Linking Early Life Stress and Psychopathology through Neural Correlates

Hee Jung Jeong, M.S.

Dissertation

Submitted to the Faculty of the

Graduate School of Vanderbilt University

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

in

Psychology

August 8 2025

Nashville, Tennessee

Committee:

Antonia Kaczkurkin, Ph.D.

Steven Hollon, Ph.D.

David Schlundt, Ph.D.

Kristopher Preacher, Ph.D

Acknowledgement

Firstly, I would like to thank my advisor, Dr. Antonia Kaczkurkin for her exceptional support throughout the graduate study. I would like to thank my committee members, Dr. Steve Hollon, Dr. David Schlundt, and Dr. Kristopher Preacher for their contribution. I especially thank Dr. Preacher for providing statistical consultation. I want to express my respect for Dr. Hollon and Dr. Schlundt for modeling passion for teaching which I was honored to observe as their teaching assistant. I also thank Dr. Sohee Park for her generosity to our family. Many special thanks to Dr. Autumn Kujawa who helped me to begin my journey at Vanderbilt. Secondly, I thank my lab mates: Gabby Reimann for being a lifelong friend, Leighton Durham for being a supportive cohort throughout all stages, and Camille Archer for her admirable character as a friend and a researcher. I also extend my thanks to Randon Dupont and Shuti Wang for their valuable contribution in managing the dataset for us. Thirdly, I would like to thank my family: my parents and brother for being endless inspirations and role models to follow. My husband, Hyeonseung Lee, for his unconditional support and for withstanding storms always ahead of me to make things smoother for me. And my son, Hayden Lee, for introducing me the new world with the joy of altruism. Lastly, I thank everyone in my life for their material and mental nourishment. I hope this will be a start for me to give back to the world what I received from you.

Table of Contents

Acknowledgement ii

List of Tables v

List of Figures vi

Part I: Overview of Early Life Stress, Neural Correlates, and Psychopathology in Youth 1

Introduction 1

Defining Early Life Stress 3

The Impact of Early Life Stress on the Brain: An Allostatic Load Model and Susceptible Brain Regions 4

Review of Longitudinal Neuroimaging Studies Linking Early Life Stress and Psychopathology Through Neural Correlates 9

Poverty Leads to Hormonal Trajectories that Map onto Hippocampal Volume and Predict Emotion Dysregulation and Depressive Symptoms 9

Threat Exposure is Associated with Left Amygdala Volume Reductions and Subsequent Internalizing and Externalizing Symptoms 10

Early ACEs Lead to Smaller Inferior Frontal Gyrus Volumes and Depressive Symptoms . 12

ACEs Associated with Anterior Cingulate Cortex Function and Externalizing Symptoms. 13

Physical and Sexual Abuse Predict Thinner Left Parahippocampal Gyrus and Antisocial Behaviors 14

Summary of Previous Longitudinal Studies 15

A Hierarchical Approach for Modeling Psychopathology and Stress 16

Part II: Uncovering the Longitudinal Relationships between Early Life Stress, Neural Correlates, and Psychopathology 17

Overview 17

Methods 18

Participants 18

Inclusion/Exclusion Criteria 20

Dependencies in Families and Sites 20

Psychopathology Assessment 21

Environmental Stressor Measures 21

Residential History Derived Scores 24

Hierarchical Modeling of Psychopathology 27

Hierarchical Modeling of Environmental Stressors 28

Statistical Analyses: Methods Common Across Studies 30

Study 1 31

Statistical Analyses 31

Results 32

Discussion 35

Study 2 41

Image Acquisition, Processing, and Quality Assurance 44

Statistical Analyses 45
Mediation Analysis Using Cluster-Robust Standard Errors. 45
Multilevel Mediation Analysis. 46
Sensitivity Analyses 46
Sex Difference 46
Results 47
Discussion 57
Part III. Synthesis: General Discussion, Limitations/Future Directions, and Conclusion 60
General Discussion 60
Limitations/Future Directions 63
Conclusion 65
References 67
Appendix 81

List of Tables

Table 1. Summary of demographic characteristics of the ABCD study sample at baseline (N = 11,868) 19
Table 2. Association between stressors at baseline and psychopathology symptoms at the third-year follow-up. 34
Table 3. Association between stressors at baseline and psychopathology symptoms at the third-year follow-up controlling for baseline psychopathology 34
Table 4. Results of mediation analyses with general environmental stress (X), regional volume (M), and total CBCL (Y). 49
Table 5. Results of mediation analyses with general environmental stress (X), regional cortical thickness (M), and total CBCL (Y)..... 50
Table 6. Results of mediation analyses with general environmental stress (X), regional surface area (M), and total CBCL (Y). 50
Table 7. Results of multilevel mediation analyses with general environmental stress (X), regional volume (M), and total CBCL (Y). 52
Table 8. Results of mediation analyses with general environmental stress (X), regional volume (M), and total CBCL (Y) controlling for baseline CBCL..... 56

List of Figures

Figure 1. Schematics of the bifactor modeling used to delineate psychopathology and environmental stress factors. 30
Figure 2. Schematic representation of the mediation model tested in Study 2 43
Figure 3. Regional cortical and subcortical gray matter volume (GMV) at the second-year follow-up mediating the association between the general environmental stress factor at baseline and total CBCL scores at the third-year follow-up. 48

Part I: Overview of Early Life Stress, Neural Correlates, and Psychopathology in Youth

Introduction

Early life stress refers to stress or adversity experienced during critical developmental periods, including the prenatal period, infancy, childhood, and adolescence (Heim et al., 2003). It is widely known that early life stress is associated with a higher likelihood of mental health disorders in later life (Kessler et al., 2010; McLaughlin et al., 2010). Furthermore, difficulties associated with early life stress are often more severe, persistent, and treatment-resistant than those not associated with early life stress (McLaughlin et al., 2010; Wade et al., 2022). Patients with mental health disorders and a history of childhood maltreatment have earlier onset of symptoms, greater comorbidity, greater suicide risk, and worse treatment response compared to individuals with the same diagnosis but no history of childhood maltreatment (Teicher & Samson, 2013). Therefore, understanding the mechanisms by which early life stress leads to psychopathology may allow us to identify those at risk which is key to early intervention and prevention of lifelong negative outcomes. One potential mechanism through which early life stress may lead to psychopathology is its adverse influence on the brain. Early life stress is believed to have a negative impact on the brain, potentially leading to long-term adverse effects during later stages of development (Cryan & Dinan, 2013). The growth and development of the human brain begins approximately two weeks after conception and continues until the brain reaches full maturity in the third decade of life (Bick & Nelson, 2016). Throughout this extended period, cognitive and emotional maturation takes place along with significant changes to the brain (Arain et al., 2013; Paus, 2005). Early life stress can cause alterations in brain development, which may affect normative cognitive and emotional development (Bick &

Nelson, 2016). Therefore, studies that investigate the connections between early life stress, brain measures, and psychopathology are essential for understanding the risk factors associated with the development of mental health symptoms.

However, most studies on early life stress and neural correlates of psychopathology collect data at only a single time point, which limits their ability to establish causal relationships among risk factors, brain, and behavior. Changes in neural substrates due to early life stress may be responsible for maladaptive cognitive, emotional, and behavioral problems. To address this issue, researchers often use mediation analysis, which involves observing the effect of an exposure (e.g., early life stress) on an outcome (e.g., psychopathology) while adding a mediator (e.g., neural correlates) to determine if the mediator has an explanatory effect (MacKinnon et al., 2007). When using mediation, a longitudinal design is preferred. Theoretically, the paths in the mediation model require time for the relationships to develop and unfold (Selig & Preacher, 2009). Furthermore, cross-sectional data leave out several key predictors such as variables measured at previous times which can lead to over- or under-estimation of the true effects (Selig & Preacher, 2009). Simulation studies indicate that performing mediation analyses using cross-sectional data can introduce biases; research shows that a variable found to play a mediating role in cross-sectional data may not be a mediator at all in a longitudinal analysis (Maxwell et al., 2011; Maxwell & Cole, 2007). In an ideal longitudinal design, the exposure, the mediator, and the outcome are assessed at different time points to tease apart the effect of early life stress on the brain and subsequent psychopathology symptoms, which can help to establish temporal precedence between the variables.

However, surprisingly few longitudinal studies have tested the mediating effect of neural measures on the relationship between early life stress and psychopathology. To improve our

understanding, this dissertation aims to provide an overview of the current state of the literature and to present the results of two studies that examined whether early life stress influences psychopathology through brain measures by leveraging the largest longitudinal study in the United States which follows over 11,000 children from ages 9-10 into young adulthood (Casey et al., 2018). First, a theoretical account on how stress can cause alterations to the brain, and specific brain regions that are found to be especially susceptible to stress will be presented. Second, a literature review on longitudinal studies that examined neural measures as mediators between early life stress and psychopathology will be presented. Third, the importance of using hierarchical modeling to reveal the inherent organization of stress and psychopathology will be discussed. Finally, two studies will be presented and discussed that aim to extend our knowledge of the association between early life stress and psychopathology and their potential underlying neural mechanisms.

Defining Early Life Stress

For clarity, the terms used throughout this proposal will first be defined, as early life stress can be conceptualized in several ways. The most specific and narrow term used in this area is *childhood maltreatment* (or childhood trauma), which includes neglect and/or abuse (physical, sexual, and/or emotional) experienced before 18 years of age and committed by a parent, caregiver, or another person in a custodial role (e.g., relative or teacher) (Fang et al., 2012; Leeb et al., 2008). Although the concept of childhood maltreatment is widely used, this term has been criticized for being too narrow in scope, leading to a call for alternative terms (Manly, 2005).

The term *childhood adversity* was suggested as an alternative concept. Childhood adversity (also sometimes referred to as adverse childhood experiences or ACEs) includes childhood maltreatment as well as other circumstances and events that could adversely affect the

child's well-being such as household dysfunction (Felitti et al., 1998). The original ACEs included a history of psychological, physical, or sexual abuse, household dysfunction, exposure to household substance abuse, family members in the home with mental illness, domestic violence against the mother, and/or household criminal activity (Felitti et al., 1998). However, ACEs have been criticized for not being based on theory or empirical evidence, not providing a comprehensive account of the many possible adverse experiences a child might encounter, and lacking consistency in what is included in the definition of this term (Afifi et al., 2022).

There is growing evidence that indirect environmental stressors outside of the immediate family can also affect the child's well-being (McLaughlin et al., 2019). For example, poverty has effects on the child that are both direct (limited access to healthcare, experiencing social isolation, and encountering stigma) and indirect (neighborhood deprivation leading to chronic stress not related to an immediate and identifiable individual experience). In our prior work, the term *environmental stress* was used to encompass childhood maltreatment, childhood adversity, and both direct and indirect environmental influences (Jeong et al., 2023). Given the wide variety of terms currently used, for simplicity and inclusivity, this dissertation will describe the findings in the literature using the term *early life stress*, which includes all terms discussed (childhood maltreatment, childhood trauma, childhood adversity, ACEs, and environmental stress).

The Impact of Early Life Stress on the Brain: An Allostatic Load Model and Susceptible Brain Regions

This section aims to provide a theoretical explanation of how stress can lead to changes in normal brain development. The development of the human brain is a lengthy process that begins approximately two weeks after conception and continues until the brain reaches full maturity in the third decade of life (Bick & Nelson, 2016). During postnatal development,

synapses multiply, and then a pruning process occurs, eliminating unnecessary synapses and shaping the brain to become more efficient and finely tuned (Petanjek et al., 2008). This pruning process is heavily influenced by experience. Unexpected experiences, such as experiencing threats or a lack of expected input (i.e., deprivation), can potentially disrupt normal brain development (Sheridan & McLaughlin, 2014).

The most prominent theory explaining how stress may cause alterations in brain structure is an allostatic load model (McEwen, 1998). As an organism interacts with the external environment, its internal stability (i.e., homeostasis) is constantly threatened (Sterling & Eyer, 1988). Threat to internal stability will result in adaptive responses such as activation of neural, neuroendocrine, and neuroendocrine-immunity responses to restore homeostasis (McEwen, 2007). However, constant exposure to external stress may place too many demands on the system, which can lead to detrimental effects. Allostatic load is a term used to describe the physiological wear and tear on the body caused by chronic stress, which has cumulative effects as the body attempts to adapt to stress over time (McEwen & Stellar, 1973).

One of the immediate responses when our body encounters stress is to release stress hormones which help us adopt a fight-or-flight state (Chrousos, 2009). The release of stress hormones is regulated by the hypothalamus-pituitary-adrenal (HPA) axis (Herman & Cullinan, 1997). Briefly, the hypothalamus secretes corticotrophin-releasing hormone (CRH), which activates the pituitary gland, releasing adrenocorticotropic hormone (ACTH). ACTH then activates the adrenal gland which releases glucocorticoids such as cortisol. These glucocorticoids trigger many physiological changes (e.g., increasing heart rate, blood pressure, and blood sugar level, suppressing the immune system) initiating a fight-or-flight response (Chrousos, 2009). Once stress hormones reach a certain level in the bloodstream, a message is sent back to the

hypothalamus and pituitary gland to decrease the production of CRH and ACTH, respectively. This negative feedback loop is crucial for preventing excessive secretion of cortisol and maintaining homeostasis of the HPA axis (Herman et al., 2016). Otherwise, the body will be constantly engaged in a fight-or-flight state, which is highly costly.

Stress hormones including glucocorticoids are lipophilic, meaning that they can easily pass the blood-brain barrier and enter the neuronal target cells (Saaltink & Vreugdenhil, 2014). Activation of neuronal targets can temporarily enhance the functioning of those regions, whereas chronic stress is known to result in damage to neurons in brain regions with a high concentration of receptors for glucocorticoids (Conrad, 2008). The hippocampus, amygdala, and prefrontal cortex are known to possess a high density of glucocorticoid receptors and studies indicate stress can induce structural changes in these regions (McEwen et al., 2016). In particular, CRH receptors exhibit the highest levels of expression during early development in the hippocampus and amygdala (Baram & Hatalski, 1998), supporting the notion that youth is a developmental period that is sensitive to stress (Tottenham & Sheridan, 2010).

Among brain regions, the hippocampus has the highest concentration of glucocorticoid receptors, and thus, is thought to be especially vulnerable to stress (Liu & Nusslock, 2017). The hippocampus plays a role in processing cognitive and emotional information, especially with regard to encoding memory (Gulyaeva, 2015). Studies indicate that exposure to chronic stress can lead to morphological changes, suppression of neuronal proliferation, and reduction in the volume of the hippocampus (Kim, Pellman, & Kim, 2015). Continuous activation of the HPA axis has been linked to shrinkage and eventual death of pyramidal neurons (McEwen, 1999; Uno, Tarara, Else, Suleman, & Sapolsky, 1989) which are the most common excitatory neurons in the hippocampus (Bekkers, 2011). The hippocampus is also involved in the negative feedback loop

of the HPA axis by downregulating the HPA axis' response to stressors (Sala et al., 2004). When glucocorticoid levels are elevated, it can lead to a decrease in the number of hippocampal receptors that typically help regulate the negative feedback to the HPA axis, which can lead to a dysregulated axis (Van Haarst et al., 1997). In summary, studies consistently indicate that stress exerts an adverse effect on the hippocampus due to its high concentration of glucocorticoid receptors and interaction with the HPA axis.

As part of the limbic system along with the hippocampus, the amygdala is responsible for processing emotional stimuli (Davis & Whalen, 2001; Tottenham & Sheridan, 2010) and has been linked to stress-related psychopathology such as anxiety, depression, and posttraumatic stress disorder (VanTieghem & Tottenham, 2018) with regard to heightened reactivity to threatening stimuli and emotion dysregulation. In conjunction with the hippocampus, the amygdala is involved in memory consolidation and retrieval in the context of stressful experiences (Johnson et al., 2005). While hippocampal volume tends to decrease under stress, the effects of amygdala volume have been mixed. Some studies show reduced volume associated with stress (Jeong et al., 2021; Lim, Radua, & Rubia, 2014), while others show no effect (Woon & Hedges, 2009) or enlarged volume (Danese & McEwen, 2012; Mehta et al., 2009; Tottenham et al., 2010). Interestingly, a study by Vyas et al. (Vyas, Mitra, Shankaranarayana Rao, & Chattarji, 2002) found that while prolonged stress in rats leads to shrinkage and reduction in the branches of pyramidal cells in the hippocampus, it promotes the growth of dendrites in the amygdala. In human studies, adults with a history of childhood adversity exhibit smaller amygdala volumes (Ahmed-Leitao et al., 2016; Driessen et al., 2000; Schmahl et al., 2003), while youths with early deprivation (e.g., institutionalized rearing) exhibit larger amygdala volumes (Mehta et al., 2009; Tottenham et al., 2010). A possibility has been suggested by

Tottenham and Sheridan (2010) that the amygdala undergoes expansive growth accompanied by hyperactivity following a stressor, thereby resulting in a larger volume during the early stage of development. Prolonged hyperactivity, however, can lead to eventual cellular atrophy and/or death (Tottenham & Sheridan, 2010). To summarize, the direction of the effects of stress in the amygdala may differ depending on the individual's stage of development. Longitudinal studies are needed to examine trajectories of change in the amygdala.

Lastly, the prefrontal cortex is enriched with glucocorticoid receptors (Patel et al., 2008) and closely interacts with the subcortical regions in response to stress (Cerqueira et al., 2007). The prefrontal cortex undergoes a process of maturation during development and exhibits the most delayed maturation compared to other areas of the brain, continuing to develop until the early twenties (Giedd, 2006). In particular, the ventral medial prefrontal cortex (vmPFC) integrates incoming information and regulates neurophysiological, autonomic, and behavioral responses to stress (McKlveen et al., 2019). The vmPFC projects to the amygdala and downregulates activity towards emotional stimuli (Motzkin et al., 2015). Such top-down inhibition of the amygdala by the vmPFC is malfunctioning in patients with mood and anxiety disorders (Myers-Schulz & Koenigs, 2012). Thus, the high concentration of glucocorticoid receptors and late maturation of the prefrontal cortex may contribute to its susceptibility to the effects of stress, which can lead to poor emotion regulation as a result of atypical regulation on subcortical regions.

In summary, stressful experiences release stress hormones that have downstream effects on important brain regions, especially the hippocampus, amygdala, and prefrontal cortex due to the high concentration of glucocorticoid receptors, which show greater expression during the early developmental stage. Furthermore, prolonged growth in these regions may also contribute

to vulnerability to the effects of stress, as these regions are still maturing as stress is experienced. The hippocampus, amygdala, and prefrontal cortex also have important ties to emotion processing and psychopathology symptoms. Their relationship will be revisited in the longitudinal studies reviewed next.

Review of Longitudinal Neuroimaging Studies Linking Early Life Stress and Psychopathology Through Neural Correlates

As demonstrated in the prior section, previous studies point to several regions that could be particularly vulnerable to the effects of stress. Furthermore, structural and functional differences in these regions are implicated in various psychopathological symptoms. As mentioned in the introduction, a mediation analysis with longitudinal data has the potential to inform the pathways by which stress impacts psychopathology through neural correlates. Previously, we conducted a literature review to investigate longitudinal studies that assessed brain metrics as mediators of the relationship between early life stress and future psychopathology symptoms (Jeong & Kaczkurkin, 2024). Following standard guidelines for systematic reviews, studies were included if they (a) measured early life stress, brain measures, and psychopathology, consecutively, from at least three different time points and (b) tested the brain measures as mediators between early life stress and psychopathology. In the next section, the main results of the reviewed studies will be discussed.

Poverty Leads to Hormonal Trajectories that Map onto Hippocampal Volume and Predict Emotion Dysregulation and Depressive Symptoms

Barch et al. (2020) investigated the connections between early life exposure to poverty, hormonal trajectories, hippocampal development, emotion regulation, and depressive symptoms. For hormones, they measured testosterone and dehydroepiandrosterone (DHEA) which are

produced by the hypothalamus-pituitary-gonadal axis that affects the hippocampus by supporting its neurogenesis and exerting neuroprotective effects. The researchers hypothesized that dysregulation of testosterone or DHEA could negatively affect hippocampal growth. They found that greater exposure to poverty in early life predicted shallower testosterone increases and a shallower slope of hippocampal growth during adolescence. Greater exposure to poverty also predicted more emotion dysregulation and depressive symptoms, even after controlling for pre-existing depressive symptoms. A greater increase in testosterone was associated with a greater increase in hippocampal growth, as well as lower emotion dysregulation and depressive symptoms. The authors conducted a serial mediation model where two or more mediators are hypothesized to sequentially contribute to the relationship in question. The results of the serial mediation analysis showed that the association between exposure to poverty in preschool and depressive symptoms in adolescence was no longer significant when testosterone slope, hippocampal volume slope, and emotion dysregulation were included in the model, suggesting a multiple mediation effect. The authors found no differences between males and females, which they interpret as indicating that the effects are equally present in both sexes. Overall, this study suggests that testosterone may serve as a protective factor against atypical hippocampal development, emotion dysregulation, and increased risk for depressive symptoms in later stages. It also highlights the detrimental downstream effects of early life poverty exposure on these processes.

Threat Exposure is Associated with Left Amygdala Volume Reductions and Subsequent Internalizing and Externalizing Symptoms

A study by Picci et al. (2022) investigated the association between threat exposure during late childhood/early adolescence and psychopathology in later adolescence and whether

amygdala or hippocampal volumes mediate this relationship. Trauma exposure and perceived stress were assessed when participants were approximately 11 years old and amygdala and hippocampal volumes were measured one year later. Psychopathology, including internalizing and externalizing symptoms, was assessed a year after imaging (i.e., two years after baseline). The study found that greater perceived stress at baseline predicted more externalizing behaviors, but not internalizing symptoms. Threat exposure was associated with smaller left amygdala volume at the one-year follow-up. Decreased volume in the left and right hippocampi predicted increased internalizing symptoms at 13-14 years.

The mediation analysis showed that left amygdala volume mediated the relationship between threat exposure at 11 years and internalizing and externalizing behaviors at 13-14 years. Interestingly, the pattern of association was divergent for internalizing and externalizing behaviors. Smaller left amygdala volumes were related to increased internalizing symptoms, while larger amygdala volumes were related to increased externalizing behaviors. Neither the left nor the right hippocampus mediated the relationship between threat exposure and later psychopathology symptoms, which is a different pattern than that observed in Barch et al. (2020). This discrepancy may be due to the different forms of early life threat examined. Also, Barch et al. (2020) had a larger age range (3-19 years) compared to Picci et al. (2022), who had a sample with a relatively smaller age range (11-14 years). Additionally, previous studies suggest that the impact of early life stress on the hippocampus may not be immediately apparent, and may present only when individuals reach adulthood (Tottenham & Sheridan, 2010). Overall, this study expands on previous research by demonstrating the involvement of the left amygdala in mediating the association between early life stress and subsequent psychopathology.

Early ACEs Lead to Smaller Inferior Frontal Gyrus Volumes and Depressive Symptoms

Luby et al. (Luby, Barch, Whalen, Tillman, & Belden, 2017) proposed that early life adversity would lead to increased depressive symptoms and poorer general health outcomes through the prefrontal cortex subregions that subsequently influence emotional processing. They measured early life stress when participants were 3 to 8 years old using adverse childhood experiences (ACEs) scores, which included experiences such as poverty, traumatic events, and parental psychiatric disorders. The study focused on volumetric changes in five prefrontal cortex subregions related to emotion regulation. These volumes were obtained when participants were between 6 and 12 years old. Emotional awareness, depression severity, and general health outcomes were assessed at ages 9-14 and 10-15 years.

The study found that early ACEs predicted greater depression severity and smaller inferior frontal gyrus volumes after controlling for age, sex, global physical health, depression severity in early childhood, and whole-brain volume. A sequential mediation model showed that higher ACE scores predicted decreases in inferior frontal gyrus volumes, which then predicted poorer emotional awareness, and this in turn predicted higher depressive symptom severity. The mediating effect was primarily driven by inferior frontal gyrus volumes rather than emotional awareness. When removing emotional awareness from the model, the inferior frontal gyrus volume continued to mediate the association between early ACEs and depressive symptom severity. When the inferior frontal gyrus volume was removed from the model, poor emotional awareness did not mediate the association between early ACEs and depressive symptoms. This study highlights the role of the prefrontal cortex, specifically the inferior frontal gyrus, in the relationship between early life stress and psychopathology.

