; Maniam, Antoniadis, & Morris, 2014; Pechtel, & Pizzagalli, 2011). Consistent with this hypothesis, a large longitudinal study (n=34,653) found that exposure to childhood adversity was related to a higher perceived intensity of daily stress in adults (McLaughlin, Conron, Koenen, & Gilman, 2010). Similarly, a recent epidemiological community study found that childhood trauma was significantly associated with higher stress sensitivity, as indexed by subjective stress appraisals (Rossler, Ajdacic-Gross, Rodgers, Haker, & Muller, 2016). Taken together, these findings provide support for an association between childhood adversity and heightened stress sensitivity later in life.

These findings also raise the possibility that heightened stress sensitivity mediates the association between childhood adversity and later HPA-activity. That is, childhood adversity may exert an indirect, but enduring, effect on the stress systems via heightened sensitivity to day-to-day stressors across development (Glaser et al. 2006). An important step in this line of investigation is to establish whether childhood adversity is associated with sensitivity to daily stressors, and whether this relationship mediates the association between adversity and basal cortisol levels. Stress sensitivity, defined here as heightened subjective perceptions of stress, may be important to understanding the long-term impact of child adversity on stress processes and psychiatric vulnerability.

Adversity Type

In addition to considering the mediating effect of stress sensitivity, it is also important to consider whether the associations between childhood adversity and stress process vary by adversity type. Most studies use samples that are characterized by very different adversity histories. Blanket terms like "maltreatment" and "adversity" capture subjects with varied histories of sexual abuse, physical abuse, neglect, and poverty in one sample. Consistent with allostaic models of stress (McEwen et al. 2002), this cumulative-risk approach assumes that the greater the number of adversity exposures, the worse the effect. A critical assumption here is that different types of adversity uniformly impact outcomes, and thus are exchangeable. However, there is preliminary evidence that different types of childhood adversity, and stressors more broadly, may have distinct consequences on the stress response system (Busso et al. 2016; Kuhlman, Geiss, Vargas, & Lopez-Duran, 2015; Miller et al. 2007). For example, a large meta-analysis by Miller et al. (2007) found that stressors characterized by threat of harm and/or traumas were uniquely associated with a high, flat diurnal profile of cortisol secretion. In interpreting their findings, the investigators suggest

that the nature of experiences may pose different demands on biological systems that result in unique neuroendocrine responses. For example, high threat experiences may favor rapid HPA activation and heighted cortisol secretion to promote mobilization and safety. Interestingly, a recent study in adolescents with a history of childhood adversity also found differential associations among subtypes of childhood adversity and indices of HPA-functioning (e.g., diurnal rhythm, reactivity, recovery; Kulhman et al. 2015). These findings highlight the potential utility of distinguishing between different types of adversity and examining their associations with stress indices. If different types of experiences are associated with distinct stress characteristics, these effects are likely obscured when cumulative-risk composite scores are employed.

While several different approaches to categorizing adversity types have been utilized in the literature (e.g., dependent vs. independent, social vs. nonsocial, physical abuse vs. emotional abuse), these categories often lack a theoretical rationale for why these experiences should predict different outcomes. However, a recent conceptual model outlined by McLaughlin, Sheridan, and Lambert (2014) that distinguishes adversity experiences along dimensions of threat and deprivation may provide a more useful strategy. In this model, *threat* refers to interpersonal exposures that involve harm or threat of harm, such as physical and sexual abuse. In contrast, *deprivation* refers to exposures that reflect an absence of expected environmental inputs such as poverty, neglect, and limited psychosocial support. While cumulative-risk models implicitly assume non-specific associations, this 'dimensions of adversity' approach contends that though experiences of threat and deprivation both increase risk for poor outcomes, they may do so through distinct biological and developmental processes. A recent study utilizing the dimensions of adversity framework found that threat, but not deprivation, was associated with attenuated cortisol reactivity

following a stress induction task (Busso et al. 2016), providing some of the first empirical evidence for the differentiation of these dimensions in stress processes. While threat and deprivation dimensions have face validity, and there is some evidence that the distinction may be a valid one, further empirical exploration is needed. If this differentiation extends to stress sensitivity or basal cortisol, such that there are dimensions-specific associations with these stress indices, it may help explain the mixed findings regarding childhood adversity and HPA functioning across studies.

Sex Differences

Finally, there is evidence of sex differences in stress processes that necessitates investigation. Stress sensitivity has been found to differ by sex, with females appearing to have greater stress sensitivity compared to males. Specifically, females are more likely to report higher perceived stress scores compared to males in response to both life events (Davis et al. 1999) and daily hassles (Almedia et al. 2002; Myin-Germeys et al. 2004). However, sex differences in biological indices of HPA-activity have been less consistent. In healthy individuals, basal cortisol levels are typically comparable between men and women (Kudielka & Kirschbaum, 2005). While some sex differences in cortisol reactivity and recovery following stressor tasks have been reported, the direction of these effects are inconsistent, and may depend of the nature of the stressor presented (e.g., Paris et al. 2010; Pruessner et al. 1997a; Wust et al. 2000). Thus, an important secondary aim is to examine whether the associations between adversity dimensions and stress processes vary by sex.

Current Study

The current study tested a theoretical model examining the association between childhood adversity and basal cortisol levels through a meditational pathway of stress sensitivity in a large sample of individuals at clinical-risk for serious mental illness. Our first

aim was to assess whether threat and deprivation are differentially associated with these proposed stress pathways. No a priori hypotheses were made about the differential effects of threat and deprivation, given that paucity of work on these proposed dimensions, yet the evidence above suggests that they entail may have distinct effects. An important secondary aim was to determine whether sex interacts with adversity dimensions to effect the proposed stress pathways. Given that females have been shown to endorse greater stress sensitivity than males in previous studies, we hypothesized that observed effects would be stronger in females.

