Neurobiological Mechanisms of Risk for Psychopathology in Adolescents Exposed to Childhood Adversity

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Citation	Busso, Daniel S. 2016. Neurobiological Mechanisms of Risk for Psychopathology in Adolescents Exposed to Childhood Adversity. Doctoral dissertation, Harvard Graduate School of Education.
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NEUROBIOLOGICAL MECHANISMS OF RISK FOR PSYCHOPATHOLOGY IN
ADOLESCENTS EXPOSED TO CHILDHOOD ADVERSITY

By

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A thesis presented to the faculty
of the Graduate School of Education of Harvard University
in partial fulfillment of the requirements
for the degree of Doctor of Education

2016

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DEDICATION
To my parents, Hilary & Esteban

ACKNOWLEDGEMENTS

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ABSTRACT

Childhood adversity (CA) exerts a deleterious toll on mental health, contributing to population-wide disparities in educational attainment, economic productivity and responsible citizenship (Shonkoff et al., 2012). The past decade has witnessed a burgeoning interest in how exposure to adversity affects neurobiological development, thereby representing one pathway through which these experiences become developmentally embedded. However, our knowledge of these intervening processes currently remains limited.

This dissertation examines neurobiological mechanisms linking childhood adversity with adolescent psychopathology, a critical step for developing effective prevention and intervention efforts supporting at-risk youth. In Study 1, I explore the differential impact of threat (exposures that involve traumatic risks to the safety of the child, as with abuse) and deprivation (exposures that involve the absence of expected environmental inputs, as with neglect or poverty) on physiological reactivity to stress and psychopathology. Although both threat and deprivation were associated with greater psychopathology, only threat exposures were mediated by changes in physiological reactivity. These findings underscore the importance of distinguishing between different forms of confounded adversities, and highlight the potential value of targeting interventions based on disorder etiology. In Study 2, I use a longitudinal design to identify whether neural structure mediates the association between childhood maltreatment and psychiatric disorders. Maltreatment was associated with reduced cortical thickness in prefrontal and temporal cortex, and these differences prospectively predicted psychopathology two years later. Identifying pre-clinical, transdiagnostic indicators of vulnerability is likely to have important ramifications for the field of preventative psychiatry, facilitating intervention efforts.

Finally, in Study 3, I explore whether adolescents' inhibitory control of threatening stimuli is moderated by maltreatment exposure. Participants completed a Go/No-Go task, a standard measure of inhibitory control, for stimuli that had previously been paired with an aversive sound (CS+) and those that had not (CS-). Contrary to hypotheses, inhibitory control was not impaired for the CS+ compared to the CS-, and this effect did not differ by maltreatment exposure. However, maltreated adolescents' inhibitory control for the CS+ predicted anti-social behavior symptoms. Further research is needed to examine the conditions for which learned threat compromises cognitive functioning in maltreated youth.

GENERAL INTRODUCTION

Childhood adversity represents a pervasive and enduring societal problem, contributing to population-wide disparities in educational attainment, economic productivity and responsible citizenship (Shonkoff et al., 2012). Nearly 60% of US adolescents report experiencing at least one adversity, including maltreatment, poverty, parental death or divorce (McLaughlin, Green, Gruber, Zaslavsky, & Kessler, 2012). Childhood adversity is also robustly associated with lifetime psychiatric disorder: epidemiologic studies indicate that exposure to adversity is associated with nearly 45% of childhood-onset mental disorders, and up to 32% of adult-onset mental disorders (Green et al., 2010). Despite recognition of the grave public health impact of childhood adversity, our knowledge of the intervening processes that drive these effects remains limited (Shonk & Cicchetti, 2001). This thesis will examine mechanisms linking childhood adversity with adolescent psychopathology, a critical step for developing effective prevention and intervention strategies supporting at-risk youth.

Interest in the neurobiological impact of childhood adversity has burgeoned in the past two decades, highlighting one important pathway through which these experiences become developmentally embedded (see, e.g., Nelson & Sheridan, 2011; Teicher et al., 2003). Prolonged activation of physiological systems following chronic adversity results in a disruption of stress regulatory systems in the body (Gunnar & Quevedo, 2007; McEwen, 2012). The autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA) axis operate synergistically to orchestrate physiological responses to environmental stressors, driving long-term biological adaptations necessary for learning and survival (Dickerson & Kemeny, 2004). The sympathetic (SNS) and parasympathetic (PNS) branches of the ANS play an important role in maintaining the body's homeostatic balance in the face of immediate stressors (i.e. activating the 'fight or flight' response) through changes in

cardiovascular tone (Sapolsky, Romero, & Munck, 2000). In contrast, the HPA-axis

maintains homeostasis by modulating levels of slower-acting hormones (e.g. cortisol) in the

bloodstream (Gunnar & Quevedo, 2007). Finally, an important strand of research assesses

the impact of childhood adversity on neural structure and function. Disruptions in neural

circuits involved in fear learning, salience processing and emotion regulation are posited to

be core mechanisms driving the association between traumatic stress and later

psychopathology (McCrory et al., 2011).

The use of biological assessments, including magnetic resonance imaging (MRI)

offers several advancements to our understanding of childhood adversity over existing

behavioral research methods. Neurobiological markers may help in the early identification of

psychopathology, or in guiding appropriate treatments or interventions for children and

adolescents with particular risk profiles (Cicchetti & Gunnar, 2008; McCrory & Viding,

2015). Neuroimaging work may also shed light on the underlying processes that are impacted

by childhood adversity. For example, it is unclear whether impairments in self-regulatory

behavior identified in samples of maltreated youth (Shields, Cicchetti, & Ryan, 1994) reflect

impairments in emotion *regulation* (i.e. top-down, cortically-mediated cognitive control

processes) or impairments in emotion *generation* (i.e. bottom-up, subcortically-mediated

differences in anxiety or impulsivity). Behavioral measures are typically unable to disentangle

these processes (Beauchaine, 2015).

Moreover, there are several reasons why adolescence is an important period in which

to study neurobiological development and psychopathology. First, adolescence is a uniquely

vulnerable time for mental disorders, with symptoms and diagnoses rising precipitously

(Giedd, Keshavan, & Paus, 2008). Evidence drawn from large, nationally representative

epidemiological surveys indicates that half of all lifetime psychiatric disorders onset by age

14, and three quarters by age 24 (Kessler et al., 2005). Adolescence is characterized as a period of high risk for major depression (Hankin et al., 1998), anxiety disorders (Campbell, Brown, & Grisham, 2003; Kessler et al., 2005), substance-use disorders (Merikangas et al., 2010), and behavioral disorders (Merikangas et al., 2010; Moffitt, 1993), among others. Second, adolescents must contend with normative developmental challenges, including a growing desire for independence, the need to navigate complex peer and parental relationships, and newfound academic and employment pressures, all of which are likely to exert a toll on psychological well being. Finally, adolescence coincides with significant structural and functional reorganization of the brain, especially in the prefrontal cortex (PFC) (Blakemore, 2008; Giedd, 2004). The PFC subserves higher-order cognitive functions, such as executive functions, and continues to develop well into the third decade of life (Giedd, 2004; Giedd et al., 1999). Thus, it is of considerable interest to explore how experiences of childhood adversity interact with normative risk processes to create enduring vulnerability to psychopathology during the teenage years.

Project Overview and Dataset

This thesis includes three studies designed to probe the psychological and neurobiological mechanisms linking childhood adversity with adolescent mental disorders. Data were drawn from an ongoing longitudinal investigation of childhood adversity and adolescent development, conducted between October 2010 and June 2015. During their first visit (Wave 1), 169 adolescents (mean age = 14.9 years) were administered a comprehensive battery of tests, including assessments of psychophysiological reactivity, family functioning, and exposure to childhood adversities. These adolescents were initially recruited to sample child maltreatment, in addition to other adversities during childhood such as exposure to

community violence, poverty, or peer victimization. During a second visit (Wave 2), a subset of 60 adolescents (mean age = 16.5 years) were administered a diagnostic clinical interview and structural and functional neuroimaging data was acquired. During a final visit (Wave 3), 51 of these adolescents (mean age = 18.9 years) returned to the lab to complete questionnaire surveys, two experimental tasks, and a second clinical interview. The three studies presented herein draw from all three waves.

In Study 1, I examine the differential impact of threat (referring to trauma exposures that involve traumatic risks to the safety of the child, such as physical and sexual abuse) and deprivation (referring to exposures that reflect the absence of expected environmental inputs, common in the case of neglect, poverty, or institutionalization) on stress reactivity and psychopathology. To date, little empirical work has identified dimensions of early experience that differentially influence neurobiological development. Identifying exposure-specific trajectories of psychopathological development has a number of clear implications for prevention and intervention, such as, for example, targeting treatments based on disorder etiology rather than just symptomatology.

In Study 2, I use a longitudinal design to identify whether differences in neural structure mediate the association between childhood maltreatment and adolescent psychopathology. To date, prospective studies of childhood maltreatment, brain development and mental health have been notably lacking, and so it is unclear whether structural brain differences identified in previous samples of maltreated children represent predictors or sequelae of psychopathology. Identifying predictive biomarkers of vulnerability in the wake of childhood maltreatment is an important goal, and may allow for the development of preventative interventions seeking to offset psychiatric risk.

Finally, In Study 3, I examine inhibitory control in adolescents exposed to childhood maltreatment. Although inhibitory control is a core cognitive process impacted by maltreatment (Cowell, Cicchetti, Rogosch, & Toth, 2015), less is known about how the emotional salience of information affects inhibitory processes. Previous research has indicated that emotional salience may enhance or impair executive functions such as inhibitory control by directing selective attention toward stimuli that have negative or positive significance for the individual (Pessoa, 2009; Vuilleumier, 2005). However, no prior research has explored whether individuals with specific histories of learned attentional bias to negative emotional stimuli – such as those who have been exposed to maltreatment – show different patterns of inhibitory control compared to typically developing controls, or how these patterns relate to externalizing psychopathology.

Together, these three studies are designed to elucidate the underlying neurobiological and cognitive mechanisms linking childhood adversity with adolescent psychopathology. The resulting findings will provide novel data about risk and resilience following childhood adversity, thereby informing prevention and intervention strategies.

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STUDY 1:

Dimensions of Adversity, Physiological Reactivity, and Externalizing Psychopathology in Adolescence: Deprivation and Threat

Abstract

Dysregulation of autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA) axis function is a putative intermediate phenotype linking childhood adversity (CA) with later psychopathology. However, the degree to which CAs predict ANS and HPA-axis dysregulation varies widely across studies. Here, we test a novel conceptual model discriminating between deprivation and threat exposure on stress reactivity and subsequent psychopathology. Adolescents (N = 169; mean age = 14.9 years) with a range of trauma (e.g., maltreatment, direct community violence) and poverty exposure participated in the Trier Social Stress Task (TSST). During the TSST, electrocardiograph, impendence cardiography, salivary cortisol and dehydroepiandrosterone sulphate (DHEA-S) data were collected. We compared the independent effects of exposure to deprivation (poverty) with exposure to threat (traumatic violence) on changes in sympathetic, parasympathetic, and HPA-axis reactivity, and assessed whether these changes statistically mediate the association between adversity and internalizing and externalizing symptoms. Exposure to both poverty and traumatic violence was associated with greater internalizing and externalizing symptoms. Threat exposure, controlling for deprivation, was associated with blunted sympathetic and cortisol reactivity. Blunted cortisol reactivity statistically mediated the association of traumatic violence with externalizing, but not internalizing, psychopathology. In contrast, we found no association between deprivation and physiological reactivity when controlling for threat exposure. We provide evidence for distinct neurobiological mechanisms through which adversity related to poverty and trauma are associated with psychopathology in adolescence. Distinguishing distinct pathways through which adversity influences mental health has implications for the prevention and treatment of youth following exposure to childhood adversity.

Introduction

Childhood adversities (CA) exert a profoundly deleterious impact on development, contributing to population-wide disparities in mental health, educational attainment and economic productivity (Shonkoff et al., 2012). Nearly 60% of US adolescents report experiencing at least one adversity, including maltreatment, poverty, parental death or divorce (McLaughlin, Green, Gruber, Zaslavsky, & Kessler, 2012). Epidemiological and clinical studies indicate that children exposed to CAs are at elevated risk for a wide spectrum of internalizing and externalizing problems, including depression, anxiety, disruptive behavior and substance use disorders (Kessler, Avenevoli, & Ries Merikangas, 2001; McLaughlin et al., 2012). Consequently, CAs represent salient environmental risk factors that imperil successful adjustment across multiple domains.

The past decade has witnessed a burgeoning interest in how CAs shape neurobiological development, leading to elevated risk for psychopathology (Teicher et al., 2003). In particular, conceptual models propose that prolonged activation of physiological systems following chronic adversity results in a disruption of stress regulatory systems in the body (McEwen, 2012). The autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA) axis operate synergistically to orchestrate physiological responses to environmental stressors, driving long-term biological adaptations necessary for learning and survival (Dickerson & Kemeny, 2004). The sympathetic (SNS) and parasympathetic (PNS) branches of the ANS play an important role in maintaining the body's homeostatic balance in the face of immediate stressors (i.e. activating the 'fight or flight' response) through changes in cardiovascular tone (Sapolsky, Romero, & Munck, 2000). In contrast, the HPA-axis maintains homeostasis by modulating levels of slower-acting hormones (e.g. cortisol) in the bloodstream (Gunnar & Quevedo, 2007).

Anomalies in ANS and HPA-axis function have been documented following

exposure to CAs spanning maltreatment (Cicchetti & Rogosch, 2001), poverty (Evans, 2003;

Evans & Kim, 2007), institutionalization (McLaughlin, Sheridan, et al., 2015), parental loss

(Tyrka et al., 2008) and parental depression (Halligan, Herbert, Goodyer, & Murray, 2004).

However, the interpretation of this literature is complicated by the lack of a clear

physiological profile associated with CA exposure. While some studies document heightened

autonomic and neuroendocrine response to psychosocial stressors following adversity (Heim

et al., 2000; Kaufman et al., 1997), others show blunted reactivity (Gunnar, Frenn, Wewerka,

& Van Ryzin, 2009; McLaughlin, Sheridan, et al., 2015), and still others find discordance

between autonomic and neuroendocrine responses (Gordis, Granger, Susman, & Trickett,

2006). Finally, some studies find no differences in stress reactivity at all (DeSantis et al.,

2011).

These divergent findings may be partially accounted for by variability in the types of

CA investigated in prior human studies (Humphreys & Zeanah, 2015; Kuhlman, Geiss,

Vargas, & Lopez-Duran, 2015; Miller, Chen, & Zhou, 2007). To date, studies of CA in

humans have typically focused on the effects of single forms of adversity (e.g. maternal

education) that are confounded with other unmeasured exposures, such as maltreatment or

community violence exposure (MacMillan et al., 2009). An alternative approach has been to

examine associations between the number of adverse childhood experiences (e.g. 'ACEs'

scores) and subsequent endocrine and cardiovascular response to stress (Lovallo, Farag,

Sorocco, Cohoon, & Vincent, 2012; Voellmin et al., 2015). Neither of these approaches

assesses whether specific domains of exposures result in specific patterns of ANS and HPA-

axis development.