ACEs Associated with Anterior Cingulate Cortex Function and Externalizing Symptoms

Fava et al. (2019) examined the relationship between childhood adversity measured with ACE scores, anterior cingulate cortex (ACC) functioning, and externalizing behavior. Externalizing behavior was assessed using the aggressive and delinquency subscales of the Child Behavior Checklist Teacher Report Form. They used an fMRI go/no-go task to observe neural mechanisms related to error monitoring, specifically focusing on the ACC, which is a central hub of cognitive control and reward processing (Allman et al., 2001). Prior studies suggest that impaired neural activity during error monitoring such as lower ACC engagement may reflect the inability of youth to update their behaviors following an error and learn from mistakes, which may confer risk for behavioral disinhibition and externalizing problems (Hall et al., 2007; Yang & Raine, 2009).

The results showed that ACEs were associated with higher rates of externalizing behavior during early adolescence. A whole-brain analysis revealed significant clusters in the ACC, mid cingulate cortex, and precuneus based on the contrast of failed vs. correct no-go trials, which captures responses to inhibitory errors. However, only the ACC showed a significant association with externalizing behavior. ACEs were associated with lower activation in the ACC during the go/no-go task, and lower ACC activation predicted higher levels of externalizing behavior. The mediation model indicated that about 63% of the total effect of ACEs on externalizing behavior operated through ACC activation. This study suggests that early life stress can negatively impact ACC functioning, specifically the ability to learn from mistakes, which may contribute to the development of externalizing symptoms in particular.

Physical and Sexual Abuse Predict Thinner Left Parahippocampal Gyrus and Antisocial Behaviors

Busso et al. (2017) conducted a study to examine the relationship between childhood maltreatment, specifically physical and sexual abuse, and psychopathology symptoms. A subsample underwent neuroimaging data collection, focusing on cortical regions and the hippocampus and amygdala. Psychopathology was assessed using the Diagnostic Interview Schedule for Children (DISC-IV), which provided diagnoses and symptom scores for various disorders including major depressive disorder, generalized anxiety disorder, posttraumatic stress disorder, conduct disorder, and oppositional defiant disorder. An antisocial behavior composite was created by combining symptoms of conduct disorder and oppositional defiant disorder.

The results showed that the group with a history of abuse had greater symptoms of antisocial behavior, major depressive disorder, and posttraumatic stress disorder at the later time points, controlling for age and sex. This group also exhibited reduced cortical thickness in the vmPFC, right inferior frontal gyrus, left and right parahippocampal gyri, right inferior temporal gyrus, and right middle temporal gyrus. Of note, there was no difference in hippocampal or amygdala volumes between the group with a history of abuse and the control group. Reduced thickness in the left and right parahippocampal gyrus predicted antisocial behaviors and greater thickness of the middle temporal gyrus predicted generalized anxiety disorder symptoms. In particular, reduced thickness of the left parahippocampal gyrus was found to mediate the association between abuse exposure and antisocial behaviors. In sum, the results of this study suggest a specific relationship between sexual and physical abuse and later antisocial behaviors through thinner cortices in the left parahippocampal gyrus.

Summary of Previous Longitudinal Studies

The current review of longitudinal mediation studies identifies several specific brain areas that are linked to early life stress. As predicted based on a heightened vulnerability due to a high concentration of glucocorticoid receptors, the amygdala, hippocampus, and subregions of the prefrontal cortex such as the inferior frontal gyrus and the vmPFC emerged as regions that are associated with early life stress. Moreover, the hippocampus, amygdala, inferior frontal gyrus, ACC, and parahippocampal gyrus were identified as mediators in the link between early life stress and subsequent psychopathology symptoms. Overall, the findings from these studies indicate that these brain regions may play a crucial role in the response to stress and potentially contribute to the development of psychopathology.

However, as illustrated by the small number of studies that met our systematic review criteria, there is currently a lack of longitudinal studies that preserve temporal precedence between early life stress, brain measures, and psychopathology symptoms. Additional longitudinal studies are needed examining potential neural correlates that mediate the relationship between early life stress and psychopathology. Previous studies are also limited by a relatively small sample size (ranging from 51 to 167). While these numbers are not inadequate, smaller samples may be underpowered to detect effects and may overlook meaningful smaller effects. Furthermore, given that the effect of stress on the brain may differ depending on the age at measurement (Tottenham & Sheridan, 2010), a narrowly defined age range would be helpful in understanding the relationship between stress and psychopathology during a specific developmental period. In addition, the studies reviewed focus on one type of stressor such as abuse only or they focus on childhood adversity, which despite being a broader concept, still neglects the large number of environmental stressors that a child may encounter. Likewise, the

studies reviewed focus on a particular class of psychopathology symptoms, such as depressive symptoms or externalizing symptoms, making it difficult to determine whether the effects are unique to some forms of psychopathology or characteristic of psychopathology more broadly. Finally, none of the studies reviewed measure stress or psychopathology hierarchically. In the next section, the advantages of a hierarchical approach for uncovering potential mediators of the relationship between early life stress and psychopathology will be discussed.

A Hierarchical Approach for Modeling Psychopathology and Stress

The effort to search for neural correlates can be significantly improved by using a hierarchical approach to define psychopathology and early life stress. An increasing body of research suggests the utility of using a general psychopathology factor or p factor to define the hierarchical structure of mental health symptoms. The general psychopathology factor encompasses symptoms that are shared across all disorders and represents a general susceptibility to mental health issues (Caspi & Moffitt, 2018; Kotov et al., 2017; Lahey et al., 2017). Alongside the p factor, hierarchical models of psychopathology can also be employed to define specific dimensions that represent groups of symptoms that naturally cluster together, such as internalizing or externalizing symptoms. These dimensions capture the high co-occurrence of different disorders and are therefore valuable in identifying common neurobiological mechanisms that underlie various psychopathology symptoms as well as disorder-specific ones (Zald & Lahey, 2017).

A hierarchical approach can also provide insights into how environmental stressors naturally cluster together, identifying common and specific dimensions underlying different stressors. It is uncommon for one type of adversity to occur in isolation (Smith & Pollak, 2021). For instance, if a child observes domestic violence, there is an increased probability that they

will experience maltreatment (Euser et al., 2011). Moreover, over 95% of children who undergo one form of child maltreatment also encounter additional forms of maltreatment (Debowska et al., 2017; Euser et al., 2011). Given the high co-occurrence of early life stressors, researchers often use a cumulative-risk approach where a count variable of the number of early life stressors is created, representing a risk score (McLaughlin & Sheridan, 2016). However, there are several caveats to consider when using a cumulative-risk approach. One of the issues with the cumulative-risk approach is that it oversimplifies the distinction between different types of stressors by adding all stressful events into one composite variable. This approach assumes that all stressors have equal weights and can be additive, which does not consider the different intensities of stressors or the interaction between stressors (Evans et al., 2013). Based on the problems with the cumulative-risk approach, there is now a call for dimensional approaches. A dimensional approach assumes that there are core underlying dimensions across different types of adversities with shared features (McLaughlin et al., 2021). Hierarchical modeling allows us to capture the dimensional nature of environmental stressors. Thus, the purpose of this dissertation is to use a hierarchical approach to understand the associations between early life stress, neural correlates, and psychopathology symptoms in youth.

Part II: Uncovering the Longitudinal Relationships between Early Life Stress, Neural Correlates, and Psychopathology

Overview

To extend our understanding of the neural correlates linking early life stress and psychopathology, the current project used hierarchical modeling to examine the association between dimensions of early life stress and future psychopathology symptoms and identify brain regions that mediate the association between early life stress and psychopathology. The current

study utilized data from the Adolescent Brain Cognitive Development℠ Study (ABCD Study®), which is the largest longitudinal neuroimaging study in the United States following over 11,000 children from ages 9-10 years into young adulthood. Data up to the third-year follow-up are currently available. The dimensions of environmental stress were identified from different measures that include a variety of stressors at baseline. Measures of brain structure were obtained from the second-year follow-up. Lastly, psychopathology symptom measures were obtained from the third-year follow-up.

In Study 1, the longitudinal association between early life stress and psychopathology was examined to determine whether dimensions of environmental stress predict future psychopathology symptoms. Exploratory structural equation modeling (ESEM) and bifactor modeling were used to delineate hierarchical factors of environmental stressors and psychopathology. Structural equation modeling (SEM) was used to test associations between the environmental stress and psychopathology factors. In Study 2, regional brain structures at the second-year follow-up were examined as potential mediators of the relationship between early life stress at baseline and psychopathology at the third-year follow-up. The following methods apply to both Study 1 and Study 2 and the details of the statistical analyses are discussed for each study separately.

Methods

Participants

The current study uses ABCD Study data from release 5.1. The ABCD Study is a multi-site research collaboration that involves collecting data from a group of 11,868 children at 21 different locations throughout the United States. The data collection started when the participants were between 9 and 10 years of age and will continue as they grow into adulthood (Volkow et

al., 2018). The ABCD Study recruited participants by using probability sampling of schools within catchment areas in each study site. They considered factors such as age, sex, race/ethnicity, socioeconomic status (SES), and urbanicity (Volkow et al., 2018). These factors were determined based on target numbers derived from the American Community Survey and school enrollment data from the National Center for Education Statistics. Each site implemented the same unbiased recruitment process. While not perfectly representative of the U.S. population, the sample is fairly balanced between males and females and has racial/ethnic and income percentages that are similar to the U.S. census numbers. Table 1 shows the demographic characteristics of the ABCD Study sample.

Table 1. Summary of demographic characteristics of the ABCD study sample at baseline (N = 11,868)

	Mean	*SD*
Age (years)	9.91	0.62
	N	*%*
Sex		
Female	5,679	47.85
Male	6,187	52.13
Missing	2	0.02
Race-Ethnicity		
Non-Hispanic White	6,173	52.01
Hispanic	2,410	20.31
Black/African American	1,784	15.03
Other	1,499	12.63
Missing	2	0.02
Household Annual Income		
< $5,000	417	3.51
$5,000-$11,999	421	3.55
$12,000-$15,999	273	2.30
$16,000-$24,999	523	4.41
$25,000-$34,999	654	5.51
$35,000-$49,999	934	7.87
$50,000-$74,999	1,498	12.62
$75,000-$99,999	1,570	13.23

$100,000-$199,999	3,311	27.90
≥ $200,000	1,250	10.53
Missing	1,017	8.57
Parental Education		
No degree	786	6.62
Highschool degree/GED	1,260	10.62
Some college	1,946	16.40
Associate's degree	1,536	12.94
Bachelor's degree	3,331	28.07
Master's degree	2,278	19.19
Professional/Doctoral degree	714	6.02
Missing	17	0.14

Note. The Race-Ethnicity category "Other" includes children identified by their parent as American Indian/Native American, Alaska Native, Native Hawaiian, Guamanian, Samoan, Other Pacific Islander, Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, Other Asian, Multi-Racial or Other Race.

Inclusion/Exclusion Criteria

Participants who met the age criteria and attended a school within the specified catchment area were considered eligible for inclusion in the study (Garavan et al., 2018). Individuals who were not proficient in English, had a caregiver who was not proficient in English, had severe sensory, intellectual, medical, or neurological conditions that could affect the accuracy of the collected data or hinder their participation, or had contraindications to MRI scanning were excluded from the study (Garavan et al., 2018).

Dependencies in Families and Sites

The ABCD Study involves data that have known dependencies, such as multiple children from the same family (siblings and multiple births like twins or triplets). Furthermore, families are grouped within different sites which introduces the nesting or multilevel structure of the

dataset (Peugh, 2010). Nesting is accounted for in the statistical analyses, as described in each study's statistical analyses section.

Psychopathology Assessment

The Child Behavior Checklist (CBCL) was used to derive psychopathology factors. The CBCL is a questionnaire that caregivers complete to assess their child's behaviors and emotions. It consists of 113 items with additional items that assess multiple symptoms within a single prompt and uses a 3-point Likert scale to indicate the extent to which each item is true for the child (not true, somewhat/sometimes true, very/often true) (Achenbach & Edelbrock, 1991). A total of 119 symptom-level items were used for modeling. The CBCL has been found to have excellent reliability, including test-retest and inter-rater reliability. It also has adequate internal consistency and good construct validity, as it correlates well with other scales and with the DSM criteria (Achenbach, 2009).

Environmental Stressor Measures

We conducted a thorough review of the data from the ABCD Study to identify various variables related to stressors in the child's environment. These factors included abuse, neglect, resource availability, physical environment attributes such as population density and pollution, and interpersonal factors like the availability of supportive relationships. The following sections describe the specific measures included.

Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS). Traumatic events during a child's lifetime were measured using the posttraumatic stress disorder criteria A traumatic events checklist from the K-SADS (Kaufman et al., 1997). Primary caregivers indicated whether their child had experienced any of 17 traumatic events based on a binary response (1 = True, 0 = False). We further selected 17 items from the K-SADS Background

Items assessing the child's relationship with his/her caregiver, peer relationships, school performance, and placement in any special services.

Family Environment Scale – Family Conflict Subscale. Family conflict was assessed using the Family Conflict Subscale from the Moos Family Environment Scale (Moos & Moos, 1994), which was adapted from the PhenX toolkit (Zucker et al., 2018). Primary caregivers answered 9 questions about family conflict (e.g., "We fight a lot in our family"), using a binary response (1 = True, 0 = False). Four questions were reversed for scoring so that higher scores on the scale reflect greater conflict.

Demographics Survey – Family Experience. Stress related to financial problems was assessed through a demographics survey modified from the PhenX toolkit (Barch et al., 2018; Stover et al., 2010). Primary caregivers answered 7 questions about situations indicating financial difficulty in the past 12 months based on a binary response (1 = Yes, 0 = No). This survey also included data on the number of people living at the child's home.

Family History Assessment. Family history of mental health issues was assessed using questions modified from the Family History Assessment Module Screener (FHAM-S) (Rice et al., 1995). Primary caregivers were asked to report on the history of mental illness in blood relatives of the child including biological father, biological mother, paternal/maternal grandfather, paternal/maternal grandmother, paternal/maternal uncle, paternal/maternal aunt, younger/older full siblings, younger/older half sibling, or same age full sibling. The response was based on a binary response (1 = Yes, 0 = No). When they responded "Yes," follow up questions asked whether relatives have experienced any of the following: a history of receiving psychiatric services or hospitalization, attempted or completed suicide, depression, mania, psychosis, nervous breakdowns, antisocial behaviors, and/or problems related to alcohol or drug use.

Child's Report of Parent Behavior Inventory (CRPBI) – short form. Youths completed questionnaires on perceptions of their caregiver's warmth, acceptance, and responsiveness based on 5 items that were shortened from the original 10 items from the Child's Report of Parent Behavior Inventory (Schaefer, 1965; Zucker et al., 2018). The items described the primary caregiver's behavior as warm or supportive, and the youth responded on a three-point Likert scale (1= Not like him/her, 2 = Somewhat like him/her, 3 = A lot like him/her).

School Risk and Protective Factors Survey. The school social environment section from the PhenX Toolkit was used to measure the child's perceived connectedness to his or her school and teachers (Zucker et al., 2018). Items assessed the youth's interactions with teachers (e.g., "I get along with my teachers"), perceptions of the classroom environment (e.g., "I feel safe at my school"), involvement in school (e.g., "I like school because I do well in class"), and feelings of alienation from academic goals (e.g., "Usually, school bores me"). Items were assessed based on a four-point Likert scale (1 = NO! (it is definitely not true), 2 = no (it is mostly not true), 3 = yes (it is mostly true), 4 = YES! (it is definitely true)).

Peer Relationships. Peer relationships were measured based on the child's response on the number of friends they have, separately for boys and girls.

Neighborhood Safety/Crime Survey. Perceptions of neighborhood safety were assessed using items from the PhenX Toolkit (Echeverria et al., 2004; Mujahid et al., 2007; Zucker et al., 2018). Caregivers responded to their perceptions of safety and the presence of crime in their neighborhoods using 3 items (e.g., "My neighborhood is safe from crime"), based on a five-point Likert scale (1 = "Strongly Disagree," 2 = "Disagree," 3 = "Neutral," 4 = "Agree," 5 = "Strongly Agree"). Additionally, youths responded to one item on their perception of the crime in their neighborhoods ("My neighborhood is safe from crime").

Community Risk and Protective Factors. The availability of substances in the community was assessed using 9 items from the PhenX Community Risk and Protective Factors questionnaire (Lisdahl et al., 2018), which is based on the Monitoring the Future Study (Arthur et al., 2007). Caregivers responded to items asking about the ease with which their child could access substances including alcohol, cigarettes, marijuana, and other drugs. Items were rated on a four-point Likert scale (0 = Very hard, 1 = Sort of hard, 2 = Sort of easy, 3 = Very easy).

Parental Monitoring. Parental monitoring, which refers to the caregiver's efforts to keep track of their child's whereabouts, was assessed using a subset of items from the Parental Monitoring questionnaire (Chilcoat & Anthony, 1996; Zucker et al., 2018). The child reported on 5 items assessing parental monitoring of their location, whom they spend time with, whether they know how to get in touch with their parents, whether they tell their parents their plans, and family dinner frequency based on a five-point Likert scale (1 = Never, 2 = Almost never, 3 = Sometimes, 4 = Often, 5 = Always or almost always).

Residential History Derived Scores

Data on participants' residential environments were obtained by accessing the digital archives of the federal government or other publicly available data repositories using the geocodes of their addresses. The ABCD Study data repository contains information about both the current and past addresses of the participants. For the current study, we used data from participants' current addresses. If participants had multiple current addresses, we averaged the data across them. Each metric derived from residential history is described below.

Years of residence. The number of years that participants have lived at their current address was assessed.

Elevation. The level of elevation was retrieved from Google Maps. Elevation is linked to increased exposure to air pollution because of the greater inhalation of carbon monoxide that occurs at lower oxygen levels (EPA, 1978).

Walkability. Walkability index scores were obtained from the Environmental Protection Agency (EPA; https://www.epa.gov/smartgrowth/smart-location-mapping#walkability). The walkability index scores indicate the ranking of each block compared to all other blocks in the United States. Walkability scores are influenced by factors such as the presence of sidewalks, the quality of sidewalks, pedestrian right-of-way, traffic volume, road conditions, building accessibility, etc. The resolution was at the census tract level.

Crime rate. The Inter-University Consortium for Political and Social Research compiled the uniform crime reports obtained from the Federal Bureau of Investigation. The grand total variable from the ABCD Study repository comprises the total count of arrests for Part I offenses (i.e., murder, rape, robbery, aggravated assault, burglary, larceny, auto theft, and arson) and Part II offenses (i.e., forgery, fraud, embezzlement, vandalism, weapon violations, sex offenses, drug and alcohol abuse violations, gambling, vagrancy, curfew violations, and runaways), based on three-year average estimates from 2010 to 2012. The resolution was based on the county level.

Area Deprivation Index. The Area Deprivation Index (ADI) was derived using the Singh method (Kind et al., 2014; Singh, 2003) based on data from the American Community Survey between 2011 to 2015. The ADI consists of 17 sub-scores and 1 national percentile score. These sub-scores range from 1 to 100, with the 100th percentile indicating the highest level of deprivation. The 17 sub-scores included in the ADI are as follows: the percentage of the population aged 25 years or older with less than 9 years of education; the percentage of the population aged 25 years or older with at least a high school diploma; the percentage of

employed persons aged 16 years or older in white collar occupations; the median family income; income disparity defined by the log of 100 times the ratio of the number of households with less than $10,000 annual income to the number of households with $50,000 or more annual income; the median home value; the median gross rent; the median monthly mortgage; the percentage of owner-occupied housing units (home ownership rate); the percentage of households with more than 1 person per room (crowding); the percentage of the civilian labor force population aged 16 years or older who are unemployed (unemployment rate); the percentage of the population below 138% of the poverty threshold; the percentage of single-parent households with children younger than 18 years; the percentage of households without a motor vehicle; the percentage of households without a telephone; the percentage of occupied housing units without complete plumbing; and the percentage of families below the poverty level.

Population density. Population density is calculated by dividing the number of people by the unit of area. The population density data was obtained from the National Aeronautics and Space Administration (NASA) Socioeconomic Data and Application Center (SEDAC). This was based on the 2010 census tract.

Pollution measures. Pollution levels based on particulate matter (PM 2.5) and nitrogen dioxide (NO2) levels were measured by satellite with a resolution at 100 km^2. The values represent three-year average estimates from 2010 to 2013. Pollution measures were obtained from NASA SEDAC. One-year average daily estimates of PM 2.5 in 2016 were available at a higher resolution (i.e., 1 km^2). These estimates were obtained from a study conducted by Di et al. (Di et al., 2016). The higher resolution measure was available for participants' current primary, secondary, and tertiary addresses. If the participant reported multiple current addresses, the average across current addresses was used.

Estimated risk of lead exposure. The risk of lead exposure was estimated by calculating a weighted sum of the age of homes and the poverty rate (https://www.vox.com/a/lead-exposure-risk-map). The scores ranged from 1 to 10, with a score of 10 representing the highest level of risk. The resolution was at the census tract level. The scores were available for participants' current primary, secondary, and tertiary addresses. The average across multiple addresses was used.

Proximity to main roads. The geospatial coordinates of the main roads were obtained from the North American Atlas as of July 2012. The shortest distance between a main road and the participant's address was obtained (Fan et al., 2021).

Hierarchical Modeling of Psychopathology

Psychopathology factors were derived in a prior published study using the baseline CBCL items from the ABCD Study (Moore et al., 2020). As reported in detail in Moore et al., the ABCD Study data was split into two samples for an ESEM to identify which items cluster together and a confirmatory bifactor analysis to define a general factor and specific factors. ESEM integrates aspects of exploratory factor analysis and SEM to delineate underlying factors (Marsh et al., 2014). Items were removed before modeling if they did not reflect symptoms of psychopathology (e.g., constipation), were less age-appropriate in 9 to 10-year-olds (e.g., substance use items), showed a lack of sufficient endorsement (too few ratings above 0), or were redundant with other items, in which case a composite was created. An ESEM analysis in one split half of the sample identified three factors of psychopathology: internalizing problems, conduct problems, and attention-deficit/hyperactivity disorder (ADHD) symptoms. In the second half of the data, a confirmatory bifactor analysis modeled the internalizing, conduct problems, and ADHD, plus a general psychopathology factor which represents the psychopathology

symptoms shared across all participants. Each CBCL item loaded onto the general psychopathology factor, as well as one of the three specific factors; all factors were orthogonal (uncorrelated) to each other. The schematic representation of the general psychopathology factor and specific factors derived from bifactor modeling using CBCL items is illustrated in Figure 1a. The results of model fitting as well as the validity and reliability of the psychopathology dimensions in the ABCD Study sample have been published elsewhere (Moore et al., 2020).

Hierarchical Modeling of Environmental Stressors

Items related to environmental stressors from the ABCD Study were included for an ESEM. Item selection was based on Urie Bronfenbrenner's ecological systems theory (Bronfenbrenner, 1979). Bronfenbrenner posited that child development occurs within a complex, multi-level system of influences that span from the immediate family/school environments to the broadest influences of cultural values, customs, and laws. As our starting point, we canvassed the ABCD Study data for any variables that may impact the child's environment at any of these levels. We eliminated measures that were administered to a subset of participants. Next, we went through a process of item selection to remove low-endorsed or redundant items. When items had high correlations with each other ($r > .90$) suggesting the items were redundant, the items were either combined or only one item was retained if it did not make conceptual sense to combine them. The ESEM was performed with 9,000 randomly selected participants to determine whether there exist latent factors underlying the environmental stressors. 1,555 participants were excluded for missing non-participation weights, leaving 7,445 participants for the ESEM analysis. The ESEM with over 100 environmental stressors revealed four factors. For the specific items that loaded onto factors 1-4 and their loading estimates, see Table S1 in the Appendix.

