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Early Experience And The Development Of Dopaminergic Circuitry

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Abstract

The developing brain is highly malleable, meaning that children are acutely sensitive to their early experiences, for better or for worse. Early adversity significantly increases the risk for psychopathology and learning challenges. Recent work in animal models powerfully suggests that the ventral tegmental area (VTA), a major source of dopaminergic projections to the rest of the brain, is a key mediator for how early stressful experiences can become biologically embedded: in mice, absent or disrupted caregiving results in latent vulnerability of the dopaminergic system to stress well into adulthood. Thus, it may be that early adversity causes a shift in the developmental trajectory of the VTA, with cascading effects on later motivational and socioemotional processes. However, little is known about whether similar disruptions in VTA circuitry are detectable in children. Thus, I leveraged fMRI methods in 4- to 10-year-old children, to examine the functional integrity of dopaminergic circuitry early in development. In Chapter 2, I tested whether stress exposure relates to VTA resting-state functional connectivity. I found an age x stress exposure interaction, such that only children with lower stress exposure showed a positive relationship between age and VTA-mPFC connectivity, consistent with an interpretation that high stress exposure is related to blunted VTA maturation. Chapter 3 examined children's neural responses to naturalistic emotional content using movie fMRI, and linked to parenting behaviors observed in the lab. I found that children who experienced more negative parenting showed reduced VTA activity during positive emotion scenes. Finally, Chapter 4 examined curiosity, a behavior that is supported by dopaminergic circuitry, and that encourages greater learning by engaging positive interest and intrinsic motivation. I tested whether individual differences in curiosity are reflected in resting-state connectivity patterns, and can be predicted by environmental experiences. Together, this work suggests that early experiences play a critical role in tuning dopaminergic neurocircuitry in children, with potentially enduring consequences for reward and socioemotional processing. This has implications both for education and for policy: how can we protect children in negative environments, and provide positive support that will allow them to best thrive as learners.

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Anne Park

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For one of my dissertation studies, the children participating in our research watched an animated short film called *Piper*. *Piper* tells the story of a baby sandpiper who has a frightening encounter with the ocean, but eventually plucks up the courage to face her fear head-on, and finds joy and friendship in its place. It's a story of leaving your comfort zone, persisting through challenges (even if you're a little clumsy at first), being curious to learn, and growing as a person, through the support of friends and family. In many ways, it's very much like the story of my own experience in graduate school, and I have innumerable people to thank for making that journey possible.

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ABSTRACT

EARLY EXPERIENCE AND THE DEVELOPMENT OF DOPAMINERGIC CIRCUITRY

Anne T. Park
Allyson P. Mackey

The developing brain is highly malleable, meaning that children are acutely sensitive to their early experiences, for better or for worse. Early adversity significantly increases the risk for psychopathology and learning challenges. Recent work in animal models powerfully suggests that the ventral tegmental area (VTA), a major source of dopaminergic projections to the rest of the brain, is a key mediator for how early stressful experiences can become biologically embedded: in mice, absent or disrupted caregiving results in latent vulnerability of the dopaminergic system to stress well into adulthood. Thus, it may be that early adversity causes a shift in the developmental trajectory of the VTA, with cascading effects on later motivational and socioemotional processes. However, little is known about whether similar disruptions in VTA circuitry are detectable in children. Thus, I leveraged fMRI methods in 4- to 10-year-old children, to examine the functional integrity of dopaminergic circuitry early in development. In Chapter 2, I tested whether stress exposure relates to VTA resting-state functional connectivity. I found an age x stress exposure interaction, such that only children with lower stress exposure showed a positive relationship between age and VTA-mPFC connectivity, consistent with an interpretation that high stress exposure is related to blunted VTA maturation. Chapter 3 examined children's neural responses to naturalistic emotional content using movie fMRI, and linked to parenting behaviors observed in the lab. I found that children who experienced more negative parenting showed reduced VTA activity during positive emotion scenes. Finally, Chapter 4 examined curiosity, a behavior that is supported by dopaminergic circuitry, and that encourages greater learning by engaging positive interest and intrinsic motivation. I tested whether individual differences in curiosity are reflected in resting-state connectivity patterns, and can be predicted by

environmental experiences. Together, this work suggests that early experiences play a critical role in tuning dopaminergic neurocircuitry in children, with potentially enduring consequences for reward and socioemotional processing. This has implications both for education and for policy: how can we protect children in negative environments, and provide positive support that will allow them to best thrive as learners.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ILLUSTRATIONS

CHAPTER 1: INTRODUCTION

When a child visits our lab to participate in a neuroimaging study, we use all kinds of strategies to make the experience as kid-friendly as possible. *A stuffed animal that explains how the "brain camera" works. Games to practice staying still like a statue for as long as possible. Snacks, and lots of praise.* This is due in large part to our knowledge that the children we study—preschool- and elementary school-aged children—are still in the process of developing many of the cognitive, socioemotional, and self-regulatory capacities necessary for staying still and focused during a brain scan. Eventually, as their prefrontal cortex slowly matures, these children will learn to reason about the world, to cope flexibly with obstacles, and to persist towards desired goals. Far from being a setback, protracted maturation is thought to be precisely what enables children to be such characteristically eager, playful, and inquisitive learners. Indeed, it has been argued that an extended childhood in humans grants children ample opportunity to explore, learn about, and adapt to a wide array of unpredictable environmental experiences (Gopnik, 2020). In thinking about this spirit of exploration, two of our young participants come to mind: one who struggled with our cognitive test battery, but spontaneously and happily figured out how to play with a slinky through trial-and-error. Another who initially refused to try the brain scan, but eventually decided to face his fears, because his mom validated his emotions and talked him through the importance of sticking with a challenge. Children are young scientists, actively forming and testing hypotheses about their ever-expanding world—and parents play an intimate role in fostering a space where they can best thrive as learners. Thus, this dissertation takes the approach of asking how certain early experiences, both positive and negative, may have cascading effects on the neural circuitry that supports learning and emotional development.

Background

The developing brain is highly plastic, or malleable, meaning that children are acutely susceptible to the conditions of the environment they grow up in, for better or for worse. As proposed by Bronfenbrenner, environment refers not only to the direct, proximal influences on a child, like family relationships, peers, and school, but also to the broader, more distal landscape of societal and cultural factors (Bronfenbrenner, 1977). For example, the approximately 12 million children living in poverty in America today (Chen & Thomson, 2021) face a wide range of hardships— shaped by policy and perpetuated by systemic racism—that include lack of access to basic needs like food and health care, housing instability, exposure to violence, educational setbacks due to under-resourced schools, and greater likelihood of experiencing abuse or neglect (Evans & Kim, 2013). Different kinds of stressors, nested at different levels, all compound on one another to impact development. To illustrate: a child living in a low-income neighborhood may endure greater lead exposure, undergo accelerated aging due to stress-related wear and tear of the body, and experience harsher parenting born out of her family's financial stress. Although structural reforms can and should be made, we also have the important opportunity to develop more effective parenting and educational programs, by better understanding how the adults in a child's life can provide positive support and play a protective role in the face of existing inequities. In the following sections, I first review how negative experiences associated with poverty can become biologically embedded in the brain (Hyde et al., 2020), and then narrow in on the specific influence of parenting behaviors on child development.

Socioeconomic status, adversity, and the developing brain

Growing up in poverty is associated with a host of negative life outcomes, including long-term disparities in physical and mental health, academic achievement, and occupational trajectory (Hao & Farah, 2020; Palacios-Barrios & Hanson, 2019; Reiss, 2013). Low socioeconomic status (SES), which is often defined as low income and/or low education level, is correlated with risk

factors that include greater exposure to violence and environmental toxins, poor neighborhood quality, and reduced access to resources (Farah, 2017). Studies in both animal models and humans are probing how specific features of early negative experiences can have dissociable effects on brain development (Cohodes et al., 2021; McEwen & Akil, 2020; McLaughlin et al., 2021). One conceptual framework has organized the existing literature into two major dimensions: threat and deprivation (McLaughlin et al., 2014). Exposure to threats of physical harm, like violence or abuse in the home, particularly impacts socioemotional processing, with behavioral consequences like differences in fear learning (Machlin et al., 2019), negative emotion processing biases (Dannlowski et al., 2013), and heightened vigilance (Pollak et al., 2009). Animal work has shown that exposure to a chronically stressful and threatening environment can inflict damage to corticolimbic regions that have high density of glucocorticoid receptors, and that are critical for affective processing, like the amygdala, hippocampus, and medial prefrontal cortex (McEwen, 2012). Humans exposed to early life stress similarly show hypertrophy or atrophy of limbic areas, as well as alterations in the functional connectivity between corticolimbic regions (Gee et al., 2013; Park et al., 2018), which is associated with disruptions in emotion regulation (VanTieghem & Tottenham, 2017). Early adversity is also associated with greater reactivity to negative stimuli (Milojevich et al., 2021) and blunted activity to positive stimuli (Kujawa et al., 2020) in humans, as well as less frequent use of adaptive emotion regulation strategies. Thus, growing up in a stressful environment has profound effects on psychopathology and emotional resilience to negative life experiences.

In contrast to threat exposure, deprivation is associated with a lack of experience-expectant inputs, i.e., inputs that the brain requires as part of the typical development of neural circuitry, often during a critical period or sensitive period. This could include experiences of neglect, with insufficient sensory, cognitive, or social stimulation to foster complex learning (McLaughlin et al., 2017). For example, animals raised in impoverished cages show differences like fewer synapses, less dendritic branching, and reduced plasticity in regions like the hippocampus, compared to

animals raised in a cognitively enriched environment, with access to novel toys and social partners (van Praag et al., 2000). Humans also benefit from experiential diversity (Heller et al., 2020), as well as access to educational resources and play experiences (like going to museums, novel toys, books, etc.). Another critical component of enrichment in humans is language: low SES is associated with disparities in child language exposure (Golinkoff et al., 2019), which may result in fewer opportunities for scaffolded knowledge building and social affiliation via parent-child conversation. Cognitive deprivation is associated with alterations in brain regions responsible for language and executive functions (e.g., the frontoparietal network) (Colich, Rosen, et al., 2020; McLaughlin et al., 2014). Cutting across many of these examples, in the domains of threat and deprivation, are two important points: 1) negative early experiences begin to sculpt brain structure, function, and plasticity via dissociable neural mechanisms, and 2) as direct caregivers, parents play a significant role in gating whether children are exposed to environmental threats or have access to cognitive enrichment and quality care.

The central influence of parenting on child development

Early in development, caregivers are critical for providing children with external emotion regulation and guidance, since children's own self-regulation processes are still immature (Gee, 2020; Sanchez et al., 2015). Importantly, positive parenting behaviors have been shown to have a buffering effect against negative outcomes for children living in poverty (Brown et al., 2020), and recent work found that an early parenting intervention in high-risk children can enhance activity in brain regions involved in socioemotional processing (Valadez et al., 2020). One fundamental process that lays the foundation for positive socioemotional development in children, and emerges from the early parent-child relationship, is attachment style (Ainsworth, 1989; Bowlby, 2008): securely attached children seek out and find comfort in their caregiver in distressing situations, while insecurely attached children cope in maladaptive ways, and are at greater risk for internalizing and externalizing problems later in life (Cooke et al., 2019). Secure attachment can be effectively promoted through parenting interventions that focus on improving

parent sensitivity, responsiveness, and attunement to the child (Barlow et al., 2016; Wright & Edginton, 2016). Parenting influences not only how children regulate their emotions and behaviors, but also their developing mental representations of self and others, informing later social relationships and coping strategies (Atzil et al., 2018; Tottenham, 2020b). Positive parenting thus provides the emotional support and scaffolding that may be uniquely important for enabling children to freely explore and learn.

On the other hand, negative parenting is associated with behavioral difficulties like greater depressive symptoms in children (Dallaire et al., 2006). Rodent models of early life stress frequently involve negative caregiving behaviors. Notably, when dams are deprived of resources, like bedding for their pups—paralleling the conditions of a low SES, under-resourced family—this results in fragmented, unpredictable maternal care, with negative effects on cognitive and emotional development (Glynn & Baram, 2019). Parent behavior can thus serve as an additional conduit for the negative effects of an impoverished environment on children, via intergenerational transmission of stress. Another possible mechanism is that early exposure to unpredictable care results in a child's reduced sense of control over the environment (Hill et al., 2008). This may promote the development of maladaptive attachment-related schemas that persist into adulthood (Szepsenwol & Simpson, 2019; Wuth et al., 2021), like an overarching belief that the world is unsafe and the future is uncertain. Life history theory is an evolutionary perspective arguing that safe, predictable environments allow for a slower pace of development—an extended period for brain plasticity—whereas harsh, unpredictable environments prioritize immediate goals due to the long-term future being uncertain (Frankenhuis et al., 2016). In other words, a child might take more risks or behave impulsively because they have grown up in an environment where rewards are inconsistent and adults are unreliable. While this may have adaptive value in some environments, it comes at certain costs: by essentially growing up too fast, children may have less opportunity to engage in the kinds of free exploration and curious learning that would be allowed in a safe and nurturing parent-child relationship, and may have difficulty coping

appropriately with obstacles. One way to shed further light on how negative parenting leads to poor learning in children is by investigating underlying biological mechanisms, with the goal of characterizing early biomarkers of disrupted development that can serve as intervention targets. This is particularly important given that little is currently known about how distinct underlying neural circuits may be differentially associated with patterns of accelerated or blunted maturation in response to early life stress (Herzberg & Gunnar, 2020). Next, I describe the brain's dopamine neuromodulatory system, due to its vast role in goal-directed behavior, motivation, learning, coping flexibly with challenges, and the promotion of brain plasticity.