In the present study, we test a recent theoretical model that predicts variability in

neurodevelopment following CA exposure (McLaughlin, Sheridan, & Lambert, 2014; Sheridan & McLaughlin, 2014). The model proposes two orthogonal dimensions of early experience, each having distinct effects on brain and biological systems: (i) *deprivation*, referring to exposures that reflect the absence of expected environmental inputs, and common in the case of neglect, poverty, or institutionalization, and (ii) *threat*, referring to trauma exposures that involve traumatic risks to the safety of the child, such as physical and sexual abuse or direct exposure to community violence. Importantly, both types of experience contribute to psychopathology (Nelson & Sheridan, 2011), and research attempting to find specificity among types of CA and risk for internalizing and externalizing psychopathology has largely failed (see, e.g., McMahon, Grant, Compas, Thurm, & Ey, 2003, for a review). However, the model predicts that deprivation and threat have differential impacts on the intervening neurobiological processes that underlie differences in psychopathology.

Specifically, evidence from human and animal studies suggests that threat exposure influences the development of cortico-limbic circuits that underlie fear learning and salience processing (McCrory et al., 2011), thereby modifying physiologic responses to novel stressors (Heim et al., 2000). In rodents, exposure to threat early in development results in prolonged alteration in amygdala, hippocampal and medial prefrontal cortex (mPFC) function in response to subsequent threat cues (Chen, Fenoglio, Dubé, Grigoriadis, & Baram, 2006), as well as hyperreactivity of the HPA-axis (Liu et al., 1997). The amygdala, hippocampus and medial prefrontal cortex (PFC) modulate behavioral and physiological responses to environmental threats via projections to the hypothalamus and brainstem (Chiang, Taylor, & Bower, 2015). The amygdala signals the hypothalamus to stimulate the release of corticotrophin releasing hormone (CRH), triggering a cascade of neurochemical

events that culminates in the release of cortisol by the adrenal cortex. Perception of environmental threats also engages the SNS and PNS by innervating neural fibers in the brain stem (Thayer, Åhs, Fredrikson, Sollers III, & Wager, 2012). Human studies of traumatic violence exposure mirror findings in animals, revealing that these exposures in childhood are associated with ANS and HPA-axis dysfunction (McLaughlin, Sheridan, Alves, & Mendes, 2014; Tarullo & Gunnar, 2006) and disruption in function and structure of the hippocampus, amygdala, and mPFC (Gorka, Hanson, Radtke, & Hariri, 2014; Herringa et al., 2013; McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015). Given the human and animal evidence, we hypothesize that threat, controlling for deprivation will be associated with disruptions in physiological reactivity.

In contrast, we hypothesize that deprivation, controlling for threat, is unlikely to result in disrupted physiological reactivity. Evidence from animal models suggests that experiences of deprivation specifically disrupt cortical development. Isolated forms of deprivation in early development (e.g., visual deprivation) results in decreased dendritic arborization in regions responsible for processing the absent information (e.g., primary visual cortex) (O'Kusky, 1985). Similarly, global deprivation in rodents results in widespread decreases in dendritic arborization, spines and overall brain volume (Wiesel & Hubel, 1965). In humans, global deprivation in the form of exposure to institutional care has been associated with widespread reductions in the thickness of cortex (McLaughlin, Sheridan, Winter, et al., 2014). Reductions in cortex such as these are hypothesized to influence cognitive development but leave stress physiology largely unaffected.

Despite the fact that deprivation and threat exposures are highly co-occurring (Coulton, Crampton, Irwin, Spilsbury, & Korbin, 2007; Dong et al., 2004), relatively few studies have attempted to disentangle the contributions of deprivation and threat on stress

reactivity. While some studies examining the impact of traumatic violence exposure on physiological reactivity have controlled for poverty or socioeconomic status (Carpenter, Shattuck, Tyrka, Geracioti, & Price, 2010; MacMillan et al., 2009; McLaughlin, Sheridan, Alves, et al., 2014), almost no investigation of the impact of poverty on physiological reactivity have controlled for traumatic violence. The purpose of the current study, then, is to test these hypothesized associations between threat (controlling for deprivation) and deprivation (controlling for threat) with autonomic (SNS and PNS) and neuroendocrine (salivary cortisol, dehydroepiandrosterone sulphate; DHEA-S) responses to a laboratory stressor.

Notably, we use the ratio of cortisol to DHEA-S as a measure of HPA-axis function. While cortisol has been extensively studied in the stress literature, DHEA, and its sulphate, DHEA-S, have received considerably less attention (Van Voorhees, Dennis, Calhoun, & Beckham, 2014). Evidence suggests that these steroids have antiglucocorticoid properties, and may therefore counterbalance the effects of cortisol on stress-induced neurotoxicity (Kimonides, Spillantini, Sofroniew, Fawcett, & Herbert, 1999). Accordingly, it has been suggested that the ratio of cortisol to DHEA may represent a better index of neuroendocrine imbalance than cortisol alone (Goodyer, Park, Netherton, & Herbert, 2001).

Next, given the robust associations between CA exposure and psychopathology (McLaughlin et al., 2012), we examined whether effects of CAs on internalizing and externalizing symptoms were statistically mediated by physiological reactivity. A robust research literature suggests that alterations in HPA-axis or ANS function are associated with both internalizing and externalizing difficulties in childhood and adolescence. Youth with internalizing problems generally exhibit elevated cortisol (Goodyer, Park, & Herbert, 2001) and SNS (Nock & Mendes, 2008) response to psychosocial stress, whereas externalizing

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problems are characterized by blunted ANS arousal and HPA-axis reactivity (Beauchaine et al., 2013; Beauchaine, Gatzke-Kopp, & Mead, 2007). Together, these data suggest that both hyper- and hypo-activation of physiological systems are associated with risk for later psychopathology.

Threat or traumatic violence was operationalized as exposure to physical abuse, sexual abuse, or direct exposure to community violence. Poverty was operationalized as whether or not a family's income fell above or below the federally defined poverty line. Although poverty is not a direct measure of deprivation (i.e. it is possible to be poor and still have exposure to enriched cognitive, social and linguistic inputs), low parental SES has been associated with exposure to fewer enriched cognitive experiences in childhood (Bradley, Corwyn, McAdoo, & Coll, 2001) including impoverished linguistic inputs and decreased overall exposure to language (Fernald, Marchman, & Weisleder, 2013; Hart & Risley, 1995). As such, poverty serves as a proxy for deprivation exposure in this study. We include both poverty and traumatic violence in all models, allowing us to examine the unique effect of one, controlling for the other. Consistent with the deprivation/threat model, we hypothesized that while deprivation and threat would be associated with internalizing and externalizing psychopathology, only threat exposure (controlling for deprivation) would influence stress reactivity, and in turn statistically mediate associations with psychopathology.

Methods

Sample

A sample of 169 adolescents (75 males, 94 females) was recruited from schools, after-school programs, medical clinics at Boston Children's Hospital and the wider community in Boston and Cambridge, MA, between July 2010 and November 2012. Recruitment sites were selected to oversample diverse ethnic/racial groups and those with

experiences of childhood adversity (i.e. participants were recruited from neighborhoods with high levels of community violence and from clinics that served a predominantly low-SES catchment area). The sample had a mean age of 14.9 years (SD=1.4). The sample was racially diverse: 41.3% White (n=69), 18.0% Black (n=30), 18.0% Hispanic/Latino (n=30), 7.8% Asian (n=13) and 15% Biracial/Other (n=25). All females were postmenarchal. Twenty six percent of participants came from households whose income fell below the federal poverty line (n=42), and approximately one third of the sample (38.3%; n=64) was from single-parent households. Participants were excluded from the study if they were currently using corticosteroids. Two participants declined to participate in the psychosocial stress task, resulting in an analytic sample of 167 participants. Parents provided informed consent, and adolescents provided assent. All study procedures were approved by the Institutional Review Boards at Boston Children's Hospital and Harvard University.

Procedure

Participants completed the Trier Social Stress Test (TSST), a widely used stress induction procedure used with children and adolescents (Kudielka, Hellhammer, & Kirschbaum, 2007). First, participants completed a 10-minute baseline period, where they were asked to sit quietly without moving. Next, participants completed three tasks in front of two experimenters: a speech preparation period, a five-minute speech to experimenters, and a mental subtraction task (see McLaughlin, Sheridan, Alves, et al., 2014). Throughout all phases of the TSST (baseline, speech preparation, speech, math), participants were seated and continuous cardiac measures were recorded non-invasively. Saliva samples were acquired at three time points: (1), immediately following the initial baseline period, 20-30 minutes after participants had arrived at the lab; (2), 15 minutes following the beginning of the

speech portion of the TSST; (3), 15 minutes following completion of the recovery period, approximately 25 minutes after sample 2. Subjects were instructed to refrain from exercising, eating or drinking caffeinated beverages within four hours of their study visit. To account for potential diurnal effects on the HPA-axis, all participants started the laboratory session in the afternoon (between 1pm-4pm). All physiological data was collected prior to questionnaires about adversity exposure and psychopathology.

Autonomic Measures

Electrocardiogram (ECG) recordings were acquired using a Biopac ECG amplifier (Goleta, CA), using a modified Lead II configuration (right clavicle, left lower torso, and right leg ground). Cardiac impedance was obtained using a Bio-Impedance Technology model HIC-2500 impedance cardiograph (Chapel Hill, NC). Electrodes were placed on the neck and torso. ECG and impedance cardiography data were sampled at 1.0kHz and acquired using Biopac MP150 hardware and Acqknowledge software. Data were scored by trained RAs blind to participant identity, and were averaged into 1-minute epochs using Mindware Heart Rate Variability (HRV) software (Mindware Technologies, Gahanna, OH).

Respiratory sinus arrhythmia (RSA) was used as a measure of PNS reactivity and was calculated from the inter-beat interval time series using spectral analysis implemented in Mindware. RSA was calculated for the high-frequency band 0.12-0.40 Hz. To ensure that RSA represents a measure of pure parasympathetic cardiac control, respiration rate was derived from the basal cardiac impedance signal and included as a covariate in all PNS analyses. Greater PNS reactivity is indicated by a task-related decrease in RSA from basal levels (i.e. vagal withdrawal).

Pre-ejection period (PEP) was calculated from impedance cardiography data as a

measure of SNS reactivity. PEP represents the time interval beginning with ventricular depolarization and ending when blood is ejected from the left ventricle, where shorter intervals correspond to greater SNS activation (Sherwood et al., 1990). As scoring of impedance cardiography data requires manual placement of the B point (the opening of the aortic valve), these data were independently scored by two raters and differences of more than 5% were adjudicated by one of the study investigators (KM).

Neuroendocrine Measures

Cortisol (nmol/L) and dehydroepiandrosterone-sulphate (DHEA-S; ng/mL) concentrations were collected at three time points during the TSST. Neuroendocrine samples were obtained with cryovial tubes (Immuno-Biological Laboratories) using the drool method, whereby participants expectorate approximately 1.5 ml of saliva into a cryovial with a plastic straw. Saliva samples were stored immediately at -20°C until they were shipped on dry ice to a laboratory in Boston, Massachusetts. Samples were assayed for cortisol and DHEA-S using commercially available luminescence immunoassay kits (CLIA; IBL, Hamburg, Germany). Intra-assay and inter-assay coefficients of variance were acceptable (cortisol: 4.24% and 3.34%; DHEA-S: 3.96% and 4.33%; respectively). HPA-axis activity was calculated by dividing cortisol by DHEA-S for each time point.

Self-Report Measures

Interpersonal violence exposure was assessed using two self-report questionnaires. First, the Childhood Trauma Questionnaire (CTQ;(Bernstein, Ahluvalia, Pogge, & Handelsman, 1997) is a 28-item self-report measure that retrospectively assesses 5 types of negative childhood experiences. Participants respond to each item in the context of "while growing

up" on a 5-point Likert scale ranging from "never" to "very often". Fifteen items corresponding to emotional abuse (e.g. "people in my family said hurtful or insulting things to me"), physical abuse (e.g. "I got hit so hard by someone in my family that I had to see a doctor or go to the hospital"), and sexual abuse (e.g. "someone molested me") were summed to generate an overall index of childhood abuse (α =.90). We also administered the Screen for Adolescent Violence Exposure (SAVE; (Hastings & Kelley, 1997), a 32-item measure of adolescents' exposure to direct or indirect violence in school, home or neighborhood contexts. We summed all 12 items corresponding to direct violence exposure (e.g. "someone has pulled a knife on me"), measured on a 5-point Likert scale ranging from "never" to "almost always" (α = .89). Finally, we z-transformed and summed the CTQ and SAVE measures (r = .23, p <.001) to create an overall interpersonal violence exposure composite, with higher scores indicating greater exposure to interpersonal violence.

Deprivation: The ratio of income to needs was computed by diving parent-reported family income by the federal poverty thresholds (as determined by the number of people in the household). Our primary measure of deprivation was a dichotomous variable indicating whether participants lived under the federal poverty line (i.e. an income to needs ratio <1). For sensitivity analyses, we also treated deprivation as a continuous measure by taking a log transformation of income-to-needs ratio (Noble et al., 2015).

Psychopathology was assessed using the Youth Self-Report form from the Child Behavior Checklist (CBCL(Achenbach, 1991). The CBCL is a widely used measure of youth emotional and behavioral problems, and has been population-normed to generate age-standardized estimates of psychopathology. Here, we use the global externalizing and internalizing subscales of the YSR.

Data Analysis

A log transformation was used to normalize the distribution of cortisol/DHEA-S prior to analysis. Autonomic reactivity to the TSST was modeled by predicting values of PEP and RSA measured during the first minute of the speech and math portions of the TSST, while controlling for these parameters during the first minute of baseline. Similarly, neuroendocrine reactivity was modeled by predicting cortisol/DHEA during the speech, controlling for baseline levels. Multiple regression models were conducted with the *sem* package in Stata, using full information maximum likelihood (FIML) to account for occasional missing data due to noise in the ANS waveforms, equipment malfunctions, etc. Less than 8% of the data were missing on any one variable.

We used standard tests of mediation (Baron & Kenny, 1986) to test whether physiological reactivity mediated the association between our two adversity measures (poverty and interpersonal violence) and psychopathology. First, we tested associations between the predictors (interpersonal violence and poverty) and the outcomes (internalizing and externalizing symptoms) (C path). Interpersonal violence and poverty were entered in separate regression models, and then included together. Next, we tested the association between the predictors and the proposed mediators (PEP, RSA and cortisol/DHEA during the speech and math portions of the TSST) (A path). As above, interpersonal violence and poverty were entered separately and then together. Finally, we tested associations between the mediators and the outcomes (B path). If these criteria were met for a single path, the significance of the indirect path (through the mediator) was tested using a bootstrapping approach (Preacher & Hayes, 2004). This approach generates bias-corrected, bootstrapped confidence intervals for total and specific indirect effects of the predictors, on the outcome, through the mediators. Confidence intervals that do not include zero indicate statistically

significant mediation. Age and gender were included as covariates in all models, and respiration rate was included as a covariate for all models using RSA. Unstandardized betas are presented in the results.

