## Title

The Impact of Adversity Exposure on Structural Neurodevelopment and Pubertal Maturation: Implications for Policy



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# The Impact of Adversity Exposure on Structural Neurodevelopment and Pubertal Maturation: Implications for Policy

A dissertation submitted in partial satisfaction of the requirements for the degree

Doctor of Philosophy in Neuroscience

by

Natalia Marian Orendain

2021

ABSTRACT OF THE DISSERTATION

The Impact of Adversity Exposure on Structural Neurodevelopment and Pubertal Maturation: Implications for Policy

by

Natalia Marian Orendain

Doctor of Philosophy in Neuroscience

University of California, Los Angeles, 2021

Professor Susan Bookheimer, Co-Chair

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Despite extensive research exploring the impact of early life adversity exposure on neurodevelopment, the extent to which exposure to various forms of adversity impacted neurodevelopment and puberty was not clear. Previous studies focused on discrete populations of youth (e.g. institutionalized youth, sexual assault survivors) studied for their exposure to often a singular form of adversity. Likewise, studies examining sources of resiliency are often limited in the sources they capture, the outcomes they measure and the sample studied. This dissertation is novel in examining different facets that interact with adversity exposure and sources of resiliency to influence structural neurodevelopment, pubertal maturation and behavioral outcomes pertinent to psychopathology risk.

The first chapter provides an overview to the dissertation, noting the state of the science, gaps in the literature this dissertation aims to address, and implications of this work.

The second chapter comprehensively examines whether different forms of resiliency *moderated* cumulative adversity's impact on structural neurodevelopment and internalizing, externalizing and total problems. Additionally, this study examined whether frontolimbic circuitry *mediated* the relationship between cumulative adversity exposure and CBCL outcomes.

The third chapter tested whether puberty *mediated* the relationship between both type-specific and cumulative adversity exposure and amygdala and hippocampal volumes. Additionally, this chapter examined the relationship between pubertal development (i.e. adrenarche and gonadarche) and type-specific and cumulative adversity exposure. Finally, this study examined whether school-based support *moderated* the impact of adversity exposure on pubertal development, specifically gonadarche.

The fourth chapter is the first study to examine the impacts of youth-perceived neighborhood threat and parental consolation on amygdala volume in periadolescent youth. The key findings across the total sample are: 1) enlarged left amygdala volumes in the presence of perceived neighborhood threat and in the absence of parental consolation; 2) diminished left amygdala volume in the absence of both neighborhood threat and parental consolation; and 3) a significant interaction effect of parental consolation and neighborhood threat on left amygdala volume.

Finally, the fifth chapter discusses both and challenges attributable to multi-site publicly available multimodal, including neuroimaging, data. Proposed improvements are suggested in an effort to minimize barriers associated with the use of "big data". This dissertation contributes to our understanding of neurodevelopment and puberty, and by identifying sources of resiliency

that can dampen the impacts of adversity exposure, has the ability to inform legislative and policy efforts.

The dissertation of Natalia Marian Orendain is approved.

Paul Chung

Beth Colgan

Susan Bookheimer, Committee Co-Chair

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University of California, Los Angeles

2021

## DEDICATION

This dissertation is dedicated to the often-voiceless youth impacted by any form of adversity.

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**PUBLICATIONS**

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## CHAPTER 1: Introduction to the Dissertation


### ABSTRACT

Due to their neurodevelopmental sensitivity, youth are particularly susceptible to environmental stressors, which can yield a lasting impact on ensuing brain structure and function. Extensive research has been conducted exploring the impact of early life adversity on prominent neural circuitry, endocrinological functioning, and ensuing psychopathology and behavior. While at times used interchangeably waith early life stress, early life adversity refers to instances of physical, verbal or sexual abuse, neglect or deprivation that occur particularly during childhood and into adolescence. Epidemiological and neuroimaging studies detail the detrimental impact of adversity exposure on youth neurodevelopment.

Experiences during adolescence generate a tremendous impact on brain development and behavior, not just during this critical period but into adulthood. Adversity heavily impacts neurodevelopment and behavior, with exposure during the developmental years translating into an increased risk for psychopathology and poorer health outcomes. Behaviors traditionally associated with adolescent's immature frontolimbic connectivity, such as high emotional reactivity and significant susceptibility to peer influence, are amplified in response to adversity exposure. The prefrontal cortex (PFC), amygdala and hippocampus are regions rich in glucocorticoid receptors and thus impacted by frequent states of high arousal and stress. The PFC is a highly studied region in adolescent development due to its immature and protracted developmental trajectory, and so too is the amygdala due to its significant role in emotional and social information processing and regulation. Sensitive windows of development, such as puberty, are periods of increased vulnerability to stressors that can yield a lasting impact on ensuing brain structure and function. The age of pubertal onset and the length of pubertal maturation also influence the neurodevelopmental trajectory and behavior of youth (Blakemore 2010; Herting 2017). While pubertal status and

neuroendocrinological processes are substantial variables in neurodevelopment, they are often overlooked in neurodevelopmental studies.

Despite extensive research exploring the impact of early life stressors and adversity exposure during development, we do not yet know to what extent exposure to various forms of adversity (i.e. abuse, neglect, chronic threat) impacts pubertal development and structural brain maturation in youth. Additionally, it has yet to be determined what feature of adversity (i.e. type, age of onset, duration, and cumulative burden) accounts for the largest variance in structural neurodevelopment of frontolimbic circuitry. Drawing from data collected as part of the Adolescent Brain Cognitive Development (ABCD) Study - a longitudinal neuroimaging study of 10,000 youth - I will quantify the impact of adversity exposure on pubertal maturation and structural frontolimbic development in youth aged. Particular attention is paid to the impact of less overt forms of early life adversity exposure, such as chronic threat. Avenues for resiliency to capitalizes on neurodevelopmental plasticity are explored.

"The distinct nature of children, their initial dependent and developmental state, their unique human potential as well as their vulnerability, all demand the need for more, rather than less, legal and other protection from all forms of violence." (United Nations Committee on the Rights of the Child of 2007, section 4, paragraph 21).

## INTRODUCTION

Experiences during adolescence generate a tremendous impact on brain development and behavior, not just during this critical period but into adulthood. Due to their neurodevelopmental sensitivity, youth are particularly susceptible to environmental stressors, which can yield a lasting impact on ensuing brain structure and function. While at times used interchangeably with early life stress, early life adversity refers to instances of physical, verbal or sexual abuse, neglect or deprivation that occur particularly during childhood and into adolescence. While extensive research has demonstrated the acute and chronic effects of single episode as well as persistent environmental stressors on structural and functional neurodevelopment, the majority of studies have focused on retrospective and discrete populations, limiting their ability for reproducibility and generalizability. Furthermore, these studies did not examine the range of adverse experiences and as such, recent human neuroimaging studies are only beginning to examine the effect of different forms of adversity on neurodevelopment.

Different forms of early life adversity, such as abuse, neglect and deprivation, are suggested to uniquely impact the brain both structurally and functionally contingent upon the characteristics of the stressor, e.g. age of onset, type, duration and frequency of exposure (Teicher 2016). Additionally, exposure is complex with experiences frequently co-occurring. Other forms of early life exposure, like neighborhood threat, have been less quantified and are traditionally overlooked in terms of adverse childhood experiences. Given the prevalence

of community violence exposure during adolescence (Heleniak 2017), it is arguable that chronic neighborhood violence exposure during development could have a detrimental and lasting impact on structural brain development and maturation.

The period of adolescence, often inseparable from puberty, is a unique window of neurodevelopment characterized behaviorally by enhanced emotional reactivity and sub-par regulatory control, among other characteristic behaviors. While adolescence is a transient window in which neurodevelopment is working towards efficiency, typical adolescent behaviors are outward manifestations of the developing brain's attempts to fine-tune its interactions with the environment. Furthermore, sensitive windows of development, such as puberty, are periods of increased vulnerability to stressors that can yield a lasting impact on ensuing brain structure and function. The age of pubertal onset and the length of pubertal maturation also influence the neurodevelopmental trajectory and behavior of youth (Blakemore 2010; Herting 2017). While pubertal status and neuroendocrinological processes are substantial variables in neurodevelopment, they are often overlooked in neurodevelopmental studies.

Behaviors traditionally associated with adolescent's immature frontolimbic connectivity, such as high emotional reactivity and significant susceptibility to peer influence, are amplified in response to adversity exposure. The prefrontal cortex (PFC), amygdala and hippocampus are regions rich in glucocorticoid receptors and thus impacted by frequent states of high arousal and stress. The PFC is a highly studied region in adolescent development due to its immature and protracted developmental trajectory, and so too is the amygdala due to its significant role in emotional and social information processing and regulation. It develops earlier than the PFC, and as such, exerts a substantial influence over adolescent functioning. Once structural and functional connections are more mature, evidence suggests that the PFC exerts inhibitory control over the amygdala resulting in

effective emotion regulation. However, these connections, including the uncinate fasciculus, are slow to develop revealing typical adolescent behavior in its stead: high emotional reactivity, susceptibility to peer influence, and enhanced salience for seeking and responding to emotionally charged stimuli. Structural and functional alterations have been observed in key regions of interest susceptible to the impact of early life adversity exposure. Given the intricacies of the brain, regional structural alterations will not only interfere with said region's functionality but will influence its ability to interact with and modulate neighboring or connected regions. This is of particular importance given the overlapping yet incongruent developmental trajectories of impacted neural regions.

Despite extensive research exploring the impact of early life stressors and adversity exposure during development, we do not yet know to what extent exposure to various forms of adversity (i.e. abuse, neglect, chronic threat) impacts pubertal development and structural brain maturation in youth. Additionally, it has yet to be determined what feature of adversity (i.e. type, age of onset, duration, and cumulative burden) accounts for the largest variance in structural neurodevelopment of frontolimbic circuitry. Heterogeneity in neural outcomes of exposure across brain regions of interest could also be attributable to differences in study design and methodology, including the categorization of adversity exposure, as well sample demographics, including age, sex, race and ethnicity. Adversity heavily impacts neurodevelopment and behavior, with exposure during the developmental years translating into an increased risk for psychopathology and poorer health outcomes.

Generally speaking, youth neurodevelopment can be viewed in terms of plasticity that diminishes with age, and thus increases one's susceptibility to permanent neural modifications in response to environmental influences. The transient period from childhood to adolescence in response to pubertal onset is regarded as a period of further sensitivity to adversity exposure and other environmental influences. Despite this transient developmental

state, youth are particularly vulnerable to environmental exposures leaving, in some instances, lasting, neural outcomes. Conversely, youth are amenable to environmental support. Drawing from data collected as part of the Adolescent Brain Cognitive Development (ABCD) Study - a longitudinal neuroimaging study of 10,000 youth - I will quantify the impact of adversity exposure on pubertal maturation and structural frontolimbic development in youth aged. Particular attention is paid to the impact of less overt forms of early life adversity exposure, such as chronic threat. Avenues for resiliency to capitalizes on neurodevelopmental plasticity are explored.

## EPIDEMIOLOGICAL STUDIES OF ADVERSITY EXPOSURE

The landmark study of early life adversity exposure was conducted from 1995 to 1997 by the Center for Disease Control and Prevention and Kaiser Permanente analyzing retrospective data on early life adversity exposure and current behavioral and health outcomes (Felitti 1998). The study included over 17,000 adults and its notable findings established a dose-response relationship between early life adversity exposure and long-term health and well-being outcomes (Felitti 1998). The study categorized early life adversity exposure or adverse childhood experiences, termed ACEs, into one of ten domains: physical abuse; sexual abuse; emotional abuse; physical neglect; emotional neglect; household mental illness; mother treated violently; household substance abuse; incarcerated household member; and parental divorce. The findings demonstrated that ACEs were common even among middle class health maintenance organization members, such that about two-thirds of study participants reported at least one ACE before the age of 18 years, while more than one in five reported three or more ACEs (Felitti 1998).

More recently, Merrick and colleagues (2018) provided an updated prevalence estimate of early life adversity exposure utilizing data on over 248,000 individuals captured

in the 2011 to 2014 Behavioral Risk Factor Surveillance System (BRFSS). They categorized adversity exposure into the following eight domains: physical abuse; sexual abuse; emotional abuse; household mental illness; household domestic violence; household substance use; incarcerated household member; and parental separation or divorce. Their categorized differed from the CDC ACEs Study in that they did not capture physical and emotional neglect (Merrick 2018). About 62% experienced at least one ACE, while one in four reported 3 or more ACEs. This study examined a significantly larger and more diverse study population and identified significantly higher instances of ACEs among individuals who identified as Black, Latinx, multiracial, and/or who were associated with low socioeconomic status (SES). The most prevalent ACE was emotional abuse (34.42%; 95% CI, 33.81%-35.03%), followed by parental separation or divorce (27.63%; 95% CI, 27.02%-28.24%).

Early life adversity exposure is associated with a host of immediate and long-term implications, including psychopathology, cardiometabolic diseases, cancer, and premature mortality (Felitti 1998, Chen 2016). Sex differences in disease risk and quality of life indicators attributable to early life adversity exposure are evident even decades later. In a cross-sectional sample of over 6000 adults, the authors noted an increased risk for all-cause mortality for women who reported either early life emotional abuse or physical abuse (Chen 2016). The increased risk of all-cause mortality among women was not directly associated with the adversity experienced, either through violence from the abuse or suicide, but was more likely attributable to chronic disease morbidity (Chen 2016). Early life adversity may predispose and epigenetically program the response tendencies of immune functioning to perpetuate chronic inflammation, leading to a heighten risk for cardiometabolic diseases, cancer, and other diseases of aging. Longitudinal prospective studies of early life adversity exposure are necessary to elucidate the mechanisms of action responsible for these sex

differences. Of note, only these two forms of early life adversity were captured and these associations were not observed among men (Chen 2016).

While these studies advanced the field of adversity exposure, their findings are retrospective which may introduce memory and response biases. Additionally, the findings were translated to the scientific and academic communities and to the general public as largely deterministic pertaining to health and well-being outcomes. More recent approaches to translating the findings of early life adversity studies have strongly focused on features of resiliency. This is particularly pertinent when examining adversity exposure prospectively and during development when youth are very much amenable to environmental support.

## NEURODEVELOPMENT AND ADVERSITY

After birth, the developing brain undergoes substantial growth and refinement until an adult-typical brain is formed in the mid-to late twenties. As the brain expands its intricacy, so too do its connections, volume and surface area; however, this initial neurodevelopmental expansion during childhood is tempered by neuronal processes that promote refinement and condensation leading to reductions in grey matter volume and white matter volumetric increases during adolescence. Generally speaking, youth neurodevelopment can be viewed in terms of plasticity that diminishes with age, and thus increases one's susceptibility to permanent neural modifications in response to environmental influences.

During typical development, volumetric increases are associated with prolific synaptogenesis as well as increases in white matter metrics predominately attributed to axonal myelination. Gyrification across the brain's surface area also increases throughout neurodevelopment, indicating axonal growth as well as whole brain expansion (Ernst 2015). Childhood is characterized by global and regional neural outgrowth manifesting as increases in grey and white matter. Throughout development, local neural connections are elongated to

form neural networks, such as those linking the hemispheres, or one lobe of the brain with another. As expected, children show less whole brain hierarchical organization in comparison with adults (Ernst 2015). Throughout development, smaller local networks undergo refinement, albeit during different time points, to form stronger, and ideally, more specialized connections.

During heightened states of arousal, growth and tissue repair are stalled, with both early life adversity and stress hormone exposure resulting in decreased cell proliferation and neurogenesis, increased apoptosis, and diminished synaptic spine density (Bath 2016). This is particularly the case for neural regions containing high concentrations of glucocorticoid receptors, the density of which is increased in the developing brain (Avishai-Eliner 1996). Three neural regions of interest pertaining to adversity exposure are the PFC, the amygdala and the hippocampus (Teicher 2016). The uncinate fasciculus is also of interest given its structural connections with the PFC and amygdala, as well as its late development. These regions in particular are susceptible to the impact of early life adversity exposure due to their developmental trajectories co-occurring during exposure as well as the high concentration of glucocorticoid receptors present (McLaughlin 2019).

The PFC's relationship with the adolescent amygdala demands specific attention. Once structural and functional connections are fully developed, the PFC exerts inhibitory control over the amygdala resulting in effective emotion regulation. The amygdala plays a key role in emotional and social information processing and regulation. In reference to the PFC's trajectory, the amygdala develops earlier in adolescence and puberty, and as such, exerts a substantial influence over adolescent functioning. In fact, the amygdala undergoes rapid growth and reaches peak volume between nine and eleven years of age; following this period, the amygdala gradually declines in volume due to developmentally regulated synaptic pruning (Teicher 2016).

At the cellular level, early life adversity has also been shown to accelerate aging during development (Nettle 2017), amplifying or causing aberrant neurodevelopment due to dysfunctional myelination and cortical maturation trajectories. Exposure during this critical window can also lead to delays in typical neurodevelopment. However, the outcomes of experimentally induced immune challenges differ based upon the timing and type of challenge introduced, suggesting a critical period and highlighting the complexity of exposure. The induction of prenatal stress produces prolonged neural inflammation (Nelson 2017). In the developing prenatal rodent brain, activating the maternal immune response not only induces sex-specific changes in astrocytic markers but in the offspring's behavioral outcomes later in life (Nelson 2017). Astrocytes are immunocompetent cells that mediate synaptic activity and neural communication. The ensuing behavioral outcomes include deficits in inhibitory response, memory, and adolescent socialization (Nelson 2017). Findings from independent animal models suggest that males may be particularly vulnerable to the impact of stress on immune response, whether induced pre-, peri- or postnatally (Nelson 2017).

Outside of the brain, both animal and human research has detailed the long-term implications of exposure. Animal models of maternal separation, and even early weaning, are associated with poorer health outcomes and increased disease risk later in life (Nettle 2017). In humans, maternal substance use postpartum is itself a significant risk factor for offspring neglect, and is an integral component of a substantial number of childhood maltreatment and out-of-home placement cases (Kim 2016). Alterations to these structures and their functionality often manifest as cognitive and behavioral abnormalities, such as verbal and intellectual deficits, memory impairment and persistent delinquency (Lansing 2016). Specific types of adversity exposure, including witnessing domestic violence, are associated with alterations in brain regions and circuitry responsible for processing the experience.

While childhood is characterized by outgrowth in grey and white matter volume, adolescence is conversely marked by a refinement in neuronal processing, attributable to synaptic pruning to facilitate efficient responding to anticipated environmental conditions. This translates to decreases in grey matter volume and cortical thickness with age; white matter volume and density continues to increase throughout both childhood and adolescence.

## PUBERTY AS A DISTINCT WINDOW OF DEVELOPMENT

Neurodevelopmental windows are periods of increased vulnerability to stressors that can yield a lasting impact on ensuing brain structure and function. While extensive research has been conducted exploring the susceptibility of the mammalian brain to environmental influences pre- and perinatally (Lupien 2009; Van Bodegom 2017), vulnerability also remains during particular phases of postnatal development, such as at the onset of puberty. Advanced pubertal maturation in response to adversity exposure - like unstable family structures and minimal parental warmth - has been observed (Mendle 2014) and is hypothesized to have evolutionary advantages. In dangerous and unpredictable environments, a faster developmental tempo would result in youth precociously attaining adult-like capabilities would maximize reproductive efforts and species survival prior to potential mortality.

Adolescence is a unique period of neurodevelopment characterized behaviorally by enhanced emotional reactivity and responding, increased impulsivity and risk taking, heightened peer influence, and sub-par regulatory control, in comparison with adult counterparts. In terms of brain maturation, both animal and human research has consistently demonstrated a general decline in grey matter volume at pubertal onset and an increase in white matter volume with time. Declines in grey matter volume are attributed to an enhancement of neuronal firing efficiency, while white matter volumetric increases

underscore connection strengthening regionally and across the brain. Adolescence is a transient window and while neurodevelopment is working towards efficiency, typical adolescent behaviors are outward manifestations of the developing brain's attempts to fine-tune its interactions with the environment. Physiologically, the period of adolescence is often inseparable from puberty.

Early in human development (i.e. prenatally and during the first year of postnatal life), the hypothalamic-pituitary-gonadal (HPG) axis expresses gonadal steroids (i.e. testosterone and estradiol) to promote sexual differentiation and organization. After years of dormancy, this circuitry is reactivated at pubertal onset, triggered by the release of gonadotropin releasing hormone (GnRH) from neurons within the median eminence of the hypothalamus. The hypothalamus is a neuroendocrinological hub important for homeostatic functioning. GnRH secretion encourages the production of gonadotropins from the pituitary gland, which overtime circulates throughout the body. Gonadotropins, such as luteinizing hormone and follicle-stimulating hormone, act on the gonads to produce estradiol and testosterone, respectively. During this time, the adrenal glands mature and produce increasing amounts of adrenal androgens, such as dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS). These two separate but complimentary neuroendocrine processes are termed gonadarche and adrenarche, respectively. Mammalian models of rodents and non-human primates have also demonstrated the impact of androgens and estrogens on synaptogenesis and pruning in impacted regions (Blakemore 2013). Independent research has demonstrated the ability of stressors during puberty to cause disruptions in the trajectory and functionality of gonadal hormones (Holder 2014).

In response to environmental stressors, the body embarks on a cascade of hormone release, first beginning in the brain. Corticotropin-releasing hormone (CRH) is first emitted by neurons in the hypothalamus in response to the perceived stressor; second, CRH triggers

the release of adrenocorticotropin (ACTH), a hormone originating from the pituitary gland. The eventual circulation of ACTH throughout the body and to the adrenal glands results in the secretion of stress-specific hormones, predominately glucocorticoids and catecholamines, such as cortisol and adrenaline, respectively, and completes the HPA axis response. The ensuing physiological responses and behaviors are characteristic of sympathetic nervous system engagement. As neural regions impacted by stress typically contain a high concentration of glucocorticoid receptors, they typically undergo protracted development and or postnatal neurogenesis in response to sustained stress exposure (McLaughlin 2019).

Prolonged and frequent activation of the HPA axis and circulation of stress hormones is detrimental to homeostatic maintenance and overall health. During this heightened state of arousal, growth and tissue repair are stalled, immunological functioning is impaired and glucocorticoids, being highly catabolic agents, negatively impact cardiometabolic functioning. Furthermore, glucocorticoids permeate the blood-brain barrier and act upon receptors in the frontal lobe, amygdala, hippocampus and cerebellum, among other areas, resulting in impaired functioning and structural alterations. Both early life adversity and stress hormone exposure result in decreased cell proliferation and neurogenesis, increased apoptosis, and diminished synaptic spines and density (Bath 2016). For example, the hippocampus is a region prominent in learning and memory, and the cerebellum, in addition to coordinating movement, has a close relationship with the limbic system. Previous studies have shown a negative association between high levels of endogenous glucocorticoids and structural volume in the hippocampus, in addition to diminished memory performance (Tu 2004).

The age of pubertal onset and the length of pubertal maturation too influence the neurodevelopmental trajectory of youth and ensuing behavior. Notable sex differences in puberty's developmental trajectory exist with females completing puberty about four years

prior to males (Pfefferbaum 2016). For example, the frontal lobe of mid-puberty females displays adolescent-specific structural alterations not yet evident in age-matched males and pre-puberty females (Herting 2017). Recent rodent models (Drzewiecki 2016) suggest the influence of sex-specific ovarian hormones, such as estradiol, on synaptic pruning in implicated regions, such as the medial PFC. The PFC, comprised in part by the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC), is a highly studied region in adolescent neurodevelopment due to its immature and protracted developmental state. It is the brain region associated with cognitive and inhibitory control, as well as the regulation of affective and reward-seeking states. It is an association area largely responsible for the coordination, integration and regulation of various types of information throughout the cortex. As such, individuals with a history of adversity exposure display diminished volumes in the PFC, amygdala and insula, possibly attributable to stunted neurodevelopment (Lansing 2016).

In concert with the frontal lobe, the fronto-mesolimbic dopamine (DA) system also exerts a powerful effect on the adolescent. The circuitry originates in the ventral tegmental area (VTA) and then travels to the ventral striatum and amygdala, following the mesolimbic pathway; mesocortical projections travel from the VTA to the PFC. Within these circuits reside high levels of gonadal and adrenal steroid receptors (Ernst 2009). Engagement of these systems in concert with pubertal maturation is associated with typical adolescent behaviors, such as diminished long-term planning and increased sensation seeking. While inhibitory and excitatory DA receptors modulate goal directed behaviors, such as approach and avoidance, unique during adolescence is the role reversal of DA receptors on cortical interneurons from inhibitory action states to excitatory (Sinclair 2014). These and other dramatic albeit gradual shifts are intended to fine-tune motivational and reward responding behaviors; however, this dynamic transitional state could also account for adolescents enhanced sensitivity to reward and propensity for risk-taking. Youth with a history of early life adversity, such as emotional

and physical neglect, display blunted responses to reward cues and altered ventral striatal reactivity (Tottenham 2016), which may in part explain their heightened penchant for substance use.

Neuroendocrinological sex differences also impact the regional maturation of frontolimbic circuitry, among other brain regions, and their ensuing influence over one another. A different cocktail of hormones, as well as delayed pubertal onset, may biologically predispose males for an extended duration towards impulsivity, risk taking and vulnerability to peer influence in comparison with female counterparts. This could in part explain why youth offenders are disproportionately male. Additionally, the peak emergence of psychopathology occurs during the adolescence and pubertal windows, at about fourteen years of age (Paus 2008).

Despite neurodevelopment being often associated with age alone, pubertal development exerts a significant influence over neurodevelopment. In a longitudinal sample of 275 healthy individuals aged 7 to 20, pubertal development was significantly correlated with structural volume in the following key regions of interest: amygdala, hippocampus, nucleus accumbens, and the basal ganglia (Klapwijk 2013). The authors noted that the influence of pubertal development, obtained via self-report Tanner staging, on neurodevelopment was independent of age for both males and females (Klapwijk 2013). While research exploring the neurobiological and endocrinological mechanisms of psychopathology is still emerging, sex differences have been observed in animal models of neurotransmitter receptor expression and in human neuroimaging studies examining cortical thickness metrics throughout various stages of pubertal development. Not just neurons, but astrocytes, microglia and other immune cells show differential expression and proliferation contingent upon sex-specific hormone development (Nelson 2017). Unfortunately, earlier

pubertal timing is associated with increased risk of psychopathology, including, mood disorders, substance use disorder, as well as risk-taking and delinquency (McLaughlin 2020).

## NEUROIMAGING STUDIES OF ADVERSITY EXPOSURE

Extensive research has been conducted exploring the impact of early life adversity on neural structure and function within the hypothalamic-pituitary-adrenal (HPA) axis and among frontolimbic circuitry (De Bellis 2002; Anderson 2004; Whittle 2013; Galinowski 2015); however, studies are only beginning to examine the impact of different forms of early life adversity on frontolimbic circuitry. These include but are not limited to: prolonged maternal separation, parental mental illness, family violence, poverty, as well as other instances of adversity. Different forms of early life adversity, such as abuse, neglect and deprivation, are suggested to uniquely impact the brain both structurally and functionally contingent upon the characteristics of the stressor, e.g. age of onset, type, duration and frequency of exposure (Teicher 2016). Heterogeneity in structural and functional neural outcomes of adversity exposure across brain regions of interest could be attributable not only to differences in methodology, but to adversity characteristics, and sample demographics, including baseline neural circuitry development.

For example, acute adversity and stress exposure result in enhanced neural activity and are associated with volumetric growth in impacted regions. When experimentally-induced in humans, acute stress exposure manifests as enhanced blood-oxygen-level dependent (BOLD) signal on a functional magnetic resonance imaging (fMRI) scan clustered in an impacted region, such as the amygdala. Adolescents with a history of early life adversity exposure exhibit weaker connectivity between the PFC and amygdala via resting state fMRI in comparison with controls (Tottenham 2016). Similarly, altered PFC-amygdala connectivity has been observed during functional task performance while adolescents with a

history of adversity exposure experienced stressful stimuli (Tottenham 2016). The amygdala plays a key role in emotional and social information processing and regulation. Should exposure become chronic in nature, as is frequently observed in individuals with a history of early life adversity, neural excitation in the amygdala, for example, would be replaced by a state of diminished activity, neuronal loss, and eventually decreased regional volume.

Similarly, altered ventral striatal reactivity translating into blunted responses to reward cues is evident in several independent studies of youth who possess a history of early life stress, such as institutionalized care, low material affiliation or emotional neglect (Tottenham 2016). As these two regions are together involved in affective association learning and the coordination of attentional gating with reward-based behaviors, volumetric reductions may impact the ability of neighboring or connected regions to modulate one another. This understanding is pertinent in terms of the relationship between the PFC and amygdala. For example, loss of amygdala volume will not only interfere with the amygdala's functional influence but the PFC's ability to exert regulatory control over this neural region and one's emotional state. Prefrontal cortical deficits have been observed in adults with a history of childhood maltreatment in the absence of previous or current psychiatric diagnoses (Teicher 2016). This is striking given the fundamental importance of the PFC in regulating inhibition, emotive states, motivation and reward seeking, as well as other cognitive processes.

Physical abuse is the most widespread form of abuse early in life, and particularly so, among males (Felitti 1998). The effects of physical abuse have received considerable attention in terms of their psychosocial, neurocognitive, behavioral and transgenerational impact. In terms of measurable neuroanatomical impact, it is not uncommon for youth with a history of physical abuse to experience traumatic brain injury (TBI) (Ewing-Cobbs 1999). The immediate effect of TBI is axonal injury resulting in cellular transport disruption,

inflammation, and eventual white matter neurodegeneration. Youth are particularly vulnerable to the neural outcomes of TBI given the prevalence of unmyelinated axons and developing fiber bundles and pathways. Pediatric TBI negatively impacts cognitive control, intellectual function, attention and memory, social functioning, and heightens risk for psychopathology (Ewing-Cobbs 2016). Among the community, TBI is a strongly associated variable in youth delinquency and high rates have been observed in juvenile offenders both pre and post-confinement (Kaba 2014). In fact, juvenile offenders studied in a 2013 meta-analysis were over 3 times as likely to report a history of TBI than controls (Farrer 2013). This is compounded by the increased prevalence of early life adversity exposure among juvenile offenders (Barnert 2016; Lansing 2016).

Furthermore, the transient period from childhood to adolescence in response to pubertal onset is regarded as a period of further sensitivity to adversity exposure and other environmental influences. In illustration of age's impact on recovery and functioning, diffusion tensor imaging (DTI) was performed at two-time points (i.e. three and 24-months) post-pediatric TBI by Ewing-Cobbs and colleagues (2016). The authors noted that children aged six to ten displayed the most compromised initial pathway integrity in response to the injury, but showed the greatest ultimate recovery at 24-months by measure of fractional anisotropy (FA) (Ewing-Cobbs 2016). FA is a DTI-specific metric that indicates the degree of water diffusion in brain tissue and is a measure of microstructural (i.e. axonal) tissue integrity. A high FA value of 1 corresponds with succinct axonal fibers or bundles, while an FA of 0 indicates isotropic diffusion, due to loss of myelination or the presence of cerebrospinal fluid, for example. Conversely, adolescents aged eleven to fifteen showed the most severe *residual* deficit in FA 24-months post injury suggesting limited plasticity in comparison with child counterparts (Ewing-Cobbs 2016). While a baseline scan pre-injury was not obtained, the authors examined both acute and chronic microstructural changes in

key association, limbic and projection pathways. Microstructural alterations have also been observed in individuals with a high cumulative adversity burden (McLaughlin 2019), in the absence of TBI.

Like other forms of abuse, sexual abuse is associated with critical periods regarding neurodevelopmental sensitivity and psychopathology risk, and is mediated by sex differences. The most striking neuroanatomical finding in response to early life sexual abuse is thinning in the area of the somatosensory cortex corresponding with female genitalia; reduced grey matter volumes have also been observed in associated regions, such as those implicated in facial recognition and processing (Everaerd 2016). Reductions in grey matter have also been observed throughout the occipital cortex and corpus callosum (De Bellis 2015). Like other forms of abuse, sexual abuse's impact on neurodevelopment is influenced by the individual's developmental state. For example, sexual abuse that occurred early in childhood is associated with reductions in hippocampal volume; however, sexual abuse occurring during adolescence is instead associated with reduced PFC volume (Lupien 2009). These findings are similar to what has been observed in animal models and align with the developmental trajectories of these two regions. Furthermore, exposure to early life adversity during hippocampal development could lead to hippocampus- dependent emotional disorders, such as major depressive disorder; this is different from disorders arising from exposure to adversity during frontal lobe development, such as post-traumatic stress disorder (PTSD) (Lupien 2009).

Unlike physical and sexual abuse which often involves direct contact and physical harm, emotional abuse can seem less caustic. While emotional abuse is often harder to detect, like other forms of adversity, it carries both short and long-term effects. Emotional abuse is a greater risk factor for depressive disorder than physical abuse (Khan 2015) and among individuals with either psychosis or bipolar disorder, it is the most frequently endorsed form

of early life adversity (Bruni 2018). Relatedly, early life adversity is associated with psychotic experiences, as well as suicidal ideation and attempts (McLaughlin 2020). Emotional abuse can stem from caregivers, family members and peers, the latter being particularly damaging to adolescents (Khan 2015). Males and females display increased sensitivity towards the development of depression following emotional abuse at the age of 14; however, females are particularly sensitive to abuse stemming from peers while males are more impacted by emotional abuse from caregivers (Khan 2015). Alterations in the auditory cortex and in circuitry connecting Broca and Wernicke's area have been observed in adults reporting early life emotional abuse (Khan 2015).

There is an inherent difference in parent and child interactions in terms of abuse and neglect or deprivation. Parental neglect, whether physical or emotional, embodies a failure to provide for a child's most basic needs, such as shelter, food, health care, emotional well-being and physical safety. Neglect and deprivation, often used interchangeably, are traditionally studied in youth within the context of foster and adoption care. Historically, neglect has shown to be most neuroanatomically damaging during infancy and early into childhood (Teicher 2016); however, this temporal window could be attributed in part to the dearth of data examining older youth experiencing neglect and deprivation. To rectify this, the hippocampal volumes of over 300 18 to 25-year old's were studied in relation to early life adversity exposure (Teicher 2018). The authors noted that exposure to neglect at or before the age of seven had greater predictive importance on hippocampal volume than severity or duration of exposure - but only for male youth; abuse not neglect impacted female's hippocampal volume (Teicher 2018). Conversely, Herzog and colleagues (2020) recently identified a differential timing of neglect on bilateral hippocampal volume in their female sample (n = 68), occurring between 9 and 13 years of age. They also found distinct windows for neglect's impact on amygdala volume in females. For the right amygdala, severe

vulnerability to neglect was conferred between 10 and 12 years of age, and again at 13 and 14 years of age, while the left amygdala displayed vulnerability between 14 and 16 years of age (Herzog 2020). The conflicting findings call for additional research in this area, ideally in nationally-representative prospective samples.

Lastly, adversity exposure also encompasses parental mental health indicators, including parental drug and alcohol abuse (both prenatal and post-natal), as well as psychopathology, including mood disorders, bipolar disorder, self-harm and suicide. The majority of studies have focused on prenatal substance exposure and maternal health on offspring development and behavioral outcomes (Russell 2015; Teicher 2018). Aside from prenatal substance exposure studies conducted in animal models, these studies were not designed to solely identify the impact of familial or household mental illness separate from frequently co-occurring adverse experiences. For example, emotional abuse and neglect are associated with irregular and unstable caregiving, and often co-occur with parental psychopathology (McLaughlin 2017). For these and many reasons, it is often difficult to isolate the impact of an adverse experience. Of note, all the imaging studies of adversity are retrospective in nature. These considerations will be discussed further in the methodological section below.

## THREAT AS A DISTINCT FORM OF ADVERSITY

It has been suggested through national survey data that the prevalence of community violence exposure during adolescence is on par with, if not greater than, adversity exposure within the home (Fagan 2014). While it has yet to be empirically demonstrated and is traditionally overlooked in terms of adverse childhood experiences, it is arguable that chronic neighborhood violence exposure during childhood or adolescence could have a detrimental

and lasting impact on structural brain development and maturation, even aside from the anticipated behavioral and psychosocial manifestations.

Neighborhood disadvantage, often quantified by socioeconomic status (SES), is often used as a proxy to capture complex environmental stress. SES is a strong and highly researched explanatory variable in a plethora of exposures and outcomes of interest ranging from access to education to quality of life to all-cause mortality risk (McLaughlin 2019; Gur 2019). In their sample of 128 youth aged nine to fourteen, Hanson and colleagues (2015) noted advanced pubertal development in individuals from low SES households (defined using the Hollingstead two-factor index) in comparison to counterparts from middle-class households. Epidemiological studies point to higher levels of basal cortisol in children from low SES households compared with those from high SES households (Tu 2004). Furthermore, smaller amygdala and hippocampal volumes have been observed in youth originating from low SES households (Hanson 2015), similar to reduced volumes observed among individuals with a history of adversity or chronic stress exposure. Poverty, like low SES, has also been strongly correlated with diminished cortical surface area and grey and white matter development, particularly in regions supporting language and decision-making (Lansing 2016). Gur and colleagues (2019) suggest that low SES and associated adversity exposure, including witnessing violence, may accelerate pubertal maturation and neurobiological aging in a regionally dependent manner. As such, diminished volumes may indicate stunted development (Lansing 2016) or advanced synaptic pruning in response to the onslaught of environmental stressors.

SES has been associated with disparity in access to and quality of summer learning that begins during the elementary education years. Youth from higher SES households typically engage in educational and enrichment experiences throughout the summer months - from museum and library visits to recreational activities and organized sports, leaving youth

from low SES households disproportionately disadvantaged (Alexander 2007a, 2007b). While the disparity is not substantial over the first couple of years of elementary education, over time, the weight of summer learning is projected to accumulate exponentially and as such, is regarded an explanatory variable in the college attendance gap, noted particularly between youth from low SES and high SES households. Given the multifactorial nature of SES, it has yet to be determined whether observed disparities in neural, cognitive and behavioral development attributed to low SES are a result of limited enrichment opportunities and afforded resources or to chronic neighborhood threat exposure and instability.

As youth age, their risk for exposure to community violence increases with more than half of youth aged 14 to17 endorsing community violence exposure in their lifetime (Heleniak 2017). Not unlike other forms of adversity exposure, greater exposure to community violence was associated with adolescent internalizing psychopathology with emotion dysregulation suggested as a possible linking mechanism (Heleniak 2017). Youth with community violence exposure report greater emotional sensitivity, intensity and persistence (Heleniak 2017). While heightened emotional reactivity is an adaptive response to existing and surviving in a high threat environment, it becomes maladaptive when threat is no longer present and environments and contexts are safe.

Youth exposed to violence exhibit alterations in threat-related information processing, including heightened attention to angry faces and limited processing of contextual information and associative facial cue encoding (Lambert 2019). Violence-exposed youth exhibited less hippocampal activation during associative learning, regardless of the facial cue presented and associated threat (Lambert 2019). These reductions in hippocampal activation during task performance are associated with broad associative memory deficits (Lambert 2019). Of note, the authors categorized youth violence exposure if early life physical abuse,

sexual abuse or witnessing domestic violence was endorsed. This is problematic as the compilation of different forms of adversity exposure may obscure the true findings.

Constant threat due to neighborhood and community characteristics is a critical variable to capture in terms of its neuroanatomical, endocrinological and behavioral influence. This is an area of much needed research not only to advance our understanding of early life adversity but in order to effectively care for and rehabilitate system-impacted as youth. The majority of youth involved with the criminal justice system have a history of early life neighborhood violence exposure (Lansing 2016) and represent a traditionally understudied population. While confined, youth are subjected to sterile environments that often lack enrichment resources, with limited regard for their developmental needs; their behaviors and activities are substantially restricted, including those educational or creative in nature (Lansing 2016). Additionally, many youth are exposed to constant threat and pervasive abuse (McCarthy 2016), in addition to the neglect experienced while detained or confined. Given the documented relationship between crime and poverty or low SES (Motley 2017), the neural correlates of poverty exposure have received considerable attention (Barch 2016; Brody 2017). However, poverty as a risk factor for quality of life outcomes does not substitute for assessing the impact of neighborhood threat exposure. As such, it is of importance for future research to disentangle the impact of low SES and neighborhood threat exposure on neurodevelopment and pubertal maturation. Neighborhood violence exposure can in part be accounted for at a population level through publicly available crime statistics.