Briefly, the "family dynamics" factor consisted of items related to the dynamics of a child's family environment such as a history of mental illness in the family, traumatic events experienced by the child, the presence of conflict within the family, and financial difficulty experienced by the immediate family. The "interpersonal support" factor consisted of items reflecting the support a child receives at home and school, such as the child's perception of his or her connectedness to school and teachers, the primary caregiver's warmth, and parental involvement in monitoring the child. The "neighborhood SES deprivation" factor was made up of items reflecting the availability of resources in a child's neighborhood such as median rent and home value, the percentage of families living below or close to the poverty level, income disparity, median family income, and the percentage of the population with at least a high school diploma. Finally, the "urbanicity" factor was made up of variables related to the quality of a child's physical environment which closely mapped onto urban living. Items included population density, perceptions of neighborhood safety, pollution levels, lead exposure risk, and walkability.

A confirmatory bifactor analysis with 2,878 hold-out participants was performed to model the four factors identified from the ESEM results, plus a general factor that captures the variance common across all the environmental stressors. If a variable loaded onto more than one factor with a loading ≥ 0.40, then the variable was assigned to the factor with the higher loading. Each item loaded onto one general factor and one specific factor. All factors were specified to be orthogonal (uncorrelated). The schematic representation of the general environmental stress factor and specific factors derived from bifactor modeling using environmental stressor measures is illustrated in Figure 1b. Results of the bifactor model are presented in Table S2 in the Appendix and the results of fitting of the model are presented in Table S3 in the Appendix.

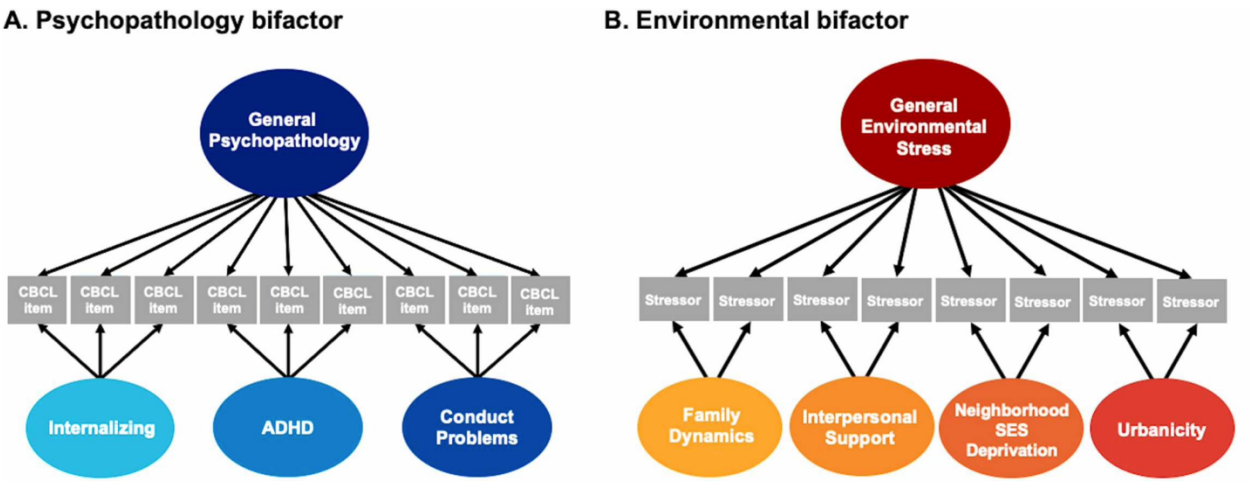

Figure 1. Schematics of the bifactor modeling used to delineate psychopathology and environmental stress factors. A) A confirmatory bifactor model of the Child Behavioral Checklist (CBCL) data yielded four orthogonal factors of psychopathology: general psychopathology, which represents symptoms across all domains, as well as specific factors for internalizing symptoms, attention-deficit/hyperactivity disorder (ADHD) symptoms, and conduct problems. B) A confirmatory bifactor model identified a general environmental stress factor, representing commonalities across all stressors, as well as four specific factors: family dynamics, interpersonal support, neighborhood socioeconomic status (SES) deprivation, and urbanicity. All factors in a bifactor model are uncorrelated with each other.

Statistical Analyses: Methods Common Across Studies

All analyses were performed using SEM in Mplus version 8.10. Full information maximum likelihood (FIML) estimation was used with all available information to handle missing data and estimate parameters (Cham et al., 2017). As mentioned before, the ABCD Study data includes two known dependencies (i.e., families and sites) that introduce complex survey data structure (also known as multilevel or hierarchical data) which must be accounted for

in analyses. Mplus provides two approaches to analyze complex survey data: 1) computing standard errors and a chi-square test of model fit taking into account stratification and non-independence of observations due to cluster sampling via STRATIFICATION and CLUSTRING commands and 2) specifying a model for each level, which is also known as multilevel modeling (Muthén, & Muthén, 2017). For our main analyses in Study 1 and Study 2, the stratification and clustering commands provided by Mplus were used to account for the non-independence of observations. Multilevel modeling was further incorporated in Study 2 to observe the mediating effect of neural correlates separately for each level of individual, family, and site. The code and a corresponding wiki for the analytic procedures can be found in https://github.com/VU-BRAINS-lab/Jeong_stressor_mediation.

Study 1

Study 1 aimed to examine the association between environmental stressors and psychopathology symptoms obtained from bifactor modeling at the third-year follow-up. It was hypothesized that a greater level of overall environmental stress represented by the general environmental stress factor would predict greater psychopathology symptoms represented by the general factor of psychopathology at the third-year follow-up as well as predicting greater symptoms in the specific dimensions of internalizing, ADHD, and conduct problems. It was also hypothesized that family dynamics, neighborhood SES deprivation, and urbanicity would predict greater psychopathology symptoms, whereas interpersonal support will predict lower psychopathology symptoms at the third-year follow-up.

Statistical Analyses

SEM was used with environmental stressors at baseline predicting psychopathology factors at the third-year follow-up. As described earlier, latent variables of environmental

stressors and psychopathology symptoms were obtained using bifactor modeling. All factors defined within bifactor modeling for environmental stress and psychopathology were specified to be uncorrelated with each other. Due to the orthogonal nature of the factors, the environmental and psychopathology dimensions were included in the same model without introducing multicollinearity problems. See Code Listing 1 in the Appendix. The same analysis was conducted with the CBCL total score at baseline included as a covariate in the model to investigate whether the obtained relationship between environmental stressors and psychopathology remains after controlling for baseline psychopathology symptoms.

Results

The statistical results of the main analyses are summarized in Table 2. There was no significant association between the general environmental stress factor at baseline and the general psychopathology factor at the third-year follow-up ($p = .875$). Greater scores on the general environmental stress factor at baseline predicted greater conduct problems and ADHD symptoms (p-values $< .001$) and lower internalizing symptoms at the third-year follow-up ($p < .001$). Greater family dynamics at baseline predicted greater psychopathology symptoms in all domains at the third-year follow-up (p-values $< .001$). Greater interpersonal support at baseline predicted lower general psychopathology, conduct problems, and ADHD symptoms at the third-year follow-up (p-values $< .001$), but also predicted greater internalizing symptoms at the third-year follow-up ($p < .001$). Greater neighborhood SES deprivation at baseline predicted greater conduct problems at the third-year follow-up ($p < .001$) but did not have an association with other psychopathology domains. Lastly, greater urbanicity at baseline predicted greater internalizing symptoms ($p = .017$) and lower ADHD symptoms at the third-year follow-up ($p = .017$).

The results of the statistical analyses when controlling for baseline CBCL total score are summarized in Table 3. When controlling for baseline psychopathology scores, greater general environmental stress predicted lower general psychopathology and lower internalizing symptoms (p-values $< .001$) and greater conduct problems and ADHD symptoms at the third-year follow-up (p-values $< .001$). Family dynamics at baseline predicted greater general psychopathology, internalizing symptoms, and conduct problems at the third-year follow-up (p-values $\leq .007$) but did not predict ADHD symptoms ($p = .604$). Greater interpersonal support at baseline predicted lower levels of general psychopathology, conduct problems, and ADHD symptoms (p-values $\leq .005$) but greater internalizing symptoms at the third-year follow-up ($p < .001$). Greater neighborhood SES deprivation at baseline predicted lower general psychopathology symptoms ($p = .001$) and greater levels of conduct problems ($p = .003$) at the third-year follow-up. Lastly, greater urbanicity at baseline predicted greater internalizing symptoms ($p = .018$) and lower ADHD symptoms at the third-year follow-up ($p = .014$).

Table 2. Association between stressors at baseline and psychopathology symptoms at the third-year follow-up.

	General Environmental Stress			Family Dynamics			Interpersonal Support			Neighborhood SES Deprivation			Urbanicity		
	β	p	R^2	β	p	R^2	β	p	R^2	β	p	R^2	β	p	R^2
General Psychopathology	0.002	.875	.000	0.279	.000	.078	-0.099	.000	.010	-0.004	.679	.000	-0.006	.577	.000
Internalizing	-0.090	.000	.008	0.109	.000	.012	0.046	.000	.002	-0.016	.114	.000	0.025	.017	.001
Conduct Problems	0.083	.000	.007	0.093	.000	.009	-0.053	.000	.003	0.040	.000	.002	-0.013	.223	.000
ADHD	0.050	.000	.003	0.050	.000	.003	-0.089	.000	.008	0.014	.190	.000	-0.025	.017	.001

All statistical values reported are standardized.

Table 3. Association between stressors at baseline and psychopathology symptoms at the third-year follow-up controlling for baseline psychopathology (i.e., total CBCL scores)

	General Environmental Stress			Family Dynamics			Interpersonal Support			Neighborhood SES Deprivation			Urbanicity		
	β	p	R^2	β	p	R^2	β	p	R^2	β	p	R^2	β	p	R^2
General Psychopathology	-0.056	.000	.003	0.097	.000	.009	-0.030	.000	.001	-0.030	.001	.001	-0.009	.288	.000
Internalizing	-0.099	.000	.010	0.081	.000	.007	0.057	.000	.003	-0.020	.050	.000	0.025	.018	.001
Conduct Problems	0.062	.000	.004	0.029	.007	.001	-0.029	.005	.001	0.032	.003	.001	-0.014	.175	.000
ADHD	0.035	.000	.001	-0.006	.604	.000	-0.071	.000	.005	0.007	.496	.000	-0.026	.014	.001

All statistical values reported are standardized.

Discussion

As expected, significant associations were found between environmental stressors at baseline and psychopathology symptoms at the third-year follow-up. The general factor of environmental stress was associated with greater conduct problems and ADHD problems but was not associated with general psychopathology symptoms and predicted lower internalizing symptoms. Furthermore, the general environmental stress factor was associated with lower internalizing symptoms and general psychopathology symptoms, after controlling for baseline psychopathology symptoms. Family dynamics predicted psychopathology symptoms to the greatest extent compared to the other stressors, suggesting that the immediate family environment may be especially important for children's mental health. Neighborhood SES deprivation was specifically associated with greater externalizing symptoms (i.e., conduct problems). Greater interpersonal support was associated with lower general psychopathology, conduct problems, and ADHD symptoms, whereas it predicted greater internalizing symptoms. Lastly, the urbanicity factor had divergent effects, predicting greater internalizing symptoms and lower ADHD symptoms, respectively.

Contrary to our hypothesis, there was no association between the general environmental stress factor and psychopathology symptoms. These results could have several explanations. First, combining divergent types of stressors together that have opposite effects on overall psychopathology may obscure associations with general psychopathology. As our results illustrate, specific dimensions such as family environment, neighborhood environment, and the quality of interpersonal interactions have unique explanatory effects that should be considered individually. It is also possible that, when measured prospectively (relying on parent informants as the child grows up), stressors may not be as strongly associated with general psychopathology.

In alignment, a recent meta-analysis found that a retrospective measure of childhood maltreatment (which captures the first-person account based on the individual's memory and subjective interpretation) predicted psychopathology to a much greater degree than prospective measures that reflect third-person accounts (Baldwin et al., 2024). Specifically, the odds ratio of prospective measures predicting psychopathology was small (OR = 1.56) which decreased further (OR = 1.27) when accounting for retrospective measures (Baldwin et al., 2024). On the other hand, the odds ratio of retrospective measures predicting psychopathology was moderate (OR = 2.21) and did not differ substantially when accounting for prospective measures (OR = 2.14) (Baldwin et al., 2024). This finding suggests that psychopathology associated with early life stress may be driven more by subjective interpretations of experiences which could be targets for cognitive interventions. Similarly, the subjective perception of an event as traumatic, rather than trauma exposure per se, was more predictive of psychopathological outcomes in individuals with post-traumatic stress symptoms (Larsen & Pacella, 2016) and obsessive-compulsive disorder (Pinciotti & Fisher, 2022).

Unexpectedly, the results of the current study found a negative association between the general environmental stress factor and the general psychopathology factor such that greater levels of general environmental stress at baseline predicted lower general psychopathology symptoms at the third-year follow-up when baseline total CBCL scores were controlled. This may be explained by the concept of hormesis which has been used to describe the salubrious or strengthening effect of environmentally induced stress on organisms in toxicology and biomedical fields (Calabrese & Baldwin, 2002) (Mattson, 2008). More specifically, hormesis describes a biphasic response by an organism in response to environmental stress such that a low-to-moderate level of stress induces positive adaptation in an organism up to a certain

threshold; once that threshold has passed, environmental stress loses its beneficial effect and becomes deleterious (Oshri, 2023). Adopting the concept of hormesis in describing the psychobiological response to stressors, Oshri (2023) contends that psychosocial stress may strengthen an adaptive response system that prepares or conditions an individual for future threats. Furthermore, Oshri et al. (2024) demonstrated that whereas early life adversity had a linear relationship with psychopathology symptoms (i.e., greater adversity, greater internalizing and externalizing symptoms), non-linear modeling showed that low-to-moderate levels of early life adversity were associated with fewer psychopathology symptoms. The results of the present study support the theory that low levels of adversity in this primarily community-based sample may have a protective effect against developing psychopathology, when baseline psychopathology levels are taken into account.

Greater scores on family dynamics were associated with greater psychopathology symptoms in all domains, although the association with ADHD disappeared when controlling for baseline psychopathology. The family dynamics factor is made up of items reflecting familial factors (e.g., history of mental illness of family, financial difficulty, and presence of conflict within the family) that have well-established associations with the child's mental health such as genetics (Carey & Dilalla, 1994; Rende & Plomin, 1993.; Smoller et al., 2019; Tackett et al., 2013), shared stressful life events among family members (Repetti et al., 2002), and interactions between genetics and stressful life events (Caspi & Moffitt, 2006; Rutter & Silberg, 2002). Furthermore, parenting can shape children's behavioral and emotional regulation through observational learning, modeling, and social referencing (Morris et al., 2007). It should be also noted that the items that loaded onto family dynamics as well as the CBCL items used to create psychopathology factors were based on the primary caregiver's report. In other words,

problematic behaviors in children reported by parents could have been substantially influenced by the primary caregiver's negative perception, interpretation, and distress related to their life stressors, leading to bias (Chilcoat & Breslau, 1997; Treutler & Epkins, 2003). To correctly identify a target for intervention (i.e., whether intervention should be targeted for the child's behaviors or the primary caregiver's interpretation), it would be critical to segregate parental subjective views from the child's cognitive, emotional, and behavioral problems.

Additionally, the results of Study 1 found that neighborhood SES deprivation predicted greater conduct problems while no other associations with other dimensions of psychopathology were found. Associations between neighborhood environment and externalizing symptoms have been reported in previous studies, whereas the effect of neighborhood environment on internalizing symptoms has been more variable (Visser et al., 2021; White et al., 2021). In a study using the ABCD Study, Beyer et al. (2024) found that neighborhood deprivation indices were related to externalizing symptoms but not internalizing symptoms. One hypothesis underlying such a specific association is that youths may develop externalizing behaviors as a protective and defensive response to a surrounding environment that is unstable, risky, and threatening. Albert Bandura in his social cognitive theory (1986) also suggested that deprived neighborhoods characterized by violence, vandalism, gangs, and drugs may provide models for aggressive problem-solving techniques in that children engage in aggressive behaviors as a means of problem-solving. In support, Galán et al. (2017) found that aggressive response generation (which indicates a tendency to generate aggressive behaviors to ambiguous social cues) mediated the relationship between neighborhood deprivation and conduct problems. The same group also found that family check-ups (which is an intervention providing parents with tools to manage children's behaviors and build positive relationships) decreased children's

aggressive behaviors (Shaw et al., 2016). Furthermore, they observed that the intervention was especially effective in the most deprived neighborhoods (Shaw et al., 2016).

Consistent with prior findings, Study 1 also showed that greater interpersonal support was associated with less general psychopathology, fewer conduct problems, and fewer ADHD symptoms, which supports the beneficial effect of parental involvement in protecting against psychopathology symptoms in youths. On the contrary, the results of the current study also showed that greater interpersonal support predicted greater internalizing symptoms, even after controlling for baseline psychopathology. Theoretical models suggest that overprotection by parents may contribute to anxiety in children through conveying the notion that the world is a dangerous place; this in turn maintains the child's anxious behaviors through overreacting to the child's anxiety (Chorpita & Barlow, 1998; Rapee, 2002). However, Gere et al. (2012) demonstrated that parental overprotection not only predicts child anxiety symptoms but other co-occurring symptoms as well, as the association between parental overprotection and child anxiety disappeared when controlling for other co-occurring symptoms. Similarly, a meta-analysis by de Roo et al. (2022) found that parental overprotection is associated with both internalizing and externalizing symptoms. In contrast, our findings showed that interpersonal support is specifically related to greater internalizing symptoms and lower psychopathology symptoms in other dimensions. It should be also noted that the items that loaded onto interpersonal support did not have explicit items measuring overprotective behaviors by parents, except for parental monitoring. Furthermore, the interpersonal support factor was made up of many items reflecting the child's perceived connectivity to and support from his or her school. In this regard, more subtle aspects of the interpersonal support factor may be related to internalizing

problems. The mechanism by which interpersonal support relates to greater internalizing symptoms is a subject for further exploration.

Lastly, the results of Study 1 showed divergent effects of urban environments on psychopathology symptoms in children; the urbanicity factor was associated with greater internalizing symptoms and lower ADHD symptoms. Throughout our previous studies (Jeong et al., 2023, 2024), we have found divergent associations between urbanicity and variables of interest. For instance, unlike other dimensions of environmental stressors which were associated with smaller regional volumes and thinner regional cortices, the urbanicity factor was associated with greater regional volumes and thicker regional cortices (Jeong et al., 2023). In another study where we looked at the associations with the brain's functional network topology (Jeong et al., 2024), urbanicity was associated with lower whole-brain modularity (indicating less segregation and specialization of functional networks) and lower local efficiency in the motor network at rest. On the other hand, urbanicity was associated with a shorter diameter in the frontoparietal network, indicating efficient processing, during a stop signal task which assesses inhibition. Consistently, the urbanicity factor was associated with better performance throughout all tasks measured including the stop signal task. In relation to mental health, there is a robust link between urbanicity and psychosis with its impact more pronounced at birth and during childhood, implying that exposure to urban environments in early life poses a greater risk for developing mental health symptoms (Krabbendam et al., 2021). Also, studies report the adverse impact of urban environments on other behavioral and emotional symptoms in youths beyond psychosis even after controlling for other associated risk factors such as family and neighborhood SES and parental symptoms of psychopathology (Evans et al., 2018; Newbury et al., 2016). Conversely, some studies found lower rates of depression associated with urban living

(De Mola et al., 2012; Petrican et al., 2021; Stier et al., 2021) and Stier et al. (2021) found that an increase in social networks mediated the association between urbanicity and lower depression. As there are various aspects related to urban living, our urbanicity factor is also comprised of heterogeneous items. The mechanism by which urbanicity leads to lower ADHD symptoms and greater internalizing symptoms may be related to the complex interaction of both positive and negative aspects of urban living.

In summary, the results of Study 1 reveal significant associations between baseline environmental stressors and future psychopathology symptoms. The general environmental stress factor, which reflects the common variance across all stressor items used in the analysis, was associated with greater conduct problems and ADHD symptoms, whereas it was associated with lower general psychopathology and internalizing symptoms. Study 1 also found that family environment was associated with greater psychopathology symptoms in all domains. Additionally, neighborhood deprivation may serve as a risk factor specific to conduct problems. In contrast, while interpersonal support was associated with greater internalizing symptoms, interpersonal factors may protect against the development of other psychopathological problems. Lastly, the urbanicity factor showed divergent patterns, predicting lower ADHD symptoms and greater internalizing symptoms.

Study 2

Study 2 examined whether brain structures mediate the relationship between environmental stressors and psychopathology longitudinally. A schematic representation of the mediation model tested is illustrated in Figure 2. The environmental stressors at baseline served as the independent variable (X), brain measures at the second-year follow-up served as the mediator (M), and psychopathology scores at the third-year follow-up served as the dependent

variable (Y). Study 1 examined the relationship between environmental stress dimensions at baseline and psychopathology dimensions at the third-year follow-up (pathway *c* in Figure 2). As noted previously, Study 1 showed no significant association between the general environmental stress and general psychopathology factors. Therefore, to ensure a *c* path for the mediation analyses, we relied on observed psychopathology scores (CBCL total score) which were positively associated with the general environmental stress, for methodological and theoretical simplicity. The main analyses were conducted with the general environmental stress factor serving as X, total CBCL score as Y, and regional volume as M to identify which brain regions are implicated in the pathway between environmental stress and greater psychopathology symptoms. Since brain volume is a composite of cortical thickness and surface area, additional analyses with regional cortical thickness and surface area were also examined.

The mediation analyses examined the effect of general environmental stress at baseline on each brain measure at the second-year follow-up (M regressed on X; pathway *a* in Figure 2) and the effect of each brain measure at the second-year follow-up and general environmental stress at baseline on total CBCL scores at the third-year follow-up (Y regressed on M and X; pathway *b* and pathway *c*' in Figure 2). The significance of the mediating path was determined by the indirect effect ($a \times b$). As in Study 1, stratification and non-independence of observation were taken into account by using the CLUSTERING and STRATIFICATION commands in Mplus. Furthermore, multilevel structural equation modeling was used to test for mediation effects at the individual level, family level, and site level, separately (Preacher et al., 2010).

Based on our review of previous studies, it was hypothesized that the hippocampus, amygdala, anterior cingulate cortex, medial orbitofrontal cortex (i.e., vmPFC), pars opercularis and pars triangularis (together comprising the inferior frontal gyrus), and parahippocampal gyrus

may mediate the relationship between the general environmental stress factor and total CBCL score. However, due to the different age ranges and sample sizes found in previous studies, whole-brain analyses were also conducted to explore other brain regions that may play a mediating role.

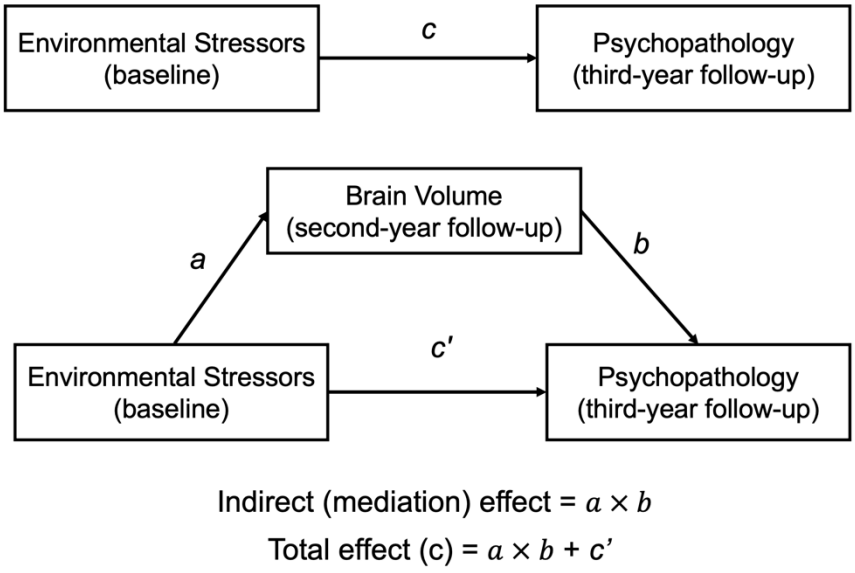

Figure 2. Schematic representation of the mediation model tested in Study 2

Mediation analyses were run with regional cortical volume, thickness, surface area, and subcortical volume. In addition, sensitivity analyses with total CBCL score at baseline added as an additional covariate were conducted to control for baseline levels of psychopathology. Additionally, change scores were computed and used for analyses for each regional volume (regional volume at baseline – regional volume at the second-year follow-up) to capture structural changes over time. Lastly, sex differences were examined in regions that were found to play significant mediating role in the main analyses, as early life adversities may have different impacts on males and females due to their neurodevelopmental differences (Bath, 2020).