Methods

Sample

The sample included 605 individuals between 12-30 years of age (mean=19.2, SD=4.5). All participants were recruited as part of the North American Prodrome Longitudinal Study (NAPLS-2). Specific details about ascertainment and inclusion and exclusion criteria have been described in detail elsewhere (Addington et al. 2012). Participants were included in the current study if measures of childhood adversity exposure, salivary cortisol, and stress sensitivity were collected at the baseline visit. Of the 605 participants, 423 (70%) met clinical-high risk (CHR) criteria for serious mental illness; 182 (30%) did not meet the criteria for CHR status. Consistent with findings of elevated rates of childhood adversity among youth at risk for psychosis, CHR youth endorsed higher levels of threat [(F (1,603)=95.40 p<. 01)], deprivation [(F (1,603)=77.20, p<. 01)] and total adversity [(F (1,603=119.84, p<. 01)] exposures. CHR youth also had higher levels of stress sensitivity compared to healthy controls [(F (1,603)=24.97, p<. 01)], however these group differences were no longer significant with adversity exposure was controlled for. There were no group differences in basal cortisol [(F (1,603)= .16, p=. 69)]. All analyses were conducted

combining across the groups in order to include variation in childhood adversity exposure, stress measures, ethnicity, and psychopathology.

Measures

Threat Exposure. Threat was operationalized to denote adverse experiences involving harm or threat of harm to an individual. Specific types of threat exposures were assessed using the *Documentation of Trauma Form*, a semi-structured interview that retrospectively assesses six types of negative childhood experiences before the age of 16. Participants where asked whether they had experienced the following: emotional abuse (e.g., "unjustified punishment" "being sworn at"), neglect (e.g., "not able to find any attention or support from people at home"), physical abuse (e.g., "being kicked or punched"), psychological bullying (e.g. "taunted or sworn at by peers"), physical bullying ("physical assaulted at school"), and sexual abuse (e.g., "touched sexually against will", "sexual contact against will"). Responses were rated on a categorical 'present' or 'absent' scale. A threat composite score was created by summing responses to the physical abuse, sexual abuse, emotional abuse, physical bullying, and psychological bullying items. The threat composite score ranged from 0 (no endorsement of threat exposures) to 5 (endorsement of all threat exposures), and was used in all statistical analyses to capture variation in threat exposures.

Deprivation Exposure. Deprivation was operationalized to denote experiences involving the absence of expected cognitive and social inputs. In the current study, deprivation items included indices of childhood poverty, emotional neglect, parental absence, and restricted peer relationships during childhood. Poverty was determined by the ratio of income to needs, which was computed by dividing reported family of origins income by US census 2014 poverty line for a family of that size, with a value of <1 indication that a family was living below the poverty line. A dichotomous measure of poverty was used rather than the linear

income to needs ratio because it is unlikely that deprivation of inputs exist at the higher end of income distribution. Neglect was assessed via the *Documentation of Trauma Form* described above. Restricted peer interactions (a proxy of psychosocial deprivation) was determined using the social subscales of *The Premorbid Adjustment Scale* (PAS; Cannon-Spoor et al. 1982), a widely used semi-structured interview designed to retrospectively assess social and academic functioning across development. Interviewers rated participants on a 0-6 scale for peer relationships during childhood (age 5-11 years). Scores falling between 4-6, which indicates social isolation and lack of same-aged peer relationships, were used to indicate restricted peer relationships. Finally, absence of a biological parental figure (e.g., no/minimal contact) was determined from a demographic information interview. A deprivation composite score was created by summing items of childhood poverty, childhood peer relations, parental absence, and neglect. This deprivation composite ranged from 0 (no endorsement of deprivation exposures) to 4 (endorsement of all deprivation exposures), and was used in all statistical analyses to capture variation in deprivation exposures.

Salivary Cortisol. Cortisol (μg/dL) concentrations were assessed via salivary samples during a baseline assessment in the research clinic. Salivary samples were collected using the drool method, whereby participants expectorate approximately 1.5mL of saliva into a tube. Multiple saliva samples (n = 3) were obtained to derive an average and increase the reliability of the cortisol estimate. Samples were collected approximately on the hour, beginning on average about 10:00am, with a range from 9:00am to 11:30am at onset of sampling (SD=26 minutes). Saliva samples were immediately stored in a–20°C freezer until they were shipped on dry ice to a laboratory in Atlanta, Georiga. In preparation for assay, samples were rapidly thawed and centrifuged. All samples were assayed for salivary cortisol (μg/dL) using a highly sensitive enzyme immunoassay (Salimetrics, State College, Pennsylvania). The test uses

about 25 μL of saliva (for singlet determinations), has a range of sensitivity from .007 to 1.8 mg/dL, and average intra-assay and interassay coefficients of variation of less than 10% and 15%. All samples were assayed in duplicate.

Stress Sensitivity. Stress sensitivity was operationalized as perceived stressfulness of daily hassles. The Daily Stress Inventory (DSI) is a 58-item measure of minor, common daily hassles occurring within the past 24 hours. Examples of such items include "was interrupted during task/activity," "was criticized," and "had your sleep disturbed." Participants indicated if the event occurred and rated each endorsed event on a 7-point Likert scale ranging from "occurred, but was not very stressful" to "caused me to panic." An index of stress perception was computed by regressing the total sum of stress ratings on the number of daily stress items endorsed. This method distinguishes among individuals who report the same number of exposures, but who differ in their subjective stress appraisals.