## METHODOLOGICAL CONSIDERATIONS

The vast majority of studies examining early life adversity are retrospective in nature (Baldwin 2019), largely due to logistical constraints on study methodology. For example, study funding places limitations on subject number, recruitment efforts, as well as length and

duration of study visits. Ethical considerations also surround the discovery of recent early life adversity exposure. Youth may not possess the awareness to identify instances of adversity exposure, particularly if family members or if other traditional sources of support are involved. Adversity exposure stemming from familial interactions complicates the relationship with the youth, given that the youth is oftentimes solely dependent on its caregiver for survival. For these and other reasons, retrospective studies are used in place of prospective cohort studies.

A recent meta-analysis of over 25,000 individuals demonstrated that retrospective and prospective studies actually capture different groups of individuals and thus cannot be used interchangeably to examine the impact of adversity exposure (Baldwin 2019). For example, the largest percentage of agreement between the two study designs was when examining childhood separation from caregiver at 93% ($k = 0.83$); the smallest percentage of agreement was when physical abuse was assessed at 75% ($k = 0.17$) (Baldwin 2019). The authors concluded that more than half of the individuals that participated in prospective observations of early life adversity exposure did not report it retrospectively; likewise, more than half of the individuals that retrospectively reported early life adversity exposure did not participate in prospective observations (Baldwin 2019). Given that the majority of studies are retrospective, the findings of this meta-analysis highlight the importance of continuing prospective studies of early life adversity exposure to assess mechanisms of risk, biobehavioral outcomes, and avenues of intervention.

While extensive research has demonstrated the acute and chronic effects of single episode as well as persistent environmental stressors (i.e. prolonged maternal separation, parental mental illness, family violence) on structural and functional neurodevelopment, the majority of studies have focused on discrete populations, limiting their ability for reproducibility and generalizability. Additionally, these studies did not comprehensively

examine the range of adverse experiences and as such, recent human neuroimaging studies are only beginning to examine the effect of different forms of adversity on neurodevelopment. Heterogeneity in neural outcomes of exposure across brain regions of interest could also be attributable to differences in adversity characteristics. When experimentally induced, acute adversity and stress exposure result in enhanced neural activity, in the amygdala for example, and are associated with volumetric growth there (Tottenham 2016). Should exposure become chronic in nature, as is frequently observed in individuals with a history of early life adversity, neural excitation would be replaced by a state of diminished activity, neuronal loss, and eventually decreased regional volume (Whittle 2013; Teicher 2016), as has also been observed in the amygdala.

Sheridan and colleagues (2014) have hypothesized early life adversity exposure to lie along a threat-deprivation axis due to distinct characteristics attributable to different forms of exposure, as well as its neurobiological correlates. For example, physical abuse, sexual abuse, and neighborhood and community violence exposure all involve threat of harm to a developing person. This holds true even in instances of indirect exposure, such as when an individual witnesses' threat and violence. Conversely, deprivation involves the absence of or low levels of social and cognitive stimulation, and as such, is a core feature of emotional and physical neglect. Sheridan and McLaughlin propose that threatening dimensions of adversity exposure are associated with reductions of PFC, amygdala and hippocampal volumes, and enhanced amygdala activation in response to threat; when examining the impact of deprivation but not threat, volume reductions and altered functionality of frontoparietal regions have been observed (Sheridan 2014; McLaughlin 2019). Despite these commonalities, adversity is complex and certain forms do not singularly map onto either

domain. Poverty or low SES is an example of a form of early life adversity that includes both dimensions of threat and deprivation.

Given that pubertal development impacts neurodevelopment, and that adversity impacts both pubertal maturation and neurodevelopment, the relationship between all three variables will be extensively studied in this dissertation utilizing data obtained from youth undergoing pubertal development. This dissertation will utilize multimodal data from the largest longitudinal study of youth neurodevelopment to date - the nationally-representative Adolescent Brain Cognitive Development (ABCD) Study. The ABCD Study launched in 2016 with a nationwide cohort of over 11,000 nine and ten-year old's at baseline to be studied for 10 years. To establish national standards of youth brain development, subjects undergo: remote follow-up every 3 months consisting of psychosocial measures; annual in-person saliva collection, for pubertal hormone analyses, paired with in-depth neurocognitive and psychosocial measures; and biennial neuroimaging, also paired with salivary pubertal hormone collection and in-depth neurocognitive and psychosocial measures. Completion of psychosocial measures by enrolled youth and their caregivers will provide information regarding adverse experiences within the immediate family and extended environment. See abcdstudy.org for more information. This dissertation aims to disentangle the impact of early life adversity exposure on structural neurodevelopment, specifically frontolimbic circuitry, and pubertal maturation in youth enrolled in the ABCD Study.

## CLINICAL IMPLICATIONS

During adolescence, the peak emergence of psychopathology and substance use occurs (Rutter 2003; Paus 2008; Glover 2012), both of which display sex-differentiated profiles and impact neurodevelopment. Survivors of early life adversity exposure account for over a third of all mental health disorders worldwide (McLaughlin 2019). Individuals with a

history of early life adversity exposure, say due to parental mental illness or violence exposure, typically engage in aberrant cognitive processing and behaviors, including hypervigilance and heightened emotional reactivity (Heleniak 2017). As such, early life adversity exposure is associated with an increased risk of developing internalizing and externalizing problematic behaviors (Gur 2019). In terms of an association with early life adversity exposure, internalizing behaviors include mood disorders, such as depression and anxiety, while externalizing behaviors include oppositional defiant disorder and conduct disorder.

In animal models at all stages of development, acute stress exposure results in increased extracellular dopamine in the nucleus accumbens, an area likened with reward processing and mediated by stress hormones (Tottenham 2016). The effect of stress on dopaminergic neurons is believed to encourage motivational and reward-seeking behaviors (Tottenham 2016), such as substance use or overeating. This is observed in human males where early adversity exposure is associated with a loss of grey matter throughout the limbic system, resulting in compensatory and increased connectivity of reward and salience networks (Helpman 2017), thereby increasing substance use risk. Disruptions in reward learning and neural responses to reward may be a mechanism by which deprivation and other forms of early life adversity influence psychopathology risk (McLaughlin 2017).

Stress introduced peripubertally in a rodent model resulted in the development of two distinct behavioral and neurobiological markers: an aggressive phenotype and increased anxiety-like behaviors and reduced sociability in another subset (Walker 2018). Microstructural changes in frontolimbic structures, specifically the PFC, amygdala and hippocampus, were coupled with the aggressive phenotype, likely due to differential glucocorticoid responses to stressors (Walker 2018). In their neuroimaging meta-analysis of 394 youth with conduct problems, characterized by aggressive, oppositional or defiant

behaviors, and 350 matched controls, Rogers and De Brito (2016) quantified grey matter volume reductions in key regions of interest, including, the left amygdala and right insula extending ventrolaterally into the PFC - neural regions associated with emotional reactivity and processing, and cognitive, emotional and inhibitory control. Further examination of childhood-onset conduct problems noted decreased grey matter volume in the left anterior insula extending into the amygdala (Rogers 2016). While causality could not be established, youth with conduct problems demonstrated aberrant structural neurodevelopment in regions noted for their influence on regulatory control, emotional reactivity and peer influence, among others. Diminished volumes in these same regions have also been observed in individuals with a history of adversity exposure (Lansing 2016).

Emotional abuse from parents and peers during childhood and into adolescence is strongly associated with mood disorders later in life, such as major depressive disorder (Khan 2015); this association with depression is double that of physical abuse's association (Norman 2012). A history of childhood emotional abuse is also associated with an increased risk for all-cause mortality in women but not men (Chen 2016), highlighting the moderating influence of neuroendocrinological processes. Males and females demonstrate sex-differentiated psychopathology, including an increased propensity for females to develop mood and anxiety disorders and males to develop attentional and oppositional disorders (Helpman 2017). In fact, women are twice as likely as men to develop trauma-related psychopathology (Helpman 2017). Among females, overactive and at times an enlarged

amygdala is associated with greater sensitivity to negative stimuli and downregulation of salience networks, biomarkers associated with mood disorders and PTSD (Helpman 2017).

## RESILIENCY FACTORS

The effects of adversity depend upon a host of factors aside from the features of the adversity exposure and the individual, and include, the perception of the exposure's controllability as well as the timing of the exposure in relation to an individual's development. The brain's ability to adapt its structure and function to environmental demands is termed neuronal plasticity. This plasticity is present throughout an organism's lifespan; however, sensitive periods of development, including puberty, afford youth the ability to rapidly learn and adapt to their environment. Sensitive periods also pose a greater risk of environmental experiences, like adversity exposure, carrying a lasting impact on the organism's biology and quality of life. Early life adversity exposure influences neurobiological, pubertal and behavioral development and functioning, frequently facilitating enhanced vigilance, increased emotional response, and impaired emotion regulation to potential threats. While this adaption is intended to enhance safety in a threatening environment, it is also associated with an increased risk towards psychopathology.

Despite the increased risk of long-term implications resulting from adversity exposure occurring during development, the neuronal plasticity attributable to sensitive windows of development aid an organism in their chances of success. This adaptive HPA functioning despite adversity is evident in the presence of support systems. Social interactions have demonstrated moderating effects on adversity's influence over physiology and behavior across a range of species, including, rodents, dolphins, non-human primates and humans (Beery 2015, McLaughlin 2020). The moderating effect has been observed from social

interactions with peers, relatives and even from the mere presence of those unfamiliar, although sex differences do emerge (Beery 2015).

Giving the increased risk of developing mood disorders following adversity exposure during development, social interactions not only serve as a source of resiliency but an antithesis to mood disorders as they work to combat the symptomatic reductions in social behavior (Beery 2015). Females demonstrate a greater benefit from social interactions following adversity exposure across species (Beery 2015); this may be due to the anxiolytic effect of social support as well as the increased prevalence of mood disorders among females following adversity. Within the home, the presence of a supportive caregiver is associated with diminished amygdala reactivity, greater functional coupling of the amygdala and the mPFC during threat processing, as well as enhanced threat discrimination during aversive learning (McLaughlin 2020). Parental support, which includes high levels of parental warmth, sensitivity and emotional support, have been shown to ameliorate the impact of adverse experiences and improve cardiometabolic, inflammatory and neurodevelopmental profiles extending into adulthood (Brody 2017). Outside the home, youth's perception of a supportive school environment, including quality of relationships with teachers and peers, are associated with academic achievements; a positive perception is also associated with reductions in risky behaviors, including sexual behaviors, drug use and violence perpetration (Piccolo 2019). Lastly, providing support to others (i.e. prosociality) has been shown to dampen physiological responses to stress in experimental conditions, reduce stress reactivity in frontolimbic regions, and increase reactivity in reward regions of the brain (Malhi 2019). Sources of resiliency display gender differences and mixed findings in part attributable to methodological considers. For example, peer support has been shown to buffer the impact of adversity exposure; however, the findings are mixed and display gender differences (Jaffee 2017). In their systematic review, Fritz and colleagues (2018) emphasize individual and

family-level resiliency factors as being the most effective in curbing psychopathology-risk associated with adversity exposure. Given that puberty is a sensitive window of development, youth are particularly amenable to environmental support and its lasting neural outcomes.

## OVERVIEW OF STUDIES

The goal of this dissertation was to examine the relationship among adversity exposure, structural frontolimbic development, pubertal maturation, sources of resiliency, and associated behavioral outcomes. Specifically, I investigated: what forms of resiliency *moderate* the impact of cumulative adversity exposure on structural frontolimbic circuitry and problematic behaviors (Study 1); the ability of pubertal development to *mediate* the relationship between both type-specific and cumulative adversity exposure and amygdala and hippocampal volumes (Study 2); and, whether a specific form of resiliency, parental support, can moderate the impact of neighborhood threat exposure on amygdala volume and problematic behaviors (Study 3). All three studies utilized baseline data from 9 and 10-year-old youth enrolled in the largest (n = 11,566) longitudinal study of youth neurodevelopment to date - the Adolescent Brain Cognitive Development (ABCD) Study.

The first study takes a broad approach of examining the relationship between cumulative adversity exposure, 6 different sources of resiliency, structural frontolimbic circuitry and associated problematic behaviors. Cumulative adversity exposure was obtained for each subject by summing the individual domains of a factor analysis, utilizing adversity data from 14 questionnaires and encompassing 47 variables. The factor analysis identified the following interpretable 6 factor domains: 1) physical and sexual violence; 2) parental mental health; 3) neighborhood threat; 4) prenatal substance exposure; 5) scarcity; and 6) household dysfunction. For Study 1, analyses were run utilizing one's cumulative adversity score, which was the summed exposure across the 6 domains. The relationship between cumulative

adversity exposure and 6 sources of resiliency were examined. The six categories of resiliency assessed were: 1) school-based support; 2) peer support; 3) parental support; 4) the presence of siblings; 5) youth's prosocial behaviors; and 6) the youth's religious and spiritual beliefs. Structural neural regions of interest (ROI) include the amygdala, hippocampus, orbitofrontal cortex and anterior cingulate cortex volumes. Clinical outcomes were obtained from the Child Behavior Checklist (CBCL) and included internalizing, externalizing and total problematic behaviors. Study 1 had three aims: 1) examine the relationship between cumulative early life adversity exposure and associated neural and behavioral outcomes; 2) examine the ability of frontolimbic circuitry to *mediate* the relationship between cumulative adversity exposure and CBCL outcomes; and 3) assess the ability of a variety of sources of resiliency, stemming intrapersonally and extending throughout the community, to *moderate* the impact of adversity exposure on associated neural and behavioral outcomes.

Study 2 focused more heavily on pubertal development, specifically adrenarche and gonadarche, in relation to both type-specific and cumulative adversity exposure, and amygdala and hippocampal volumes. Thus, this study examined the individual contributions of different forms of adversity, in additional to one's cumulative adversity burden. This study utilized the 6 forms of adversity identified in the factor analysis - 1) physical and sexual violence; 2) parental mental health; 3) neighborhood threat; 4) prenatal substance exposure; 5) scarcity; and 6) household dysfunction. Pubertal development was obtained via parent report and included information pertaining to the development of secondary sex characteristics, such as height, body hair, skin changes, breast development, menarche, voice changes and facial hair. Additionally, school-based resiliency was included as a potential source of support against the ramifications of adversity exposure on pubertal and neural outcomes. We focused our analyses on school-based support to limit the number of comparisons performed and to examine a type of community resiliency that is poised to play

a significant role in youth development as they age throughout adolescence (Curran 2017, Verhoeven 2019). Study 2 had the following 3 aims: 1) to examine the relationship between different forms of early life adversity exposure, including an individual's cumulative burden, and adrenarche and gonadarche, while controlling for covariates such as age, sex, race, ethnicity; 2) to examine the ability of puberty to *mediate* the relationship between both type-specific and cumulative adversity exposure and amygdala and hippocampal volumes; and 3) to assess the ability of school-based support to *moderate* the impact of both type-specific and cumulative adversity on pubertal development (i.e. gonadarche).

Finally, Study 3 narrowed in on the ability of one form of resiliency to moderate the impact of one pervasive form of adversity exposure - neighborhood threat - on subcortical limbic structures and problematic behaviors. Neighborhood crime and violence exposure is a source of trauma and chronic stress (McEwen 2010), particularly for adolescents due to their increased risk of involvement (Hardaway 2016). Furthermore, research has demonstrated the increased risk for minority youth to be both witnesses and victims of neighborhood violence (Hardaway 2016, Motley 2017). We utilized youth perceptions of neighborhood threat and youth perceptions of parental support, specifically, parental consolation. Youth-perceived parental consolation, namely, the caregiver's ability to alleviate the youth's distress, demonstrated both an individualized and culturally-inclusive quality. We previously found that other forms of parental support captured in the ABCD Study, such as the frequency with which the caregiver smiled and the frequency with which the caregiver told the youth that they loved them, did not demonstrate cultural sensitivity. Study 3 has two aims: 1) examine whether parental consolation *moderates* the relationship between neighborhood threat exposure and amygdala and hippocampal volumes; and 2) examine the relationship between parental consolation and youth prevalence of antisocial behaviors, such as aggression and delinquency. Youth exposed to neighborhood threat are at a greater risk for psychopathology

and detrimental behavioral outcomes, such as aggression and delinquency (Hardaway 2016). While youth may not be exposed to direct or immediate sources of neighborhood violence, their perceptions of neighborhood threat serve as a valuable exposure source associated with brain and behavioral alterations.

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## CHAPTER 2: Resiliency to Cumulative Adversity's Neural and Behavioral Outcomes in ABCD Study Youth


### ABSTRACT

Early life adversity exposure is associated with a host of detrimental health and quality of life outcomes throughout the lifespan. However, as youth are neurally primed towards plasticity, they are particularly amenable to sources of resiliency that can mitigate problematic neural and behavioral outcomes associated with adversity exposure. This is the first study to examine the ability of different forms of resiliency to moderate cumulative adversity's impact on frontolimbic circuitry and associated behaviors. Additionally, this study examined the ability of frontolimbic circuitry to *mediate* the relationship between cumulative adversity exposure and behavioral outcomes. We examined the following 6 forms of resiliency: 1) parental support; 2) the presence of siblings; 3) peer support; 4) school-based support; 5) the youth's prosocial behaviors; 6) the youth's religious/spiritual beliefs. Individuals with higher scores across the domains of physical and sexual violence, parental mental health, and scarcity had more internalizing problems. Conversely, individuals with higher scores pertaining to neighborhood threat, prenatal substance exposure, and household dysfunction had higher externalizing problems. School-based support and parental support demonstrated the ability to moderate the relationship between cumulative adversity exposure and bilateral hippocampal volume. Additionally, school-based support, parental support, peer support and the presence of siblings all moderated the relationship between cumulative adversity exposure and behavioral outcomes. Finally, mediation analyses revealed that early life adversity exposure is associated with altered amygdala and hippocampal volume, which increases the risk of problematic internalizing and externalizing behaviors.

## INTRODUCTION

Early life adversity exposure is associated with a host of detrimental health and quality of life outcomes throughout the lifespan. Early life adversity exposure is associated with alterations in the structure and function of frontolimbic circuitry (McLaughlin 2019) and is also associated with an increased risk towards internalizing and externalizing psychopathology (Jaffee 2017), including mood disorders and defiant disorders. Long-term effects include increased risk for problematic interpersonal relationships and even premature mortality (Felitti 1998, Agorastos 2019). Alterations in neural and behavioral functioning serve adaptive purposes in instances of threat and deprivation, but can become less adaptive outside of such environments. As adolescents are neurally primed towards plasticity, they are particularly amenable to environmental input, making adolescence a key time to implement and reinforce sources of resiliency that can mitigate problematic neural and behavioral outcomes associated with adversity exposure.

Adolescence is a unique neurodevelopmental period characterized by enhanced emotional reactivity and responding, increased impulsivity and risk taking, and heightened peer influence in comparison with adult counterparts (Tottenham 2016). While neurodevelopment is working towards efficiency, typical adolescent behaviors are outward manifestations of the developing brain's attempts to fine-tune its interactions with the environment. For example, adolescent's normative enhanced emotional reactivity and increased impulsivity can in part be attributable to the amygdala's earlier developmental trajectory in comparison with the prefrontal cortex. The brain develops according to region-specific trajectories, making the hippocampus particularly vulnerable earlier in life due to its developmental timeline (Tottenham 2010; Kirbakaran 2020).

Adversity exposure occurring during developmental windows, such as puberty, often carrying a larger and lasting burden into adulthood (Helpman 2017). Frontolimbic circuitry, including the amygdala, hippocampus, orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC), is highly susceptible to alterations from excessive levels of glucocorticoids, such as cortisol, and thus, often impacted by early life adversity exposure (Teicher 2016). Furthermore, the density of glucocorticoid receptors is enhanced during adolescence as these anatomical regions undergo development, further compounding adolescent's vulnerability (Tottenham 2016). Given that neural circuitry is in flux throughout adolescence and puberty, adversity exposure can prime the developing brain to continue to anticipate future onslaughts (Tottenham 2016).

Adolescence provides opportunity to reinforce resiliency to stress and adversity exposure by capitalizing on enhanced neural plasticity. Social, educational, public health and neuroscientific research has identified sources of resiliency with varying levels of proximity to the individual that serve protective roles against the detrimental health and quality of life outcomes associated with adversity exposure (Horn 2016, Fritz 2018). Within the community, sources can include peer- and school-based support. Social support in general has been shown to buffer the impact of parental psychopathology on youth psychopathology risk and health outcomes (Fritz 2018). Within the home, a supportive relationship with one's caregiver(s) has shown protective effects against both transient experimental stressors (Gunnar 2015) and more chronic forms of early life adversity exposure (Busso 2014, Brody 2017, Hanson 2019). The presence of siblings has also demonstrated a buffering effect against adversity exposure's relationship with psychopathology risk (Gass 2006). Lastly, resiliency can exist at the intrapersonal and interpersonal levels, including an individual's tendency towards prosocial

behaviors (i.e. caring for and helping others) (Flouri 2016) or affiliation with religious and spiritual beliefs (Jocson 2018). High levels of religious involvement moderated psychopathology associated with community violence exposure (Jocson 2018) and the presence of prosociality was associated with less internalizing and externalizing problematic behaviors in response to chronic adversity exposure (Flouri 2016). However, the relationship between resiliency and the neural and behavioral outcomes associated with adversity exposure is less clear (see Figure 1). The majority of studies have examined resiliency to adversity in older youth and among discrete populations of youth exposed to specific forms of adversity. Additionally, sex differences in resiliency to adversity-associated outcomes have not been explored.

This is the first study to examine the ability of different forms of resiliency to moderate cumulative adversity's impact on frontolimbic circuitry and associated behaviors. By examining sources of resiliency among youth exposed to a variety of adversity, we aim to advance the scientific field of early life adversity exposure and reframe the narrative from that of adversity-exposed youth carrying life-long disadvantages instead to all youth carrying enhanced amenability to sources of support and resiliency. As such, our study will examine youth as they enter adolescence utilizing baseline data. Our first aim is to examine the relationship between cumulative early life adversity exposure and associated neural and behavioral outcomes. We anticipated a positive dose-response relationship between one's cumulative burden and both structural brain changes (McLaughlin 2019) and internalizing and externalizing behaviors (Felitti 1998). Specifically, we anticipated that greater early life adversity burden would be associated with enlarged bilateral amygdala volume, diminished bilateral hippocampal volume and minimally diminished OFC and ACC volumes. Given the developmental immaturity of the latter two regions which demonstrate synaptic reorganization throughout one's 20s, we thus anticipate

the observable impact on these regions to be minimal at age 9 and 10. Our second aim is to examine the ability of frontolimbic circuitry to *mediate* the relationship between cumulative adversity exposure and CBCL outcomes, for which we anticipated frontolimbic circuitry to partially *mediate* the relationship between both outcomes. Finally, we aim to assess the ability of sources of resiliency to *moderate* the impact of adversity exposure on associated neural and behavioral outcomes. Given the extant literature on sources of resiliency, we postulated that all forms of resiliency would have an impact on amygdala and hippocampal volumes, particularly, school-based support, peer support and parental support. We did not anticipate changes in the OFC or ACC given that this circuitry is very much burgeoning. This study will examine six sources of resiliency: 1) school-based support; 2) peer support; 3) parental support; 4) presence of siblings; 5) youth's prosocial behaviors; and 6) youth's religious and spiritual beliefs. Structural neural regions of interest (ROI) include the amygdala, hippocampus, OFC and ACC volumes. Behavioral outcomes include internalizing and externalizing problematic behaviors as well as total problems. This study captured cross-sectional retrospective early life adversity exposure obtained from 11,566 9 and 10-year-old youth enrolled in the Adolescent Brain Cognitive Development (ABCD) Study.

## METHODS

*Protocol.* The present study used the National Data Archive, ABCD version 2.01 baseline data set (Yang 2019) collected between 2016 and 2018 from the ABCD study, the largest longitudinal neuroimaging study of youth development. Over 10,000 youth from 21 different research sites in the United States are enrolled in this 10-year longitudinal study (Volkow 2018). Procedures, sampling and recruitment (Volkow 2018, Barch 2018, Garavan 2018) for the ABCD

study have been described previously. Caregivers provided written informed consent and children provided assent for participation in the study. All procedures were approved by a central institutional review board, and each site has a detailed protocol in place to address reported adversity exposure. The University of California, Los Angeles, institutional review board has indicated that analyses using the publicly released ABCD Study data are not human subjects research and therefore do not require their own approval.

*Measures*

*Sociodemographic Characteristics.* A caregiver-completed demographic questionnaire was used to gather information regarding youth's age, sex, race and ethnicity, as well as family income and primary caregiver's education. These demographic features were employed as covariates in subsequent analyses.

*Early Life Adversity Exposure.* Early life adversity was measured through a series of 14 questionnaires. Across the questionnaires, 47 variables were identified that captured different forms of adversity exposure, including: physical, sexual and emotional abuse; emotional and physical neglect; loss of parent; domestic violence; parental mental health and drug use; and threatening experiences (e.g., witnessing community violence, experiencing death threats). Due to the sensitive nature of the questions and the age of the youth, most of the adversity variables were parent-reported. Youth-report was used to measure family dysfunction and parental emotional abuse. All adversity variables were binarized to indicate the presence or absence of exposure and for standardization across questions and questionnaires. All 47 variables underwent a factor analysis for dimensionality reduction and to identify latent constructs. Descriptive statistics examined the domains of the factor analysis separately while mediation and moderation analyses utilized a cumulative adversity score comprised by summing the domains. Youth with

an adversity score of zero across all domains, such that no form of adversity exposure was endorsed or captured, served as the study's reference group.

*Neuroimaging.* Volumes in $mm^3$ of frontolimbic circuitry, including the amygdala, hippocampus, OFC and ACC, and intracranial space were acquired using FreeSurfer v5.3.0 on $T_1$w MRI sequences obtained from 11,533 ABCD Study youth at baseline. Neuroimaging processing pipelines, employed to correct for motion, artefacts and site and scanner differences, were conducted centrally for all study participants by the Data and Informatics Core at the University of California, San Diego. Details regarding processing pipelines and analyses for common regions of interest can be found at Hagler *et al.* 2019. All neuroimaging metrics used in this study were obtained from the National Data Archive, ABCD version 2.01.

*Clinical Outcomes.* The parent-reported Child Behavior Checklist (Achenbach 2000) was used to assess children's internalizing problems, externalizing problems, as well as total problems, the latter encompassing the sum of all internalizing and externalizing behaviors. Problems over the prior 6 months were captured by this measure and raw scores were converted to t scores, with a t score less than 60 representing normal functioning (Achenbach 2000).

*Sources of Resiliency.* The six categories of resiliency assessed were: 1) school-based support; 2) peer support; 3) parental support; 4) the presence of siblings; 5) youth's prosocial behaviors; and 6) the youth's religious and spiritual beliefs. Analyses were conducted to examine the impact of resiliency at the level of individual questions, at the level of individual categories by averaging the corresponding questions, and across all statistically-significant resiliency categories to obtain a cumulative score. All resiliency variables were binarized to indicate the presence or absence of each source of support and for standardization across questionnaires. The questions comprising each of the 6 different forms of resiliency were averaged to provide

subjects with a resiliency score across each category. Given the understanding that not one source of resiliency in isolation but likely complex interrelations of different forms of resiliency impact the relationship between adversity and psychopathology (Fritz 2018), we examined the impact of cumulative resiliency. A cumulative resiliency score was obtained from the sources of resiliency shown to significantly impact neural regions and behaviors. Our findings indicated that three sources of resiliency significantly impacted neural regions and behaviors. Thus, a cumulative resiliency score was obtained for each subject by summing the presence (or absence) of each statistically-significant resiliency category, for a maximum total cumulative resiliency score of 3.

*Statistical Analyses.* All data were analyzed using R version 3.5.1 (R Project for Statistical Computing) (R 2018). To organize, categorize and weigh the study's adversity variables, we utilized the domains derived from the exploratory factor analysis due to its noted ability to capture latent constructs (Finch 2020). Factor analyses were performed on all adversity questions using square multiple correlations as prior communality estimates with oblique rotation (Promax) of factors. Parallel analyses were performed and we assessed the fit with three different factoring methods - principal factor solution, minimum residual, and generalized weighted least squares - and with 5 to 8 factors. The number of factors was determined using scree plots, proportion of common variance explained by the factors, parallel analysis, and interpretability of factors. We utilized oblique rotations as they allow the resulting factors to be correlated. For each exploratory factor analysis performed, we extracted the chi-square value, the standardized root mean square residual (SRMR), and the root mean square error of approximation (RMSEA), Tucker Lewis Index (TFI), and comparative fit index (CFI). Indices corresponding to goodness of fit were SRMR values >0.1, RMSEA values ≤0.05, TFI and CFI

values >0.9 (Finch 2020). Our selected model's fit corresponds to: RMSEA value = 0.02, TFI and CFI values >0.85. Variables were considered to load on a factor if the factor loading was ≥0.40. No variables loaded on more than one factor. Using the factors from the final analysis with the entire sample, factor scores were calculated for each youth and compared across CBCL outcomes using ANOVA models.

Factor scores corresponding with cumulative adversity exposure were examined via linear regression models employing the R package "lm". Regression and interaction models employed cumulative adversity exposure, 6 forms of resiliency, CBCL outcomes, and 4 frontolimbic ROI volumes in $mm^3$. Statistical significance was set at 2-sided $p < 0.05$.

We next examined whether frontolimbic circuitry *mediated* the impact of cumulative adversity on clinical outcomes, specifically, internalizing, externalizing and total problems. Mediation analyses were conducted employing the R package "mediation". Finally, we examined whether disparities in the impact of cumulative adversity exposure on ROIs and behavioral outcomes were *moderated* by 6 different sources of resiliency. An ANOVA employing a Chi-square test and simple slopes analysis were used to identify significant interactions. In all linear, mediation and moderation models, youth's age, sex, race and ethnicity, as well as family income and primary caregiver's education were controlled. All models examining frontolimbic circuitry as the outcome controlled for intracranial volume; instances of significant findings in the absence of controlling for intracranial volume are otherwise specified. To adjust for multiple comparisons across all analyses we utilized Benjamini-Hochberg corrections at $p < 0.05$.

## RESULTS

*Sociodemographic Characteristics.* The demographic and clinical characteristics of the sample are shown in Table 1. Youth with an adversity score of zero across all domains, such that no form of adversity exposure was endorsed or captured, served as the study's reference group (n = 915).

*Overview.* Descriptive statistics were run using the 6 factor domains while mediation and moderation analyses utilized a cumulative adversity score comprised of the 6 domains. A six-factor solution was identified for the final factor analysis utilizing a principal factor solution and oblique rotation. As shown in Table 2, this solution gives clearly interpretable factors entitled: 1) physical and sexual violence; 2) parental mental health; 3) neighborhood threat; 4) prenatal substance exposure; 5) scarcity; and 6) household dysfunction. Individuals with higher factor scores across the following domains had more internalizing problems: physical and sexual violence; parental mental health; and scarcity. Conversely, individuals with higher factor scores across the following domains had higher externalizing problems: neighborhood threat; prenatal substance exposure; and household dysfunction. Internalizing and externalizing problematic behaviors can be assessed by anxious, depressed, withdrawn, rule breaking and aggressive behavior.

*Mediation Analyses.* Mediation models were conducted for 4 separate neural ROIs that served as possible mediators between the association of cumulative early life adversity (independent variable) and each CBCL outcome, i.e. internalizing, externalizing and total problems (dependent variables). See the steps outlined in Table 4 detailing the mediating effects of frontolimbic circuitry on the association between early life adversity and CBCL outcomes,

adjusted for covariates. Mediation analyses were performed according to Baron and Kenny (1986) criteria and a quasi-Bayesian approximation was used to calculate confidence intervals.

*Frontolimbic Circuitry on Internalizing Behaviors.* Mediation models showed that right amygdala volume partially mediated the association between early life adversity exposure and internalizing behaviors ($p \leq 0.001$; total effect: 1.02, BCa 95% CI: 0.94–1.11; indirect effect: 0.00, BCa 95% CI: 0.00–0.01). See Figure 2a.

*Frontolimbic Circuitry on Externalizing Behaviors.* Mediation models showed that left amygdala volume partially mediated the association between early life adversity exposure and externalizing behaviors ($p \leq 0.001$; total effect: 1.15, BCa 95% CI: 1.07–1.23; indirect effect: 0.00, BCa 95% CI: 0.00–0.01). Left hippocampal volume partially mediated the association between early life adversity exposure and externalizing behaviors ($p \leq 0.001$; total effect: 1.14, BCa 95% CI: 1.07–1.23; indirect effect: 0.00, BCa 95% CI: 0.00–0.01). Right hippocampal volume also partially mediated the association between early life adversity exposure and externalizing behaviors ($p \leq 0.001$; total effect: 1.15, BCa 95% CI: 1.07–1.22; indirect effect: 0.00, BCa 95% CI: 0.00–0.01). See Figure 2b.

Mediation models examining bilateral OFC and ACC volumes did not mediate the association between early life adversity exposure and externalizing behaviors when controlling for covariates ($p > 0.10$).

*Frontolimbic Circuitry on Total Problems.* Mediation models showed that left amygdala volume partially mediated the association between early life adversity exposure and total problems ($p \leq 0.001$; total effect: 1.36, BCa 95% CI: 1.27–1.44; indirect effect: 0.00, BCa 95% CI: 0.00–0.01). Furthermore, right amygdala volume partially mediated the association between early life adversity exposure and total problems ($p \leq 0.001$; total effect: 1.36, BCa 95% CI: 1.27–

1.45; indirect effect: 0.01, BCa 95% CI: 0.00–0.01). Left hippocampal volume partially mediated the association between early life adversity exposure and total problems ($p \leq 0.001$; total effect: 1.36, BCa 95% CI: 1.27–1.45; indirect effect: 0.00, BCa 95% CI: 0.00–0.01). Right hippocampal volume also partially mediated the association between early life adversity exposure and total problems ($p \leq 0.001$; total effect: 1.36, BCa 95% CI: 1.27–1.44; indirect effect: 0.00, BCa 95% CI: 0.00–0.01). See Figure 2c.

Mediation models examining bilateral OFC and ACC volumes did not mediate the association between early life adversity exposure and total problems when controlling for covariates ($p > 0.12$).

*Moderation Analyses.* Moderation analyses were conducted to examine whether 6 different forms of resiliency interact with cumulative adversity exposure to alter the impact on frontolimbic circuitry and CBCL outcomes. Interactions were interpreted through the plotting of estimates (i.e. neural ROI volumes and behavioral outcomes) by cumulative adversity exposure and presence of resiliency sources. The results of these analyses are presented in Table 5. For each possible source of resiliency, moderation models were ran and presented first for neural outcomes and then for behavioral outcomes.

*Parental Support*. An interaction effect between cumulative adversity and parental support averaged across 5 domains were found on left ($p = 0.0223$) and right ($p = 0.00428$) hippocampal volumes. A higher adversity burden captured at ages 9 and 10 was associated with a larger left hippocampal volume ($F(1,11527) = 398.8$, $p = 0.02545$, adjusted $R^2 = 0.38$, $f^2 = 0.61$)

and a larger right hippocampal volume ($F(1,11527) = 482.5$, $p = 0.00517$, adjusted $R^2 = 0.43$, $f^2 = 0.75$) among youth in comparison with controls.

When examining the individual characteristics that summed to total parental support, the primary caregiver's ability to validate and smile impacted cumulative adversity's association with hippocampal volume. An interaction effect between cumulative adversity and caregiver validation were found on left ($p = 0.00316$) and right ($p = 0.01778$) hippocampal volumes. A higher adversity burden captured at ages 9 and 10 was associated with a larger left hippocampal volume ($F(1,11527) = 399.2$, $p = 0.003158$, adjusted $R^2 = 0.38$, $f^2 = 0.61$) and a larger right hippocampal volume ($F(1,11527) = 482.2$, $p = 0.01781$, adjusted $R^2 = 0.43$, $f^2 = 0.75$) among youth in comparison with controls. An interaction effect between cumulative adversity and caregiver smiling was found on right hippocampal volumes ($p = 0.01438$). Frequent parental smiling also moderated the impact of cumulative adversity on right hippocampal volume ($F(1,11527) = 482.3$, $p = 0.01322$, adjusted $R^2 = 0.43$, $f^2 = 0.75$), but not left ($F(1,11527) = 398.6$, $p > 0.10$, adjusted $R^2 = 0.38$, $f^2 = 0.61$). The presence of total parental support as well as individual features did not moderate cumulative adversity's impact on bilateral amygdala, OFC or ACC volumes.

When examining behavioral outcomes, a main effect of cumulative adversity and an interaction effect between cumulative adversity and total parental support (summed across 5 domains) were found on internalizing behaviors. A higher adversity burden captured at ages 9 and 10 was associated with greater internalizing behaviors ($F(1,11521) = 56.6$, $p = 0.03129$, adjusted $R^2 = 0.08$, $f^2 = 0.09$) among youth in comparison with controls. When examining the individual characteristics that summed to total parental support, a main effect of cumulative adversity ($p < 0.001$) and an interaction effect between cumulative adversity and love and

affection ($p = 0.03206$) were found on externalizing behaviors. Parental love and affection moderated the impact of adversity exposure on externalizing behaviors ($F(1,11521) = 77.1$, $p = 0.03281$, adjusted $R^2 = 0.10$, $f^2 = 0.11$). No significant effects were found for parental support's ability to moderate cumulative adversity's impact on total problematic behaviors.

*School-based Support.* The total average school support did not moderate cumulative adversity's impact on frontolimbic circuitry, specifically, bilateral amygdala, hippocampus, OFC or ACC volumes. Null findings remained whether or not intracranial volume was corrected for.

When examining the individual characteristics that comprised and averaged to total school-based support, the youth's perception of their intelligence in relation to their peers, and whether they got along with their teachers impacted cumulative adversity's association with hippocampal volume. Specifically, an interaction effect between cumulative adversity and youth's perception of their intelligence ($p = 0.04597$) were found on right hippocampal volumes. A higher adversity burden captured at ages 9 and 10 was associated with a *smaller* right hippocampal volume ($F(1,11505) = 481.7$, $p = 0.04317$, adjusted $R^2 = 0.43$, $f^2 = 0.75$) when controlling for intracranial volume among youth in comparison with controls. Lastly, a main effect of cumulative adversity ($p = 0.03560$) and an interaction effect between cumulative adversity and whether youth got along with their teachers ($p = 0.04292$) were found on left hippocampal volumes. A higher adversity burden captured at ages 9 and 10 was associated with a *smaller* left hippocampal volume ($F(1,11506) = 110$, $p = 0.04775$, adjusted $R^2 = 0.14$, $f^2 = 0.16$) among youth in comparison with controls. When controlling for intracranial volume, the findings were null ($F(1,11505) = 397.8$, $p > 0.07$, adjusted $R^2 = 0.38$, $f^2 = 0.61$).