<div align="center">

Results

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Physiological Reactivity

We first examined task-related changes in physiological reactivity from baseline using paired samples t-tests. Significant increases in SNS activity (i.e. smaller PEP than baseline) were observed for 90% of participants for the speech ($t = 13.78; p < .001$) and 82% of participants for the math ($t = 11.52; p < .001$) portions of the TSST. Similarly, vagal suppression (i.e. smaller RSA than baseline) was observed for 70% of participants for speech ($t = 6.29; p < .001$) and 61% of participants for math ($t = 4.25; p < .001$). Finally, increased HPA-axis reactivity (i.e. greater cortisol:DHEA-S than baseline) occurred in 78% of participants ($t = 7.06; p < .001$).

Adversity Exposure and Psychopathology

Table 1 displays means and standard deviations for key study variables. Bivariate correlations are presented in Table 2. Following examination of the uncontrolled, bivariate associations, we ran multiple regression models testing the association between CAs (poverty and violence exposure) and internalizing and externalizing psychopathology. Poverty was associated with externalizing ($\beta=4.74, p=.005$), but not internalizing symptoms ($\beta=2.40, p=.18$). Children whose household income fell below the federal poverty line exhibited greater levels of externalizing symptoms than those above the poverty line. This pattern of results did not change when controlling for violence exposure. Exposure to violence was

significantly associated with both externalizing (β=3.06, p<.001) and internalizing symptoms (β=2.87, p<.001), which did not change when controlling for poverty. Children with greater exposure to violence had higher levels of psychopathology.

Adversity Exposure and Physiological Reactivity

Table 3 displays coefficients, standard errors, and significance values for hierarchical linear regression models predicting physiological reactivity (RSA, PEP, Cortisol:DHEA-S) from poverty and interpersonal violence. Neither violence nor poverty predicted PNS reactivity to speech or math. Exposure to violence was associated with blunted SNS reactivity to the speech and math portions of the TSST. Findings did not change when controlling for poverty. In contrast, poverty was unassociated with SNS reactivity, with or without controlling for violence. Finally, interpersonal violence was associated with blunted HPA-axis response to the TSST, even when accounting for poverty. In contrast, poverty was unrelated to HPA-axis reactivity, even when accounting for interpersonal violence.

Physiological Reactivity and Psychopathology

Next, we tested the hypothesis that physiological reactivity would be associated with symptoms of psychopathology. Symptoms of externalizing psychopathology were associated with blunted physiological reactivity. Blunted SNS and PNS reactivity to math (SNS: β=.15, p=.017; PNS: β=1.14, p=.050) and decreased HPA-axis activation following the TSST (β=-2.55, p=.008) were associated with greater externalizing symptoms. Neither SNS, PNS, nor HPA-axis reactivity were associated with internalizing symptoms.

Mediation Analysis

Finally, we ran separate mediation models to test whether physiological reactivity to the TSST mediated the association of violence exposure with internalizing and externalizing symptoms. Controlling for poverty, a significant indirect effect of violence exposure through HPA-axis reactivity was observed (N=156; 95% CI: .03, .45) (Figure 1). We found no significant indirect effect of violence through SNS reactivity to speech or to math.

Sensitivity Analysis

We conducted sensitivity analyses to determine whether our dichotomous operationalization of poverty explained our findings. The pattern of findings was identical when using income-to-needs ratio as a continuous measure.

Discussion

The present study provides evidence for distinct effects of deprivation and threat on ANS and HPA-axis development. Disturbances in autonomic and neuroendocrine system function are a putative mechanism underlying the association between childhood adversities and psychopathology (Gunnar & Quevedo, 2007; Lupien, McEwen, Gunnar, & Heim, 2009). However, findings from previous studies have been highly mixed, suggesting the need to disentangle the relative impacts of different forms of adversity.

We extend previous research in a number of ways. First, we tested a novel theoretical model that differentiates between experiences of deprivation and threat in shaping neurobiological development (McLaughlin, Sheridan, & Lambert, 2014; Sheridan & McLaughlin, 2014). Consistent with this model, our data support the hypothesis that while both forms of adversity—reflected in poverty and interpersonal violence exposure—are

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associated with higher levels of psychopathology, only threat is associated with differences in physiological reactivity. Specifically, we found that threat was associated with blunted SNS and cortisol reactivity to the TSST, and that HPA-axis reactivity mediated the association between threat and externalizing psychopathology. In contrast, we found no association between threat and PNS reactivity, or any associations between physiological reactivity and internalizing symptoms. These findings are consistent with previous studies reporting blunted physiological reactivity to stress in individuals with exposure to interpersonal violence, such as maltreatment (Gunnar et al., 2009; Heim et al., 2000; MacMillan et al., 2009) and with those reporting blunted physiological reactivity in children with externalizing disorders (Beauchaine et al., 2013, 2007). Notably, we found no association of poverty with physiological reactivity, with or without controlling for interpersonal violence. This departs from a number of prior studies of poverty-exposed youth (Evans & Kim, 2007; Rudolph et al., 2014). These findings suggest that studies examining poverty and physiological reactivity to stress should assess and control for exposure to violence, which may be a critical confounder.

Second, our findings show that interpersonal violence was associated with blunted SNS reactivity to the TSST. To date, surprisingly few prior studies have explored the impact of adversity exposure on ANS reactivity, and these have often used nonspecific measures such as heart rate (Heim et al., 2000; Orr et al., 1998). Our use of pre-ejection period is advantageous as it represents a measure of 'pure' sympathetic response. The importance of differentiating between contributions of the SNS and PNS is underscored by our finding that only SNS indicators are associated with exposure to threat. In contrast, in previous studies we (and others) have found that PNS reactivity to psychosocial stress functions as a *moderator,* such that risk of internalizing psychopathology following exposure to childhood

adversities varies as a function of PNS activity (McLaughlin, Alves, & Sheridan, 2014; McLaughlin, Rith-Najarian, Dirks, & Sheridan, 2013). Taken together, these results suggest that measures of ANS activity, particularly of the SNS, may be used as a clinically useful index of stress sensitivity following exposure to violence in childhood alongside commonly used HPA-axis measures such as cortisol.

The findings from this study should be viewed in light of several limitations. First, our data are cross-sectional, precluding us from determining the directional and transactional pathways linking CA exposure, physiological reactivity and externalizing psychopathology. Our mediation analyses assume a temporal ordering of relationships, but it is possible that externalizing symptoms precede rather than follow from blunted physiological reactivity to stress. It is plausible that youths with externalizing problems may put themselves at increased risk for exposure to interpersonal violence (e.g. by engaging in community violence). Future prospective studies are needed to explore bidirectional associations between these variables. Second, our assessment of psychopathology used a self-report questionnaire. Replication of these findings using a structured clinical interview is therefore warranted. Third, our model focuses on only two aspects of early experience, and there are likely to be numerous others. For example, other characteristics of adversity, including the developmental timing and chronicity of exposure, have been conceptualized as important components of CA that explain differences in neuroendocrine activity and psychopathology in later life (Bosch et al., 2012; Fries, Hesse, Hellhammer, & Hellhammer, 2005; Jonson-Reid, Kohl, & Drake, 2012). Further studies are needed to examine the impact of additional dimensions of adversity on neurobiological development and mental health. Fourth, we did not collect information on females' use of oral contraceptives, which may have affected analyses involving HPA-axis reactivity. However, given the age of the sample, we find this to be unlikely. Finally, our

study design did not allow us to examine moderators of the association between childhood

adversity and psychopathology. An enhanced understanding of factors that may buffer

individuals from early adversity is another important goal for future research.

Conclusions

We provide evidence for differential influences of threat and deprivation on

physiological reactivity to stress. Although both deprivation and threat exposure were

associated with greater levels of externalizing symptoms, only threat exposure was associated

with differences in physiological reactivity. Blunted physiological reactivity, in turn, mediated

only the association of threat with externalizing problems. These findings provide

preliminary support for the deprivation/threat model as a useful theoretical framework

through which to understand the association of childhood adversity with neurobiological

development. Moreover, these findings highlight the importance of distinguishing between

different forms of adversity. Such an approach may eventually yield information that can be

used to targeting intervention approaches based on disorder etiology, in addition to

symptomatology.

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Tables

Table 1. Distribution for Childhood Adversity, Physiological Reactivity and Psychopathology Variables (N=167)

	Mean	SD
SAVE Traumatic Violence	13.40	2.57
CTQ Abuse	19.64	7.03
RSA - Baseline	6.92	1.34
RSA - Speech	6.03	1.41
RSA - Math	6.38	1.43
PEP - Baseline	102.61	14.77
PEP - Speech	86.39	19.58
PEP - Math	90.99	18.30
Cortisol - Baseline	6.59	6.00
Cortisol – Post Speech and Math	10.98	8.09
DHEA-S - Baseline	16.61	34.62
DHEA-S – Post Speech and Math	17.44	33.95
YSR Externalizing	52.12	9.63
YSR Internalizing	52.92	10.26

Note: SAVE = Screen for Adolescent Violence Exposure; CTQ = Childhood Trauma Questionnaire; YSR = Youth Self Report; RSA = Respiratory sinus arrhythmia; DHEA-S = Dehydroepiandrosterone sulphate; PEP = Pre-ejection period.

Table 2. Bivariate Correlations Among Physiology, Childhood Adversity, Psychopathology, and Demographic Variables (N=167)

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Age	--												
2. Female	-.12	--											
3. Poverty	-.01	-.06	--										
4. Interpersonal Violence	.22**	-.05	.21**	--									
5. PEP (Baseline)	.29**	-.09	.10	.07	--								
6. PEP (Speech)	.18*	-.19*	.12	.16*	.68**	--							
7. PEP (Math)	.18*	-.10	.13	.18*	.74**	.90**	--						
8. RSA (Baseline)	-.10	.08	.15	.01	-.02	.01	-.04	--					
9. RSA (Speech)	-.02	-.15	.21*	.16*	.20*	.46**	.43**	.16*	--				
10. RSA (Math)	-.05	.01	.13	.14	.10	.30**	.33**	.37**	.67**	--			
11. Cort:DHEA (Baseline)	.00	.12	.20*	.10	-.07	-.08	-.08	.13	-.04	.06	--		
12. Cort:DHEA (Post)	-.09	.13	.20*	-.02	-.05	-.15	-.14	.17*	-.07	.04	.84**	--	
13. YSR Externalizing	.15	.07	.21**	.48**	.03	.09	.13	.07	.15	.18*	-.01	-.13	--
14. YSR Internalizing	.19*	.04	.10	.44**	-.07	-.00	-.01	-.04	.11	.02	-.09	-.15	.54**

Note: * $p < .05$; ** $p < .01$; YSR = Youth Self Report; PEP = Pre-ejection period; RSA = Respiratory sinus arrhythmia

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Table 3. Summary of hierarchical regression analysis for effects of poverty and interpersonal violence   on physiological reactivity (N=167)

	Speech			Math		
	β	S.E	*p*-value	β	S.E	*p*-value
RSA						
IV	.09	.07	.19	.09	.07	.19
Poverty	.45	.25	.071	.15	.25	.55
IV (adj. for poverty)	.07	.07	.32	.08	.07	.22
Poverty (adj. for IV)	.40	.25	.11	.09	.25	.70
PEP						
IV	1.51	.72	.035	1.65	.61	.007
Poverty	2.48	2.64	.35	2.47	2.30	.28
IV (adj. for poverty)	1.44	.73	.050	1.59	.63	.012
Poverty (adj. for IV)	1.33	2.67	.62	1.20	2.31	.60

	Post Speech and Math		
	β	S.E	*p*-value
Cortisol:DHEA-S			
IV	-.08	.04	.033
Poverty	.09	.14	.50
IV (adj. for poverty)	-.09	.04	.021
Poverty (adj. for IV)	.15	.14	.28

Note: RSA = respiratory sinus arrhythmia; PEP=pre-ejection period; DHEA-S=dehydroepiandrosterone sulphate; IV = interpersonal violence. Analyses control for age, sex, baseline reactivity and respiration rate (for models with RSA).
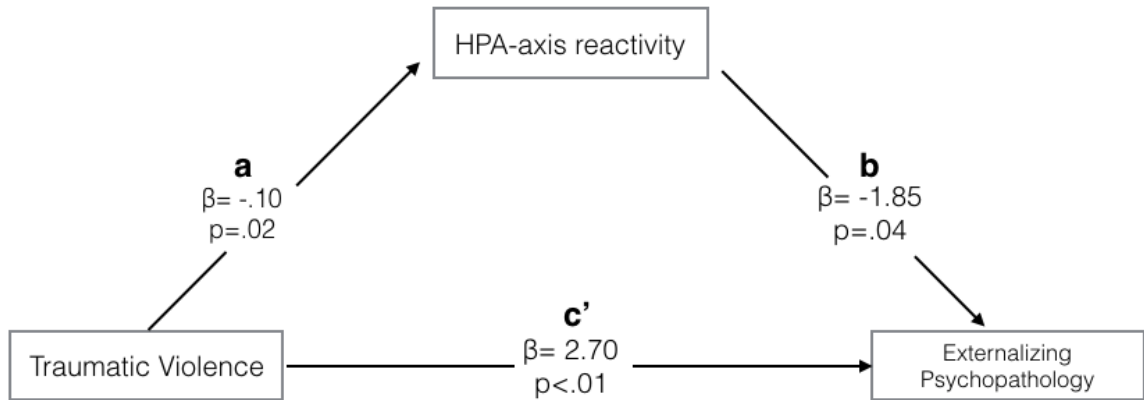
Figure 1. HPA-axis reactivity mediates the association between traumatic violence exposure and externalizing psychopathology. The significance of the indirect effect was tested using a bootstrapping approach, and analyses adjust for age, sex, poverty, and HPA-axis activity at baseline.