Data Analyses

Path models were constructed to test mediating and moderating associations using software package Mplus version 5.21 (Muthen & Muthen, 2010). We tested a cumulative-risk and dimensions of adversity model, which are based on different conceptualizations of childhood adversity. The cumulative-risk model aggregates all adversity exposures into a single score, while the differentiated dimension of adversity model distinguishes adversity exposures along dimensions of threat and deprivation. In the differentiated dimensions of adversity model both threat and deprivation were entered into the model. This approach allowed us to examine the effect of each adversity dimension (e.g. threat), while controlling for the effect of the other (e.g., deprivation). For both the cumulative and dimensions of adversity models we first estimated a main effects path model to examine whether stress

sensitivity mediated the association between adversity and basal cortisol, followed by an interaction path model to see if the direct and indirect pathways were moderated by sex.

Path analysis provides estimates, or path coefficients, that indicate the direction and significance of the association between variables, as well as several fit indices, which evaluate the fit of the proposed model. A Chi-squared significance test, considered good when non-significant, suggests the specified model is congruent with the observed data and is a reasonable fit. The Root Mean Square Error of Approximation (RMSEA) is considered adequate below 0.10. The Comparative Fit Index (CFI) considers the number of paths in the model and is considered good at 0.93 or above. To test for mediation across all models, both direct and indirect effects were examined. The significance of indirect effects was tested using a bootstrapping approach (Hayes, 2013). This approach generates bias-corrected, bootstrapped confidence interval for total and specific indirect effects of the predictors, on the outcome, through the mediator. Confidence intervals that do not include zero indicate statistically significant mediation. To test for moderation, main effect and interaction terms were included on all pathways.

Prior to analyses, a log transformation was applied to normalize the distribution of cortisol prior to analyses, a standard procedure with cortisol data (Miller & Plessow, 2013). Stress sensitivity and saliva sampling time variables were standardized. Saliva sampling time and sex were entered into all models to control for these effects. Statistical significance was based on $p < 0.05$ and all test were two-tailed. Standardized betas are presented in results, unstandardized betas reported for tests of simple slopes.

Results

Sample Characteristics

Demographic and adversity characteristics are shown in Table 1. The majority of individuals in the current study reported at least one adversity exposure (74%; n=448). Across the entire sample, 59% (n=357) endorsed at least one threat exposure and 54% (n=328) endorsed at least one deprivation exposure during childhood. Co-occurring adversities were common, with 49% (n=300) of individuals reporting two or more adversity exposures. Females endorsed higher levels of total adversity exposure [(F (1,603)=5.4, p=. 02)] and threat exposure [(F (1,603)=4.23, p=. 04)] compared to males. There were no sex differences in deprivation exposures [(F (1,603)=4.01, p=. 06)], stress sensitivity [(F (1,603)=0.68, p=. 41)] or basal cortisol ([F (1,603)=. 09, p=. 75)]. There was a significant age difference in basal cortisol [(F (1,603)=1.74, p<. 01)], whereby cortisol increased with age, consistent with previous reports (Walker et al., 2013). A moderate correlation was observed between threat and deprivation (r=. 46, p<. 01) in the total sample, which is consistent with the literature on the co-occurrence rates among different types of adversity (Green et al., 2010). However, this modest correlation also suggests a degree of independence of the two adversity dimensions.

Bivariate and partial correlations between adversity dimensions and stress measures stratified by sex are presented in Table 2. There were sex differences in the correlations between stress sensitivity. In females, total adversity (r=. 35, p<. 01) and threat (r=. 22, p<. 01) were associated with stress sensitivity; in males deprivation (r=. 12 p<. 02) was associated with stress sensitivity. Stress sensitivity was associated with cortisol in females (r=. 16, p<. 01) but not in males. Cortisol was not associated with any indices of adversity for either sex.

Cumulative-Risk Path Model

We first constructed a main effects path model to determine if stress sensitivity mediated the association between total adversity and basal cortisol. This model (Figure 1) showed adequate fit (X^2= 5.4, p >.05 RMSEA=. 07, CFI=. 95) and accounted for 5% of the variance in stress sensitivity and 10% of the variance in basal cortisol. There was no direct effect of total childhood adversity on basal cortisol (β= -.00, p=. 96), but the mediating effect of stress sensitivity on basal cortisol was significant (Indirect Est.: b = .01, p<. 01, 95% CI=. 003-.016). This path model was tested again with the inclusion of interaction terms, to determine whether sex moderated these pathways. This model (Figure 2) showed improved fit (X^2= 6.2, p >.05 RMSEA=. 02, CFI=. 99). Sex significantly moderated the association between total childhood adversity and stress sensitivity (β= -.21, p<. 01), but not the association between stress sensitivity and cortisol (β= -.04, p=. 48). For females only, higher levels of total adversity predicted increased levels of stress sensitivity (simple slopes: b= .15, p<. 01). However, there was no indirect effect of total adversity on cortisol through stress sensitivity in females (b= .00, SE= .01, 95% CI = -.02 - .03).

Dimensions of Adversity Path Model

We constructed a second main effects path model to examine whether the associations among adversity, stress sensitivity, and basal cortisol differed when threat and deprivation exposures were considered separately. This model (Figure 3) demonstrated adequate fit (X^2= 4.2 p>.05, RMSEA= .02, CFI= .98) and accounted for 5% of the variance in stress sensitivity and 10% of the variance in basal cortisol. There was no direct effect of threat (β=-.03, p=. 49) or deprivation (β=. 03, p=. 45) on basal cortisol. Both threat (β=. 10, p=. 03) and deprivation (β=. 15, p<. 01) were associated with greater stress sensitivity. The association between stress sensitivity and basal cortisol was also significant (β= .12, p< .01). Finally, there was an

indirect effect for both threat (b= .02, SE= .01, 95% CI = .001-.014) and deprivation (b= .01, SE= .00, 95% CI = .003-.027) on cortisol through stress sensitivity.