Image Acquisition, Processing, and Quality Assurance

Imaging data were collected across 21 data collection sites following an imaging protocol developed by the ABCD Data Analysis and Informatics Center (DAIC) and the ABCD Imaging Acquisition Workgroup to harmonize collection across multiple 3 tesla (3T) scanner platforms (Siemens Prisma, General Electric (GE) 750, and Phillips) (Casey et al., 2018). 3D T1-weighted images of whole brain structure were acquired with the following parameters: TR (repetition time) 2400 to 2500 ms; TE (echo time) 2 to 2.9 ms; FOV (field of view) 256 × 240 to 256; FOV phase of 93.75% to 100%; matrix 256 × 256; 176 to 225 slices; TI (inversion delay) 1060 ms; flip angle of 8°; voxel resolution of 1×1×1×mm; total acquisition time was 7 minutes and 12 seconds for Siemens Prisma, 6 minutes and 9 seconds for GE 750, and 5 minutes and 38 seconds for Phillips.

To perform centralized processing and analysis by DAIC, the Multi-Modal Processing Stream was used for imaging data processing and analysis. Preprocessing included correction for gradient nonlinearity distortions, intensity scaling and homogeneity correction, registration to an averaged reference brain in standard space, and manual quality control (QC). Following the preprocessing, cortical surface reconstruction and subcortical segmentation were performed through automated and atlas-based segmentation procedures in FreeSurfer v.5.3. Cortical volume, thickness, and surface area in each cortical parcel of the standard FresSurfer Desikan-Killiany parcellation scheme (Desikan et al., 2006) and the average volume in each subcortical region (Fischl et al., 2002) were calculated. Lastly, post-processing QC was performed by trained technicians for motion, intensity homogeneity, white matter underestimation, pial overestimation, and magnetic susceptibility artifact. Subjects were excluded for substantial artifacts in the image that prevent radiological read, abnormal MRI findings (scores of 3 =

consider clinical referral or 4 = consider immediate clinical referral), and/or problems with motion, intensity inhomogeneity, white matter underestimation, or pial overestimation (scores of 2 = moderate problems or 3 = severe problems).

Statistical Analyses

Mediation analyses with structural equation modeling (Gunzler et al., 2013) were conducted to identify aspects of brain regions that mediate the relationship between the general environmental stress factor at baseline and total CBCL scores at the third-year follow-up. Latent variables of environmental stress and psychopathology symptoms were obtained via bifactor modeling in the same manner as described in Study 1. Potential mediators included cortical volume, thickness and surface area for each region defined from the Desikan atlas (68 regions for each measure) and for each regional subcortical volume (19 regions). Significant mediation was determined by the significance of the indirect path ($a \times b$). Two separate statistical approaches were used to address dependencies of the sample (i.e., multilevel structure of the dataset).

Mediation Analysis Using Cluster-Robust Standard Errors. Mediation analyses were performed with cluster-robust standard errors using the complex data analysis (TYPE=COMPLEX) in Mplus. Stratification by site and cluster by family were defined using STRATIFICATION and CLUSTER commands to account for the multi-level structure of the dataset in computing standard errors. Maximum likelihood estimation with robust standard errors (MLR) was used to estimate parameters which is robust to non-normality and non-independence of observations when used with complex data analysis in Mplus (https://users.ugent.be/~yrosseel/lavaan/utrecht2010.pdf). Bias-corrected bootstrapping with a resampling of 1000 was implemented to estimate the confidence intervals of the effects. See

Code Listing 2 in the Appendix for an example of the mediation analysis using cluster-robust standard errors.

Multilevel Mediation Analysis. In addition, multilevel mediation analysis was run with regional volume as a mediator in Mplus. Three-level random intercept model (TYPE=THREELEVEL RANDOM) was used and clusters (i.e., family and site) were defined using the CLUSTER command. Bayesian estimation was used to calculate credible intervals which are analogous to confidence intervals. For modeling, *a* path assessing the effect of the general environmental stress factor on brain volume, *b* path assessing the effect of brain volume on total CBCL score, and *c'* path assessing the effect of general environmental stress and volume on total CBCL score were calculated for the individual level (level 1), family level (level 2), and site level (level 3). Indirect effects ($a \times b$) were estimated for levels 1-3. See Code Listing 3 in the Appendix for an example of the multilevel mediation analysis.

Sensitivity Analyses

For sensitivity analyses, we ran the main mediation analyses with regional volume 1) controlling for baseline psychopathology and 2) using regional volume change scores (i.e., regional volume at baseline minus regional volume at the second-year follow-up).

Sex Difference

Sex differences were examined in regional volumes found to play a significant mediating role between the general environmental stress factor and total CBCL scores from the main analyses. The Wald test was used to determine whether the mediating effect obtained from the main analyses was significantly different by sex.

Results

Main Analysis. Taking into account clustering of families and stratification of sites, the results of Study 2 showed significant indirect effects between the general environmental stress factor and total CBCL score through reduced volumes in the following regions: bilateral posterior cingulate, bilateral caudate, bilateral accumbens area, left inferior parietal, left paracentral, left postcentral, left rostral middle frontal, left superior frontal, left temporal pole, right caudal anterior cingulate, right precentral, right supramarginal, left hippocampus, and right putamen (Figure 3; see Table 4 for statistics). Specifically, greater general environmental stress predicted smaller regional volumes (*a*) in these regions, and lower regional volumes in these regions predicted greater total CBCL scores (*b*). The significant mediating effects (*ab*) imply that the association between the general environmental stress factor and total CBCL scores is partially explained through the smaller volumes in these regions.

When looking at two independent components of cortical volume (cortical thickness and surface area), cortical thickness in the left paracentral, left precentral, left superior frontal, and right postcentral mediated the relationship between the general environmental stress factor and total CBCL score (see Table 5 for statistics). Additionally, surface area in the bilateral posterior cingulate and right caudal anterior cingulate mediated the relationship between the general environmental stress factor and total CBCL score (see Table 6 for statistics).

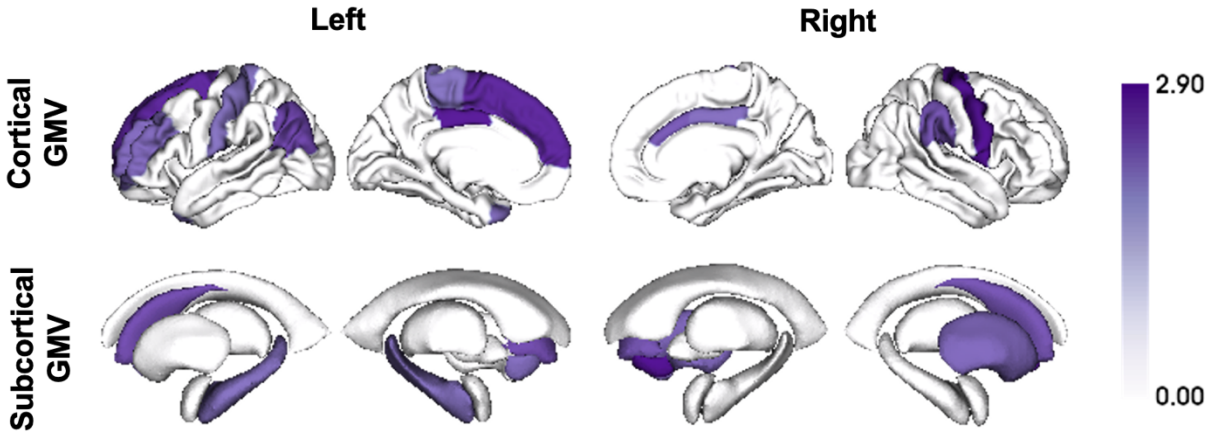

Figure 3. Regional cortical and subcortical gray matter volume (GMV) at the second-year follow-up mediating the association between the general environmental stress factor at baseline and total CBCL scores at the third-year follow-up. The colors represent the strength of the indirect effect in z-scores.

Table 4. Results of mediation analyses with general environmental stress (X), regional volume (M), and total CBCL (Y).

Mediator	Effect of X on mediator (*a*)	Unique effect of mediator on Y (*b*)	Indirect effect (*ab*)	Direct effect (*c'*)
Inferior parietal (L)	-0.105 *** [-0.127, -0.083]	-0.029* [-0.052, -0.006]	0.003 * [0.001, 0.006]	0.024 * [0.009,0.045]
Paracentral (L)	-0.163 *** [-0.186, -0.141]	-0.024 * [-0.045, 0.002]	0.004 * [0.000, 0.007]	0.024 * [0.005, 0.044]
Postcentral (L)	-0.195 *** [-0.217, -0.174]	-0.024 * [-.049, -0.001]	0.005 * [0.000, 0.010]	0.023 * [0.004, 0.045]
Posterior cingulate (L)	-0.126 *** [-0.149, -0.104]	-0.033 ** [-0.055, -0.010]	0.004 ** [0.001, 0.007]	0.023 * [0.006, 0.045]
Rostral middle frontal (L)	-0.181 *** [-0.201, -0.159]	-0.025 * [-0.048, -0.002]	0.005 * [0.000, 0.009]	0.023 * [0.004, 0.045]
Superior frontal (L)	-0.175 *** [-0.196, -0.152]	-0.031 ** [-0.055, -0.010]	0.005 ** [0.002, 0.009]	0.022 * [0.005, 0.043]
Temporal pole (L)	-0.112 ***[-0.133, -0.090]	-0.025 * [-0.045, 0.000]	0.003 * [0.000, 0.005]	0.025 * [0.007, 0.047]
Caudal anterior cingulate (R)	-0.084 *** [-0.106, -0.062]	-0.028 * [-0.053, -0.004]	0.002 ** [0.000, 0.004]	0.025 * [0.007, 0.047]
Posterior cingulate (R)	-0.099 *** [-0.121, -0.077]	-0.025 * [-0.048, -0.001]	0.002 * [0.000, 0.005]	0.025 * [0.006, 0.047]
Precentral (R)	-0.184 *** [-0.204, -0.164]	-0.036 ** [-0.060, -0.010]	0.007 ** [0.002, 0.011]	0.021 * [0.003, 0.043]
Supramarginal (R)	-0.129 *** [-0.151, -0.107]	-0.027 * [-0.049, -0.003]	0.003 * [0.000, 0.007]	0.024 * [0.005, 0.045]
Caudate (L)	-0.170 *** [-0.192, -0.148]	-0.031 * [-0.055, -0.006]	0.005 * [0.001, 0.010]	0.022 * [0.003, 0.044]
Hippocampus (L)	-0.182 *** [-0.202, -0.161]	-0.025 * [-0.049, -0.002]	0.005 * [0.000, 0.009]	0.023 * [0.004, 0.044]
Accumbens area (L)	-0.102 *** [-0.124, -0.078]	-0.026 * [-0.048, 0.000]	0.003 * [0.000, 0.005]	0.025 * [0.007, 0.046]
Caudate (R)	-0.177 *** [-0.198, -0.154]	-0.030 * [-0.054, -0.005]	0.005 * [0.001, 0.010]	0.022 * [0.003, 0.044]
Putamen (R)	-0.148 *** [-0.169, -0.126]	-0.027 * [-0.052, -0.004]	0.004 * [0.000, 0.008]	0.023 * [0.004, 0.045]
Accumbens area (R)	-0.116 *** [-0.138, -0.093]	-0.036 ** [-0.059, -0.011]	0.004 ** [0.001, 0.007]	0.023 * [0.004, 0.045]

Values in the table indicate estimated beta values and values within square brackets indicate 95% confidence intervals from bias-corrected bootstrapping. All statistical values reported are standardized.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 5. Results of mediation analyses with general environmental stress (X), regional cortical thickness (M), and total CBCL (Y).

Mediator	Effect of X on mediator (*a*)	Unique effect of mediator on Y (*b*)	Indirect effect (*ab*)	Direct effect (*c′*)
Paracentral (L)	-0.126 *** [-0.147, -0.106]	-0.045 *** [-0.070, -0.021]	0.006 *** [0.003, 0.009]	0.022 * [0.003, 0.043]
Postcentral (L)	-0.146 *** [-0.170, -0.126]	-0.027 * [-0.053, -0.004]	0.004 * [0.001, 0.008]	0.023 * [0.004, 0.045]
Superior frontal (L)	-0.037 ** [-0.061, -0.015]	-0.036 ** [-0.060, -0.014]	0.001 * [0.000, 0.003]	0.026 * [0.007, 0.046]
Precentral (R)	-0.067 *** [-0.090, -0.045]	-0.046 *** [-0.071, -0.024]	0.003 ** [0.001, 0.005]	0.024 * [0.005, 0.045]

Values in the table indicate estimated beta values and values within square brackets indicate 95% confidence intervals from bias-corrected bootstrapping. All statistical values reported are standardized.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 6. Results of mediation analyses with general environmental stress (X), regional surface area (M), and total CBCL (Y).

Mediator	Effect of X on mediator (*a*)	Unique effect of mediator on Y (*b*)	Indirect effect (*ab*)	Direct effect (*c′*)
Posterior cingulate (L)	-0.117 *** [-0.139, -0.094]	-0.036 ** [-0.057, -0.014]	0.004 ** [0.002, 0.007]	0.023 * [0.005, 0.045]
Caudal anterior cingulate (R)	-0.097 *** [-0.118, -0.076]	-0.034 ** [-0.057, -0.011]	0.003 ** [0.001, 0.006]	0.024 * [0.006, 0.046]
Posterior cingulate (R)	-0.094 *** [-0.116, -0.073]	-0.030 ** [-0.053, -0.007]	0.003 * [0.001, 0.005]	0.025 * [0.006, 0.047]

Values in the table indicate estimated beta values and values within square brackets indicate 95% confidence intervals from bias-corrected bootstrapping. All statistical values reported are standardized.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Multilevel Modeling. When looking at individual, family, and site level separately, the effect of the general environmental stress factor on regional volume (*a*) and the effect of the mediator on total CBCL score (*b*) were significant in the following regions: bilateral postcentral, bilateral precentral, bilateral superior frontal, bilateral thalamus, bilateral hippocampus, left fusiform, left pars opercularis, left postcentral, left superior frontal, left temporal pole, right cuneus, right inferior parietal, right inferior temporal, right medial orbitofrontal, right pericalcarine, right superior parietal, right supramarginal, left pallidum, and left amygdala (see Table 7 for statistics). However, the indirect effect (*ab*) was not significant for any of these regions at the family level.

In contrast, a number of regions were found to have significant indirect effects at the site level. Specifically, the indirect effect (*ab*) was significant for the following regions: bilateral postcentral, bilateral precentral, bilateral superior frontal, bilateral thalamus, bilateral hippocampus, left fusiform, left pars opercularis, left frontal pole, left cuneus, left inferior parietal, left inferior temporal, right orbitofrontal, right pericalcarine, right superior parietal, right supramarginal, and left amygdala (see Table 7 for statistics). Overall, the multilevel modeling results indicate that the relationships between the general environmental stress, regional volume, and total CBCL scores are significant at the family and site levels and that the mediating effect of regional volume between environmental stress and total CBCL was significant at the site level only.

Table 7. Results of multilevel mediation analyses with general environmental stress (X), regional volume (M), and total CBCL (Y).

Mediator	Level	Effect of X on mediator (*a*)	Unique effect of mediator on Y (*b*)	Indirect effect (*ab*)	Direct effect (*c'*)
Fusiform (L)	Individual	0.048 [-0.107, 0.231]	0.007 [0.000, 0.013]	0.000 [-0.001, 0.001]	-0.002 [-0.002, 0.024]
	Family	-0.200 [-0.231, -0.168] *	-0.015 [-0.031, -0.005] *	-0.001 [-0.027, 0.022]	0.004 [-0.002, 0.008]
	Site	-0.245 [-0.420, -0.076] *	0.008 [-0.099, 0.102]	0.003 [0.001, 0.006] *	-0.001 [-0.033, 0.028]
Pars opercularis (L)	Individual	-0.030 [-0.249,0.159]	-0.011 [-0.017,-0.004] *	0.000 [-0.002, 0.003]	-0.011 [-0.024, 0.023]
	Family	-0.122 [-0.152, -0.089] *	0.031 [0.011, 0.059] *	0.000 [-0.026, 0.026]	0.031 [0.011, 0.059] *
	Site	-0.198 [-0.337, -0.084]*	-0.002 [-0.124, 0.122]	-0.004 [-0.007, -0.001]*	-0.001 [-0.035, 0.037]
Postcentral (L)	Individual	-0.010 [-0.158, 0.142]	-0.024 [-.044, -0.005] *	0.005 * [0.001, 0.009]	-0.002 [-0.023, 0.024]
	Family	-0.215 [-0.244, -0.186] *	-0.012 [-0.024, -0.003] *	0.001 [-0.022, 0.025]	0.004 [-0.001, 0.009]
	Site	-0.205 [-0.350, -0.059] *	-0.005 [-0.118, 0.106]	0.003 [0.001, 0.005] *	-0.003 [-0.036, 0.026]
Precentral (L)	Individual	0.032 [-0.125, 0.174]	0.009 [0.002, 0.016] *	0.000 [-0.001, 0.002]	-0.003 [-0.023, 0.023]
	Family	-0.226 [-0.254, -0.194] *	-0.019 [-0.034, -0.007] *	0.001 [-0.022, 0.031]	0.002 [-0.003, 0.007]
	Site	-0.245 [-0.401, -0.085] *	-0.004 [-0.121, 0.094]	0.004 [0.001, 0.008] *	-0.004 [-0.040, 0.026]
Superior frontal (L)	Individual	0.011 [-0.136, 0.165]	0.001 [-0.006, 0.006]	0.000 [-0.001, 0.000]	-0.002 [-0.023, 0.024]
	Family	-0.171 [-0.201, -0.137] *	-0.015 [-0.028, -0.006] *	-0.004 [-0.031, 0.024]	0.004 [-0.001, 0.009]
	Site	-0.270 [-0.432, -0.100] *	0.016 [-0.092, 0.113]	0.003 [0.001, 0.005] *	0.002 [-0.036, 0.033]
Temporal pole (L)	Individual	0.034 [-0.137, 0.206]	0.004 [-0.002, 0.011]	0.000 [-0.001, 0.001]	0.000 [-0.024, 0.023]
	Family	-0.116 [-0.147, -0.087] *	-0.027 [-0.046, -0.008] *	-0.001 [-0.018, 0.013]	0.003 [-0.002, 0.009]
	Site	-0.159 [-0.374, 0.011]	0.010 [-0.064, 0.076]	0.003 [0.001, 0.006] *	0.001 [-0.027, 0.030]
Cuneus (R)	Individual	0.028 [-0.133, 0.181]	-0.003 [-0.011, 0.004]	0.002 [-0.001, 0.001]	0.000 [-0.024, 0.024]
	Family	-0.175 [-0.205, -0.145] *	0.013 [0.002, 0.026] *	0.013 [-0.016, 0.048]	0.009 [0.004, 0.014] *
	Site	-0.253 [-0.406, -0.130] *	-0.055 [-0.169, 0.064]	-0.002 [-0.005, 0.000] *	-0.015 [-0.056, 0.026]
Inferior parietal (R)	Individual	-0.006 [-0.148, 0.160]	-0.003 [-0.009, 0.003]	0.000 [-0.001, 0.001]	-0.002 [-0.022, 0.024]
	Family	-0.170 [-0.201, -0.139] *	-0.010 [-0.024, -0.001] *	-0.004 [-0.024, 0.006]	0.005 [0.000, 0.009]
	Site	-0.117 [-0.290, 0.044]	0.046 [-0.033, 0.135]	0.002 [0.000, 0.004] *	0.002 [-0.025, 0.028]
Inferior temporal (R)	Individual	-0.077 [-0.223, 0.073]	0.002 [-0.005, 0.009]	0.000 [-0.001, 0.000]	-0.002 [-0.022, 0.024]
	Family	-0.203 [-0.232, -0.170] *	-0.011 [-0.027, -0.002] *	-0.001 [-0.030, 0.030]	0.004 [-0.001, 0.009]

	Site	-0.226 [-0.367, -0.091] *	0.003 [-0.135, 0.113]	0.002 [0.000, 0.006] *	-0.002 [-0.042, 0.031]
	Individual	0.073 [-0.096, 0.267]	0.003 [-0.003, 0.009]	0.000 [-0.001, 0.001]	-0.002 [-0.022, 0.024]
Medial orbitofrontal (R)	Family	-0.166 [-0.199, -0.133] *	-0.013 [-0.029, -0.001] *	0.001 [-0.013, 0.017]	0.004 [-0.001, 0.009]
	Site	-0.160 [-0.362, 0.037]	-0.008 [-0.087, 0.063]	0.002 [0.000, 0.005] *	-0.004 [-0.032, 0.020]
	Individual	-0.019 [-0.177, 0.149]	-0.007 [-0.015, 0.000]	0.000 [-0.001, 0.001]	0.000 [-0.024, 0.024]
Pericalcarine (R)	Family	-0.110 [-0.142, -0.081] *	0.012 [0.002, 0.025] *	0.006 [-0.014, 0.033]	0.008 [0.003, 0.013] *
	Site	-0.221 [-0.404, -0.074] *	-0.031 [-0.120, 0-.056]	-0.001 [-0.003, 0.000] *	-0.008 [-0.041, 0.026]
	Individual	-0.103 [-0.255, 0.036]	0.002 [-0.005, 0.008]	0.000 [-0.001, 0.000]	-0.002 [-0.023, 0.024]
Postcentral (R)	Family	-0.198 [-0.228, -0.167] *	-0.012 [-0.027, -0.003] *	-0.002 [-0.026, 0.019]	0.004 [-0.001, 0.009]
	Site	-0.173 [-0.313, -0.034] *	0.018 [-0.095, 0.135]	0.002 [0.001, 0.005] *	0.000 [-0.032, 0.030]
	Individual	-0.049 [-0.187, 0.0108]	0.002 [-0.005, 0.008]	0.000 [-0.001, 0.000]	-0.002 [-0.022, 0.024]
Precentral (R)	Family	-0.196 [-0.227, -0.163] *	-0.019 [-0.032, -0.008] *	0.000 [-0.022, 0.023]	0.003 [-0.002, 0.008]
	Site	-0.206 [-0.358, -0.049] *	0.000 [-0.108, 0.106]	0.004 [0.002, 0.006] *	-0.002 [-0.036, 0.025]
	Individual	0.113 [-0.045, 0.268]	0.001 [-0.006, 0.007]	0.000 [-0.001, 0.001]	-0.003 [-0.023, 0.023]
Superior frontal (R)	Family	-0.192 [-0.220, -0.157] *	-0.010 [-0.025, -0.001] *	-0.003 [-0.030, 0.024]	0.005 [0.000, 0.009]
	Site	-0.288 [-0.468, -0.105] *	0.011 [-0.086, 0.099]	0.002 [0.000, 0.005] *	0.001 [-0.038, 0.030]
	Individual	-0.116 [-0.305, 0.037]	0.004 [-0.002, 0.010]	0.000 [-0.002, 0.000]	-0.002 [-0.018, 0.023]
Superior parietal (R)	Family	-0.181 [-0.210, -0.151] *	-0.013 [-0.029, -0.004] *	-0.003 [-0.021, 0.011]	0.005 [-0.001, 0.009]
	Site	-0.214 [-0.368, -0.047] *	0.021 [-0.062, 0.091]	0.002 [0.001, 0.005] *	0.002 [-0.029, 0.031]
	Individual	-0.191 [-0.357, -0.022] *	0.002 [-0.002, 0.009]	-0.001 [-0.002, 0.000]	-0.002 [-0.023, 0.024]
Supramarginal (R)	Family	-0.132 [-0.163, -0.100] *	-0.020 [-0.038, -0.011] *	-0.002 [-0.026, 0.021]	0.004 [-0.001, 0.009]
	Site	-0.151 [-0.265, -0.024] *	0.017 [-0.131, 0.159]	0.003 [0.001, 0.005] *	0.000 [-0.033, 0.029]
	Individual	0.010 [-0.133, 0.155]	0.012 [0.004, 0.019] *	0.000 [-0.002, 0.002]	-0.002 [-0.023, 0.023]
Thalamus (L)	Family	-0.161 [-0.191, -0.127] *	-0.019 [-0.033, -0.009] *	0.002 [-0.010, 0.020]	0.004 [-0.001, 0.008]
	Site	-0.144 [-0.327, 0.047]	-0.024 [-0.096, 0.056]	0.003 [0.002, 0.005] *	-0.007 [-0.033, 0.017]
	Individual	-0.023 [-0.207, 0.133]	0.006 [-0.001, 0.013]	0.000 [-0.001, 0.001]	0.000 [-0.024, 0.024]
Pallidum (L)	Family	-0.100 [-0.128, -0.069] *	-0.018 [-0.034, -0.002] *	0.000 [-0.005, 0.011]	0.005 [-0.001, 0.010]
	Site	-0.088 [-0.430, 0.214]	-0.011 [-0.051, 0.025]	0.002 [0.000, 0.004]	-0.002 [-0.029, 0.025]
	Individual	-0.036 [-0.179, 0.125]	0.005 [-0.003, 0.012]	0.000 [-0.001, 0.001]	-0.002 [-0.022, 0.024]
Hippocampus (L)	Family	-0.193 [-0.224, -0.161] *	-0.011 [-0.025, -0.003] *	0.009 [-0.005, 0.031]	0.004 [-0.001, 0.009]
	Site	-0.162 [-0.315, -0.004] *	-0.068 [-0.152, 0.032]	0.002 [0.001, 0.005] *	-0.013 [-0.042, 0.009]