STUDY 2:

Childhood Maltreatment, Neural Structure, and Adolescent Psychopathology

Abstract

Childhood maltreatment exerts a deleterious impact on a broad array of mental health outcomes. The neurobiological mechanisms that mediate this association remain poorly characterized. Here, we use longitudinal design to prospectively identify neural mediators of the association between childhood maltreatment and psychiatric disorders in a community sample of adolescents. Structural magnetic resonance imaging (MRI) data and assessments of mental health were acquired for 51 adolescents (aged 13-20; M=16.96; SD=1.51), 19 of whom were exposed to physical or sexual abuse. Participants were assessed for maltreatment exposure (Time 1), participated in MRI scanning and a diagnostic structured interview (Time 2), and two years later were followed-up to assess psychopathology (Time 3). We examined associations between childhood maltreatment and neural structure, and identified whether maltreatment-related differences in neural structure prospectively predicted psychiatric symptom two years later, and change in symptoms across time. Childhood maltreatment predicted reduced cortical thickness in medial and lateral prefrontal and temporal lobe regions. Thickness of the left parahippocampal gyrus mediated the longitudinal association of maltreatment with anti-social behavior. In summary, childhood maltreatment is associated with disruptions in cortical structure in medial prefrontal and paralimbic regions, and these disruptions are selectively associated with increased vulnerability to internalizing and externalizing psychopathology. Identifying predictive biomarkers of vulnerability following childhood maltreatment may uncover neurodevelopmental mechanisms linking environmental experience with the onset of psychopathology.

Introduction

Childhood maltreatment poses a persistent and intractable public health problem that affects upwards of six million children in the United States each year (Institute of Medicine, 2014). Exposure to maltreatment is a robust predictor for the development of chronic psychiatric problems in adolescence and adulthood, including depression, anxiety and antisocial behavior (MacMillan et al., 2001; McLaughlin, Green, Gruber, Zaslavsky, & Kessler, 2012). Epidemiologic studies indicate that childhood adversity, including maltreatment, is associated with nearly 45% of childhood-onset mental disorders, and up to 32% of adult-onset mental disorders (Green et al., 2010). Recent efforts have attempted to identify the neurobiological sequelae of childhood maltreatment, highlighting one important pathway through which these experiences become developmentally embedded (Hart & Rubia, 2012).

The widespread associations of childhood maltreatment on neural structure are now well-established (Bick & Nelson, 2015; McCrory, De Brito, & Viding, 2010). Early neuroimaging studies documented reduced overall brain volume, reduced total gray matter (GM), and specific reductions in the volume of prefrontal, temporal, occipital and parietal cortex in maltreated relative to non-maltreated children (Andersen et al., 2008; De Bellis et al., 1999, 2002; Tomoda, Navalta, Polcari, Sadato, & Teicher, 2009; van Harmelen et al., 2010). More recent studies have focused on a cortico-limbic network that includes the medial prefrontal cortex (mPFC) and medial temporal lobe (Hanson et al., 2015; McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015; Morey, Haswell, Hooper, & De Bellis, 2015). The mPFC and medial temporal lobe operate synergistically to initiate and regulate physiological and behavioral responses to environmental threats (McEwen, 2012).

The medial temporal lobe includes the amygdala, hippocampus, and

parahippocampal cortex. The amygdala is involved in perception and associative learning of threat-related stimuli (Davis & Whalen, 2001; Johansen, Cain, Ostroff, & LeDoux, 2011). Although stress-related perturbations in amygdala structure are well-documented in rodents (McEwen, 2012), findings in children and adults exposed to maltreatment are mixed (e.g. (De Bellis et al., 2002; De Brito et al., 2013; Hanson et al., 2015; Woon & Hedges, 2008). In contrast, functional imaging studies of maltreated children consistently document elevated amygdala response to negative emotional cues, including to facial displays of anger and negative emotional stimuli (McCrory et al., 2011, 2013; McLaughlin et al., 2015). Reduction in hippocampal volume following stress exposure is well documented in rodents (McEwen, 2012) and in both children and adults with childhood maltreatment exposure (Gorka, Hanson, Radtke, & Hariri, 2014; Hanson et al., 2015; Morey et al., 2015; Teicher, Anderson, & Polcari, 2012). The hippocampus is necessary for modulation of the hypothalamic-pituitary-adrenal (HPA) axis, and is sensitive to the neurotoxic effects of glucocorticoids (Frodl & O'Keane, 2013; Woolley, Gould, & McEwen, 1990). Finally, reductions in the volume of the parahippocampal gyrus and other regions of the medial temporal lobe have been consistently observed in previous studies of children and adults with histories of childhood maltreatment (De Brito et al., 2013; Hanson et al., 2010; Van Dam, Rando, Potenza, Tuit, & Sinha, 2014).

Childhood maltreatment also appears to influence the development of brain regions that modulate limbic response to threatening or emotionally evocative stimuli. For example, activity in subdivisions of the mPFC, including orbitofrontal (OFC) and ventromedial (vmPFC) regions, is associated with reduced amygdala activity during both automatic (e.g., fear extinction) and effortful (e.g. cognitive reappraisal) forms of emotion regulation (Buhle et al., 2014; Milad & Quirk, 2012). OFC and vmPFC volume and thickness are reduced in

children and adults with exposure to physical and sexual abuse (Chaney et al., 2014; Dannlowski et al., 2012; De Brito et al., 2013; Edmiston et al., 2011; Hanson et al., 2010; Kelly et al., 2013, 2015). The vmPFC is centrally involved in the inhibition of conditioned fear, and may therefore play an important role in the pathophysiology of fear-related psychopathology, including anxiety disorders (Phelps, Delgado, Nearing, & LeDoux, 2004). Similarly, the OFC is implicated in both emotion regulation and emotion-based decision making, as evidenced by neuroimaging and lesion studies (Bechara, Damasio, & Damasio, 2000; Ochsner et al., 2004; Shiba, Kim, Santangelo, & Roberts, 2015).

In sum, existing work indicates that childhood maltreatment is associated with widespread structural brain changes, specifically in the mPFC and medial temporal lobe. However, we know comparatively little about the implications of these differences for psychopathology onset or other sequelae of maltreatment. A crucial goal for translational research is to identify predictive markers of vulnerability that can be used to identify subgroups of maltreated individuals most at-risk for future psychopathology (McCrory & Viding, 2015). However, extant research is predominantly cross-sectional, and so it is unclear whether structural brain differences identified in previous samples of maltreated children represent predictors or consequences of psychopathology.

To date, only three studies of maltreatment have examined prospective associations between regional GM and psychopathology. Rao and colleagues (2010) focused on hippocampal volume in adolescence, finding that volume of this region mediated the association of childhood maltreatment with major depressive disorder. Van Dam et al. (2014) identified maltreatment-related reductions in GM volume in the medial temporal lobe in adulthood that predicted severity of later substance-use disorder relapse. Finally, Gorka et al. (2014) found in a sample of young adults (mean age=19.5 years) that reduced

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hippocampal and mPFC GM mediated the association between maltreatment and later anxiety symptoms. No prospective studies have assessed whether cortical development during early to middle adolescence predicts later psychopathology. This window is associated with a precipitous increase in the incidence of multiple forms of psychopathology (Giedd, Keshavan, & Paus, 2008; Kessler et al., 2005), and also with structural brain changes, particularly in the prefrontal cortex (Blakemore, 2008; Blakemore & Choudhury, 2006). Thus, it is of considerable interest to explore how experiences of maltreatment interact with normative risk processes to create vulnerability to psychopathology during this time.

The aim of the present study was to examine whether alterations in neural structure mediate the prospective association of childhood maltreatment with psychopathology during adolescence. We specifically focus on maltreatment experiences that involve environment threat (physical and sexual abuse), as they most closely meet criteria for trauma as an experience involving threats to one's physical integrity or the physical integrity of others, or sexual violation (American Psychiatric Association, 2013). Childhood maltreatment, neural structure and psychopathology were measured at three distinct time points, allowing us to identify latent markers of vulnerability to psychopathology. To our knowledge, no prior study of mid-adolescence has explored prospective associations between maltreatment, cortical development and psychopathology using a three-time point longitudinal design. We assessed the impact of childhood maltreatment on cortical thickness and subcortical volume, and then tested whether these differences mediated the association between maltreatment exposure and psychiatric symptoms across adolescence.

Methods

Participants

Participants were initially recruited for a larger study on child maltreatment (see

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(McLaughlin, Sheridan, Alves, & Mendes, 2014)). At Time 1, 169 adolescents (aged 13-17;

M=15.14; SD=1.46) provided detailed assessments of family history and maltreatment.

Initial recruitment efforts focused on local schools, after-school programs and medical

clinics in neighborhoods in Boston and Cambridge, MA that were known to have high rates

of community violence and poverty. At Time 2 (mean time to follow-up = 14.5 months;

SD=9.9), a subsample of 59 adolescents was selected to complete a neuroimaging session

that included a structural scan, as well as a diagnostic clinical interview. All females were

postmenarchal at time of scan. Exclusion criteria included use of psychiatric medication

(with the exception of medication for attention-deficit hyperactivity disorder [ADHD],

which was discontinued 24-hours before scanning), use of metal orthodontics or other metal

contraindications for magnetic resonance imaging (MRI), claustrophobia, presence of an

active substance use disorder or pervasive developmental disorder, and inability to speak

English. Nine participants were recruited only for the neuroimaging portion at Time 2

(Time 1 data was reported at Time 2 for these participants). For more information on

baseline associations between childhood maltreatment and neural structure using the full

sample, see Gold et al. (manuscript in preparation).

Finally, at Time 3 (mean time to follow-up = 23.1 months; SD=3.24), 51 participants

completed additional assessments (retention rate of 86%). The eight subjects lost to follow-

up between Times 2 and 3 did not differ by maltreatment status, age, gender, or internalizing

psychopathology (*p*'s >.25), but had greater symptoms of externalizing psychopathology

(*p*=.04). Parents provided informed consent, and adolescents provided assent (or informed

consent for those ≥18 years of age). Experimental procedures were approved by the

Institutional Review Boards of Boston Children's Hospital and Harvard University.

The analytic sample for the current study includes the 51 adolescents who were

assessed at Time 2 (Time 2; aged 13-20; M=16.96; SD=1.51) and Time 3 (aged 15-22;

M=18.92; SD=1.50), 18 with exposure to serious physical or sexual abuse. Sample

demographics, by maltreatment status, are presented in Table 1. Maltreated adolescents and

controls were matched on age, gender, race, IQ and socioeconomic status.

Measures

     Childhood Maltreatment was assessed using the Childhood Trauma Questionnaire, a 28-

item self-report measure (CTQ; 46), and the Childhood Experiences of Care and Abuse

(CECA; 47), a retrospective, interviewer-led measured administered by trained research

assistants. The CTQ assesses frequency of emotional, sexual and physical abuse and has

excellent psychometric properties, including test-retest reliability and convergent validity

with a structured trauma interview (Bernstein et al., 1997). The CECA assesses numerous

aspects of caregiving experiences, including maltreatment, and has high interrater reliability

and agreement between reporters (Bifulco, Brown, Lillie, & Jarvis, 1997; Brown, Craig,

Harris, Handley, & Harvey, 2007). Participants were classified as maltreated if they reported

physical or sexual abuse on the CECA, or scored above a validated threshold on the physical

and sexual abuse subscales of the CTQ (Walker et al., 1999). Childhood maltreatment was

treated as both a dichotomous (maltreated/control) and a continuous measure (CTQ Abuse

Subscale, log-transformed to improve normality) in our analyses.

     Psychopathology was measured using the Diagnostic Interview Schedule for Children

Version-IV (DISC-IV; (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) to assess

past-year internalizing (major depressive disorder [MDD], generalized anxiety disorder

[GAD]) and externalizing (conduct disorder [CD], oppositional defiant disorder [ODD],

attentional-deficit hyperactivity disorder [ADHD]) symptoms and diagnoses at Time 2 and 3.

The DISC-IV is a highly structured interview that assesses numerous psychiatric disorders, and was conducted by trained research assistants. For participants over the age of 18, we administered the Young Adult version of the DISC, which is appropriate for those up to 24 years. Symptoms of ODD and CD were combined to form an 'anti-social behavior' composite by dividing symptoms of each disorder by the number of total possible symptoms, and then summing them.

MRI Acquisition

Structural magnetic resonance images were acquired using a 3T Siemens Trio scanner located at the Harvard Center for Brain Science. Participants were positioned in a 32-channel head coil and T1-weighted volumes were acquired using a multi-echo magnetization-prepared rapid acquisition with gradient echo sequence (TR=2530ms, TE=1640-7040ms, flip angle=7 degrees, field of view=220 mm^2, 176 slices, voxel-size=1 mm^3). To reduce motion-related artifacts, a navigator echo was used prior to scan acquisition, which compared slices to this echo online and permitted up to 20% of slices to be reacquired.

Image Processing

T1-weighted scans were processed using the Freesurfer analysis pipeline (http://surfer.nmr.mgh.harvard.edu), which performs automated cortical reconstruction and volumetric segmentation of the human brain (Fischl, 2012; Fischl et al., 2002; Fischl & Dale, 2000). Gray/white and gray/cerebrospinal fluid (CSF) boundaries were constructed using spatial intensity gradients across tissue classes. Segmentation of tissue types was visually inspected for each participant, and manual edits were made as necessary to improve the placing of gray/white and gray/CSF borders. After tissue reconstruction, the cortex was

parcellated based on the structure of gyri and sulci (Desikan et al., 2006). Freesurfer

morphometric procedures have been validated against manual measurement (Kuperberg et

al., 2003) and histological analysis (Rosas et al., 2002), have demonstrated good test-retest

reliability across scanner manufacturers and field strengths (Han et al., 2006) and have been

widely used in prior samples of adolescents (Kühn et al., 2014; Schilling et al., 2013).

Neural Regions of Interest (ROIs)

Cortical thickness and subcortical volume was estimated for the following regions

defined by the Desikan-Killiany atlas in Freesurfer (Desikan et al., 2006), and chosen based

on a prior meta-analysis of neural structures sensitive to maltreatment (see Gold et al.,

manuscript in preparation): vmPFC (average of left and right orbitofrontal regions); left and

right lateral OFC (average of lateral OFC, frontal pole and pars orbitalis); left and right

inferior frontal gyrus (average of pars opercularis and pars triangularis); anterior cingulate

cortex (average of left and right rostral and caudal anterior cingulate); posterior cingulate

cortex (average of left and right posterior cingulate and isthmus cingulate); left and right

middle frontal gyrus (average of rostral middle frontal and caudal middle frontal); medial

superior frontal gyrus (average of left and right superior frontal); left and right insula cortex;

left and right temporal pole; left and right parahippocampal gyrus; left and right inferior,

middle and superior temporal gyri; left and right amygdala; left and right hippocampus.