The dopamine neuromodulatory system
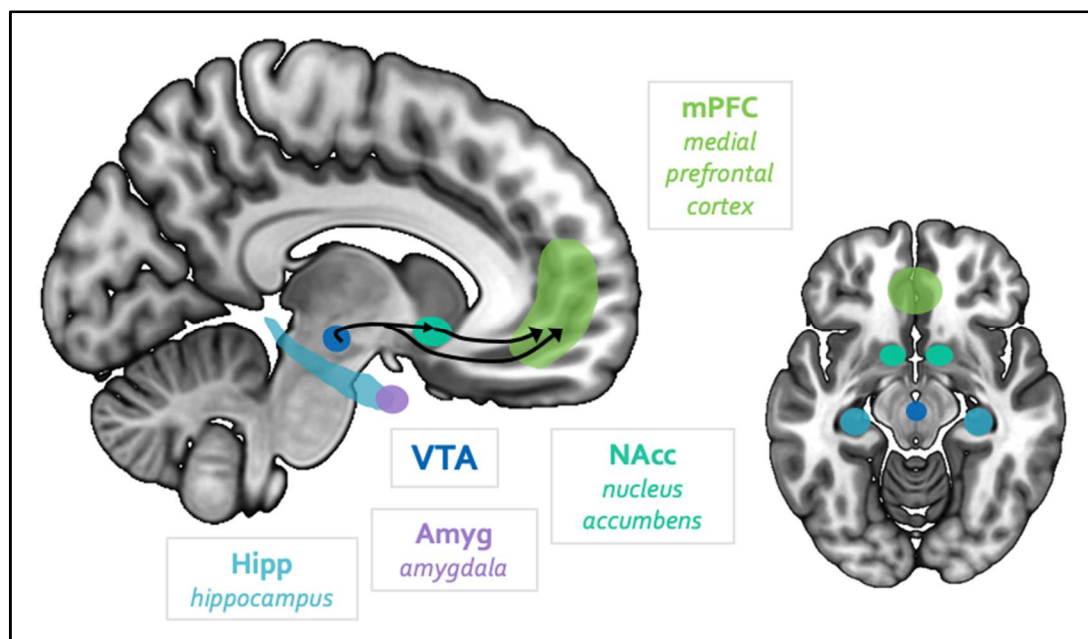
Figure 1.1. Schematic of major hubs of the dopaminergic system. The ventral tegmental area (VTA; dark blue in the figure), which is located in the midbrain, sends out dopaminergic projections to both subcortical and cortical regions. The dopamine system, among other processes, is implicated in motivated behavior and socioemotional processing.

Dopamine neurons convey a powerful learning signal. They are known to encode reward prediction errors, signaling the receipt of unexpected rewards, and guiding future behavior

(Hollerman & Schultz, 1998). The dopamine system thus plays a critical role in learning about the environment, and driving motivated, goal-directed behavior towards desired rewards (Hamid et al., 2016; Schultz, 2016). Dopamine neurons originate in the midbrain in the ventral tegmental area (VTA), and project to many other regions important for reward processing and socioemotional function, including the nucleus accumbens (NAcc), amygdala (Amyg), hippocampus (Hipp), and medial prefrontal cortex (mPFC) (Yamaguchi et al., 2011) (Figure 1.1). Causal evidence from animal work shows that early life stress induces transcriptional changes in the VTA that prime mice to be less resilient to later stressors (i.e., the mice showed decreases in social approach) (Peña et al., 2017). Alterations in the developmental trajectory of the VTA may thus create latent vulnerability early in life, such that negative behavioral outcomes may not become visible until later on, depending on the individual's later encounters with stressful experiences.

Ventral tegmental area connectivity

Work in animal models shows that VTA dopamine neurons have a protracted developmental trajectory (Hoops & Flores, 2017), such that dopamine innervation of the prefrontal cortex continues even well into adolescence. Thus, many important behaviors that rely on prefrontal function, like reasoning, planning, and processing emotions, are slow to mature. Protracted maturation also means that still-developing dopamine neurons may be particularly vulnerable to external influences and negative experiences. Exposure to chronic stress results in structural and functional changes in the dopaminergic circuitry of rodents, like the loss of VTA dopamine neurons (Douma & de Kloet, 2019). Disrupting the development of dopamine neurons also drives dysfunction in critical projection targets like the medial prefrontal cortex (mPFC; Reynolds et al., 2018). In humans, the mPFC is involved in the top-down, flexible control of coping behaviors (Heilbronner & Hayden, 2016), and is also an important hub of the default mode network, which supports social, self-related, and affective processes (Lieberman et al., 2019). Early alterations in the connectivity (or communication) between reward regions and mPFC may therefore have long-

term implications for self-regulation and for building mental models of self and others, especially given the close integration of reward neurocircuitry with emotion and social cognition (Bickart et al., 2014; Sander & Nummenmaa, 2021).

Curiosity as a reward-related behavior that enhances learning

The dopamine system underlies so many of the behaviors that are important for supporting children's socioemotional processing and school readiness, including self-control, persistence towards desired goals, coping with stress, and more. Curiosity, defined here as the desire to seek out knowledge, is a behavior that fosters greater learning, and that relies intimately on dopaminergic circuitry (Gruber et al., 2014; Gruber & Ranganath, 2019; Jirout & Klahr, 2012). One important method by which children satisfy their curiosity is by asking questions (Ronfard et al., 2018). Especially in early childhood, parental figures serve as major resources for providing children with information about the world. Thus, investigating individual differences in curious behavior in children, as well as environmental predictors of curiosity, may shed light on how we can positively support dopaminergic functioning, and may reveal promising intervention targets for improving children's learning and intrinsic motivation. Next, I outline the types of methods used in this dissertation to characterize individual differences in children's environmental experiences, neural activity, and behaviors.

Methods Approach

In addition to parents telling us about their child's environmental experiences via questionnaires, they also participate in a parent-child interaction task at the lab: a snapshot of the kind of relationship they share, in a naturalistic situation that gives opportunities for both pedagogy and play. Although a task of this nature may be subject to the usual constraints on social desirability, it nevertheless gives us rich information on nuanced social dynamics, and allows us to quantify

observed parenting behaviors. In addition to behavioral measures, the children in our research participate in functional magnetic resonance imaging (fMRI). This dissertation will make use of two different fMRI methods: resting-state fMRI, where the child is given no external stimulus, and simply lets their mind wander; and movie fMRI, where the child watches an animated short film. Resting-state fMRI is thought to reflect the past history of co-activation between different brain regions (Gabard-Durnam et al., 2016; Guerra-Carrillo et al., 2014), and is thus useful for relating to children's long-term environmental experiences. Movie fMRI allows us to examine children's brain responses to naturalistic emotional and social content. Neuroimaging with children is challenging, because young children tend to move more than adults, and MRI scan quality is highly contingent upon staying still (although research is currently underway to develop novel MRI scans that will be more robust to motion). It is also potentially highly rewarding. Neuroimaging methods offer us the unique opportunity to expand upon behavioral studies, by shedding light on early brain changes that have not yet manifested in behavior, and potentially improving predictions about when and how individual children respond best to intervention (Cooper & Mackey, 2016). Finally, the sample of children represented in this work is both socioeconomically and racially diverse, and reflects the richness of experience in Philadelphia. However, given the emphasis of this dissertation on parenting practices, and on environmental experiences that have their roots in systemic inequalities, I also acknowledge that the field of psychology still needs far more cross-cultural sensitivity (Nielsen et al., 2017), as well as racial diversity of both participants and researchers (Roberts et al., 2020; Stern et al., 2021).

Dissertation Approach

The first study (Chapter 2) examines the relationship between early life adversity and the development of VTA dopaminergic circuitry in young children (Park et al., 2021). Early adversity is strongly associated with the development of psychopathology, including symptoms related to

attenuations in reward processing, motivation, and social exploration. Work in rodent models compellingly reveals that the VTA is a key mediator between experiences of early life stress and later vulnerability, via cascading changes in the developmental trajectory of the dopamine system. Thus, we sought to test whether a similar disruption is detectable in human children. Here, we collected resting-state fMRI data in 4- to 9-year-old children, as well as parent-report data on the child's experiences of stress. Stress exposure was quantified in two ways: low socioeconomic status (SES), which tends to be associated with a broad array of stressors, and adverse childhood experiences (ACEs), which includes experiences of abuse, neglect, and household dysfunction. We tested for age x stress interactions in the functional connectivity of the VTA, as well as other regions implicated in the dopamine system, including the nucleus accumbens (NAcc), hippocampus (Hipp), and medial prefrontal cortex (mPFC). An age x stress interaction would suggest that the developmental trajectory of dopaminergic circuitry varies as a function of stress exposure, and is detectable even in early childhood.

The second study (Chapter 3) examines children's neural responses to naturalistic emotional events, and relates them to the singularly formative social dynamic of childhood: the parent-child relationship. Parents and caregivers play a unique role in modulating the development of emotion-related neurocircuitry. The ability to effectively process and regulate emotions is critical for guiding how young children learn about and engage with the world. Indeed, blunted neural response to positive emotions and rewards is a risk factor for the development of psychopathology. In order to better characterize the link between parenting and emotional developmental trajectories, we need a deeper understanding of young children's naturalistic emotional experience. However, most of the work to-date has focused on simplified emotional stimuli. In Chapter 3, we leveraged movie fMRI to capture children's neural activity in response to positive and negative emotional events, in 4- to 11-year-olds. We then tested for associations between neural activity and parenting behaviors observed during a laboratory parent-child

interaction task, in order to examine whether the early parent-child relationship is associated with differences in the function of emotion-related brain regions.

Based on the evidence that the VTA dopaminergic circuitry is consequential for both reward and emotion processing early in development, is susceptible to life experiences, and has implications for learning and plasticity, the third and final study (Chapter 4) investigates a behavior that ties together all three principles: curiosity. Encouraging children to ask questions, engage in thoughtful hypothesis testing, and develop interests that make them happy all have the potential to improve long-term learning and intrinsic motivation. In Chapter 4, I explore how curiosity may be represented in the brain, by examining resting-state functional coupling between regions that have known associations with curiosity, like the VTA, NAcc, and mPFC. I additionally examine potential environmental predictors of child curiosity, in order to more fully characterize the types of early experiences that might encourage or hinder child exploration. Findings were limited, and I discuss possible challenges with the curiosity measures used in this study.

Finally, in Chapter 5, I discuss overall takeaways and future directions. In sum, this dissertation leverages naturalistic measures of both brain and behavior in order to examine the possibility that disruptions to VTA neurocircuitry can serve as a biomarker for early negative consequences of stressful experiences. Looking beyond, the overarching goal of this research program is to identify promising targets for intervention and support: given what we know about the role of early experience in sculpting dopaminergic circuitry, how can we reduce systemic disparities in stress exposure and access to resources, and how can parents directly support their child in ways that will encourage curious learning and build resilience.

CHAPTER 2: Early childhood stress is associated with blunted development of ventral tegmental area functional connectivity

Abstract

Early life stress increases risk for later psychopathology, due in part to changes in dopaminergic brain systems that support reward processing and motivation. Work in animals has shown that early life stress has a profound impact on the ventral tegmental area (VTA), which provides dopamine to regions including nucleus accumbens (NAcc), anterior hippocampus, and medial prefrontal cortex (mPFC), with cascading effects over the course of development. However, little is known about how early stress exposure shifts the developmental trajectory of mesocorticolimbic circuitry in humans. In the current study, 88 four- to nine-year-old children participated in resting-state fMRI. Parents completed questionnaires on their children's chronic stress exposure, including socioeconomic status (SES) and adverse childhood experiences (ACEs). We found an age x SES interaction on VTA connectivity, such that children from higher SES backgrounds showed a positive relationship between age and VTA-mPFC connectivity. Similarly, we found an age x ACEs exposure interaction on VTA connectivity, such that children with no ACEs exposure showed a positive relationship between age and VTA-mPFC connectivity. Our findings suggest that early stress exposure relates to the blunted maturation of VTA connectivity in young children, which may lead to disrupted reward processing later in childhood and beyond.

Introduction

Early stress exposure is associated with heightened risk for poor mental health later in life (Green et al., 2010; McLaughlin et al., 2012). One mechanism by which early life stress leads to mental health vulnerability is via alterations in dopaminergic neurocircuitry (Hollon et al., 2015; Ironside et al., 2018; Russo & Nestler, 2013), which supports reward processing, cognitive flexibility, and goal-directed behavior (Lloyd & Dayan, 2016; Salamone & Correa, 2012). Disruptions to this key neural circuitry have been associated with symptoms that frequently underlie adult psychopathology, like anhedonia, impulsivity, and reduced motivation (Belujon & Grace, 2017; Novick et al., 2018). However, little is known about how stressful experiences impact dopaminergic circuitry in early childhood, a critical time point for understanding how stress causes long-term biological change.

The ventral tegmental area (VTA) in the midbrain has emerged as a key potential target for examining how stressors can have cascading effects on reward circuitry (Douma & de Kloet, 2019; Holly & Miczek, 2016). The VTA is the primary source of dopamine projections to other reward-related regions, including the nucleus accumbens (NAcc), anterior hippocampus (aHipp), and medial prefrontal cortex (mPFC), which collectively form the mesocorticolimbic pathway (Yamaguchi et al., 2011). Recent work in rodent models has suggested that the adverse sequelae of early life stress may be critically mediated by long-lasting alterations in the VTA. Specifically, work by Peña et al. (2017) found that exposure to early life stress (during a period roughly comparable to human infancy) induced long-lasting changes in the expression of *Otx2*, a developmental transcription factor implicated in dopamine neuron development (Di Salvio et al., 2010; Omodei et al., 2008) and experience-dependent plasticity (Beurdeley et al., 2012; Lee et al., 2017), in the VTA. These mice were primed to be less resilient when they encountered additional stressors later in adulthood, i.e., they developed depression-like behavior like decreases in exploration and social approach (Peña et al., 2017). Indeed, experimentally

13

suppressing *Otx2* in the VTA increased the likelihood of poor response to later stress, while overexpressing *Otx2* reversed the effects of early life stress, highlighting the pivotal role of the VTA as a mediator for downstream behavior problems. Complementary work finds that stress exposure in early adolescent rats results in aberrant activity in VTA and anterior hippocampus, with evidence for a possible critical period in the vulnerability of this circuit (Gomes et al., 2019). Taken together, early life stress causes enduring alterations in the VTA that create latent vulnerability for dysregulated reward-related behaviors, perhaps via changes in the connectivity between VTA and other parts of the dopaminergic reward circuitry.