	Individual	0.017 [-0.134, 0.174]	0.010 [0.003, 0.018] *	0.000 [-0.001, 0.002]	-0.002 [-0.023, 0.023]
Amygdala (L)	Family	-0.166 [-0.193, -0.135] *	-0.011 [-0.025, -0.001] *	0.001 [-0.008, 0.013]	0.005 [0.000, 0.009]
	Site	-0.096 [-0.455, 0.287]	-0.022 [-0.052, 0.011]	0.002 [0.000, 0.004] *	-0.005 [-0.029, 0.016]
	Individual	0.021 [-0.130, 0.176]	0.008 [-0.001, 0.014]	0.000 [-0.001, 0.001]	-0.003 [-0.023, 0.023]
Thalamus (R)	Family	-0.156 [-0.187, -0.123] *	-0.011 [-0.024, -0.003] *	0.000 [-0.009, 0.010]	0.005 [0.000, 0.010] *
	Site	-0.079 [-0.275, 0.127]	-0.007 [-0.072, 0.066]	0.002 [0.000, 0.004] *	-0.004 [-0.029, 0.018]
	Individual	-0.032 [-0.170, 0.129]	0.005 [-0.003, 0.012]	0.000 [-0.001, 0.001]	-0.002 [-0.023, 0.024]
Hippocampus (R)	Family	-0.193 [-0.223, -0.162] *	-0.011 [-0.025, -0.002] *	0.005 [-0.004, 0.023]	0.004 [0.000, 0.009]
	Site	-0.128 [-0.298, 0.053]	-0.053 [-0.123, 0.026]	0.002 [0.000, 0.005] *	-0.010 [-0.035, 0.012]

Values in the table indicate estimated beta values and values within square brackets indicate 95% confidence intervals from bias-corrected bootstrapping.
* indicates the significance of credible intervals calculated by the Bayesian estimator

Sensitivity Analyses. Using volume change scores (regional volume at baseline minus regional volume at the second-year follow-up) as mediators, no regions significantly mediated the relationship between the general environmental stress factor and total CBCL score. The null finding observed could be due to the possibility that a duration of two years between time points is too narrow to observe meaningful changes. When controlling for baseline psychopathology symptoms, the association between the general environmental stress factor and total CBCL scores reversed (see total effect *c* in Table 8 for statistics), such that greater environmental stress at baseline was associated with lower total CBCL scores at the third-year follow-up. Greater environmental stress was associated with smaller volumes in the left posterior cingulate, the left frontal pole, and the left pallidum (*a*), and smaller volumes in these regions were associated with greater total CBCL scores (*b*). The mediating effect (*ab*) of the left posterior cingulate and the left pallidum were significant (see Table 8 for statistics).

Sex difference. Examining the regions that showed a significant mediation effect in the main analyses, there was no evidence of significant sex differences.

Table 8. Results of mediation analyses with general environmental stress (X), regional volume (M), and total CBCL (Y) controlling for baseline CBCL

Mediator	Effect of X on mediator (*a*)	Unique effect of mediator on Y (*b*)	Indirect effect (*ab*)	Direct effect (*c'*)	Total effect (*c*)
Posterior cingulate (L)	-0.123 *** [-0.143, -0.103]	-0.022* [-0.040, -0.006]	0.003 * [0.001, 0.005]	-0.032 *** [-0.046, -0.017]	-0.029 *** [-0.043,-0.014]
Frontal pole (L)	-0.161 *** [-0.184, -0.140]	-0.018 * [-0.035, 0.000]	0.003 * [0.000, 0.006]	-0.032 *** [-0.046, -0.017]	-0.029 *** [-0.043, -0.014]
Pallidum (L)	-0.108 *** [-0.130, -0.084]	-0.021 * [-0.039, -0.003]	0.002 * [0.000, 0.004]	-0.032 *** [-0.046, -0.016]	-0.029 *** [-0.043,-0.014]

Values in the table indicate estimated beta values and values within square brackets indicate 95% confidence intervals from bias-corrected bootstrapping. All statistical values reported are standardized.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Discussion

Consistent with prior studies and our hypotheses, smaller volumes in the hippocampus, the anterior cingulate cortex, and subregions of the prefrontal cortex were found to mediate the association between general environmental stress at baseline and psychopathology symptoms at later time points. Additionally, smaller volumes in other brain regions were found to play a mediating role in the relationship between environmental stress and psychopathology symptoms. Specifically, several mediators were identified from regions implicated in the frontal network and frontoparietal network (rostral middle frontal, superior frontal, caudal anterior cingulate), default mode network (posterior cingulate, inferior parietal, temporal lobe), motor network (paracentral, postcentral, precentral), and the subcortical network that can be further divided into hippocampus/amygdala and reward processing circuitry (caudate, accumbens, putamen). Multilevel modeling analyses identified additional regions and extended this finding by showing that the associations between environmental stress, regional volume, and psychopathology symptoms are significant at the family and site levels and that the mediating effects of regional volumes were significant at the site level. When baseline psychopathology symptoms were included as a covariate, the reverse association between the general environmental stress factor and total CBCL scores was observed, albeit the mediating effects of the posterior cingulate, frontal pole, and pallidum linking the general environmental stressor and total CBCL were in a similar direction as in the main analyses (i.e., greater environmental stress predicted smaller volumes, and smaller volumes predicted greater psychopathology symptoms). No sex differences were found. Next, the structural findings obtained from the main analyses will be discussed, with each region grouped into a network framework in order to give a broader overview of their potential functional aspects.

Frontal network

Several frontal regions emerged as mediators between early life stress and total CBCL scores, consistent with the hypothesis that prefrontal regions are susceptible to stress due to the high concentration of glucocorticoid receptors as well as the extended maturation of the prefrontal cortex throughout the developmental stage. There are numerous psychiatric and neurobehavioral symptoms related to dysfunction in frontal areas including apathy, perseverance, impulsiveness, disinhibition, emotion dysregulation, executive functioning deficits, and abulia (Hoffmann, 2013; Joseph, 1999). Accordingly, structural differences represented by smaller volume and dysfunction of the frontal cortex are implicated in a wide array of psychiatric disorders including schizophrenia (Sanfilipo et al., 2020.; Weinberger, 1988), ADHD (Krain & Castellanos, 2006), and mood and anxiety disorders (Kenwood et al., 2022; Pizzagalli & Roberts, 2022). The major function of the frontal lobes is the integration of sensory, cognitive, and emotional information through its interconnectivity with motor, temporal, and subcortical regions including the cerebellum and brainstem, which together help to make an optimal decision in response to changing environments (Hoffmann, 2013). In other words, the frontal cortex serves as a control tower in monitoring internal and external environments by integrating information and ultimately making decisions which have direct implications for cognitive, behavioral, and emotional outcomes.

Default mode network

The posterior cingulate cortex, inferior parietal cortex, and temporal lobe (Fransson & Marrelec, 2008; Qin & Northoff, 2011) are part of the default mode network which activates when individuals are not engaged in an active task (Raichle et al., 2001). The default mode network has been linked to self-referential processing such as internal introspection,

autobiographical memories, and future-oriented thoughts (Buckner et al., 2008) and has anti-correlations with task-related brain activities (Fox et al., 2005). Furthermore, heightened activation in the default mode network as well as decreased anti-correlation with task-related brain activity has been found in patients with psychiatric disorders including schizophrenia and depression (Broyd et al., 2009). The inability to flexibly switch between external environmental processing and internal states as well as heightened self-referential processing associated with the default mode network may underlie self-reference and rumination symptoms (Whitfield-Gabrieli & Ford, 2012).

Subcortical regions

Consistent with the hypothesis and previous findings showing that hippocampal volume is susceptible to stress due to high levels of glucocorticoid receptors and protracted postnatal neurogenesis, Study 2 showed that smaller hippocampal volume mediated the relationship between environmental stress and psychopathology symptoms. In alignment, previous studies have reported an association between childhood adversity, smaller hippocampal volume, and psychopathology (Paquola et al., 2016; Pollok et al., 2022). Study 2 supports these previous findings, suggesting that the hippocampus is vulnerable to the effect of stress which may confer risk for developing psychopathology. In addition, regions implicated in the positive valence system (Kujawa et al., 2020), including reward processing and motivational behaviors, were found to play mediating roles, specifically the nucleus accumbens as part of the ventral striatum and the caudate and putamen as part of the dorsal striatum. It has been suggested that stress reduces positive valence system function, and exposure to early life stress may have a greater impact than exposure later in development (Boecker-Schlier et al., 2016; Goff et al., 2013;

Hanson et al., 2016). Here, we found that structural differences represented by smaller volumes related to stress are implicated in greater psychopathology symptoms.

Motor network

Although often overlooked in discussing psychopathology since the focus is often on cognitive and affective processing, motor development is highly sensitive to early life stress (Demaestri et al., 2020) and psychomotor disturbances are hallmark symptoms of major depressive disorder, bipolar disorder, and schizophrenia (Northoff et al., 2021). Imbalance of transmitters such as dopamine and serotonin involved in motor movements and interaction with other networks may produce abnormal motor outcomes such as agitation and slowing (Northoff et al., 2021). The finding of motor-related regions in Study 2 suggests that motor regions may be sensitive to stress and may have implications for psychopathology symptoms in youths.

To conclude, a number of brain regions implicated in the frontal network, default mode network, reward processing network, and motor network emerged as mediators between environmental stress and future psychopathology symptoms, highlighting the importance of these regions in understanding the effect of stress on the developing brain.

Part III. Synthesis: General Discussion, Limitations/Future Directions, and Conclusion

General Discussion

This dissertation utilized a longitudinal design to identify brain structures that are potentially affected by early life stress and may lead to increased psychopathology symptoms in youths. It is well-known that psychopathology symptoms associated with early life stress are more severe, persistent, and treatment-resistant than those not associated with early life stress. Previous studies linking early life stress and neurobiological development suggest that long-lasting psychological problems related to early life stress may occur through alterations in brain

structures that lead to cognitive and emotional maladjustment. In this dissertation, Study 1 illustrated a significant association between environmental stress and psychopathology. Study 1 also revealed that the general environmental stress factor may not be the sole predictor of overall psychopathology; each of the specific factors also showed unique associations suggesting that examination of all manifestations of environmental stress will be important going forward. Study 2 extended these findings by showing that brain structures implicated in the frontal network, default mode network, motor network, reward circuitry, and emotional processing were found to mediate the relationship between early life stress and later psychopathology symptoms. Differences in these brain structures are implicated in a wide range of cognitive and emotional problems as well as various psychiatric disorders. The finding of structural differences mediating environmental stress and psychopathology symptoms in youths suggests that neural circuitry shaped by early adversity may lead to perpetuating problems and may serve as a risk factor for developing psychopathology that meet the criteria for diagnoses during adolescence and adulthood.

On a different perspective, the brain has the capability to self-organize in response to external demands and internal processing, and this ability might be a key to resilience in the presence of adversity (Cicchetti & Curtis, 2015). The structural organization of the brain reflects the history of the organism and what the organism was capable of at the time in response to what was most important to the organism (Luu & Tucker, 1996). Similarly, it is unlikely that evolution will favor mechanisms that inflict damage to the organism, unless they bring about benefits for survival and reproduction (Bath, 2020). Consistently, there is growing support that brain characteristics associated with adversity should be viewed through a lens of adaptation, rather than deficit (Ellis et al., 2009, 2017), especially when interpreting neural characteristics in youths

with high malleability and potential for growth. Therefore, it is important to distinguish between true developmental disabilities/impairments and natural variation within the broad, normal range of development (Taylor et al., 2023). From this perspective, the regions identified in the current dissertation may not reflect aberrations, but rather, adaptations to the child's environment. However, it is also possible for something to be both adaptive at the time and yet still confer risk for later problems. For example, the accelerated maturation theory posits that severe early life stress may lead to early maturation of the developing brain (Callaghan & Tottenham, 2016). While this may have been an adaptive response in the moment in response to a chronic stressor, it can a risk factor for later psychological problems. Thus, this suggests that the practical meaning of brain differences associated with early life stress may not be fully transparent – those brain changes may or may not be beneficial to the child.

Furthermore, another consideration of the current dissertation is the use of a broad definition of environmental stress that goes beyond the concept of childhood adversity. McLaughlin (2016) defined childhood adversity as "experiences that are likely to require significant adaptation by an average child and that represent a *deviation* from the expectable environment." While our broader definition of environmental stress is more inclusive, it will also inevitably capture a greater amount of variability as more stressors are included. Some stressors will be common and may not be associated with psychopathology, including everyday stressors that are likely experienced by most children to varying degrees. At the same time, other stressors that are more severe and have stronger associations with psychopathology may not be endorsed as frequently by children. In this regard, the broad and inclusive nature of the general environmental stress factor used in this dissertation means that we are capturing the gradient of

stressor severity, from least to most severe, which also may have mapped onto natural variation in structural associations with stress.

Taken together, it may be premature to conclude that the structural differences found in the current study with a predominantly normative U.S. youth sample demonstrate neural "deficits" in response to environmental stress. Instead, low to moderate levels of stress may make individuals more resilient, as the hormesis model illustrates (Oshri, 2023). Furthermore, previous studies indicate that the subjective interpretation of stressful events may be more critical in the manifestation of future psychopathology (Baldwin et al., 2024; Larsen & Parcella, 2016; Pinciotti & Fisher, 2022); therefore, the association between subjective interpretations of the events and neural structural/functional organization should be explored further. Utilizing the concepts of homeostasis and allostasis, low to moderate levels of stress may allow an individual to sustain a greater range of homeostasis. As Sterling (2014) describes, a mental disorder may arise from a reduced capacity to return to homeostasis (i.e., inadequate allostasis); thus, a therapeutic goal would be to restore responsiveness to a full range of signals which depends on the plasticity of the brain in learning and forgetting. Activities such as physical exercise (Cotman & Berchtold, 2002) and mental activities like forgiveness (Ricciardi et al., 2013), mindfulness (Hölzel et al., 2011), and cognitive/behavioral therapies (Appelbaum et al., 2023) which modify subjective interpretations can aid to increase plasticity in hopes of ameliorating the long-term negative effects of stress on the developing brain.

Limitations/Future Directions

This dissertation has a number of strengths, but also some limitations that could suggest avenues for future directions. Firstly, while factor analyses have the advantage of extracting underlying dimensions, it is difficult to specify which individual items are specifically related to

psychopathology. For instance, we showed that interpersonal support was associated with greater internalizing symptoms; however, it is unclear which specific aspects of interpersonal support are associated with internalizing symptoms. Therefore, more granular measures and methodologies that tease apart these factors would be complementary to factor analyses that provide a broad overview of the structure underlying observed variables. Secondly, mediation models with longitudinal designs are not without caveats in terms of deriving causal inferences as parameters are confined to the specific lags chosen (Deboeck & Preacher, 2015). Continuous time mediation analysis (Deboeck & Preacher, 2016) is a statistical approach that can estimate lag-independent parameters to measure mediating relationships over time. Such an approach could be incorporated in future work to uncover processes that evolve continuously over time. Thirdly, mediation analyses with observational data do not allow for causal inferences as we cannot randomly assign children to adversity exposure. While maintaining temporal precedence between variables is an improvement over cross-sectional analyses and continuous time mediation analyses can capture dynamic relationships, we can still only speculate about causal mechanisms when the variables of interest cannot be experimentally manipulated.

Finally, this dissertation has alluded to brain networks in interpreting structural results; however, it is important to acknowledge that brain structure conditions, but does not determine, neural network dynamics (Batista-García-Ramó & Fernández-Verdecia, 2018). In fact, the dynamic functional organization of the brain might be key to understanding the brain's adaptability, robustness, and resilience withstanding structural damages (Park & Friston, 2013). Intriguingly, researchers have demonstrated distinctive effects of pharmacotherapy on brain structure and functional networks (Neufeld et al., 2023; Voineskos et al., 2020). Antipsychotics, which are effective in treating not only psychosis but other disorders such as major depressive

disorder with psychotic episodes, were related to reduced cortical thickness (Voineskos et al. 2020). However, in the same group of patients, antipsychotics were found to stabilize functional network connectivity over time which has implications for positive effects on the regulation of emotions, attention, and other psychosis-related symptoms (Neufeld et al. 2023). These results illustrate that structural changes are not necessarily related to functional networks and functional networks might find ways to compensate for differences in brain structure (Neufeld et al. 2023). The flexibility of functional networks provides an exciting avenue to investigate the network connectivity characteristics in response to environmental stressors. In our previous work, we examined associations between environmental stressors and functional network topology at baseline and found that greater environmental stress was associated with less modularity, which may indicate less specialization/efficiency but also greater flexibility (Jeong et al. 2024). While promising, this study focused on network topology measured with graph theory, which is related to, but distinct from functional connectivity. Future work should investigate whether functional connectivity plays a role in linking environmental stress to future psychopathology symptoms in youth.

Conclusion

Utilizing a longitudinal design and a dimensional approach to define early life stress, the general and specific factors of early life stress were associated with future psychopathology symptoms. Furthermore, neural substrates that mediate the relationship between early life stress and psychopathology were identified. This dissertation showed that different types of stressors are associated with divergent patterns of psychopathology, which may have implications for the etiology of mental health symptoms in youth. There is also evidence that the general environmental stress factor representing a non-specific, wide range of stressors was associated

with less general psychopathology symptoms when baseline psychopathology is taken into account. Regarding neural substrates, we found that smaller volumes in regions implicated in the frontal, default mode, motor, and reward processing networks mediated the relationship between greater general environmental stress and greater psychopathology symptoms. These regions have been shown to differ in wide variety of psychiatric disorders including schizophrenia, anxiety, depression, and mania. In this regard, the neural substrates found in the current study may inform risk factors that underlie the development of future psychopathology. At the same time, it is premature to conclude that structural differences observed at this stage of development are indicators of future psychopathology because these characteristics may reflect individuals' adaptation to the external environment. It is possible that early life exposure to stress promotes more resilience in the future by preparing and conditioning the individual to future threats. Allostasis – which reflects the ability to return to one's homeostasis – may be more critical in determining psychopathology outcomes, rather than stress exposure per se. Allostasis depends on the plasticity of the brain, which can be fostered through various interventions. Additionally, the subjective interpretation of stressful events may have important implications for neural plasticity. Taken together, by uncovering the nuanced interplay between early life stress, neural structure, and psychopathology in a younger sample, this dissertation advances our understanding of the environmental and neural risk factors that may contribute to the development of mental health symptoms in youth. Such work aims to alleviate the negative impacts of early life stress on children.

References

Achenbach, T. M. (2009). *The Achenbach system of empirically based assessment (ASEBA): Development, findings, theory, and applications.* Burlington, VT: University of Vermont Research Center for Children, Youth, and Families.

Achenbach, T. M., & Edelbrock, C. (1991). Child behavior checklist. *Burlington (Vt)*, *7*, 371–392.

Afifi, T. O., Stewart-Tufescu, A., Taillieu, T., Salmon, S., Fortier, J., & Roos, L. E. (2022). Adverse Childhood Experiences. In *Comprehensive Clinical Psychology* (Second Edi, Vol. 11). Elsevier. https://doi.org/10.1016/b978-0-12-818697-8.00038-8

Ahmed-Leitao, F., Spies, G., van den Heuvel, L., & Seedat, S. (2016). Hippocampal and amygdala volumes in adults with posttraumatic stress disorder secondary to childhood abuse or maltreatment: A systematic review. *Psychiatry Research - Neuroimaging*, *256*, 33–43. https://doi.org/10.1016/j.pscychresns.2016.09.008

Allman, J. M., Hakeem, A., Erwin, J. M., Nimchinsky, E., Hof, P., & Hixon, F. P. (2001). The anterior cingulate cortex: The evolution of an interface between emotion and cognition. *Annals of the New York Academy of Sciences*, *935*, 107–117. https://doi.org/10.1111/j.1749-6632.2001.tb03476.x

Appelbaum, L. G., Shenasa, M. A., Stolz, L., & Daskalakis, Z. (2023). Synaptic plasticity and mental health: methods, challenges and opportunities. In *Neuropsychopharmacology* (Vol. 48, Issue 1, pp. 113–120). Springer Nature. https://doi.org/10.1038/s41386-022-01370-w

Arain, M., Haque, M., Johal, L., Mathur, P., Nel, W., Rais, A., Sandhu, R., & Sharma, S. (2013). Maturation of the adolescent brain. *Neuropsychiatric Disease and Treatment*, *9*, 449–461. https://doi.org/10.2147/NDT.S39776

Arthur, M. W., Briney, J. S., Hawkins, J. D., Abbott, R. D., Brooke-Weiss, B. L., & Catalano, R. F. (2007). Measuring risk and protection in communities using the Communities That Care Youth Survey. *Evaluation and Program Planning*, *30*(2), 197–211. https://doi.org/10.1016/j.evalprogplan.2007.01.009

Baldwin, J. R., Coleman, O., Francis, E. R., & Danese, A. (2024). Prospective and Retrospective Measures of Child Maltreatment and Their Association with Psychopathology: A Systematic Review and Meta-Analysis. *JAMA Psychiatry*. https://doi.org/10.1001/jamapsychiatry.2024.0818

Baram, T. Z., & Hatalski, C. G. (1998). Neuropeptide-mediated excitability: A key triggering mechanism for seizure generation in the devloping brain. *Trends in Neurosciences*, *21*(11), 471–476. https://doi.org/10.1016/S0166-2236(98)01275-2

Barch, D. M., Albaugh, M. D., Avenevoli, S., Chang, L., Clark, D. B., Glantz, M. D., Hudziak, J. J., Jernigan, T. L., Tapert, S. F., Yurgelun-Todd, D., Alia-Klein, N., Potter, A. S., Paulus, M. P., Prouty, D., Zucker, R. A., & Sher, K. J. (2018). Demographic, physical and mental health assessments in the adolescent brain and cognitive development study: Rationale and description. *Developmental Cognitive Neuroscience*, *32*(October 2017), 55–66. https://doi.org/10.1016/j.dcn.2017.10.010

Barch, D. M., Shirtcliff, E. A., Elsayed, N. M., Whalen, D., Gilbert, K., Vogel, A. C., Tillman, R., & Luby, J. L. (2020). Testosterone and hippocampal trajectories mediate relationship of poverty to emotion dysregulation and depression. *Proceedings of the National Academy of Sciences of the United States of America*, *117*(36), 22015–22023. https://doi.org/10.1073/pnas.2004363117

Bath, K. G. (2020). Synthesizing Views to Understand Sex Differences in Response to Early Life Adversity. In *Trends in Neurosciences* (Vol. 43, Issue 5, pp. 300–310). Elsevier Ltd. https://doi.org/10.1016/j.tins.2020.02.004

Batista-García-Ramó, K., & Fernández-Verdecia, C. I. (2018). What we know about the brain structure-function relationship. In *Behavioral Sciences* (Vol. 8, Issue 4). MDPI Multidisciplinary Digital Publishing Institute. https://doi.org/10.3390/bs8040039

Beyer, L., Keen, R., Ertel, K. A., Okuzono, S. S., Pintro, K., Delaney, S., & Slopen, N. (2024). Comparing two measures of neighborhood quality and internalizing and externalizing behaviors in the adolescent brain cognitive development study. *Social Psychiatry and Psychiatric Epidemiology*. https://doi.org/10.1007/s00127-024-02614-4

Bick, J., & Nelson, C. A. (2016). Early adverse experiences and the developing brain. *Neuropsychopharmacology*, *41*(1), 177–196. https://doi.org/10.1038/npp.2015.252

Boecker-Schlier, R., Holz, N. E., Buchmann, A. F., Blomeyer, D., Plichta, M. M., Jennen-Steinmetz, C., Wolf, I., Baumeister, S., Treutlein, J., Rietschel, M., Meyer-Lindenberg, A., Banaschewski, T., Brandeis, D., & Laucht, M. (2016). Interaction between COMT Val158Met polymorphism and childhood adversity affects reward processing in adulthood. *NeuroImage*, *132*, 556–570. https://doi.org/10.1016/j.neuroimage.2016.02.006

Bronfenbrenner, U. (1979). *The Ecology of Human Development: Experiments by Nature and Design*. Harvard University Press.