Statistical Analyses

Mediation analyses were performed using standard procedures based on ordinary

least squares regression (Baron & Kenny, 1986). First, we examined the total effect of

childhood maltreatment on psychiatric symptoms and diagnoses (c path). Next, we examined

associations between childhood maltreatment and neural structure across 24 ROIs (*a* path). False-discovery rate (FDR) correction was applied to reduce Type 1 error (p < .05). Next, we examined associations between cortical thickness and psychopathology at Time 3 (*b* path). For this stage, we only focused on ROIs that were significantly associated with maltreatment (significant *a* path), and corrected for multiple comparisons. Next, if *a, b* and *c* paths were significant, we tested the indirect effects of maltreatment on psychopathology through neural structure using the *sgmediation* program in Stata 13.0 (StataCorp, College Station, TX). Boot-strapped, bias-corrected confidence intervals (CIs) were estimated (5000 resamples) for the indirect effect, which are appropriate for small samples and non-normality in the standard errors of indirect effects (Preacher & Hayes, 2008). 95% CIs that exclude zero indicates a significantly mediated effect. Finally, we conducted analyses to test whether neural structure mediated the association between maltreatment and *change* in psychopathology between Times 2 and 3. Time 2 psychopathology was entered as a covariate in all prior mediation analyses with a significant indirect effect. All analyses controlled for age and gender, and those predicting cortical thickness additionally controlled for parent education, given its known associations with neural structure (Noble, Houston, Kan, & Sowell, 2012).

<div align="center">**Results**</div>

Childhood Maltreatment and Psychopathology

Maltreated adolescents reported significantly greater symptoms of ASB (β=.19, *p*=.01), MDD (β=2.71, *p*=.04), and PTSD (β=1.09, *p*<.001) at Time 3, adjusting for age and gender. No association was observed between maltreatment and GAD (β=1.06, *p*=.16). At follow-up, maltreated adolescents were marginally more likely to have a diagnosis of GAD

(χ^2=3.82, p=.05) and MDD (χ^2=3.26, p=.07). However, no differences in diagnoses were found for ODD, CD, or PTSD. These lack of differences were likely due to overall low rates of diagnoses in our sample (see Table 1), and thus subsequent analyses focused on symptoms of psychiatric disorders reported in the diagnostic structured interview.

Childhood Maltreatment and Neural Structure

We examined group differences in brain structure among adolescents exposed to childhood maltreatment, compared to controls. Regression coefficients, standard errors and significance values for all cortical and subcortical regions are presented in Table 2. After FDR-correction, reduced cortical thickness was observed for maltreated adolescents in vmPFC, right inferior frontal gyrus, left and right parahippocampal gyri, right inferior temporal gyrus, and right middle temporal gyrus. No association was found between maltreatment and volume of the amygdala and hippocampus.

Cortical Thickness and Psychopathology

Next, we examined associations between neural structures associated with maltreatment and psychopathology (Table 3). In addition to the covariates described above, analyses controlled for time in months between scanning and follow-up, and significance values were FDR corrected. Thickness of the left and right parahippocampal gyrus predicted ASB symptoms, and thickness of the middle temporal gyrus predicted GAD symptoms.

Mediation Analyses

Finally, for associations with significant *a*, *b* and *c* paths, we tested indirect effects of maltreatment on psychopathology through neural structure. Thickness of the left

parahippocampal gyrus significantly mediated the association of maltreatment and ASB symptoms (CI: .01, .18) (34% of the total effect was mediated). In contrast, no mediation of the right parahippocampal gyrus and ASB was observed (CI: -.02, .15).

The above mediation analyses were performed without controls in place for Time 2 symptoms of psychopathology. Thus, these mediations may simply reflect existing associations between cortical thickness measured at Time 2 and symptoms of psychopathology at Time 2. To address this possibility, we assessed whether cortical thickness mediated the association between childhood maltreatment and *change* in psychopathology across adolescence by including a control for symptoms of psychopathology at Time 2. After including this control in every path, the indirect effect of childhood maltreatment on ASB through left parahippocampal gyrus thickness remained significant (CI: .00, .16) (see Figure 1).

Discussion

Childhood maltreatment is strongly associated with risk for psychopathology (McLaughlin et al., 2012), and prior cross-sectional research has been limited by an inability to disentangle the associations of maltreatment and psychopathology on neural structure. Here, we provide evidence for a neural mechanism linking exposure to childhood maltreatment with psychopathology. Specifically, we find that childhood maltreatment is associated with reduced cortical thickness in numerous regions of lateral and medial PFC and temporal cortex. Reduced thickness of the parahippocampal gyrus is prospectively associated with increased vulnerability to anti-social behavior two years later.

Maltreatment-related abnormalities in the vmPFC observed here are consistent with prior studies of maltreated children and adolescents (De Brito et al., 2013; Edmiston et al., 2011; Hanson et al., 2010; Kelly et al., 2013; Morey et al., 2015). The vmPFC is engaged

during fear extinction and the suppression of negative emotion (Milad & Quirk, 2012), and is thought to modulate and inhibit the amygdala during these processes (Milad & Quirk, 2012; Phelps et al., 2004). Although associations between vmPFC thickness and GAD did not survive correction for multiple comparisons, prior studies have linked vmPFC structure to GAD in both healthy adolescents (Ducharme et al., 2013) and clinical samples (Strawn et al., 2014). It is possible that this reflects a lag in typical age-related synaptic pruning, and that maltreated adolescents may be less able to recruit the vmPFC in the service of emotional control, resulting in greater anxiety symptoms. Further research is needed to understand the role of vmPFC structure and function as a neurobiological mechanism linking childhood maltreatment with later psychopathology.

Additionally, childhood maltreatment was associated with reduced cortical thickness in the temporal lobe, specifically the middle temporal gyrus and parahippocampal regions. Notably, our analyses revealed that thickness of the left parahippocampal gyrus mediated the association of childhood maltreatment and ASB symptoms, with and without controlling for baseline symptoms. A recent meta-analysis of whole-brain, voxel-based morphometry studies identified maltreatment-related reductions in parahippocampal gyrus volume across multiple studies (Lim et al., 2014), a finding corroborated by subsequent research (Van Dam et al., 2014). Moreover, changes in the structure of the medial temporal lobe, including the parahippocampal gyrus, have been observed in both cross-sectional and prospective studies of early adversity (Gianaros et al., 2007; Hanson et al., 2015). In sum, our findings reflect the impact of maltreatment on cortico-limbic areas implicated previously in behavioral and emotional control functions. The medial temporal lobe and interconnected limbic structures are involved in the pathophysiology of both internalizing and externalizing psychopathology, including ODD/CD (Hoptman, 2003), ASB (Ermer, Cope, Nyalakanti, Calhoun, & Kiehl,

2013) and depression (Bora, Fornito, Pantelis, & Yücel, 2012), potentially because they reflect underlying deficits in emotion processing or regulation that are relevant to these disorders.

Notably, we found no associations between childhood maltreatment and volume of the amygdala and hippocampus. Altered hippocampal volume has been observed in prior samples of maltreated children and adolescents (Edmiston et al., 2011; Gorka et al., 2014; Hanson et al., 2015), although others have found no association (De Brito et al., 2013; Woon & Hedges, 2008). Maltreatment-related differences in amygdala structure remain decidedly mixed (Bick & Nelson, 2015), in spite of wide support in the rodent literature (McEwen, 2012). These divergent findings may be accounted for by differences in developmental timing of maltreatment, co-occurrence of psychopathology, age at scan or MRI analysis type (whole-brain versus region-based approach), explored in prior studies. For example, a recent study found peak sensitivity of exposure to maltreatment on amygdala volume in pre-adolescent children, ages 10-11 years (Pechtel, Lyons-Ruth, Anderson, & Teicher, 2014).

This study had notable strengths, including its longitudinal design, the use of a structured clinical interview to assess symptoms and diagnoses of psychiatric disorders, and the use of cortical thickness to index neural structure, complementing and extending previous volumetric approaches. Nevertheless, several methodological limitations should be noted. First, our sample size was small, which is important when considering the null findings in regions that have been previously identified as sensitive to maltreatment. Second, rates of psychiatric diagnosis in our sample were quite low, restricting our analyses to focus on symptoms of psychopathology instead of rates of diagnosis. It may be that our use of community recruitment techniques resulted in us identifying a particularly resilient sample. Third, future research will be needed to assess whether structural markers can predict the

onset of a psychiatric diagnosis. Fourth, our use of a whole-brain ROI approach required stringent multiple comparison correction, and therefore only the most robust associations may have emerged in our analysis. Finally, future research should focus more specifically on emotional abuse and neglect, other forms of childhood maltreatment that are significantly associated with risk for psychopathology and neural structure (Choi, Jeong, Rohan, Polcari, & Teicher, 2009; Sheridan, Fox, Zeanah, McLaughlin, & Nelson, 2012; Teicher, Samson, Polcari, & McGreenery, 2006). Examining the differential impact of multiple forms of childhood maltreatment, as well as variations in timing and chronicity of exposure, represent important goals for future research.

Adolescence is a uniquely vulnerable window for the onset of internalizing and externalizing psychopathology (Giedd et al., 2008), and childhood maltreatment is a known risk factor for myriad psychiatric disorders across the lifespan (McLaughlin et al., 2012). Our findings suggest that structural changes within the medial temporal lobe may be one mechanism underlying this association. Recent theoretical approaches have highlighted the need to identify intermediate neural phenotypes that predict risk for later psychopathology, raising the possibility of targeted intervention approaches for those most at-risk (McCrory & Viding, 2015). The present study contributes to this objective by suggesting that this latent vulnerability in adolescence may be indexed by measures of neural structure.

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Tables

Table 1. Distribution of key study variables, by maltreatment (N=51)

	Maltreated (n=18)		Controls (n=33)		χ^2	p-value
	%	(n)	%	(n)		
Female	61.11	11	60.61	20	0.00	.97
Race/Ethnicity					9.56	.09
White	11.11	2	36.36	12		
Black	38.89	7	21.21	7		
Hispanic/Latino	11.11	2	12.12	4		
Asian	0.00	0	12.12	4		
Middle Eastern	0.00	0	3.03	1		
Other/Biracial	38.89	7	15.15	5		
Parent Educational					2.79	.43
High School or Less	22.22	4	15.15	5		
Some College	22.22	4	18.18	6		
College Degree	22.22	4	45.45	15		
Graduate School	33.33	6	21.21	7		
Internalizing Disorder Dx						
Generalized Anxiety	11.11	2	0.00	0	3.82	.05
Major Depression	16.67	3	3.03	1	3.26	.07
PTSD	5.56	1	0.00	0	1.87	.17
Externalizing Disorder Dx[2]						
ODD	0.00	0	3.03	1	.55	.46
Conduct Disorder	0.00	0	0.00	0	0.00	.99
	Mean	(SD)	Mean	(SD)	t-value	p-value
Age at Time 3 (years)	18.63	(1.62)	19.08	(1.43)	1.02	.31
CTQ Abuse Subscale*	32.39	(9.95)	16.97	(2.31)	8.31	<.001
IQ (WASI total score)	100.11	(16.89)	99.36	(13.88)	0.17	.87
Internalizing Disorder Sx[1]						
Generalized Anxiety	4.66	(2.00)	3.58	(2.73)	1.49	.14
Major Depression	8.61	(4.02)	6.03	(4.53)	2.02	.05
PTSD	3.44	(3.91)	.64	(1.82)	3.50	<.001
Externalizing Disorder Sx[2]						
ODD	5.44	(2.04)	3.36	(2.55)	2.98	<.01
Conduct Disorder	1.64	(1.61)	0.83	(0.78)	2.42	.02

Note: all p-values refer to 2-sided tests; diagnoses of mental disorders refer to past-year diagnoses
* CTQ measured at Time 1
Abbreviations: Dx = diagnosis; Sx = symptoms; CTQ = Childhood Trauma Questionnaire; ODD = oppositional defiant disorder; CD = conduct disorder; PTSD = post-traumatic stress disorder

Table 2. Coefficients summarizing associations between maltreatment and neural structure

	Maltreatment Exposure (n=18)		
	β	S.E.	*p*-value
Cortical Thickness (mm)			
Ventromedial PFC	-.12	.03	.001*
Left lateral OFC	-.05	.05	.040
Right lateral OFC	-.10	.05	.068
Left inferior frontal gyrus	-.06	.04	.083
Right inferior frontal gyrus	-.12	.04	.002*
Anterior cingulate cortex	-.02	.05	.712
Posterior cingulate cortex	-.01	.04	.822
Left middle frontal gyrus	-.05	.03	.161
Right middle frontal gyrus	-.05	.03	.165
Medial superior frontal gyrus	-.08	.04	.039
Left insular cortex	-.04	.05	.412
Right insular cortex	.03	.04	.475
Left temporal pole	-.20	.08	.020
Right temporal pole	.00	.11	.951
Left parahippocampal gyrus	-.24	.08	.005*
Right parahippocampal gyrus	-.24	.07	.001*
Left inferior temporal gyrus	-.09	.04	.019
Right inferior temporal gyrus	-.09	.03	.004*
Left middle temporal gyrus	-.02	.04	.682
Right middle temporal gyrus	-.11	.04	.008*
Left superior temporal gyrus	-.05	.04	.263
Right superior temporal gyrus	-.08	.04	.069
Subcortical Volume (mm^3)			
Amygdala	-25.58	55.44	.647
Hippocampus	-125.29	45.31	.374

Note: Analyses adjust for age, gender, total intracranial volume and parent education
* = significant after FDR-correction

Table 3. Associations between maltreatment-sensitive ROIs and symptoms of psychopathology

	GAD			MDD			PTSD			Anti-social behavior		
	β	S.E.	p-value	β	S.E.	p-value	β	S.E.	p-value	β	S.E.	p-value
VmPFC	5.83	2.84	.046	1.99	5.13	.700	-1.59	1.22	.199	-.29	.27	.298
Right IFG	3.89	2.82	.174	4.22	2.94	.397	-1.74	1.17	.145	.10	.26	.703
Right ITG	4.67	3.15	.145	3.71	5.55	.507	-1.16	1.34	.390	.13	.30	.662
Right MTG	7.79	2.49	.003*	8.57	4.58	.068	-.46	1.15	.692	.29	.25	.252
Left PHG	-.60	1.26	.636	-4.87	2.07	.023	-1.13	.50	.029	-.35	.10	.001*
Right PHG	1.62	1.51	.289	-3.63	2.59	.168	-1.02	.62	.108	-.33	.12	.016*

*= Significant after FDR-correction within each psychopathology scale; GAD = Generalized Anxiety Disorder; MDD = Major Depressive Disorder; PTSD = Post-Traumatic Stress Disorder.