When examining behavioral outcomes, a main effect of cumulative adversity ($p < 0.001$) and an interaction effect between cumulative adversity and the presence of total school support

($p = 0.00693$) were found on internalizing behaviors. The association between higher adversity burden captured at ages 9 and 10 and greater internalizing behaviors was moderated if school support was present ($F(1,11521) = 60.02$, $p = 0.008778$, adjusted $R^2 = 0.08$, $f^2 = 0.09$). When examining the individual characteristics that comprised and averaged to total school-based support, the youth's perception of their intelligence in relation to their peers, and whether they got along with their teachers impacted cumulative adversity's association with problematic behaviors. Specifically, a main effect of cumulative adversity ($p < 0.001$) and an interaction effect between cumulative adversity and youth's perception of their intelligence ($p = 0.012889$) were found on internalizing behaviors. A higher adversity burden captured at ages 9 and 10 was associated with higher internalizing behaviors ($F(1,11500) = 59.51$, $p = 0.01431$, adjusted $R^2 = 0.08$, $f^2 = 0.09$) among youth in comparison with controls. Lastly, a main effect of cumulative adversity ($p < 0.001$) and an interaction effect between cumulative adversity and whether youth got along with their teachers ($p = 0.02009$) were found on internalizing behaviors. The association between higher adversity burden captured at ages 9 and 10 and greater internalizing behaviors was moderated if youth got along with their teachers ($F(1,11500) = 58.38$, $p = 0.01813$, adjusted $R^2 = 0.07$, $f^2 = 0.08$). No significant effects were found for school-based support's ability to moderate cumulative adversity's impact on externalizing behaviors and total problematic behaviors.

*Prosociality.* A main effect of cumulative adversity ($p = 0.02854$ and $p = 0.00122$) and an interaction effect between cumulative adversity and youth's prosociality ($p = 0.02296$ and $p = 0.01975$) were found on left and right hippocampal volumes, respectively. A higher adversity burden captured at ages 9 and 10 was associated with a smaller left hippocampal volume ($F(1,11528) = 115.8$, $p = 0.02633$, adjusted $R^2 = 0.14$, $f^2 = 0.16$) and a smaller right hippocampal

volume ($F(1,11528) = 115.8$, $p = 0.0221$, adjusted $R^2 = 0.14$, $f^2 = 0.16$) among youth among youth who did not endorse prosociality in comparison with controls. When controlling for intracranial volume, the findings were null ($F(1,11527) = 398.6$, $p > 0.09$, adjusted $R^2 = 0.38$, $f^2 = 0.61$). Significance did not survive multiple comparisons correction via Benjamini-Hochberg correction at $p < 0.05$ ($F(1,11528) = 115.8$, $p > 0.17$).

When examining the individual characteristics that comprised and averaged to total prosociality, the youth's propensity to be kind to others and care about their feelings impacted cumulative adversity's association with hippocampal volume. A main effect of cumulative adversity ($p = 0.04105$ and $p = 0.00173$) and an interaction effect between cumulative adversity and being kind and caring towards others ($p = 0.00366$ and $p = 0.00400$) were found on left and right hippocampal volumes, respectively. A higher adversity burden captured at ages 9 and 10 was associated with a *larger* left hippocampal volume ($F(1,11501) = 110.5$, $p = 0.003774$, adjusted $R^2 = 0.14$, $f^2 = 0.16$) and a *larger* right hippocampal volume ($F(1,11501) = 124.3$, $p = 0.003846$, adjusted $R^2 = 0.15$, $f^2 = 0.18$) among youth who did not endorse prosociality in comparison with controls. When controlling for intracranial volume, the findings were null ($F(1,11500) = 397.4$, $p > 0.17$, adjusted $R^2 = 0.38$, $f^2 = 0.61$).

Lastly, the presence of youth's total prosociality as well as the individual features of being kind and caring towards other, and helping those in need did not moderate cumulative adversity's impact on bilateral amygdala, OFC or ACC volumes. No significant effects were found for the presence of youth's prosociality to moderate cumulative adversity's impact on internalizing, externalizing and total problematic behaviors. This includes youth's total prosociality as well as the individual features of this domain.

*Cumulative Resiliency.* A cumulative resiliency score was obtained from the three sources of resiliency shown to significantly impact neural regions and behaviors - parental support, school-based support, and prosociality. An individual's cumulative resiliency impacted cumulative adversity's association with right hippocampal volume, while controlling for covariates. While a main effect of cumulative adversity just missed significance ($p = 0.06478$), a significant interaction effect between cumulative adversity and cumulative resiliency was observed on right hippocampal volumes ($p = 0.01956$). The presence of cumulative resiliency did not moderate cumulative adversity's impact on the left hippocampus or bilateral amygdala, OFC and ACC volumes. No significant effects were found for the presence of cumulative resiliency to moderate cumulative adversity's impact on internalizing, externalizing and total problematic behaviors.

## DISCUSSION

This is the first study to comprehensively examine whether different forms of resiliency *moderated* cumulative adversity's impact on structural neurodevelopment and internalizing, externalizing and total problems. Additionally, this study examined whether frontolimbic circuitry *mediated* the relationship between cumulative adversity exposure and CBCL outcomes. Individuals with higher scores across the domains of physical and sexual violence, parental mental health, and scarcity had more internalizing problems. Conversely, individuals with higher scores pertaining to neighborhood threat, prenatal substance exposure, and household dysfunction had higher externalizing problems. As the median onset of all psychiatric disorders is 14 years of age (Kessler 2005), adolescents, particularly those with a history of adversity exposure, are at a heightened risk for psychopathology (Fritz 2018).

When examining the possible moderating relationship between six forms of resiliency and cumulative adversity, the following sources of resiliency impacted frontolimbic circuitry: subtypes of school-based support (i.e. self-perception of intelligence compared with peers and relationship with teachers) and bilateral hippocampal volumes; total parental support, in addition to the ability of the caregiver to validate and smile, and bilateral hippocampal volume.

When examining the possible moderating relationship between different forms of resiliency and cumulative adversity exposure, the following sources impacted CBCL outcomes: subtypes of school-based support (i.e. self-perception of intelligence compared with peers and relationship with teachers) and internalizing behaviors; subtypes of parental support (i.e. love and affection) and externalizing behaviors; peer support and internalizing behaviors; and, the presence of siblings, specifically, both younger and twin siblings and internalizing behaviors and total problems. While associations with externalizing problematic behaviors were rarely noted, internalizing and externalizing behaviors possess a shared neurobiology and in instances, co-occur (Merz 2018). For example, reduced self-regulatory control over emotions and reward-related behaviors are shared features (Merz 2018).

Mediation of frontolimbic circuitry on the association between early life adversity and CBCL outcomes identified the following: 1) the ability of the right amygdala volume to partially mediate the association between early life adversity exposure and internalizing behaviors; 2) the ability of the left amygdala and bilateral hippocampus to partially mediate the association between early life adversity exposure and externalizing behaviors; and 3) the ability of bilateral amygdala and bilateral hippocampal volumes to partially mediate the association between early life adversity exposure and total problems. Thus, early life adversity exposure is associated with

altered amygdala and hippocampal volume, which increases the risk of problematic internalizing and externalizing behaviors.

*The Hippocampus as a Developmental Target of Adversity.* The hippocampus plays an essential role in the formation and retrieval of memories, learning, and emotion processing. It is especially vulnerable earlier in life (Tottenham 2010; Kirbakaran 2020), which may in part explain this study's findings. High concentrations of glucocorticoids can downregulate hippocampal receptors that, under normal conditions, function to aid the negative feedback loop of the hypothalamic pituitary adrenocortical (HPA) axis (Tottenham 2010). After a stressor is removed and high circulating glucocorticoids are no longer necessary, glucocorticoids act on receptors in the hippocampus to suppress HPA axis activation, and eventual inhibition of HPA axis activity (Tottenham 2010). However, during development, such as adolescence, the density of glucocorticoid receptors is enhanced and stress-induced HPA axis activation disrupts hippocampal functioning. Adversity is hypothesized to affect dendritic arborization of pyramidal cells in CA3, neurogenesis in the dentate gyrus, and in extreme instances, global neurotoxicity. In non-human primates, direct cortisol administration to the hippocampus has resulted in dendritic atrophy and soma shrinkage (Kirbakaran 2020).

Our study found that individual differences in hippocampal volumes partially mediated the contribution of early life adversity exposure to increased behavioral problems, replicating a previous finding by Hanson and colleagues (2015) among a similarly-aged sample of youth. As the hippocampus projects to the amygdala and PFC (among other neural regions), hippocampal and amygdala co-modulation will not only affect hippocampally- mediated memory formation but amygdala responsivity to emotional stimuli. Given the existing literature, alterations in other frontolimbic regions may be taking place but the effects are difficult to observe for a variety of

reasons. There may be a silent period between exposure to maltreatment and discernible neurobiological differences, with observable cross-sectional differences becoming fully discernible in the period between puberty and adulthood (Andersen 2004).

Studies examining the impact of early life adversity exposure on hippocampal development have routinely noted decreased hippocampal volume in response to exposure, irrespective of comorbid psychiatric disorders (Tottenham 2010; Calem 2017; Cassiers 2018). The hippocampus is also often structurally and functionally impaired in a variety of psychiatric disorders (Teicher 2016). Hippocampal alterations may be associated with aberrant fear extinction due to its role in memory functioning (Ahmed-Leitao 2016). Additionally, volumetric reductions resulting from adversity exposure are associated with behavioral problems and may be attributable to less overproduction of synapses during puberty (Ahmed-Leitao 2016).

Regarding lateralization of the hippocampus, the left hippocampus has shown responsivity via functional MRI to socioaffective stimuli (Heany 2018) and in rodents, only high levels of anxiety impacted the right hippocampus (whereas low levels impacted the hippocampus bilaterally) (Sakaguchi 2017). The right hippocampus reaches maximal volume 1 year earlier than the left hippocampus (Ahmed-Leitao 2016) and the number of cells between the hippocampi differ, as do and types and densities of synaptic receptors present (Sakaguchi 2017). The left and right hippocampus secrete different amounts of neurotransmitters and stress hormone in response to stress; this functional asymmetry is proposed to have evolutionary advantages in sympathetic nervous system responding (Sakaguchi 2017).

The hippocampus, in particular, has demonstrated reversibility in structural alterations due to stress following extended periods of relief (Hanson 2015). It is thus paramount to identify

sources of resiliency in all features of a developing person's life that can combat the detrimental effects of early life adversity.

*Sources of Resiliency to Adversity*

*Parental Support*. Parental support, including high levels of parental warmth, sensitivity and emotional support, have been shown to ameliorate the impact of adverse experiences and improve cardiometabolic, inflammatory and neurodevelopmental profiles extending into adulthood (Brody 2017). Our study found that the primary caregiver's ability to validate and smile lessened cumulative adversity's association with bilateral hippocampal volume reductions and increased internalizing behaviors. The primary caregiver's love and affection moderated the impact of adversity exposure on externalizing behaviors. An evidence-based family intervention program, the Strong African American Families, ameliorated the impact of years lived in poverty on youth's hippocampal volume reductions and depressive symptomology by enhancing supportive parenting (Brody 2017). While the study was underpowered to detect individual parenting practices that may be responsible for the buffering effects, some of which lasted into adulthood (Brody 2017), the inclusion of consistent emotional support is validated by previous studies. Among a sample of girls with early life adversity exposure, the presence of a warm and supportive parent served a protective role against psychopathology (Jaffee 2017). Similarly, the association between violence exposure and PTSD symptoms was moderated by positive parenting (Fritz 2018). Of note, women are twice as likely as men to develop trauma-related psychopathology, and tend to develop mood disorders while men often present with more externalizing psychopathology (Helpman 2017).

*School-based Support.* Youth's perception of a supportive school environment, including the quality of teacher and peer relationships, are associated with academic achievements and reductions in risky behaviors, such as violence perpetration (Piccolo 2019). Our study found that youth's perception

of their intelligence in relation to their peers and whether they got along with their teachers impacted cumulative adversity's association with hippocampal volume and internalizing behaviors. School-based support has been shown to mitigate deficiencies in inhibitory control, cognitive flexibility and working memory among young from low socioeconomic status (SES) households (Piccolo 2019). Working memory, or the ability to hold and manipulate information in one's mind, is negatively impacted by prolonged and unpredictable stress (Dominguez 2019). As children and adolescents spend a large proportion of their time in school, school climate is positioned to contribute vastly to brain development, for better or worse. Youth from disadvantaged neighborhoods are more likely to attend lower quality schools and be exposed to adversity (Piccolo 2019), in turn, influencing neurodevelopment and cognitive functioning. The detrimental effects of an unsupportive school environment may be magnified in the context of socioeconomic disadvantage (Piccolo 2019).

*Prosociality*. Providing support, or prosociality, has been shown to dampen physiological responses to stress in experimental conditions, reduce stress reactivity in frontolimbic regions, and increase reactivity in reward regions of the brain (Malhi 2019). Our study found that youth's propensity to be kind to others and care about their feelings impacted cumulative adversity's association with bilateral hippocampal volume, only when intracranial volume was not controlled for. This may highlight a nonlinear relationship between total intracranial volume and regional brain volume (Goddings 2019). Resilient youth tend to carry an internal locus of control characterized by high self-esteem and self-reliance, as well as the tendency to attribute successes to their own efforts (Jaffee 2017). In their systematic review, Fritz and colleagues (2018) emphasize individual and family-level resiliency factors as being the most effective in curbing psychopathology-risk associated with adversity exposure. While our findings did not demonstrate the ability of prosociality to moderate cumulative adversity's impact on any problematic behaviors among 9 and 10-year-olds, prosociality may have a greater impact on

lessening problematic behaviors as youth become more peer-oriented as they age throughout adolescence.

*Other Forms of Support*

*Presence of Siblings.* A longitudinal study of 132 families identified the ability of sibling affection to moderate the relationship between stressful life events in a younger sibling's life and internalizing symptomatology (Gass 2006). The questions assessing the presence of siblings were not nuanced enough to identify whether the youth lived with their siblings or had an existing relationship with them. While the presence of an older sibling has been associated with increased risk for adolescent substance use (Whiteman 2016), our findings show that the mere presence of a sibling (i.e. younger and twin) moderated cumulative adversity's impact on internalizing and total problematic behaviors. While moderation analyses examining frontolimbic circuitry were null, future research should examine the relationship quality youth have with their siblings and its ability to moderate the impact of adversity exposure.

*Peer Support.* Regardless of history of adversity, more peer support is associated with lower levels of depressive symptomology and other forms of psychopathology (Jaffee 2017; Fritz 2018). The ability of social support to buffer the impact of adversity exposure displays gender differences, albeit mixed findings (Jaffee 2017). Our study found that the presence of peer support moderated cumulative adversity's association with left OFC volume and internalizing and problematic behaviors - but only for male youth. Limitations in assessing the impact the presence of a close peer network may play may in part be attributable to the youth's understanding of perceived closeness. Some youth were unsure of what a close friendship entailed and as such, listed all individuals they regularly associated with, such as all classmates. Future research would benefit from framing the question away from a count of close friendships, as that carries great individual variability, to one more specific and age-appropriate, such as,

"Do you have a close number of friends you can share secrets with and count on?". Additionally, future studies should not limit the assessment of youth's peer network to peers of the same sexual and gender orientation.

*Religious and Spiritual Beliefs.* Null findings attributable to the presence of religious or spiritual beliefs is likely twofold. First, the impact of the youth's religious and spiritual beliefs may best be assessed by asking the youth directly and when they're older, given that at the age of 9 and 10 youth are often defacto participants in their caregiver's religious and spiritual practices and beliefs. Secondly, religiosity and spirituality may carry particular significance for youth of specific cultures (i.e. Indigenous, Native or Mexican American) especially if these beliefs are used to remedy, explain or recover from hardships and stressors. As studies have examined religiosity in tandem with other sources of resiliency (Malhi 2019), additional research is needed to examine religiosity and spirituality as sources of resiliency against early life adversity exposure.

## LIMITATIONS

The presence of early life adversity exposure captured in this study represent one time point (i.e. baseline) and may not be evident of chronic exposure. In instances where the caregiver may be unaware of exposure or may be associated either directly or indirectly with its perpetuation, the findings may not accurately reflect exposure. As youth age, we encourage sensitive physical and sexual abuse questions to be asked directly of youth participants. As neuroimaging is captured biannually, even delayed notification of early life adversity exposure will be beneficial in associating adversity's impact with neurodevelopment and ensuing behavioral outcomes. Given the impact of other physiological processes (e.g. puberty, epigenetics) on the relationship between early life adversity and associated outcomes (Piccolo

2018; Laube 2020), future studies would benefit from examining the influence of these processes in concert.

Lastly, recent prevalence estimates of type-specific and cumulative early life adversity exposure obtained from over 200,000 adults participating in the Behavioral Risk Factor Surveillance System indicate rates double that of the current study's (Merrick 2018). Given that exposure was assessed retrospectively in adults and this is the first nationwide study to prospectively (from baseline) examine the prevalence of adversity exposure in a population-based study of youth, we do not have a comparison with which to assess our study's prevalence rates by. For this and many reasons, the ABCD Study is poised to significantly contribute and advance our knowledge of youth physiological and social development, while capturing the many factors that influence it. Finally, participants enrolled in the ABCD Study possess a higher educational attainment and larger household income than national averages (Merrick 2018).

## CONCLUSION

Youth and adults with histories of early life adversity tend to experience lower levels of social support from friends and family members, as well as less stable social support throughout the lifespan (Jaffee 2017). This may contribute to elevated psychopathology rates, often displaying sex-differences. The hippocampus is suggested to play a role in resiliency through information processing, as well as stress and emotion regulation. The hippocampus is especially vulnerable earlier in life (Tottenham 2010; Kirbakaran 2020), which may in part explain this study's findings. Individuals with higher scores across the domains of physical and sexual violence, parental mental health, and scarcity had more internalizing problems. Conversely, individuals with higher scores pertaining to neighborhood threat, prenatal substance exposure,

and household dysfunction had higher externalizing problems. School-based support and parental support independently moderated the relationship between adversity exposure and bilateral hippocampal volumes. School-based support, parental support, the presence of siblings and peer support moderated the relationship between adversity exposure and CBCL outcomes. Finally, the amygdala and hippocampus partially mediated the association between early life adversity exposure and CBCL outcomes. Given the increased functional connectivity between the hippocampus, amygdala and medial PFC among those with early life adversity exposure and or PTSD (McLaughlin 2019), it is anticipated that as these youth age, it will be essential to utilize longitudinal ABCD Study data to examine how this frontolimbic circuitry evolves in adversity-exposed youth. Resilience is a dynamic construct and while the impact of individual sources of resiliency may adjust throughout development, the quality of these sources can ultimately be improved upon (Fritz 2018).

## TABLES

| Table 1. Demographic Characteristics of ABCD Study Youth at Baseline (n=11566) | |
|---|---|
| **Characteristic** | **No. (%)** |
| **Age, y** | |
| 9 | 6090 (52.7) |
| 10 | 5469 (47.3) |
| **Sex[a]** | |
| Male | 6042 (52.3) |
| Female | 5512 (47.7) |
| **Race/ethnicity** | |
| White | 6016 (52.0) |
| Black | 1730 (15.0) |
| Hispanic | 2340 (20.2) |
| Asian | 244 (2.1) |
| Other | 1229 (10.6) |
| **Household income[a], $** | |
| 0-24,999 | 1593 (15.1) |
| 25,000-49,999 | 1544 (14.6) |
| 50,000-74,999 | 1454 (13.8) |
| 75,000-99,999 | 1529 (14.5) |
| 100,000+ | 4444 (42.1) |
| **Primary caregiver's educational attainment[a]** | |
| Less than HS diploma | 765 (6.6) |
| HS diploma/GED | 1231 (10.7) |
| Some college or AA degree | 3397 (29.4) |
| Bachelors degree | 3235 (28.0) |
| Graduate and professional school | 2911 (25.2) |
| **Clinical Outcomes** | |
| Internalizing problems ≥ t-score of 60 | 1940 (16.7) |
| Externalizing problems ≥ t-score of 60 | 1211 (10.5) |
| Total problems ≥ t-score of 60 | 1414 (12.2) |
| **Adversity Exposure** | |
| Physical and sexual violence | 843 (7.3) |
| Parental mental health | 9413 (81.4) |
| Neighborhood safety | 2304 (19.9) |
| Prenatal substance exposure | 1224 (10.6) |
| Scarcity | 1348 (11.7) |
| Household dysfunction | 4867 (42.1) |

[a]Five youth were missing data indicating sex; 995 youth were missing data describing family income; 20 youth were missing data describing primary caregiver's education.

**Table 2: Early life adversity factor structure (loadings) in 9 and 10 year olds at baseline (n = 11500)**

| | Rotated factor-pattern (standardized regression coefficients) | | | | | |
|---|---|---|---|---|---|---|
| ***Lifetime exposure*** | **Factor 1: Physical and sexual violence** | **Factor 2: Parental mental health** | **Factor 3: Neighborhood Safety** | **Factor 4: Prenatal substance exposure** | **Factor 5: Scarcity** | **Factor 6: Household dysfunction** |
| Beaten by family member | 0.797 | | | | | |
| Beaten by non-family member | 0.795 | | | | | |
| Received bruises from beating | 0.575 | | | | | |
| Sexually assaulted by family member | 0.653 | | | | | |
| Sexually assaulted by non-family member | 0.571 | | | | | |
| Sexually assaulted by peer | 0.39 | | | | | |
| Witness community shooting/stabbing | 0.492 | | | | | |
| Threatened to kill by family member | 0.545 | | | | | |
| Threatened to kill by non-family member | 0.593 | | | | | |
| Parental alcohol misuse | | 0.463 | | | | |
| Parental drug misuse | | 0.478 | | | | |
| Parental depression | | 0.605 | | | | |
| Parental bipolar disorder | | 0.437 | | | | |
| Parental psychosis | | 0.377 | | | | |
| Parent sought mental health counseling | | 0.630 | | | | |
| Parent hospitalized for mental health | | 0.657 | | | | |
| Parent attempted/committed suicide | | 0.501 | | | | |
| Neighborhood safety | | | 0.769 | | | |
| Neighborhood violence | | | 0.796 | | | |
| Prenatal tobacco exposure | | | | 0.344 | | |
| Prenatal alcohol exposure | | | | 0.388 | | |
| Prenatal cannabis exposure | | | | 0.422 | | |
| Prenatal crack/cocaine exposure | | | | 0.574 | | |
| Prenatal heroin/morphine exposure | | | | 0.402 | | |
| Prenatal opioid exposure | | | | 0.459 | | |
| Food insecurity | | | | | 0.679 | |
| Utility services (gas, electric) turned off | | | | | 0.691 | |
| Family members hit one another | | | | | | 0.495 |
| Family members fight | | | | | | 0.615 |
| Family members criticize | | | | | | 0.462 |

**Table 3: Factor score comparison by clinical outcomes (n = ; mean [SE] shown, controlling for age, sex and race/ethnicity, primary caregiver's education, and family income)**

| | Rotated factor-pattern (standardized regression coefficients) | | | | | |
|---|---|---|---|---|---|---|
| | **Internalizing problems** | **p-value** | **Externalizing problems** | **p-value** | **Total problems** | **p-value** |
| Factor 1: Physical and sexual violence | 0.613 (0.106) | < 0.0001 | 0.5001 (0.102) | 0.0001 | 0.681 (0.111) | 0.0001 |
| Factor 2: Parental mental health | 2.762 (0.116) | < 0.0001 | 2.420 (0.112) | 0.0001 | 3.262 (0.121) | 0.0001 |
| Factor 3: Neighborhood Safety | 1.335 (0.129) | < 0.0001 | 1.401 (0.125) | 0.0001 | 1.651 (0.136) | 0.0001 |
| Factor 4: Prenatal substance exposure | 1.002 (0.130) | < 0.0001 | 1.677 (0.125) | 0.0001 | 1.699 (0.137) | 0.0001 |
| Factor 5: Scarcity | 0.365 (0.173) | 0.0346 | 0.317 (0.167) | 0.058 | 0.428 (0.182) | 0.0189 |
| Factor 6: Household dysfunction | 1.439 (0.136) | < 0.0001 | 2.481 (0.130) | 0.0001 | 2.447 (0.143) | 0.0001 |

**Table 4: Mediating effect of frontolimbic circuitry on the association between early life adversity and CBCL outcomes, adjusted for age, sex, race/ethnicity, primary caregiver's education and family income. Mediation analyses according to Baron and Kenny (1986) criteria and Bootstrapping.**

| | Step 1 | | | | Step 2 | | | | Step 3 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Internalizing Problems (DV); Cumulative Adversity (IV) | | | | Brain Volume (M); Cumulative Adversity (IV) | | | | Internalizing Problems (DV); Brain Volume (M)b; Cumulative Adversity (IV)a | | | |
| | B | SE | p | 95% BCa | B | SE | p | 95% BCa | B | SE | p | 95% BCa |
| Left amygdala volume (mm3) | 1.018 | 0.042 | < 0.001 | [0.94 to 1.10] | -2.181 | 0.857 | 0.011 | [-3.86 to -0.49] | 1.017a; -0.0009b | 0.042a; 0.000b | < 0.001a,b | [0.93 to 1.10]a; [-0.00 to 0.000]b |
| Right amygdala volume (mm3) | 1.018 | 0.042 | < 0.001 | [0.94 to 1.10] | -3.609 | 0.859 | < 0.001 | [-5.29 to -1.93] | 1.015a; -0.001b | 0.042a; 0.000b | < 0.001a; 0.024b | [0.93 to 1.10]a; [-0.00 to 0.000]b |
| Left hippocampal volume (mm3) | 1.018 | 0.042 | < 0.001 | [0.94 to 1.10] | -3.575 | 1.635 | 0.0288 | [-6.78 to -0.37] | 1.017a; -0.0003b | 0.042a; 0.000b | < 0.001a; 0.046b | [0.93 to 1.10]a; [-0.00 to 0.000]b |
| Right hippocampal volume (mm3) | 1.018 | 0.042 | < 0.001 | [0.94 to 1.10] | -5.157 | 1.604 | 0.001 | [-8.30 to -2.01] | 1.017a; -0.0003b | 0.042a; 0.000b | < 0.001a; 0.047b | [0.93 to 1.10]a; [-0.00 to 0.000]b |
| Left OFC volume (mm3) | 1.018 | 0.042 | < 0.001 | [0.94 to 1.10] | 0.416 | 2.095 | 0.843 | [-3.69 to 4.52] | 1.018a; -0.0242b | 0.042a; 0.000b | < 0.001a; 0.284b | [0.93 to 1.10]a; [-0.00 to 0.000]b |
| Right OFC volume (mm3) | 1.018 | 0.042 | < 0.001 | [0.94 to 1.10] | -2.752 | 2.155 | 0.201 | [-6.97 to 1.47] | 1.018a; -0.0003b | 0.042a; 0.000b | < 0.001a; 0.058b | [0.93 to 1.10]a; [-0.00 to 0.000]b |
| Left ACC volume (mm3) | 1.018 | 0.042 | < 0.001 | [0.94 to 1.10] | -4.069 | 3.045 | 0.181 | [-10.04 to 1.90] | 1.018a; -0.0003b | 0.042a; 0.000b | < 0.001a; 0.031b | [0.93 to 1.10]a; [-0.00 to 0.000]b |
| Right ACC volume (mm3) | 1.018 | 0.042 | < 0.001 | [0.94 to 1.10] | -5.350 | 3.267 | 0.102 | [-11.75 to 1.05] | 1.018a; -0.0002b | 0.042a; 0.000b | < 0.001a; 0.078b | [0.93 to 1.10]a; [-0.00 to 0.000]b |
| | Step 1 | | | | Step 2 | | | | Step 3 | | | |
| | Externalizing Problems (DV); Cumulative | | | | Brain Volume (M); Cumulative Adversity (IV) | | | | Externalizing Problems (DV); Brain Volume (M)b; Cumulative Adversity (IV)a | | | |
| | B | SE | p | 95% BCa | B | SE | p | 95% BCa | B | SE | p | 95% BCa |
| Left amygdala volume (mm3) | 1.146 | 0.041 | < 0.001 | [1.06 to 1.22] | -2.180 | 0.858 | 0.011 | [-3.86 to -0.49] | 1.142a; -0.002b | 0.041a; 0.000b | < 0.001a,b | [1.06 to 1.22]a; [-0.00 to -0.00]b |
| Right amygdala volume (mm3) | 1.146 | 0.041 | < 0.001 | [1.06 to 1.22] | -3.609 | 0.858 | < 0.001 | [-5.29 to -1.93] | 1.140a; -0.002b | 0.041a; 0.000b | < 0.001a,b | [1.06 to 1.22]a; [-0.00 to -0.00]b |
| Left hippocampal volume (mm3) | 1.146 | 0.041 | < 0.001 | [1.06 to 1.22] | -3.575 | 1.636 | 0.028 | [-6.78 to -0.37] | 1.142a; -0.001b | 0.041a; 0.000b | < 0.001a,b | [1.06 to 1.22]a; [-0.00 to -0.00]b |
| Right hippocampal volume (mm3) | 1.146 | 0.041 | < 0.001 | [1.06 to 1.22] | -5.157 | 1.604 | 0.001 | [-8.30 to -2.01] | 1.142a; -0.001b | 0.041a; 0.000b | < 0.001a,b | [1.06 to 1.22]a; [-0.00 to -0.00]b |
| Left OFC volume (mm3) | 1.146 | 0.041 | < 0.001 | [1.06 to 1.22] | 0.416 | 2.095 | 0.842 | [-3.69 to 4.52] | 1.142a; -0.001b | 0.041a; 0.000b | < 0.001a,b | [1.06 to 1.22]a; [-0.00 to -0.00]b |
| Right OFC volume (mm3) | 1.146 | 0.041 | < 0.001 | [1.06 to 1.22] | -2.752 | 2.156 | 0.202 | [-6.98 to 1.47] | 1.142a; -0.001b | 0.041a; 0.000b | < 0.001a,b | [1.06 to 1.22]a; [-0.00 to -0.00]b |
| Left ACC volume (mm3) | 1.146 | 0.041 | < 0.001 | [1.06 to 1.22] | -4.069 | 3.046 | 0.182 | [-10.04 to 1.90] | 1.142a; -0.001b | 0.041a; 0.000b | < 0.001a,b | [1.06 to 1.22]a; [-0.00 to -0.00]b |
| Right ACC volume (mm3) | 1.146 | 0.041 | < 0.001 | [1.06 to 1.22] | -5.351 | 3.267 | 0.102 | [-11.76 to 1.05] | 1.142a; -0.001b | 0.041a; 0.000b | < 0.001a,b | [1.06 to 1.22]a; [-0.00 to -0.00]b |
| | Step 1 | | | | Step 2 | | | | Step 3 | | | |
| | Total Problems (DV); Cumulative Adversity (IV) | | | | Brain Volume (M); Cumulative Adversity (IV) | | | | Total Problems (DV); Brain Volume (M)b; Cumulative Adversity (IV)a | | | |
| | B | SE | p | 95% BCa | B | SE | p | 95% BCa | B | SE | p | 95% BCa |
| Left amygdala volume (mm3) | 1.357 | 0.044 | < 0.001 | [1.27 to 1.44] | -2.181 | 0.858 | 0.011 | [-3.86 to -0.49] | 1.353a; -0.002b | 0.044a; 0.000b | < 0.001a,b | [1.27 to 1.44]a; [-0.00 to -0.00]b |
| Right amygdala volume (mm3) | 1.357 | 0.044 | < 0.001 | [1.27 to 1.44] | -3.609 | 0.858 | < 0.001 | [-5.29 to -1.93] | 1.353a; -0.002b | 0.044a; 0.000b | < 0.001a,b | [1.27 to 1.44]a; [-0.00 to -0.00]b |
| Left hippocampal volume (mm3) | 1.357 | 0.044 | < 0.001 | [1.27 to 1.44] | -3.576 | 1.636 | 0.028 | [-6.78 to -0.37] | 1.353a; -0.002b | 0.044a; 0.000b | < 0.001a,b | [1.27 to 1.44]a; [-0.00 to -0.00]b |
| Right hippocampal volume (mm3) | 1.357 | 0.044 | < 0.001 | [1.27 to 1.44] | -5.157 | 1.605 | 0.001 | [-8.30 to -2.01] | 1.353a; -0.002b | 0.044a; 0.000b | < 0.001a,b | [1.27 to 1.44]a; [-0.00 to -0.00]b |
| Left OFC volume (mm3) | 1.357 | 0.044 | < 0.001 | [1.27 to 1.44] | 0.416 | 2.095 | 0.843 | [-3.69 to 4.52] | 1.353a; -0.002b | 0.044a; 0.000b | < 0.001a,b | [1.27 to 1.44]a; [-0.00 to -0.00]b |
| Right OFC volume (mm3) | 1.357 | 0.044 | < 0.001 | [1.27 to 1.44] | -2.752 | 2.157 | 0.202 | [-6.98 to 1.47] | 1.353a; -0.002b | 0.044a; 0.000b | < 0.001a,b | [1.27 to 1.44]a; [-0.00 to -0.00]b |
| Left ACC volume (mm3) | 1.357 | 0.044 | < 0.001 | [1.27 to 1.44] | -4.069 | 3.046 | 0.182 | [-10.04 to 1.90] | 1.353a; -0.002b | 0.044a; 0.000b | < 0.001a,b | [1.27 to 1.44]a; [-0.00 to -0.00]b |
| Right ACC volume (mm3) | 1.357 | 0.044 | < 0.001 | [1.27 to 1.44] | -5.351 | 3.268 | 0.102 | [-11.76 to 1.05] | 1.353a; -0.002b | 0.044a; 0.000b | < 0.001a,b | [1.27 to 1.44]a; [-0.00 to -0.00]b |

**Table 5: Moderating effect of 6 forms of resiliency on cumulative adversity's impact on a) frontolimbic circuitry and b) CBCL outcomes. Analyses adjusted for age, sex, race/ethnicity, primary caregiver's education and family income.**

| | Left amygdala (mm3) | | Right amygdala (mm3) | | Left hippocampus (mm3) | | Right hippocampus (mm3) | |
|---|---|---|---|---|---|---|---|---|
| **Sources of Resiliency** | B [95% CI] | p | B [95% CI] | p | B [95% CI] | p | B [95% CI] | p |
| **School Support (average)** | | | | | | | | |
| *Cumulative adversity* | 0.076 [-7.43 to 7.59] | 0.984 | -0.010 [-7.75 to 5.52] | 0.997 | 9.638 [-4.47 to 23.75] | 0.181 | 7.986 [-5.45 to 21.42] | 0.244 |
| *Resiliency* | 1.478 [-4.21 to 7.16] | 0.611 | 1.047 [-4.83 to 6.92] | 0.727 | 4.073 [-6.61 to 14.75] | 0.455 | 1.067 [-9.10 to 1.12] | 0.837 |
| *Interaction* | -0.296 [-2.51 to 1.92] | 0.793 | -0.745 [-3.03 to 1.54] | 0.523 | -3.209 [-7.37 to 0.94] | 0.130 | -3.176 [-7.12 to 0.78] | 0.116 |
| **Parental Support (average)** | | | | | | | | |
| *Cumulative adversity* | -3.824 [-13.68 to 6.03] | 0.447 | -2.073 [-12.26 to 8.11] | 0.690 | 20.24 [1.71 to 38.76] | 0.032 | 22.99 [5.36 to 40.62] | **0.011** |
| *Resiliency* | 26.79 [-2.54 to 56.12] | 0.074 | 13.84 [-16.47 to 44.15] | 0.371 | 23.52 [-31.58 to 78.62] | 0.403 | 52.56 [0.11 to 105.01] | **0.049** |
| *Interaction* | 3.244 [-7.14 to 13.62] | 0.540 | -36.51 [-11.09 to 10.36] | 0.947 | -22.73 [-42.22 to -3.22] | **0.022** | -27.06 [-46.61 to 84.94] | **0.004** |
| **Prosociality* (average)** | | | | | | | | |
| *Cumulative adversity* | 0.252 [-5.85 to 6. 35] | 0.935 | -2.312 [-8.61 to 3.99] | 0.472 | 8.277 [-3.19 to 19.74] | 0.157 | 6.579 [-4.33 to 17.49] | 0.237 |
| *Resiliency* | -6.313 [-15.22 to 2.59] | 0.165 | -6.533 [-15.84 to 2.57] | 0.158 | 1.921 [-14.82 to 19.74] | 0.822 | -1.491 [-17.43 to 14.44] | 0.854 |
| *Interaction* | -0.747 [-4.27 to 2.78] | 0.679 | -14.06 [-3.78 to 3.50] | 0.939 | -5.599 [-12.23 to 1.03] | 0.098 | -5.473 [-11.78 to 0.84] | 0.089 |

| | Left OFC (mm3) | | Right OFC (mm3) | | Left ACC (mm3) | | Right ACC (mm3) | |
|---|---|---|---|---|---|---|---|---|
| **Sources of Resiliency** | B [95% CI] | p | B [95% CI] | p | B [95% CI] | p | B [95% CI] | p |
| **School Support (average)** | | | | | | | | |
| *Cumulative adversity* | 0.177 [-18.58 to 18.92] | 0.985 | -5.262 [-26.09 to 15.57] | 0.621 | -5.966 [-32.42 to 20.49] | 0.659 | -11.93 [-41.22 to 17.36] | 0.424 |
| *Resiliency* | 1.493 [-12.70 to 15.69] | 0.837 | -7.673 [-23.44 to 8.09] | 0.340 | 1.809 [-18.22 to 21.84] | 0.859 | -2.916 [-25.09 to 19.25] | 0.796 |
| *Interaction* | 0.935 [-4.59 to 6.46] | 0.740 | 1.271 [-4.87 to 7.41] | 0.685 | 1.937 [-5.85 to 9.72] | 0.626 | 3.275 [-5.35 to 11.90] | 0.457 |
| **Parental Support (average)** | | | | | | | | |
| *Cumulative adversity* | -2.47 [-27.26 to 21.96] | 0.833 | 6.173 [-21.18 to 33.52] | 0.658 | -15.00 [-49.73 to 19.73] | 0.397 | -19.34 [-57.79 to 19.11] | 0.324 |
| *Resiliency* | 45.53 [-27.67 to 118.74] | 0.223 | 26.49 [-54.86 to 107.84] | 0.523 | 45.36 [-57.95 to 148.67] | 0.389 | 47.24 [-67.13 to 161.61] | 0.418 |
| *Interaction* | 6.58 [-19.33 to 32.49] | 0.619 | -7.328 [-36.11 to 21.46] | 0.618 | 16.77 [-19.79 to 53.33] | 0.368 | 19.95 [-20.52 to 60.42] | 0.334 |
| **Prosociality* (average)** | | | | | | | | |
| *Cumulative adversity* | -19.78 [-35.00 to -4.55] | **0.011** | -6.070 [-22.99 to 10.85] | 0.482 | -10.27 [-31.76 to 11.22] | 0.348 | -17.45 [-41.24 to 6.33] | 0.150 |
| *Resiliency* | 0.188 [-22.05 to 22.42] | 0.987 | 6.474 [-18.24 to 31.19] | 0.607 | -14.43 [-45.82 to 16.95] | 0.367 | -4.630 [-39.38 to 30.12] | 0.793 |
| *Interaction* | 13.73 [4.92 to 22.54] | **0.002** | 3.160 [-6.63 to 12.95] | 0.527 | 6.299 [-6.14 to 18.73] | 0.321 | 9.803 [-3.96 to 23.57] | 0.163 |

| | Internalizing Problems | | Externalizing Problems | | Total Problems | | | |
|---|---|---|---|---|---|---|---|---|
| **Sources of Resiliency** | B [95% CI] | p | B [95% CI] | p | B [95% CI] | p | | |
| **School Support (average)** | | | | | | | | |
| *Cumulative adversity* | 1.567 [1.34 to 1.99] | **< 0.001** | 1.195 [0.78 to 1.61] | **< 0.001** | 1.498 [1.05 to 1.94] | **< 0.001** | | |
| *Resiliency* | -1.078 [-1.40 to -0.75] | **< 0.001** | -1.691 [-2.00 to -1.38] | **< 0.001** | -1.812 [-2.15 to -1.47] | **< 0.001** | | |
| *Interaction* | -0.175 [-0.30 to -0.05] | **0.007** | -0.030 [-0.15 to 0.09] | 0.633 | -0.058 [-0.19 to 0.07] | 0.387 | | |
| **Parental Support (average)** | | | | | | | | |
| *Cumulative adversity* | 1.098 [0.53 to 1.66] | **< 0.001** | 1.218 [0.67 to 1.76] | **< 0.001** | 1.298 [0.71 to 1.89] | **< 0.001** | | |
| *Resiliency* | -0.946 [-2.63 to 0.74] | 0.272 | -5.436 [-7.05 to -3.82] | **< 0.001** | -3.962 [-5.73 to -2.20] | **< 0.001** | | |
| *Interaction* | -0.092 [-0.68 to 0.51] | 0.763 | -0.110 [-0.68 to 0.46] | 0.705 | 0.038 [-0.58 to 0.66] | 0.904 | | |
| **Prosociality* (average)** | | | | | | | | |
| *Cumulative adversity* | 1.129 [0.77 to 1.48] | **< 0.001** | 1.320 [0.98 to 1.66] | **< 0.001** | 1.362 [0.99 to 1.72] | **< 0.001** | | |
| *Resiliency* | -0.462 [-0.98 to 0.05] | 0.077 | -1.733 [-2.23 to -1.24] | **< 0.001** | -1.317 [-1.85 to -0.78] | **< 0.001** | | |
| *Interaction* | -0.067 [-0.27 to 0.14] | 0.512 | -0.112 [-0.31 to 0.08] | 0.258 | -0.009 [-0.22 to 0.20] | 0.930 | | |