This path model was tested again with the inclusion of interaction terms, to determine whether sex moderated these pathways. This model (Figure 4) demonstrated improved fit (X^2= 7.1, p >.05 RMSEA=. 00, CFI=1.0) and accounted for 10% of the variance in stress sensitivity and 10% of the variance in basal cortisol. Sex significantly moderated the association of threat and stress sensitivity (β= -. 25, p<. 01). For females only, higher levels of threat were associated with higher levels of stress sensitivity (simple slopes: b= .20, p<. 01). Sex did not moderate the association between deprivation and stress sensitivity (β=. 02, p= .78), or the association between stress sensitivity and basal cortisol (β=-.05 p=. 49). Finally, there was an indirect effect in females of threat on basal cortisol through stress sensitivity (b= .03, SE= .01, 95% CI = .001 - .04).

Because this model revealed a non-significant moderating effect of sex on the association between deprivation and stress sensitivity and stress sensitivity and basal cortisol, we constructed an alternate model removing the interaction term from these pathways. This modified model (Figure 5) demonstrated goodness of fit (X^2= 10.3, p >.05, RMSEA=. 03, CFI= .96) and accounted for 6% of the variance in stress sensitivity and 10% of the variance in basal cortisol. There was no direct effect of threat (β=-.03, p=. 49) or deprivation (β=. 03, p=. 45) on basal cortisol. Sex moderated the effect of threat on stress sensitivity (β=-. 20, p<. 01). For females only, higher levels of threat were associated with higher levels of stress sensitivity (simple slopes: b= .18 p<. 01.). Deprivation was associated with stress sensitivity ((β=. 12, p< .01), and stress sensitivity was associated with cortisol (β=. 13, p<. 01). There was an indirect effect in females of threat on basal cortisol through stress sensitivity (b= .02,

SE= .01, 95% CI = .004 - .03). Across sexes there was also an indirect effect of deprivation on basal cortisol through stress sensitivity (b= .01, SE= .01, 95% CI = .002 - .03).

Discussion

While there is general agreement around the broad principle that childhood adversity leads to alterations in stress processes and systems, the mechanisms linking the two has remained less clear and cortisol findings have been mixed. This study tested a theoretical model that proposes stress sensitivity mediates the association between childhood adversity and basal cortisol. Further, this model also examined whether different dimensions of adversity (threat and deprivation) and sex have differential associations with these proposed pathways. In support of our model, we found that childhood adversity was associated with increased stress sensitivity, which subsequently predicted higher basal cortisol levels; however, these associations varied by adversity dimension and sex. Deprivation had an indirect effect on basal cortisol through stress sensitivity across both sexes. However, the indirect effect of threat on basal cortisol was specific to females. All models controlled for sex, suggesting that this finding was not simply a consequence of sex differences in adversity exposure severity. Notably, the cumulative-risk model obscured these more complicated associations.

The pattern of findings observed across models highlights the utility of comparing cumulative-risk and dimensions of adversity approaches, in addition to considering sex differences. For example, the cumulative-risk and dimensions of adversity main effects models suggested that threat and deprivation did not differ in their associations with stress sensitivity. However, when sex was included as a moderator, a sex by adversity-dimension interaction emerged, resulting in a more nuanced pattern of findings. Utilizing only the

cumulative-risk approach, or failing to consider sex differences, would have led to different, and incomplete, conclusions about the nature of the relationship between childhood adversity and stress processes. Similar problems have likely contributed to inconsistencies in the literature.

Our finding that childhood adversity is associated with increased stress sensitivity is consistent with previous work that has shown a relationship between childhood adversity and subjective perceptions of stress in adulthood (McLaughlin et al. 2010; Rossler et al. 2016; Gibson et al. 2014). While the exact mechanisms underlying these associations are unknown, there is basis for speculation. Periods of atypical cortisol levels and altered HPA function following childhood adversity, even if transient, may impact developing corticolimbic circuits in ways that heighten sensitivity to stress later in life (Gunnar & Vazquez, 2006; Chen & Baram, 2016). This could involve heighted detection of negative cues by the PFC, compromised inhibitory feedback regulation of the HPA-axis by the PFC and hippocampus, and/or epigenetic changes in the systems that regulate stress physiology (Heim et al. 2008; Cecil et al. 2016). Childhood environments characterized by unpredictability and uncontrollability may also instill negative cognitive, coping, and attributional styles that subsequently influence the interpretation, experience, and resolution of future stressors (Chorpita & Barlow, 1998). Decreases in perceived coping resources and perceptions of low control have both been found to increase subjective experiences of stress (Folkman et al. 1986). Future work is needed to elucidate the biological and cognitive processes through which childhood adversity experiences influence stress sensitivity. Nonetheless, the results underscore a role for stress sensitivity in the stress-related sequelae following childhood adversity. It will, however, be critical that future studies obtain measures of stress sensitivity

early in childhood to confirm that increased sensitivity is a product of childhood adversities developmental influences, rather than a congenital predisposition.

Our findings also suggest that females may be uniquely sensitive to threat experiences. Although the effects are small, these findings raise important questions regarding what factors underlie these observed sex differences. There are a number of possible explanations ranging from sex differences in fear circuitry, the nature of threat experiences, to reporting biases. For example, sex differences are observed across development in the neurobiology of corticolimbic fear circuitry, such that females show poorer discrimination between danger and safety signals (Gamwell et al. 2015), heightened physiological and neural sensitivity to threat cues (Domes et al. 2010; Lebron-Milad et al. 2012; Stevens & Hamann 2012; Tolin & Foa, 2006), and lower thresholds for threat detection (Glover et al. 2012). These findings suggest a sensitivity to threat, that may be distinguishable from deprivation experiences. There is also evidence that females are more sensitive than males to stressors that are interpersonal in nature (Stroud et al. 2002). Given the strong interpersonal nature of threat experiences, this may increase their potency among females.