Figures

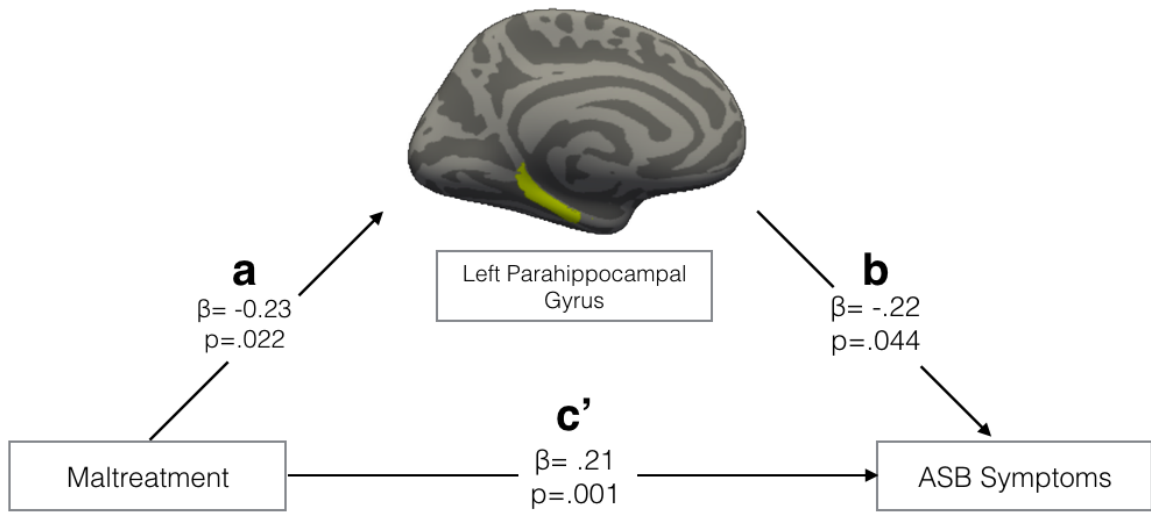Figure 1. Variations in left parahippocampal gyrus thickness mediate the association between childhood maltreatment and anti-social behavior (ASB) at Time 3. The significance of the indirect effect was tested using a bootstrapping approach and controlled for age at scan, gender, parent education, Time 2 ASB symptoms, and time between scan and follow-up. Note: c' = direct effect of maltreatment on ASB.

STUDY 3:

Fear Conditioning, Inhibitory Control, and Externalizing Psychopathology in Maltreated Adolescents

Abstract

Deficits in inhibitory control are one putative mechanism underlying the association between childhood maltreatment and externalizing psychopathology. Here, we test whether inhibitory control of threat stimuli differs as a function of maltreatment history. Forty-eight adolescents (29 female; mean age = 18.92; SD = 1.54 years), 17 with exposure to physical or sexual abuse, completed a Go/No-Go (GNG) task. The threat salience of the No-Go stimuli was previously manipulated using an associative fear-conditioning paradigm. We hypothesized that previously conditioned No-Go stimuli would result in impaired inhibitory performance, and that this effect would be strongest for adolescents previously exposed to maltreatment. Finally, we explored whether inhibitory control to the conditioned stimulus (CS+) or unconditioned stimulus (CS-) would predict externalizing psychopathology. We hypothesized that inhibitory control to the CS- would predict attention-deficit hyperactivity disorder (ADHD) symptoms and inhibitory control to the CS+ would predict antisocial behavior (ASB) symptoms. Analyses revealed no main effect of stimulus (CS+/CS-) on inhibitory control, nor an interaction of stimulus with maltreatment. However, results showed that maltreatment was associated with global impairments in inhibitory control compared to controls, and that threat-related inhibitory control was associated with ASB symptoms in maltreated adolescents only. Further research is needed to examine the conditions for which learned threat compromises cognitive functioning in maltreated youth.

Introduction

Childhood maltreatment is a serious public health problem, affecting over six million children in the United States per year (Institute of Medicine, 2014). A history of maltreatment is considered one of the strongest risk factors for problem behaviors in adolescence and early adulthood (Lansford et al., 2002), predicting juvenile delinquency (Lansford et al., 2007), substance abuse (Kunitz, Levy, McCloskey, & Gabriel, 1998), intimate partner violence (Stith, Smith, Penn, Ward, & Tritt, 2004), and multiple externalizing disorders (McLaughlin, Green, Gruber, Zaslavsky, & Kessler, 2012).

These clinical sequelae may be mediated by a disruption of cognitive control processes and their associated neural substrates. Inhibitory control, one such process, refers to the ability to suppress or withhold actions that are behaviorally or contextually inappropriate (Munakata et al., 2011). Executive functions, including inhibitory control, are negatively impacted by childhood maltreatment (Beers & De Bellis, 2002; DePrince, Weinzierl, & Combs, 2009; Mezzacappa, Kindlon, & Earls, 2001; Navalta, Polcari, Webster, Boghossian, & Teicher, 2006). Primate models have shown that exposure to excessive quantities of the stress hormone cortisol contributes to lasting deficits in response inhibition, likely by disrupting prefrontal cortex function (Lyons, Lopez, Yang, & Schatzberg, 2000). Inhibitory control allows individuals to modulate their behavior and regulate impulse on executing behavior, and is therefore one candidate mechanism linking childhood maltreatment with later externalizing psychopathology.

In the current study, we investigate maltreated adolescents' inhibitory control in the context of threat. Considerable evidence suggests that victims of maltreatment display hyperresponsiveness to threat cues. Previous research indicates a selective vigilance to angry faces in maltreated children, which is in turn associated with heightened risk for

psychopathology (Briggs-Gowan et al., 2015; Pollak, 2008). Electrophysiological and functional neuroimaging studies also indicate heightened neural response to threatening facial displays (Curtis & Cicchetti, 2013; McCrory et al., 2011; Pollak, Cicchetti, Klorman, & Brumaghim, 1997) and stimuli depicting violence (McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015). Given the disproportionate attentional and cognitive resources consumed by threat processing in maltreated children, it is likely that threat stimuli presented during cognitive tasks will interfere with task performance (McCrory & Viding, 2015). Indeed, studies using the emotional Stroop paradigm, which assesses interference effects of threat-related words (e.g. 'rape') on a concurrent non-emotional task, have found impaired performance for high-threat words in those with maltreatment-related post-traumatic stress disorder (PTSD), relative to controls (Cassiday, McNally, & Zeitlin, 1992; Foa, Feske, Murdock, Kozak, & McCarthy, 1991).

Little is known, however, about how threat cues impinge on other cognitive processes, including inhibitory control. The only existing research on this topic has been conducted in non-maltreated samples. For example, Pessoa, Padmala, Kenzer, & Bauer (2012) explored the effect of high-threat stimuli (those previously paired with a mild shock) on inhibitory performance in a stop-signal task. Inhibitory performance was impaired for the high-threat stimulus compared to a neutral stimulus. Similarly, Verbruggen & Houwer (2007) found that inhibition to high-arousal stimuli (both positive and negative) is impaired compared to neutral stimuli. These results are interpreted as reflecting interference effects of emotional stimuli on the voluntary allocation of attention (Pessoa, 2008, 2009). However, no studies have examined whether individuals with histories of learned attentional bias to threat, such as those exposed to maltreatment, show different patterns of inhibitory control for threatening stimuli than typically developing controls.

Here, we also investigate the association between inhibitory control and externalizing disorders. Attention-deficit hyperactivity disorder (ADHD) has been conventionally understood as a generalized impulsivity disorder (Barkley, 1997), and studies show consistently that ADHD patients show reduced performance on neurocognitive tasks measuring inhibitory control (Lijffijt, Leon, Verbaten, & van Engeland, 2005; Schachar, Mota, Logan, Tannock, & Klim, 2000; Trommer, Hoeppner, Lorber, & Armstrong, 1988). Thus, we expect general inhibitory performance to predict ADHD symptoms. In contrast, conduct disorder (CD) and oppositional defiant disorder (ODD) are impulse control disorders posited to arise from abnormal processing of affective information, leading to aggressive behaviors (Blair, 2001). For example, social information processing theories suggest maltreated individuals develop inadequate coding of social cues, resulting in a hypervigilance to social threat (Dodge & Pettit, 2003). In turn, this hypervigilance to hostile cues (and hypovigilance to non-hostile cues) contributes to later anti-social behavior problems (Dodge et al., 1995). Thus, we expect inhibitory control *in the context of threat* to predict anti-social behavior symptoms.

The Present Study

In the present study, inhibitory control was assessed using a Go/No-Go (GNG) task, an experimental paradigm used extensively in laboratory settings. In a standard GNG task, subjects make a speeded response (e.g. a button press) when they observe one class of 'Go' stimuli, but withhold a response when they view another class of infrequently presented 'No-Go' stimuli. As Go stimuli occur much more frequently than No-Go stimuli, they build a motorically prepotent response that must be inhibited in order to successfully withhold a response. We manipulated the emotional salience of No-Go stimuli using an

associative fear-conditioning paradigm, where an aversive unconditioned stimulus (UCS) is paired with a conditioned stimulus (CS+) but not an unconditioned stimulus (CS-). This will allow comparisons of inhibitory performance for No-Go stimuli that have prior threat salience (the CS+) compared with those that do not (the CS-).

We predicted that previously conditioned No-Go stimuli (CS+) would result in impaired inhibitory performance as predicted by prior literature (Hypothesis 1), and that this effect would be strongest for adolescents previously exposed to maltreatment (Hypothesis 2). Finally, we explored whether inhibitory control to the CS- or CS+ would predict externalizing psychopathology. We anticipated that generalized, non-threat related inhibition, as measured by inhibitory control to the CS-, would predict ADHD symptoms (Hypothesis 3). However, we also hypothesized that disruptions to inhibition in the context of threat, as measured by inhibitory control to the CS+, would predict antisocial behavior symptoms (Hypothesis 4).

Methods

Sample

Forty-eight adolescents (29 female; mean age = 18.92; SD = 1.54 years) were recruited as part of an ongoing longitudinal investigation of childhood adversity and adolescent development (see McLaughlin, Sheridan, Alves, & Mendes, 2014). Seventeen (35%) subjects reported exposure to serious physical or sexual abuse. Subjects initially responded to flyers and advertisements located in schools, after-school programs and medical clinics in Boston and Cambridge, MA. This community sample was diverse with respect to race/ethnicity, and parent education: 29.2% White ($n=14$), 27.1% Black ($n=13$), 12.5% Hispanic/Latino ($n=6$), 6.3% Asian ($n=3$), 2.1% Middle Eastern ($n=1$), and 23%

Biracial/Other (*n*=11). Thirty-five percent of the sample (*n*=18) had parents with an associate's degree or high school diploma/GED only. Informed consent was provided by a parent/guardian, and adolescents provided assent (or informed consent for those ≥18 years of age). Equipment malfunctions resulted in the loss of electrodermal activity (EDA) data for two participants. One participant discontinued the fear conditioning task during the session, and was therefore omitted from subsequent analyses. An additional two participants were excluded from the Go/No-Go analysis due to very low accuracy.

Measures

Childhood Maltreatment was assessed using the Childhood Trauma Questionnaire, a 28-item self-report measure (CTQ; Bernstein, Ahluvalia, Pogge, & Handelsman, 1997), and the Childhood Experiences of Care and Abuse interview (CECA; Bifulco, Brown, & Harris, 1994). The CTQ retrospectively assesses childhood abuse experiences in adolescents and adults, and has good convergent and discriminant validity (Bernstein *et al*, 1997). The CECA is a semi-structured interview led by trained research assistants, and measures numerous aspects of caregiving experiences, including neglect, physical and sexual abuse and exposure to domestic violence. Interrater reliability of the CECA is excellent (Bifulco, Brown, Lillie, & Jarvis, 1997). Participants were classified as maltreated if they reported exposure to physical or sexual abuse on the CECA, or scored above a validated threshold on the CTQ (Walker et al., 1999).

Externalizing Psychopathology. The Diagnostic Interview Schedule for Children Version-IV (DISC-IV; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) was used to assess past year symptoms of externalizing disorders (oppositional defiant disorder, conduct disorder, and attention-deficit hyperactivity disorder). The DISC-IV is a highly structured interview that was conducted by trained research assistants. For participants over the age of

81

18, we administered the Young Adult version of the DISC, which is appropriate for those up to 24 years. Past year symptom count was used to assess ADHD. Symptoms of ODD and CD were combined to form an anti-social behavior (ASB) composite by dividing symptoms of each disorder by the number of total possible symptoms, and then summing them.

Parental Education. The highest level of parental education was measured as the highest level of education attained by either parent. It was recorded as one of four categories (less than high school=1; some college=2; college=3; or graduate degree=4) and entered into models as a continuous variable.

Physiological Measures. Electrodermal activity (EDA) was measured continuously during the fear-conditioning task using a galvanic skin response module connected to a MP150 amplifier (Biopac Systems, Goleta, CA). Two Ag/AgCl electrodes filled with isotonic gel were attached to the distal phalanges of the index and middle fingers of the left hand. EDA was sampled at 250Hz and processed using AcqKnowledge 4.0 software (Biopac Systems, Galeta, CA). SCR responses were thresholded at 0.02 microsiemens (μs), and were calculated as the difference in amplitude from a 1-second pre-CS baseline to peak response in the 0.5-5 seconds after stimulus onset. We included zero responses in our analysis, thereby providing an estimate of mean response magnitude (Dawson, Schell, & Filion, 2000). A log-transformation was applied to SCR data (plus a constant) to improve normality for parametric analyses.

Design and Procedure

Fear Conditioning Task. Subjects completed a differential fear conditioning task (Shechner et al., 2015), where an aversive unconditioned stimulus (UCS) is paired with a

conditioned stimulus (CS+) but not an unconditioned stimulus (CS-). Images of a blue and yellow bell served as the CS+ and CS- and were counterbalanced across participants. The UCS was a 1-second image of a red bell, paired with an aversive 100dB buzz delivered through external speakers. The task involved four phases: preacquisition, acquisition, extinction, and reinstatement (Figure 1). Within each phase, the CS+ and CS- were presented sequentially in one of two counterbalanced orders. The CS duration was 7-8 seconds, and the inter-trial interval (ITI) ranged from 13-17 seconds (mean = 15 seconds). During preacquisition (Phase 1), the CS+ and CS- were shown in the absence of the UCS (4 trials each). During acquisition (Phase 2), the CS+ was followed by the UCS according to an 80% reinforcement schedule (10 trials each). During extinction (Phase 3), the CS+ and CS- were shown in the absence of the UCS (8 trials each). Finally, during reinstatement (Phase 4), the CS+ was once again paired with the UCS (10 trials each). After each phase, subjects rated how unpleasant and how fearful they were of the CS+ and CS- on a 9-point Likert scale ranging from 0 ("not at all"), to 9 ("extremely"). These ratings were summed to create a self-reported fear composite for each CS in each phase.

Go/No-Go Task. Immediately following fear conditioning, subjects completed a Go/No-Go (GNG) task. Subjects were required to rapidly respond, by pressing the spacebar, to one class of stimuli ("Go" stimuli), while inhibiting their response to specific target stimuli ("No-Go" stimuli). The No-Go stimuli were blue and yellow bells (CS+ and the CS-) from the fear conditioning portion of the experiment. The Go stimuli were six objects that were comparable to these bells in terms of complexity, size, and color; each object appeared in blue and yellow (Figure 2A). Target and non-target stimuli appeared individually on the computer screen for 500ms, followed by a fixation cross (jittered ITI range=1500-3500ms) (Figure 2B). Subjects completed 288 trials, separated across three

blocks. A ratio of 75% Go to 25% No-Go trials was maintained. No-Go trials were preceded by two, three and four Go trials. All stimuli were presented on a 19" color monitor, through a task programmed in E-Prime (Version 2.0, Psychology Software Tools, Pittsburgh, PA).