**FIGURES**

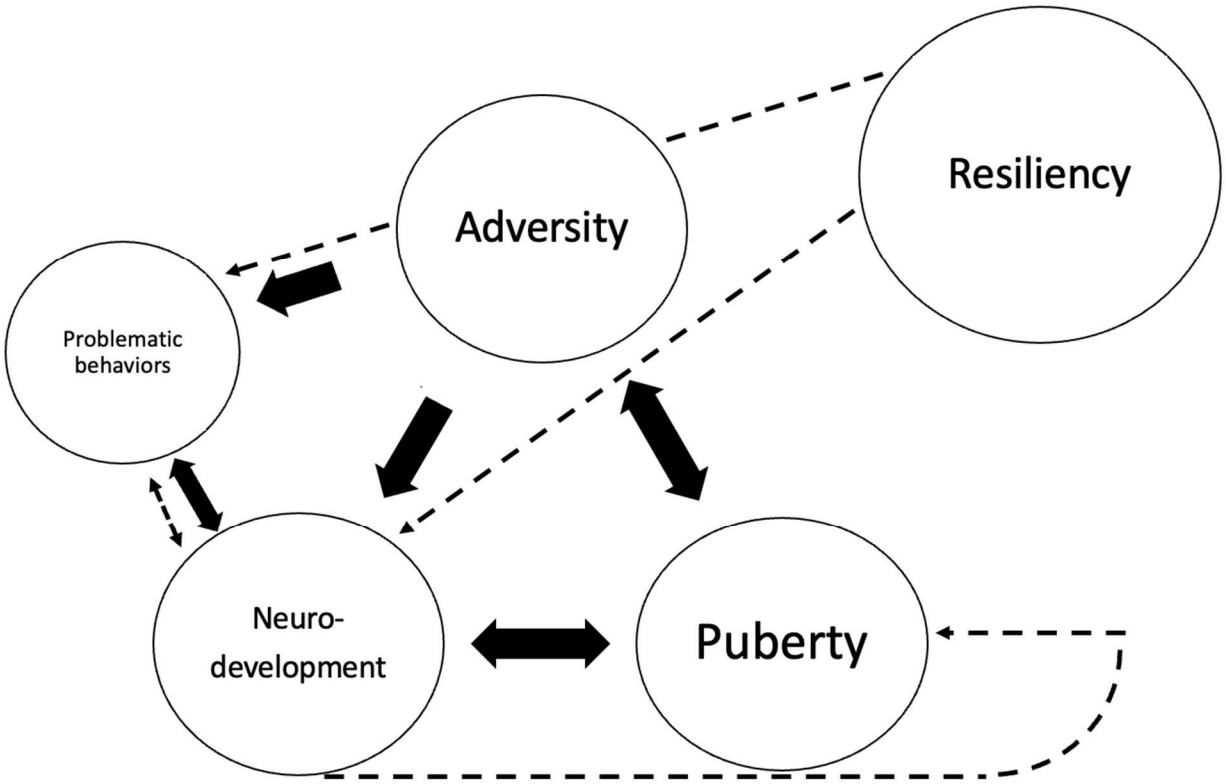
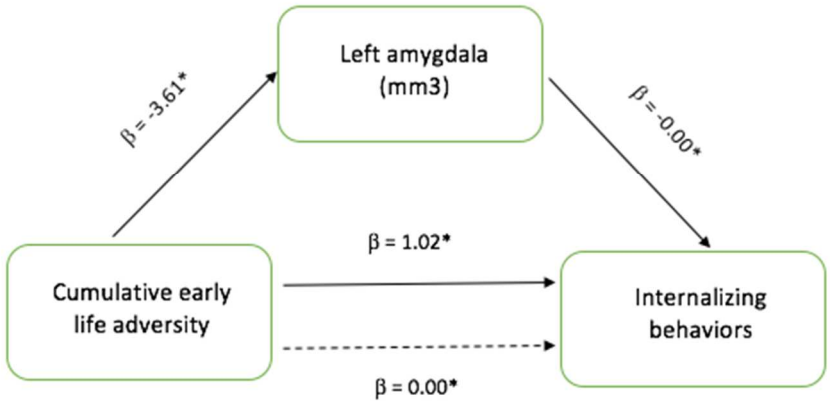
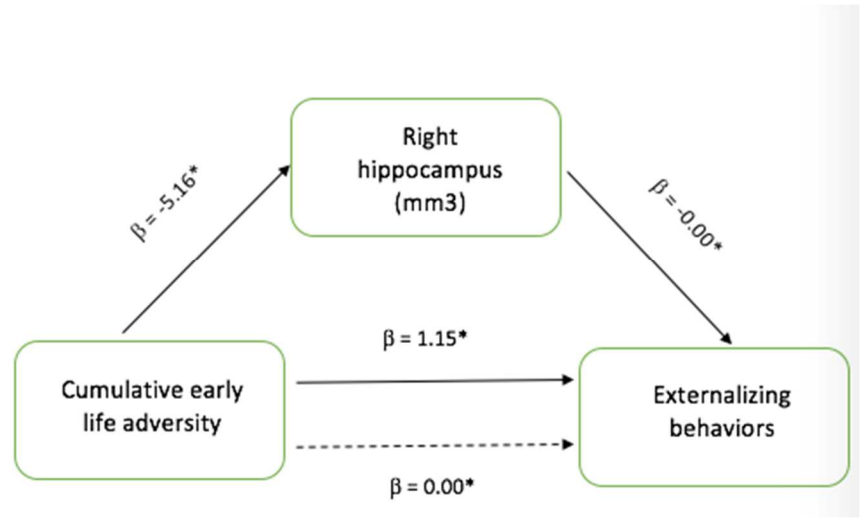



Figure 1: Suggested mechanistic schema depicting the relationship between early life adversity, neurodevelopment, problematic behaviors, puberty and resiliency.

A)




B)




C)

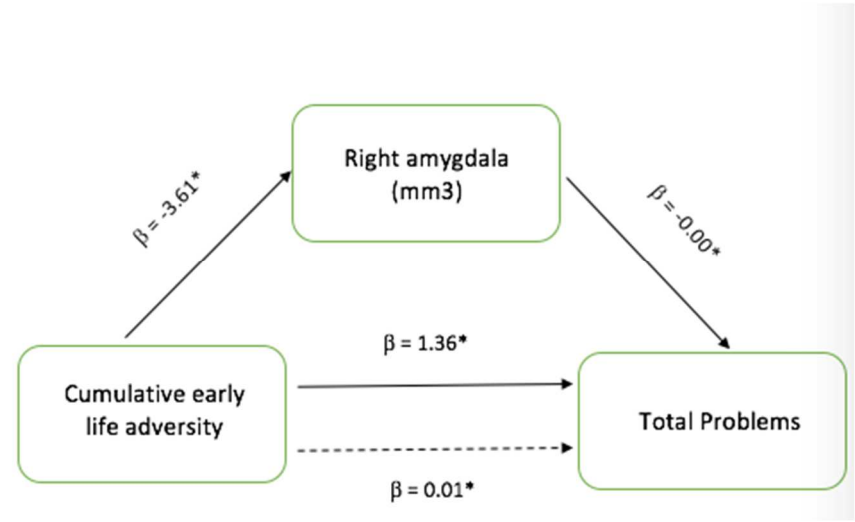



Figure 2: Mediation of frontolimbic circuitry on the association between early life adversity and CBCL outcomes, adjusted for age, sex, race/ethnicity, primary caregiver's education and family income. 2a) details the impact of the left amygdala on internalizing behaviors; 2b) depicts the impact of the right hippocampus on externalizing behaviors; and 2c) details the mediating impact of the right amygdala on total problems. Mediation analyses according to Baron and Kenny (1986) criteria and Bootstrapping. The dashed line and corresponding coefficient represent the average causal mediation effects (ACME) or the indirect effect of the independent variable (cumulative early life adversity) on the dependent variable (behavioral outcome) through the mediator (neural region of interest).

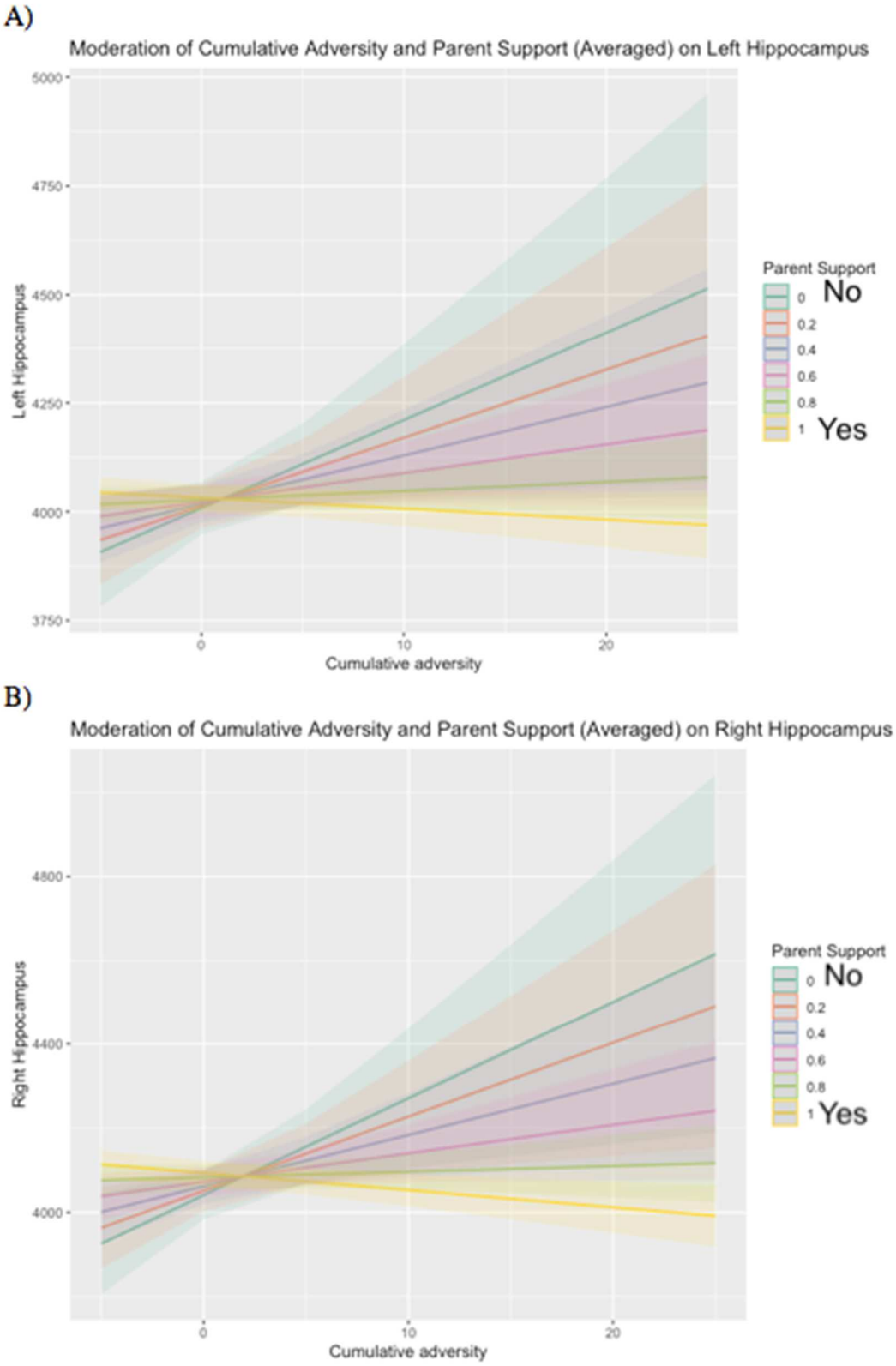



Figure 3: The moderating role of parental support on cumulative adversity's impact on a) left and b) right hippocampal volumes.

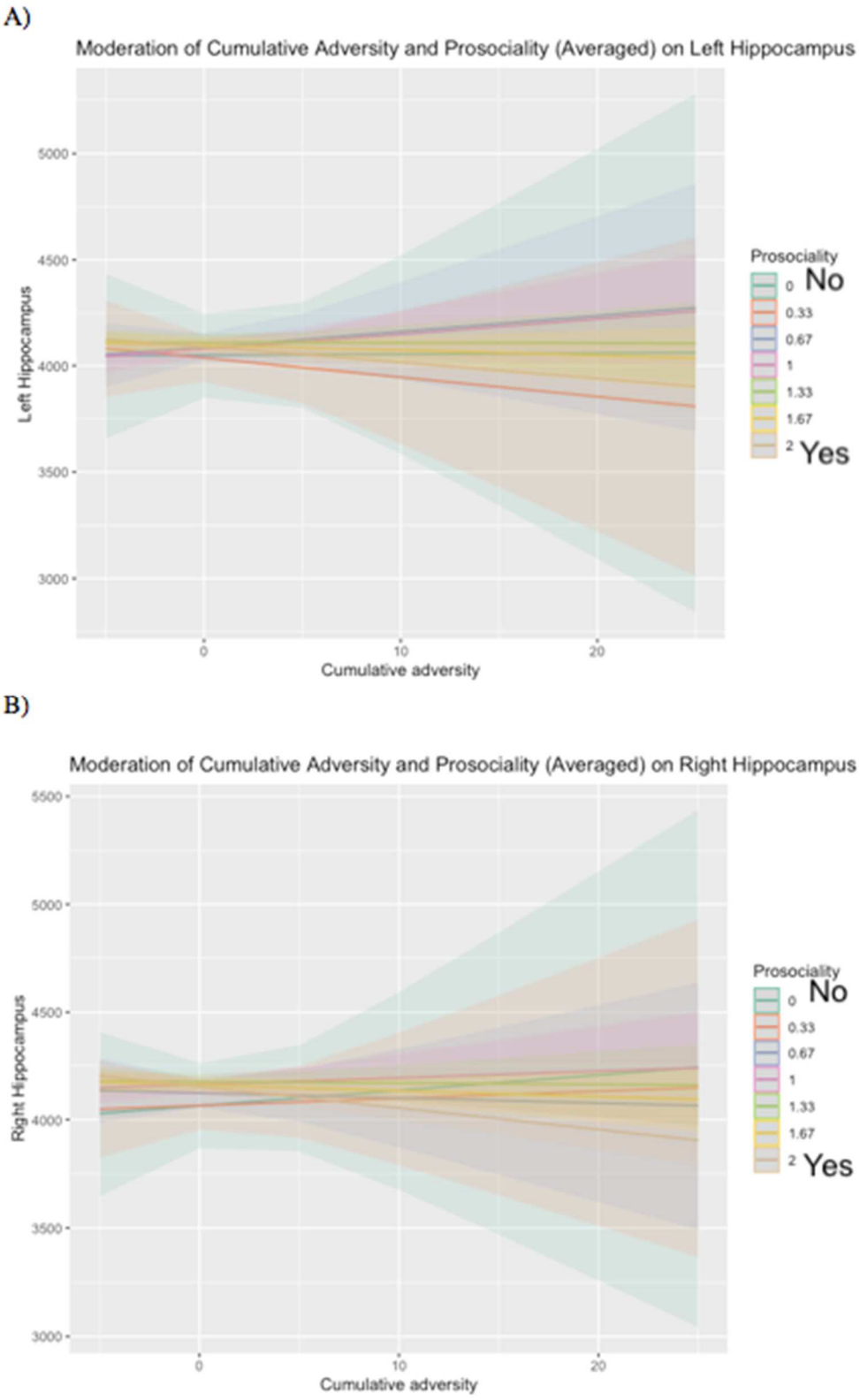



Figure 4: The moderating role of youth's total prosociality on cumulative adversity's impact on a) left and b) right hippocampal volumes. Findings did not remain when intracranial volume was controlled for.

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## SUPPLEMENT

## METHODS

School-based support can include an individual's feeling of belonging and accomplishment at school and often relates to the relationship a youth has with their teachers (Horn 2016). Sources of school-based support captured were the youth's perception of: their intelligence in relation to their peers, whether they got along with their teachers, and whether they generally enjoyed school. School engagement and educational attainment are associated with greater financial stability, better quality of life outcomes, and less stress exposures throughout life (Moses 2017), and thus are particularly relevant for youth who have experienced early life adversity exposure. Additionally, healthy relationships with teachers and older nonfamilial mentors are associated with prosociality, academic achievement and increased effective coping skills among adversity exposed youth (Moses 2017). Additional sources of support outside the home were obtained and included the number of close friends given the research on the positive impact a peer support network during childhood plays in healthy socioemotional adjustment (Steinebach 2019) and brain development (Osher 2020). Total number of close male and female friends was examined across the total sample, and the number of close same-sex friends was examined further due to the tendency of primary school aged children to routinely play and associate with members of the same sex (Fabes 2003).

Youth's perception of the primary caregiver's ability to offer parental support were obtained from five questions in the Child Report of Parent Behavior Inventory (CRPBI) Acceptance Subscale (Schaefer 1965). These include the frequency with which the primary caregiver demonstrates: love and affection, consolation, validation of feelings, approachability,

and smiling when interacting with the youth. The occurrence of parental monitoring was also included as a separate variable and was obtained via the following question directed at youth participants, “How often do your parents/guardians know where you are?”. The presence and count of full, half and twin siblings both younger and older was obtained given the (at times conflicting) research on the buffering effects of siblings towards the detrimental impact of household dysfunction and other forms of early life adversity. Given the mixed findings in this area, we were unclear whether the presence of siblings would facilitate or diminish adversity exposure.

Youth’s internal prosocial behaviors were assessed via three questions obtained from the Youth Prosocial Behavior Survey, developed for the ABCD Study. The three questions include youth’s perceptions of the relative accuracy of the following statements: 1) “I try to be nice to other people. I care about their feelings.”; 2) “I am helpful if someone is hurt, upset, or feeling sick.”; and 3) “I often offer to help others (parents, teachers, children)”. Responses to the individual questions were utilized as were the average of the three responses. Lastly, parents were asked to report on the importance of the youth’s religious and spiritual beliefs. Responses were binarized to indicate importance or lack thereof.

*Statistical Analyses.* Descriptive statistics and initial correlations were first performed. To adjust for outliers, neural outcome data points greater than four standard deviations from the mean were replaced with the Winsorized mean. The variance inflation factor and correlations between all covariates and predictor variables were examined to detect potential problems related to multicollinearity. Our variance inflation factor of 1.0 is not indicative of significant multicollinearity between predictor variables and covariates (Salmeron 2018). In addition, autocorrelation via the Durbin Watson Test, Cook’s distance, and leverage values were

calculated for the dependent variables based on the independent variables to identify outliers and influential observations.

## RESULTS

*Factor Analyses.* The 6 factor domains explained 22.4% of the cumulative variance in the adversity data. Thirty adversity variables were included in the domains, while the remaining 17 variables were not included in the subsequent analyses due to lack of endorsement. The first five domains only include variables that were obtained from parent responses while the final domain assessing household dysfunction included youth-derived responses. Cronbach's alpha was acceptable (i.e., >0.70) for the physical and sexual violence and neighborhood safety factors, but poor on the remaining four factors.

As shown in Table 3 of the factor scores, individuals with higher factor scores across the following domains had more internalizing problems: physical and sexual violence (*factor 1*); parental mental health (*factor 2*); and scarcity (*factor 5*). Conversely, individuals with higher factor scores across the following domains had higher externalizing problems: neighborhood safety (*factor 3*); prenatal substance exposure (*factor 4*); and household dysfunction (*factor 6*). All associations presented controlled for age, sex, race/ethnicity, primary caregiver's education and family income.

*Moderation Analyses.* Moderation analyses were conducted to examine whether six different forms of resiliency to interact with cumulative adversity exposure to alter the impact on frontolimbic circuitry and CBCL outcomes. In all models, youth's age, sex, race and ethnicity, as well as family income and primary caregiver's education were controlled. All models examining frontolimbic circuitry as the outcome controlled for intracranial volume; instances of significant

findings in the absence of controlling for intracranial volume are otherwise specified. Interactions were interpreted through the plotting of estimates (i.e. neural ROI volumes and behavioral outcomes) by cumulative adversity exposure and presence of resiliency sources. The results of these analyses are presented in Table 5. For each possible source of resiliency, moderation models were ran and presented first for neural outcomes and then for behavioral outcomes.

*School-based Support.* The total average school support did not moderate cumulative adversity's impact on frontolimbic circuitry, specifically, bilateral amygdala, hippocampus, OFC or ACC volumes. Null findings remained whether or not intracranial volume was corrected for.

When examining the individual characteristics that comprised and averaged to total school-based support, the youth's perception of their intelligence in relation to their peers, and whether they got along with their teachers impacted cumulative adversity's association with hippocampal volume. Specifically, an interaction effect between cumulative adversity and youth's perception of their intelligence ($p = 0.04597$) were found on right hippocampal volumes. A higher adversity burden captured at ages 9 and 10 was associated with a *smaller* right hippocampal volume ($F(1,11505) = 481.7$, $p = 0.04317$, adjusted $R^2 = 0.43$, $f^2 = 0.75$) when controlling for intracranial volume among youth in comparison with controls. Lastly, a main effect of cumulative adversity ($p = 0.03560$) and an interaction effect between cumulative adversity and whether youth got along with their teachers ($p = 0.04292$) were found on left hippocampal volumes. A higher adversity burden captured at ages 9 and 10 was associated with a *smaller* left hippocampal volume ($F(1,11506) = 110$, $p = 0.04775$, adjusted $R^2 = 0.14$, $f^2 = 0.16$) among youth in comparison with controls. When controlling for intracranial volume, the findings were null ($F(1,11505) = 397.8$, $p > 0.07$, adjusted $R^2 = 0.38$, $f^2 = 0.61$).

When examining behavioral outcomes, a main effect of cumulative adversity ($p < 0.001$) and an interaction effect between cumulative adversity and the presence of total school support ($p = 0.00693$) were found on internalizing behaviors. The association between higher adversity burden captured at ages 9 and 10 and greater internalizing behaviors was moderated if school support was present ($F(1,11521) = 60.02$, $p = 0.008778$, adjusted $R^2 = 0.08$, $f^2 = 0.09$). When examining the individual characteristics that comprised and averaged to total school-based support, the youth's perception of their intelligence in relation to their peers, and whether they got along with their teachers impacted cumulative adversity's association with problematic behaviors. Specifically, a main effect of cumulative adversity ($p < 0.001$) and an interaction effect between cumulative adversity and youth's perception of their intelligence ($p = 0.012889$) were found on internalizing behaviors. A higher adversity burden captured at ages 9 and 10 was associated with higher internalizing behaviors ($F(1,11500) = 59.51$, $p = 0.01431$, adjusted $R^2 = 0.08$, $f^2 = 0.09$) among youth in comparison with controls. Lastly, a main effect of cumulative adversity ($p < 0.001$) and an interaction effect between cumulative adversity and whether youth got along with their teachers ($p = 0.02009$) were found on internalizing behaviors. The association between higher adversity burden captured at ages 9 and 10 and greater internalizing behaviors was moderated if youth got along with their teachers ($F(1,11500) = 58.38$, $p = 0.01813$, adjusted $R^2 = 0.07$, $f^2 = 0.08$). No significant effects were found for school-based support's ability to moderate cumulative adversity's impact on externalizing behaviors and total problematic behaviors.

*Peer Support.* An interaction effect between cumulative adversity and the presence of peer support for male youth ($p = 0.03160$) was found on left OFC volumes. A higher adversity

burden captured at ages 9 and 10 was associated with smaller left OFC volume ($F(1,6003) = 151.4$, $p = 0.03296$, adjusted $R^2 = 0.30$, $f^2 = 0.43$) when controlling for intracranial volume among male youth.

When examining the total sample and the presence of peer support, an interaction effect between cumulative adversity and the presence of a male peer support was found on left OFC volumes ($p = 0.032998$). A higher adversity burden captured at ages 9 and 10 was associated with a slightly smaller left OFC volume ($F(1,6003) = 151.4$, $p = 0.03296$, adjusted $R^2 = 0.30$, $f^2 = 0.43$) when controlling for intracranial volume among male youth.

When examining behavioral outcomes, a main effect of cumulative adversity ($p < 0.001$) and an interaction effect between cumulative adversity and the presence of male friends for male youth ($p = 0.00517$) were found on internalizing behaviors. Similarly, a main effect of cumulative adversity ($p < 0.001$) and an interaction effect between cumulative adversity and the presence of male friends for the total sample ($p = 0.00332$) were found on internalizing behaviors. The association between higher adversity burden captured at ages 9 and 10 and greater internalizing behaviors was moderated if male friends were present among the male sub-sample ($F(1,6001) = 27.9$, $p = 0.05255$, adjusted $R^2 = 0.07$, $f^2 = 0.08$) and total sample ($F(1,11500) = 57.1$, $p = 0.01461$, adjusted $R^2 = 0.08$, $f^2 = 0.09$). A main effect of cumulative adversity ($p < 0.001$) and an interaction effect between cumulative adversity and the presence of male friends for the total sample ($p = 0.03417$) were also found on total problems. A higher adversity burden captured at ages 9 and 10 moderated the association with greater total problematic behaviors if male friends were present among the total sample ($F(1,11500) = 85.89$, $p = 0.03233$, adjusted $R^2 = 0.11$, $f^2 = 0.12$) in comparison with controls. No significant effects

were found for peer support's ability to moderate cumulative adversity's impact on externalizing behaviors or total problems.

*Parental Support*. An interaction effect between cumulative adversity and parental support averaged across 5 domains were found on left ($p = 0.0223$) and right ($p = 0.00428$) hippocampal volumes. A higher adversity burden captured at ages 9 and 10 was associated with a larger left hippocampal volume ($F(1,11527) = 398.8$, $p = 0.02545$, adjusted $R^2 = 0.38$, $f^2 = 0.61$) and a larger right hippocampal volume ($F(1,11527) = 482.5$, $p = 0.00517$, adjusted $R^2 = 0.43$, $f^2 = 0.75$) among youth in comparison with controls.

When examining the individual characteristics that summed to total parental support, the primary caregiver's ability to validate and smile impacted cumulative adversity's association with hippocampal volume. An interaction effect between cumulative adversity and caregiver validation were found on left ($p = 0.00316$) and right ($p = 0.01778$) hippocampal volumes. A higher adversity burden captured at ages 9 and 10 was associated with a larger left hippocampal volume ($F(1,11527) = 399.2$, $p = 0.003158$, adjusted $R^2 = 0.38$, $f^2 = 0.61$) and a larger right hippocampal volume ($F(1,11527) = 482.2$, $p = 0.01781$, adjusted $R^2 = 0.43$, $f^2 = 0.75$) among youth in comparison with controls. An interaction effect between cumulative adversity and caregiver smiling was found on right hippocampal volumes ($p = 0.01438$). Frequent parental smiling also moderated the impact of cumulative adversity on right hippocampal volume ($F(1,11527) = 482.3$, $p = 0.01322$, adjusted $R^2 = 0.43$, $f^2 = 0.75$), but not left ($F(1,11527) = 398.6$, $p > 0.10$, adjusted $R^2 = 0.38$, $f^2 = 0.61$). The presence of total parental support as well as individual features did not moderate cumulative adversity's impact on bilateral amygdala, OFC or ACC volumes.

When examining behavioral outcomes, a main effect of cumulative adversity and an interaction effect between cumulative adversity and total parental support (summed across 5 domains) were found on internalizing behaviors. A higher adversity burden captured at ages 9 and 10 was associated with greater internalizing behaviors ($F(1,11521) = 56.6$, $p = 0.03129$, adjusted $R^2 = 0.08$, $f^2 = 0.09$) among youth in comparison with controls. When examining the individual characteristics that summed to total parental support, a main effect of cumulative adversity ($p < 0.001$) and an interaction effect between cumulative adversity and love and affection ($p = 0.03206$) were found on externalizing behaviors. Parental love and affection moderated the impact of adversity exposure on externalizing behaviors ($F(1,11521) = 77.1$, $p = 0.03281$, adjusted $R^2 = 0.10$, $f^2 = 0.11$). No significant effects were found for parental support's ability to moderate cumulative adversity's impact on total problematic behaviors.

*Presence of Siblings.* The presence of an older, younger or twin sibling did not moderate cumulative adversity's impact on frontolimbic circuitry, specifically, bilateral amygdala, hippocampus, OFC or ACC volumes. Null findings remained whether or not intracranial volume was corrected for.

When examining behavioral outcomes, a main effect of cumulative adversity ($p < 0.001$) and an interaction effect between cumulative adversity and the presence of younger siblings ($p = 0.01322$) were found on internalizing behaviors. Similarly, a main effect of cumulative adversity ($p < 0.001$) and an interaction effect between cumulative adversity and the presence of a twin sibling ($p = 0.00516$) were found on internalizing behaviors. A higher adversity burden captured at ages 9 and 10 moderated the association with greater internalizing behaviors if a younger sibling was present ($F(1,11521) = 60.4$, $p = 0.01809$, adjusted $R^2 = 0.08$, $f^2 = 0.09$) or if a twin was present ($F(1,11521) = 60.1$, $p = 0.006082$, adjusted $R^2 = 0.08$, $f^2 = 0.09$) in comparison with

controls. Main effects of cumulative adversity ($p < 0.001$) and interaction effects between cumulative adversity and the presence of both younger siblings ($p = 0.01826$) and a twin ($p = 0.00381$) were observed for total problems. A higher adversity burden captured at ages 9 and 10 moderated the association with greater total problematic behaviors if a younger sibling was present ($F(1,11521) = 90.8$, $p = 0.02549$, adjusted $R^2 = 0.12$, $f^2 = 0.14$) or if a twin was present ($F(1,11521) = 90.4$, $p = 0.004511$, adjusted $R^2 = 0.12$, $f^2 = 0.14$) in comparison with controls. No significant effects were found for the presence of siblings in moderating cumulative adversity's impact on externalizing behaviors.

*Prosociality.* A main effect of cumulative adversity ($p = 0.02854$ and $p = 0.00122$) and an interaction effect between cumulative adversity and youth's prosociality ($p = 0.02296$ and $p = 0.01975$) were found on left and right hippocampal volumes, respectively. A higher adversity burden captured at ages 9 and 10 was associated with a smaller left hippocampal volume ($F(1,11528) = 115.8$, $p = 0.02633$, adjusted $R^2 = 0.14$, $f^2 = 0.16$) and a smaller right hippocampal volume ($F(1,11528) = 115.8$, $p = 0.0221$, adjusted $R^2 = 0.14$, $f^2 = 0.16$) among youth among youth who did not endorse prosociality in comparison with controls. When controlling for intracranial volume, the findings were null ($F(1,11527) = 398.6$, $p > 0.09$, adjusted $R^2 = 0.38$, $f^2 = 0.61$). Significance did not survive multiple comparisons correction via Benjamini-Hochberg correction at $p < 0.05$ ($F(1,11528) = 115.8$, $p > 0.17$).

When examining the individual characteristics that comprised and averaged to total prosociality, the youth's propensity to be kind to others and care about their feelings impacted cumulative adversity's association with hippocampal volume. A main effect of cumulative adversity ($p = 0.04105$ and $p = 0.00173$) and an interaction effect between cumulative adversity and being kind and caring towards others ($p = 0.00366$ and $p = 0.00400$) were found on left and

right hippocampal volumes, respectively. A higher adversity burden captured at ages 9 and 10 was associated with a *larger* left hippocampal volume ($F(1,11501) = 110.5$, $p = 0.003774$, adjusted $R^2 = 0.14$, $f^2 = 0.16$) and a *larger* right hippocampal volume ($F(1,11501) = 124.3$, $p = 0.003846$, adjusted $R^2 = 0.15$, $f^2 = 0.18$) among youth who did not endorse prosociality in comparison with controls. When controlling for intracranial volume, the findings were null ($F(1,11500) = 397.4$, $p > 0.17$, adjusted $R^2 = 0.38$, $f^2 = 0.61$).

Lastly, the presence of youth's total prosociality as well as the individual features of being kind and caring towards other, and helping those in need did not moderate cumulative adversity's impact on bilateral amygdala, OFC or ACC volumes. No significant effects were found for the presence of youth's prosociality to moderate cumulative adversity's impact on internalizing, externalizing and total problematic behaviors. This includes youth's total prosociality as well as the individual features of this domain.

*Religious and Spiritual Beliefs.* The presence of religious or spiritual beliefs did not moderate cumulative adversity's impact on frontolimbic circuitry, specifically, bilateral amygdala, hippocampus, OFC or ACC volumes. Null findings remained whether or not intracranial volume was corrected for. No significant effects were found for the presence of youth's religious and spiritual beliefs to moderate cumulative adversity's impact on internalizing, externalizing and total problematic behaviors.

*Cumulative Resiliency.* Given the understanding that not one source of resiliency in isolation but likely complex interrelations of different forms of resiliency impact the relationship between adversity and psychopathology (Fritz 2018), we examined the impact of cumulative resiliency. A cumulative resiliency score was obtained from the three sources of resiliency

shown to significantly impact neural regions and behaviors - parental support, school-based support, and prosociality.

The sub-questions pertaining to each of the three sources of resiliency were binarized and the average score of sub-questions equated to the total score. For example, responses to the three questions that assessed school-based support were averaged for a total school-based resiliency score per individual. Similarly, responses to the three questions that examined prosociality were averaged to attain a total prosocial score and responses to the five questions related to parental support were averaged to attain a total parental support score. An individual's cumulative resiliency score was the summation of total parental support, total school-based support, and total prosociality. The range for each individual's total cumulative resiliency score is 0 to 3. An individual's cumulative resiliency impacted cumulative adversity's association with right hippocampal volume, while controlling for age, sex, race/ethnicity, primary caregiver's education and family income. While a main effect of cumulative adversity just missed significance ($p = 0.06478$), a significant interaction effect between cumulative adversity and cumulative resiliency was observed on right hippocampal volumes ($p = 0.01956$). The presence of cumulative resiliency did not moderate cumulative adversity's impact on the left hippocampus or bilateral amygdala, OFC and ACC volumes. No significant effects were found for the presence of cumulative resiliency to moderate cumulative adversity's impact on internalizing, externalizing and total problematic behaviors.

Further analyses were not performed for sibling support, peer support and religious and spiritual importance given the: a) null main and interaction effects with cumulative adversity across neural outcomes and b) inability to quantify and binarize the numerical variables of sibling count and number of close peers. For example, when attempting to quantify the range of

peer support that interacted with cumulative adversity exposure to positively impact neural outcomes, a range of 3 to 5 was obtained via observations of histogram frequency plots as well as model interaction plots. However, only 3055 (26%) subjects endorsed 3 to 5 friends given the vast range of youth supplied responses. And given an absence of significant associations between these three forms of resiliency, establishing a range of optimal peer support and siblings would have been arbitrary.

## CHAPTER 3: The Mediating Influence of Puberty on Adversity Exposure and Frontolimbic Development Among ABCD Study Youth


### ABSTRACT

Puberty is a sensitive window of development marked by enhanced neural plasticity. Early life adversity exposure is associated with alterations in structural and functional frontolimbic circuitry as well as an individual's pubertal maturation trajectory. Adversity exposure is also associated with an increased risk for internalizing and externalizing problematic behaviors, such as anxious, depressed and withdrawn symptomology. Sources of school-based support are associated not only with academic achievement, but positive physical and mental health, and decreased incidences of problematic behaviors. As youth spend a vast proportion of their developmental life in school, school climate is poised to exert strong effects on neurodevelopment and behaviors. This study comprehensively tested whether puberty *mediated* the relationship between both type-specific and cumulative adversity exposure and amygdala and hippocampal volumes. Additionally, this study examined the relationship between pubertal development (i.e. adrenarche and gonadarche) and type-specific and cumulative adversity exposure. Finally, this study examined whether school-based support *moderated* the impact of adversity exposure on pubertal development, specifically gonadarche. Specific types of adversity exposure were associated with advanced adrenarchal development, specifically, parental mental health, neighborhood threat, prenatal substance exposure, and scarcity. Among females, advanced gonadarchal development was associated with physical and sexual violence, parental mental health, neighborhood safety and prenatal substance exposure. Type-specific and cumulative adversity exposure among males was not associated with gonadarche. This may in

part be attributable to male's delayed pubertal maturation with respect to females. Mediation analyses revealed that specific forms of early life adversity exposure, specifically, neighborhood threat, household dysfunction, prenatal substance exposure and scarcity, are associated with advanced gonadarche, which in turn increases the risk of amygdala and hippocampal alterations. However, the ability of school-based support to interact with adversity exposure to influence pubertal development (i.e. gonadarche) was demonstrated among female youth who specifically reported a positive relationship with their teachers.

## INTRODUCTION

Early life adversity exposure is associated with a host of detrimental health and quality of life outcomes, not just acutely but often persisting throughout the lifespan (Felitti 1998; Teicher 2016; McLaughlin 2020). Exposure during development is associated with alterations in the structure and function of frontolimbic circuitry (McLaughlin 2019) and one's pubertal maturation trajectory, specifically the timing of onset and tempo between developmental stages (Laube 2020). Early life adversity exposure is associated with an increased risk for internalizing and externalizing problematic behaviors, such as anxious, depressed and withdrawn symptomology (Jaffee 2017). Puberty is considered a sensitive window of development and carries enhanced neural plasticity, or the potential for structural and functional change (Dorn 2019). While youth are at risk for alterations in response to adversity exposure during adolescence, conversely, they are neurodevelopmentally primed towards plasticity in response to sources of support. Given that youth spend a large proportion of their developmental years in school, school climate is poised to exert strong effects on neurodevelopment and behaviors (Piccolo 2019), and may offset the impact of adversity exposure.

Puberty occurs in two distinct phases - adrenarche and gonadarche. The former entails the activation of the adrenal glands and is associated with skin, hair and height changes that begin around 6-8 years of age; the latter entails the development of secondary sex characteristics occurring 1-2 years later, and earlier in girls (Mendle 2019). While gonadarche begins around 9 and 10 (Mendle 2019), there is great interindividual variability in pubertal onset (Laube 2020). Advanced pubertal maturation has been observed in response to early life adversity exposure (Mendle 2014) and is hypothesized to have evolutionary advantages. Greater pubertal maturation is associated with a more developed global brain phenotype, evident by smaller subcortical gray

matter volumes, including the amygdala and hippocampus (Herting 2014). Post-pubertal individuals display smaller hippocampal volumes in comparison to youth at the onset of puberty, with larger effects evident in males (Herting 2017). When examining individual features of pubertal development, advancement of pubic hair was associated with smaller right hippocampal volumes, while breast development was related to smaller bilateral amygdala volumes (Herting 2017). Conversely, Goddings and colleagues (2019) report sex differences and *increases* in amygdala and hippocampal volumes with greater self-assessed pubertal development (via Tanner stage). Given these disparate findings, additional work is needed pertaining to the development of secondary sex characteristics as they relate to structural neurodevelopment and are impacted by adversity exposure. Our study utilizes data from the largest cohort of youth neurodevelopment and is poised to address these questions.