Additional work in rodents shows that VTA dopamine neurons have a protracted developmental trajectory, continuing to grow and innervate mPFC throughout adolescence (Hoops & Flores, 2017). This protracted development plays an important role in shaping the maturation of mPFC (Reynolds et al., 2018), but also leaves dopamine neurons vulnerable to environmental insult for an extended period of time. Throughout life, rodents exposed to chronic stress show loss of dopamine neurons in the VTA, and functional changes in the synaptic connections of VTA dopamine neurons to other projection targets in the mesocorticolimbic circuitry (reviewed in Burke & Miczek, 2014; Douma & de Kloet, 2019). Thus, chronic stress exposure has significant effects on how VTA dopamine neurons communicate with other brain regions, and may impair the mPFC's top-down regulation of the VTA. However, it is unclear how stress exposure interacts with the timing of reward circuitry development in humans.

In humans, early life stress is associated with differences in the activation and connectivity of reward processing regions, as measured by functional magnetic resonance imaging (fMRI), with the bulk of prior work focusing on the NAcc and mPFC (Hanson et al., 2016; Hanson, Knodt, et al., 2017; Herzberg & Gunnar, 2020; Ironside et al., 2018). Several studies have found associations between early stress exposure and alterations in NAcc functional connectivity with medial prefrontal cortex (Fareri et al., 2017; Hanson, Knodt, et al., 2017; Marshall et al., 2018).

14

For example, Hanson et al. (2017) found that childhood maltreatment was related to alterations in NAcc-mPFC task-dependent functional connectivity in young adults, but that this depended on also experiencing greater levels of recent life stress (Hanson, Knodt, et al., 2017), consistent with the work by Peña et al. (2017) in mice showing that early stress may sensitize the VTA to later stress. Early life stress has also been linked to reduced functional connectivity between the VTA and the hippocampus in late childhood and adolescence (Marusak et al., 2017). However, little is known about how early stress exposure impacts the developmental trajectory of VTA connectivity during childhood.

Here, we examined whether early life stress was associated with VTA resting-state functional connectivity development between the ages of 4 and 9. We additionally examined three other mesocorticolimbic regions, NAcc, aHipp, and mPFC, to test for the specificity of the effects on VTA. Resting-state is thought to reflect the history of co-activation between brain regions, making it a useful measure for probing individual differences in functional anatomy (Gabard-Durnam et al., 2016; Guerra-Carrillo et al., 2014). Its stimulus-free nature also helps mitigate the possibility that individuals from different backgrounds may differ in their familiarity with, and interpretation of, task stimuli. We conceptualized early life stress in two ways. First, we examined childhood socioeconomic status (SES). Low SES increases risk for chronic stress because it is associated with experiences like reduced access to resources, increased chaos in the home, and more exposure to violence (Evans, 2004; McLaughlin & Sheridan, 2016). Second, we examined exposure to Adverse Childhood Experiences, or ACEs, which capture children's cumulative exposure to household dysfunction, abuse, and/or neglect, in order to test whether these types of stressful home experiences uniquely explain reward circuitry differences above and beyond other negative impacts of lower SES. We investigated whether these measures of early life stress were associated with differences in the functional connectivity of VTA, NAcc, aHipp, and mPFC, and whether connectivity patterns with age differed as a function of stress exposure.

Methods

Participants

The Institutional Review Board at the University of Pennsylvania approved this study. All parents provided informed, written consent. Children younger than age 8 provided verbal assent, and children ages 8 and older provided written assent. Participants were recruited from Philadelphia and the surrounding regions through advertisements on public transportation, partnerships with local schools, outreach programs, community family events, and social media ads.

Resting-state scans were acquired for 137 participants. Eighty-eight participants were included in the final sample (see exclusion criteria below). Children were between the ages of 4 and 9 (M = 6.80, SD = 1.38, range = 4.1 to 9.9). The racial and ethnic makeup of the sample was as follows: 56% Black, 41% White, 11% Asian, 10% Other, and 10% Hispanic/Latino. Percentages sum to greater than 100% because parents could endorse multiple races. For comparison, Philadelphia is 42.9% Black, 35.3% White, 6.9% Asian, 0.5% Other, and 12.4% Hispanic, and the United States overall is 12.6% Black, 62.0% White, 5.2% Asian, 1% Other, and 16.9% Hispanic (2010 US Census, StatisticalAtlas.com). We controlled for race and ethnicity in all analyses. Because the most numerous racial group was Black, we treated Black as the reference category, and included dummy variables for White, Asian, Other, and Hispanic/Latino.

Participants were excluded for: missing data on both measures of SES (parental education and income) (n = 1), race/ethnicity (n = 4), or the Adverse Childhood Experiences questionnaire (n = 8); not completing the resting-state scan (e.g., due to falling asleep or wanting to end the scan early, n = 21); an artifact in the resting-state data (due to hair glitter, n = 1); incorrect registration of the participant at the scanner (n = 1); or parent-reported diagnosis of Attention-Deficit/Hyperactivity Disorder during the visit, despite not reporting a diagnosis during screening

(*n* = 2). Participants were also excluded for having no usable resting-state data due to average head displacement (3 translations, 3 rotations) of greater than 1.2 mm (*n* = 10), as well as for having an unusable structural scan (*n* = 1).

Questionnaires

Questionnaire response distributions are shown in Figure 2.1. The parent/guardian filling out the questionnaires was as follows: 80% Mother, 17% Father, 1% Guardian, 2% Grandmother. Parental education and family income were assessed using the MacArthur Foundation Research Network on Socioeconomic Status and Health sociodemographic questionnaire (Operario et al., 2004). Parents were asked to report their highest education level (possible responses ranged from "less than high school" to "professional degree (J.D., M.D., Ph.D.)"), as well as the highest education level of their partner if applicable (85% of parents reported the education level of their partner). Average parental education ranged from 11 to 20 years (*Mdn* = 14, *SD* = 2.61, *n* = 88). Thirty-four percent had a high school diploma or less education, compared to 51% of adults ages 25 and older in Philadelphia, and 40.5% in the United States (2010 US Census, StatisticalAtlas.com). Total family income was assessed by asking "Which of these categories best describes your total combined family income for the past 12 months? This should include income (before taxes) from all sources, wages, rent from properties, social security, disability and/or veteran's benefits, unemployment benefits, workman's compensation, help from relatives (including child payments and alimony), and so on." Possible responses included: Less than $5,000, $5,000 through $11,999, $12,000 through $15,999, $16,000 through $24,999, $25,000 through $34,999, $35,000 through $49,999, $50,000 through $74,999, $75,000 through $99,999, $100,000 through $149,999, $150,000 through $199,999, $200,000 and greater, and Unsure. Annual family income was estimated as the median value of the selected income bracket (*Mdn* = $62.5K, *SD* = $63K, *n* = 83). For comparison, the median household income in Philadelphia in 2010 was $64K, and in the United States was $55K. Socioeconomic status (SES) was defined as

the average of Z-scored income and Z-scored years of parental education (parental education

was averaged across parents if available for both parents).
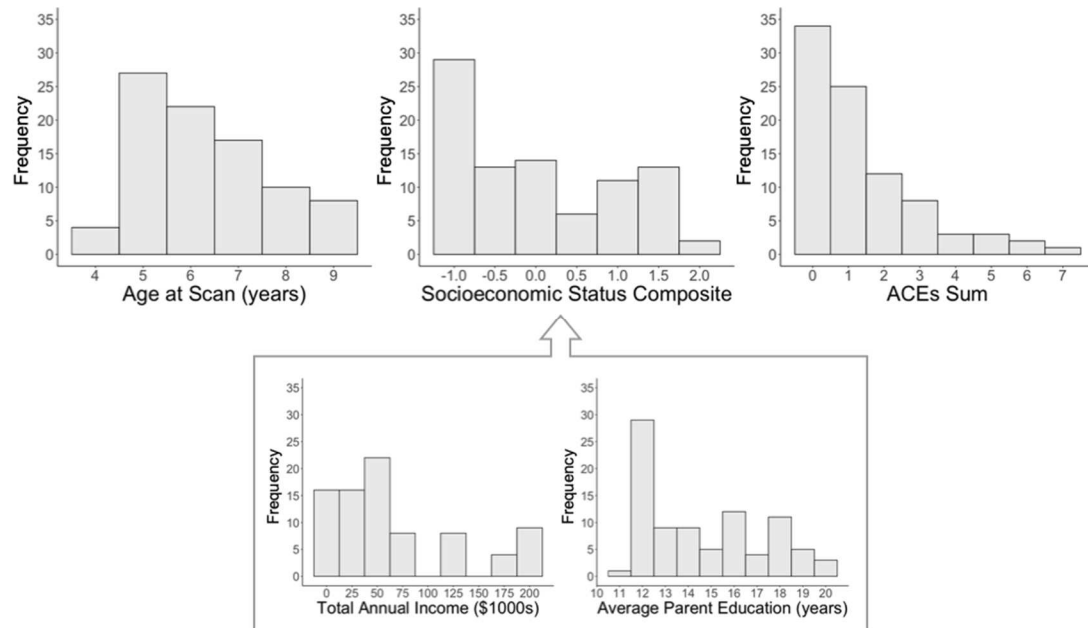
Figure 2.1. Histograms of demographic information (*n* = 88; for income, *n* = 83). The
Socioeconomic Status composite is the average of Z-scored income and parent education. ACEs,
Adverse Childhood Experiences.

Parents completed the child version of the Adverse Childhood Experiences (ACEs) questionnaire

(Murphy et al., 2016), which asked parents about their child's lifetime experiences with broader

household dysfunction and parent separation, abuse, and neglect. An ACEs score was calculated

by summing the binary ratings for these ten types of experiences (Table 2.1). ACEs sum ranged

from 0 to 7 (*Mdn* = 1, *SD* = 1.62). Number of ACEs was as follows: 38.6% reported that their child

experienced 0 ACEs, 28.4% reported 1 ACE, and 33.9% reported 2+ ACEs. For comparison, a

nationally representative survey (2011-2014) of youth under the age of 18, using a similar ACEs

measure, found that 38.5% reported 0 ACEs, 23.5% reported 1 ACE, and 38% reported 2+ ACEs

(Merrick et al., 2018).

	Percentage endorsing	t	p
Parental separation/divorce	31%	-4.69	<.001 ***
Lived with a person who ever went to prison	24%	-8.08	<.001 ***
Lived with a person who has abused substances	24%	-3.35	.002 **
Lived with a person who has a mental illness	23%	-1.71	.10
Witnessed interpersonal violence	20%	-0.39	.70
Physical neglect	9%	1.02	.34
Emotional abuse	5%	-1.12	.33
Emotional neglect	1%	--	--
Sexual abuse	1%	--	--
Physical abuse	0%	--	--

* $p < .05$, ** $p < .01$, *** $p < .001$

Table 2.1. Associations between specific Adverse Childhood Experiences (ACEs) and Socioeconomic Status (SES). SES was compared between families who endorsed each item and those who did not. Negative *t*-statistics indicate lower SES for families that endorsed an item as compared to those that did not. Dashed lines indicate ACEs with too few instances to test for SES differences.

Neuroimaging data acquisition

Prior to the scanning session, participants were acclimated to the scanning environment with a mock scanner that simulates typical MRI noises. Participants practiced keeping still in the mock scanner for about 10 minutes, by watching a movie that would pause each time they moved their heads more than 1 mm. During the actual MRI session, a researcher stayed in the scanner room with the participant to reassure the child and to gently squeeze the child's foot if the child moved.

Imaging was performed at the Center for Advanced Magnetic Resonance Imaging and Spectroscopy (CAMRIS) at the University of Pennsylvania. Scanning was conducted using a Siemens MAGNETOM Prisma 3T MRI scanner with the vendor's 32-channel coil. A whole-brain, high-resolution, T1-weighted 3D-encoded multi-echo structural scan (MPRAGE) was collected

(acquisition parameters: TR = 2530 ms, TEs = 1.69 ms/3.55 ms/5.41 ms/7.27 ms, BW = 650 Hz/px, 3x GRAPPA, flip angle = 7°, voxel size = 1 mm isotropic, matrix size = 256 x 256, 176 sagittal slices, FOV = 256 mm, total scan time = 4:38). This sequence used interleaved volumetric navigators to prospectively track and correct for subject head motion (Tisdall et al., 2012). A T2*-weighted multiband gradient echo resting-state scan was also collected (acquisition parameters: multiband acceleration factor = 3, TR = 2000 ms, TE = 30.2 ms, BW = 1860 Hz/px, flip angle = 90°, voxel size = 2 mm isotropic, matrix size = 96 x 96, 75 axial slices, FOV = 192 mm, volumes = 150 - 240, 5 dummy scans). The multiband acceleration factor was set at 3 to balance the need for smaller voxels to localize VTA, achievable only with some acceleration, with the need for higher signal-to-noise ratios, which is reduced by higher acceleration factors, and lower motion sensitivity, which is enhanced by higher acceleration factors (Preibisch et al., 2015). Participants saw a black fixation cross on a gray screen throughout the scan.

We updated our acquisition strategy in order to increase the amount of usable data, in two ways: 1) monitoring head motion in real-time using the Framewise Integrated Real-time MRI Monitor (FIRMM) software (Dosenbach et al., 2017), and 2) collecting two resting-state scans when possible. This resulted in 54 participants who continued to be scanned until our movement criterion was achieved (at least 5 minutes of functional data with head motion less than 1 mm, maximum 8 minutes, per resting-state scan). Runs were dropped from subsequent analyses if they exceeded 1.2 mm average motion (see Summary of motion considerations), resulting in a final breakdown of 51 participants with one usable resting-state scan and 37 participants with two usable resting-state scans. All analyses controlled for the total amount of data collected (total number of resting-state volumes), as well as average motion, weighted by run length. We controlled for the amount of data provided by each child so that children with more available data would not be overrepresented in the models. Participants had an average head displacement of 0.37 mm (SD = 0.28 mm, significantly non-normally distributed, W = 0.86, p < .001).

Preprocessing

The functional imaging data were preprocessed using Nipype, a Python-based framework for flexibly integrating neuroimaging analysis tools (Gorgolewski et al., 2011). The software packages used in this preprocessing pipeline included FMRIB Software Library (FSL v5.0.8; Jenkinson et al., 2012), FreeSurfer (v6.0.0; Dale et al., 1999), Advanced Normalization Tools (ANTs v2.1.0; Avants et al., 2011), and Nipype's implementation of Artifact Detection Tools (ART; http://www.nitrc.org/projects/artifact_detect/).

Simultaneous realignment and slice timing correction was conducted using an algorithm implemented in Nipy (Roche, 2011). Outlier volumes in the functional data were defined using ART based on composite motion (greater than 1 mm of head displacement between volumes) and global signal intensity (greater than 3 standard deviations from the mean).