Alternatively, these sex differences may be accounted for by differences in the nature of threat exposures experienced by females relative to males. That is, females may experience different types of threat (e.g., sexual abuse) that uniquely influence stress sensitivity. In the current sample, females endorsed higher rates of sexual abuse, physical abuse, and psychological abuse (but not physical bullying). While controlling for sex in our models helps account for differences in severity (i.e., total threat severity), it does not control for differences in the specific types of threat exposures, which may ultimately prove important. Relatedly, sex differences in reporting of both childhood adversity and perceived stress may also underlie these associations. Females tend to endorse higher levels of childhood trauma

even though, with the exception of sexual abuse, there are few sex differences in rates of physical abuse, psychological abuse, and neglect (Tolin & Foa, 2006; Koenen & Widom, 2009). Thus, the current study may underestimate threat exposure in males. In regards to subjective perceived stress reporting, a large meta-analysis concluded that there are robust sex differences in the appraisal of stressful events relative to actual stress exposures, with females endorsing higher levels of perceived stress (Davis et al. 1999). More work is needed to tease apart whether these associations are driven by sex differences in the way threat experiences shape subjective stress perception, or whether they are artifacts of severity differences and reporting tendencies.

Finally, we also found that stress sensitivity mediates the association between childhood adversity and basal cortisol, although the effects are small and should be interpreted with caution. These findings are consistent with existing evidence linking subjective stress appraisals to changes in cortisol reactivity (Wirtz et al. 2007; Juster et al. 2012; Slattery et al. 2014). However, more work is needed to determine how influential subjective stress appraisals are in modulating biological stress responses, and the relative concordance between those two measures. While we found indirect effects, there were no direct effects of adversity exposure on basal cortisol levels in any of our models. This is not surprising given the complexities of estimating the association between history of childhood adversity and basal cortisol (Tarulla & Gunnar, 2006; Gunnar & Quivedo, 2007). For example, in the current study there is likely significant variability in the time lag between adversity exposure and cortisol measurement, which as been shown to influence the direction and magnitude of associations (Miller et al. 2007 for review). It is possible that childhood adversity exerts direct long-term effects on other indices of HPA-functioning not measured in this study, such

as cortisol reactivity, early awakening response, and diurnal rhythm. These indices may be more sensitive to, and permanently changed by, early adverse experiences.

Implications & Limitations

The current findings suggest that stress sensitivity, as indexed by subjective stress perception, may be a relevant intermediary process in the complex relationship between childhood adversity and stress vulnerability. This indicie is likely to capture both biological and cognitive processes that increase vulnerability to future stress and psychopathology across the life course, particularly in females. The observed sex difference is consistent with higher rates of stress-related forms of psychopathology (e.g., depression, PTSD) observed in females compared to males (Bangassar & Valentino, 2014). Consequently, stress sensitivity may be an important target for preventative interventions following childhood adversity. Fortunately, a number of psychosocial interventions may be tailored to address and reshape stress appraisals. For example, elements from cognitive behavioral therapy, mindfulness-based stress reduction, and biofeedback techniques are particularly well suited to modifying stress perception and appraisals.

The findings from this study should be considered in light of several limitations. First, all adversity indices were self-reported, retrospective, and categorical variables. The reliance of retrospective reporting of childhood adversity introduces the possibility of both under and over reporting, which may have affected our results. While the categorical variables provide a rough estimate of exposure history, they do not include measures of frequency, intensity, or timing of specific exposure types (e.g., times of sexual abuse, intensity of physical abuse), which are likely to be important. Additionally, the adversity experiences included in this study do not encompass all forms of threat (e.g., community violence, witnessing domestic abuse) or deprivation, nor do they include parental psychopathology or non-interpersonal

forms of trauma (e.g., car accidents, injuries, natural disasters). Future studies utilizing more extensive measures of threat and deprivation will be needed to replicate these findings. Finally, while basal cortisol is logical indicator of stress response, there are significant challenges to it's measurement due to diurnal and circadian rhythms (Young et al. 2004). Finally, although our theoretical model implies a development sequence, our measures of self-reported childhood adversity, stress perception, and basal cortisol were assessed concurrently, and thus are not temporally ordered.

Conclusion

The current findings point to a complex relationship between childhood adversity and stress processes that varies by adversity dimension and sex. Importantly, these relationships were obscured in the cumulative and main effects models, highlighting the importance of assessing specific types of adversity, and examining potential sex differences. Our findings also shed new light on how childhood adversity may lead to long-term psychiatric vulnerability through stress sensitivity. While subjective stress appraisals have traditionally received less attention in the childhood adversity literature, they may represent an important aspect of the stress processes disrupted by childhood adversity. Future work should continue to delineate both the biological and cognitive pathways through which childhood experiences of threat and deprivation shape future perceptions of stress, and investigate whether these differ in males and females. This work will help advance our understanding of etiology and inform our intervention approaches.

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Appendix C: Manuscript 2 Tables

Table 1. Sample Characteristics (n=605)