Statistical Analyses

Based on evidence of fear learning differences between early and late acquisition and extinction trials (Lang et al., 2009; McLaughlin, Sheridan, et al., 2015), average SCR was computed for six phases: pre-acquisition, early conditioning (trials 1-10); late conditioning (trials 11-20); early extinction (trials 1-8); late extinction (trials 9-16); and reinstatement. Analysis of psychophysiological and GNG data was performed using paired t-tests, analysis of variance (ANOVA) and analysis of covariance (ANCOVA), where appropriate. First, we evaluated our fear conditioning procedure by assessing whether SCR response and self-reported fear differed by Stimulus (CS+ vs. CS-) and Phase. Next, we assessed whether fear conditioning differed by Maltreatment by testing a two-way interaction between Maltreatment and Stimulus, and a three-way interaction between Maltreatment, Stimulus, and Phase.

For GNG analyses, we first examined the effect of Stimulus (CS+ vs. CS-) on performance across all individuals using paired t-tests. Outliers were removed if they fell 2.5 standard deviations away from the mean. Next, we explored whether GNG performance differed by maltreatment exposure using ANOVA. Finally, we tested whether inhibitory control for both the CS+ and CS- predicted externalizing psychopathology (ADHD and ASB) using ordinary least squares (OLS) regression. Regression analyses controlled for age, gender and parent education to account for potential confounds.

Results

Sample Demographics and Psychopathology

Table 1 displays sociodemographic and questionnaire data for the sample, by maltreatment. Groups did not differ on age, gender, race/ethnicity, or parent education. As expected, maltreated adolescents scored higher on the CTQ Abuse Subscale than controls. Regression analyses indicated that maltreated adolescents also reported greater ADHD ($\beta=3.14$; $p=.002$) and ASB ($\beta=.21$; $p=.004$) symptoms, controlling for age, gender and parent education.

Fear Conditioning

Fear conditioning in the whole sample was tested using a repeated-measures analysis of variance (ANOVA). Differences in SCR response were evaluated as a function of Stimulus (CS+, CS-) and Phase (Pre-acquisition, Early Acquisition, Late Acquisition, Early Extinction, Late Extinction, Reinstatement). Analyses revealed a main effect of Stimulus ($F_{1,44}= 6.06$; $p = .02$), with higher SCR responses to the CS+ compared to the CS, and a main effect of Phase ($F_{3.4,220}= 6.48$; $p < .001$), with higher SCR response during early acquisition, late acquisition and reinstatement trials. We also observed a Stimulus-by-Phase interaction ($F_{3.5,155.6}= 4.75$; $p = .002$), where significant differences between the CS+ and CS- emerged only during early acquisition trials ($t_{44} =3.06$, $p=.004$), late acquisition ($t_{44}=2.35$, $p=.024$) and reinstatement trials ($t_{44} =2.61$, $p=.012$) (see Figure 3). For self-reported fear, we similarly found an effect of Stimulus ($F_{1,46}= 157.38$; $p < .001$), Phase ($F_{3,44}= 86.05$; $p < .001$), and a Stimulus-by-Phase interaction ($F_{3,44}= 46.31$; $p < .001$). Post-hoc analyses revealed that significant differences in self-reported fear between the

CS+ and CS- occurred only in acquisition (t_{46} =12.96, p<.001), extinction (t_{46} =3.84, p<.001), and reinstatement trials (t_{46} =11.56, p<.001). These results are consistent with previous studies of fear learning (McLaughlin, Sheridan, et al., 2015) and indicate an acquired association of the CS+ and the UCS. Descriptive statistics for SCR and self-reported fear, by Phase, are presented in Tables 2 and 3.

Finally, we examined differences in fear conditioning, by exposure to childhood maltreatment. A repeated measures ANOVA, with Stimulus and Phase as within-subjects factors, and Maltreatment as a between-subjects factor, found no main effect of Maltreatment on SCR response, nor any interactions of Maltreatment with Stimulus or Phase (p's >.15). In contrast, analysis of self-reported fear revealed a three-way Stimulus-by-Phase-by-Maltreatment interaction ($F_{3,43}$= 3.02; p = .04). Post-hoc analyses suggest that this effect is driven by greater self-reported fear to the CS+ during acquisition trials for maltreated adolescents, compared to controls (t_{45} =2.60, p=.01).

Go/No-Go Performance

Behavioral results for Go and No-Go trials are summarized in Table 4. First, paired t-tests examined whether response inhibition to No-Go trials differed by stimulus (CS+ vs. CS-). Errors of commission (i.e. % erroneous presses to No-Go trials) served as the outcome of interest. Contrary to our hypothesis, we observed no significant differences in errors of commission (t_{45} =.47, p=.68) between the CS+ and CS-.

Next, we explored whether GNG performance differed by maltreatment exposure. Overall performance (i.e. errors of commission collapsed across both the CS+ and CS-) was worse for subjects exposed to maltreatment compared to controls (t_{44} =3.12, p=.003). A repeated measures ANOVA, with Stimuli (CS+, CS-) as a within-subjects factor, and Maltreatment (maltreated, controls) as a between-subjects factor, found no significant

Maltreatment-by-Stimuli interaction ($F_{1,44}$= .202; p .66). These findings did not change when controlling for parental education.

Go/No-Go Performance and Externalizing Psychopathology

Finally, we examined whether Go/No-Go performance was associated with externalizing psychopathology (ADHD and ASB symptoms), controlling for age, gender and parental education. In separate regression models, errors of commission for the CS- were unrelated to both ADHD (β=6.41; p=.195) and ASB (β=.30; p=.390), suggesting that general deficiencies in inhibitory control were unrelated to externalizing symptoms. However, errors of commission for the CS+, controlling for the CS-, predicted ASB symptoms (β=.84; p=.029, but not ADHD symptoms (β=5.98; p=.272). Thus, inhibitory control to threatening stimuli (controlling for overall inhibitory performance) predicted antisocial behavior. Moreover, there was a significant interaction between maltreatment and errors of commission for the CS+ in predicting ASB symptoms: the association between errors for the CS+ and ASB symptoms held only for maltreated (β=1.77; p=.006), but not control subjects (β=-.05; p=.922).

Discussion

To date, few studies have focused on proximal cognitive mechanisms underlying the association between childhood maltreatment and externalizing psychopathology. Here, in order to investigate interactions between maltreatment and threat processing, we adapted a widely used inhibitory control paradigm (the Go/No-Go task) to include a fear-conditioning component. The central hypothesis was that previously conditioned stimuli would impair inhibitory performance, and this effect would be strongest for adolescents

previously exposed to maltreatment. Additionally, we hypothesized that inhibitory control to threatening stimuli (the CS+) would predict ASB symptoms, whereas inhibitory control to non-threatening stimuli (the CS-) would predict ADHD symptoms.

Contrary to our predictions, we found no difference in inhibitory performance for the CS+ compared to the CS- (Hypothesis 1). These findings are discordant with those of Pessoa et al. (2012), who found that inhibitory control on a Stop Signal Task (SST) was impaired for stimuli that were previously paired with a mild shock. A number of possible explanations may account for this difference. First, it is possible that our threat manipulation (a loud sound paired with the CS+) was insufficiently potent to disrupt inhibition through attentional capture. However, we did find greater physiological reactivity and self-reported fear for the CS+ compared to the CS-, suggesting that our threat manipulation was effective. Second, the SST task used by Pessoa et al. (2012) and the GNG task used here tax slightly different inhibitory processes. Specifically, the SST requires subjects to cancel an already initiated response, whereas the GNG task requires a decision *not* to initiate a response. It remains to be seen whether future research manipulating No-Go salience can replicate existing findings.

Similarly, we did not observe an interaction between maltreatment and stimulus type (CS+/CS-) on GNG performance (Hypothesis 2). This is surprising, given existing evidence of emotion-modulated biases in attentional control in prior samples of maltreated youth (McCrory et al., 2011; Shackman, Shackman, & Pollak, 2007). It may be that that our use of bells as the CS+ and CS- were not as ecologically valid as angry faces, which are used extensively in developmental psychopathology research (e.g. McCrory et al., 2011, 2013; Pollak & Sinha, 2002; Shackman et al., 2007). Indeed, attentional capture to threatening facial displays is likely to carry specific survival value for maltreated youth, whereas our use

of bells as the CS+ and CS- represent *novel* learned threats. Future studies should therefore examine inhibitory control of stimuli that have prior threat salience, possible using facial displays of emotion. Notably, we also found no differential conditioning of the CS+ and CS- by maltreatment (as measured by SCR), which departs from a recent study using a similar conditioning paradigm (McLaughlin, Sheridan, et al., 2015). Thus, our null findings with respect to maltreatment/stimulus interactions may simply reflect a failure of differential fear conditioning to begin with.

Our findings did indicate that maltreated adolescents exhibited overall impairments in inhibitory control, as reflected by greater errors of commission on No-Go trials. Moreover, our findings were unchanged after controlling for parental education, suggesting the effects of maltreatment on inhibitory control were not driven by other related adversities. Prior studies have observed diminished inhibitory capacity arising from childhood maltreatment, including in diverse samples of early to mid adolescent males (Mezzacappa et al., 2001), and adult females (Navalta et al., 2006). This finding may align with global cognitive deficits in cognition previously observed in maltreated samples, such as in IQ (Koenen, Moffitt, Caspi, Taylor, & Purcell, 2003; Mills et al., 2011), abstract reasoning (Beers & De Bellis, 2002), working memory (Dunn et al., 2015) and reading ability (Perez & Widom, 1994).

Notably, we found that inhibitory control for the CS+, controlling for inhibitory control to the CS-, was associated with ASB symptoms, an effect that was driven by maltreated subjects only. In contrast, inhibitory control to the CS- was unrelated to both ADHD and ASB symptoms. These results may indicate that maltreated youth displaying anti-social behaviors are selectively impaired when cognitive tasks require the regulation of affect. Several studies have discriminated between adolescents with and without anti-social

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behavior tendencies using measures of executive function (Lynam & Henry, 2001; Séguin, Pihl, Harden, Tremblay, & Boulerice, 1995). We extend this finding to suggest that these differences may be most apparent under conditions of threat, and specifically in populations with histories of violence exposure. Future research should continue to disentangle the associations between hot (i.e. emotionally driven) and cold (i.e. emotionally neutral) aspects of executive functioning and their relationship to externalizing psychopathology.

Conclusions

Extensive evidence indicates that childhood maltreatment results in perturbations in threat processing (Jovanovic & Ressler, 2010; McCrory & Viding, 2015; Sheridan & McLaughlin, 2014) and cognitive functioning, including inhibitory control (Mezzacappa et al., 2001; Navalta et al., 2006). Here, we tested whether inhibitory control of threatening stimuli was moderated by maltreatment exposure. Although we found that childhood maltreatment was associated with overall impairments in inhibitory control, no interactions were found between maltreatment and threat salience. However, results showed that for maltreated adolescents, degree of inhibitory impairment to threat salient stimuli predicted anti-social behavior symptoms. Further research is needed to examine the conditions in which learned threat compromises cognitive functioning in maltreated youth.

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Tables

Table 1. Distribution of Demographic Variables, by Maltreatment (n=48)

	Maltreated (n=19)		Controls (n=32)			
	%	(*n*)	%	(*n*)	χ^2	*p*-value*
Female	57.9	11	56.3	18	0.20	.65
Race/Ethnicity					9.42	.09
White	10.5	2	37.5	12		
Black	31.6	6	21.9	7		
	21.1	4	6.25	2		
Hispanic/Latino						
Asian	15.8	3	0	0		
Middle East	5.3	1	0	0		
Other/Biracial	36.8	7	12.5	4		
Parent Education						
HS or Less	15.8	3	15.6	5	3.95	.27
Some College	26.3	5	15.6	5		
College	15.8	3	43.8	14		
Grad School	31.6	6	21.9	7		
	Mean ± SD		Mean ± SD		*t*-value	*p*-value
Age (years)	18.65 ± 1.65		19.07 ± 1.48		.92	.36
CTQ Abuse Subscale	.12 ± 10.43		16.79 ± 2.09		7.7	<.001

Note: all p-values refer to 2-sided tests

Table 2. Skin conductance response (SCR) during the fear-conditioning task, by maltreatment (n=46)

	Pre-Acquisition		Early Conditioning		Late Conditioning		Early Extinction		Late Extinction		Reacquisition	
	CS+	CS-	CS+	CS-	CS+	CS-	CS+	CS-	CS+	CS-	CS+	CS-
Sample	.04 (.10)	.01 (.04)	.12 (.17)	.04 (.09)	.09 (.19)	.03 (.06)	.03 (.10)	.03 (.08)	.02 (.10)	.05 (.12)	.10 (.17)	.04 (.09)
Maltreat.	.04 (.11)	.01 (.02)	.14 (.16)	.06 (.12)	.10 (.19)	.02 (.04)	.06 (.16)	.03 (.07)	.06 (.15)	.08 (.14)	.13 (.19)	.07 (.14)
Controls	.04 (.08)	.02 (.05)	.11 (.18)	.02 (.07)	.08 (.20)	.03 (.07)	.00 (.00)	.03 (.09)	.00 (.00)	.04 (.10)	.08 (.15)	.01 (.03)

Note: SCR values are log-transformed. Numbers in parentheses represent standard deviations

Table 3. Self-reported fear following each phase of the fear-conditioning task, by maltreatment (n=48)

	Pre-Acquisition		Conditioning		Extinction		Reacquisition	
	CS+	CS-	CS+	CS-	CS+	CS-	CS+	CS-
Total	2.7 (2.2)	2.4 (1.4)	11.4 (4.8)	2.8 (1.3)	5.1 (4.0)	3.0 (3.0)	11.8 (4.8)	2.9 (2.3)
Maltreated	3.2 (2.6)	3.0 (2.0)	13.9 (3.3)	2.9 (1.2)	6.3 (4.5)	3.8 (4.4)	14.4 (3.7)	2.6 (1.7)
Controls	2.4 (1.9)	2.0 (0.4)	9.9 (4.9)	2.7 (1.4)	4.2 (3.6)	2.5 (1.6)	10.3 (4.8)	3.1 (2.7)

Note: Subjects rated how unpleasant and how fearful they were of the CS+ and CS-; these ratings were summed to create a self-reported fear composite for each CS in each phase. Numbers in parentheses represent standard deviations

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Table 4. Behavioral Data for Go/No-Go Task, by Stimulus and Maltreatment (n=45)

	Total Sample (n=46)		Maltreatment (n=17)		Controls (n=29)	
	CS+	CS-	CS+	CS-	CS+	CS-
No-Go Trials:						
Errors of commission (%)	28.5 ± 11.6	27.7 ± 11.2	34.8 ± 9.5	33.2 ± 9.7	24.7 ± 11.2	24.5 ± 10.9
Reaction time for errors (ms)	360 ± 33	364 ± 34	356 ± 26	360 ± 30	363 ± 37	366 ± 37
Go Trials:						
Errors of omission (%)	2.4 ± 3.2		1.83 ± 2.4		2.8 ± 3.4	
Reaction time for hits (ms)	414 ± 45		395 ± 36		425 ± 46	