Broyd, S. J., Demanuele, C., Debener, S., Helps, S. K., James, C. J., & Sonuga-Barke, E. J. S. (2009). Default-mode brain dysfunction in mental disorders: A systematic review. In *Neuroscience and Biobehavioral Reviews* (Vol. 33, Issue 3, pp. 279–296). https://doi.org/10.1016/j.neubiorev.2008.09.002

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: Anatomy, function, and relevance to disease. In *Annals of the New York Academy of Sciences* (Vol. 1124, pp. 1–38). https://doi.org/10.1196/annals.1440.011

Busso, D. S., McLaughlin, K. A., Brueck, S., Peverill, M., Gold, A. L., & Sheridan, M. A. (2017). Child Abuse, Neural Structure, and Adolescent Psychopathology: A Longitudinal Study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *56*(4), 321–328. https://doi.org/10.1016/j.jaac.2017.01.013

Calabrese, E. J., & Baldwin, L. A. (2002). Defining hormesis. *Human and Experimental Toxicology*, *21*(2), 91–97. https://doi.org/10.1191/0960327102ht217oa

Callaghan, B. L., & Tottenham, N. (2016). The Stress Acceleration Hypothesis: Effects of early-life adversity on emotion circuits and behavior. In *Current Opinion in Behavioral Sciences* (Vol. 7, pp. 76–81). Elsevier Ltd. https://doi.org/10.1016/j.cobeha.2015.11.018

Carey, G., & Dilalla, D. L. (1994). Personality and Psychopathology: Genetic Perspectives. In *Journal of Abnormal Psychology* (Vol. 103, Issue 1).

Casey, B. J., Cannonier, T., Conley, M. I., Cohen, A. O., Barch, D. M., Heitzeg, M. M., Soules, M. E., Teslovich, T., Dellarco, D. V., Garavan, H., Orr, C. A., Wager, T. D., Banich, M. T., Speer, N. K., Sutherland, M. T., Riedel, M. C., Dick, A. S., Bjork, J. M., Thomas, K. M., … Dale, A. M. (2018a). The Adolescent Brain Cognitive Development (ABCD) study: Imaging acquisition across 21 sites. *Developmental Cognitive Neuroscience*, *32*(March), 43–54. https://doi.org/10.1016/j.dcn.2018.03.001

Casey, B. J., Cannonier, T., Conley, M. I., Cohen, A. O., Barch, D. M., Heitzeg, M. M., Soules, M. E., Teslovich, T., Dellarco, D. V., Garavan, H., Orr, C. A., Wager, T. D., Banich, M. T., Speer, N. K., Sutherland, M. T., Riedel, M. C., Dick, A. S., Bjork, J. M., Thomas, K. M., …

Dale, A. M. (2018b). The Adolescent Brain Cognitive Development (ABCD) study: Imaging acquisition across 21 sites. *Developmental Cognitive Neuroscience*, *32*(March), 43–54. https://doi.org/10.1016/j.dcn.2018.03.001

Caspi & Moffitt 2006. (n.d.).

Caspi, A., & Moffitt, T. E. (2018). All for one and one for all: Mental disorders in one dimension. *American Journal of Psychiatry*, *175*(9), 831–844. https://doi.org/10.1176/appi.ajp.2018.17121383

Cerqueira, J. J., Mailliet, F., Almeida, O. F. X., Jay, T. M., & Sousa, N. (2007). The prefrontal cortex as a key target of the maladaptive response to stress. *Journal of Neuroscience*, *27*(11), 2781–2787. https://doi.org/10.1523/JNEUROSCI.4372-06.2007

Cham, H., Reshetnyak, E., Rosenfeld, B., & Breitbart, W. (2017). Full Information Maximum Likelihood Estimation for Latent Variable Interactions With Incomplete Indicators. *Multivariate Behavioral Research*, *52*(1), 12–30. https://doi.org/10.1080/00273171.2016.1245600

Chilcoat, H. D., & Anthony, J. C. (1996). Impact of parent monitoring on initiation of drug use through late childhood. *Journal of the American Academy of Child and Adolescent Psychiatry*, *35*(1), 91–100. https://doi.org/10.1097/00004583-199601000-00017

Chilcoat, H. D., & Breslau, N. (1997). *Does Psychiatric History Bias Mothers' Reports? An Application of a New Analytic Approach*.

Chorpita, B. F., & Barlow, D. H. (1998). The Development of Anxiety: The Role of Control in the Early Environment. In *Psychological Bulletin '* (Vol. 124, Issue 1).

Chrousos, G. P. (2009). Stress and disorders of the stress system. *Nature Reviews Endocrinology*, *5*(7), 374–381. https://doi.org/10.1038/nrendo.2009.106

Conrad, C. D. (2008). Chronic stress-induced hippocampal vulnerability: The glucocorticoid vulnerability hypothesis. *Reviews in the Neurosciences*, *19*(6), 395–411. https://doi.org/10.1515/REVNEURO.2008.19.6.395

Cryan, J. F., & Dinan, T. G. (2013). Unraveling the Longstanding Scars of Early Neurodevelopmental Stress. *Biological Psychiatry*, *74*(11), 788–789. https://doi.org/10.1016/j.biopsych.2013.10.004

Danese, A., & McEwen, B. S. (2012). Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiology and Behavior*, *106*(1), 29–39. https://doi.org/10.1016/j.physbeh.2011.08.019

Davis, M., & Whalen, P. J. (2001). The amygdala: Vigilance and emotion. *Molecular Psychiatry*, *6*(1), 13–34. https://doi.org/10.1038/sj.mp.4000812

De Mola, C. L., Stanojevic, S., Ruiz, P., Gilman, R. H., Smeeth, L., & Miranda, J. J. (2012). The effect of rural-to-urban migration on social capital and common mental disorders: PERU MIGRANT study. *Social Psychiatry and Psychiatric Epidemiology*, *47*(6), 967–973. https://doi.org/10.1007/s00127-011-0404-6

de Roo, M., Veenstra, R., & Kretschmer, T. (2022). Internalizing and externalizing correlates of parental overprotection as measured by the EMBU: A systematic review and meta-analysis. In *Social Development* (Vol. 31, Issue 4, pp. 962–983). John Wiley and Sons Inc. https://doi.org/10.1111/sode.12590

Deboeck, P. R., & Preacher, K. J. (2015). No need to be discrete: A method for continuous time mediation analysis. *Structural Equation Modeling*, *23*(1), 61–75. https://doi.org/10.1080/10705511.2014.973960

Debowska, A., Willmott, D., Boduszek, D., & Jones, A. D. (2017). What do we know about child abuse and neglect patterns of co-occurrence? A systematic review of profiling studies and recommendations for future research. *Child Abuse and Neglect*, *70*(March), 100–111. https://doi.org/10.1016/j.chiabu.2017.06.014

Demaestri, C., Pan, T., Critz, M., Ofray, D., Gallo, M., & Bath, K. G. (2020). Type of early life adversity confers differential, sex-dependent effects on early maturational milestones in mice. *Hormones and Behavior*, *124*. https://doi.org/10.1016/j.yhbeh.2020.104763

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., Hyman, B. T., Albert, M. S., & Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*(3), 968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021

Di, Q., Kloog, I., Koutrakis, P., Lyapustin, A., Wang, Y., & Schwartz, J. (2016). Assessing PM2.5 Exposures with High Spatiotemporal Resolution across the Continental United States. *Environmental Science and Technology*, *50*(9), 4712–4721. https://doi.org/10.1021/acs.est.5b06121

Driessen, M., Herrmann, J., Stahl, K., Zwaan, M., Meer, S., Hill, A., Osterheider, M., & Petersen, D. (2000). Magnetic resonance imaging volumes of the hippocampus and the amygdala in women with borderline personality disorder and early traumatization. *Archives of General Psychiatry*, *57*(12), 1115–1122. https://doi.org/10.1001/archpsyc.57.12.1115

Echeverria, S. E., Diez-Roux, A. V., & Link, B. G. (2004). Reliability of self-reported neighborhood characteristics. *Journal of Urban Health*, *81*(4), 682–701. https://doi.org/10.1093/jurban/jth151

Ellis, B. J., Bianchi, J. M., Griskevicius, V., & Frankenhuis, W. E. (2017). Beyond Risk and Protective Factors: An Adaptation-Based Approach to Resilience. *Perspectives on Psychological Science*, *12*(4), 561–587. https://doi.org/10.1177/1745691617693054

Ellis, B. J., Figueredo, A. J., Brumbach, B. H., & Schlomer, G. L. (2009). Fundamental dimensions of environmental risk: The impact of harsh versus unpredictable environments on the evolution and development of life history strategies. *Human Nature*, *20*(2), 204–268. https://doi.org/10.1007/s12110-009-9063-7

EPA. (1978). *Altitude as a factor in air pollutoin*.

Euser, E. M., van IJzendoorn, M. H., Prinzie, P., & Bakermans-Kranenburg, M. J. (2011). Elevated child maltreatment rates in immigrant families and the role of socioeconomic differences. *Child Maltreatment*, *16*(1), 63–73. https://doi.org/10.1177/1077559510385842

Evans, B. E., Buil, J. M., Burk, W. J., Cillessen, A. H. N., & van Lier, P. A. C. (2018). Urbanicity is Associated with Behavioral and Emotional Problems in Elementary School-Aged Children. *Journal of Child and Family Studies*, *27*(7), 2193–2205. https://doi.org/10.1007/s10826-018-1062-z

Evans, G. W., Li, D., & Whipple, S. S. (2013). Cumulative risk and child development. *Psychological Bulletin*, *139*(6), 1342–1396. https://doi.org/10.1037/a0031808

Fan, C. C., Marshall, A., Smolker, H., Gonzalez, M. R., Tapert, S. F., Barch, D. M., Sowell, E., Dowling, G. J., Cardenas-Iniguez, C., Ross, J., Thompson, W. K., & Herting, M. M. (2021). Adolescent Brain Cognitive Development (ABCD) study Linked External Data (LED): Protocol and Practices for Geocoding and Assignment of Environment Data. *PsyArXiv*.

Fang, X., Brown, D. S., Florence, C. S., & Mercy, J. A. (2012). The economic burden of child maltreatment in the United States and implications for prevention. *Child Abuse and Neglect*, *36*(2), 156–165. https://doi.org/10.1016/j.chiabu.2011.10.006

Fava, N. M., Trucco, E. M., Martz, M. E., Cope, L. M., Jester, J. M., Zucker, R. A., & Heitzeg, M. M. (2019). Childhood adversity, externalizing behavior, and substance use in adolescence: Mediating effects of anterior cingulate cortex activation during inhibitory errors. *Development and Psychopathology*, *31*, 1439–1450. https://doi.org/https://doi.org/10.1017/S0954579418001025

Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., Koss, M. P., & Marks, J. S. (1998). Relationship of Childhood Abuse and Household Dysfunction to Many of the Leading Causes of Death in Adults: The Adverse Childhood Experiences (ACE)Study. *American Journal of Preventive Medicine*, *14*(4), 245–258. https://doi.org/10.1016/j.amepre.2019.04.001

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., Van Der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., & Dale, A. M. (2002). Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. *Neuron*, *33*(3), 341–355. https://doi.org/10.1016/S0896-6273(02)00569-X

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. In *PNAS July* (Vol. 5). www.pnas.orgcgidoi10.1073pnas.0504136102

Fransson, P., & Marrelec, G. (2008). The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: Evidence from a partial correlation network analysis. *NeuroImage*, *42*(3), 1178–1184. https://doi.org/10.1016/j.neuroimage.2008.05.059

Galán, C. A., Shaw, D. S., Dishion, T. J., & Wilson, M. N. (2017). Neighborhood Deprivation during Early Childhood and Conduct Problems in Middle Childhood: Mediation by Aggressive Response Generation. *Journal of Abnormal Child Psychology*, *45*(5), 935–946. https://doi.org/10.1007/s10802-016-0209-x

Garavan, H., Bartsch, H., Conway, K., Decastro, A., Goldstein, R. Z., Heeringa, S., Jernigan, T., Potter, A., Thompson, W., & Zahs, D. (2018). Recruiting the ABCD sample: Design considerations and procedures. *Developmental Cognitive Neuroscience*, *32*(April), 16–22. https://doi.org/10.1016/j.dcn.2018.04.004

Gere, M. K., Villabø, M. A., Torgersen, S., & Kendall, P. C. (2012). Overprotective parenting and child anxiety: The role of co-occurring child behavior problems. *Journal of Anxiety Disorders*, *26*(6), 642–649. https://doi.org/10.1016/j.janxdis.2012.04.003

Giedd, J. N. (2006). Structural Magnetic Resonance Imaging of the Adolescent Brain. *Annals of the New York Academy of Sciences*, *1021*(1), 77–85.

Goff, B., Gee, D. G., Telzer, E. H., Humphreys, K. L., Gabard-Durnam, L., Flannery, J., & Tottenham, N. (2013). Reduced nucleus accumbens reactivity and adolescent depression following early-life stress. *Neuroscience*, *249*, 129–138. https://doi.org/10.1016/j.neuroscience.2012.12.010

Gulyaeva, N. V. (2015). Ventral hippocampus, Stress and phychopathology: Translational implications. *Neurochemical Journal*, *9*(2), 85–94. https://doi.org/10.1134/S1819712415020075

Gunzler, D., Chen, T., Wu, P., & Zhang, H. (2013). Introduction to mediation analysis with structural equation modeling. *Shanghai Archives of Psychiatry*, *25*(6), 390–394. https://doi.org/10.3969/j.issn.1002-0829.2013.06.009

Hall, J. R., Bernat, E. M., & Patrick, C. J. (2007). Externalizing psychopathology and the error-related negativity. *Psychological Science*, *18*(4), 326–333. https://doi.org/10.1111/j.1467-9280.2007.01899.x

Hanson, J. L., Albert, D., Iselin, A. M. R., Carré, J. M., Dodge, K. A., & Hariri, A. R. (2016). Cumulative stress in childhood is associated with blunted reward-related brain activity in adulthood. *Social Cognitive and Affective Neuroscience*, *11*(3), 405–412. https://doi.org/10.1093/scan/nsv124

Heim, C., Meinlschmidt, G., & Nemeroff, C. B. (2003). Neurobiology of early-life stress. *Psychiatric Annals*, *33*(1), 18–26.

Herman, J. P., & Cullinan, W. E. (1997). Neurocircuitry of stress: Central control of the hypothalamo-pituitary-adrenocortical axis. *Trends in Neurosciences*, *20*(2), 78–84. https://doi.org/10.1016/S0166-2236(96)10069-2

Herman, J. P., Mcklveen, J. M., Ghosal, S., Kopp, B., Wulsin, A., Makinson, R., Scheimann, J., & Myers, B. (2016). *Regulation of the hypothalamic-pituitary-adrenocortical stress response*. *6*(2), 603–621. https://doi.org/10.1002/cphy.c150015.Regulation

Hoffmann, M. (2013). The Human Frontal Lobes and Frontal Network Systems: An Evolutionary, Clinical, and Treatment Perspective. *ISRN Neurology*, *2013*, 1–34. https://doi.org/10.1155/2013/892459

Hölzel, B. K., Carmody, J., Vangel, M., Congleton, C., Yerramsetti, S. M., Gard, T., & Lazar, S. W. (2011). Mindfulness practice leads to increases in regional brain gray matter density. *Psychiatry Research - Neuroimaging*, *191*(1), 36–43. https://doi.org/10.1016/j.pscychresns.2010.08.006

Jeong, H. J., Durham, E. L., Moore, T. M., Dupont, R. M., McDowell, M., Cardenas-Iniguez, C., Micciche, E. T., Berman, M. G., Lahey, B. B., & Kaczkurkin, A. N. (2021). The association between latent trauma and brain structure in children. *Translational Psychiatry*, *11*(1).

Jeong, H. J., Moore, T. M., Durham, E. L., Reimann, G. E., Dupont, R. M., Cardenas-Iniguez, C., Berman, M. G., Lahey, B. B., & Kaczkurkin, A. N. (2022). General and Specific Factors of Environmental Stress and their Associations with Brain Structure and Dimensions of Psychopathology. *Biological Psychiatry Global Open Science*, 1–10. https://doi.org/10.1016/j.bpsgos.2022.04.004

Jeong, H. J., Moore, T. M., Durham, E. L., Reimann, G. E., Dupont, R. M., Cardenas-Iniguez, C., Berman, M. G., Lahey, B. B., & Kaczkurkin, A. N. (2023). General and Specific Factors of Environmental Stress and Their Associations With Brain Structure and Dimensions of Psychopathology. *Biological Psychiatry Global Open Science*, *3*(3), 480–489. https://doi.org/10.1016/j.bpsgos.2022.04.004

Jeong, H. J., Reimann, G. E., Durham, E. L., Archer, C., Stier, A. J., Moore, T. M., Pines, J. R., Berman, M. G., & Kaczkurkin, A. N. (2024). Early life stress and functional network topology in children. *Developmental Cognitive Neuroscience*, *66*. https://doi.org/10.1016/j.dcn.2024.101367

Johnson, L. R., Farb, C., Morrison, J. H., McEwen, B. S., & LeDoux, J. E. (2005). Localization of glucocorticoid receptors at postsynaptic membranes in the lateral amygdala. *Neuroscience*, *136*(1), 289–299. https://doi.org/10.1016/j.neuroscience.2005.06.050

Joseph, R. (1999). Frontal Lobe Psychopathology: Mania, Depression, Confabulation, Catatonia, Perseveration, Obsessive Compulsions, and Schizophrenia. *Psychiatry*, *62*(2), 138–172. https://doi.org/10.1080/00332747.1999.11024862

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., Williamson, D., & Ryan, N. (1997). Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry*, *36*(7), 980–988. https://doi.org/10.1097/00004583-199707000-00021

Kenwood, M. M., Kalin, N. H., & Barbas, H. (2022). The prefrontal cortex, pathological anxiety, and anxiety disorders. In *Neuropsychopharmacology* (Vol. 47, Issue 1, pp. 260–275). Springer Nature. https://doi.org/10.1038/s41386-021-01109-z

Kessler, R. C., McLaughlin, K. A., Green, J. G., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., Aguilar-Gaxiola, S., Alhamzawi, A. O., Alonso, J., Angermeyer, M., Benjet, C., Bromet, E., Chatterji, S., De Girolamo, G., Demyttenaere, K., Fayyad, J., Florescu, S., Gal, G., Gureje, O., … Williams, D. R. (2010). Childhood adversities and adult psychopathology in the WHO world mental health surveys. *British Journal of Psychiatry*, *197*(5), 378–385. https://doi.org/10.1192/bjp.bp.110.080499

Kim, E. J., Pellman, B., & Kim, J. J. (2015). Stress effects on the hippocampus: A critical review. *Learning and Memory*, *22*(9), 411–416. https://doi.org/10.1101/lm.037291.114

Kind, A. J. H., Jencks, S., Brock, J., Yu, M., Bartels, C., Ehlenbach, W., Greenberg, C., & Smith, M. (2014). Neighborhood socioeconomic disadvantage and 30-day rehospitalization: A retrospective cohort study. *Annals of Internal Medicine*, *161*(11), 765–774. https://doi.org/10.7326/M13-2946

Kotov, R., Waszczuk, M. A., Krueger, R. F., Forbes, M. K., Watson, D., Clark, L. A., Achenbach, T. M., Althoff, R. R., Ivanova, M. Y., Michael Bagby, R., Brown, T. A., Carpenter, W. T., Caspi, A., Moffitt, T. E., Eaton, N. R., Forbush, K. T., Goldberg, D., Hasin, D., Hyman, S. E., … Zimmerman, M. (2017). The hierarchical taxonomy of psychopathology (HiTOP): A dimensional alternative to traditional nosologies. *Journal of Abnormal Psychology*, *126*(4), 454–477. https://doi.org/10.1037/abn0000258

Krabbendam, L., Van Vugt, M., Conus, P., Söderström, O., Abrahamyan Empson, L., Van Os, J., & Fett, A. K. J. (2021). Understanding urbanicity: How interdisciplinary methods help to unravel the effects of the city on mental health. In *Psychological Medicine* (Vol. 51, Issue 7, pp. 1099–1110). Cambridge University Press. https://doi.org/10.1017/S0033291720000355

Krain, A. L., & Castellanos, F. X. (2006). Brain development and ADHD. *Clinical Psychology Review*, *26*(4), 433–444. https://doi.org/10.1016/j.cpr.2006.01.005

Kujawa, A., Klein, D. N., Pegg, S., & Weinberg, A. (2020). Developmental trajectories to reduced activation of positive valence systems: A review of biological and environmental contributions. *Developmental Cognitive Neuroscience*, *43*. https://doi.org/10.1016/j.dcn.2020.100791

Lahey, B. B., Krueger, R. F., Rathouz, P. J., Waldman, I. D., & Zald, D. H. (2017). A hierarchical causal taxonomy of psychopathology across the life span. *Psychological Bulletin*, *143*(2), 142–186. https://doi.org/10.1037/bul0000069

Larsen, S. E., & Pacella, M. L. (2016). Comparing the effect of DSM-congruent traumas vs. DSM-incongruent stressors on PTSD symptoms: A meta-analytic review. In *Journal of Anxiety Disorders* (Vol. 38, pp. 37–46). Elsevier Ltd. https://doi.org/10.1016/j.janxdis.2016.01.001

Leeb, R. T., Paulozzi, L. J., Melanson, C., Simon, T. R., & Arias, I. (2008). *Childhood maltreatment surveillance: uniform definitions for public health and recommended data*

elements (Version 1.). Centers for Disease Control and Prevention, National Center for Injury Prevention and Control.

Lim, L., Radua, J., & Rubia, K. (2014). Gray Matter Abnormalities in Childhood Maltreatment: A Voxel-Wise Meta-Analysis. *The American Journal of Psychiatry*, *171*(8), 854–863.