The following confounds were regressed out of the functional data: 6 realignment parameters (3 translations, 3 rotations) and their first-order derivatives, outlier volumes flagged by ART (one nuisance regressor per outlier), composite motion, and linear and quadratic polynomials to detrend the data. Five principal components were also derived from segmentations of both cerebrospinal fluid (CSF) and white matter (WM), and regressed from the data, to correct for physiological noise like heart rate and respiration (aCompCor; Behzadi et al., 2007). The CSF and WM segmentations were derived from Freesurfer's individual parcellations of the lateral ventricles and total white matter, respectively; these segmentations were transformed into functional space. Confound regression occurred within a skull-stripped functional mask which was created using FSL's Brain Extraction Tool (BET; Smith, 2002); BET's fractional intensity threshold was set at 0.4.

The functional data were bandpass filtered (0.01-0.1 Hz), spatially smoothed with an isotropic 6 mm Gaussian kernel (FWHM), and normalized to the OASIS-30 Atropos template (in MNI152 2 mm space) in a two-step process. First, the median functional image was coregistered to the reconstructed surfaces using FreeSurfer's bbregister (Greve & Fischl, 2009); next, the structural image was registered to the OASIS-30 Atropos MNI152 template using ANTs. The transformation matrices generated by these two steps were concatenated, allowing images to be transformed directly from functional to MNI space in a single interpolation step.

Seed-based analyses

We examined the functional connectivity of the ventral tegmental area (VTA), nucleus accumbens (NAcc), anterior hippocampus (aHipp), and medial prefrontal cortex (mPFC) (seeds shown in Figure 2.2A). The VTA was defined using a probabilistic atlas that was constructed from hand-drawn ROIs of the VTA (Murty et al., 2014). Nucleus accumbens was defined from the Harvard-Oxford subcortical atlas provided through FSL. Anterior hippocampus was defined from a probabilistic atlas of the medial temporal lobe (Hindy & Turk-Browne, 2016), divided into anterior and posterior sections at Y = -21, and masked by the Harvard-Oxford hippocampus in order to limit the seed from extending into surrounding white matter. Medial prefrontal cortex was defined as FreeSurfer's individual parcellation of bilateral rostral anterior cingulate cortex (rACC) based on the Desikan-Killiany atlas (Desikan et al., 2006). The seed for mPFC will be referred to throughout as rACC. The average temporal signal-to-noise ratio (tSNR) within the seed regions were as follows: VTA (M = 24.02, SD = 4.39), NAcc (M = 41.79, SD = 9.05), aHipp (M = 33.26, SD = 5.10), rACC (M = 48.65, SD = 13.43) (whole-brain tSNR maps are provided in Supplemental Figure 1). We extracted the average time series within each ROI from unsmoothed data, to ensure that signal was not blurred outside of the ROI.

We used the average time series within each seed to generate whole-brain subject-level functional connectivity maps for the VTA, NAcc, aHipp, and rACC, using FSL's *fsl_glm* tool. Because motion and physiological noise were already filtered out of the functional data during earlier preprocessing steps, subject-level GLMs only contained the seed time series as a regressor. For participants with two resting-state runs, seed connectivity maps were generated separately for each run, and then the runs were averaged together using a Nipype implementation of a fixed-effects model (using FSL's *flameo*) to produce a single connectivity map per participant to be entered into group-level analyses.

Whole-brain group-level analyses were performed with FMRIB's Local Analysis of Mixed Effects tool (FSL's FLAME 1). Only voxels that had unanimous coverage across subjects were tested, resulting in a mask that covered the entire brain. We ran the following GLMs (testing for both positive and negative associations): 1) group average; 2) main effects of age, 3) SES, and 4) ACEs exposure; and the 5) age x SES interaction and 6) age x ACEs interaction. All group GLMs included the following covariates: age (except when age was the main effect being tested), gender, average head motion (in millimeters), number of resting-state volumes, and race/ethnicity. To examine the robustness of the results, we additionally ran GLMs for SES and the age x SES interaction (GLMs 3 and 5) that controlled for the main effect of ACEs exposure, and GLMs for ACEs exposure and the age X ACEs interaction (GLMs 4 and 6) that controlled for the main effect of SES. We did not include both age x SES and age x ACEs in the same model because the regressors were collinear.

Z-statistic maps were corrected for multiple comparisons with parametric clusterwise inference using FSL's *cluster* tool (relies on Gaussian Random Field Theory) at a cluster-defining threshold of $z = 3.1$ ($p < .001$), neighborhood size of 26, and an FWE-corrected threshold of $p < .05$, based on evidence from Eklund et al. that false positives are not well controlled at a less stringent threshold (Eklund et al., 2016). Following recommendations for neuroimaging reporting (Poldrack,

2017), uncorrected statistical maps are available on NeuroVault

(https://neurovault.org/collections/ZSVLTNSF/) (Gorgolewski et al., 2016). All statistical analyses

were conducted in R.

Summary of motion considerations

Studying brain development in early childhood requires addressing higher levels of motion than

typically seen at later ages. The effect of motion during our structural scans was minimized using

prospective motion correction, which provided high-quality data for our structural processing

(Tisdall et al., 2012). We dealt with motion during our fMRI scans in four ways, each designed to

mitigate the specific effects of motion on fMRI studies. First, we implemented real-time motion

monitoring at the scanner (FIRMM) in order to more systematically track participants' motion

during the scans and maximize the amount of data that met our motion thresholds (Dosenbach et

al., 2017). Second, we set a motion exclusion threshold based on our data quality, as data quality

differs by features of the acquisition, and therefore there is no universal motion cutoff that

balances participant inclusion with data quality (i.e., multiband factor, head coil selection). The

motion threshold was set at 1.2 mm based on qualitative evaluations of connectivity maps of a left

motor cortex seed, as the anatomy of motor cortex is well-known and established by early

childhood (Gao et al., 2015; Grayson & Fair, 2017). Participants with connectivity maps that did

not look as expected all had composite motion over 1.2 mm. Evaluations were done by an

experimenter blind to any demographic information about the participants. For participants with

two usable resting-state runs, head motion was averaged between the two runs, weighted by run

length. The participants who were excluded for motion (n = 10) were slightly younger than

included participants (Exc. median: 5.5 years, Inc. median: 6.6 years, U = 277.0, p = .06).

Excluded participants did not differ from included participants on parental education (Exc.

median: 15.5, Inc. median: 14, U = 483.0, p = .61), family income (Exc. median: $42.5K, Inc.

median: $62.5K, U = 444.5, p = .35), or ACEs (Exc. median: 1, Inc. median: 1, U = 399.5, p =

.62). Third, within the included sample, we tested how motion was related to our variables of interest: age, SES, and ACEs. Higher average head motion was significantly related to younger age (r_s = -0.31, p = .003) and to lower SES (r_s = -0.23, p = .03), but there was no age x SES interaction on head motion ($t(84)$ = -0.11, p = .91). Average head motion was not significantly related to ACEs sum (r_s = -0.12, p = .23), and there was no age x ACEs interaction on head motion ($t(84)$ = -1.06, p = .29). Fourth, because motion was related to age and SES, we included average motion (across runs) in all models.

Results

Demographics and stress measures. Lower SES was associated with greater exposure to ACEs (r_s = -0.32, p = .002). Specifically, SES was lower among children who experienced parental separation ($t(86)$ = -4.69, p < .001), family incarceration ($t(86)$ = -8.08, p < .001), and family drug abuse ($t(86)$ = -3.35, p = .002) (Table 1). ACEs exposure was lower for White children than for Black children ($t(83)$ = -2.63, p = .01). SES was higher for White ($t(83)$ = 4.74, p < .001) and Asian ($t(83)$ = 4.75, p < .001) children than for Black children. ACEs exposure was slightly, but not significantly, higher in Hispanic children as compared to Non-Hispanic children ($t(83)$ = 1.43, p = .16). SES was slightly, but not significantly, lower in Hispanic children as compared to Non-Hispanic children ($t(83)$ = -1.77, p = .08). Age was not significantly related to SES (r_s = -.17, p = .12), but it was significantly positively related to ACEs (r_s = 0.26, p = .01). SES and ACEs exposure did not differ by gender.

Group average results. Across the entire group, VTA was positively functionally connected to subcortical regions including nucleus accumbens, hippocampus, amygdala, and cerebellum, as well as the striatum and thalamus (Figure 2.2A). In cortex, VTA was most strongly correlated with medial prefrontal cortex, precuneus, and visual cortex, broadly consistent with D_1 receptor

binding sites in the human brain (Palomero-Gallagher et al., 2015). Notably, we did not observe strong connectivity with lateral prefrontal and parietal regions in this age range, consistent with developmental work on VTA connectivity (Tomasi & Volkow, 2014). The positive group averages for NAcc, aHipp, and rACC were similar, showing broad connections to subcortical regions and to the default mode network. NAcc and aHipp additionally showed connectivity with somatomotor cortex. There were no regions that showed negative functional connectivity in the group average for the VTA, NAcc, aHipp, or rACC.
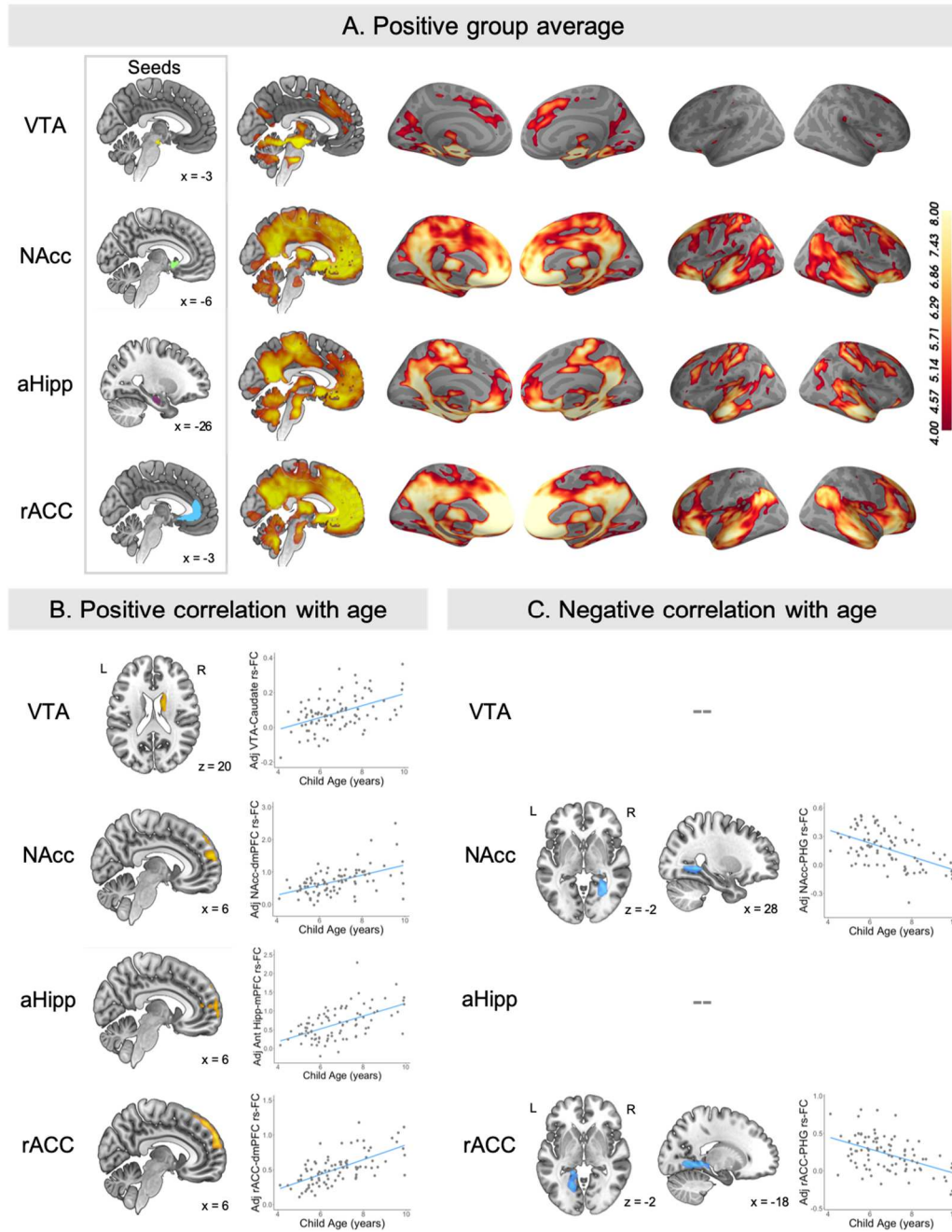
Figure 2.2. (A) Positive group average functional connectivity for the ventral tegmental area (VTA), nucleus accumbens (NAcc), anterior hippocampus (aHipp), and rostral anterior cingulate cortex (rACC). Seed regions are shown on the left (VTA = yellow, NAcc = green, aHipp = purple, rACC = blue). (B) Positive relationships between age and functional connectivity. (C) Negative relationships between age and functional connectivity. No regions showed negative relationships between age and VTA functional connectivity, or between age and aHipp functional connectivity. Models control for age (in the group average), gender, average head motion, number of resting-state volumes, and race/ethnicity, and are corrected for multiple comparisons at $z = 3.1$, $p < 0.05$, $N = 88$. Scatterplots show the relationship between age and extracted parameter estimates (adjusted for covariates).

27

Main effects of age. VTA functional connectivity showed a positive association with age in the right caudate (Figure 2.2B; peak voxel coordinates (MNI): 14, 2, 20, maximum z-statistic = 4.09, cluster volume = 171 voxels). No regions showed a negative age-related association with VTA functional connectivity. NAcc, rACC, and aHipp functional connectivity showed positive associations with age in dorsal medial prefrontal cortex (dmPFC) (Figure 2.2B, NAcc peak voxel coordinates (MNI): 6, 62, 18, maximum z-statistic = 4.42, cluster volume = 372 voxels; aHipp peak voxel coordinates (MNI): -2, 52, 10, maximum z-statistic = 4.44, cluster volume = 475 voxels; rACC peak voxel coordinates (MNI): 8, 48, 46, maximum z-statistic = 5.38, cluster volume = 1788 voxels). aHipp functional connectivity also showed a positive association with age in two additional clusters (Fig S2): right cerebellum (peak voxel coordinates (MNI): 42, -62, -44, maximum z-statistic = 4.72, cluster volume = 349 voxels); and left dorsal PFC (peak voxel coordinates (MNI): -20, 24, 60, maximum z-statistic = 4.52, cluster volume = 521 voxels). NAcc and rACC connectivity showed similar negative associations with age (Figure 2.2C). NAcc connectivity showed a negative relationship with age in right parahippocampal gyrus (PHG; peak voxel coordinates (MNI): 28, -48, -2, maximum z-statistic = 4.43, cluster volume = 388 voxels), and rACC connectivity showed a negative relationship with age in left PHG (peak voxel coordinates (MNI): -18, -42, -2, maximum z-statistic = 4.28, cluster volume = 436 voxels). No negative relationship with age was found for aHipp.