Frontolimbic circuitry is often impacted by early life adversity exposure due to the high concentration of glucocorticoid receptors present, as well as their enhanced density during adolescence (Tottenham 2016). Anatomical regions that comprise the circuitry, such as the amygdala, hippocampus, undergo development throughout puberty. The amygdala, for example, undergoes rapid growth and reaches peak volume between nine and eleven years of age; following this period, its volume gradually declines due to developmentally regulated synaptic pruning (Teicher 2016). These and other subcortical regions have demonstrated responsivity to pubertal hormone levels, with changes most pronounced early in pubertal development (Herting 2014).

Pubertal development is suggested to demonstrate a mediating role between brain development and adolescent behaviors. Sex steroids and pubertal development have been shown to affect neurogenesis, apoptosis, synapse number, dendritic branching and outgrowth, as well as

processes pertaining to pre-myelination and myelination (Herting 2017; Goddings 2019). In animal models of gonadectomy and when sex hormones are inhibited, observed structural and functional neural changes are likened to pubertal influences, or lack thereof (Goddings 2019). In humans, pubertal stage has been found to moderate the association between limbic circuitry and risky sexual behaviors (Vijayakumar 2018). In females, pubertal maturation in advance of one's peers is associated with earlier engagement in dating and sexual activity, and carries a greater likelihood for females to become involved with older boyfriends, the latter carrying an additional set of risks (Goddings 2019). Across the sexes, early pubertal timing is recognized as a risk factor for adverse health outcomes in adulthood, ranging from depression to cardiometabolic disorders and early mortality (Zhang 2019). Long-term effects can be seen in increased risk for compromised interpersonal relationships, poor academic achievements and psychiatric disorders (Felitti 1998; Teicher 2016; McLaughlin 2020). The ability of pubertal development to mediate the relationship between early life adversity exposure and neurodevelopment has yet to be examined.

Adolescence is a time of increased social influences (Vijayakumar 2018) and carries enhancements in learning associated with complex social and cognitive skills (Laube 2020). Adolescence is also a time of increased parental conflict (Vijayakumar 2018), suggesting a greater need for sources of resiliency and support outside the home. Like other sources of resiliency, a supportive school environment is associated not only with academic achievement, but positive physical and mental health, and decreased incidences of externalizing behaviors (; Piccolo 2019). School-based support can include an individual's feeling of belonging and accomplishment at school and can directly relate to the relationship a youth has with their teachers (Horn 2016). How teachers facilitate learning through instructional practices (i.e. the

curriculum, teaching expectations, and student evaluations), for example, was demonstrated to moderate the associations between adverse home environments and poor inhibitory control and associated neural structures (Piccolo 2019). Expanding upon the domain of school-based support, school climate includes the quality of relationships with teachers and peers, school safety and community, and other contextual factors that address the student's perception of learning, achievement, and quality of the school environment. As youth spend a vast proportion of their developmental life in school, school climate is poised to exert strong effects on neurodevelopment and behavior (Piccolo 2019). Furthermore, whether school-based support is able to moderate the impact of adversity exposure on pubertal development (i.e. gonadarche) has yet to be assessed.

To examine pubertal development, our study utilized secondary sex characteristics to emphasize the psychosocial components of pubertal development. Outward representations of pubertal development not only signal physical development but carry social ramifications. Physical changes in response to pubertal hormones may lead to altered behaviors not only by the developing youth but by those they interact with, both of which may contribute to neurodevelopmental changes (Blakemore 2010). Youth who appear to be more pubertally advanced due to the outward development of secondary sex characteristics, say due to adversity exposure, are more often treated as adults, and stigmatized in school and throughout the community (Deardorff 2019, Mendle 2019). How these psychosocial ramifications of pubertal development interact with resiliency efforts has yet to be examined. Additionally, there exists wide individual variability in hormone levels both within and across pubertal stages (Vijayakumar 2018; Laube 2020). Sex hormones fluctuate due to diet, exercise (Vijayakumar 2018) and circadian rhythm (Herting 2017). Among females, cycle irregularity is greatest 1–2

years following menarche (Herting 2014), thus contributing to hormonal fluctuations. Lastly, there is not a clear correspondence between sex hormone levels and pubertal development. A systematic review by Vijayakumar and colleagues (2018) identified a predominantly non-significant relationship between gonadal hormones and amygdala and hippocampus volumes. Plasma levels measured may not directly reflect actual hormone concentrations at the level of the brain (Herting 2014). While there is not clear correspondence between sex hormone levels and the development of secondary sex characteristics, the latter (is suggested to reflect hormonal effects on synaptic, dendritic, and axonal developmental processes (Herting 2014).

While extensive research has examined the impact of acute and chronic adversity exposure on brain development and behavior, this is the first study to comprehensively examine the impact of adversity exposure on pubertal maturation, neurodevelopment and associated behaviors, and to assess the impact of school-based support on both neural and behavioral outcomes. Previous studies of pubertal development have focused largely on discrete samples, such as precocious pubertal development among females exposed to early life adversity (Zhang 2019), or on specific types of adversity, such as socioeconomic disadvantage and advanced pubertal onset (Zhang 2019). This study captured different forms of early life adversity exposure, obtained from both the youth and caregiver, among the largest nationally-representative sample of youth brain development to date. Utilizing baseline data for youth enrolled in the Adolescent Brain Cognitive Development (ABCD) study, this study has three aims: 1) to examine the relationship between different forms of early life adversity exposure, including an individual's cumulative burden, on adrenarche and gonadarche, while controlling for covariates such as age, sex, race, ethnicity; 2) to examine the ability of puberty to *mediate* the relationship between both type-specific and cumulative adversity exposure and amygdala and hippocampal volumes; and 3)

to assess the ability of school-based support to *moderate* the impact of both type-specific and cumulative adversity on pubertal development (i.e. gonadarche).

## METHODS

*Protocol.* The present study used the National Data Archive, ABCD version 2.01 baseline data set (Yang 2019) collected between 2016 and 2018 from the ABCD study, the largest longitudinal neuroimaging study of youth development. 11,566 youth from 21 different research sites in the United States are enrolled in this 10-year longitudinal study (Volkow 2018). Procedures, sampling and recruitment (Volkow 2018, Barch 2018, Garavan 2018) for the ABCD study have been described previously. Caregivers provided written informed consent and children provided assent for participation in the study. All procedures were approved by a central institutional review board, and each site has a detailed protocol in place to address reported adversity exposure. The University of California, Los Angeles, institutional review board has indicated that analyses using the publicly released ABCD Study data are not human subjects research and therefore do not require their own approval.

### *Measures*

*Sociodemographic Characteristics.* A caregiver-completed demographic questionnaire was used to gather information regarding youth's age, sex, race and ethnicity, as well as primary caregiver's education and family income. These demographic features were employed as covariates in subsequent analyses, unless otherwise specified.

*Early Life Adversity Exposure.* The occurrence of early life adversity was attained through a series of 14 questionnaires completed by youth and their caregivers. Across the 14 questionnaires, 47 variables were identified that captured different forms of adversity exposure,

including: physical, sexual and emotional abuse; emotional and physical neglect; loss of parent; domestic violence; parental mental health and drug use; and threatening experiences. Threatening experiences include witnessing community violence, being the victim of bullying, feeling safe at school and in the neighborhood, and experiencing death threats. Due to the sensitive nature of the questions and the age of the youth, most of the adversity variables were parent-reported. For example, only caregivers were asked about the youth's history of sexual abuse and prenatal substance exposure. All adversity variables were binarized to indicate the presence or absence of exposure and for standardization across questions and questionnaires. All 47 variables underwent principal component analysis (PCA) and factor analysis for the purposes of dimensionality reduction and to identify latent variables or constructs. Descriptive statistics, mediation and moderation analyses examined type-specific and cumulative adversity score across individuals. Youth with an adversity score of zero across all domains, such that no form of adversity exposure was endorsed or captured, served as the study's controls.

*Pubertal Development.* Pubertal maturation of secondary sex characteristics was obtained via completion of the Pubertal Development Scale (PDS) (Petersen 1988) for all youth subjects by their primary caregivers. The PDS is a more frequently used measurement of pubertal stage (Vijayakumar 2018). Characteristics corresponding to adrenarche development in either sex included those pertaining to: growth spurt, body hair and changes in the skin. To assess gonadarche development in males, two questions pertaining to change in voice and in facial hair were asked. To capture gonadarche development in females, caregivers answered two questions concerning the youth's breast development and menarche. The participants' caregivers were instructed to indicate the developmental stage of each of these physical characteristics on a four-point scale: ranging from (1) has not started to develop, (2) shows first signs of development, (3)

shows clear development, to (4) has finished developing. The four PDS stages map onto: *Pre-pubertal, Early puberty*, *Mid- to Late pubertal* and *Post-pubertal.* Developmental characteristics was organized by whether they developed during adrenarche and gonadarche. Scores corresponding to changes in skin, hair and height development were averaged together to represent adrenarche. The same questions were asked of both male and female youth. Characteristics indicating gonadarche development were average together and included voice and facial chair for males and breast development and menarche for females. The two questions corresponding to gonadarche development in males were averaged to obtain a gonadarchal development score for male youth. Similarly, but separately, the two questions addressing gonadarche development in females were scored and averaged to obtain a gonadarchal development score for female youth. Thus, each youth obtained a score for adrenarchal development and gonadarchal development. The average scores for adrenarchal and gonadarchal development were utilized in subsequent analyses, as done previously by X and colleagues (). For the mediation and moderation analyses, pubertal developmental stages 2-4 were compared with stage 1 (reference group). Mediation and moderation models were initially run utilizing all 4 stages of pubertal development; however, given the small proportion of endorsement of gonadarche stage 4 among males (< 0.25%) and females (< 2%), and to improve model performance and stability, stages 3 and 4 of gonadarche were collapsed.

*Neuroimaging.* Volumes in $mm^3$ of subcortical regions, such as the amygdala and hippocampus, and intracranial space were acquired using FreeSurfer v5.3.0 on $T_1$w MRI sequences obtained from 11,533 ABCD Study youth at baseline. Neuroimaging processing pipelines, employed to correct for motion, artefacts and site and scanner differences, were conducted centrally for all study participants by the Data and Informatics Core at the University

of California, San Diego. Details regarding processing pipelines and analyses for common regions of interest can be found at Hagler *et al.* 2019. All neuroimaging metrics used in this study were obtained from the National Data Archive, ABCD version 2.01.

*School-based Support.* To limit the number of comparisons performed, we focused our analyses on school-based support, a type of community resiliency that is poised to play a significant role in youth development as age throughout adolescence (Curran 2017, Verhoeven 2019). While various evidence-based intervention programs delivered in school have intentionally impacted youth's development and functioning, features inherent to a school environment can nonetheless unintentionally impact youth development (Verhoeven 2019). For example, sources of school-based support, such as youth's perception of their intelligence in relation to their peers, whether they got along with their teachers, and whether they generally enjoyed school have individually demonstrated a relationship with youth development (Durlak 2011, Verhoeven 2019). As such, we purposefully narrow our focus to provide a richer discussion of the amygdala and hippocampus and how adversity exposure juxtaposed against developmental timing interacts with features inherent to a school environment. These include youth's perception of: 1) their intelligence in relation to their peers, 2) whether they got along with their teachers, and 3) whether they generally enjoyed school. Each youth received a school-based resiliency score, ranging from 0 to 3, that indicated whether each of these individual sources had been present as reported by the youth. We then examined the influence of the individual sources of school support through sensitivity analyses in instances warranted. While studies have investigated the relationship between adversity exposure and these sources of school-based support (Busso 2014, Mota 2016, Moses 2017), to our knowledge, these sources of school-based support have not been investigated against pubertal development.

*Statistical Analyses.* All data were analyzed using R version 3.5.1 (R Project for Statistical Computing) (R 2018). After performing a PCA and exploratory factor analysis, we moved forward utilizing the domains derived from the factor analysis due to its noted ability to capture latent constructs (Finch 2020), which is pertinent in organizing, categorizing and weighing the study's adversity variables. Exploratory common factor analyses were performed on all adversity questions using square multiple correlations as prior communality estimates with oblique rotation (Promax) of factors. Parallel analysis was subsequently performed. We assessed the fit with three different factoring methods - principal factor solution, minimum residual, and generalized weighted least squares - and with 5 to 8 factors. We utilized oblique rotations as they allow the resulting factors to be correlated. The factor rotations rearrange the original mathematically-derived loadings to make the resulting patterns more comprehensible. The number of factors was determined using scree plots, proportion of common variance explained by the factors, parallel analysis, and interpretability of factors. We utilized the "psych" package and "vss" function. For each exploratory factor analysis performed, we extracted the chi-square value, the standardized root mean square residual (SRMR), and the root mean square error of approximation (RMSEA), Tucker Lewis Index (TFI), and comparative fit index (CFI). Indices corresponding to goodness of fit were SRMR values $< 0.08$, RMSEA values $\leq 0.05$, TFI and CFI values $>0.9$ (Finch 2020). Our selected model's fit corresponds to: SRMR value = 0.02, RMSEA value = 0.02, TFI and CFI values $>0.85$. Variables were considered to load on a factor if the factor loading was $\geq 0.40$. No variables loaded on more than one factor. Using the factors from the final analysis with the entire sample, factor scores were calculated for each youth and compared across CBCL outcomes using ANOVA models.

Using the unweighted data, factor scores corresponding with cumulative adversity exposure were examined via ordinal and multinomial logistic regression models employing the R packages "multinom" and "plor" from the nnet and MASS libraries, respectively. All regression and interaction models employed cumulative adversity exposure, school-based resiliency, adrenarche and gonadarche development, and bilateral amygdala and hippocampal volumes in $mm^3$. Descriptive statistics and initial correlations were first performed. To adjust for outliers, neural outcome data points (i.e. bilateral amygdala, hippocampal and intracranial volume) greater than four standard deviations from the mean were replaced with the Winsorized mean (). Type-specific and cumulative adversity exposure and school-based resiliency were examined as cross-sectional predictors after covarying for the effects of age, sex, race, ethnicity, primary caregiver's education, family income. The variance inflation factor and correlations between all covariates and predictor variables were examined to detect potential problems related to multicollinearity. Our variance inflation factor of 1.0 is not indicative of significant multicollinearity between predictor variables and covariates (Salmeron 2018). In addition, autocorrelation via the Durbin Watson Test, Cook's distance, and leverage values were calculated for the dependent variables based on the independent variables to identify outliers and influential observations. Statistical significance was set at 2-sided $p < 0.05$.

The mediation models employed both linear (when examining the independent variable on the dependent variable and the indirect effects) and ordinal logistic (when examining the independent variable on the mediator) regression as the R "mediation" package does not accept multinomial logistic regression. The moderation models utilized multinomial logistic regression as the proportional odds assumption is not met in order to perform an ordinal logistic regression for these analyses. One adrenarche variable comprised of 4 categorical outcomes was utilized for

both male and female subjects. Gonadarche variables were sex-specific and also contained 4 categorical outcomes. Both ordinal and multinomial logistic regression models utilized outcome 1 ("Has not started to develop") as the reference level for both adrenarche and gonadarche. This permutation method allowed for a comprehensive examination of the relationships between all pubertal developmental groups included in the analysis. The prevalence of stage 4 adrenarche and gonadarche development was small (< 0.25% among males and < 2% among females), so as to improve multinomial model performance and stability, stages 3 and 4 of gonadarche were collapsed.

To test the hypothesis that adversity exposure promotes precocious pubertal development, proportional relative risk and adjusted odds ratios were calculated with multinomial and ordinal logistic regression analyses. Additionally, we quantified the impact of cumulative adversity exposure on frontolimbic volumes and behavioral outcomes, controlling for covariates. We examined whether frontolimbic circuitry *mediated* the impact of cumulative adversity on clinical outcomes, specifically, internalizing, externalizing and total problems. Mediation analyses were conducted employing the R package "mediation". Then we examined whether disparities in the impact of cumulative adversity exposure on ROIs and behavioral outcomes were *moderated* by 6 different sources of resiliency. An ANOVA employing a Chi-square test and simple slopes analysis were used to identify significant interactions. To adjust for multiple comparisons when examining [insert specific analyses], we utilized Benjamini-Hochberg corrections at $p < 0.05$.

## RESULTS

*Factor Analyses.* A six-factor solution was identified for the final factor analysis utilizing a principal factor solution and oblique rotation. This solution gives clearly interpretable factors entitled: 1) physical and sexual violence; 2) parental mental health; 3) neighborhood safety; 4) prenatal substance exposure; 5) scarcity; and 6) household dysfunction. The 6 factor domains explained 22.4% of the cumulative variance in the adversity data. Thirty adversity variables were included in the domains, while the remaining 17 variables were not included in the subsequent analyses due to lack of endorsement. The first five domains only include variables that were obtained from parent responses while the final domain assessing household dysfunction included youth-derived responses. Cronbach's alpha was acceptable (i.e., >0.70) for the physical and sexual violence and neighborhood safety factors, but poor on the remaining four factors.

As shown in Table 3 of the factor scores, individuals with higher factor scores across the following domains had more internalizing problems: physical and sexual violence (*factor 1*); parental mental health (*factor 2*); and scarcity (*factor 5*). Conversely, individuals with higher factor scores across the following domains had higher externalizing problems: neighborhood safety (*factor 3*); prenatal substance exposure (*factor 4*); and household dysfunction (*factor 6*). All associations presented controlled for age, sex, race/ethnicity, primary caregiver's education and family income.

*Sociodemographic Characteristics.* The demographic and clinical characteristics of the sample are shown in Table 1. Youth with a history of early life adversity exposure differed from controls in that exposed-youth were more likely to be younger and male then controls. The mean adrenarche stage did not differ significantly between the adversity exposed youth and controls ($p = 0.063$); however, average gonadarche stage did differ significantly between the adversity

exposed youth and controls when examining both males and females ($p = 0.0005$, $p = 0.0008$) (see Table 2). Adversity exposed males demonstrated lower mean gonadarche than controls, while adversity exposed females displayed higher mean gonadarche than controls.

*Overview.* In this study, we examined type-specific and cumulative adversity's impact on adrenarche and gonadarche, while controlling for covariates such as, age, sex, race/ethnicity, primary caregiver's education and family income, unless otherwise specified. Specifically, we examined whether gonadarche development mediated type-specific and cumulative adversity's impact on bilateral amygdala and hippocampal volumes. We then examined the ability of school-based support to moderate the impact of type-specific and cumulative adversity on gonadarche.

When examining type-specific and cumulative adversity's impact on adrenarche and gonadarche, while controlling for covariates (i.e. age, sex, race/ethnicity, primary caregiver's education and family income), significant findings were found when examining adrenarche among the total sample and female gonadarche. Specifically, parental mental health was associated with advanced adrenarchal development ($p < 0.001$) and the proportional relative risk ratio switching from a stage 1 adrenarche to stage 2 adrenarche was 9.65%, and -13.45% for stages 3 and 4 combined. Thus, youth with parental mental health exposure were more likely than those without to be at stage 2 of adrenarche (Figure 1). Neighborhood threat was associated with advanced adrenarche development ($p = 0.02$) and the proportional relative risk from stage 1 to stages 3 and 4 combined was 9.01%. Thus, youth with neighborhood threat exposure were more likely than those without to be at stages 3 or 4 of adrenarche (Figure 2). Prenatal substance exposure was associated with advanced adrenarche development ($p = 0.01$) and the proportional relative risk from stage 1 to stage 2 was 7.66%. Youth with prenatal substance exposure were more likely than those without to be at stage 2 of adrenarche (Figure 3). Scarcity was associated

with advanced adrenarche development ($p = 0.004$) and the proportional relative risk from stage 1 to stages 3 and 4 combined is 9.57%. Youth exposed to scarcity were more likely to be at stages 3 combined with 4 of adrenarche (Figure 4). Lastly, cumulative adversity exposure was associated with advanced adrenarche development ($p < 0.001$) and the proportional relative risk from stage 1 to stage 2 is 3.8%. Thus, youth with cumulative adversity exposure were more likely to be at stage 2 of adrenarche (Figure 5). Physical and sexual violence exposure and household dysfunction did not demonstrate a significant relationship with adrenarche.

Type-specific and cumulative adversity did not demonstrate a significant relationship with gonadarche among males, with the greatest association found among males with neighborhood threat exposure ($p > 0.20$). Females in this sample were disproportionality impacted such that all forms of adversity, except for scarcity exposure and household dysfunction, were significantly associated with gonadarche development. Physical and sexual violence exposure among females was associated with advanced gonadarche development ($p = 0.0427$) and the proportional relative risk from stage 1 to stages 3 and 4 combined is 12.94%. Parental mental health was associated with advanced adrenarche development ($p < 0.001$) and the proportional relative risk from stage 1 to stage 2 is 14.99% (Figure 6). Neighborhood threat was associated with advanced gonadarchal development among females such that the proportional relative risk ratio switching from a stage 1 adrenarche to stage 2 adrenarche was 12.26% ($p = 0.0033$), and 19.42% for stages 3 and 4 combined ($p = 0.0093$). Prenatal substance use was associated with advanced gonadarchal development among females such that the proportional relative risk ratio switching from a stage 1 adrenarche to stage 2 adrenarche was 20.52% ($p < 0.001$), and 27.36% for stages 3 and 4 combined ($p = 0.0027$) (Figure 7). Lastly, cumulative adversity exposure was associated with advanced gonadarchal development among

females ($p < 0.0001$), such that the proportional relative risk ratio switching from a stage 1 adrenarche to stage 2 adrenarche was 8.04% and 11.64% for stages 3 and 4 (Figure 8). Scarcity and household dysfunction did not demonstrate a significant relationship with gonadarche among females.

*Mediation Analyses.* Mediation models were conducted for gonadarche development that served as possible mediators between the association of type-specific and cumulative early life adversity (independent variable) and bilateral amygdala and hippocampal volumes (dependent variables). All mediation models controlled for age. See the steps outlined in Tables 3 and 4 detailing the mediating effects of gonadarche development on the association between early life adversity and neural outcomes, adjusted for age. Mediation analyses were performed according to Baron and Kenny (1986) criteria and a quasi-Bayesian approximation was used to calculate confidence intervals.

*Neighborhood Threat Exposure.* Mediation models showed that gonadarche development in boys partially mediated the association between neighborhood threat exposure and left amygdala volume ($p \leq 0.0001$; total effect: -23.99, BCa 95% CI: -30.16 to -17.32; indirect effect: -1.55, BCa 95% CI: -2.50 to -0.62). Specifically, stage 2 of gonadarche development significantly impacted left amygdala volume while controlling for neighborhood threat exposure and age of the youth ($F(1,6044) = 28.3$, $\beta = -34.66$, standard error (SE) = 8.55, $p < 0.0001$). Furthermore, mediation models showed that gonadarche development in boys partially mediated the association between neighborhood threat exposure and right amygdala volume ($p \leq 0.0001$; total effect: -25.58, BCa 95% CI: -31.52 to -19.14; indirect effect: -1.68, BCa 95% CI: -2.47 to -0.67). Specifically, stage 2 of gonadarche development significantly impacted right amygdala volume while controlling for neighborhood threat exposure and age of the youth ($F(1,6044) =$

23.9, β = -36.46, standard error (SE) = 8.54, $p < 0.0001$). Among girls, mediation models showed that gonadarche development partially mediated the association between neighborhood threat exposure and left amygdala volume ($p \leq 0.0001$; total effect: -27.45, BCa 95% CI: -23.40 to -11.86; indirect effect: -0.88, BCa 95% CI: -2.06 to -0.10). Specifically, stage 2 of gonadarche development significantly impacted left amygdala volume while controlling for neighborhood threat exposure and age of the youth ($F(1,5512) = 17.4$, β = -11.69, standard error (SE) = 5.86, $p = 0.046$). Furthermore, mediation models showed that gonadarche development in girls partially mediated the association between neighborhood threat exposure and right amygdala volume ($p \leq 0.0001$; total effect: -18.52, BCa 95% CI: -24.49 to -13.04; indirect effect: -1.00, BCa 95% CI: -2.04 to -0.11). Specifically, stages 3 and 4 of gonadarche development significantly impacted right amygdala volume while controlling for neighborhood threat exposure and age of the youth ($F(1,5512) = 13.0$, β = -23.87, standard error (SE) = 12.60, $p = 0.058$).

Mediation models showed that gonadarche development in boys partially mediated the association between neighborhood threat exposure and left hippocampal volume ($p \leq 0.0001$; total effect: -47.34, BCa 95% CI: -60.38 to -34.39; indirect effect: -3.84, BCa 95% CI: -5.71 to -1.84). Both stages 2 ($F(1,6044) = 28.3$, β = -81.87, standard error (SE) = 16.08, $p < 0.001$) and 3 combined with 4 (β = -121.52, standard error (SE) = 51.77, $p = 0.02$) of gonadarche development significantly impacted left hippocampal volume while controlling for neighborhood threat exposure and age of the youth. Mediation models showed that gonadarche development in boys partially mediated the association between neighborhood threat exposure and right hippocampal volume ($p \leq 0.0001$; total effect: -52.28, BCa 95% CI: -64.24 to -39.61; indirect effect: -3.98, BCa 95% CI: -6.34 to -2.11). Both stages 2 ($F(1,6044) = 34.9$, β = -93.18, standard error (SE) = 15.88, $p < 0.0001$) and 3 combined with 4 (β = -126.88, standard error (SE) = 51.12, $p = 0.01$) of

gonadarche development significantly impacted right hippocampal volume while controlling for neighborhood threat exposure and age of the youth. When examining the hippocampus, mediation models showed that gonadarche development in girls partially mediated the association between neighborhood threat exposure and left hippocampal volume ($p \leq 0.0001$; total effect: -47.65, BCa 95% CI: -60.26 to -36.41; indirect effect: -3.22, BCa 95% CI: -6.02 to -1.98). Specifically, stages 3 and 4 of gonadarche development significantly impacted left hippocampal volume while controlling for neighborhood threat exposure and age of the youth ($F(1,5512) = 25.6$, $\beta = -92.85$, standard error (SE) = 24.93, $p = 0.0002$). Additionally, mediation models showed that gonadarche development in girls partially mediated the association between neighborhood threat exposure and right hippocampal volume ($p \leq 0.0001$; total effect: -46.50, BCa 95% CI: -58.53 to -35.80; indirect effect: -3.23, BCa 95% CI: -5.72 to -1.85). Specifically, stages 3 and 4 of gonadarche development significantly impacted right hippocampal volume while controlling for neighborhood threat exposure and age of the youth ($F(1,5512) = 26.5$, $\beta = -98.60$, standard error (SE) = 24.46, $p < 0.0001$).

*Prenatal Substance Exposure.* When examining the hippocampus, mediation models showed that gonadarche development in girls fully mediated the association between prenatal substance exposure and left hippocampal volume ($p \leq 0.0001$; total effect: -16.22, BCa 95% CI: -31.97 to -1.07; indirect effect: -2.62, BCa 95% CI: -4.68 to -1.15). Both stages 2 ($F(1,5512) = 12.8$, $\beta = -46.83$, standard error (SE) = 11.45, $p < 0.0001$) and 3 combined with 4 ($\beta = -115.34$, standard error (SE) = 24.85, $p = < 0.0001$) of gonadarche development significantly impacted left hippocampal volume while controlling for prenatal substance exposure and age of the youth. Additionally, mediation models showed that gonadarche development in girls partially mediated the association between prenatal substance exposure and right hippocampal volume ($p \leq 0.0001$;

total effect: -19.37, BCa 95% CI: -37.61 to -4.33; indirect effect: -2.71, BCa 95% CI: -4.44 to -0.95). Both stages 2 ($F(1,5512) = 14.4$, $\beta = -40.09$, standard error (SE) = 11.23, $p = 0.0004$) and 3 combined with 4 ($\beta = -119.90$, standard error (SE) = 24.37, $p = < 0.0001$) of gonadarche development significantly impacted right hippocampal volume while controlling for prenatal substance exposure and age of the youth. Among girls, mediation models examining bilateral amygdala outcomes were not associated with significant findings ($p > 0.05$). Among male youth, mediation models examining the independent variable prenatal substance exposure, were not associated with significant findings pertaining to either bilateral amygdala or hippocampal outcomes ($p > 0.05$).

*Scarcity.* When examining the hippocampus, mediation models showed that gonadarche development in girls partially mediated the association between scarcity and left hippocampal volume ($p \leq 0.0001$; total effect: -18.19, BCa 95% CI: -29.98 to -7.32; indirect effect: -2.93, BCa 95% CI: -4.87 to -1.04). Both stages 2 ($F(1,5512) = 13.0$, $\beta = -47.27$, standard error (SE) = 11.43, $p < 0.0001$) and 3 combined with 4 ($\beta = -114.34$, standard error (SE) = 24.87, $p = < 0.0001$) of gonadarche development significantly impacted left hippocampal volume while controlling for scarcity exposure and age of the youth. Additionally, mediation models showed that gonadarche development in girls partially mediated the association between prenatal substance exposure and right hippocampal volume ($p \leq 0.0001$; total effect: -20.35, BCa 95% CI: -34.53 to -8.05; indirect effect: -2.97, BCa 95% CI: -4.44 to -0.80). Both stages 2 ($F(1,5512) = 14.4$, $\beta = -40.70$, standard error (SE) = 11.21, $p = 0.0003$) and 3 combined with 4 ($\beta = -118.96$, standard error (SE) = 24.39, $p = < 0.0001$) of gonadarche development significantly impacted right hippocampal volume while controlling for scarcity exposure and age of the youth. Among girls, mediation models examining bilateral amygdala outcomes were not associated with

significant findings ($p > 0.05$). Among male youth, mediation models examining the independent variable scarcity, were not associated with significant findings pertaining to either bilateral amygdala or hippocampal outcomes ($p > 0.05$).

*Household Dysfunction.* Mediation models showed that gonadarche development in boys partially mediated the association between exposure to household dysfunction and left amygdala volume ($p \leq 0.0001$; total effect: -22.94, BCa 95% CI: -30.36 to -16.06; indirect effect: -1.06, BCa 95% CI: -1.79 to -0.17). Specifically, stage 2 of gonadarche development significantly impacted left amygdala volume while controlling for household dysfunction and age of the youth ($F(1,6044) = 27.1$, $\beta = -37.96$, standard error (SE) = 8.53, $p < 0.0001$). Furthermore, mediation models showed that gonadarche development in boys partially mediated the association between neighborhood threat exposure and right amygdala volume ($p \leq 0.0001$; total effect: -24.87, BCa 95% CI: -31.15 to -17.36; indirect effect: -1.11, BCa 95% CI: -1.71 to -0.19). Specifically, stage 2 of gonadarche development significantly impacted right amygdala volume while controlling for household dysfunction and age of the youth ($F(1,6044) = 23.9$, $\beta = -36.46$, standard error (SE) = 8.54, $p < 0.0001$). Among girls, mediation models showed that gonadarche development partially mediated the association between exposure to household dysfunction and left amygdala volume ($p \leq 0.0001$; total effect: -13.50, BCa 95% CI: -20.47 to -6.09; indirect effect: -0.66, BCa 95% CI: -1.52 to -0.20). Specifically, stage 2 of gonadarche development significantly impacted left amygdala volume while controlling for household dysfunction and age of the female youth ($F(1,5512) = 13.3$, $\beta = -13.97$, standard error (SE) = 5.84, $p = 0.0168$). Mediation models of gonadarche development in girls also partially mediated the association between household dysfunction and right amygdala volume ($p \leq 0.0001$; total effect: -12.98, BCa 95% CI: -19.84 to -5.43; indirect effect: -0.81, BCa 95% CI: -1.64 to -0.21). Both stages 2 ($F(1,5512) = 7.5$, $\beta = -$

12.54, standard error (SE) = 5.77, p = 0.0297) and 3 combined with 4 (β = -30.46, standard error (SE) = 12.55, p = 0.0152) of gonadarche development significantly impacted right amygdala volume while controlling for household dysfunction and age of the youth.

Mediation models showed that gonadarche development in boys partially mediated the association between exposure to household dysfunction and left hippocampal volume ($p \leq 0.0001$; total effect: -36.91, BCa 95% CI: -49.45 to -23.62; indirect effect: -2.67, BCa 95% CI: -4.10 to -0.51). Both stages 2 ($F(1,6044) = 22.2$, β = -89.10, standard error (SE) = 16.05, $p < 0.001$) and 3 combined with 4 (β = -142.14, standard error (SE) = 51.73, p = 0.006) of gonadarche development significantly impacted left hippocampal volume while controlling for household dysfunction and age of the youth. Mediation models showed that gonadarche development in boys partially mediated the association between exposure to household dysfunction and right hippocampal volume ($p \leq 0.0001$; total effect: -37.30, BCa 95% CI: -50.63 to -21.92; indirect effect: -3.07, BCa 95% CI: -4.16 to -0.47). Both stages 2 ($F(1,6044) = 27.1$, β = -101.21, standard error (SE) = 15.86, $p < 0.0001$) and 3 combined with 4 (β = -149.79, standard error (SE) = 51.11, p = 0.003) of gonadarche development significantly impacted right hippocampal volume while controlling for household dysfunction and age of the youth. Among girls, mediation models showed that gonadarche development partially mediated the association between exposure to household dysfunction and left hippocampal volume ($p \leq 0.0001$; total effect: -28.92, BCa 95% CI: -44.31 to -14.93; indirect effect: -2.45, BCa 95% CI: -4.97 to -1.44). Specifically, stages 2 ($F(1,5512) = 15.4$, β = -45.57, standard error (SE) = 11.44, $p < 0.0001$) and 3 combined with 4 (β = -110.73, standard error (SE) = 24.87, $p < 0.0001$) of gonadarche development significantly impacted left hippocampal volume while controlling for household

dysfunction and age of the youth. Mediation models of gonadarche development in girls also partially mediated the association between household dysfunction and right hippocampal volume ($p \leq 0.0001$; total effect: -35.37, BCa 95% CI: -47.14 to -20.65; indirect effect: -4.34, BCa 95% CI: -4.79 to -1.22). Both stages 2 ($F(1,5512) = 18.0$, $\beta = -31.02$, standard error (SE) = 6.90, $p < 0.0001$) and 3 combined with 4 ($\beta = -114.62$, standard error (SE) = 24.38, $p < 0.0001$) of gonadarche development significantly impacted right hippocampal volume while controlling for household dysfunction and age of the youth.

*Cumulative Adversity.* Among girls, mediation models showed that gonadarche development partially mediated the association between cumulative adversity exposure and left amygdala volume ($p \leq 0.0001$; total effect: -4.86, BCa 95% CI: -7.06 to -2.22; indirect effect: -0.65, BCa 95% CI: -0.98 to -0.06). Specifically, stage 2 of gonadarche development significantly impacted left amygdala volume while controlling for cumulative exposure and age of the female youth ($F(1,5512) = 13.4$, $\beta = -12.67$, standard error (SE) = 5.88, $p = 0.0311$. Mediation models of gonadarche development in girls also partially mediated the association between cumulative adversity and right amygdala volume ($p \leq 0.0001$; total effect: -5.15, BCa 95% CI: -7.58 to -2.98; indirect effect: -0.27, BCa 95% CI: -0.91 to -0.03). Specifically, stages 3 combined with 4 of gonadarche development significantly impacted right amygdala volume while controlling for cumulative adversity exposure and age of the female youth ($F(1,5512) = 9.1$, $\beta = -27.55$, standard error (SE) = 12.59, $p = 0.0287$).

Among girls, mediation models showed that gonadarche development partially mediated the association between cumulative adversity exposure and left hippocampal volume ($p \leq 0.0001$; total effect: -12.94, BCa 95% CI: -16.99 to -7.66; indirect effect: -2.22, BCa 95% CI: -3.05 to -0.56). Specifically, stages 2 ($F(1,5512) = 17.4$, $\beta = -41.61$, standard error (SE) = 11.49, p

= 0.0003) and 3 combined with 4 (β = -104.24, standard error (SE) = 24.95, p < 0.0001) of gonadarche development significantly impacted left hippocampal volume while controlling for cumulative adversity exposure and age of the youth. Mediation models of gonadarche development in girls also partially mediated the association between cumulative exposure and right hippocampal volume (p ≤ 0.0001; total effect: -13.31, BCa 95% CI: -18.16 to -8.66; indirect effect: -1.65, BCa 95% CI: -2.78 to -0.43). Both stages 2 (F(1,5512) = 19.7, β = -34.61, standard error (SE) = 11.27, p = 0.0021) and 3 combined with 4 (β = -108.16, standard error (SE) = 24.46, p < 0.0001) of gonadarche development significantly impacted right hippocampal volume while controlling for household dysfunction and age of the youth.

Finally, among male youth, mediation models examining the independent variables physical and sexual violence exposure, parental mental health and cumulative adversity were not associated with significant findings pertaining to either bilateral amygdala or hippocampal outcomes (p > 0.05). Among female youth, mediation models examining the independent variables physical and sexual violence exposure and parental mental health were not associated with significant findings pertaining to either bilateral amygdala or hippocampal outcomes (p > 0.05).

*Moderation Analyses.* Moderation analyses were conducted to examine whether school-based support as a form of resiliency interacts with type-specific and cumulative adversity exposure to alter the impact on pubertal development, specifically gonadarche. In all models, youth's age, sex, race and ethnicity, as well as family income and primary caregiver's education were controlled. Interactions were interpreted through the plotting of estimates (i.e. pubertal outcomes) by type-specific and cumulative adversity exposure and presence of school-based support. The results of these analyses are presented in Table 5. Moderation models were run and

presented first for type-specific adversity, followed by cumulative adversity, i.e. 1) physical and sexual violence; 2) parental mental health; 3) neighborhood threat; 4) prenatal substance exposure; 5) scarcity; and 6) household dysfunction; and 7) cumulative adversity. Moderation models first employed total school-based support and in instances where total support was shown to statistically interact with adversity exposure, we further examined the individual characteristics that comprised and summed to total school-support. Sources of school-based support included: the youth's perception of their intelligence in relation to their peers, whether they got along with their teachers, and whether they generally enjoyed school.

Among male youth, an individual's scarcity score significantly interacted with average gonadarche development ($p < 0.0001$). A main effect of school resiliency was found at stage 2 of gonadarche, when one ($p = 0.021$), two ($p = 0.018$) and three ($p = 0.020$) sources of school-based support were present. The proportional relative risk from stage 1 to stage 2 for one, two and three sources of school-based support is -47.94%, -46.08% and -44.50%, respectively. Among male youth, an individual's physical and sexual violence exposure ($p = 0.20$), parental mental health ($p = 0.064$), neighborhood threat ($p = 0.25$), prenatal substance exposure ($p = 0.39$), household dysfunction ($p = 0.42$) and cumulative adversity ($p = 0.26$) did not moderate gonadarche development.

Sensitivity analyses were conducted to examine whether individual characteristics that comprised total school-based support - the youth's perception of their intelligence in relation to their peers, whether they got along with their teachers, and whether they generally enjoyed school - interacted with male youth's scarcity score to influence gonadarche. When examining the youth's perception of their intelligence in relation to their peers, a main effect of scarcity score was observed at gonadarche stages 3 and 4 combined ($\beta = -1.54$, $SE = 0.05$, $p < 0.0001$)

and an interaction effect between scarcity score and this form of school support at gonadarche stages 3 and 4 combined ($\beta = 1.64$, SE = 0.05, $p < 0.0001$). The proportional relative risk from stage 1 to stages 3 combined with 4 were -78.47% for scarcity score alone and 415.50% for scarcity score interacting with youth's perception of their intelligence in relation to their peers. Youth's perception of whether they got along with their teachers interacted with scarcity score to significantly influence gonadarche among males ($p < 0.0001$). However, neither main effects nor interaction effects were found ($p > 0.62$). Finally, youth's perception of whether they generally enjoyed school interacted with scarcity score to significantly influence gonadarche among males ($p < 0.0001$). However, neither main effects nor interaction effects were found ($p > 0.60$). The significant driver of school-based support to significantly moderate scarcity's impact on gonadarche among males was youth's perception of their intelligence in relation to their peers.