	Total (n=605)	Males (n=345)	Females (n=260)
Age, years (mean ± SD)	19.3 ± 4.5	19.02 ± 4.5	19.58 ± 4.5
*Race, n (%)***			
First Nations	10 (1.7%)	8 (2.3%)	2 (0.8%)
East Asian	28 (3.0%)	9 (2.6%)	9 (3.5%)
Southeast Asian	12 (2.0%)	4 (1.2%)	8 (3.1%)
South Asian	15 (2.5%)	8 (2.3%)	7 (2.7%)
Black	113 (18.7%)	59 (17.1%)	55 (20.8%)
Central/South American	22 (3.6%)	18 (5.2%)	4 (1.5%)
Middle Eastern	5 (0.8%)	2 (0.6%)	3 (1.2%)
White	345 (56.9%)	204(59.1%)	140 (53.8%)
Interracial	65 (0.3%)	33 (9.6%)	32 (12.3%)
Threat Exposure n (%)[a]			
Sexual Abuse	67 (11.1%)	20 (5.8%)	47 (18.1%)
Physical Abuse	104 (17.2%)	48 (13.1%)	56 (21.5%)
Psychological Abuse	153 (25.3%)	73 (21.2%)	80 (30.8%)
Physical Bullying	136 (22.5%)	90 (26.1%)	46 (17.7%)
Psychological Bullying	301 (49.8%)	168 (48.7%)	133 (51.2%)
Deprivation Exposure n (%)[a]			
Emotional Neglect	184 (37.0%)	90 (26.1%)	94 (36.2%)
Restricted Peer Relations	109 (17.2%)	67 (19.4%)	42 (16.1%)
Parental Absence	41 (7.0%)	20 (.03%)	21 (.08%)
Poverty	102 (17.0%)	55 (15.9%)	47 (18.1%)
Adversity Characteristics (mean ± SD)			
Threat*	1.27 ± 1.4	1.11 ± 1.3	1.34 ± 1.4
Deprivation	0.78 ± .85	0.71 ± .82	0.83 ± .87
Total Adversity*	2.05 ± 1.9	1.82 ± 1.78	2.17 ± 2.11

[a] Percentages add up to > 100% because one subject can score multiple items.
*p <.05 ** p<.0

Table 2. Partial Correlations for Adversity Exposure and Stress Measures

	Stress Sensitivity			Cortisol[b]		
	Males *r*	Females *r*	Total *r*	Males *r*	Females *r*	Total *r*
Total Adversity[a]	.08	.35**	.21**	-.00	.08	.05
Threat	-.02	.22**	.10*	.01	.09	.05
Deprivation	.12*	.10	.13**	-.03	.05	.04
Stress Sensitivity				.10	.16**	.13**

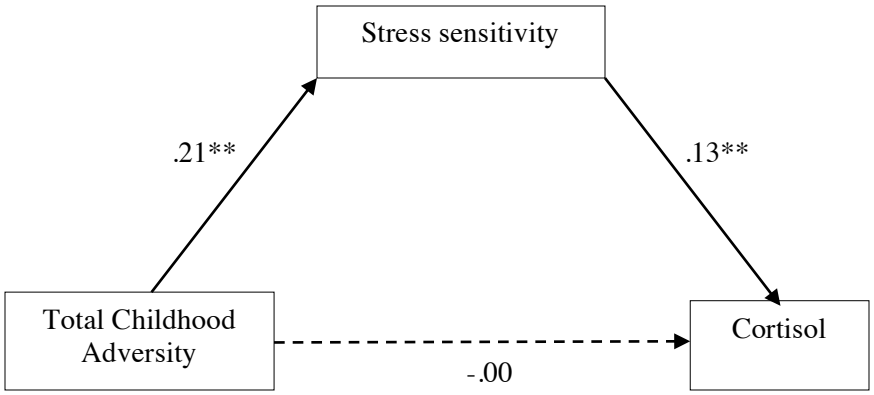
Note. Correlations for threat control for deprivation; correlations for deprivation control for threat. There was a significant two-tailed correlation between threat and deprivation (males: $r = .40$, females: $r = .51$, total sample: $r = .46$).

[a] Total Adversity equals sum of threat and deprivation.

[b] Correlations with cortisol control for saliva sampling time.

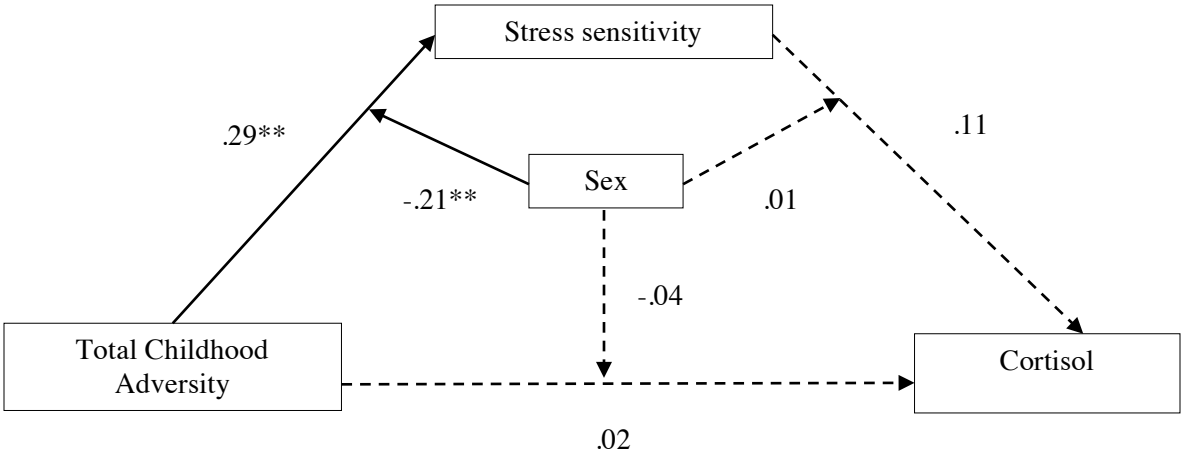
*$p < .05$ **$p < .01$

Appendix D: Manuscript 2 Figures



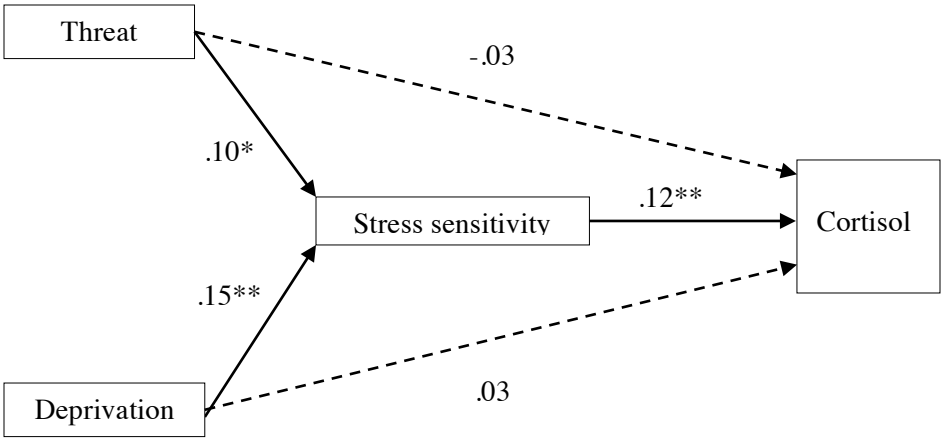
(Controlling for sex and saliva sampling time)