Main effects of stress measures. Higher SES was related to lower VTA functional connectivity with bilateral intraparietal sulcus (Figure 2.3A; right IPS: peak voxel coordinates (MNI): 30, -54, 42, maximum z-statistic = 4.70, cluster volume = 242 voxels; left IPS: peak voxel coordinates (MNI): -22, -56, 38, maximum z-statistic = 4.50, cluster volume = 553 voxels). The main effect of SES was similar when additionally controlling for ACEs exposure, although limited only to left IPS (Fig S3A). Higher ACEs exposure was related to lower VTA functional connectivity with right somatomotor cortex (Figure 2.3B; peak voxel coordinates (MNI): 64, -2, 26, maximum z-statistic = 4.55, cluster volume = 213 voxels). The main effect of ACEs exposure was highly

similar when additionally controlling for SES (Fig S3B). No regions showed a positive association with VTA functional connectivity for SES or ACEs exposure. There were no significant positive or negative main effects of SES or ACEs exposure on NAcc, aHipp, or rACC functional connectivity.
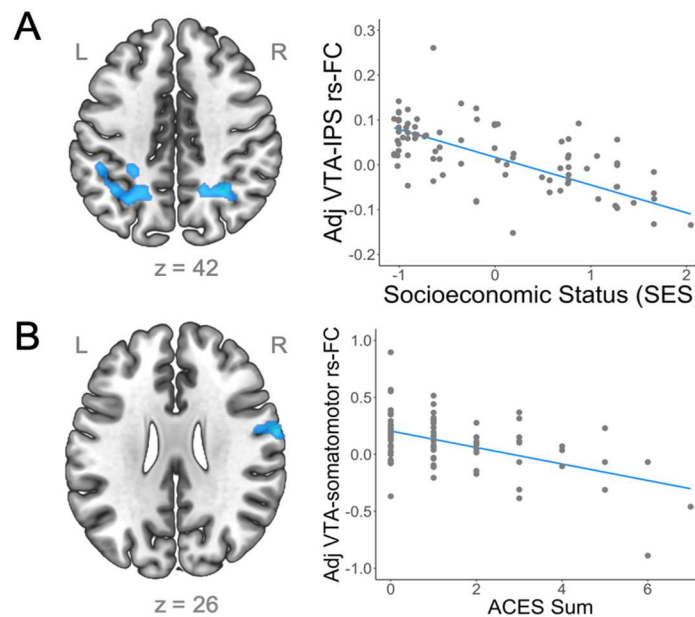
Figure 2.3. (A) Higher Socioeconomic Status (SES) is associated with lower ventral tegmental area (VTA) functional connectivity with bilateral intraparietal sulcus (IPS). (B) Higher exposure to Adverse Childhood Experiences (ACEs) is associated with lower VTA functional connectivity with right somatomotor cortex. Models control for age, gender, average head motion, number of resting-state volumes, and race/ethnicity. Results are corrected for multiple comparisons at $z = 3.1$, $p < 0.05$. Scatterplots show the relationship between the independent variables (SES, ACEs) and extracted parameter estimates (adjusted for covariates).

Interactions between age and stress measures. There was an age x SES interaction on connectivity between VTA and left dorsal mPFC (dmPFC) (Figure 2.4A; peak voxel coordinates (MNI): -10, 40, 24, maximum z-statistic = 4.38, cluster volume = 509 voxels). VTA-dmPFC connectivity showed a stronger positive association with age in children from higher SES backgrounds, compared to children from lower SES backgrounds. The age x SES interaction was nearly identical after additionally controlling for the main effect of exposure to ACEs (Fig S4A). To examine whether the relationship between age and VTA connectivity is significantly different from

zero within SES groups, participants were divided into 2 groups by median split: higher SES (n = 46) and lower SES (n = 42). VTA-dmPFC connectivity was positively related to age in children from a higher SES background ($t(77)$ = 4.56, p < .001, 95% CI [0.02, 0.06]), and not significantly related to age in children from a lower SES background ($t(77)$ = -1.52, p = .13, 95% CI [-0.04, 0.005]; Figure 2.4A).
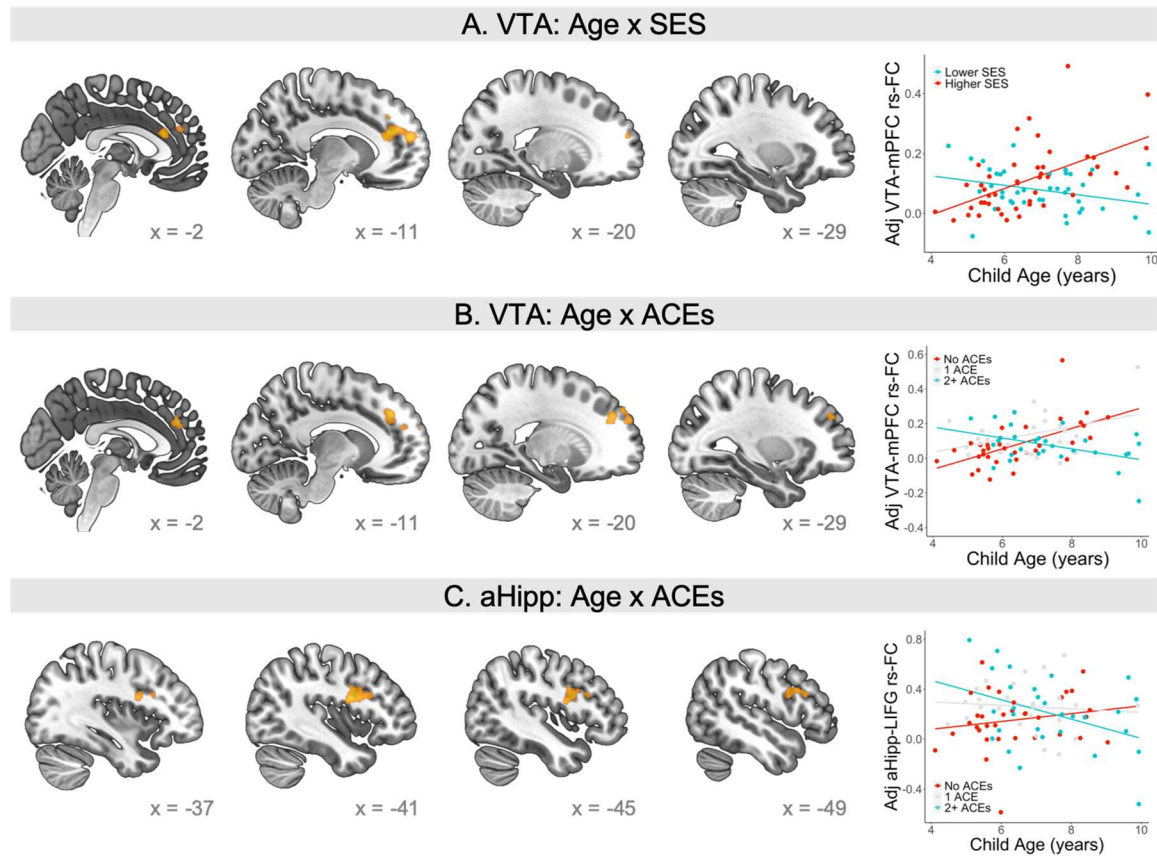
Figure 2.4. Age x stress exposure interactions on ventral tegmental area (VTA) functional connectivity. (A) Age x Socioeconomic Status (SES) interaction on VTA functional connectivity. Scatterplot shows the relationship between child age and extracted parameter estimates, plotted by median split on SES for visualization purposes. (B) Age x Adverse Childhood Experiences (ACEs) interaction on VTA functional connectivity. (C) Age x ACEs interaction on anterior hippocampus (aHipp) functional connectivity. Scatterplots show the relationship between age and extracted parameter estimates (adjusted for covariates). For visualization purposes, participants were grouped by having exposure to 0, 1, or 2+ ACEs. Results are corrected for multiple comparisons at z = 3.1, p < 0.05. All models control for gender, average head motion, number of resting-state volumes, and race/ethnicity.

We found a similar age x ACEs interaction on connectivity between VTA and left dorsal mPFC (Figure 2.4B; peak voxel coordinates (MNI): -14, 36, 36, maximum z-statistic = 4.43, cluster volume = 564 voxels). VTA-dmPFC connectivity showed a stronger positive association with age in children with lower exposure to ACEs, compared to children with higher exposure to ACEs. The dmPFC cluster overlapped with the age x SES result but additionally extended to the lateral surface of PFC. The age x ACEs interaction was almost identical after additionally controlling for the main effect of SES (Fig S4B). To test whether the relationship between age and VTA connectivity is significantly different from zero within ACEs exposure levels, participants were divided into 3 groups: exposure to 0 ACEs (n = 34), 1 ACE (n = 25), or 2 or more ACEs (n = 29). The 2+ ACEs group reflects greatest cumulative risk, while the 1 ACE group is heterogeneous in its experiences (32% parental separation/divorce, 24% living with someone with mental illness, 20% witnessing adults treated violently, 12% physical neglect, 4% living with someone who abuses substances, 4% living with someone who has been incarcerated, 4% sexual abuse). VTA-dmPFC connectivity was positively related to age in children with no ACEs exposure (t(74) = 3.45, p = .001, 95% CI [0.02, 0.09]), positively related to age in children with exposure to 1 ACE (t(74) = 2.19, p = .03, 95% CI [0.004, 0.08], and unrelated to age in children with 2+ ACEs (t(74) = -1.95, p = .055, 95% CI [-0.06, 0.0006]); Figure 2.4B).

There was an age x ACEs interaction on connectivity between aHipp and left inferior frontal gyrus (IFG) (Figure 2.4C; peak voxel coordinates (MNI): -40, 4, 22, maximum z-statistic = 4.23, cluster volume = 352 voxels). aHipp-LIFG connectivity showed a stronger negative association with age in children with higher exposure to ACEs, compared to children with lower exposure to ACEs. The age x ACEs interaction was nearly identical after additionally controlling for the main effect of SES (Fig S4C). aHipp-LIFG connectivity was unrelated to age in children with no ACEs exposure (t(74) = 0.84, p = .40, 95% CI [-0.04, 0.11]), unrelated to age in children with exposure to 1 ACE (t(74) = -0.35, p = .73, 95% CI [-0.10, 0.07], and negatively related to age in children with 2+ ACEs (t(74) = -2.33, p = .02, 95% CI [-0.14, -0.01]); Figure 2.4C). There was no significant age x

SES interaction for the aHipp seed, and no significant age x SES or age x ACEs exposure interactions for the NAcc or rACC seeds.

Discussion

Resting-state functional connectivity of the ventral tegmental area (VTA) showed different patterns with age as a function of stress exposure in 4- to 9-year-old children. Specifically, children from higher socioeconomic status (SES) backgrounds showed a positive relationship between age and VTA functional connectivity with dorsal medial prefrontal cortex (dmPFC), while children from lower SES backgrounds did not show this pattern. Similarly, only children with low exposure to Adverse Childhood Experiences (ACEs) showed a positive relationship between age and VTA functional connectivity with dmPFC. Our results suggest that stress-related differences in VTA connectivity begin to emerge during childhood. It is possible that children from lower SES backgrounds or with high ACEs exposure accumulate negative experiences as they grow up, or that they do not accumulate positive experiences in the same way as their peers from lower stress backgrounds. It is also possible that early experiences, before age 4, set children on different developmental trajectories. Longitudinal work beginning in infancy or even at conception, with detailed information on the specific timing of stressors, is needed to better understand the causes of the cross-sectional relationships presented here.

Our findings are consistent with recent work in rodents showing that exposure to early life stress causes changes in the VTA that create susceptibility to later stressors (Peña et al., 2017). There is evidence that chronic stress results in the loss of dopaminergic neurons in the VTA (Sugama & Kakinuma, 2016), as well as altered dopamine activity in VTA projection targets like NAcc and mPFC (Holly & Miczek, 2016). Stress also has been shown to alter mPFC neuron morphology (Cook & Wellman, 2004; Liston et al., 2006). Communication between VTA and mPFC is complex

32

and bidirectional, with both excitatory and inhibitory connections determining dopamine activity (Beier et al., 2015). Studies in animal models have not yet determined whether early life stress impacts projections from VTA, or projections to VTA from mPFC. Unfortunately, resting-state fMRI cannot differentiate between excitatory and inhibitory connections, and analytical approaches that can shed light onto directionality, i.e., bottom-up vs. top-down, require more data than can be acquired in young children (Mitra et al., 2015). Our work is also consistent with cross-species evidence that the development of VTA projections in rodents (Hoops & Flores, 2017), and the maturation of dopamine availability in humans (Larsen et al., 2020), continues through childhood and adolescence.

The age x ACEs and age x SES interactions on VTA connectivity were observed in a region of mPFC that is often called dorsal anterior cingulate cortex (dACC). The dACC has been hypothesized to play an important role in appraising environmental states and integrating internal and external motivational factors, in order to guide behavior via top-down modulation of the VTA (Beier et al., 2015; Haber & Behrens, 2014; Heilbronner & Hayden, 2016). Blunted age-related changes in VTA-mPFC functional coupling in childhood may thus reflect alterations in effective dACC top-down regulation of dopamine activity. Recent work also suggests that the dopaminergic midbrain drives dorsal mPFC's role in learning about the amount of effort needed to perform a task, highlighting the bottom-up influences that additionally support motivated behavior (Hauser et al., 2017). We did not observe any age x stress interactions on nucleus accumbens (NAcc) or rostral anterior cingulate cortex (rACC) connectivity, but we did observe that connectivity between anterior hippocampus and left inferior frontal gyrus (LIFG) differed by ACEs exposure. aHipp-LIFG connectivity showed a stronger negative association with age in children with higher exposure to ACEs, compared to children with lower exposure to ACEs. It has been suggested that dopaminergic neuromodulation may play a critical role in refining hippocampal-prefrontal circuitry during adolescence, in support of goal-oriented behavior and decision making (Murty et al., 2016).