Among female youth, household dysfunction significantly interacted with average gonadarche development ($p = 0.015$). At stage 2 of gonadarche, main effects of household dysfunction ($p = 0.02$) and resiliency when two ($p = 0.048$) and three ($p = 0.042$) sources of school-based support were found. Additionally, an interaction effect of household dysfunction and school-based support was found at gonadarche stage 2 with one ($p = 0.028$), two ($p = 0.010$) and three ($p = 0.023$) sources of school-based support. The proportional relative risk from stage 1 to stage 2 for the significant variables are as follows: household dysfunction (-51.62%), two (-59.07%) and three (-59.91%) sources of school-based support, and the interaction between school-based support and household dysfunction when one (113.97%), two (132.84%), and three (108.20%) sources are present. Among female youth, an individual's physical and sexual violence exposure ($p = 0.81$), parental mental health ($p = 0.27$), neighborhood threat ($p = 0.35$),

prenatal substance exposure ($p = 0.32$), scarcity ($p = 0.56$) and cumulative adversity ($p = 0.25$) did not moderate gonadarche development.

Sensitivity analyses were conducted to examine whether individual characteristics that comprised total school-based support - the youth's perception of their intelligence in relation to their peers, whether they got along with their teachers, and whether they generally enjoyed school - interacted with household dysfunction to influence female gonadarche. When examining the youth's perception of their intelligence in relation to their peers, neither a main effect of household dysfunction nor an interaction effect between household dysfunction and this form of school support were identified ($p = 0.50$). When examining the youth's perception of whether they got along with their teachers, neither a main effect of household dysfunction nor an interaction effect between household dysfunction and this form of school support were identified ($p = 0.16$). However, at stage 2 of gonadarche among females, a main effect of youth's perception of whether they got along with their teachers was found ($\beta = -0.59$, $SE = 0.20$, $p = 0.004$), with a proportional relative risk from stage 1 to stage 2 of -44.40%. Finally, when examining whether female youth generally enjoyed school, neither a main effect of household dysfunction nor an interaction effect between household dysfunction and this form of school support were identified ($p = 0.28$). However, at stage 2 of gonadarche among females, a main effect of whether youth generally enjoyed school was found ($\beta = -0.21$, $SE = 0.08$, $p = 0.014$), with a proportional relative risk from stage 1 to stage 2 of -18.55%. Thus, whether youth got along with their teachers carried the greatest proportional relative risk from stage 1 to stage 2 of female gonadarchal development.

## DISCUSSION

This study comprehensively tested whether puberty *mediated* the relationship between both type-specific and cumulative adversity exposure and amygdala and hippocampal volumes. Additionally, this study examined the relationship between pubertal development (i.e. adrenarche and gonadarche) and both type-specific and cumulative adversity exposure. Finally, this study examined whether school-based support *moderated* the impact of adversity exposure on pubertal development, specifically gonadarche. Early life adversity exposure was obtained from both the youth and caregiver and utilizing the results of a factor analysis, the following 6 adversity domains were identified and studied: 1) physical and sexual violence; 2) parental mental health; 3) neighborhood safety; 4) prenatal substance exposure; 5) scarcity; and 6) household dysfunction. Descriptive statistics and mediation and moderation analyses were run using the 6 factor domains as well as a cumulative adversity score comprised of the 6 domains.

*Adversity and Pubertal Development.* Specific types of adversity exposure were associated with advanced adrenarchal development, specifically, parental mental health, neighborhood threat, prenatal substance exposure, and scarcity. The often-chronic nature of parental mental health and neighborhood threat may explain why these forms of adversity exposure impacted adrenarche. The timing of prenatal substance exposure may explain the association with advanced adrenarchal development. Both neighborhood threat and scarcity exposure increased the likelihood of stages 3 and 4 adrenarche, with scarcity exposure carrying the greatest relative risk. Deprivation of bioenergetic resources due to food scarcity could result in delayed maturation, as seen in war-related famine (Colich 2019); however, food insecurity is common in the US (McLaughlin 2012) and it may be that more extreme forms of deprivation can delay pubertal development. Lastly, parental mental health carried the greatest relative risk

which may in part be due to the greater prevalence among the sample. Of note, parental mental health was associated with a negative proportional relative risk of -13.45% of adrenarche development at stages 3 combined with 4.

Among females, advanced gonadarchal development was associated with physical and sexual violence, parental mental health, neighborhood safety and prenatal substance exposure. Prenatal substance exposure was associated with the greatest relative risk for advanced gonadarche among females. Exposure to alcohol and tobacco were the two most common sources of prenatal substance exposure in ABCD Study youth at baseline. A recent longitudinal study of over 15,000 youth found that maternal alcohol intake during the first trimester was associated with advanced pubertal onset among girls but not among boys (Brix 2020). Human studies of prenatal alcohol exposure have found conflicting findings for both sexes (Akison 2019, Brix 2020). Prenatal tobacco exposure is associated with advanced pubertal onset in girls, and earlier voice changes in boys, although the authors do suggest that more studies on boys are needed (Chen 2018). Lastly, type-specific and cumulative adversity exposure among males was not associated with gonadarche. This may in part be attributable to male's delayed pubertal maturation with respect to females.

*Relationship Between Adversity, Pubertal Maturation and Brain Development.* Neighborhood threat exposure and household dysfunction were the only forms of adversity where mediation models employing gonadarche development and both bilateral amygdala and hippocampal volume was significant among both males and females. Among females, prenatal substance exposure and scarcity played a significant role among females when examining the mediating ability of gonadarche on bilateral hippocampal volume. Thus, specific forms of early life adversity exposure (i.e. neighborhood threat, household dysfunction, prenatal substance

exposure and scarcity) are associated with advanced gonadarche, which increases the risk of amygdala and hippocampal alterations.

*Neighborhood Threat Exposure.* Mediation models showed that gonadarche development partially mediated the association between neighborhood threat exposure and left and right amygdala volume among both males and females. Among males, stage 2 of gonadarche mediated with association when examining bilateral amygdala volume. Among females, stage 2 of gonadarche mediated the association between neighborhood threat exposure and left amygdala volume while stages 3 combined with 4 mediated the association with right amygdala volume. The observed mediating relationships were more significant among girls, possibly due to greater gonadarche development among girls in comparison to boys. Additionally, the amygdala (and hippocampus) has demonstrated earlier maturational peaks in girls in comparison to boys (Frere 2020).

When examining hippocampal volume, mediation models showed that gonadarche development partially mediated the association between neighborhood threat exposure and left and right hippocampal volume among both males and females. Among males, all advanced stages of gonadarche (stages 2, and 3 combined with 4) mediated with association when examining bilateral hippocampal volume. Among females, stages 3 combined with 4 of gonadarche mediated the association between neighborhood threat exposure and bilateral hippocampal volume.

*Prenatal Substance Exposure.* Only mediation models examining the ability of gonadarche development to mediate the association between prenatal substance exposure and bilateral hippocampal volume among females was significant. In fact, gonadarche development in girls *fully* mediated the association between prenatal substance exposure and *left* hippocampal

volume. Both gonadarchal stages 2 and 3 combined with 4 mediated the association between prenatal substance exposure and bilateral hippocampal volume. Among male youth, mediation models examining the independent variable prenatal substance exposure, were not associated with significant findings pertaining to either bilateral amygdala or hippocampal outcomes. Among girls, mediation models examining bilateral amygdala outcomes were not associated with significant findings. While conflicting findings regarding the directionality of pubertal onset (i.e. precocious or delayed) are evident in response to prenatal substance exposure (Akison 2019), findings more clearly point to an effect among girls (Brix 2020). The observed significant findings among girls may be attributable to our findings of earlier gonadarche among girls exposed to prenatal substance exposure. Additionally, the hippocampus develops earlier than the amygdala (Tottenham 2016) and as such, may be more vulnerable to the impacts of earlier forms of adversity exposure. Humphreys and colleagues (2019) suggest a sensitive period of adversity exposures on hippocampal volumes ranging from in utero to the age of 5.

*Scarcity.* Only mediation models examining the ability of gonadarche development to mediate the association between scarcity and bilateral hippocampal volume among females was significant. Both gonadarchal stages 2 and 3 combined with 4 mediated the association between scarcity and bilateral hippocampal volume. Among male youth, mediation models examining the independent variable scarcity were not associated with significant findings pertaining to either bilateral amygdala or hippocampal outcomes. Among girls, mediation models examining bilateral amygdala outcomes were not associated with significant findings.

*Household Dysfunction.* Mediation models showed that gonadarche development partially mediated the association between household dysfunction and left and right amygdala volume among both males and females. Among males, stage 2 of gonadarche mediated with

association when examining bilateral amygdala volume. Among females, stage 2 of gonadarche mediated the association between household dysfunction and left amygdala volume while stages 3 combined with 4 mediated the association with right amygdala volume. A greater likelihood of advanced gonadarche among girls in comparison to boys in response to household dysfunction could be attributable to greater average gonadarche development among girls in comparison to boys, i.e. 2.36 and 1.55, respectively. Furthermore, the amygdala and hippocampus display earlier maturational peaks in girls in comparison to boys (Frere 2020).

When examining hippocampal volume, mediation models showed that gonadarche development partially mediated the association between neighborhood threat exposure and left and right hippocampal volume among both males and females. Among both males and females, all advanced stages of gonadarche (stages 2, and 3 combined with 4) mediated with association when examining bilateral hippocampal volume. Greater similarities in gonadarche influence among the sexes when examining bilateral hippocampal volumes may in part be attributed to the earlier maturational peak of the hippocampus, in comparison to the amygdala. In addition to neighborhood threat exposure, household dysfunction was the only other form of adversity exposure where mediation models showed significant findings pertaining to both bilateral amygdala and hippocampal volumes among both males and females. Household dysfunction and neighborhood threat are often more chronic in nature than other forms of adversity exposure (Hardaway 2016), such as physical and sexual abuse, which may occur sporadically and show more variability in their frequency. Chronic forms of adversity exposure occurring during development are poised to exert a differential and possibly greater impact on development (Teicher 2016).

*Cumulative Adversity.* Mediation models showed that gonadarche development partially mediated the association between cumulative adversity and left and right amygdala volume among females. Stage 2 of gonadarche mediated the association between cumulative adversity and left amygdala volume whereas stages 3 combined with 4 mediated the association with right amygdala volume. This difference could be attributable to the maturation trajectory of the amygdala. Uematsu and colleagues (2012) found that the left amygdala reached peak volume among girls around 9.6 years of age while the right amygdala peaked around 11.4 years of age. They speculate that the left amygdala might grow in advance of the right amygdala due to the left amygdala's role in responding to fearful events and faces and thus being of pertinence early in life (Uematsu 2012). However, our study suggests more advanced pubertal onset associated with the right amygdala. These findings require further exploration.

When examining hippocampal volume, mediation models showed that gonadarche development partially mediated the association between neighborhood threat exposure and left and right hippocampal volume among females. All advanced stages of gonadarche (stages 2, and 3 combined with 4) mediated with association when examining bilateral hippocampal volume. These more robust findings associated with hippocampal development and all stages of advanced gonadarche among females may be due to the earlier maturation trajectory of the hippocampus in comparison to the amygdala and females more advanced pubertal maturation in comparison to males.

*Resiliency to Adversity's Impact on Puberty.* Moderation analyses were conducted to examine whether school-based support as a form of resiliency interacts with type-specific and cumulative adversity exposure to alter the impact on pubertal development, specifically gonadarche. In all models, youth's age, sex, race and ethnicity, as well as family income and

primary caregiver's education were controlled. Interactions were interpreted through the plotting of estimates (i.e. pubertal outcomes) by type-specific and cumulative adversity exposure and presence of school-based support. The results of these analyses are presented in Table 5. Moderation models were run and presented first for type-specific adversity, followed by cumulative adversity. Moderation models first employed total school-based support and in instances where total support was shown to statistically interact with adversity exposure, we further examined the individual characteristics that comprised and summed to total school-support. Sources of school-based support included: the youth's perception of their intelligence in relation to their peers, whether they got along with their teachers, and whether they generally enjoyed school.

Among male youth, an individual's scarcity score was the only source of aversity that significantly interacted with average gonadarche development ($p < 0.0001$). A main effect of school resiliency was found at stage 2 of gonadarche, when one ($p = 0.021$), two ($p = 0.018$) and three ($p = 0.020$) sources of school-based support were present. The proportional relative risk from stage 1 to stage 2 for one, two and three sources of school-based support is -47.94%, -46.08% and -44.50%, respectively. Sensitivity analyses examining individual characteristics of school-based support revealed a main effect of scarcity score at gonadarche stages 3 and 4 combined and an interaction effect between scarcity and youth's perception of their intelligence in relation to their peers at gonadarche stages 3 and 4 combined. The proportional relative risk from stage 1 to stages 3 combined with 4 were -78.47% for scarcity score alone and 415.50% for scarcity score interacting with youth's perception of their intelligence in relation to their peers. As neither main effects nor interaction effects were found for the other two sources of school-based support, the apparent driver of school-based support in moderating scarcity's impact on

gonadarche among males was youth's perception of their intelligence in relation to their peers. The sensitivity analyses explain why the proportional relative risk decreases as additional sources of school-based support are included. In our study, scarcity exposure captured both food insecurity and utility services being turned off due to lack of payment. Previous research examining scarcity exposure has focused on food insecurity and nutritional deprivation and their relationship with delayed pubertal onset, to ensure that sufficient bioenergetic resources are reserved for reproduction (Colich 2019). We are not aware of any studies utilizing youth's perception of their intelligence in relation to their peers as a source of resiliency against adversity exposure. However, research on different forms of school-based resiliency have demonstrated its ability to moderate adversity's association with problematic behaviors.

Among female youth, household dysfunction significantly interacted with average gonadarche development ($p = 0.015$). At stage 2 of gonadarche, main effects of household dysfunction ($p = 0.02$) and resiliency when two ($p = 0.048$) and three ($p = 0.042$) sources of school-based support were found. Additionally, an interaction effect of household dysfunction and school-based support was found at gonadarche stage 2 with one ($p = 0.028$), two ($p = 0.010$) and three ($p = 0.023$) sources of school-based support. The proportional relative risk from stage 1 to stage 2 for the significant variables are as follows: household dysfunction (-51.62%), two (-59.07%) and three (-59.91%) sources of school-based support, and the interaction between school-based support and household dysfunction when one (113.97%), two (132.84%), and three (108.20%) sources are present. A recent meta-analysis examining household dysfunction and other forms of adversity exposure noted a small association with advanced pubertal timing among girls (Zhang 2019); however, studies have suggested that girls are more impacted by household dysfunction than boys (Coêlho 2018). Our study defined household dysfunction as

family members oftentimes hitting, criticizing and fighting with one another, while the 2019 meta-analysis included incidences of the following as household dysfunction: parental death or serious illness, parental separation or divorce, parental incarceration, parental substance abuse, domestic violence, mental illness (Zhang 2019). Given our study's targeted and data-driven definition and associated findings, future research should examine the impact of a more nuanced definition of household dysfunction, as opposed to one that could serve as a catch-all for other forms of adversity exposure.

Sensitivity analyses examining whether individual characteristics that comprised total school-based support interacted with household dysfunction among females to influence gonadarche revealed neither main effects nor interaction effects for youth's perception of their intelligence in relation to their peers. Main effects corresponding to youth's perception of whether they got along with their teachers and whether they generally enjoyed school were found with proportional relative risks of -44.40% and -18.55% for stage 1 to stage 2, respectively. Thus, whether female youth got along with their teachers carried the greatest proportional relative risk from stage 1 to stage 2 of female gonadarchal development.

Among male and female youth, an individual's physical and sexual violence exposure parental mental health, neighborhood threat, prenatal substance exposure and cumulative adversity did not moderate gonadarche development. The reasons why scarcity exposure impacted gonadarche in male youth while household dysfunction influenced gonadarche development in female youth is unclear. Future research utilizing the longitudinal ABCD Study dataset, along with other population-based longitudinal studies, are needed to identify whether sexually-differentiated sensitive windows of development are associated with different forms of adversity exposure on pubertal and neurodevelopmental outcomes.

*Understanding Sex Differences.* Grey matter volume develops in a curvilinear manner, peaking in late childhood and decreasing throughout adolescence. Based on cross-sectional findings, Herting and colleagues (2014) hypothesized that males and females would have similar amygdala and hippocampal volumes at the start of adolescence. Our findings, however, clearly demonstrate sex differences in both amygdala and hippocampal volumes irrespective of adversity exposure. Findings from longitudinal studies of structural neurodevelopment suggest a nonlinear relationship with puberty that is interactive with both age and sex (Goddings 2019). Furthermore, features of pubertal development display sex differential associations with neurodevelopment. Regarding amygdala volume, a systematic review by Vijayakumar and colleagues (2018) found negative associations with breast development in females but positive associations with hair and skin changes in males. Generally, studies found negative associations with pubertal stage among females, and positive associations with pubertal stage among males (Vijayakumar 2018). As such, puberty may contribute to observed sex differences in amygdala development. Regarding hippocampal development, generally volume reductions are evident with increasing pubertal maturation; while sex differences are present, they are less stark than observed for amygdala development (Vijayakumar 2018). This may be attributable to the developmental timing of these neural regions and the overlap with pubertal development. Furthermore, a steeper trajectory of change in subcortical regions is seen early in puberty, followed by a plateau or even reversal in growth by late puberty (Herting 2017).

The age of pubertal onset varies considerably among individuals, ranging from 8 to 14.9 years in females and 9.7–14.1 years in males (Laube 2020). While advanced pubertal maturation is associated with a more developed brain phenotype, precocious pubertal development is suggested to influence neurodevelopment differently than a normative pubertal maturation

trajectory (Vijayakumar 2018). Advanced pubertal development has been associated with a history of early life adversity exposure, although previous studies have largely focused on precocious pubertal development among females (Zhang 2019). Reductions in hippocampal volume have been observed most consistently for children exposed to threat-related adversity; reductions in hippocampal volume are inconsistently associated with deprivation exposure, and rarely are observed among samples exposed to both threat and deprivation (McLaughlin 2019). Regarding amygdala volume, reductions have been observed most consistently among youth exposed to threat; like hippocampal volumes, associated volume reductions are inconsistent among youth exposed to deprivation or among samples exposed to both threat and deprivation (McLaughlin 2019). Directional findings in subcortical volumes are more reliably demonstrated with the hippocampus (Teicher 2016).

Without addressing adversity exposure, the literature has yielded conflicting findings as to the relationship between pubertal development and neurodevelopment, specifically of subcortical structures. In their longitudinal sample of 126 adolescents aged 10 to 14 and utilizing two time points of neuroimaging data separated by 2 years, Herting and colleagues (2014) did not find an association between pubertal measures and hippocampal development. However, another study found that pubertal development, as assessed by self-reported Tanner Stage, predicted changes in subcortical volumes of the hippocampus and amygdala among youth aged 7 to 22 years (Goddings 2014).

Precocious pubertal development is associated with psychopathology, including depression, anxiety, conduct disorders and substance use, as well as lower academic functioning (Laube 2020). Adolescence also marks the peak age of onset for psychopathology (Kessler 2005) with symptomology following sex-differential patterns. Females are more likely to develop

internalizing disorders, such as anxiety and depression, while males more routinely engage in substance abuse and externalizing disorders (Herting 2014). It is suggested that early pubertal maturation might truncate the length of childhood as a developmental strategy in response to hostile and unstable family structures and environments. In doing so, precocious pubertal development may narrow the window of cognitive development before basic cognitive functions are fully developed (Laube 2020).

## LIMITATIONS

The presence of early life adversity exposure captured in this study represent one time point (i.e. baseline) and may not be evident of chronic exposure. In instances where the caregiver may be unaware of exposure or may be associated either directly or indirectly with its perpetuation, the findings may not accurately reflect exposure. As youth age, we encourage sensitive physical and sexual abuse questions to be asked directly of youth participants. As neuroimaging is captured biannually, even delayed notification of early life adversity exposure will be beneficial in associating adversity's impact with neurodevelopment and ensuing behavioral outcomes.

PDS underrepresents gonadal development, particularly among males (Vijayakumar 2018). As such, individuals with low PDS scores can actually be quite physically developed according to Tanner Stage. Nevertheless, the assessment of an individual's perception of their physical appearance captures the influence of these physical changes on how youth are perceived by their parents, which itself is an important construct to examine (Goddings 2019). Additionally, sex hormones influence brain development and measurements of secondary sex characteristics are a proxy for hormonal levels (Herting 2014). Future studies should examine the

influence of adversity exposure, sources of resiliency and neurodevelopment within the context of sex hormones and development of secondary sex characteristics. Of note, some neural changes are suggested to occur independently of sex hormone changes (Goddings 2019).

Our understanding of the findings rests of the assumption that neurodevelopmental changes proceed pubertal and behavioral changes. As this is a cross-sectional study, it is important to keep in mind that while mediation analyses confirm the plausibility of the proposed causal pathway, they do not preclude alternative ordering. As such, future research should employ a longitudinal design and/or specifically examine the plausibility of pubertal and behavioral changes proceeding neurodevelopmental changes.

Lastly, recent prevalence estimates of type-specific and cumulative early life adversity exposure obtained from over 200,000 adults participating in the Behavioral Risk Factor Surveillance System indicate rates double that of the current study's (Merrick 2018). Given that exposure was assessed retrospectively in adults and this is the first nationwide study to prospectively (from baseline) examine the prevalence of adversity exposure in a population-based study of youth, we do not have a comparison with which to assess our study's prevalence rates by. For this and many reasons, the ABCD Study is poised to significantly contribute and advance our knowledge of youth physiological and social development, while capturing the many factors that influence it. Finally, participants enrolled in the ABCD Study possess a higher educational attainment and larger household income than national averages (Merrick 2018).

## CONCLUSION

Physical changes in response to pubertal hormones may lead to altered behaviors not only by the developing youth but by those they interact with, both of which may contribute to

neurodevelopmental changes. Additionally, adversity exposure is traditionally associated with advanced pubertal development, including onset. As adolescence is a time of increased social influences and parental conflict, there is a greater need for sources of resiliency and support outside the home. School-based support is poised to play a significant role in youth development as they age throughout adolescence. This study has identified sources of adversity that are associated with advanced pubertal development and display sex differentiation. Among females, advanced gonadarchal development was associated with physical and sexual violence, parental mental health, neighborhood safety and prenatal substance exposure; type-specific and cumulative adversity exposure was not associated with gonadarche among males. Mediation analyses revealed that specific forms of early life adversity exposure (i.e. neighborhood threat, household dysfunction, prenatal substance exposure and scarcity) are associated with advanced gonadarche, which increases the risk of amygdala and hippocampal alterations. However, school-based support, specifically whether youth reported a positive relationship with their teachers moderated the impact of adversity exposure on pubertal development among females. Additional work is needed to identify sources of support within the school environment that may mitigate the physiological effects of early life adversity exposure.

## TABLES

**Table 1. Demographic Characteristics of ABCD Study Youth at Baseline (n=11566)**

| Characteristic | No. (%) |
|---|---|
| **Age, y** | |
| 9 | 6090 (52.7) |
| 10 | 5469 (47.3) |
| **Sex[a]** | |
| Male | 6042 (52.3) |
| Female | 5512 (47.7) |
| **Race/ethnicity** | |
| White | 6016 (52.0) |
| Black | 1730 (15.0) |
| Hispanic | 2340 (20.2) |
| Asian | 244 (2.1) |
| Other | 1229 (10.6) |
| **Household income[a], $** | |
| 0-24,999 | 1593 (15.1) |
| 25,000-49,999 | 1544 (14.6) |
| 50,000-74,999 | 1454 (13.8) |
| 75,000-99,999 | 1529 (14.5) |
| 100,000+ | 4444 (42.1) |
| **Primary caregiver's educational attainment[a]** | |
| Less than HS diploma | 765 (6.6) |
| HS diploma/GED | 1231 (10.7) |
| Some college or AA degree | 3397 (29.4) |
| Bachelors degree | 3235 (28.0) |
| Graduate and professional school | 2911 (25.2) |
| **Adversity Exposure** | |
| Physical and sexual violence | 843 (7.3) |
| Parental mental health | 9413 (81.4) |
| Neighborhood safety | 2304 (19.9) |
| Prenatal substance exposure | 1224 (10.6) |
| Scarcity | 1348 (11.7) |
| Household dysfunction | 4867 (42.1) |

[a]Five youth were missing data indicating sex; 995 youth were missing data describing family income; 20 youth were missing data describing primary caregiver's education.

**Table 2: Demographic characteristics and pubertal development among controls and youth with any adversity exposure**

| | Count (%) | |
|---|---|---|
| **Characteristic** | **Controls (n=915)** | **Adversity Exposed, any (n=10,651)** |
| **Age, y** | | |
| 9 | 440 (48.1) | 5655 (53.1) |
| 10 | 475 (52.0) | 4996 (46.9) |
| **Sex[a]** | | |
| Male | 439 (48.0) | 5610 (52.7) |
| Female | 476 (52.0) | 5041 (47.3) |
| **Race/ethnicity** | | |
| White | 395 (43.2) | 5623 (52.8) |
| Black | 152 (16.6) | 1581 (14.8) |
| Hispanic | 235 (25.7) | 2106 (19.8) |
| Asian | 61 (6.7) | 183 (1.7) |
| Other | 72 (7.9) | 1158 (10.9) |
| | | |
| **Pubertal Dev.** | | |
| Adrenarche, mean (SD) | 1.57 (0.67) | 1.53 (0.62) |
| Gonadarche, mean (SD) | 1.61 (0.5) M<br>2.28 (0.8) F | 1.55 (0.51) M<br>2.37 (0.78) F |

**Table 3: Mediating effect of male gonadarche on the association between early life adversity and amygdala and hippocampal volumes, adjusted for age. Mediation analyses according to Baron and Kenny (1986) criteria and Bootstrapping.**

| | Step 1 | | | | Step 2 | | | | Step 3 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Left Amygdala Volume (mm3) (DV); Adversity (IV) | | | | Gonadarche Development (M); Adversity (IV) | | | | Left Amygdala Volume (mm3) (DV); Gonadarche Development (M)b; Adversity (IV)a | | | |
| | B | SE | p | 95% BCa | B | SE | p | 95% BCa | B | SE | p | 95% BCa |
| Factor 1: Physical and sexual violence | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 2: Parental mental health | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 3: Neighborhood Safety | -24.02 | 3.28 | < 0.0001 | [-30.45 to -17.59] | 0.32 | 0.04 | < 0.0001 | [0.25 to 0.39] | -22.43a; -34.66b | 3.30a; 8.55b | < 0.0001ab | [-28.90 to -15.97]a; [-51.43 to -17.89]b |
| Factor 4: Prenatal substance exposure | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 5: Scarcity | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 6: Household dysfunction | -22.77 | 3.65 | < 0.0001 | [-29.92 to -15.62] | 0.18 | 0.05 | < 0.0001 | [0.09 to 0.27] | -21.88a; -37.96b | 3.65a; 8.53b | < 0.0001ab | [-29.03 to -14.73]a; [-54.68 to -21.24]b |
| Cumulative Adversity | - ns - | | | | - ns - | | | | - ns - | | | |
| | Step 1 | | | | Step 2 | | | | Step 3 | | | |
| | Right Amygdala Volume (mm3) (DV); Adversity (IV) | | | | Gonadarche Development (M); Adversity (IV) | | | | Right Amygdala Volume (mm3) (DV); Gonadarche Development (M)b; Adversity (IV)a | | | |
| | B | SE | p | 95% BCa | B | SE | p | 95% BCa | B | SE | p | 95% BCa |
| Factor 1: Physical and sexual violence | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 2: Parental mental health | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 3: Neighborhood Safety | -25.40 | 3.27 | < 0.0001 | [-31.82 to -18.99] | 0.32 | 0.04 | < 0.0001 | [0.25 to 0.39] | -23.90a; -36.46b | 3.29a; 8.54b | < 0.0001ab | [-30.35 to -17.45]a; [-53.20 to -19.73]b |
| Factor 4: Prenatal substance exposure | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 5: Scarcity | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 6: Household dysfunction | -24.62 | 3.64 | < 0.0001 | [-31.76 to -17.49] | 0.18 | 0.05 | < 0.0001 | [0.09 to 0.27] | -23.76a; -39.93b | 3.64a; 8.52b | < 0.0001ab | [-30.89 to -16.63]a; [-56.62 to -23.24]b |
| Cumulative Adversity | - ns - | | | | - ns - | | | | - ns - | | | |
| | Step 1 | | | | Step 2 | | | | Step 3 | | | |
| | Left Hippocampal Volume (mm3) (DV); Adversity (IV) | | | | Gonadarche Development (M); Adversity (IV) | | | | Left Hippocampal Volume (mm3) (DV); Gonadarche Development (M)b; Adversity (IV)a | | | |
| | B | SE | p | 95% BCa | B | SE | p | 95% BCa | B | SE | p | 95% BCa |
| Factor 1: Physical and sexual violence | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 2: Parental mental health | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 3: Neighborhood Safety | -47.48 | 6.17 | < 0.0001 | [-59.57 to -35.39] | 0.32 | 0.04 | < 0.0001 | [0.25 to 0.39] | -43.49a; -81.87b | 6.20a; 16.08b | < 0.0001ab | [-55.64 to -31.34]a; [-113.37 to -50.37]b |
| Factor 4: Prenatal substance exposure | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 5: Scarcity | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 6: Household dysfunction | -36.44 | 6.87 | < 0.0001 | [-49.91 to -22.98] | 0.18 | 0.05 | < 0.0001 | [0.09 to 0.27] | -34.23a; -89.10b | 6.86a; 16.05b | < 0.0001ab | [-47.68 to -20.79]a; [-120.56 to -57.65]b |
| Cumulative Adversity | - ns - | | | | - ns - | | | | - ns - | | | |
| | Step 1 | | | | Step 2 | | | | Step 3 | | | |
| | Right Hippocampal Volume (mm3) (DV); Adversity (IV) | | | | Gonadarche Development (M); Adversity (IV) | | | | Right Hippocampal Volume (mm3) (DV); Gonadarche Development (M)b; Adversity (IV)a | | | |
| | B | SE | p | 95% BCa | B | SE | p | 95% BCa | B | SE | p | 95% BCa |
| Factor 1: Physical and sexual violence | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 2: Parental mental health | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 3: Neighborhood Safety | -52.74 | 6.09 | < 0.0001 | [-64.69 to -40.79] | 0.32 | 0.04 | < 0.0001 | [0.25 to 0.39] | -48.31a; -93.18b | 6.12a; 15.88b | < 0.0001ab | [-60.30 to -36.31]a; [-124.29 to -62.06]b |
| Factor 4: Prenatal substance exposure | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 5: Scarcity | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 6: Household dysfunction | -40.44 | 6.79 | < 0.0001 | [-53.76 to -27.13] | 0.18 | 0.05 | < 0.0001 | [0.09 to 0.27] | -37.99a; -101.21b | 6.77a; 15.86b | < 0.0001ab | [-51.27 to -24.70]a; [-132.29 to -70.13]b |
| Cumulative Adversity | - ns - | | | | - ns - | | | | - ns - | | | |

**Table 4: Mediating effect of female gonadarche on the association between early life adversity and amygdala and hippocampal volumes, adjusted for age. Mediation analyses according to Baron and Kenny (1986) criteria and Bootstrapping.**

| | Step 1 | | | | Step 2 | | | | Step 3 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Left Amygdala Volume (mm3) (DV); Adversity | | | | Gonadarche Development (M); Adversity | | | | Left Amygdala Volume (mm3) (DV); Gonadarche Development (M)b; Adversity (IV)a | | | |
| | B | SE | p | 95% BCa | B | SE | p | 95% BCa | B | SE | p | 95% BCa |
| Factor 1: Physical and sexual violence | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 2: Parental mental health | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 3: Neighborhood Safety | -17.53 | 3.04 | < 0.0001 | [-23.49 to -11.57] | 0.36 | 0.03 | < 0.0001 | [0.29 to 0.42] | -16.57a; -11.69b | 3.08a; 5.86b | < 0.0001a; 0.046b | [-22.60 to -10.54]a; [-23.18 to -0.21]b |
| Factor 4: Prenatal substance exposure | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 5: Scarcity | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 6: Household dysfunction | -13.64 | 3.59 | 0.0001 | [-20.66 to -6.61] | 0.23 | 0.04 | < 0.0001 | [0.15 to 0.30] | -12.84a; -13.97b | 3.60a; 5.84b | 0.0004a; 0.0168b | [-19.89 to -5.79]a; [-25.42 to -2.52]b |
| Cumulative Adversity | -4.62 | 1.16 | < 0.0001 | [-6.89 to -2.35] | 0.14 | 0.01 | < 0.0001 | [0.11 to 0.16] | -4.21a; -12.67b | 1.17a; 5.88b | 0.0003a; 0.0311b | [-6.50 to -1.91]a; [-24.19 to -1.16]b |
| | **Step 1** | | | | **Step 2** | | | | **Step 3** | | | |
| | **Right Amygdala Volume (mm3) (DV);** | | | | **Gonadarche Development (M); Adversity** | | | | **Right Amygdala Volume (mm3) (DV); Gonadarche Development (M)b; Adversity (IV)a** | | | |
| | **B** | **SE** | **p** | **95% BCa** | **B** | **SE** | **p** | **95% BCa** | **B** | **SE** | **p** | **95% BCa** |
| Factor 1: Physical and sexual violence | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 2: Parental mental health | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 3: Neighborhood Safety | -18.57 | 3.00 | < 0.0001 | [-24.45 to -12.69] | 0.36 | 0.03 | < 0.0001 | [0.29 to 0.42] | -17.52a; -23.87b± | 3.04a; 12.60b± | < 0.0001a; 0.058b± | [-23.48 to -11.58]a; [-48.57 to 0.83]b± |
| Factor 4: Prenatal substance exposure | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 5: Scarcity | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 6: Household dysfunction | -13.03 | 3.54 | 0.0002 | [-19.98 to -6.09] | 0.23 | 0.04 | < 0.0001 | [0.15 to 0.30] | -12.16a; -30.46b± | 3.55a; 12.55b± | 0.0006a; 0.0152b± | [-19.13 to -5.20]a; [-55.06 to -5.87]b± |
| Cumulative Adversity | -5.3 | 1.14 | < 0.0001 | [-7.55 to -3.06] | 0.14 | 0.01 | < 0.0001 | [0.11 to 0.16] | -4.88a; -27.55b± | 1.16a; 12.59b± | < 0.0001a; 0.0287b± | [-7.15 to -2.61]a; [-52.22 to -2.87]b± |
| | **Step 1** | | | | **Step 2** | | | | **Step 3** | | | |
| | **Left Hippocampal Volume (mm3) (DV);** | | | | **Gonadarche Development (M); Adversity** | | | | **Left Hippocampal Volume (mm3) (DV); Gonadarche Development (M)b; Adversity (IV)a** | | | |
| | **B** | **SE** | **p** | **95% BCa** | **B** | **SE** | **p** | **95% BCa** | **B** | **SE** | **p** | **95% BCa** |
| Factor 1: Physical and sexual violence | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 2: Parental mental health | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 3: Neighborhood Safety | -48.49 | 5.94 | < 0.0001 | [-60.14 to -36.84] | 0.36 | 0.03 | < 0.0001 | [0.29 to 0.42] | -44.43a; -92.85b± | 6.01a; 24.93b± | < 0.0001a; 0.0002b± | [-56.20 to -32.65]a; [-141.72 to -43.98]b± |
| Factor 4: Prenatal substance exposure | -16.27 | 7.02 | 0.0205 | [-30.03 to -2.50] | 0.19 | 0.04 | < 0.0001 | [0.12 to 0.27] | -13.61a; -115.34b± | 7.02a; 24.85b± | < 0.0001ab± | [-27.37 to 0.16]a; [-164.05 to -66.64]b± |
| Factor 5: Scarcity | -17.9 | 7.22 | 0.0133 | [-32.06 to -3.73] | 0.19 | 0.04 | < 0.0001 | [0.11 to 0.26] | -15.26a; -114.33b± | 7.22a; 24.87b± | 0.0347a; < 0.0001b± | [-29.42 to -1.10]a; [-163.08 to -65.59]b± |
| Factor 6: Household dysfunction | -29.64 | 7.03 | < 0.0001 | [-43.43 to -15.86] | 0.23 | 0.04 | < 0.0001 | [0.15 to 0.30] | -26.48a; -110.73b± | 7.04a; 24.87b± | 0.0002a; < 0.0001b± | [-40.28 to -12.68]a; [-159.47 to -61.99]b± |
| Cumulative Adversity | -12.35 | 2.27 | < 0.0001 | [-16.80 to -7.90] | 0.14 | 0.01 | < 0.0001 | [0.11 to 0.16] | -10.73a; -104.24b± | 2.29a; 24.95b± | < 0.0001ab± | [-15.22 to -6.23]a; [-153.14 to -55.35]b± |
| | **Step 1** | | | | **Step 2** | | | | **Step 3** | | | |
| | **Right Hippocampal Volume (mm3) (DV);** | | | | **Gonadarche Development (M); Adversity** | | | | **Right Hippocampal Volume (mm3) (DV); Gonadarche Development (M)b; Adversity (IV)a** | | | |
| | **B** | **SE** | **p** | **95% BCa** | **B** | **SE** | **p** | **95% BCa** | **B** | **SE** | **p** | **95% BCa** |
| Factor 1: Physical and sexual violence | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 2: Parental mental health | - ns - | | | | - ns - | | | | - ns - | | | |
| Factor 3: Neighborhood Safety | -47.24 | 5.83 | < 0.0001 | [-58.67 to -35.81] | 0.36 | 0.03 | < 0.0001 | [0.29 to 0.42] | -43.28a; -98.60b± | 5.89a; 24.46b± | < 0.0001ab± | [-54.83 to -31.73]a; [-146.54 to -50.66]b± |
| Factor 4: Prenatal substance exposure | -19.14 | 6.88 | 0.0054 | [-32.64 to -5.65] | 0.19 | 0.04 | < 0.0001 | [0.12 to 0.27] | -16.67a; -119.90b± | 6.89a; 24.37b± | 0.0155a; < 0.0001b± | [-30.16 to -3.17]a; [-167.67 to -72.14]b± |
| Factor 5: Scarcity | -20 | 7.09 | 0.0048 | [-33.89 to -6.11] | 0.19 | 0.04 | < 0.0001 | [0.11 to 0.26] | -17.39a; -118.96b± | 7.09a; 24.39b± | 0.0142a; < 0.0001b± | [-31.28 to -3.50]a; [-166.77 to -71.16]b± |
| Factor 6: Household dysfunction | -34.07 | 6.89 | < 0.0001 | [-47.58 to -20.56] | 0.23 | 0.04 | < 0.0001 | [0.15 to 0.30] | -31.02a; -114.62b± | 6.90a; 24.38b± | < 0.0001ab± | [-44.55 to -17.49]a; [-162.41 to -66.84]b± |
| Cumulative Adversity | -13.19 | 2.23 | < 0.0001 | [-17.55 to -8.82] | 0.14 | 0.01 | < 0.0001 | [0.11 to 0.16] | 11.67a; -108.16b± | 2.25a; 24.46b± | < 0.0001ab± | [-16.07 to -7.26]a; [-158.10 to -60.22]b± |

**Table 5: Moderating effect of school-based support on type-specific and cumulative adversity's impact gonadarche development. Values presented indicate comparison between stages 1 and 2, unless otherwise specified. Analyses adjusted for age, sex, race/ethnicity, primary caregiver's education and family income. *Indicates comparison between stages 1 and stages 3 combined with 4.**

| | Male Gonadarche | | | Female Gonadarche | |
|---|---|---|---|---|---|
| **Sources of Resiliency** | B [SE] | p | | B [SE] | p |
| **School Support (average)** | | | | | |
| *Scarcity* | 0.062 [0.21] | 0.770 | | | |
| *Resiliency - One* | -0.653 [0.28] | **0.021** | | | |
| *Resiliency - Two* | -0.618 [0.26] | **0.018** | | | |
| *Resiliency - Three* | -0.589 [0.25] | **0.020** | | | |
| *Interaction - One source* | -0.520 [0.58] | 0.368 | | | |
| *Interaction - Two sources* | -0.002 [0.22] | 0.992 | | | |
| *Interaction - Three sources* | -0.079 [0.22] | 0.719 | | | |
| **Intelligence in Relation to Peers*** | | | | | |
| *Scarcity* | -1.536 [0.05] | **< 0.001** | | | |
| *Resiliency* | -0.047 [0.35] | 0.895 | | | |
| *Interaction* | 1.640 [0.05] | **< 0.001** | | | |
| **Relationship with Teachers** | | | | | |
| *Scarcity* | 0.031 [0.08] | 0.709 | | | |
| *Resiliency* | -0.169 [0.14] | 0.232 | | | |
| *Interaction* | -0.031 [0.09] | 0.743 | | | |
| **Generally Liking School** | | | | | |
| *Scarcity* | -0.019 [0.07] | 0.782 | | | |
| *Resiliency* | 0.020 [0.09] | 0.829 | | | |
| *Interaction* | 0.043 [0.08] | 0.605 | | | |
| | Male Gonadarche | | | Female Gonadarche | |
| | B [SE] | p | | B [SEI] | p |
| **School Support (average)** | | | | | |
| *Household Dysfunction* | | | | -0.726 [0.32] | **0.022** |
| *Resiliency - One* | | | | -0.613 [0.47] | 0.191 |
| *Resiliency - Two* | | | | -0.893 [0.45] | **0.048** |
| *Resiliency - Three* | | | | -0.914 [0.45] | **0.042** |
| *Interaction - One source* | | | | 0.761 [0.35] | **0.028** |
| *Interaction - Two sources* | | | | 0.845 [0.33] | **0.010** |
| *Interaction - Three sources* | | | | 0.733 [0.32] | **0.023** |
| **Intelligence in Relation to Peers** | | | | | |
| *Household Dysfunction* | | | | 0.056 [0.09] | 0.545 |
| *Resiliency* | | | | 0.087 [0.09] | 0.349 |
| *Interaction* | | | | -0.009 [0.10] | 0.930 |
| **Relationship with Teachers** | | | | | |
| *Household Dysfunction* | | | | -0.176 [0.17] | 0.295 |
| *Resiliency* | | | | -0.587 [0.20] | **0.004** |
| *Interaction* | | | | 0.217 [0.17] | 0.211 |
| **Generally Liking School** | | | | | |
| *Household Dysfunction* | | | | 0.012 [0.08] | 0.888 |
| *Resiliency* | | | | -0.205 [0.08] | **0.014** |
| *Interaction* | | | | 0.018 [0.09] | 0.847 |

**FIGURES**

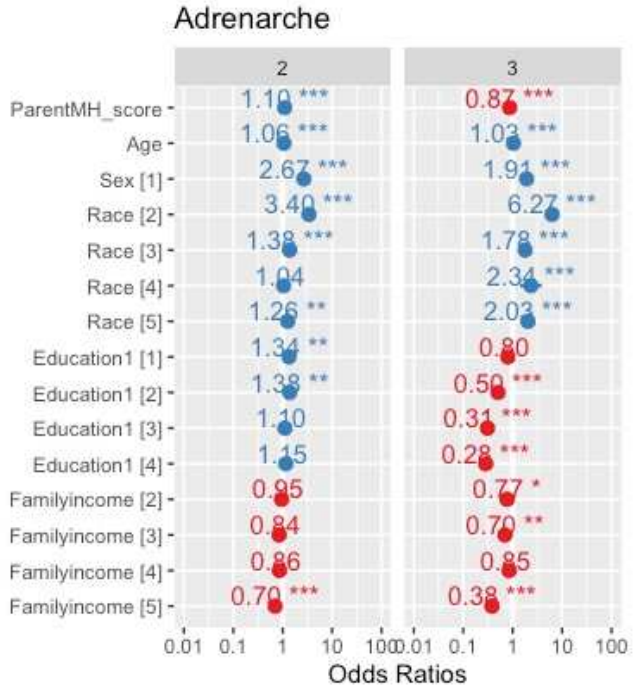


Figure 1: Relationship between parental mental health exposure and adrenarche development, controlling for age, sex, race/ethnicity, primary caregiver's education and family income. Odds ratios presented and significance level based at $p < 0.05$.