Lisdahl, K. M., Sher, K. J., Conway, K. P., Gonzalez, R., Feldstein Ewing, S. W., Nixon, S. J., Tapert, S., Bartsch, H., Goldstein, R. Z., & Heitzeg, M. (2018). Adolescent brain cognitive development (ABCD) study: Overview of substance use assessment methods. *Developmental Cognitive Neuroscience*, *32*(April 2017), 80–96. https://doi.org/10.1016/j.dcn.2018.02.007

Liu, P. Z., & Nusslock, R. (2017). How Stress Gets Under the Skin: Early Life Adversity and Glucocorticoid Receptor Epigenetic Regulation. *Current Genomics*, *19*(8), 653–664. https://doi.org/10.2174/1389202919666171228164350

Luby, J. L., Barch, D., Whalen, D., Tillman, R., & Belden, A. (2017). Association between early life adversity and risk for poor emotional and physical health in adolescence a putative mechanistic neurodevelopmental pathway. *JAMA Pediatrics*, *171*(12), 1168–1175. https://doi.org/10.1001/jamapediatrics.2017.3009

MacKinnon, D. P., Fairchild, A. J., & Fritz, M. S. (2007). Mediation analysis. *Annual Review of Psychology*, *58*, 593–614. https://doi.org/10.1146/annurev.psych.58.110405.085542

Manly, J. T. (2005). Advances in research definitions of child maltreatment. *Child Abuse and Neglect*, *29*(5 SPEC. ISS.), 425–439. https://doi.org/10.1016/j.chiabu.2005.04.001

Marsh, H. W., Morin, A. J. S., Parker, P. D., & Kaur, G. (2014). Exploratory structural equation modeling: An integration of the best features of exploratory and confirmatory factor analysis. In *Annual Review of Clinical Psychology* (Vol. 10, pp. 85–110). Annual Reviews Inc. https://doi.org/10.1146/annurev-clinpsy-032813-153700

Mattson, M. P. (2008). Hormesis defined. In *Ageing Research Reviews* (Vol. 7, Issue 1, pp. 1–7). https://doi.org/10.1016/j.arr.2007.08.007

Maxwell, S. E., & Cole, D. A. (2007). Bias in cross-sectional analyses of longitudinal mediation. *Psychological Methods*, *12*(1), 23–44. https://doi.org/10.1037/1082-989X.12.1.23

Maxwell, S. E., Cole, D. A., & Mitchell, M. A. (2011). Bias in cross-sectional analyses of longitudinal mediation: Partial and complete mediation under an autoregressive model. *Multivariate Behavioral Research*, *46*(5), 816–841. https://doi.org/10.1080/00273171.2011.606716

McEwen, B. S. (1998). Stress, Adaptation, and Disease. *Annals of the New York Academy of Sciences*, *840*(1), 33–44.

McEwen, B. S. (1999). Stress and hippocampal plasticity. *Annual Review of Neuroscience*, *22*, 105–122. https://doi.org/10.1146/annurev.neuro.22.1.105

McEwen, B. S. (2007). Physiology and neurobiology of stress and adaptation: Central role of the brain. *Physiological Reviews*, *87*(3), 873–904. https://doi.org/10.1152/physrev.00041.2006

McEwen, B. S., & Stellar, E. (1973). Stress and the individual: Mechanisms leading to disease. *Archives of Internal Medicine*, *153*(18).

McEwen, Nasca, C., & Gray, J. D. (2016). Stress Effects on Neuronal Structure: Hippocampus, Amygdala, and Prefrontal Cortex. *Neuropsychopharmacology*, *41*(1), 3–23. https://doi.org/10.1038/npp.2015.171

McKlveen, J. M., Moloney, R. D., Scheimann, J. R., Myers, B., & Herman, J. P. (2019). "Braking" the Prefrontal Cortex: The Role of Glucocorticoids and Interneurons in Stress

Adaptation and Pathology. *Biological Psychiatry*, *86*(9), 669–681. https://doi.org/10.1016/j.biopsych.2019.04.032

McLaughlin, Green, J. G., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., & Kessler, R. C. (2010). Childhood adversities and adult psychopathology in the National Comorbidity Survey Replication (NCS-R) III: Associations with functional impairment related to DSM-IV disorders. *Psychological Medicine*, *40*(5), 847–859. https://doi.org/10.1017/S0033291709991115

McLaughlin, K. A. (2016). Future Directions in Childhood Adversity and Youth Psychopathology. *Journal of Clinical Child and Adolescent Psychology*, *45*(3), 361–382. https://doi.org/10.1080/15374416.2015.1110823

McLaughlin, K. A., & Sheridan, M. A. (2016). Beyond Cumulative Risk: A Dimensional Approach to Childhood Adversity. *Current Directions in Psychological Science*, *25*(4), 239–245. https://doi.org/10.1177/0963721416655883

McLaughlin, K. A., Sheridan, M. A., Humphreys, K. L., Belsky, J., & Ellis, B. J. (2021). The Value of Dimensional Models of Early Experience: Thinking Clearly About Concepts and Categories. *Perspectives on Psychological Science*, *16*(6), 1463–1472. https://doi.org/10.1177/1745691621992346

McLaughlin, K. A., Weissman, D., & Bitrán, D. (2019). Childhood Adversity and Neural Development: A Systematic Review. *Annual Review of Developmental Psychology*, *1*(1), 277–312. https://doi.org/10.1146/annurev-devpsych-121318-084950

Mehta, M. A., Golembo, N. I., Nosarti, C., Colvert, E., Mota, A., Williams, S. C. R., Rutter, M., & Sonuga-Barke, E. J. S. (2009). Amygdala, hippocampal and corpus callosum size following severe early institutional deprivation: the English and Romanian Adoptees study pilot. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *50*(8), 943–951. https://doi.org/10.1111/j.1469-7610.2009.02084.x

Moore, T. M., Kaczkurkin, A. N., Durham, E. L., Jeong, H. J., McDowell, M. G., Dupont, R. M., Applegate, B., Tackett, J. L., Cardenas-Iniguez, C., Kardan, O., Akcelik, G. N., Stier, A., Rosenberg, M. D., Hedeker, D., Bernman, M. G., & Lahey, B. B. (2020). Criterion Validity and Relationships between Alternative Hierarchical Dimensional Models of General and Specific Psychopathology. *Journal of Abnormal Psychology*, *129*, 677–688.

Moos, R. H., & Moos, B. S. (1994). *Family Environment Scale Manual.* Consulting Psychologists Press.

Morris, A. S., Silk, J. S., Steinberg, L., Myers, S. S., & Robinson, L. R. (2007). The role of the family context in the development of emotion regulation. *Social Development*, *16*(2), 361–388. https://doi.org/10.1111/j.1467-9507.2007.00389.x

Motzkin, J. C., Philippi, C. L., Wolf, R. C., Baskaya, M. K., & Koenigs, M. (2015). Ventromedial prefrontal cortex is critical for the regulation of amygdala activity in humans. *Biological Psychiatry*, *77*(3), 276–284. https://doi.org/10.1016/j.biopsych.2014.02.014

Mujahid, M. S., Diez Roux, A. V., Morenoff, J. D., & Raghunathan, T. (2007). Assessing the measurement properties of neighborhood scales: From psychometrics to ecometrics. *American Journal of Epidemiology*, *165*(8), 858–867. https://doi.org/10.1093/aje/kwm040

Muthén, L. K., & Muthén, B. O. (2017). *Mplus User's Guide (Eighth ed.)*. Los Angeles, CA: Muthén & Muthén.

Myers-Schulz, B., & Koenigs, M. (2012). Functional anatomy of ventromedial prefrontal cortex: Implications for mood and anxiety disorders. In *Molecular Psychiatry* (Vol. 17, Issue 2, pp. 132–141). https://doi.org/10.1038/mp.2011.88

Neufeld, N. H., Oliver, L. D., Mulsant, B. H., Alexopoulos, G. S., Hoptman, M. J., Tani, H., Marino, P., Meyers, B. S., Rothschild, A. J., Whyte, E. M., Bingham, K. S., Flint, A. J., & Voineskos, A. N. (2023). Effects of antipsychotic medication on functional connectivity in major depressive disorder with psychotic features. *Molecular Psychiatry*, *28*(8), 3305–3313. https://doi.org/10.1038/s41380-023-02118-8

Newbury, J., Arseneault, L., Caspi, A., Moffitt, T. E., Odgers, C. L., & Fisher, H. L. (2016). Why Are Children in Urban Neighborhoods at Increased Risk for Psychotic Symptoms? Findings from a UK Longitudinal Cohort Study. *Schizophrenia Bulletin*, *42*(6), 1372–1383. https://doi.org/10.1093/schbul/sbw052

Northoff, G., Hirjak, D., Wolf, R. C., Magioncalda, P., & Martino, M. (2021). All roads lead to the motor cortex: psychomotor mechanisms and their biochemical modulation in psychiatric disorders. In *Molecular Psychiatry* (Vol. 26, Issue 1, pp. 92–102). Springer Nature. https://doi.org/10.1038/s41380-020-0814-5

Oshri, A. (2023). The Hormesis Model for Building Resilience Through Adversity: Attention to Mechanism in Developmental Context. *Review of General Psychology*, *27*(3), 245–259. https://doi.org/10.1177/10892680221142020

Oshri, A., Howard, C. J., Zhang, L., Reck, A., Cui, Z., Liu, S., Duprey, E., Evans, A. I., Azarmehr, R., & Geier, C. F. (2024). Strengthening through adversity: The hormesis model in developmental psychopathology. *Development and Psychopathology*. https://doi.org/10.1017/S0954579424000427

Paquola, C., Bennett, M. R., & Lagopoulos, J. (2016). Understanding heterogeneity in grey matter research of adults with childhood maltreatment—A meta-analysis and review. In *Neuroscience and Biobehavioral Reviews* (Vol. 69, pp. 299–312). Elsevier Ltd. https://doi.org/10.1016/j.neubiorev.2016.08.011

Park, H. J., & Friston, K. (2013). Structural and functional brain networks: From connections to cognition. In *Science* (Vol. 342, Issue 6158). American Association for the Advancement of Science. https://doi.org/10.1126/science.1238411

Patel, P. D., Katz, M., Karssen, A. M., & Lyons, D. M. (2008). Stress-induced changes in corticosteroid receptor expression in primate hippocampus and prefrontal cortex. *Psychoneuroendocrinology*, *33*(3), 360–367. https://doi.org/10.1016/j.psyneuen.2007.12.003

Paus, T. (2005). Mapping brain maturation and cognitive development during adolescence. *Trends in Cognitive Sciences*, *9*(2), 60–68. https://doi.org/10.1016/j.tics.2004.12.008

Petanjek, Z., Judaš, M., Kostović, I., & Uylings, H. B. M. (2008). Lifespan alterations of basal dendritic trees of pyramidal neurons in the human prefrontal cortex: A layer-specific pattern. *Cerebral Cortex*, *18*(4), 915–929. https://doi.org/10.1093/cercor/bhm124

Petrican, R., Miles, S., Rudd, L., Wasiewska, W., Graham, K. S., & Lawrence, A. D. (2021). Pubertal timing and functional neurodevelopmental alterations independently mediate the effect of family conflict on adolescent psychopathology. *Developmental Cognitive Neuroscience*, *52*, 17. https://doi.org/https://doi.org/10.1016/j.dcn.2021.101032

Peugh, J. L. (2010). A practical guide to multilevel modeling. *Journal of School Psychology*, *48*(1), 85–112. https://doi.org/10.1016/j.jsp.2009.09.002

Picci, G., Taylor, B. K., Killanin, A. D., Eastman, J. A., Frenzel, M. R., Wang, Y., Stephen, J. M., Calhoun, V. D., & Wilson, T. W. (2022). Left amygdala structure mediates longitudinal associations between exposure to threat and long-term psychiatric symptomatology in

youth. *Human Brain Mapping*, *43*, 4091–4102. https://doi.org/https://doi.org/10.1002/hbm.25904

Pinciotti, C. M., & Fisher, E. K. (2022). Perceived traumatic and stressful etiology of obsessive-compulsive disorder. *Psychiatry Research Communications*, *2*(2). https://doi.org/10.1016/j.psycom.2022.100044

Pizzagalli, D. A., & Roberts, A. C. (2022). Prefrontal cortex and depression. In *Neuropsychopharmacology* (Vol. 47, Issue 1, pp. 225–246). Springer Nature. https://doi.org/10.1038/s41386-021-01101-7

Pollok, T. M., Kaiser, A., Kraaijenvanger, E. J., Monninger, M., Brandeis, D., Banaschewski, T., Eickhoff, S. B., & Holz, N. E. (2022). Neurostructural traces of early life adversities: A meta-analysis exploring age- and adversity-specific effects. In *Neuroscience and Biobehavioral Reviews* (Vol. 135). Elsevier Ltd. https://doi.org/10.1016/j.neubiorev.2022.104589

Preacher, K. J., Zyphur, M. J., & Zhang, Z. (2010). A general multilevel SEM framework for assessing multilevel mediation. *Psychological Methods*, *15*(3), 209–233. https://doi.org/10.1037/a0020141

Qin, P., & Northoff, G. (2011). How is our self related to midline regions and the default-mode network? In *NeuroImage* (Vol. 57, Issue 3, pp. 1221–1233). https://doi.org/10.1016/j.neuroimage.2011.05.028

Raichle, M. E., Macleod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (1996). A default mode of brain function. In *National Academy of Sciences*. www.pnas.org

Rapee, R. M. (2002). *The Development and Modification of Temperamental Risk for Anxiety Disorders: Prevention of a Lifetime of Anxiety?*

Rende & Plomin 1993. (n.d.).

Repetti, R. L., Taylor, S. E., & Seeman, T. E. (2002). Risky families: Family social environments and the mental and physical health of offspring. In *Psychological Bulletin* (Vol. 128, Issue 2, pp. 330–366). American Psychological Association Inc. https://doi.org/10.1037/0033-2909.128.2.330

Ricciardi, E., Rota, G., Sani, L., Gentili, C., Gaglianese, A., Guazzelli, M., & Pietrini, P. (2013). How the brain heals emotional wounds: The functional neuroanatomy of forgiveness. *Frontiers in Human Neuroscience*, *7*, 1–9. https://doi.org/10.3389/fnhum.2013.00839

Rice, J. P., Reich, T., Bucholz, K. K., Neurnan, R. J., Fishman, R., Rochberg, N., Hesselbrock, V. M., Nurnberger, J. I., Schuckit, M. a, & Begleiter, H. (1995). Diagnoses of Alcohol Dependence. *Direct*, *19*(4), 1018–1023.

Rutter, M., & Silberg, J. (2002). *GENE-ENVIRONMENT INTERPLAY IN RELATION TO EMOTIONAL AND BEHAVIORAL DISTURBANCE*. www.annualreviews.org

Saaltink, D. J., & Vreugdenhil, E. (2014). Stress, glucocorticoid receptors, and adult neurogenesis: A balance between excitation and inhibition? *Cellular and Molecular Life Sciences*, *71*(13), 2499–2515. https://doi.org/10.1007/s00018-014-1568-5

Sala, M., Perez, J., Soloff, P., Ucelli Di Nemi, S., Caverzasi, E., Soares, J. C., & Brambilla, P. (2004). Stress and hippocampal abnormalities in psychiatric disorders. *European Neuropsychopharmacology*, *14*(5), 393–405. https://doi.org/10.1016/j.euroneuro.2003.12.005

Sanfilipo, M., Lafargue, T., Rusinek, H., Arena, L., Loneragan, C., Lautin, A., Feiner, D., Rotrosen, J., & Wolkin, A. (n.d.). *Volumetric Measure of the Frontal and Temporal Lobe Regions in Schizophrenia Relationship to Negative Symptoms*.

Schaefer, E. S. (1965). Children's reports of parental behavior: An inventory. *Child Development*, *36*(2), 413–424. https://doi.org/ttps://doi.org/10.2307/1126465

Schmahl, C. G., Vermetten, E., Elzinga, B. M., & Bremner, J. D. (2003). Magnetic resonance imaging of hippocampal and amygdala volume in women with childhood abuse and borderline personality disorder. *Psychiatry Research - Neuroimaging*, *122*(3), 193–198. https://doi.org/10.1016/S0925-4927(03)00023-4

Selig, J. P., & Preacher, K. J. (2009). Mediation Models for Longitudinal Data in Developmental Research. *Research in Human Development*, *6*(2–3), 144–164. https://doi.org/10.1080/15427600902911247

Shaw, D. S., Sitnick, S. L., Brennan, L. M., Choe, D. E., Dishion, T. J., Wilson, M. N., & Gardner, F. (2016). The long-term effectiveness of the Family Check-Up on school-age conduct problems: Moderation by neighborhood deprivation. *Development and Psychopathology*, *28*(4), 1471–1486. https://doi.org/10.1017/S0954579415001212

Sheridan, M. A., & McLaughlin, K. A. (2014). Dimensions of early experience and neural development: Deprivation and threat. *Trends in Cognitive Sciences*, *18*(11), 580–585. https://doi.org/10.1016/j.tics.2014.09.001

Singh, G. K. (2003). Area Deprivation and Widening Inequalities in US Mortality, 1969-1998. *American Journal of Public Health*, *93*(7), 1137–1143. https://doi.org/10.2105/AJPH.93.7.1137

Smith, K. E., & Pollak, S. D. (2021). Rethinking Concepts and Categories for Understanding the Neurodevelopmental Effects of Childhood Adversity. *Perspectives on Psychological Science*, *16*(1), 67–93. https://doi.org/10.1177/1745691620920725

Smoller, J. W., Andreassen, O. A., Edenberg, H. J., Faraone, S. V., Glatt, S. J., & Kendler, K. S. (2019). Psychiatric genetics and the structure of psychopathology. In *Molecular Psychiatry* (Vol. 24, Issue 3, pp. 409–420). Nature Publishing Group. https://doi.org/10.1038/s41380-017-0010-4

Sterling, P. (2014). Homeostasis vs allostasis implications for brain function and mental disorders. In *JAMA Psychiatry* (Vol. 71, Issue 10, pp. 1192–1193). American Medical Association. https://doi.org/10.1001/jamapsychiatry.2014.1043

Sterling, P., & Eyer, J. (1988). Allostasis: A new paradigm to explain arousal pathology. In *Life Stress, Cognition and Health* (pp. 629–649). John Wiley & Sons.

Stier, A. J., Schertz, K. E., Rim, N. W., Cardenas-Iniguez, C., Lahey, B. B., Bettencourt, M. A., & Berman, M. G. (2024). *Evidence and theory for lower rates of depression in larger US urban areas*. https://doi.org/10.1073/pnas.2022472118/-/DCSupplemental.y

Stover, P. J., Harlan, W. R., Hammond, J. A., Hendershot, T., & Hamilton, C. M. (2010). PhenX: a toolkit for interdisciplinary genetics research. *Current Opinion in Lipidology*, *21*(2), 136–140. https://doi.org/10.1053/j.gastro.2016.08.014.CagY

Tackett, J. L., Lahey, B. B., van Hulle, C., Waldman, I., Krueger, R. F., & Rathouz, P. J. (2013). Common genetic influences on negative emotionality and a general psychopathology factor in childhood and adolescence. *Journal of Abnormal Psychology*, *122*(4), 1142–1153. https://doi.org/10.1037/a0034151

Taylor, E. K., Abdurokhmonova, G., & Romeo, R. R. (2023). Socioeconomic Status and Reading Development: Moving from "Deficit" to "Adaptation" in Neurobiological Models of Experience-Dependent Learning. In *Mind, Brain, and Education* (Vol. 17, Issue 4, pp. 324–333). John Wiley and Sons Inc. https://doi.org/10.1111/mbe.12351

Teicher, M. H., & Samson, J. A. (2013). Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. *American Journal of Psychiatry*, *170*(10), 1114–1133. https://doi.org/10.1176/appi.ajp.2013.12070957

Tottenham, N., Hare, T. A., Quinn, B. T., McCarry, T. W., Nurse, M., Gilhooly, T., Millner, A., Galvan, A., Davidson, M. C., Eigsti, I. M., Thomas, K. M., Freed, P. J., Booma, E. S., Gunnar, M. R., Altemus, M., Aronson, J., & Casey, B. J. (2010). Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. *Developmental Science*, *13*(1), 46–61. https://doi.org/10.1111/j.1467-7687.2009.00852.x

Tottenham, N., & Sheridan, M. A. (2010). A review of adversity, the amygdala and the hippocampus: A consideration of developmental timing. *Frontiers in Human Neuroscience*, *3*(JAN), 1–18. https://doi.org/10.3389/neuro.09.068.2009

Treutler, C. M., & Epkins, C. C. (2003). Are Discrepancies Among Child, Mother, and Father Reports on Children's Behavior Related to Parents' Psychological Symptoms and Aspects of Parent-Child Relationships? 1. In *Journal of Abnormal Child Psychology* (Vol. 31, Issue 1).

Uno, H., Tarara, R., Else, J. G., Suleman, M. A., & Sapolsky, R. M. (1989). Hippocampal damage associated with prolonged and fatal stress in primates. *Journal of Neuroscience*, *9*(5), 1705–1711. https://doi.org/10.1523/jneurosci.09-05-01705.1989

Van Haarst, A. D., Oitzl, M. S., & De Kloet, E. R. (1997). Facilitation of feedback inhibition through blockade of glucocorticoid receptors in the hippocampus. *Neurochemical Research*, *22*(11), 1323–1328. https://doi.org/10.1023/A:1022010904600

VanTieghem, M. R., & Tottenham, N. (2018). Neurobiological Programming of Early Life Stress: Functional Development of Amygdala-Prefrontal Circuitry and Vulnerability for Stress-Related Psychopathology. In E. Vermetten, D. G. Baker, & V. B. Risbrough (Eds.), *Behavioral Neurobiology of PTSD* (pp. 117–136). Springer.

Visser, K., Bolt, G., Finkenauer, C., Jonker, M., Weinberg, D., & Stevens, G. W. J. M. (2021). Neighbourhood deprivation effects on young people's mental health and well-being: A systematic review of the literature. In *Social Science and Medicine* (Vol. 270). Elsevier Ltd. https://doi.org/10.1016/j.socscimed.2020.113542

Voineskos, A. N., Mulsant, B. H., Dickie, E. W., Neufeld, N. H., Rothschild, A. J., Whyte, E. M., Meyers, B. S., Alexopoulos, G. S., Hoptman, M. J., Lerch, J. P., & Flint, A. J. (2020). Effects of Antipsychotic Medication on Brain Structure in Patients with Major Depressive Disorder and Psychotic Features: Neuroimaging Findings in the Context of a Randomized Placebo-Controlled Clinical Trial. *JAMA Psychiatry*, *77*(7), 674–683. https://doi.org/10.1001/jamapsychiatry.2020.0036

Volkow, N. D., Koob, G. F., Croyle, R. T., Bianchi, D. W., Gordon, J. A., Koroshetz, W. J., Pérez-Stable, E. J., Riley, W. T., Bloch, M. H., Conway, K., Deeds, B. G., Dowling, G. J., Grant, S., Howlett, K. D., Matochik, J. A., Morgan, G. D., Murray, M. M., Noronha, A., Spong, C. Y., … Weiss, S. R. B. (2018). The conception of the ABCD study: From substance use to a broad NIH collaboration. *Developmental Cognitive Neuroscience*, *32*(April 2017), 4–7. https://doi.org/10.1016/j.dcn.2017.10.002

Vyas, A., Mitra, R., Shankaranarayana Rao, B. S., & Chattarji, S. (2002). Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. *Journal of Neuroscience*, *22*(15), 6810–6818. https://doi.org/10.1523/jneurosci.22-15-06810.2002

Wade, M., Wright, L., & Finegold, K. E. (2022). The effects of early life adversity on children's mental health and cognitive functioning. *Translational Psychiatry*, *12*(1), 1–12. https://doi.org/10.1038/s41398-022-02001-0

Weinberger, D. R. (1988). *Schizophrenia and the frontal lobe*.