Across our entire sample of children, irrespective of stress exposure, we found that the VTA showed increased connectivity with the caudate with age. This finding is consistent with prior work showing greater VTA-caudate connectivity in adults (ages 15 to 46) relative to youth (ages 7 to 22, but note overlapping age ranges; Tomasi & Volkow, 2014). The caudate plays an important role in behaviors like performance monitoring and cognitive control (Brovelli et al., 2011). Indeed, recent work in young adults has shown that the structural connectivity between VTA and caudate is related to conflict monitoring (Mamiya et al., 2019). Thus, increased functional coupling between the VTA and caudate may support the rapid development of cognitive control between the ages of 4 and 9 (Akshoomoff et al., 2018; Fjell et al., 2012). We also found that NAcc, aHipp, and rACC show very similar positive relationships between age and connectivity with dmPFC. Past work found different developmental changes in NAcc resting-state connectivity, i.e., decreased connectivity between NAcc and subgenual ACC, but the age range was much broader, from 4 and 23 (Fareri et al., 2015). Another study found no developmental changes in VTA-NAcc connectivity at rest in adolescence and young adulthood (ages 10-30), but found that VTA-NAcc connectivity during a motivational task decreased with age (Murty et al., 2018). Reward system development is likely nonlinear through adolescence and differs by task state (Hartley & Somerville, 2015; Somerville et al., 2010; Somerville & Casey, 2010). We also observed age-related decreases in connectivity between rACC and NAcc with the parahippocampal gyrus (PHG), a region involved in spatial processing and memory. PHG is at the border of visual and default mode networks in adults, depending on the parcellation (Yeo et al., 2011), but little is known about how its network membership changes with development. Fareri and colleagues found a positive relationship between age and NAcc-PHG connectivity in their broad age range of 4 to 23 (Fareri et al., 2015), suggesting that changes early in childhood may not extend linearly through adolescence and early adulthood.

We observed a negative main effect of SES on VTA connectivity with bilateral intraparietal sulcus (IPS), a task-positive region spanning the frontoparietal network (FPN) and the dorsal attention

34

network (DAN; Yeo et al., 2011), and implicated in processing number and space (Hubbard et al., 2005). Parietal cortex more broadly is rich in dopamine receptor expression (Palomero-Gallagher et al., 2015), but few parietal neurons project back down to VTA (Watabe-Uchida et al., 2012), suggesting that our result reflects differences in bottom-up innervation of IPS by VTA neurons. The cognitive implications of lower VTA-IPS connectivity are unclear. We additionally observed a main effect of ACEs exposure on VTA connectivity, such that higher ACEs exposure was associated with lower connectivity between VTA and right ventral somatomotor cortex, a region that does directly project to VTA (Watabe-Uchida et al., 2012), and has been linked to action-related learning (Coddington & Dudman, 2019). Further research is needed to replicate this unexpected finding and determine the behavioral relevance of adversity effects on VTA-somatomotor connectivity. In contrast with prior studies in older children (Marusak et al., 2017; Richter et al., 2019), we did not observe a main effect of stress on hippocampal connectivity, nor did we find stress effects on connectivity of NAcc or rACC.

SES and ACEs exposure were moderately correlated at about r_s = .3. The main effects of ACEs and SES on VTA connectivity were distinct, and held even when controlling for the other stress measure. The interactions between stress measures and age were highly similar, suggesting that both measures have similar effects on the maturation of VTA connectivity with mPFC. It will be critical in future work to examine how a broader set of stressors have unique impacts on the early organization of dopaminergic circuitry (Palacios-Barrios & Hanson, 2019). This would include experiences such as negative parenting behaviors, lack of social support, a chaotic and/or dangerous home environment, broader community disadvantage, and racial discrimination. In this study, as in many others, race was associated with SES and ACEs exposure. We controlled for race, rather than examine its impacts directly, because our samples within racial groups were small, and because we did not collect data on individuals' experiences with racism, which likely constitute major stressors for families of color.

This study has a number of limitations. First, our data are cross-sectional, so although we have demonstrated a possible age-related blunting of reward circuitry development, we have not yet followed children as they grow up. Second, our measures of early stress exposure rely on parents accurately and completely reporting on their children's experiences. It is possible that some parents under-report on child ACEs due to a lack of complete knowledge about their child's experiences, poor memory for retrospective events, or the sensitive nature of some of the items (e.g., abuse and neglect). Our definition of SES, which combines parent education and income, is also limited since it is a snapshot measure that may not capture potentially important household dynamics, like changes in partner or changes in income. Future work should also examine whether similar findings are found in population representative samples. Third, our measures of SES and ACEs exposure reflect cumulative and chronic stressors, and thus we cannot draw conclusions about the nature of the stressors impacting VTA connectivity. Future work could take a more dimensional approach, to see if particular types of stressors are driving these effects (McLaughlin & Sheridan, 2016), and to explore what other environmental experiences associated with lower SES are impacting VTA-mPFC connectivity in early childhood. It will also be important to further investigate the timing of adversity, i.e., whether alterations in VTA connectivity emerge due to the cumulative impact of stressors encountered over time, or due to the pivotal impact of a stressor experienced during an early sensitive window. Fourth, it is possible that certain VTA connectivity relationships may only emerge during task-dependent states (Ballard et al., 2011; Murty et al., 2018; Salehi et al., 2020). Future work should examine developmental patterns in VTA connectivity during motivational contexts. Fifth, we are limited by the spatial resolution of our fMRI data, as the VTA is a small brain region flanked closely by the substantia nigra (part of the nigrostriatal dopamine pathway). Thus, it is possible that some of our findings reflect connectivity of the midbrain more broadly rather than VTA alone. We also note that the signal-to-noise ratio (SNR) in VTA was lower than that of the other seed regions; indeed, recent work found that multiband fMRI reduces mesolimbic activity (specifically, nucleus accumbens activity) during reward-processing tasks (Srirangarajan et al., 2021). Fifth, resting-state connectivity relies on

36

blood oxygen-level dependent (BOLD) signal and therefore can be influenced by individual differences in vasculature and physiology (Murphy et al., 2013; Shmueli et al., 2007), though these relationships may be functionally important and not just confounds (Tak et al., 2015). Cardiovascular function is impacted by SES and ACEs in adolescents and adults (Lagraauw et al., 2015; Low et al., 2009; Monnat & Chandler, 2015), but the links are less well-studied in children, and it is unclear how physiological differences would result in the specific pattern of findings presented here.

In sum, our findings suggest that early stress exposure may disrupt the typical developmental trajectory of the dopamine system, which is essential for reward processing and goal-directed behavior. Future work should examine how early life stress impacts the interplay between VTA, a broader set of subcortical regions, and cortical networks, as well as its consequences for a variety of behaviors, like impulse control (Zisner & Beauchaine, 2015), effortful behavior (Assadi et al., 2009; Westbrook et al., 2020), exploration (Laureiro-Martínez et al., 2015), and curiosity (Gruber & Ranganath, 2019). We hypothesize that a blunted VTA-mPFC developmental trajectory could serve as a biomarker for reduced resilience to stress: these children may be more at risk for the development of psychopathology following stressors experienced later in life. In order to help buffer against the long-lasting and potentially compounding effects of early disruptions to reward neurocircuitry, it will be critical to design early childhood interventions that help children develop effective strategies for coping with chronic stress, and that focus on positive development of motivated behavior.

CHAPTER 3: The relationship between parenting and children's neural activity to emotional content

Abstract

How do early experiences shape emotional processing? For young children, much of their emotional worlds center their parents, but we know little about how variation in normative parenting relates to variation in neural responses to emotion. Because young children can struggle with tasks in the scanner, we studied emotional processing during a short film with positive and negative emotional events (n = 70, ages 4 to 11), and with rich parent-child interactions. We chose a movie without language or humans with racial or gender identities to limit differential processing based on language exposure or demographics. For a subsample (n = 30), parenting was measured during a brief parent-child interaction, consisting of a 5 minute wordless picture book, a 5 minute challenging puzzle, and 5 minutes of free play with novel toys. We characterized positive parenting (positive affect, like laughing, and positive content, like praise) and negative parenting (negative affect, like harsh tone, and negative content, like rough handling). We found that negative parenting was associated with less activation of the ventral tegmental area (VTA) and cerebellum during positive emotional events. Associations between negative parenting and VTA activation held after controlling for socioeconomic status, history of parental depression, and stressful life events. Our results suggest that experiences of negative parenting may shape reward-related responses to positive emotional information, above and beyond other stressors in children's lives.

Introduction

Effective emotion processing is critical for supporting children's learning (Martin & Ochsner, 2016) and ability to cope adaptively with challenges. Understanding individual differences in emotional processing in childhood is important because early emotional experience may influence long-term trajectories of behavioral adjustment. Indeed, emotional information is thought to serve as a potent input for children to build their understanding of the world (Wu et al., 2020). Children's experience of positive emotion predicts later development of positive social relationships (Griffith et al., 2021). And blunted neural activation to positive emotional and rewarding stimuli confers risk for later psychopathology (Kujawa et al., 2020). However, further research is needed on how early experiences relate to affective neural processing in early childhood.

Emotional experience is represented dynamically in the brain, emerging from the interaction between networks responsible for core affective bodily responses and top-down emotion regulation (Lindquist & Barrett, 2012), as well as circuitry for reward processing (Berridge & Kringelbach, 2015; Sander & Nummenmaa, 2021) and social cognition (Bickart et al., 2014). In adults, regions associated with the salient aspects of emotional experience include the amygdala, anterior insula, anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and medial prefrontal cortex (mPFC; Lindquist et al., 2012). Reward processing, which is supported by dopaminergic regions like the ventral tegmental area (VTA) and nucleus accumbens (NAcc), motivates approach and avoidance responses, and is also inherently emotional in nature (Cromwell et al., 2020). Recent studies have begun using naturalistic movies during functional magnetic resonance imaging (fMRI) to examine emotional experience in developmental populations.

Movie fMRI has the potential to elicit more naturalistic emotional responses, allows for more nuanced links to behavior (Gruskin et al., 2020), and helps minimize issues related to participant compliance and motion (Vanderwal et al., 2019). In a study using a multivariate approach,

39

children showed differences relative to adults in neural responses to movie clips portraying negative emotions: children showed greater engagement in visual processing regions and lower engagement in emotion regulation regions (Camacho et al., 2019). Although there is some evidence of differences between children and adults, like young children showing greater responsiveness to positive stimuli (Garcia & Tully, 2020; Picardo et al., 2016), little is known about neural changes in emotional reactivity across childhood. A study in 4- to 12-year-olds found no main effects of age, but did find that age interacted with irritable temperament, such that greater irritability was associated with age-related increases in activity to negative movie clips in subcortical and frontal regions (Karim & Perlman, 2017). Movies thus show promise for tapping into individual differences in multifaceted, naturalistic emotional experiences early in development (Finn et al., 2020).

Early life stress is one major factor that introduces latent vulnerability in emotion and reward neurocircuitry (Hanson et al., 2021; Herzberg & Gunnar, 2020; Milojevich et al., 2021). In animal models, when early stress is experimentally induced using maternal separation and fragmented care paradigms, rats are more vulnerable to blunted affect and reduced social exploration later in life, via cascading changes in the development of reward neurocircuitry (Birnie et al., 2020; Glynn & Baram, 2019; Peña et al., 2017). A recent study found that placing dams in a stressful low resource environment drove an increase in negative parenting behaviors, and resulted in long-term attenuation of VTA dopamine activity in their offspring, suggesting a potent role for early disrupted programming of VTA development (Rincón-Cortés & Grace, 2021). In humans, a large body of work has examined the impacts of extreme forms of caregiver-related adversity (abuse, neglect, and parental separation) on emotional development (Callaghan & Tottenham, 2016b; Cohodes et al., 2021), such as more intense emotional responses to negative stimuli (Lavi et al., 2019; Weissman et al., 2019). However, little is known about the effects of normative parenting behaviors on the development of affective neurocircuitry, especially in early childhood.

Parents play a central role in their children's early emotional life (Atzil et al., 2018; Callaghan & Tottenham, 2016b; Tan et al., 2020), influencing social adjustment later in development (Perry et al., 2020; Yaniv et al., 2021). Children who are securely attached experience more positive affect, and improved emotion regulation (Cooke et al., 2019). Positive parenting includes behaviors like warmth and sensitivity to children's needs. Studies on relationships between positive parenting and children's neural responses have generated mixed results (Farber et al., 2020; Kujawa et al., 2020; Tan et al., 2020). For example, in adolescents, one study found that greater maternal warmth and support related to *lower* amygdala reactivity to negative faces (Romund et al., 2016), whereas another found that greater familial warmth related to *higher* amygdala reactivity to negative faces (Farber et al., 2019). During a parent-adolescent interaction task designed to elicit anxiety, greater parental use of reframing and problem solving with their child related to lower anterior insula and perigenual cingulate activation in response to threat stimuli (Butterfield et al., 2019). Importantly, warm parenting was also found to have a protective effect in children exposed to violence in the home, consistent with a normalizing effect on amygdala sensitization to threats (Stevens et al., 2021).

The current literature on normative negative parenting, which includes harsh, intrusive, or controlling behaviors, is similarly nascent. One study found that harsh parenting observed at age two (in a sample of only boys) was related to reduced amygdala activity to emotional faces at age twenty (Gard et al., 2017). In contrast, negative maternal emotion was related to greater amygdala activity to negative stimuli in adolescents (Turpyn et al., 2018). Negative parental affect observed during a parent-child interaction task was associated with greater response in the amygdala to negative emotional faces in older children (Pozzi et al., 2020). Observed negative parental affect was also associated with blunted response to positive social rewards in the amygdala, anterior insula, anterior cingulate, and nucleus accumbens in adolescents (Tan et al., 2014). Negative parenting may thus sensitize the brain to negative information, and increase risk for the development of blunted emotional response to positive experiences.