Figure 1. Main effects path model examining the mediating effect of stress sensitivity on the association between total childhood adversity and basal cortisol. The model demonstrated adequate fit: $X^2 = 5.4$, $p > .05$ RMSEA=. 07, CFI=. 95. Paths are marked with standardized coefficients. The mediating effect of stress sensitivity on basal cortisol was significant (Indirect Estimate: b = .01, p<. 01, 95% CI=. 003-.016). *p< .05, **p<.01



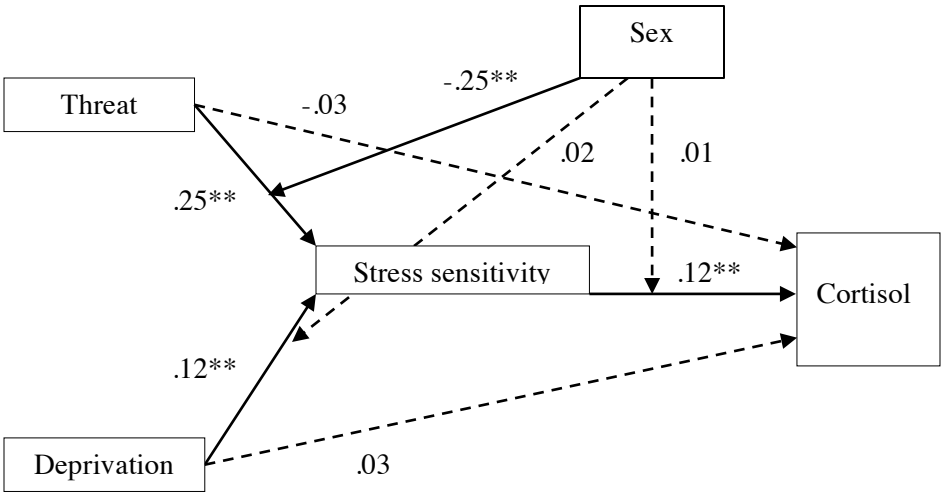
(Controlling for sex and saliva sampling time)

Figure 2. Interaction path model examining the moderating effect on sex. The model demonstrated adequate fit: $X^2 = 6.2$, $p > .05$ RMSEA=. 02, CFI=. 99. Paths are marked with standardized coefficients. There was no indirect effect of total adversity on cortisol through stress sensitivity in males (b= -.01, SE= .00, 95% CI = -0.01 - .001) or females (b= .02, SE= .01, 95% CI = -.02 - .03). *p< .05, **p<.01



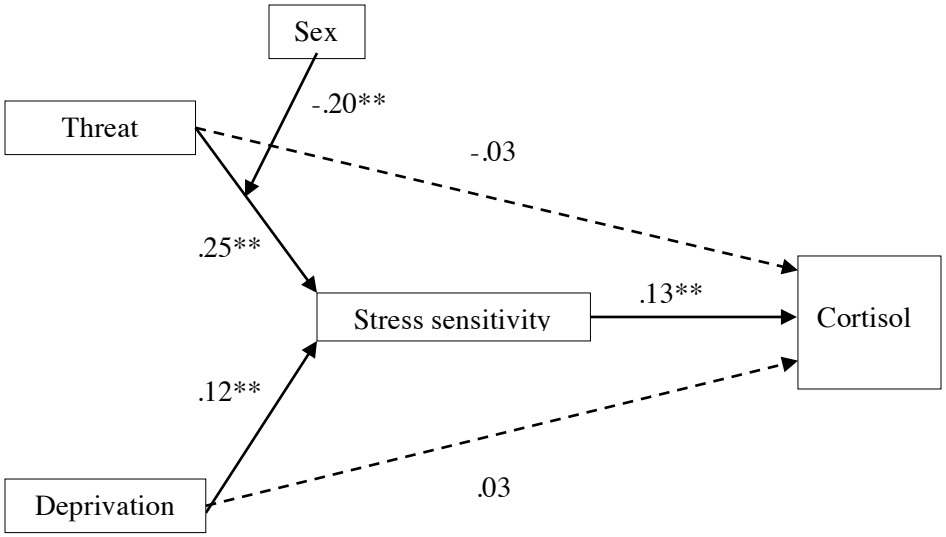
(Controlling for sex and saliva sampling time)

Figure 3. Main effects path model examining the mediating effect of stress sensitivity on the association between threat, deprivation and basal cortisol. The model demonstrated adequate fit: X^2= 4.2 p>.05, RMSEA= .02, CFI= .98. Paths are marked with standardized coefficients. There was an indirect effect for both threat (Indirect Estimate: b= .02, SE= .01, 95% CI = .001-.014) and deprivation (Indirect Estimate: b= .01, SE= .00, 95% CI = .003-.027) on cortisol through stress sensitivity.*p< .05, **p<.01



(Controlling for sex and saliva sampling time)