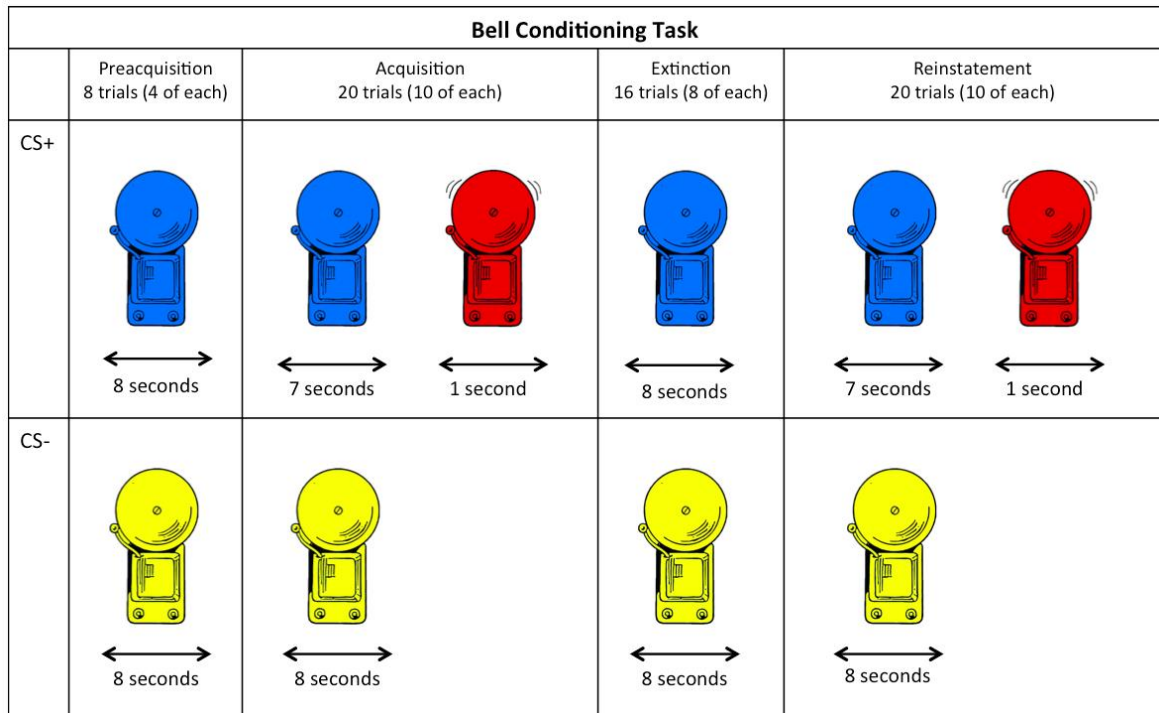Note: CS+ = Conditioned Stimulus; CS-= Unconditioned Stimulus

Figure 1. Depiction of the Preacquisition, Acquisition, Extinction and Reinstatement phases of the bell conditioning task. Note that the CS+ was counterbalanced across participants. CS=conditioned stimulus
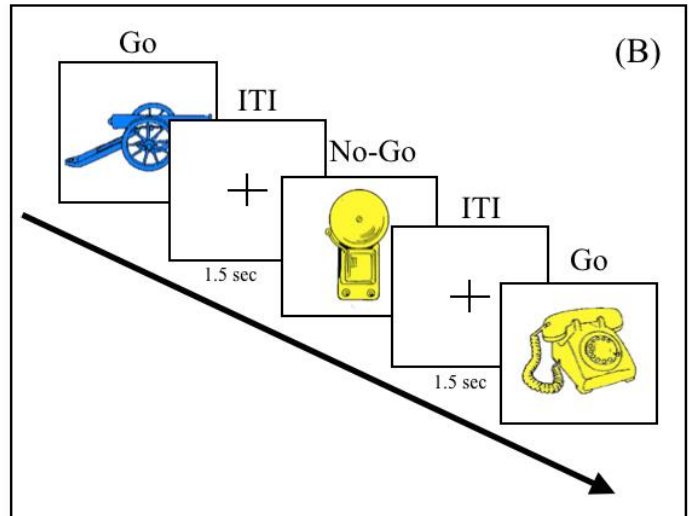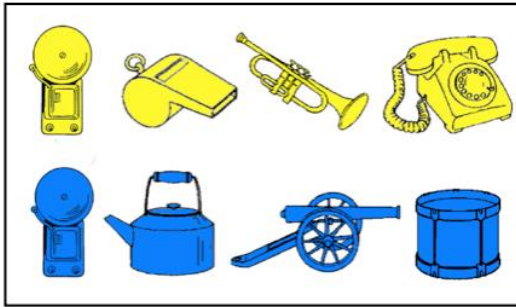
Figure 2. Depiction of the Go/No-Go task. (A) The blue and yellow bells (left) served as the No-Go stimuli. The remaining six objects were Go stimuli, and appeared in both blue and yellow. (B) Representative sequence of trials in Go/No-Go task. No-Go trials were preceded by two, three, or four Go trials (not shown).
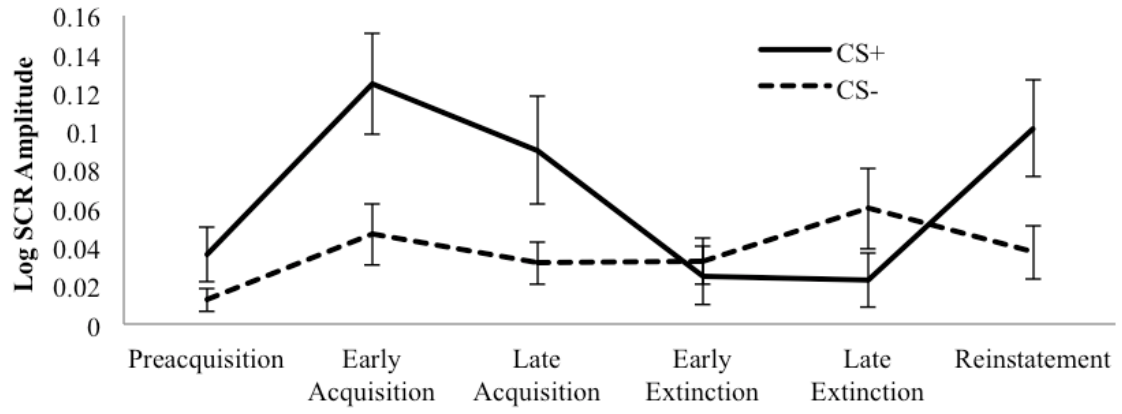
Figure 3. SCR response during fear conditioning as a function of Stimulus and Phase

GENERAL CONCLUSIONS AND IMPLICATIONS FOR POLICY AND PRACTICE[*]

For over half a century, researchers have documented the deleterious impact of adversity on the development of children. Childhood adversity is an important determinant of negative life outcomes, including psychiatric disorders, school failure and anti-social behavior, among many others (Garner et al., 2011; Shonkoff, 2010). Yet despite the social and economic cost of childhood adversity, our knowledge of the psychological and biological pathways that link early adversity with psychopathology remains limited. To address this limitation, the present thesis included three studies designed to explicate neurobiological and psychological mechanisms that link childhood adversity with adolescent mental health. In this chapter, the key findings from these studies are briefly summarized, before an extended discussion on the opportunities and challenges involved in the translation of basic science research to practice and policy.

Summary of Key Findings

Across all three studies, exposure to childhood adversity was associated with impairments to mental health, as reflected by significantly greater levels of internalizing and externalizing symptoms. This is perhaps unsurprising, considering the vast epidemiological and clinical data that now documents this relationship (Green et al., 2010; Kessler, Davis, & Kendler, 1997; McLaughlin, Green, Gruber, Zaslavsky, & Kessler, 2012). In addition, Study 3 documented maltreatment-related impairments in inhibitory control that may underlie the onset of externalizing disorders. Given the significant societal and economic costs incurred as a result of early adversity, the present findings further underscore the need to implement

timely, effective interventions in the wake of adverse early life experiences. Moreover, demonstrating the deleterious effects of childhood adversity may provide further impetus for government agencies to further prioritize prevention and intervention efforts serving vulnerable families.

Additionally, childhood adversity, specifically traumatic violence, was associated with widespread changes across multiple neurobiological systems. This is consistent with numerous prior investigations of trauma-exposed child and adolescent populations (see Bick & Nelson, 2015; Nelson & Sheridan, 2011). In this thesis, adversity-related differences in neurobiology were identified in autonomic nervous system and hypothalamic-pituitary-adrenal (HPA) axis function (Study 1), and brain structure (Study 2). Notably, Study 2 contributes to the existing literature by examining *prospective* associations between childhood maltreatment, neural structure and psychopathology. Such an approach is novel, as the majority of prior neuroimaging work has been cross-sectional, and we generally lack studies measuring brain and behavior at different time points. Identifying intermediate neural phenotypes that predict risk for later psychopathology is an important goal, raising the possibility of targeted intervention approaches for those most at-risk (McCrory & Viding, 2015). However, future research should explore whether neural risk markers account for more variance in psychopathology than existing behavioral risk markers, as this is necessary to justify their clinical usefulness.

Finally, the work presented in this thesis underscores the need for future work to better characterize and measure childhood adversity. As discussed in Study 1, it is important for future research to understand dimensions of early experience that shape neurodevelopment in different ways, particularly ways other than frequently invoked stress pathways. Although Study 1 found no effect of deprivation on stress reactivity, further

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research is needed to understand the mechanisms through which this exposure *does* affect mental health. In addition to identifying different dimensions of experience, the timing and/or chronicity of childhood adversity is also an important aspect of experience that warrants further study (Andersen & Teicher, 2008)

Translating Basic Science Research on Risk and Resilience: Opportunities and Challenges

It is now commonly held that scientific knowledge from genomics, neurobiology, and cognitive neuroscience can stimulate new ways of thinking about policy initiatives, disease prevention, the alleviation of poverty and other inequalities, and the implementation and evaluation of interventions that aim to promote positive developmental outcomes (Shonkoff, 2010). Yet the partnership between scientists and policy makers does not come easily, and both parties need to create a discursive space in which to discuss both what needs to be translated (and how), and to probe the practical, political and ethical challenges that arise when scientific research enters public discourse.

There are several reasons to be cautious about the utility of biotechnologies (MRI, genotyping, glucocorticoid assays) for policy and prevention science. First, the correspondence between biology and behavior is complex, often poorly understood and can change across the life course. As an example, salivary cortisol levels are consistently associated with externalizing problems in preschoolers and elementary school-aged children, but not in adolescents (Alink et al., 2008) Additionally, the interpretation of brain structure-function relationships is likely to vary across adolescence and adulthood. In adults, greater regional gray matter is often found to reflect a functional advantage, whereas the same differences in adolescents could represent a maturational 'lag' in synaptic pruning. Until the biology-behavior link is more clearly understood, the ability to interpret this research will

remain limited.

A further source of challenge comes from the considerable financial cost associated with brain imaging, genotyping and other technologies. Currently, the kind of mental health care that is provided in the United States and many other developed nations does not adequately meet the needs of children and adolescents, particularly those in poverty (Mulye et al., 2009). Consequently, Luthar and Brown (2007, p. 6) persuasively argue that "for the thousands of at-risk children and families lacking any kind of health insurance, it would seem that there is limited hope, in the foreseeable future, that these expensive technologies will be harnessed for individualized tailoring of mental health treatments according to their unique psychobiological profiles". Balancing cost-effective, evidence-based interventions with greater financial investment in mental health services is crucial if this is to change.

Finally, it is inevitable that knowledge from brain scans and other biotechnologies will raise unprecedented ethical dilemmas for researchers, policy makers, practitioners and families (Illes & Bird, 2006): how might neuroimaging guide decisions about treatment, and to whom? How might labeling (or even mislabeling) children affect their treatment in schools, homes and hospitals? How might brain imaging reconstitute our perception of "typical" and "atypical" development? Robust ethical guidelines are critical in protecting those children and families who have both the most to gain and the most to lose.

Nevertheless, knowledge from the biological sciences also offers considerable promise. Although a full description of possible implications is beyond the scope of this chapter, here are a few possible applications. To begin with, the neurosciences add converging biological evidence to support existing epidemiological, behavioral and psychological accounts of risk and resilience. Scientific narratives – what Shonkoff and Bales (2011) call a "core story" – represent powerful rhetorical devices that capture the attention

of the public, policy makers. Biological data may be seen as particularly persuasive because they are perceived as offering more precision and clarity than data from other sources, enjoying a scientific cachet that is not afforded to explanations at other levels of analysis (Busso & Pollack, 2015).

Second, evidence suggests that neurobiological or epigenetic information may be used to assess and differentiate treatment responses to clinical or educational interventions. Currently, interventions with child and adolescent populations typically use self, teacher, parent or clinician reports to assess the effectiveness of a given program. However, the addition of "objective" neurophysiological data to self, parent, teacher and clinicians reports may yield a more accurate and reliable image of treatment efficacy by complementing data at the level of behavior to also include more subtle neurobiological information. Biological data may be particularly valuable, for instance, because biological changes may precede changes at the behavioral level, or in cases where neurobiological systems may be more sensitive than behavioral assessments (Cicchetti & Gunnar, 2008; Gabrieli, 2009).

Finally, cognitive, neurological and epigenetic markers may aid in the early identification of psychopathology, or guide treatments or interventions for child and adolescent populations with particular risk profiles. Childhood adversity may result in measurable, systems-level changes to neurobiology with no immediate clinical manifestation, but may nevertheless signal vulnerability to *future* psychopathology (McCrory & Viding, 2015). Such an approach has been successful both in this thesis and in other studies using this sample (Busso, McLaughlin, & Sheridan, 2014; McLaughlin et al., 2014), and aligns with the National Institute of Mental Health's Research Domain Criteria (RDoC) initiative (Insel, 2014). Indeed, the identification of pre-clinical, transdiagnostic indicators of vulnerability is

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likely to have important implications for the field of preventative psychiatry, facilitating intervention efforts.

Conclusions

Over the past decade, research from cognitive neuroscience and psychology has made important inroads for our understanding of how childhood adversity shapes development. The three studies included in this thesis represent an effort to understand the underlying neurobiological mechanisms that link childhood adversity with poor mental health. The goal of building a science-based framework for childhood policy is currently an important agenda in research and policy, and this movement draws expertise from neuroscience, public health, education, and psychology (Shonkoff, 2010). Further research is needed to understand how the developmental embedding of early adversity affects lifelong learning and health, thereby motivating the design of innovative prevention and intervention strategies.

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