In the current study, we examined brain responses to emotional and parent-child interaction events during a short film, in children between the ages of 4 and 11. We specifically selected a movie that has core themes related to a parent-child interaction, and includes a range of positive and negative events. We examined children's brain responses during positive and negative emotional events, as well as during parent-child interaction events, and related this activity to individual differences in positive and negative parenting experiences observed during a laboratory parent-child interaction task. We additionally examined relationships with socioeconomic status (SES), in order to test the specificity of parenting effects, i.e., whether differential brain responses to the movie are related to parenting specifically, or can be explained by broader experiences of early adversity.

Methods

Participants

Participants were recruited from Philadelphia and the surrounding regions as part of two larger studies. One study was on environmental influences on brain development in typically developing children, and recruitment occurred through local schools, outreach programs, community family events, and advertisements on public transportation and social media. The Institutional Review Board at the University of Pennsylvania approved this study. The other study was on brain development in children with and without autism spectrum disorder (ASD). Only typically developing children were included in the current study. The Institutional Review Board at the Children's Hospital of Philadelphia (CHOP) approved this study. Recruitment for this study occurred through CHOP's internal recruitment infrastructure. All parents provided informed,

written consent, and children provided assent. Data were collected from June 2018 to March 2020.

Movie fMRI scans were acquired for 80 participants. Seventy participants were included in the final example. Participants were excluded for: not completing the movie fMRI scan (e.g., due to falling asleep or wanting to end the scan early, $n = 4$); incorrect registration of the participant at the scanner ($n = 1$); or technical problems that resulted in an incomplete movie scan (less than 5 minutes of usable movie data, $n = 5$). In the final sample, children were between the ages of 4 and 11 ($M = 8.36$, $SD = 1.74$, range = 4.27 to 11.85). We had data on racial and ethnic makeup in the subsample that participated in the parent-child interaction task ($n = 30$): 47% Black, 47% White, 23% Asian, 3% Other, and 0% Hispanic/Latino. Percentages sum to greater than 100% because parents could endorse multiple races.

Parent-child interaction task

Procedure. In a sub-sample of participants ($n = 30$), we collected a 15-minute parent-child interaction task modeled after the Three Bags Task (Love et al., 2005). We included the following tasks (Figure 3.1):

1. A wordless picture book (Mr. Wuffles! by David Wiesner).
2. A challenging block puzzle. Parents were given written instructions that said, "See how many of these puzzles your child can make," along with a booklet of the six hardest Wechsler Intelligence Scale for Children (WISC; (Wechsler & Kodama, 1949)) block design puzzles, as well as one easy demonstration puzzle.
3. A free-play "curiosity box". The box had a variety of different drawers containing a variety of small novel toys and common household objects.
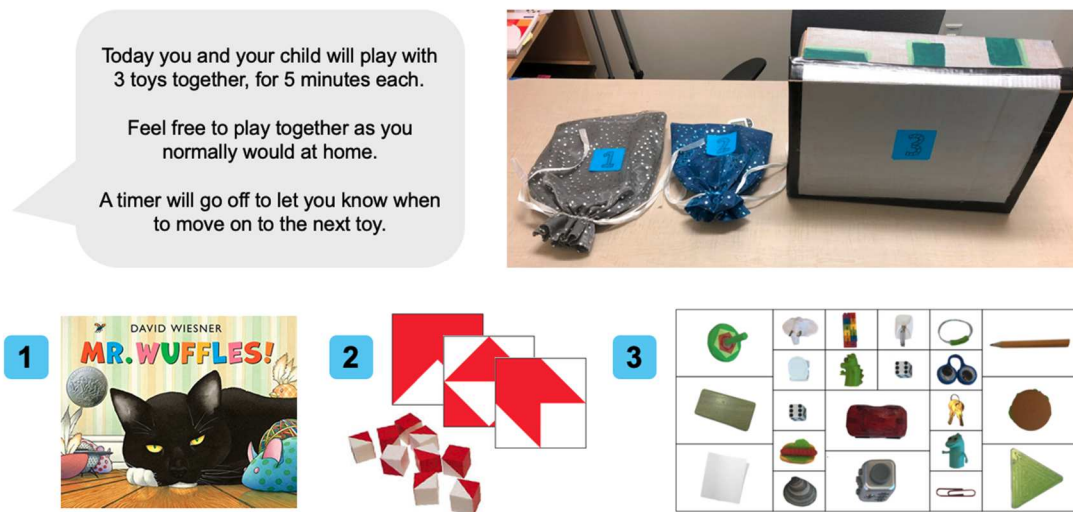
Figure 3.1. Parent-child interaction task (*n* = 30). There were three 5-minute toys: 1) a wordless picture book, 2) a challenging block puzzle, and 3) a free-play box with drawers containing a variety of novel toys and common household objects. Parents and children were instructed to play together as they normally would at home, and timers were used to indicate when to move to the next toy.

At the beginning of the session, the parent and child were instructed to play as they normally would at home, and an experimenter explained that timers would go off every 5 minutes and 30 seconds, to let them know when to move on to the next task (30 seconds were provided in between tasks to allow for transition time). The experimenter then left the room for the duration of the parent-child interaction task, which was video-taped. Twenty-five (83%) children participated in the tasks with their mother, and five (17%) children participated with their father.

Coding scheme for parent behaviors. Observer ratings of parent behaviors were captured using the PARCHISY coding scheme (Deater-Deckard et al., 1997), which consists of 7-point Likert-type scales (1 = no occurrence of the behavior, to 7 = continual occurrence of the behavior). We created a positive parenting composite that averaged between two positive behaviors in the PARCHSY coding scheme: positive content and positive affect. Positive content

is defined by PARCHISY as "use of praise, explanation, and open-ended questions," and positive affect is defined as "smiling, laughing." We also created a negative parenting composite, which consisted of the average between negative content and negative affect. Negative content is defined as "use of physical control of task or child's hand/arm/body, use of criticism" and negative affect is defined as "rejection: frowning, cold/harsh voice." Parent behavior ratings were determined separately for each of the three tasks, and then averaged together if at least two out of the three tasks were usable. Individual tasks were dropped if the dyad spent less than 3 minutes on the task (book: n = 1); or deviated substantially from the main task (block puzzle task: n = 1 engaged in free play with the blocks instead of making puzzles).

Six pairs of trained coders provided PARCHISY ratings based on video recordings of the parent-child interaction task. Coders were diverse with respect to racial, ethnic, and gender identities, but were all undergraduate students, and not parents themselves. Coders in each pair watched the videos together over Zoom, independently gave their Likert ratings, compared ratings, and came to a consensus through discussion for any ratings that differed by more than 1 point (if ratings differed by 1 point, the ratings were averaged). Nine videos (30% of the sample) were coded by all pairs to assess interrater reliability using Cronbach's alpha (*ltm* package in R): parent positive content, r = .90; parent positive affect, r = .95; parent negative content, r = .93; parent negative affect, r = .97, child positive affect, r = .74; child negative affect, r = .97). Ratings were averaged across coding pairs. Positive parenting and negative parenting did not differ by child's age, gender, or race (ps > .07).

Questionnaires

Socioeconomic status. Parental education and family income were assessed using the MacArthur Foundation Research Network on Socioeconomic Status and Health sociodemographic questionnaire (Operario et al., 2004). Parents reported on their highest

education level (possible responses ranged from "less than high school" to "professional degree (J.D., M.D., Ph.D.)"), as well as the highest education level of their partner if applicable (86% of parents reported the education level of their partner). Average parental education ranged from 10 to 20 years ($Mdn = 16$, $SD = 2.53$, $n = 70$). Total family income was assessed by asking "Which of these categories best describes your total combined family income for the past 12 months? This should include income (before taxes) from all sources, wages, rent from properties, social security, disability and/or veteran's benefits, unemployment benefits, workman's compensation, help from relatives (including child payments and alimony), and so on." Possible responses included: Less than $5,000, $5,000 through $11,999, $12,000 through $15,999, $16,000 through $24,999, $25,000 through $34,999, $35,000 through $49,999, $50,000 through $74,999, $75,000 through $99,999, $100,000 through $149,999, $150,000 through $199,999, $200,000 and greater, and Unsure. Annual family income was estimated as the median value of the selected income bracket ($Mdn = \$125K$, $SD = \$71K$, $n = 63$). Socioeconomic status (SES) was defined as the average of Z-scored income and Z-scored years of parental education (parental education was averaged across parents if available for both parents). Higher SES was associated with higher frequency of positive parenting ($r_s(68) = 0.49$, $p = .006$), and lower frequency of negative parenting ($r_s(68) = -0.54$, $p = .002$).

Stressful life events. Parents filled out a modified version of the Life Events Scale for Young Children (LES-C) (Coddington, 1972), which asked parents to report whether specific events had happened to their child within the last 12 months, as well as how stressful the child found these events, from 0 to 4. Examples of items include: "Your child had a serious accident or illness," "A family member or close relative died," and "You separated or got divorced from your partner." An LES-C score was calculated by summing all stress ratings.

Parental depression. In the sub-sample of participants with parent-child interaction data ($n = 30$), parents were asked to self-report on whether any family members have difficulties with

depression (binary yes/no response). We controlled for parental depression (depression history in

the parent who participated in the parent-child interaction task; 13% of the sample reported

history of depression) in region-of-interest sensitivity analyses, due to prior evidence showing that

maternal depression is related to adverse child functioning via parenting behaviors (Goodman et

al., 2020), as well as to attachment difficulties (Pratt et al., 2019). Parental depression was

associated with lower frequency of positive parenting behaviors ($t(28) = 2.17$, $p = .04$), but not

significantly related to negative parenting behaviors ($t(28) = 1.49$, $p = .15$).

Movie fMRI stimuli

During the scan session, participants watched Pixar's "Piper", a 5-minute animated short film

about a baby sandpiper who overcomes her fear of the ocean. The movie includes both positive

and negative emotional events, as well as rich parent-child interactions. We selected a movie

without language or humans with racial or gender identities to limit processing differences due to

language exposure or demographics. Participants from the ASD study watched the Piper movie

without audio ($n = 40$), due to the study's pre-existing data collection procedures. In order to

account for differences in the movie-watching experience due to having no audio, we controlled

for dataset in all analyses that include data from both studies.

Neuroimaging data acquisition

Before the scan, participants practiced staying still for about 10 minutes in a mock scanner that

simulates MRI noises. They practiced by watching a movie that would pause whenever they

moved their head by more than 1 mm. During the actual MRI session, a researcher stayed with

the child to reassure them, as well as to remind them to stay still if the child started to move.

Imaging was performed at the Center for Advanced Magnetic Resonance Imaging and

Spectroscopy (CAMRIS) at the University of Pennsylvania. Scanning was conducted using a

Siemens MAGNETOM Prisma 3 T MRI scanner with the vendor's 32-channel coil. A whole-brain,

high-resolution, T1-weighted 3D-encoded multi-echo structural scan (MPRAGE) was collected

(acquisition parameters: TR = 2530 ms, TEs = 1.69 ms/3.55 ms/5.41 ms/7.27 ms, BW =650 Hz/px,

3x GRAPPA, flip angle = 7°, voxel size =1 mm isotropic, matrix size = 256 × 256, 176 sagittal

slices, FOV =256 mm, total scan time = 4:38). This sequence used interleaved volumetric

navigators to prospectively track and correct for subject head motion (Tisdall et al., 2012). A 5-

minute T2*-weighted multiband gradient echo functional scan was also collected (acquisition

parameters: multiband acceleration factor = 3, TR = 2000 ms, TE = 30.2 ms, BW =1860 Hz/px, flip

angle = 90°, voxel size = 2 mm isotropic, matrix size = 96 × 96, 75 axial slices, FOV =192 mm,

volumes = 150, 5 dummy scans). Participants watched the 5-minute Piper movie during the

functional scan. PsychoPy2 (v1.90.2; Peirce et al., 2019) was used to ensure that the beginning

of the functional scan would trigger the start of the movie, so all participants' functional data

would be time-locked to the same movie events.

Preprocessing

The functional imaging data were preprocessed using Nipype, a Python-based framework for

flexibly integrating neuroimaging analysis tools (Gorgolewski et al., 2011). The software packages

used in this preprocessing pipeline included FMRIB Software Library (FSL v5.0.8; Jenkinson et

al., 2012), FreeSurfer (v6.0.0; Dale et al., 1999), Advanced Normalization Tools (ANTs v2.1.0;

Avants et al., 2011), and Nipype's implementation of Artifact Detection Tools (ART;

http://www.nitrc.org/projects/artifact_detect/).

Simultaneous realignment and slice timing correction was conducted using an algorithm

implemented in Nipy (Roche, 2011). Outlier volumes in the functional data were defined using

ART based on composite motion (greater than 1 mm of head displacement between volumes) and global signal intensity (greater than 3 standard deviations from the mean).

The following confounds were regressed out of the functional data: 6 realignment parameters (3 translations, 3 rotations) and their first-order derivatives, outlier volumes flagged by ART (one nuisance regressor per outlier), composite motion, and linear and quadratic polynomials to detrend the data. Five principal components were also derived from segmentations of both cerebrospinal fluid (CSF) and white matter (WM), and regressed from the data, to correct for physiological noise like heart rate and respiration (aCompCor; Behzadi et al., 2007). The CSF and WM segmentations were derived from Freesurfer's individual parcellations of the lateral ventricles and total white matter, respectively; these segmentations were transformed into functional space. Confound regression occurred within a skull-stripped functional mask which was created using FSL's Brain Extraction Tool (BET; Smith, 2002); BET's fractional intensity threshold was set at 0.4.

The functional data were high-pass filtered with a cutoff of 100 s, spatially smoothed with an isotropic 6 mm Gaussian kernel (FWHM), and normalized to the OASIS-30 Atropos template (in MNI152 2 mm space) in a two-step process. First, the median functional image was coregistered to the reconstructed surfaces using FreeSurfer's bbregister (Greve & Fischl, 2009); next, the structural image was registered to the OASIS-30 Atropos MNI152 template using ANTs. The transformation matrices generated by these two steps were concatenated, allowing images to be transformed directly from functional to MNI space in a single interpolation step.