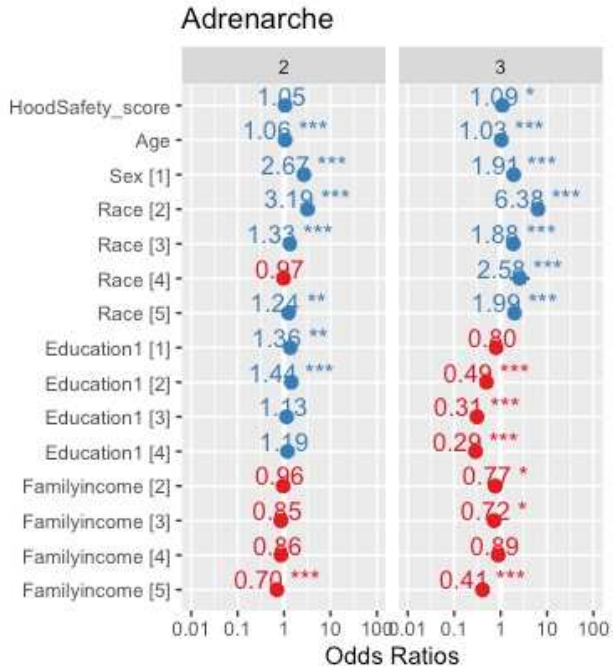


Figure 2: Relationship between neighborhood threat and adrenarche development, controlling for age, sex, race/ethnicity, primary caregiver's education and family income. Odds ratios presented and significance level based at $p < 0.05$.

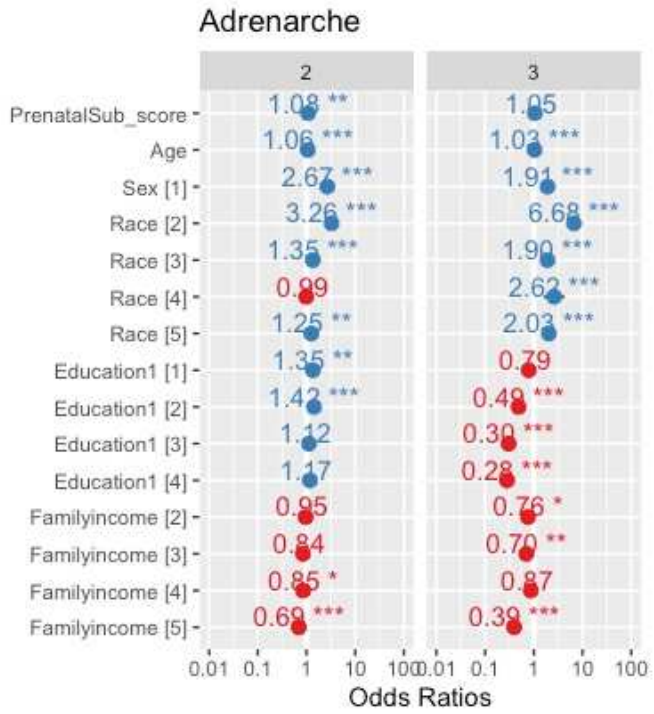


Figure 3: Relationship between prenatal substance exposure and adrenarche development, controlling for age, sex, race/ethnicity, primary caregiver's education and family income. Odds ratios presented and significance level based at $p < 0.05$.

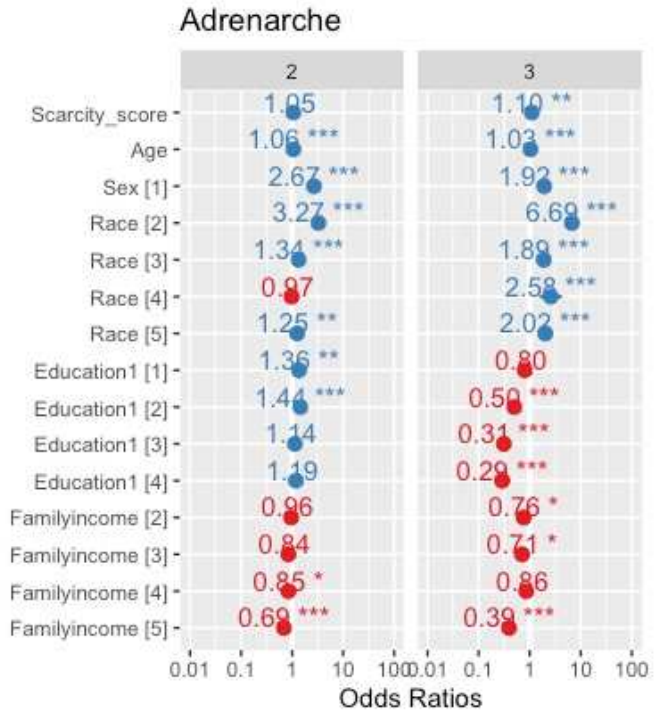


Figure 4: Relationship between scarcity exposure and adrenarche development, controlling for age, sex, race/ethnicity, primary caregiver's education and family income. Odds ratios presented and significance level based at $p < 0.05$.

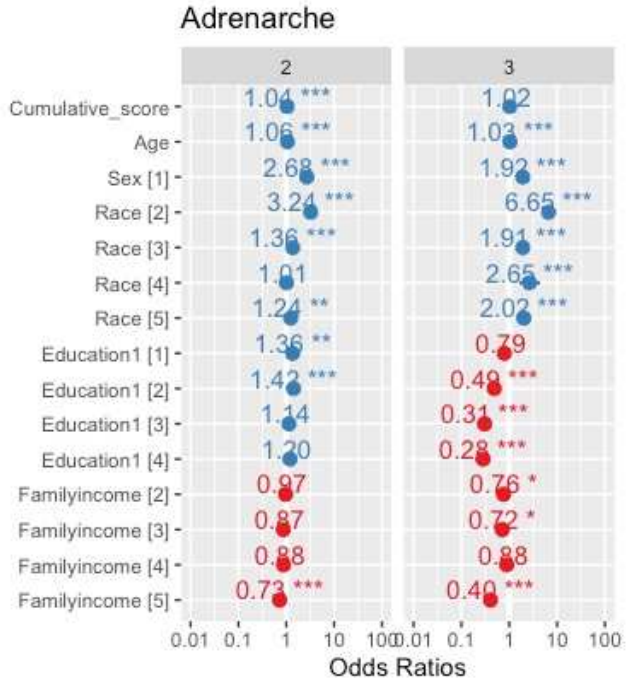


Figure 5: Relationship between cumulative adversity exposure and adrenarche development, controlling for age, sex, race/ethnicity, primary caregiver's education and family income. Odds ratios presented and significance level based at $p < 0.05$.

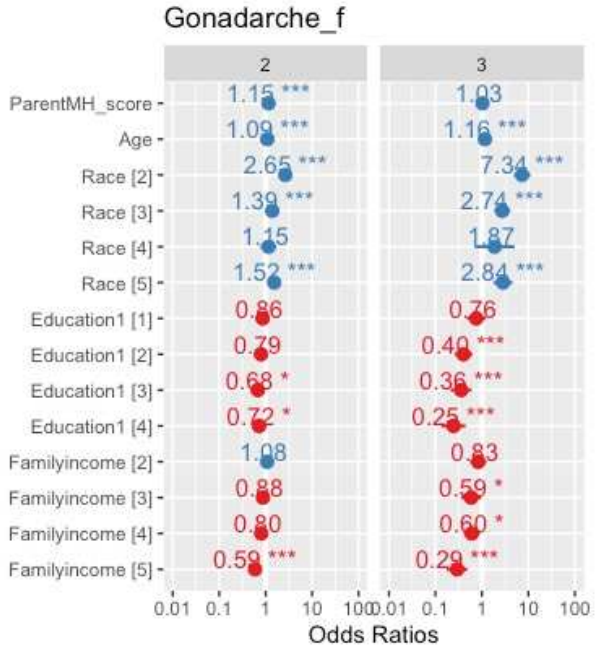


Figure 6: Relationship between parental mental health and female gonadarche development, controlling for age, race/ethnicity, primary caregiver's education and family income. Odds ratios presented and significance level based at $p < 0.05$.

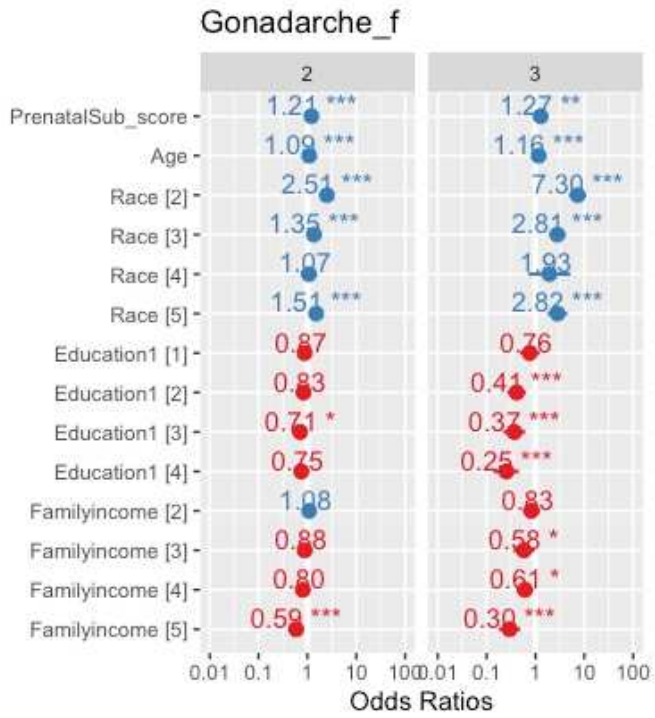


Figure 7: Relationship between prenatal substance exposure and female gonadarche development, controlling for age, race/ethnicity, primary caregiver's education and family income. Odds ratios presented and significance level based at $p < 0.05$.

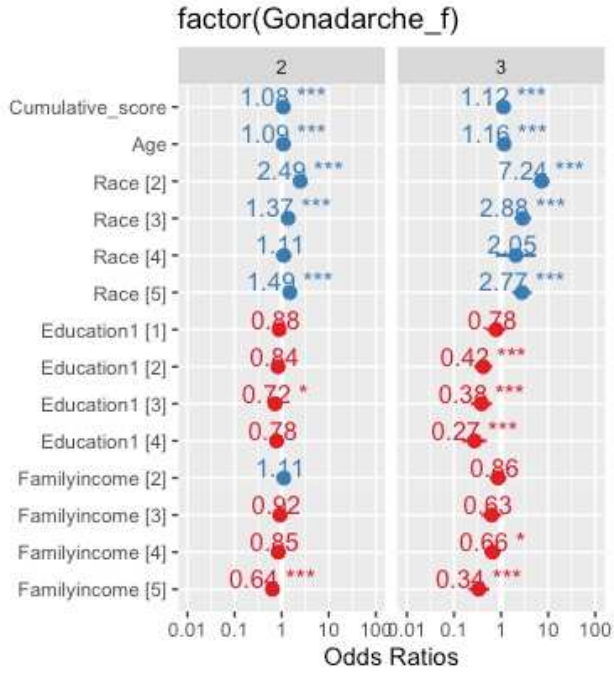


Figure 8: Relationship between cumulative adversity exposure and female gonadarche development, controlling for age, race/ethnicity, primary caregiver's education and family income. Odds ratios presented and significance level based at $p < 0.05$.

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# CHAPTER 4: Perceptions of Neighborhood Safety and Parental Support in Early Adolescence: Sex Differences and Neurobiological Correlates in the ABCD Study


## ABSTRACT

Neighborhood violence and threat exposure is a source of trauma and chronic stress and exposed youth demonstrate brain alterations in frontolimbic circuitry. While parental involvement, including supportiveness and expressing affection, is associated with healthy socioemotional adjustment, self-regulatory and coping behaviors in developing humans and animal models, research has demonstrated mixed findings as to whether parental involvement can effectively moderate the behavioral and physiological impacts of threat exposure. Our findings demonstrate that irrespective of documented neighborhood threat exposure, youth-perceived threat exposure is associated with structural alterations in the left amygdala. Youth-reported parental support, specifically the caregiver's ability to console, demonstrates an interaction effect with perceived neighborhood threat to influence left amygdala volume. Extant neuroimaging literature suggests that the amygdala's linkage with behavioral responses to threat is more left-lateralized. A dose-response relationship was observed such that greater endorsement of neighborhood threat and parental support were associated with greater differences in amygdala volume. While males endorsed higher rates of neighborhood and school threat, females endorsed greater levels of parental consolation than males. There were no significant differences in parent-perceived neighborhood threat by sex. The interaction effect of parental consolation and neighborhood threat among girls was so significant that it drove the interaction effect seen across the total sample. Lastly, racial and ethnic differences in perceived threat exposure were evident such that the greatest perceived prevalence of neighborhood and

school threat were endorsed by Black and Hispanic/Latinx youth, followed by White and Asian youth. The greatest perceived prevalence of parental consolation was endorsed by White then Hispanic/Latinx youth, followed by Asian and Black youth. Finally, all clinical outcomes were significantly more common among youth who reported neighborhood threat exposure. This study utilized youth-perceived parental consolation, namely, the caregiver's ability to alleviate the youth's distress, given the individualized and culturally-inclusive quality of this form of support. Future research is encouraged to utilize the publicly-available longitudinal ABCD Study dataset to examine sources of parental support that can best strengthen youth development as they age.

## INTRODUCTION

Neighborhood crime and violence exposure is a source of trauma and chronic stress (McEwen 2010), particularly for adolescents due to their increased risk of involvement (Hardaway 2016). Research has demonstrated the increased risk for minority youth to be both witnesses and victims of neighborhood violence (Hardaway 2016, Motley 2017). Youth exposed to neighborhood violence in early adolescence demonstrate brain alterations in later adolescence equating to smaller hippocampal and amygdala volumes (Saxbe 2018), possibly due to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Cacciaglia 2017). These findings remained when controlling for concurrent neighborhood violence exposure, age and gender; only smaller hippocampal volumes remained after controlling for family aggression (Saxbe 2018). In addition to the physiological and neurodevelopmental sequela of neighborhood violence exposure, exposed youth are at a greater risk for psychopathology (i.e. mood disorders) and detrimental behavioral outcomes, such as aggression and delinquency (Russell 2015; Hardaway 2016).

Parental involvement, including supportiveness and expressing affection, promotes healthy socioemotional adjustment, self-regulatory and coping behaviors in developing humans (Hardaway 2016, Vidal 2017), as well as in rodent and non-human primate models (Gunnar 2015). Neuroendocrine hormones, such as oxytocin, are implicated in parental support's neurobiological resilience (Yirmiya 2018, Scattliffe 2019). Brody and colleagues (2017) demonstrated that supportive parenting, specifically high levels of parental warmth, sensitivity and emotional support, ameliorated the detrimental effects of poverty on hippocampal and amygdalar development. Unfortunately, this study did not isolate the neurodevelopmental impact of neighborhood violence or threat exposure from that of poverty. Despite the established but

complex association between low socioeconomic status (SES) and crime (Peterson 2009; McCrea 2019), the neurobiological impact attributable solely to neighborhood threat exposure is unclear.

The goal of the current study was to disentangle the role of neighborhood threat exposure on neurodevelopment, separate from poverty, given the hypothesized impact chronic threat would have on development. While youth may not be exposed to direct or immediate sources of neighborhood violence, their perceptions of neighborhood threat serve as a valuable exposure source associated with brain and behavioral alterations. Caregiver perceptions of threat may be more reflective of actual neighborhood violence exposure given youth's developmental state (Taber 2010); however, they are implicated in a different set of questions and do not directly address how the exposure specifically impacts the youth. Furthermore, research has demonstrated mixed findings as to whether parental involvement can effectively moderate neighborhood threat exposure and various behavioral outcomes (Jain 2012, Hardaway 2016). Differences in findings may be due to the complex nature of perceived neighborhood threat, which can fluctuate from sporadic to enduring.

While extensive research has examined the ability of different sources of parental support, such as warmth and affection, to serve as interventions for adverse exposures and behavioral outcomes (Lansford 2018, Calders 2020), not all forms of support demonstrate cross-cultural sensitivity (Bornstein 2012). This study utilized youth-perceived parental consolation, namely, the caregiver's ability to alleviate the youth's distress, given the individualized and culturally-inclusive quality of this form of support. Utilizing baseline data for youth enrolled in the Adolescent Brain Cognitive Development (ABCD) study, this study has two aims: 1) examine whether parental support moderates the relationship of neighborhood threat exposure

and neurodevelopment of frontolimbic circuitry, specifically whether parental consolation can curtail the association between neighborhood threat exposure and reduced amygdala and hippocampal volumes; and 2) examine the relationship between parental support and youth prevalence of antisocial behaviors, such as aggression and delinquency, specifically whether parental consolation can abate the association between neighborhood threat exposure and behavioral outcomes. within the context of neighborhood violence exposure among youth at baseline enrolled in the Adolescent Brain Cognitive Development (ABCD) study. Given that parental support has demonstrated an impact on neurodevelopment regardless of adversity exposure, we controlled for family structure, a proxy for household dysfunction, when examining the impact of parental support and neighborhood threat exposure on outcomes.

## METHODS

*Protocol.* The present study used the National Data Archive, ABCD version 2.01 baseline data set (Yang 2019) collected between 2016 and 2018 from the ABCD study, the largest longitudinal neuroimaging study of youth development. Over 10,000 youth from 21 different research sites in the United States are enrolled in this 10-year longitudinal study (Volkow 2018). Procedures, sampling and recruitment (Volkow 2018, Barch 2018, Garavan 2018) for the ABCD study have been described previously. Caregivers provided written informed consent and children provided assent for participation in the study. All procedures were approved by a central institutional review board, and each site has a detailed protocol in place to address reported adversity exposure. The University of California, Los Angeles, institutional review board has indicated that analyses using the publicly released ABCD Study data are not human subjects research and therefore do not require their own approval.

*Measures*

*Sociodemographic Characteristics.* A caregiver-completed demographic questionnaire was used to gather information regarding youth's age, sex, race and ethnicity, as well as family income and primary caregiver's education. Family structure was obtained from a series of questions aimed at quantifying the presence and relationality of primary caregivers residing with the youth a majority of the time. Specifically, youth were classified as living with the following: two biological parents; a single biological mother; a biological mother and nonbiological partner; a single biological father; a biological father and nonbiological partner; a nonbiological parent and undisclosed biological parent; two nonbiological parents; and a single nonbiological parent. Further information regarding the sex/gender identification of the caregivers, other than the primary caregiver, is not captured at baseline. The presence and number of siblings was not used in this study. Family structure, specifically the presence and relationality of primary caregivers, has been used as a proxy for household dysfunction (citation needed).

*Neighborhood and School Threat.* Youth and caregiver-reported perceived neighborhood threat was captured via the following question, *My neighborhood is safe from crime*. 5-point Likert response options were binarized with responses of *Strongly disagree* and *Disagree* equating to perceived neighborhood threat or violence exposure; the remaining three response options served as the control. This item was modified from the PhenX Toolkit Neighborhood Safety and Crime questionnaire (Mujahid 2007) and serves as a standalone question for youth, and one of three related questions for caregivers. All regression and interaction models employed the youth's perceived neighborhood threat.

Youth-reported school threat was included in the study as a covariate. Youth's response to *I feel safe at my school* was binarized with responses of *Definitely not true* equating to

perceived school threat or violence exposure; the remaining three response options served as the control. This item is part of the larger 12-item School Risk and Protective Factors Survey, designed for the ABCD Study.

*Parental Support.* Perceived caregiver support was measured using 5 items from the caregiver acceptance subscale of the Children's Report of Parent Behavior Inventory (Schaefer 1965); however, upon close review of the data distribution of these 5 items, only the item corresponding to parental consolation was selected. The remaining 4 items displayed largely variability in distributions by race and ethnicity and thus may not be culturally sensitive nor serve as an appropriate measure for parental support. Parental consolation, namely, the caregiver's ability to alleviate the youth's distress, represents a broad and individualized form of support. Importantly, youth-perceived parental consolation is not culturally exclusionary. See supplementary table 1 for the 5 subscale items.

*Neuroimaging.* Volumes in $mm^3$ of subcortical regions, such as the amygdala and hippocampus, and intracranial space were acquired using FreeSurfer v5.3.0 on $T_1$w MRI sequences obtained from 11,533 ABCD Study youth at baseline. Neuroimaging processing pipelines, employed to correct for motion, artefacts and site and scanner differences, were conducted centrally for all study participants by the Data and Informatics Core at the University of California, San Diego. Details regarding processing pipelines and analyses for common regions of interest can be found at Hagler *et al.* 2019. All neuroimaging metrics used in this study were obtained from the National Data Archive, ABCD version 2.01.

*Clinical Outcomes.* The parent-reported Child Behavior Checklist (Achenbach 2000) was used to assess children's externalizing problems, specifically rule breaking and aggressive behavior, internalizing problems, as well as total problems, the latter encompassing the sum of

all internalizing and externalizing behaviors. Problems over the prior 6 months were captured by this measure and raw scores were converted to t scores, with a t score less than 60 representing normal functioning.

*Statistical Analyses.* All data were analyzed using R version 3.5.1 (R Project for Statistical Computing) (R 2018). Using the unweighted data, factors associated with neighborhood and school threat and parental support were examined via linear regression models employing the R package "lm". All regression and interaction models employed youth-perceived neighborhood threat and parental support. Descriptive statistics and initial correlations were first performed. To adjust for outliers, outcome data points (i.e. bilateral amygdala, hippocampal and intracranial volume) greater than four standard deviations from the mean were replaced with the Winsorized mean. Youth-reported neighborhood threat and parental consolation were examined as cross-sectional predictors after covarying for the effects of age, sex, race, ethnicity, primary caregiver's education, family income, family structure, youth-perceived school threat, and intracranial volume (ICV). The variance inflation factor and correlations between all covariates and predictor variables were examined to detect potential problems related to multicollinearity. In addition, autocorrelation via the Durbin Watson Test, Cook's distance, and leverage values were calculated for the dependent variables based on the independent variables to identify outliers and influential observations. Seven influential observations were identified and following significant differences in point estimates and standard errors via sensitivity analyses, were excluded from the final model and results. Statistical significance was set at 2-sided $p < 0.05$.

We examined whether disparities in the impact of neighborhood threat on amygdala and hippocampal volumes were moderated by parental support. An ANOVA employing a Chi-square test and simple slopes analysis were used to identify significant interactions. Lastly, we examined whether parental support moderated the impact of neighborhood threat on clinical outcomes, specifically externalizing problems, such as rule breaking and aggressive behaviors. To adjust for multiple comparisons, we utilized Benjamini-Hochberg corrections at $p < 0.05$.

**RESULTS**

*Sociodemographic Characteristics.* After excluding 310 participants with missing imaging data, data from 11,559 children (47.7% female; 52.0% white) and 1 of their caregivers were included for analyses. All children were 9 to 10 years old. Detailed demographic information is reported in Table 1. A small proportion (<1%) of participants were missing data on certain measures, such as primary caregiver's education and household income.

*Overview.* Males endorsed higher rates of neighborhood and school threat; there were no significant differences in parent-perceived neighborhood threat by sex (Table 2). Significant differences in youth-perceived neighborhood and school threat, as well as parent-perceived neighborhood threat, were observed across race and ethnicity ($p < 0.001$) (Table 2). Parents endorsed higher perceived neighborhood threat than youth, at a rate approximately 1.7x that of youth. All group comparisons were controlled for via Benjamini-Hochberg correction at $p < 0.05$.

*Youth Perceptions of Neighborhood and School Threat.* The estimated prevalence rates of youth and parent-perceived neighborhood and school threat are outlined in Table 2. There was greater threat endorsement in the neighborhood and at school among male youth. Significant

differences in prevalence of perceived threat were observed between racial and ethnic groups, with significance persisting even after controlling for multiple comparisons ($p < 0.001$). The greatest perceived prevalence of neighborhood and school threat were endorsed by Black and Hispanic/Latinx youth, followed by White and Asian youth.

*Concordance between Parent and Youth Endorsement of Neighborhood Threat.* There was also a small correlation ($r(11502) = 0.213$, $p < 0.001$) between youth and parent reported neighborhood threat, with youth overall reporting feeling safer than their parents (Table 2). Parents endorsed higher perceived neighborhood threat than youth, at a rate approximately 1.7x that of youth. Parent-reported neighborhood threat differed significantly across racial and ethnic grouping, even when controlling for multiple comparisons via Benjamini-Hochberg correction at $p < 0.05$ ($F(1,11521) = 105.2$, $p < 0.001$). Parent-reported neighborhood threat did not differ significantly by the youth's age or sex.

*Differences in Youth-Reported Parental Support.* Rates of parental consolation did not differ significantly by age but did so by sex, race and ethnicity after controlling for multiple comparisons. The approximate prevalence rates were 98.0% (95% CI, 97.6%-98.3%) and 98.3% (95% CI, 97.9%-98.6%) for youth-perceived parental consolation among nine and ten-year-olds at baseline, respectively. Girls endorsed greater levels of parental consolation than boys ($F(1,11520) = 6.583$, $p = 0.0206$). The approximate prevalence rates were 97.8% (95% CI, 97.4%-98.2%) and 98.5% (95% CI, 98.1%-98.8%) among male and female youth, respectively. Lastly, differences in parental consolation prevalence rates were observed across racial and ethnic groups ($F(1,11522) = 7.282$, $p = 0.0206$). The greatest perceived prevalence of parental consolation was endorsed by White then Hispanic/Latinx youth, followed by Asian and Black youth. The approximate prevalence rates of youth-perceived parental consolation were 98.7%

(95% CI, 98.4-98.9%-26.6%) among White youth, 98.1% (95% CI, 97.4%-98.6%) among Hispanic/Latinx youth, 97.5% (95% CI, 94.4%-98.9%) among Asian youth, 96.6% (95% CI, 95.7%-97.4%) among Black youth, and 97.7% (95% CI, 96.7%-98.4%) among the 1229 youth that did not identify with any of the former racial or ethnic categories.

*Associations Between Perceived Neighborhood Threat and Amygdala Volumes.* We examined the relationships of youth-reported neighborhood threat and parental consolation to bilateral amygdala volume, controlling for age, sex, race, ethnicity, primary caregiver's education, family income, family structure, youth-perceived school threat, and ICV.

In the left amygdala, there were no significant main effects of neighborhood threat or parental consolation ($F(1,10499) = 261.8$, $p > 0.16$, $R^2 = 0.38$, $f^2 = 0.61$); but there was a significant interaction of neighborhood threat and parental consolation ($F(1,10498) = 252.2$, $p = 0.0081$, $R^2 = 0.38$, $f^2 = 0.61$). Post hoc sensitivity analyses were conducted to examine the nature of the interaction that neighborhood threat was associated with larger amygdala volume only in the absence of parental support (Figure 1). These analyses yielded a dose-response relationship of both neighborhood threat and parental support, such that greater endorsement of the two variables were associated with greater differences in amygdala volume. The analysis of the right amygdala did not yield a significant main effect of neighborhood threat or of parental consolation ($F (1,10499) = 208.7$, $p > 0.98$, $R^2 = 0.33$, $f^2 = 0.49$), nor a significant interaction of the two ($F (1,10498) = 200.86$, $p = 0.088$, $R^2 = 0.33$, $f^2 = 0.49$) (Table 3).

We examined sex-differences in youth-reported neighborhood threat and parental consolation as predictors of bilateral amygdala volume, again controlling for age, sex, race, ethnicity, primary caregiver's education, family income, family structure, youth-perceived school threat, and ICV. In males analyzed singly, there was a significant main effect of

neighborhood threat ($F(1,5475) = 139$, $p = 0.033$, $R^2 = 0.38$, $f^2 = 0.61$), an effect that was strengthened when controlling for clinical outcomes, specifically, externalizing problems ($F(1,5473) = 133.6$, $p = 0.030$, $R^2 = 0.38$, $f^2 = 0.61$). However, there were neither main effects of neighborhood threat nor parental consolation for girls ($F(1,4999) = 128.1$, $p > 0.94$, $R^2 = 0.38$, $f^2 = 0.61$). In girls, the analyses yielded a significant crossover interaction of neighborhood threat and parental consolation ($F(1,4998) = 123.3$, $p = 0.028$, $R^2 = 0.38$, $f^2 = 0.61$). Among boys, there was not a significant interaction of neighborhood threat and parental consolation ($F(1,5474) = 133.6$, $p = 0.118$, $R^2 = 0.38$, $f^2 = 0.61$)(Figure 1). Again, this indicates that the effect of neighborhood threat on left amygdala volume is opposite and dependent on the value of parental support. The analysis of the right amygdala did not yield a significant main nor interaction effect of neighborhood threat and parental consolation for either male or female youth.

*Relationships Between Perceived Neighborhood Threat and Clinical Outcomes in Youth*. All clinical outcomes were significantly more common among youth who reported neighborhood threat exposure. Among youth who did <u>not</u> endorse neighborhood threat exposure, the prevalence rates and confidence intervals of the clinical outcomes (t-score ≥ 60) are as follows: 16.2% (95% CI, 15.5%-16.9%) internalizing; 9.5% (95% CI, 8.9%-10.0%) externalizing; 9.0% (95% CI, 8.5%-9.6%) rule-breaking; 9.7% (95% CI, 9.1%-10.3%) aggressive problems; and 11.2% (95% CI, 10.6%-11.8%) total problems. Among youth who <u>did</u> endorse neighborhood threat exposure, the prevalence rates and confidence intervals of the clinical outcomes (t-score ≥ 60) are as follows: 21.2% (95% CI, 19.0%-23.7%) internalizing; 18.8% (95% CI, 16.7%-21.2%) externalizing; 18.6% (95% CI, 16.5%-20.9%) rule-breaking; 18.1% (95% CI, 16.0%-20.4%) aggressive problems; and 20.6% (95% CI, 18.4%-23.0%) total problems. Sex differences in prevalence rates were evident across all clinical domains and retained significance after multiple

comparisons correction (see Table 4). Racial and ethnic differences were greatest for rule breaking problems ($p < 0.001$). Both youth and parent-perceived neighborhood threat display a low correlation with internal, external and total problems, albeit a stronger correlation between parent-perceived neighborhood threat and all clinical outcomes ($r(11517) = 0.117$, $p < 0.001$).

*Relationships Between Perceived Neighborhood Threat, Amygdala Volume and Externalizing Behaviors in Youth.* Lastly, we examined the relationships of youth-reported neighborhood threat and left amygdala volume on rule-breaking and aggressive problems, while controlling for age, sex, race, ethnicity, primary caregiver's education, family income, family structure, and youth-perceived school threat. When examining rule-breaking across the total sample, there were significant main effects of neighborhood threat ($p < 0.0001$) and left amygdala volume ($p = 0.0051$) were evident. Additionally, there was a significant interaction of neighborhood threat and left amygdala volume on rule-breaking behaviors ($F(1,10508) = 45.67$, $p < 0.001$, $R^2 = 0.09$, $f^2 = 0.10$). When examining aggressive problems across the total sample, only a significant main effect of neighborhood threat ($p < 0.0001$) but not left amygdala volume ($p = 0.24$) was evident. However, there was a significant interaction of neighborhood threat and left amygdala volume on aggressive behaviors ($F(1,10508) = 28.6$, $p = 0.011$, $R^2 = 0.06$, $f^2 = 0.06$). All moderation analyses remained statistically significant at $p < 0.01$ even when controlling for multiple comparisons via Benjamini-Hochberg correction.

## DISCUSSION

To our knowledge, this is the first study to examine the impacts of youth-perceived neighborhood threat and parental consolation on amygdala volume in periadolescent youth. The key findings across the total sample are: 1) enlarged left amygdala volumes in the presence of

perceived neighborhood threat and in the absence of parental consolation; 2) diminished left amygdala volume in the absence of both neighborhood threat and parental consolation; and 3) a significant interaction effect of parental consolation and neighborhood threat on left amygdala volume. When examining the sexes separately, we see a significant interaction effect of parental consolation and neighborhood threat among girls, driving the interaction effect seen across the total sample. Among boys, we identified a significant positive association between left amygdala volume and neighborhood threat even when controlling for concomitant problematic behaviors, such as rule-breaking and aggression. In addition to sex differences in perceived threat exposure, parental consolation, and model performance, we identified racial and ethnic differences in perceived threat exposure and parental consolation. These differences are explored and discussed in greater detail below. Of note, significant differences in youth- and parent-reported perceived neighborhood threat were evident with parent perceived threat on average 1.7x greater than that of youth.

*Relationship Between Neighborhood Threat, Parental Support and Study Outcomes.* Parental support, such as consolation and love, has been demonstrated to serve as a buffer against adversity exposure, including poverty (Brody 2017), as well as long-term health outcomes (Walsh 2019). Its protective and moderating effects have been demonstrated not just during infancy (Howell 2017), but span from prenatal care (Phua 2017, Glynn 2019) throughout adolescence (van Rooij 2017, Vannucci 2019). Traditionally, the impact of parental support has been measured in terms of behavioral outcomes, including socioemotional functioning (Callaghan 2016, Tottenham 2020), problematic behaviors and psychopathology (Farrell 2011, Tottenham 2015, Glynn 2019). Youth with a history of adversity exposure often experience lower levels of social support from both friends and family; this may in part explain why a

history of early adversity exposure confers psychopathology risk (Jaffee 2017). Adversity exposure, like neighborhood threat, is associated with increased threat sensitivity and dysregulated reward responsivity. However, socially supportive relationships can buffer the impact on brain and behavioral outcomes. While findings are mixed, the combative effects of social support have demonstrated sex-specificity (Jaffee 2017). Given the shift in support preference from family to peers as youth develop throughout adolescence (Gunnar 2015), future research should examine the ability of peer support to moderate the impact of neighborhood threat on neurobiological outcomes and problematic behaviors.

Regarding the laterality of the findings, extant neuroimaging literature suggests that the amygdala's linkage with behavioral responses to threat is more left-lateralized; whereas, the amygdala's recruitment by the emotional component of threat awareness is more right-lateralized (Karolis 2019). Furthermore, left amygdala activation is generally linked to cognitive processing and recognition of emotional stimuli (Skuse 2005), whereas the right amygdala is generally responsive to arousing stimuli, like facial expressions (Williams 2004). Damage to the left and right amygdala results in discrete deficits in cognition and arousal, respectively (Glascher 2003).

Early life adversity is a risk factor for psychopathology, including internalizing and externalizing problems. Internalizing problems include mood disorders while externalizing problems include rule breaking and aggressive behaviors. In animal models, exposures of threat and deprivation delivered peripubertally lead to the development of one of two phenotypes: an aggressive phenotype with altered frontolimbic circuitry, or, a phenotype marked by increased anxiety-like behaviors and reduced sociability (Walker 2018). Given the nature of current study's stress exposure, we see that perceived neighborhood threat is associated with greater parental endorsement of externalizing behaviors, particularly rule-breaking, in youth. This

finding agrees with an extensive body of literature detailing the association between threat and violence exposure and externalizing problematic behaviors (Wilson 2009). Furthermore, our study demonstrates that amygdala volume moderates the association between perceived neighborhood threat and rule-breaking and aggressive problems in a diverse sample of peripubertal youth.

Lastly, the impact of perceived neighborhood threat and parental consolation on left and right hippocampal volumes were examined; however, the findings were not significant, regardless of controlling for ICV. Additionally, there were no significant findings regarding parental consolation, neighborhood threat, nor clinical behavioral outcomes with bilateral hippocampal volume. This could be due to the developmental trajectory of the hippocampus which peaks earlier than the amygdala between 3 to 5 years of age (Teicher 2016). Additionally, research has demonstrated that sub-regions of the hippocampus develop inversely of one another and on their own developmental timelines (Tamnes 2018); this itself could distort any potential findings. Future research should take advantage of the longitudinal ABCD Study dataset and should examine sub-regional hippocampal volumes and their development under adversity exposure.