Figure 4. Interaction path model examining the moderating effect on sex. The model demonstrated goodness of fit: X^2= 7.1, p >.05 , RMSEA=. 00, CFI=1.0. Paths are marked with standardized coefficients. There was an indirect effect in females of threat on cortisol through stress sensitivity (Indirect Estimate: b= .03, SE= .01, 95% CI = .001 - .04).) *p< .05, **p<.01



(Controlling for sex and saliva sampling time)

Figure 5. Modified path model examining the mediating effect of stress sensitivity on the association between threat, deprivation and basal cortisol. The model demonstrated good fit: Chi 2= 10.3, p >.05 RMSEA=. 03, CFI= .96. Paths are marked with standardized coefficients. There was an indirect effect in females of threat on basal cortisol through stress sensitivity (Indirect Estimate: b= .02, SE= .01, 95% CI = .004 - .03). Across sexes there was also an indirect effect of deprivation on basal cortisol through stress sensitivity (Indirect Effect: b= .01, SE= .01, 95% CI = .002 - .03). *p< .05, **p<.01

General Conclusion

This dissertation examined whether different types of childhood adversity have distinct effects on neural and stress mechanisms that underlie risk for psychopathology. Current approaches to studying childhood adversity are poorly suited to examining the consequences of specific types of adversity and elucidating mechanisms. To address these limitations the current studies tested a novel conceptual model (McLaughlin et al. 2014) that distinguishes adverse experiences along dimensions of threat and deprivation. These dimensions cut across multiple types of adversity and are based on principles of experience-dependent plasticity. The findings across both studies provide preliminary evidence for the dimensions of adversity model and subtle dimension-specific associations. Study 1 demonstrated deprivation-specific associations with cortical and hippocampal volumes, such that higher levels of deprivation, but not threat, were associated with smaller volumes in these regions. An interaction between threat and deprivation on superiorfrontal cortical thickness was also found. Study 2 found that both threat and deprivation were associated with increased stress sensitivity, which subsequently predicted higher basal cortisol levels; however, threat effects were specific to females. Importantly, across both studies, the dimensions of adversity and cumulative-risk models revealed disparate findings that supported different interpretations regarding the effect of childhood adversity on corticolimbic structure and stress processes.

Our results suggest that the conceptualization and statistical modeling of childhood adversity influences the findings and their subsequent interpretations. Across both studies, we demonstrated that incomplete conclusions are drawn when threat and deprivation are combined into a single cumulative measure or examined separately (without controlling for co-occurrence). For example, in Study 1 the deprivation-specific associations with cortical and hippocampal volumes were obscured in the cumulative model. Notably, the deprivation

effects were obscured not only because they were different in magnitude from the threat effect, but also different in direction. Similarly, in Study 2, the cumulative model obscured the threat-specific association with stress sensitivity in females. Taken together, these findings suggest that childhood adversity should not be treated as a unitary construct, and that a more nuanced approach to conceptualizing and differentiating dimensions of adversity is warranted. Our findings also provide preliminary empirical support for the differentiation of threat and deprivation dimensions. This adds to a growing literature that has examined the distinct effects of threat and deprivation on developmental processes such as automatic emotion regulation, cognitive control, sympathetic activity, and cortisol reactivity (Lambert et al. 2016; Busso et al. 2016). It will be important to expand the findings from the current studies to determine the functional consequences of the observed structural brain differences and increased stress sensitivity.

While the field has shifted from focusing on singular types of adversity to cumulative exposures over the past two decades, the current findings support a synthesis of these approaches. That is, rather than placing the premium on the total number of discrete adversities, regardless of nature, it may be best to consider the number of adversities that occur within a specific dimensions (e.g., threat, deprivation). It is also likely that there are other relevant dimensions of adversity to be tested. As we develop and advance the dimensions of adversity approach, it will be important to draw from neuroscience and animal literatures. We need to think carefully about how different types of experiences may calibrate neurodevelopment, neuroendocrine, and neurocognitive functioning in ways that are congruent with the experience, or disrupt normative developmental processes. That said, a move to a dimensions of adversity model does not assume that threat and deprivation will always have distinct effects. In fact, it is likely that certain effects will be common across

different types of adversity. However, by relying solely on the cumulative approach and not attending to potential differences in the nature of these experiences, we diminish our ability to identify differences.

In line with the RDoC initiative, threat and deprivation should be examined across multiple levels of analysis. In fact, the current RDoC matrix already includes multiple constructs related to threat (e.g., acute threat, potential threat, sustained threat), as well as loss. The loss construct defined as "a state of deprivation of a motivationally significant con specific, object, or situation; social or non-social and may include permanent or sustained loss of shelter, behavioral control, status, loved ones, or relationships" complements our dimension of deprivation. A major advantage of the congruence between the threat and deprivation dimensions and RDoC is the potential to leverage findings from other investigations and the ability to draw upon relevant animal models to facilitate translational research. It will also be important to investigate how different dimensions of adversity influence other RDoC constructs that fall under the positive valence, cognitive, social process and arousal/regulatory domains. This can help us understand how different types of childhood adversity can lead to varied psychiatric outcomes (i.e., multifinality).

Finally, the ultimate goal of this research is to develop preventative interventions, and to improve treatment, for individuals who have experienced childhood adversity. Current diagnostic systems and dominant treatment paradigms are poorly suited to addressing the effects of childhood adversity. General diagnostic practices typically entail assigning multiple, distinct co-morbid diagnoses, which obscures etiological clarity and treatment targets. Meanwhile, treatment approaches emphasize symptom improvement rather than restoration of the underlying disrupted processes. There is also a large gap in addressing the highly vulnerable group of youth who have experienced adversity but do not yet meet criteria

for a psychiatric disorder. Few interventions or programs leverage critical window for prevention. Identifying whether different types of childhood adversity are associated with specific vulnerabilities will be critical for designing short-term interventions that specifically target and modify disrupted processes.