White, R. M. B., Witherspoon, D. P., Wei, W., Zhao, C., Pasco, M. C., Maereg, T. M., Bámaca-Colbert, M., Browning, C., Furr-Holden, D., Leech, T., Leventhal, T., Matthews, S. A., Roy, A., Sugie, N., & Winkler, E. (2021). Adolescent Development in Context: A Decade Review of Neighborhood and Activity Space Research. In *Journal of Research on Adolescence* (Vol. 31, Issue 4, pp. 944–965). John Wiley and Sons Inc. https://doi.org/10.1111/jora.12623

Whitfield-Gabrieli, S., & Ford, J. M. (2012). Default mode network activity and connectivity in psychopathology. In *Annual Review of Clinical Psychology* (Vol. 8). https://doi.org/10.1146/annurev-clinpsy-032511-143049

Woon, F. L., & Hedges, D. W. (2009). Amygdala Volume in Adults with Posttraumatic Stress Disorder: A Meta-Analysis. *Journal of Neuropsychiatry*, *21*(1), 5–12. https://doi.org/10.1176/appi.neuropsych.21.1.5

Yang, Y., & Raine, A. (2009). Prefrontal structural and functional brain imaging findings in antisocial, violent, and psychopathic individuals: A meta-analysis. *Psychiatry Research - Neuroimaging*, *174*(2), 81–88. https://doi.org/10.1016/j.pscychresns.2009.03.012

Zald, D. H., & Lahey, B. B. (2017). Implications of the Hierarchical Structure of Psychopathology for Psychiatric Neuroimaging. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *2*(4), 310–317. https://doi.org/10.1016/j.bpsc.2017.02.003

Zucker, R. A., Gonzalez, R., Feldstein Ewing, S. W., Paulus, M. P., Arroyo, J., Fuligni, A., Morris, A. S., Sanchez, M., & Wills, T. (2018a). Assessment of culture and environment in the Adolescent Brain and Cognitive Development Study: Rationale, description of measures, and early data. *Developmental Cognitive Neuroscience*, *32*(May 2017), 107–120. https://doi.org/10.1016/j.dcn.2018.03.004

Zucker, R. A., Gonzalez, R., Feldstein Ewing, S. W., Paulus, M. P., Arroyo, J., Fuligni, A., Morris, A. S., Sanchez, M., & Wills, T. (2018b). Assessment of culture and environment in the Adolescent Brain and Cognitive Development Study: Rationale, description of measures, and early data. *Developmental Cognitive Neuroscience*, *32*(May 2017), 107–120. https://doi.org/10.1016/j.dcn.2018.03.004

Appendix

Table S1. Exploratory structural equation modeling with 4 factors.

Item	Brief wording	Family Dynamics	Interpersonal Support	Neighborhood SES Deprivation	Urbanicity
ksads754	Car accident	0.27	0.05	0.13	-0.14
ksads755	Significant accident	0.31	0.01	-0.03	-0.02
ksads756	Witnessed/caught in a fire	0.33	0.05	0.03	0.01
ksads757	Witnessed/caught in a natural disaster	0.22	0.01	0.07	-0.30
ksads760	Witnessed violence in the community	**0.43**	0.12	0.15	0.13
ksads766	Witnessed violence in the home	**0.53**	0.01	0.16	0.00
ksads769	Sexually assaulted by a peer	**0.42**	-0.02	-0.01	-0.03
ksads770	Learned about sudden death of loved one	0.31	0.01	0.06	-0.01
ksads763_765	Beaten or threatened to death by a family member	**0.50**	0.05	0.10	-0.04
ksads764_768	Threatened to death or sexually assaulted by a non-family member	**0.40**	0.02	0.14	-0.15
fes1	Family members fight a lot	**0.52**	-0.06	-0.09	0.02
fes2	Family member rarely become angry	0.34	-0.03	-0.04	0.06
fes3	Family members throw things	**0.50**	-0.03	-0.02	0.06
fes4	Family members hardly lose temper	0.36	-0.03	-0.01	0.04
fes5	Family members criticize each other	0.39	-0.05	0.06	0.05
fes6	Family members hit each other	**0.46**	0.00	0.04	0.04
fes7	Family members try to smooth things when there is a disagreement	0.23	-0.06	-0.04	0.07
fes8	Family members try to outdo each other	0.32	0.01	0.12	0.02
fes9	Family members don't raise voice	0.27	-0.02	-0.25	0.03
fexp1_2	Could not afford food/telephone service	**0.48**	-0.03	0.28	0.17

fexp3_4	Could not pay and/or evicted for not paying rent/mortgage	**0.49**	-0.03	0.23	0.17
fexp5	Could not pay for gas/electric service	**0.45**	-0.03	0.19	0.13
fexp6_7	Could not afford to go to the hospital/see a dentist	0.37	-0.06	0.22	-0.05
roster	Number of people living at the home	0.02	0.03	0.01	-0.07
fmhx4	Family history of alcohol-related problems	**0.58**	0.02	-0.11	-0.02
fmhx5	Family history of drug-related problems	**0.67**	0.00	0.06	-0.06
fmhx7	Family history of mania	**0.55**	-0.03	-0.06	-0.01
fmhx8	Family history of psychosis	**0.54**	0.01	0.01	0.02
fmhx9	Family history of antisocial problems	**0.66**	0.01	0.09	-0.10
fmhx10	Family history of nerve problems	**0.57**	0.01	-0.09	0.02
fmhx11	Family history of receiving psychiatric service	**0.69**	0.02	-0.25	-0.02
fmhx12	Family history of hospitalization due to psychiatric problems	**0.70**	0.04	-0.09	-0.02
fmhx13	Family history of suicide	**0.61**	0.00	-0.09	-0.01
cvg_acc1	Caregiver makes me feel better after talking over my worries	0.01	**0.63**	0.02	0.02
cvg_acc2	Caregiver smiles at me very often	-0.02	**0.53**	-0.08	0.03
cvg_acc3	Caregiver makes me feel better when I'm upset	0.03	**0.65**	0.00	0.01
cvg_acc4	Caregiver believes in showing love for me	0.00	**0.64**	0.01	0.03
cvg_acc5	Caregiver is easy to talk to	-0.02	**0.56**	-0.02	0.04
cvg_acc	There is a second adult who cares for me	-0.10	0.12	-0.15	-0.04
conflict	Caregiver and child get along	0.37	-0.14	-0.11	0.01

ftime_lv	Child lives with caregiver full time	-0.07	-0.02	0.12	0.03
school_g	Grades child gets on average	0.17	-0.19	0.25	0.00
grad_drp	Drop in child's grades	-0.20	0.20	-0.22	0.04
service2	Child receives: Full-time learning support	0.07	-0.09	0.22	-0.03
service4	Child receives: Special education for specific subjects	0.20	-0.15	0.11	-0.06
service5	Child receives: Part-time aide	0.20	-0.12	0.13	0.03
service6	Child receives: Resource room	0.27	-0.08	0.00	-0.02
service7	Child receives: Tutoring support	0.15	-0.05	0.13	-0.11
service8	Child receives: Gifted program service	-0.10	0.03	-0.13	-0.04
service9	Child receives: other special service	0.14	-0.06	0.01	-0.02
det_susp	Detention or suspension history	-0.36	0.18	-0.22	-0.06
bst_frnd	Child has a best friend	-0.07	0.16	0.12	-0.08
grp_frnd	Child has a group of friends	-0.05	0.16	-0.20	-0.01
bully	Problems with bullying	0.35	-0.13	0.10	-0.01
mh_srvc	Child has received mental health service	**0.47**	-0.13	-0.11	0.03
school2	Students have lots of chance to decide things in my school	0.04	**0.40**	0.09	0.05
school3	I get along with my teachers	-0.04	**0.61**	-0.04	-0.02
school4	My teachers notice when I'm doing good job	0.02	**0.52**	0.15	-0.04
school5	There are many chances for students in get involved	0.04	0.36	0.01	0.03
school6	I feel safe at my school	0.00	**0.58**	-0.13	-0.02
school7	The school lets my parents know when I've done something well	0.04	**0.46**	0.10	-0.04
school8	I like school because I do well	-0.01	**0.62**	0.12	-0.03
school9	I feel just as smart as other kids	0.03	**0.47**	0.04	-0.01
school10	There are many chances to be part of class	0.06	**0.59**	-0.01	0.05
school15	School bores me	0.05	**-0.50**	-0.01	0.01

school17	Getting good grads is not important to me	0.06	-0.29	-0.12	0.05
resil5a	The number of friends that are boys	0.02	-0.01	-0.04	0.00
resil6a	The number of friends that are girls	0.00	0.23	0.01	0.01
resil5b	The number of close friends that are boys	0.01	-0.02	-0.06	0.01
resil6b	The number of close friends that are girls	-0.01	0.22	0.05	0.00
neigh	Neighborhood is safe from crime (child)	-0.07	0.25	-0.30	-0.11
neigh1	I feel safe walking in my neighborhood	-0.12	0.04	-0.37	**-0.46**
neigh3	Neighborhood is safe from crime (parent)	-0.15	0.03	-0.38	**-0.50**
crpf1	Accessibility to alcohol	0.08	0.00	**-0.45**	0.08
crpf2	Accessibility to cigarettes	**0.41**	-0.05	-0.03	0.04
crpf4	Accessibility to marijuana	**0.40**	-0.02	-0.07	0.12
crpf6	Medical marijuana legal in the state	0.09	0.06	0.12	-0.19
monitor1	How often parents know where I am	-0.05	**0.45**	-0.05	0.00
monitor2	How often parents know who I am with	0.01	0.35	-0.13	0.03
monitor3	How often parents get in touch when they are not at home	0.02	0.30	-0.09	0.05
monitor4	How often I let parents about my plan	-0.01	**0.43**	0.07	0.02
monitor5	How often child and parents eat dinner together	-0.06	0.28	-0.11	0.01
rh_yr	Years of residence	-0.11	0.00	-0.17	0.12
rh_ele	Elevation level	0.24	0.08	-0.27	0.27
rh_walk	Walkability scores	-0.08	0.00	0.17	**0.50**
rh_crime	Crime rates	0.13	0.05	-0.24	**0.56**
rh_eduh*	Percentage of populations with at least high school diploma	-0.11	-0.05	**0.77**	0.02
rh_work*	Percentage of populations with white collar occupations	-0.04	-0.03	0.16	-0.28
rh_incom	Median family income	0.03	-0.03	**-0.97**	0.10
rh_indis	Income disparity	0.02	0.02	**0.83**	0.05

rh_homv	Median home value	-0.12	-0.07	**-0.53**	0.13
rh_rent	Median gross rent	-0.22	-0.05	**-0.50**	0.15
rh_homo*	Home ownership rate	-0.06	0.00	**0.63**	0.27
rh_crowd	Crowding in the home	-0.18	-0.01	**0.50**	0.13
rh_unemp	Unemployment rate	-0.03	-0.03	**0.67**	0.06
rh_b138	Percentage of populations below or around the poverty level	-0.02	-0.01	**0.87**	0.04
rh_sp	Percentage of single-parent household	0.03	-0.01	**0.76**	0.10
rh_ncar	Percentage of houses without a motor vehicle	0.04	0.02	**0.62**	0.31
rh_ntel	Percentage of houses without a telephone	-0.02	0.00	**0.41**	0.03
rh_nplmb	Percentage of houses without complete plumbing	-0.05	-0.01	0.22	0.03
rh_adi_p	National percentile of ADI scores	0.12	0.00	**0.79**	-0.24
rh_pden	Population density	-0.12	0.01	0.21	**0.53**
rh_no2	Pollution measure (NO2)	-0.04	0.02	-0.12	**0.83**
rh_pm25	Pollution measure (PM2.5)	0.06	0.03	-0.07	**0.42**
rh_pxrd	Proximity to major roads	0.01	0.01	-0.16	-0.17
rh_leadh	Lead exposure risk	0.08	0.02	0.21	**0.46**
rh_pm25a	Pollution measure (PM2.5) at high resolution	-0.09	0.01	0.28	0.30

Note. N = 7,445. Standardized loadings ≥ 0.4 are in bold. * denotes items that are reverse coded before log transformation. Items with standardized loadings in bold were retained for the next round of a confirmatory factor analysis in the second random sample (N = 2,373).

Table S2. Standardized factor loadings from the confirmatory bifactor model.

Item	Brief wording	General Environmental Stress	Family Dynamics	Interpersonal Support	Neighborhood SES Deprivation	Urbanicity
ksads760	Witnessed violence in the community	**0.47**	0.30			
ksads766	Witnessed violence in the home	0.22	**0.48**			
ksads769	Sexually assaulted by a peer	0.08	**0.50**			
ksads763_765	Beaten or threatened to death by a family member	0.14	**0.46**			
ksads764_768	Threatened to death or sexually assaulted by a non-family member	0.24	0.39			
fes1	Family members fight a lot	0.11	**0.40**			
fes3	Family members throw things	0.15	0.36			
fes6	Family members hit each other	0.21	0.31			
fexp1_2	Could not afford food/telephone service	**0.55**	0.38			
fexp3_4	Could not pay and/or evicted for not paying rent/mortgage	**0.45**	**0.43**			
fexp5	Could not pay for gas/electric service	**0.46**	0.36			
fmhx4	Family history of alcohol-related problems	-0.05	**0.62**			
fmhx5	Family history of drug-related problems	0.21	**0.75**			
fmhx7	Family history of mania	0.03	**0.68**			
fmhx8	Family history of psychosis	0.16	**0.57**			
fmhx9	Family history of antisocial problems	0.23	**0.72**			
fmhx10	Family history of nerve problems	0.05	**0.64**			

fmhx11	Family history of receiving psychiatric service	-0.12	**0.79**	
fmhx12	Family history of hospitalization due to psychiatric problems	0.04	**0.79**	
fmhx13	Family history of suicide	-0.01	**0.67**	
mh_srvc	Child has received mental health service	-0.03	**0.43**	
crpf2	Accessibility to cigarettes	-0.01	0.35	
crpf4	Accessibility to marijuana	-0.01	0.21	
cvg_acc1	Caregiver makes me feel better after talking over my worries	-0.06		**0.62**
cvg_acc2	Caregiver smiles at me very often	-0.09		**0.56**
cvg_acc3	Caregiver makes me feel better when I'm upset	-0.09		**0.68**
cvg_acc4	Caregiver believes in showing love for me	-0.10		**0.67**
cvg_acc5	Caregiver is easy to talk to	-0.08		**0.56**
school2	Students have lots of chance to decide things in my school	0.04		**0.43**
school3	I get along with my teachers	-0.07		**0.67**
school4	My teachers notice when I'm doing good job	0.10		**0.61**
school6	I feel safe at my school	-0.23		**0.51**
school7	The school lets my parents know when I've done something well	0.04		**0.53**
school8	I like school because I do well	0.08		**0.70**
school9	I feel just as smart as other kids	-0.02		**0.50**
school10	There are many chances to be part of class	0.00		**0.58**
school15	School bores me	0.06		**-0.49**

monitor1	How often parents know where I am	-0.06	0.34		
monitor4	How often I let parents about my plan	0.02	**0.41**		
crpf1	Accessibility to alcohol	-0.36		-0.19	
rh_eduh*	Percentage of populations with at least high school diploma	**0.76**		0.20	
rh_incom	Median family income	**-0.79**		**-0.55**	
rh_indis	Income disparity	**0.75**		0.39	
rh_homv	Median home value	-0.31		**-0.53**	
rh_rent	Median gross rent	-0.26		**-0.60**	
rh_homo*	Home ownership rate	**0.81**		0.02	
rh_crowd	Crowding in the home	**0.59**		-0.11	
rh_unemp	Unemployment rate	**0.66**		0.30	
rh_b138	Percentage of populations below or around the poverty level	**0.85**		0.31	
rh_sp	Percentage of single-parent household	**0.74**		0.33	
rh_ncar	Percentage of houses without a motor vehicle	**0.71**		0.25	
rh_ntel	Percentage of houses without a telephone	**0.40**		0.21	
rh_adi_p	National percentile of ADI scores	**0.55**		**0.55**	
neigh1	I feel safe walking in my neighborhood	**-0.47**			-0.16
neigh3	Neighborhood is safe from crime (parent)	**-0.51**			-0.25
rh_walk	Walkability scores	0.32			0.36
rh_crime	Crime rates	-0.15			**0.67**
rh_pden	Population density	0.37			**0.40**
rh_no2	Pollution measure (NO2)	0.03			**0.97**
rh_pm25	Pollution measure (PM2.5)	0.02			**0.49**

rh_leadh	Lead exposure risk	0.37	**0.49**

Note. N = 2,373; Standardized loadings ≥ 0.4 are in bold. * denotes items that are reverse coded before log transformation.

Table S3. Psychometric indices for each latent factor in the bifactor model and the higher-order model.

Index	General	Family Dynamics	Interpersonal Support	Neighborhood SES Deprivation	Urbanicity
			Bifactor Model		
H	0.942	0.922	0.888	0.717	0.944
ECV (S&E)	0.339	0.274	0.213	0.080	0.095
ECV (New)	0.339	0.834	0.976	0.248	0.719
Omega	0.879	0.906	0.851	0.804	0.644
OmegaH	0.217	0.827	0.848	0.011	0.644
Factor determinancy	0.957	0.961	0.943	0.863	0.972
PUC	0.731				
			Higher-Order Model		
H		0.929	0.889	0.972	0.765
Factor determinancy	0.880	0.964	0.943	0.986	0.888

Note. H = index of construct replicability; ECV = explained common variance; PUC = percent correlations that are uncontaminated; OmegaH = ω hierarchical.

Code Listing 1. An example code of structural equation modeling with environmental stressors predicting psychopathology factors.

```
TITLE: ABCD Bifactor;
DATA:FILE is
study1_data.dat;
VARIABLE: NAMES ARE
subnum age_b_y age_b_m age_2_y age_2_m age_3_y
age_3_m female gender psweight npweight npweight2
famid relation demo_prim siten NHWHITE AFRICAN
HISPANIC OTHER cbcl_t3 cbcl_tb
GENERAL FAMHX SES CAREGVR
ENVIRON GENERAL3 EXT3 ADHD3 INT3;

USEVARIABLES ARE
GENERAL FAMHX SES
CAREGVR ENVIRON GENERAL3
EXT3 ADHD3 INT3;

MISSING ARE .;
  STRATIFICATION=SITEN;
  CLUSTER=FAMID;

  ANALYSIS:
  ITERATIONS=500000;
  TYPE=COMPLEX;

MODEL:

GENERAL3 INT3 EXT3 ADHD3 ON GENERAL FAMHX SES CAREGVR ENVIRON;

OUTPUT: STDYX;
```

Code Listing 2. An example code of mediation analysis using cluster-robust standard errors.

```
TITLE: mediation;
DATA:   FILE is
mplus_data.dat;
VARIABLE: NAMES ARE
subnum age_b_y age_b_m age_2_y age_2_m age_3_y age_3_m
female gender psweight npweight np_ps_weight
famid relation demo_prim siten
NHWHITE AFRICAN HISPANIC OTHER
cbcl_total_3 COIL1_b COIL2_b COIL3_b COIL4_b COIL5_b
COIL1_2 COIL2_2 COIL3_2 COIL4_2 COIL5_2 serial_b serial_2
vol1_2 vol2_2 vol3_2 vol4_2 vol5_2 vol6_2 vol7_2 vol8_2
vol9_2 vol10_2 vol11_2 vol12_2 vol13_2 vol14_2 vol15_2
vol16_2 vol17_2 vol18_2 vol19_2 vol20_2 vol21_2 vol22_2
vol23_2 vol24_2 vol25_2 vol26_2 vol27_2 vol28_2 vol29_2
vol30_2 vol31_2 vol32_2 vol33_2 vol34_2 vol35_2 vol36_2
vol37_2 vol38_2 vol39_2 vol40_2 vol41_2 vol42_2 vol43_2
vol44_2 vol45_2 vol46_2 vol47_2 vol48_2 vol49_2 vol50_2
vol51_2 vol52_2 vol53_2 vol54_2 vol55_2 vol56_2 vol57_2
vol58_2 vol59_2 vol60_2 vol61_2 vol62_2 vol63_2 vol64_2
vol65_2 vol66_2 vol67_2 vol68_2 vol69_2 vol70_2 vol71_2
vol72_2 vol73_2 vol74_2 vol75_2 vol76_2 vol77_2 vol78_2
vol79_2 vol80_2 vol81_2 vol82_2 vol83_2 vol84_2 vol85_2
vol86_2 vol87_2 total_l_2 total_r_2 total_2 subcortical_sum_2
GENERAL FAMHX SES CAREGVR ENVIRON;

USEVARIABLES ARE
GENERAL
cbcl_total_3
vol16_2;

MISSING ARE .;
STRATIFICATION=SITEN;
CLUSTER=FAMID;

DEFINE: STANDARDIZE
vol16_2;

ANALYSIS:
ESTIMATOR=MLR;
TYPE=COMPLEX;
BOOTSTRAP=1000;

MODEL:
cbcl_total_3 ON GENERAL vol16_2;
```

```
vol16_2 ON GENERAL;

MODEL INDIRECT:
cbcl_total_3 IND GENERAL;

OUTPUT:
STANDARDIZED
cinterval(bcbootstrap);
```

Code Listing 3. An example code of multilevel mediation analysis.

```
TITLE: 3-level msem;
DATA:   FILE is
/Users/jeonh13/Downloads/Dissertation/mplus data/mplus_data.dat;
VARIABLE: NAMES ARE
subnum age_b_y age_b_m age_2_y age_2_m age_3_y age_3_m
female gender psweight npweight np_ps_weight
famid relation demo_prim siten
NHWHITE AFRICAN HISPANIC OTHER
cbcl_total_3 COIL1_b COIL2_b COIL3_b COIL4_b COIL5_b
COIL1_2 COIL2_2 COIL3_2 COIL4_2 COIL5_2 serial_b serial_2
vol1_2 vol2_2 vol3_2 vol4_2 vol5_2 vol6_2 vol7_2 vol8_2
vol9_2 vol10_2 vol11_2 vol12_2 vol13_2 vol14_2 vol15_2
vol16_2 vol17_2 vol18_2 vol19_2 vol20_2 vol21_2 vol22_2
vol23_2 vol24_2 vol25_2 vol26_2 vol27_2 vol28_2 vol29_2
vol30_2 vol31_2 vol32_2 vol33_2 vol34_2 vol35_2 vol36_2
vol37_2 vol38_2 vol39_2 vol40_2 vol41_2 vol42_2 vol43_2
vol44_2 vol45_2 vol46_2 vol47_2 vol48_2 vol49_2 vol50_2
vol51_2 vol52_2 vol53_2 vol54_2 vol55_2 vol56_2 vol57_2
vol58_2 vol59_2 vol60_2 vol61_2 vol62_2 vol63_2 vol64_2
vol65_2 vol66_2 vol67_2 vol68_2 vol69_2 vol70_2 vol71_2
vol72_2 vol73_2 vol74_2 vol75_2 vol76_2 vol77_2 vol78_2
vol79_2 vol80_2 vol81_2 vol82_2 vol83_2 vol84_2 vol85_2
vol86_2 vol87_2 total_l_2 total_r_2 total_2 subcortical_sum_2
GENERAL FAMHX SES CAREGVR ENVIRON;

USEVARIABLES ARE
GENERAL
cbcl_total_3
vol16_2;

MISSING ARE .;
CLUSTER=SITEN FAMID;
IDVARIABLE = subnum;

DEFINE: STANDARDIZE
vol16_2;
cbcl_total_3=cbcl_total_3/100;

ANALYSIS:
ESTIMATOR = BAYES;
TYPE=THREELEVEL RANDOM;

MODEL:

%WITHIN%
```

```
GENERAL vol16_2 cbcl_total_3;
vol16_2 ON GENERAL(a1);
cbcl_total_3 ON vol16_2(b1);
cbcl_total_3 ON GENERAL(c1);

%BETWEEN SITEN%
GENERAL vol16_2 cbcl_total_3;
vol16_2 ON GENERAL(a2);
cbcl_total_3 ON vol16_2(b2);
cbcl_total_3 ON GENERAL(c2);

%BETWEEN FAMID%
GENERAL vol16_2 cbcl_total_3;
vol16_2 ON GENERAL(a3);
cbcl_total_3 ON vol16_2(b3);
cbcl_total_3 ON GENERAL(c3);

MODEL CONSTRAINT:
NEW(ind1-ind3);
ind1=a1*b1;
ind2=a2*b2;
ind3=a3*b3;
```