*Duality in Amygdala Volume.* Recent neuroimaging work (Brody 2017, Whittle 2017) is examining the moderating influence of parenting on poverty's impact on neural regions of interest, including the amygdala. These studies demonstrated the ability of supportive parenting to ameliorate the association between poverty and amygdala volumes; however, the association between poverty and amygdala volume was contradictory between the studies. Brody and colleagues (2017) found a positive association between SES and left amygdala volume, such that poverty during the ages of 11 to 18 equated to smaller amygdala volumes (n = 667). Among 166

youth aged 11 to 20, Whittle and colleagues (2017) found a negative association between SES and right amygdala volume. Of note, Whittle and colleagues (2017) found this association employing neighborhood socioeconomic disadvantage as opposed to individual household SES, the former a measure incorporating Australian census data on approximately 250 homes per region. While socioeconomic disadvantage or low SES carries an established albeit complex relationship with crime (Peterson 2009; McCrea 2019), it is also associated with other forms of adversity exposure. Low SES households are disproportionality impacted by food and financial insecurity, housing instability, domestic abuse, and increased mortality and morbidity, among other hardships (Williams 2001, Blair 2016, Farah 2017, Farah 2018). To specifically examine the impact of community violence exposure on neurodevelopment, Saxbe and colleagues (2018) obtained structural and functional (i.e. resting state) scans of urban-dwelling youth in Los Angeles. While the authors did not examine parental support, they found an association between smaller amygdala volumes and community violence exposure among 22 youth.

Conflicting findings pertaining to the directionality of amygdala volume associated with adversity exposure is not uncommon in the literature. As such, researchers are exploring the nuances of adversity in addition to cumulative adversity burden. For example, the type, duration, frequency and age of onset of adversity exposure have all been suggested to uniquely impact neuroanatomical and behavioral profiles (Teicher 2016). An unexpected finding of the present study was the stark differences in left amygdala volume associated with parental consolation and neighborhood threat. Among the 10,150 youth at baseline who endorsed no appreciable perception of neighborhood threat, the average left amygdala volume was 1573 $mm^3$. This is not significantly different from the left amygdala volume of the 1161 youth (i.e. 1529 $mm^3$) who endorsed experiencing neighborhood threat but also reported receiving parental consolation. At

one end of the spectrum, an absence of parental consolation (and neighborhood threat) is associated with smaller left amygdala volumes across male and female youth at baseline. An enlarged left amygdala volume is seen among male and female youth who endorsed neighborhood threat in the absence of parental consolation.

These extremes are evident in Figure 1 and demonstrate the deprivation-threat model, proposed by Sheridan and McLaughlin (Sheridan 2014). The model distinguishes between deprivation and threat as distinct forms of childhood adversity; deprivation involves an absence of inputs from the environment where as threat includes experiences directly involving harm or threat of harm. These distinct experiences are suggested to uniquely impact developing frontolimbic circuitry, including the amygdala. A possible mechanism for this differential impact could lie in HPA-axis responsivity to stressors and the moderating role of neuroendocrine hormones on the structural and functional circuitry of glucocorticoid-rich neural regions, such as the amygdala. The effects of stress on HPA-axis functioning is contingent upon the characteristics of the stressor, leading to either hypo- or hyper-reactivity of the circuitry. For example, HPA-axis hypo-reactivity is associated with deprivation early in life whereas HPA-axis hyper-reactivity is related to increased corticotrophin-releasing hormone signaling and impaired glucocorticoid negative feedback (van Bodegom 2017). The neuropeptide oxytocin is implicated in complex social behaviors and like the HPA-axis, is shown to be dysregulated in adults who have experienced early life adversity (Seltzer 2014). Conversely, oxytocin and other neuroendocrine hormones are implicated in the neurobiological resilience of parental support (Yirmiya 2018, Scattliffe 2019).

Our study echoes findings from Brody and colleagues (2017) that demonstrate the ability of supportive parenting to ameliorate the detrimental effects of poverty on amygdala volume.

This baseline finding from the largest longitudinal study of youth development to date further suggests that threatening experiences, such as neighborhood violence or crime, impact amygdala development differently than experiences of deprivation, such as absence of caregiver support or consolation. Future research should utilize the upcoming longitudinal neuroimaging ABCD Study data release to further investigate the impact of different experiences of stress and adversity on the developing brain, while remaining cognizant of developmental sex differences.

*Sex Differences.* The main effect of neighborhood threat on left amygdala volume was only observed among male youth. Furthermore, male youth carried a greater endorsement of perceived school threat in comparison to females. Conversely, the significant crossover interaction of neighborhood threat and parental consolation on left amygdala volume was only significant for female youth. This may in part be attributable to the greater endorsement of parental consolation among female youth ($p = 0.01$) as well as existing literature suggesting that male and female youth appreciate different forms of support from their caregivers (Gunnar 2015).

Externalizing problems via the CBCL were more frequent in boys compared to girls, and these behaviors encompass rule-breaking and aggressive problems, both of which were significantly more prevalent among male youth in other cohorts (White 2019). The higher prevalence of externalizing problems among preadolescent males agrees with existing literature; however, internalizing problems, corresponding with anxiety and depressive symptoms, historically demonstrate a higher prevalence among females (Bangasser 2014, van Bodegom 2017). Our findings of both increased externalizing and internalizing behaviors among male youth may be due to the age of onset of adversity exposure. Adversity first experienced in childhood is more strongly associated with internalizing behaviors than adversity first

experienced in adolescence, which is more strongly associated with externalizing problems (Jaffee 2017). However, research over the past 30 years exploring sex as a moderator of psychopathology due to early life adversity exposure reinforces that the relationship is nuanced and complex (White 2019).

*Racial and Ethnic Considerations.* Significant racial and ethnic differences exist in perceived threat and clinical outcomes in the ABCD Study cohort, akin to other cohorts (Merrick 2018). Among individuals identifying as Black or Hispanic/Latinx, youth-perceived neighborhood and school threat, as well as parent-perceived neighborhood threat was more endorsed than among White and Asian counterparts. Regarding clinical outcomes, a greater endorsement of externalizing problems was observed among Black youth, corresponding with a > 2-fold and 1.5x increase in rule-breaking and aggressive problems, respectively. The prevalence of total problem as assessed by the CBCL was highest for Black (15%) and Hispanic/Latinx (12.4%) youth followed by White (10.9%) and Asian (5.0%) youth. Given that the CBCL was validated in predominately White samples (citations needed), future research should explore the utility of this measure in other racial and ethnic groups.

Parental endorsement of rule-breaking behaviors may be influenced by teacher or school reports addressing youth behavior. Studies have shown that in-school behaviors from Black and Hispanic/Latinx youth are perceived as problematic beginning at a lower threshold than imposed on White counterparts (Voight 2015).

## LIMITATIONS

The goal of the current study was to examine the role of neighborhood threat exposure on neurodevelopment. While youth may not be exposed to direct or immediate sources of

neighborhood violence, their perceptions of neighborhood threat served as a valuable source with which to explore associated brain and behavioral outcomes. However, these findings capture perceived threat at one time point and may not be evident of chronic exposure. While fundamentally a different question than perceived threat, future studies would benefit to incorporate an objective measure of threat and violence exposure, such as census-derived crime reports. It is essential that this metric be captured at the neighborhood or community level, as opposed to at the county-level, given the potential for vastly different neighborhoods and communities to reside within the same county.

As youth age, a greater emphasis is placed on peer relationships and support. Future studies should examine the ability of peer and kinship support to serve as moderators of neighborhood threat exposure on neurodevelopmental and behavioral outcomes as youth age. Additionally, it is important to delineate the impact of adversity exposure, including neighborhood threat, during sensitive windows of development, such as at the onset of puberty.

## CONCLUSION

Addressing the impact of different forms of early life adversity on neurodevelopment and pubertal maturation in a nationally-representative longitudinal sample of youth would not only improve and contribute towards our scientific understanding but could result in a dramatic shift in public perception, policy efforts and infrastructural reform of juvenile confinement and child welfare. This research aims to provide a foundation to subsequent examinations of the impact of confinement on youth neurodevelopment and pubertal maturation to understand the efficacy and suitability of this form of rehabilitation.

## TABLES

**Table 1. Demographic Characteristics of ABCD Study Youth at Baseline (n=11559)**

| Characteristic | No. (%) |
|---|---|
| **Age, y** | |
| 9 | 6090 (52.7) |
| 10 | 5469 (47.3) |
| **Sex[a]** | |
| Male | 6042 (52.3) |
| Female | 5512 (47.7) |
| **Race/ethnicity** | |
| White | 6016 (52.0) |
| Black | 1730 (15.0) |
| Hispanic/Latinx | 2340 (20.2) |
| Asian | 244 (2.1) |
| Other | 1229 (10.6) |
| **Parental Dynamic** | |
| Two bio. parents | 7315 (63.3) |
| Single mom | 2040 (17.7) |
| Single mom + other adult | 1423 (12.3) |
| Single dad | 140 (1.2) |
| Single dad + other adult | 96 (0.8) |
| Nonbio. caregiver + bio parent involvement | 99 (0.9) |
| Single nonbio caregiver | 169 (1.5) |
| Two nonbio. caregivers | 274 (2.4) |
| **Household income[a], $** | |
| 0-24,999 | 1593 (15.1) |
| 25,000-49,999 | 1544 (14.6) |
| 50,000-74,999 | 1454 (13.8) |
| 75,000-99,999 | 1529 (14.5) |
| 100,000+ | 4444 (42.1) |
| **Primary caregiver's educational attainment[a]** | |
| Less than HS diploma | 765 (6.6) |
| HS diploma/GED | 1231 (10.7) |
| Some college or AA degree | 3397 (29.4) |
| Bachelors degree | 3235 (28.0) |
| Graduate and professional school | 2911 (25.2) |

[a]Five youth were missing data indicating sex; 995 youth were missing data describing family income; 20 youth were missing data describing primary caregiver's education.

**Table 2: Mean Differences in Perceived Threat Across Groups**

| | Rate (95% CI), % | | | | | |
|---|---|---|---|---|---|---|
| **Characteristic** | **Neighborhood Threat, youth** | **Adjusted *F*[b]** | **Neighborhood Threat, parent** | **Adjusted *F*[b]** | **School Threat, youth** | **Adjusted *F*[b]** |
| **Age, y** | | | | | | |
| 9 | 11.5 (10.8-12.4) | 14.9[c] | 18.2 (17.2-19.2) | 2.6 | 3.1 (2.7-3.6) | 13.6[c] |
| 10 | 9.4 (8.6-10.2) | | 17.1 (16.1-18.1) | | 2.0 (1.7-2.4) | |
| **Sex[a]** | | | | | | |
| Male | 10.8 (10.1-11.7) | 1.4[c] | 17.6 (16.7-18.6) | 0.02 | 3.0 (2.6-3.5) | 7.6[c] |
| Female | 10.2 (9.4-11.0) | | 17.7 (16.7-18.8) | | 2.2 (1.8-2.6) | |
| **Race/ethnicity** | | | | | | |
| White | 5.7 (5.1-6.3) | | 11.2 (10.4-12.0) | | 1.3 (1.1-1.7) | |
| Black | 24.5 (22.5-26.6) | | 34.4 (32.2-36.7) | | 6.6 (5.5-8.0) | |
| Hispanic/Latinx | 13.0 (11.7-14.4) | 60.7[c] | 20.9 (19.3-22.6) | 105.2[c] | 2.5 (1.9-3.2) | 20.7[c] |
| Asian | 3.7 (1.8-7.1) | | 12.7 (8.9-17.7) | | 0.8 (0.1-3.2) | |
| Other | 11.1 (9.5-13.1) | | 20.7 (18.5-23.1) | | 3.7 (2.7-4.9) | |

[a]Five youth were missing data indicating sex; [b]The adjusted F statistic is a variant of the second-order Rao-Scott adjusted X2 statistic; [c]Statistically significant at P < .05 after Benjamini-Hochberg correction.

| Table 3: Model results for left and right amygdala volume ($mm^3$) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Left** | | | | **Right** | | | |
| Parameter | Estimate | 95% CI | t-statistic | p-value | Estimate | 95% CI | t-statistic | p-value |
| Intercept | 155.00 | 81.35, 228.68 | 4.13 | **< 0.001** | 435.51 | 359.19, 511.83 | 11.19 | **< 0.001** |
| Neighborhood threat | 85.80 | 27.20, 144.40 | 2.87 | **0.004** | 47.70 | -13.01, 108.40 | 1.54 | 0.124 |
| Parental Consolation | 41.61 | 12.03, 71.19 | 2.76 | **0.006** | 12.84 | -17.81, 43.48 | 0.82 | 0.412 |
| Sex (Female) | -36.68 | -44.20, -29.15 | -9.56 | **< 0.001** | -47.70 | -55.49, -39.91 | -11.99 | **< 0.001** |
| Age | 1.10 | 0.64, 1.55 | 4.72 | **< 0.001** | 0.25 | -0.22, 0.73 | 1.06 | 0.291 |
| School Threat | -12.63 | -35.40, 10.14 | -1.09 | 0.277 | -11.11 | -34.70, 12.48 | -0.92 | 0.356 |
| Race[a] (Black) | -42.84 | -54.63, -31.06 | -7.13 | **< 0.001** | -24.94 | -37.16, -12.73 | -4 | **< 0.001** |
| Race[a] (Hispanic) | -7.88 | -17.77, 2.01 | -1.56 | 0.118 | 3.96 | -6.29, 14.21 | 0.76 | 0.449 |
| Race[a] (Asian) | -6.81 | -31.53, 17.92 | -0.54 | 0.589 | 17.73 | -7.88, 43.34 | 1.36 | 0.175 |
| Race[a] (Other) | -33.10 | -44.66, -21.54 | -5.61 | **< 0.001** | -13.83 | -25.80, -1.85 | -2.26 | **0.024** |
| Education[b] (HS) | -14.62 | -32.97, 3.72 | -1.56 | 0.118 | -8.17 | -27.18, 10.83 | -0.84 | 0.399 |
| Education[b] (AA) | -12.69 | -29.62, 4.25 | -1.47 | 0.142 | -2.21 | -19.75, 15.34 | -0.25 | 0.805 |
| Education[b] (BA) | -4.36 | -22.60, 13.89 | -0.47 | 0.639 | 5.85 | -13.05, 24.76 | 0.61 | 0.544 |
| Education[b] (PhD/MD/JD/MSW) | -3.34 | -22.11, 15.44 | -0.35 | 0.728 | 8.97 | -10.78, 28.12 | 0.87 | 0.382 |
| Income[c] (25,000-49,999), $ | -7.74 | -20.84, 5.36 | -1.16 | 0.247 | -11.45 | -25.02, 2.12 | -1.66 | 0.098 |
| Income[c] (50,000-74,999), $ | 7.27 | -7.16, 21.69 | 0.99 | 0.324 | -3.88 | -18.83, 11.06 | -0.51 | 0.611 |
| Income[c] (75,000-99,999), $ | 0.83 | -14.41, 16.08 | 0.11 | 0.915 | -2.86 | -18.65, 12.93 | -0.36 | 0.722 |
| Income[c] (100,000+), $ | 8.43 | -6.26, 23.12 | 1.12 | 0.261 | 7.93 | -7.29, 23.15 | 1.02 | 0.307 |
| Family[d] (Single mom) | 2.00 | -8.90, 12.89 | 0.36 | 0.719 | 1.88 | -9.40, 13.17 | 0.33 | 0.744 |
| Family[d] (Single mom + other adult) | -3.16 | -14.40, 8.08 | -0.55 | 0.582 | -8.00 | -19.65, 3.64 | -1.35 | 0.178 |
| Family[d] (Single dad) | 4.53 | -26.29, 35.34 | 0.29 | 0.773 | 1.33 | -30.60, 33.25 | 0.08 | 0.935 |
| Family[d] (Single dad + other adult) | 30.02 | -7.24, 67.27 | 1.58 | 0.114 | 27.68 | -10.92, 66.27 | 1.41 | 0.16 |
| Family[d] (Nonbio. caregiver + bio parent involvement) | 18.57 | -17.80, 54.94 | 1 | 0.317 | 33.20 | -4.48, 70.89 | 1.73 | 0.084 |
| Family[d] (Single nonbio caregiver) | -2.68 | -31.55, 26.19 | -0.18 | 0.856 | 6.66 | -23.25, 36.57 | 0.44 | 0.663 |
| Family[d] (Two nonbio. caregivers) | -12.32 | -34.98, 10.35 | -1.07 | 0.287 | -7.98 | -31.46, 15.50 | -0.67 | 0.505 |
| Intracranial volume ($mm^3$) | 8418.00 | 0.00, 0.00 | 62.2 | **< 0.001** | 0.00 | 0.00, 0.00 | 54.52 | **< 0.001** |
| Neighborhood threat x Parental consolation | -80.45 | -140.03, -20.86 | -2.65 | **0.008** | -53.70 | 115.43, 8.03 | -1.71 | 0.088 |

[a]For Race, White used as ground truth; [b]for Education, less than a highschool (HS) education was used as the ground truth; [c]a combined family income of less than $25,000 per year was used as the ground truth; [d]for family, the in-home presence of two biological caregivers was used as the ground truth.

**Table 4: Demographic Differences in Internalizing and Externalizing Symptomatology**

| | Rate (95% CI), % | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Characteristic** | **Internal Problems** | ***F*[b]** | **External Problems** | ***F*[b]** | **Rule Breaking Problems** | ***F*[b]** | **Aggressive Problems** | ***F*[b]** | **Total Problems** | ***F*[b]** |
| **Age, y** | | | | | | | | | | |
| 9 | 16.4 (15.5-17.3) | 1.5 | 10.7 (10.0-11.5) | 6.5[c] | 10.0 (9.3-10.8) | 0.5 | 10.9 (10.1-11.7) | 2.4 | 12.5 (11.7-13.4) | 3.3 |
| 10 | 17.2 (16.2-18.2) | | 10.2 (9.4-11.0) | | 10.0 (9.3-11.0) | | 10.3 (9.5-11.1) | | 11.9 (11.1-12.8) | |
| **Sex[a]** | | | | | | | | | | |
| Male | 20.3 (19.3-21.3) | 95.3[c] | 12.8 (12.0-13.7) | 76.4[c] | 12.7 (11.9-13.5) | 26.2[c] | 12.8 (12.0-13.7) | 83.5[c] | 14.2 (13.3-15.1) | 113.9[c] |
| Female | 13.0 (12.1-13.9) | | 7.9 (7.2-8.7) | | 7.1 (6.5-7.9) | | 8.2 (7.5-9.0) | | 10.1 (9.3-11.0) | |
| **Race/ethnicity** | | | | | | | | | | |
| White | 16.5 (15.5-17.4) | | 9.0 (8.3-9.8) | | 7.9 (7.2-8.6) | | 9.7 (8.9-10.5) | | 10.9 (10.1-11.7) | |
| Black | 13.8 (12.2-15.6) | | 15.1 (13.5-16.9) | | 16.8 (15.0-18.6) | | 13.9 (12.3-15.6) | | 15.0 (13.3-16.8) | |
| Hispanic/Latinx | 19.2 (17.7-20.9) | 2.7 | 9.6 (8.5-10.9) | 9.8[c] | 9.4 (8.3-10.7) | 46.6[c] | 9.7 (8.5-11.0) | 5.1[c] | 12.4 (11.1-13.8) | 8.6[c] |
| Asian | 11.9 (8.2-16.8) | | 2.5 (1.0-5.5) | | 3.7 (1.8-7.1) | | 2.9 (1.3-6.1) | | 5.0 (2.7-8.7) | |
| Other | 18.7 (16.6-21.0) | | 14.4 (12.5-16.5) | | 13.5 (11.7-15.6) | | 13.9 (12.1-16.0) | | 16.1 (14.1-18.3) | |

[a]Five youth were missing data indicating sex; [b]The adjusted F statistic is a variant of the second-order Rao-Scott adjusted X2 statistic; [c]Statistically significant at P < .05 after Benjamini-Hochberg correction.

**FIGURE**

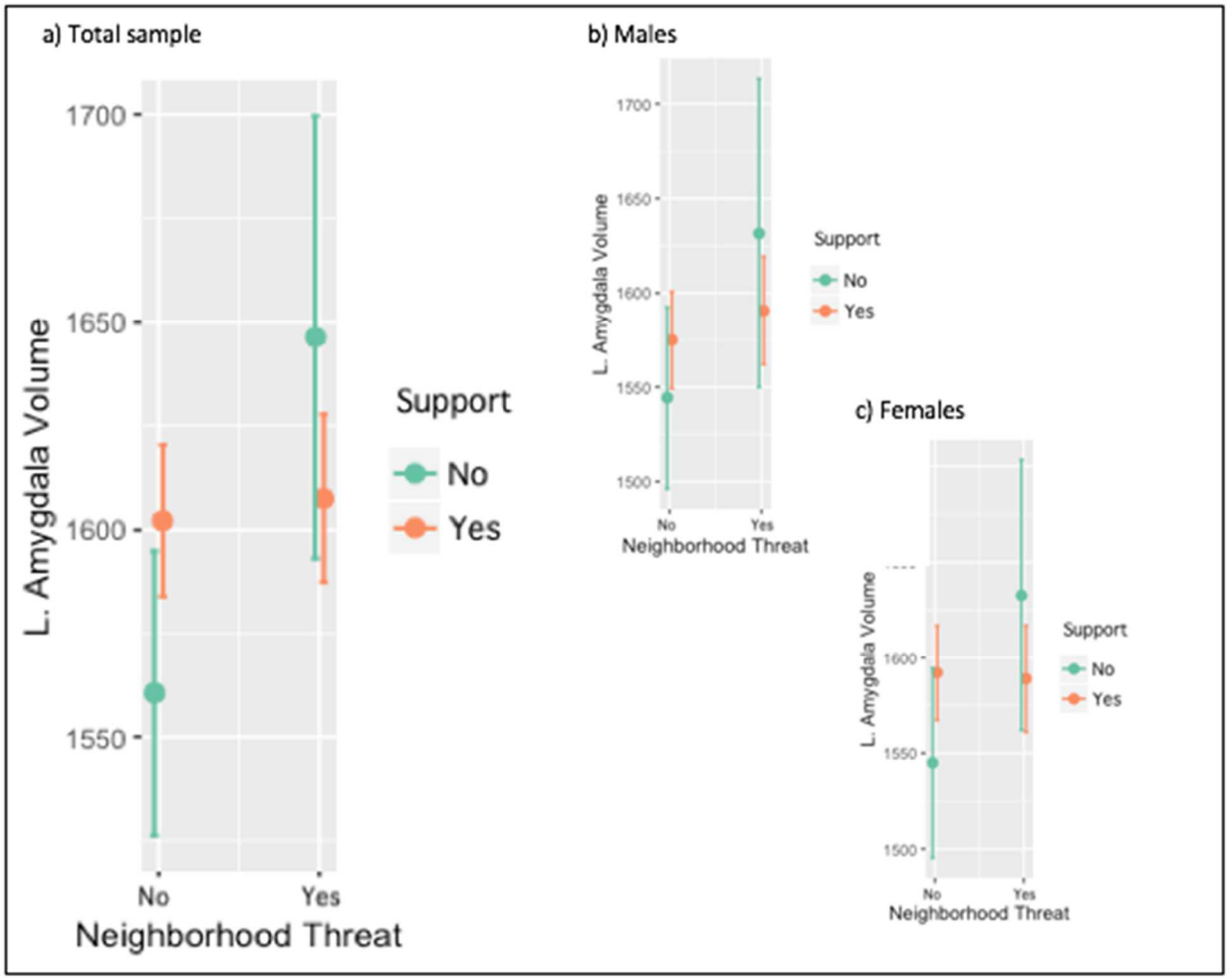


**Figure 1: Association of threat and left amygdala volume ($mm^3$), stratified by sex.**

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**SUPPLEMENT**

TABLE 1: Parental Support via The Children's Report of Parent Behavior Inventory, Caregiver Acceptance Subscale

My [caregiver] is a person who....

1. Makes me feel better after talking over my worries with him/her.
2. Smiles at me very often.
3. Is able to make me feel better when I am upset.*
4. Believes in showing his/her love for me.
5. Is easy to talk to.

Response options:
1 = Not like him/her
2 = Somewhat like him/her
3 = A lot like him/her

*Item included as a proxy for parental support in this study.

## CHAPTER 5: General Discussion of the Dissertation

## SUMMARY

*Overview.* This dissertation examines the different facets that interact with adversity exposure and sources of resiliency to influence structural neurodevelopment, pubertal maturation and behavioral outcomes pertinent to psychopathology risk. The chapters' aims and analyses transition from general to specific, such that the second chapter begins with a general overview of the data-driven relationship between cumulative early life adversity, frontolimbic circuitry, problematic behaviors and a range of resiliency sources. The next chapter becomes more specific in examining the relationship between different forms of early life adversity, specific subcortical structures, pubertal onset and problematic behaviors. The final research chapter examines the relationship between a singular, prevalent form of adversity, a single source of resiliency, specific subcortical structures and problematic behaviors. This dissertation highlights the nuanced complexities of experiences of both adversity and resiliency on physiological development and functioning, with a particular emphasis on neurodevelopment and puberty.

*Chapter 2: Resiliency to Cumulative Adversity's Neural and Behavioral Outcomes in ABCD Study Youth.* This is the first study to comprehensively examine whether different forms of resiliency *moderated* cumulative adversity's impact on structural neurodevelopment and internalizing, externalizing and total problems. Additionally, this study examined whether frontolimbic circuitry *mediated* the relationship between cumulative adversity exposure and CBCL outcomes. Individuals with higher scores across the domains of physical and sexual violence, parental mental health, and scarcity had more internalizing problems. Conversely, individuals with higher scores pertaining to neighborhood threat, prenatal substance exposure, and household dysfunction had higher externalizing problems. As the median onset of all

psychiatric disorders is 14 years of age (Kessler 2005), adolescents, particularly those with a history of adversity exposure, are at a heightened risk for psychopathology (Fritz 2018).

When examining the possible moderating relationship between six forms of resiliency and cumulative adversity, the following sources of resiliency impacted bilateral hippocampal volume: subtypes of school-based support, specifically, self-perception of intelligence compared with peers and relationship with teachers, and total parental support, including the ability of the caregiver to validate and smile. When examining the possible moderating relationship between different forms of resiliency and cumulative adversity exposure, the following sources impacted CBCL outcomes: subtypes of school-based support (i.e. self-perception of intelligence compared with peers and relationship with teachers) and internalizing behaviors; subtypes of parental support (i.e. love and affection) and externalizing behaviors; peer support and internalizing behaviors; and, the presence of siblings, specifically, both younger and twin siblings and internalizing behaviors and total problems.

Mediation of frontolimbic circuitry on the association between early life adversity and CBCL outcomes identified the following: 1) the ability of the right amygdala volume to partially mediate the association between early life adversity exposure and internalizing behaviors; 2) the ability of the left amygdala and bilateral hippocampus to partially mediate the association between early life adversity exposure and externalizing behaviors; and 3) the ability of bilateral amygdala and bilateral hippocampal volumes to partially mediate the association between early life adversity exposure and total problems. Thus, early life adversity exposure is associated with altered amygdala and hippocampal volume, which is associated with greater risk of problematic internalizing and externalizing behaviors.

*Chapter 3: The Mediating Influence of Puberty on Adversity Exposure and Frontolimbic Development Among ABCD Study Youth.* This study tested whether puberty *mediated* the relationship between both type-specific and cumulative adversity exposure and amygdala and hippocampal volumes. Additionally, this study examined the relationship between pubertal development (i.e. adrenarche and gonadarche) and type-specific and cumulative adversity exposure. Finally, this study examined whether school-based support *moderated* the impact of adversity exposure on pubertal development, specifically gonadarche. School-based support was specifically selected as a source of resiliency given the findings from the previous chapter and the existing literature. Early life adversity exposure was organized into the following 6 domains derived from a factor analysis: 1) physical and sexual violence; 2) parental mental health; 3) neighborhood threat; 4) prenatal substance exposure; 5) scarcity; and 6) household dysfunction.

Specific types of adversity exposure were associated with advanced adrenarchal development, specifically, parental mental health, neighborhood threat, prenatal substance exposure, and scarcity. The often-chronic nature of parental mental health and neighborhood threat may explain why these forms of adversity exposure impacted adrenarche. The timing of prenatal substance exposure may explain the association with advanced adrenarchal development. Among females, advanced gonadarchal development was associated with physical and sexual violence, parental mental health, neighborhood safety and prenatal substance exposure. Prenatal substance exposure was associated with the greatest relative risk for advanced gonadarche among females. Exposure to alcohol and tobacco were the two most common sources of prenatal substance exposures in ABCD Study youth at baseline. A recent longitudinal study of over 15,000 youth found that maternal alcohol intake during the first trimester was associated with advanced pubertal onset among girls but not among boys (Brix 2020). Of note,

type-specific and cumulative adversity exposure among males was not associated with gonadarche. This may in part be attributable to male's delayed pubertal maturation with respect to females.

When examining the mediating ability of gonadarche, neighborhood threat and household dysfunction were the only forms of adversity that significantly interacted with bilateral amygdala and hippocampal volume among both males and females. Only among females, prenatal substance exposure and scarcity played a significant role among females when examining the mediating ability of gonadarche on bilateral hippocampal volume. Thus, specific forms of early life adversity exposure (i.e. neighborhood threat, household dysfunction, prenatal substance exposure and scarcity) are associated with advanced gonadarche, which is associated with greater amygdala and hippocampal alterations. However, the ability of school-based support to interact with adversity exposure to influence pubertal development (i.e. gonadarche) was demonstrated among female youth who specifically reported a positive relationship with their teachers.

*Chapter 4: Perceptions of Neighborhood Safety and Parental Support in Early Adolescence: Sex Differences and Neurobiological Correlates in the ABCD Study*. To our knowledge, this is the first study to examine the potential impacts of youth-perceived neighborhood threat and parental consolation on amygdala volume in periadolescent youth. The key findings across the total sample are: 1) enlarged left amygdala volumes in the presence of perceived neighborhood threat and in the absence of parental consolation; 2) diminished left amygdala volume in the absence of both neighborhood threat and parental consolation; and 3) a significant interaction effect of parental consolation and neighborhood threat on left amygdala volume. Post hoc sensitivity analyses were conducted to examine the nature of the interaction

that neighborhood threat was associated with larger amygdala volume only in the absence of parental support. These analyses yielded a dose-response relationship of both neighborhood threat and parental support, such that greater endorsement of the two variables were associated with greater differences in amygdala volume.

When examining the sexes separately, we see a significant interaction effect of parental consolation and neighborhood threat among girls, driving the interaction effect seen across the total sample. Among boys, we identified a significant positive association between left amygdala volume and neighborhood threat even when controlling for concomitant problematic behaviors, such as rule-breaking and aggression. Males endorsed higher rates of neighborhood and school threat; there were no significant differences in parent-perceived neighborhood threat by sex. In addition to sex differences in perceived threat exposure, parental consolation, and model performance, we identified racial and ethnic differences in perceived threat exposure and parental consolation. The greatest perceived prevalence of neighborhood and school threat were endorsed by Black and Hispanic/Latinx youth, followed by White and Asian youth. Of note, significant differences in youth- and parent-reported perceived neighborhood threat were evident with parent perceived threat on average 1.7x greater than that of youth.

Rates of parental consolation did not differ significantly by age but did so by sex, race and ethnicity after controlling for multiple comparisons. Girls endorsed greater levels of parental consolation than boys and differences in parental consolation prevalence rates were observed across racial and ethnic groups. The greatest perceived prevalence of parental consolation was endorsed by White then Hispanic/Latinx youth, followed by Asian and Black youth. Finally, all clinical outcomes were significantly more common among youth who reported neighborhood threat exposure.

## SIGNIFICANCE

This dissertation is novel in its ability to comprehensively examine an array of factors that influence and interact with both early life adversity exposure and sources of resiliency to impact neurodevelopment and pubertal maturation. Due to the breadth of data collected by the multi-site ABCD Study and its publicly available nature, this dissertation was equipped to account for factors (i.e. sex, race and ethnicity, household income and parental education) not previously controlled for and addressed in prior studies of early life adversity exposure. Despite extensive research exploring the impact of early life adversity exposure on neurodevelopment, the extent to which exposure to various forms of adversity impacted neurodevelopment and puberty was not clear. Additionally, previous studies focused on discrete populations of youth (e.g. institutionalized youth, sexual assault survivors) studied for their exposure to often a singular form of adversity. This dissertation contributes to our understanding of neurodevelopment and puberty, and by identifying sources of resiliency that can dampen the impacts of adversity exposure, has the ability to inform legislative and policy efforts. For example, additional resources can be invested into community-based efforts that follow evidence-based approaches to promote supportive school environments. Youth involved with the juvenile justice system present a particular need given their oftentimes pre-existing adversity exposure and minimal sources of support present within and outside of the system. As such,

rehabilitative efforts aimed at system-impacted youth should include multiple sources of support to promote resiliency to adversity.

## LIMITATIONS

Study-specific limitations were explored at the end of each chapter pertaining to study questionnaires used, adversity reporting and the cross-sectional nature of the findings, among other limitations. Thus, this space will be utilized to address top-level limitations pertinent to utilizing publicly-available "big data". While data derived from publicly available multi-site longitudinal studies has many benefits, it also presents challenges. Challenges that significantly impacted this dissertation include: disorganization and inconsistency within data sharing platforms, substantial delays in data release, and minimal creative flexibility in study design. These challenges/barriers will be explored at greater length below.

To obtain access to the multi-site ABCD Study data, a data use agreement and secure account was established with the National Institute of Mental Health Data Archive (NDA). NDA contains human subjects' data collected from hundreds of research projects across a plethora of scientific domains, e.g. autism, typical neurodevelopment, genetics and osteoarthritis. NDA is utilized as the infrastructure to share study data, relevant tools and methodology, as well as analyses and findings so as to encourage collaborative scientific discovery and communication. As UCLA is one of the 21 institutions directly participating in the ABCD Study, we were aware of data processing and release delays in slight advance of other NDA users. While delays are expected given the breadth of data collected for this study, the actual delays were so substantial and outside the anticipated delay window that they caused significant challenges not only to this project but to proposed ABCD sub-studies. For example, each data release (i.e. version 1, 1.1, 2,

2.1) was at least 6 months delayed. Additionally, the initial releases - version 1 and version 2 - contained erroneous data and as such, were superseded by versions 1.1 and 2.1, respectively. Given the expected lag in discovering and subsequently correcting the erroneous data in versions 1 and 2, research findings utilizing these versions were submitted for publication and released in peer-reviewed journals. Given the data collection and release timeline put in place by the ABCD Study's data and informatics core (DAIC) following year 1 and year 2 data collection, this dissertation had proposed to incorporate longitudinal study data; however, due to the substantial delays in data release, this dissertation only utilized and reported findings on cross-sectional baseline data. This change substantially impacted the generalizability of this dissertation's findings. Lastly, data derived from publicly-available multi-site studies carries minimal creative flexibility in study design, even for study sites. This is not unique to the ABCD Study but has been observed with other publicly-available multi-site neuroimaging studies (Etkin 2019, Wiseman 2019).

While the "big data" movement has encouraged data sharing, replication efforts and cross-institutional collaborations, the success of big data will ultimately be determined by the utility of the data available. It is suggested that future efforts minimize these barriers through the following proposed improvements: 1) transparency and accountability in data release timelines and quality. This can be attained in part by hiring experienced statisticians and analysts and providing all data users with an informational monthly newsletter which addresses and provides solutions for common issues related to data quality and the timely delivery of data releases; 2) accuracy and consistency across data files and platforms. For example, the DAIC and NDA staff should implement and utilize detailed standard operating procedures ensuring that data are uniformly presented to users. Within the ABCD Study, for example, data files should contain, at

minimum, subject identification number, age in months, sex, gender, race/ethnicity and visit type (i.e. baseline or follow-up). Each of these demographic variables should be standardized across all files to minimize errors and promote consistency. Each file's data dictionary can provide additional details regarding the variables and included response options. It is advised that the response options for common variables are standardized and consistent. For example, labeling the female sex as a 1 on one datasheet and a 0 on others, can lead to errors and delays in distributing research findings.

## FUTURE DIRECTIONS

Experiences during adolescence generate a tremendous impact on brain development and behavior, not just during this critical period but extending into adulthood. Generally speaking, youth neurodevelopment can be viewed in terms of plasticity that diminishes with age, and thus increases one's susceptibility to permanent neural modifications in response to environmental influences. Recent neuroimaging studies are beginning to examine the impact of different forms of early life adversity and their associated nuances (i.e. type, age of onset, duration, frequency) on frontolimbic and associated circuitry. Less overt forms of early life adversity exposure, such as chronic threat due to neighborhood violence exposure, should be explored given their prevalence and pertinence to neurodevelopmental and behavioral outcomes. Furthermore, the integration of neuroendocrinological processes ascribed to pubertal development into neuroimaging studies of early life adversity exposure would provide a more comprehensive understanding of the impacts of exposure and observed sex differences.

To combat the methodological limitations and biases associated with retrospective studies of early life adversity exposure, future studies should employ a prospective longitudinal study

design. Despite the inherent vulnerability of a developmental state, current approaches to translating the findings of early life adversity studies should investigate features of resiliency. This can help limit and possibly rectify previous findings on early life adversity exposure pertaining to health and well-being outcomes, which have been received by the public as largely pre-deterministic and fatalistic. This modified approach emphasizing resiliency is particularly germane when examining adversity exposure during development when youth are very much amenable to environmental support. Future research should utilize the publicly-available multimodal dataset derived from the largest longitudinal study of youth development to date - the ABCD Study.

## CONCLUDING REMARKS

Early life adversity exposure is associated with a host of detrimental outcomes, acutely following exposure and throughout the lifespan. These include problematic behaviors associated with increased psychopathology risk, structural and functional neural alterations, and adaptations to one's pubertal maturation trajectory. However, sources of resiliency, particularly when accessible during development, can mitigate the detrimental outcomes associated with adversity exposure. This dissertation is novel in its ability to extensively examine an array of factors that influence and interact with both early life adversity exposure and sources of resiliency to impact neurodevelopment and pubertal maturation. In addition to cumulative adversity exposure, the following domains of adversity exposure were identified and included in this dissertation's analytical models: 1) physical and sexual violence; 2) parental mental health; 3) neighborhood threat; 4) prenatal substance exposure; 5) scarcity; and 6) household dysfunction. Additionally, the following six categories of resiliency studied and analyzed were: 1) school-based support; 2)

peer support; 3) parental support; 4) the presence of siblings; 5) youth's prosocial behaviors; and 6) the youth's religious and spiritual beliefs. This dissertation utilized data obtained from the largest neuroimaging study of youth to date - the ABCD Study. Due to the breadth of data available, this dissertation was well powered to explore the relationships between resiliency, adversity, physiological development (i.e. structural frontolimbic circuitry and pubertal maturation) and behavioral outcomes. While the findings are limited by the cross-sectional nature of the data, this dissertation has importantly identified the following: sex differences in adversity's impact on pubertal development; type-specific differences in adversity's impact on structural neurodevelopment and pubertal maturation; sex differences in behavioral outcomes associated with adversity exposure; prevalence of adversity exposure among a nationally-representative sample of youth; moderating ability of differential sources of resiliency to mitigate adversity's impact on brain and behavioral outcomes; moderating ability of differential sources of resiliency to mitigate adversity's impact on pubertal development; and a clearer understanding of the relationship between early life adversity, resiliency and structural neurodevelopment among nine and ten-year old youth. This dissertation lays the groundwork for future investigations to explore the nuanced relationship between structural neurodevelopment, pubertal maturation, early life adversity exposure and sources of resiliency. Future studies are encouraged to utilize the longitudinal ABCD Study data, incorporate the sex hormone data and to identify additional features of adversity (i.e. age of onset, duration, frequency, relationship to perpetrator) that may contribute to neural and behavioral adaptations.

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