Summary of motion considerations

We minimized the effects of motion during our structural scans using prospective motion correction (Tisdall et al., 2012). Movie fMRI has previously been shown to reduce head motion,

especially in younger children (Greene et al., 2018). Participants had an average head displacement of 0.20 mm (SD = 0.14 mm, significantly non-normally distributed, W = 0.80, p < .001), and an average of 3.10% outlier volumes (SD = 4.09%, significantly non-normally distributed, W = 0.73, p < .001). Thus, no participants exceeded our motion threshold of 1 mm average head displacement (3 translations, 3 rotations), or 20% outlier volumes. Higher average head motion was significantly related to younger age (r_s(68) = -0.31, p = .009) and to lower SES (r_s(68) = -0.27, p = .02). Higher percent outlier volumes was slightly but not significantly related to younger age (r_s(68) = -0.23, p = .051) and to lower SES (r_s(68) = -0.21, p = .08). All analyses controlled for the number of outlier volumes as defined by ART.

Movie fMRI analysis

Regressor definition. Five trained research assistants independently watched the Piper movie and used the video annotation software ELAN to label movie time points that fell into three categories: positive affect, negative affect, and parent-child interactions. Positive affect was defined as time points when the main character, Piper, appeared to be feeling positive (e.g., related to happiness, joy, excitement, etc.). Negative affect was defined as time points when Piper appeared to be feeling negative (e.g., related to fear, suspense/tension, sadness, etc.). Parent-child interactions were defined as any time points when Piper and her mother were interacting. Annotators were instructed to focus on labeling movie segments that lasted around 5 to 15 seconds (in order to extract events that would be suitable for block design fMRI analysis). All annotators were watching Piper for the first time.

Events were defined as blocks of contiguous time points where there was agreement from at least three out of the five annotators (Figure 3.2). This was achieved by rounding event start and stop times to the nearest 1-second bin, and flagging only time points with at least three endorsements. The minimum event length was 1 second.
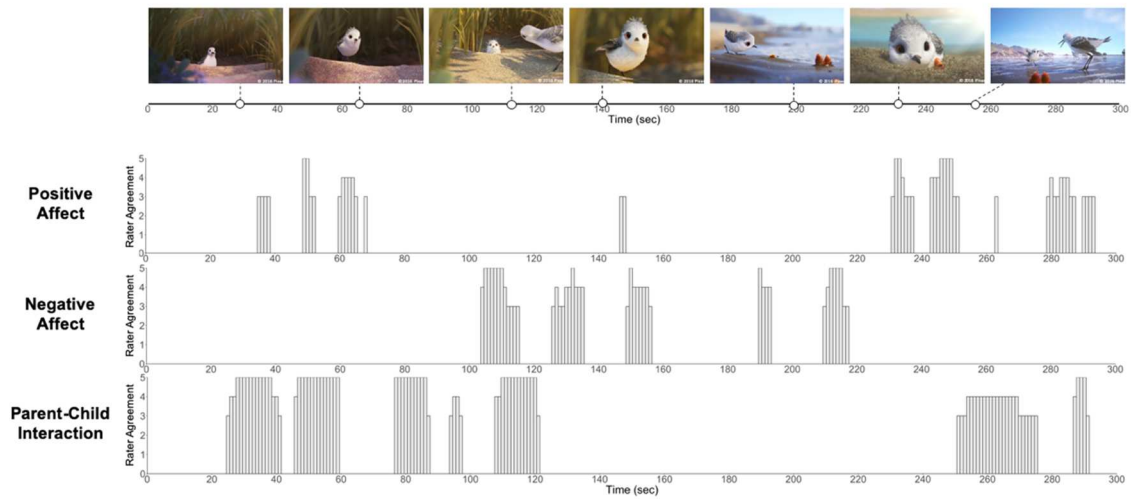
Figure 3.2. Positive affect, negative affect, and parent-child interaction event regressors extracted from the Piper animated short film. Time points were only included if there was overlap between at least three out of the five independent annotators. Top row shows a summary of key events during the Piper movie narrative.

Whole-brain analyses. Each subject-level design matrix included one event regressor (as well as its temporal derivative), for positive affect events, negative affect events, and parent-child events. The regressors were convolved with FSL's double-gamma hemodynamic response function. We used FSL's *fsl_glm* tool to generate a contrast map for each of the three event regressors from the preprocessed data. First-level contrast maps for positive affect, negative affect, and parent-child interaction events were then submitted to group-level analyses. Group-level analyses were performed with FMRIB's Local Analysis of Mixed Effects tool (FSL's FLAME 1). Only voxels that had unanimous coverage across subjects were tested, resulting in a mask that covered the entire brain. We ran the following GLMs (testing for both positive and negative associations, n = 70): 1) group average; 2) gender differences, 3) main effect of age, and 4) main effect of SES. GLMs included the following covariates (except for models where the covariate was the main effect being tested): age, gender, number of outlier volumes, and dataset (to control for broader differences between the two studies, mainly whether the Piper movie had audio or not). The group average GLM only controlled for number of outliers and dataset. In the sub-

sample of participants with parent-child interaction data, we ran the following GLMs (testing for both positive and negative associations, and controlling for age, gender, and number of outlier volumes, n = 30): 5) main effect of positive parenting, and 6) main effect of negative parenting.

Z-statistic maps were corrected for multiple comparisons with parametric clusterwise inference using FSL's cluster tool (relies on Gaussian Random Field Theory) at a cluster-defining threshold of z = 3.1 ($p <$ .001), neighborhood size of 26, and an FWE-corrected threshold of $p <$ .05. All statistical analyses were conducted in R.

Region-of-interest (ROI) analyses. Due to the extensive role of the amygdala in studies on parenting and emotional development, we additionally performed region-of-interest analyses using an independent amygdala ROI (bilateral amygdala from the Harvard-Oxford subcortical atlas available through FSL; Figure 3.5). We examined whether positive and negative parenting were related to ROI activity during positive affect, negative affect, and parent-child interaction events.

Results

Group average results

Positive affect events of the movie were associated with activity in regions of the default mode network, including precuneus, angular gyrus, middle temporal gyrus, and medial prefrontal cortex, as well as regions in orbitofrontal cortex, lateral prefrontal cortex, somatomotor cortex, and cerebellum (Figure 3.3A). The negative affect events also showed overlap with the default mode network, in precuneus, angular gyrus, and medial prefrontal cortex, as well as middle temporal gyrus and lingual gyrus (Figure 3.3B). Finally, the parent-child interaction events were associated

with activity in the bilateral temporoparietal junction (TPJ), middle temporal gyrus, temporal poles, postcentral gyrus, and visual areas, including lateral occipital cortex and fusiform face area (Figure 3.3C).
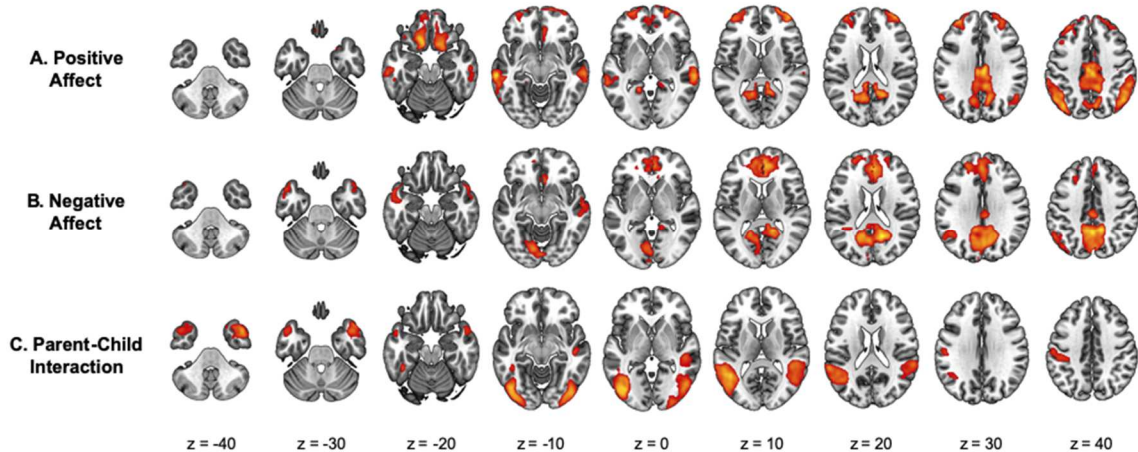
Figure 3.3. Positive group average activity for the events during the movie related to (A) positive affect, (B) negative affect, and (C) parent-child interactions. Models controlled for number of outlier volumes and dataset, and were corrected for multiple comparisons at z = 3.1, p < 0.05, n = 70.

Associations with parenting measures

During positive affect events in the movie, greater occurrence of negative parenting behaviors during the parent-child interaction task was related to reduced activation in the VTA (Figure 3.4A; peak voxel coordinates (MNI): 12, -6, -14, maximum z-statistic = 5.32, cluster volume = 190 voxels) and left cerebellum (Figure 3.4B; peak voxel coordinates (MNI): -34, -44, -42, maximum z-statistic = 4.25, cluster volume = 183 voxels). Negative parenting was not related to activity during negative affect events or parent-child interaction events. We also found no significant effects of positive parenting on activity during any of the movie events.

In order to test the robustness of the results to additional covariates, we used an independent VTA ROI (Figure 3.4A, overlaid in yellow) to extract Z-statistic values from subject-level contrast maps of positive affect, negative affect, and parent-child interaction events. The VTA ROI came from a probabilistic atlas that was constructed from hand-drawn ROIs of the VTA (Murty et al., 2014). Consistent with the whole-brain result, there was a significant association between negative parenting behaviors and reduced activity in the VTA ROI to positive affect events ($t(25)$ = -3.54, p = .002). The association remained significant even after additionally controlling for SES ($t(24)$ = -3.38, p = .002), stressful life events, LES-C ($t(24)$ = -3.58, p = .002), and parental depression ($t(24)$ = -3.28, p = .003). Due to the role of child temperament in reward circuitry function (Guyer et al., 2014), we also controlled for child affective responses during the parent-child interaction task, and found that the association remained even after controlling for child positive affect ($t(24)$ = -3.87, p < .001) and negative affect ($t(24)$ = -3.23, p = .004). SES, LES-C, and parent depression were not associated with VTA activation to positive events.
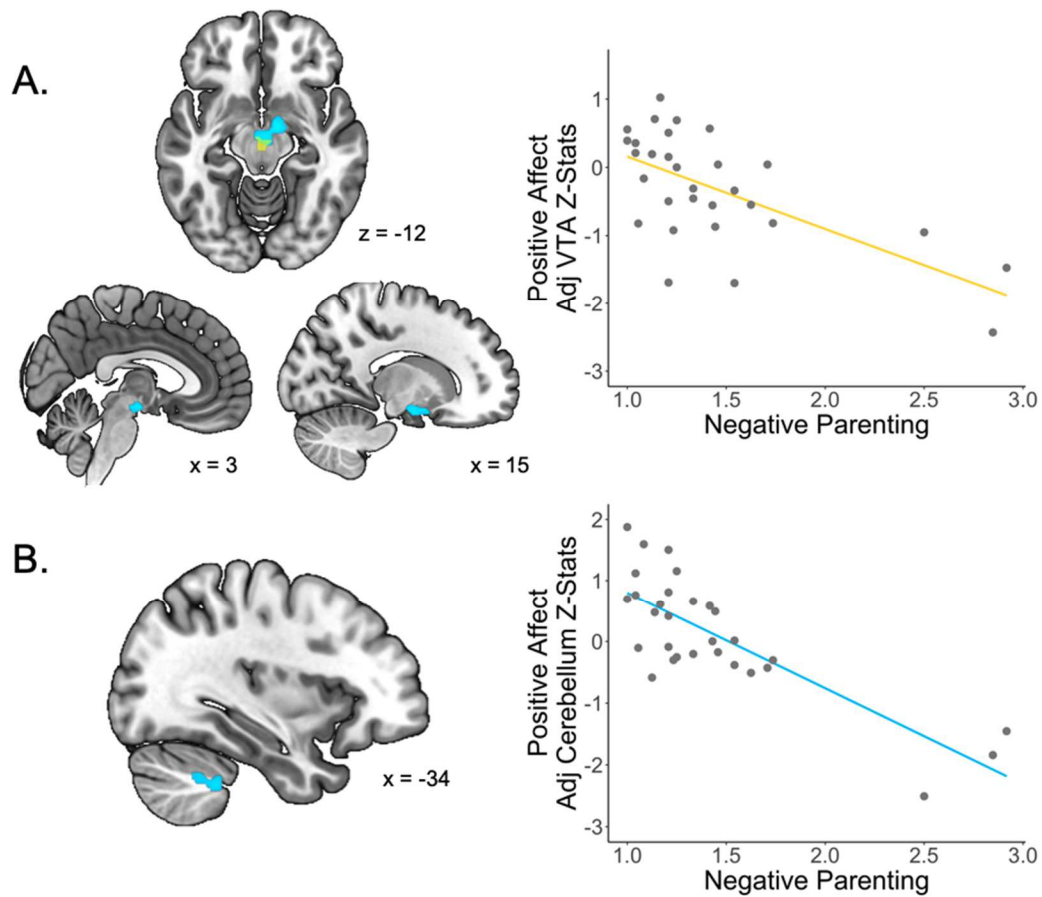
Figure 3.4. Negative parenting is associated with reduced activity in the (A) VTA and (B) cerebellum during positive affect events of the movie. Scatterplots show the relationship between negative parenting and extracted Z-statistic values (adjusted for covariates: age, gender, number of outlier volumes). The independent VTA ROI is shown overlaid in yellow (Murty et al., 2014). Cerebellar statistics were extracted from the cluster that was significant in the whole-brain analysis and presented only to show the distribution of the data. Models were corrected for multiple comparisons at $z = 3.1$, $p < 0.05$, $n = 30$.

We additionally conducted a region-of-interest analysis for the amygdala. The amygdala was significantly activated above baseline only during the positive affect events (Figure 3.5A; $t(69) = 3.39$, $p < .001$), and was significantly more active during positive affect events relative to negative affect events ($t(68) = 3.73$, $p < .001$) and parent-child interaction events ($t(68) = 4.01$, $p < .001$). Negative parenting was significantly related to lower activity in the amygdala during positive affect

events (Figure 3.5B; *t*(25) = -2.85, *p* = .009). Negative parenting was not related to amygdala

activity during the negative affect or parent-child interaction events, and there were no significant

effects for positive parenting.
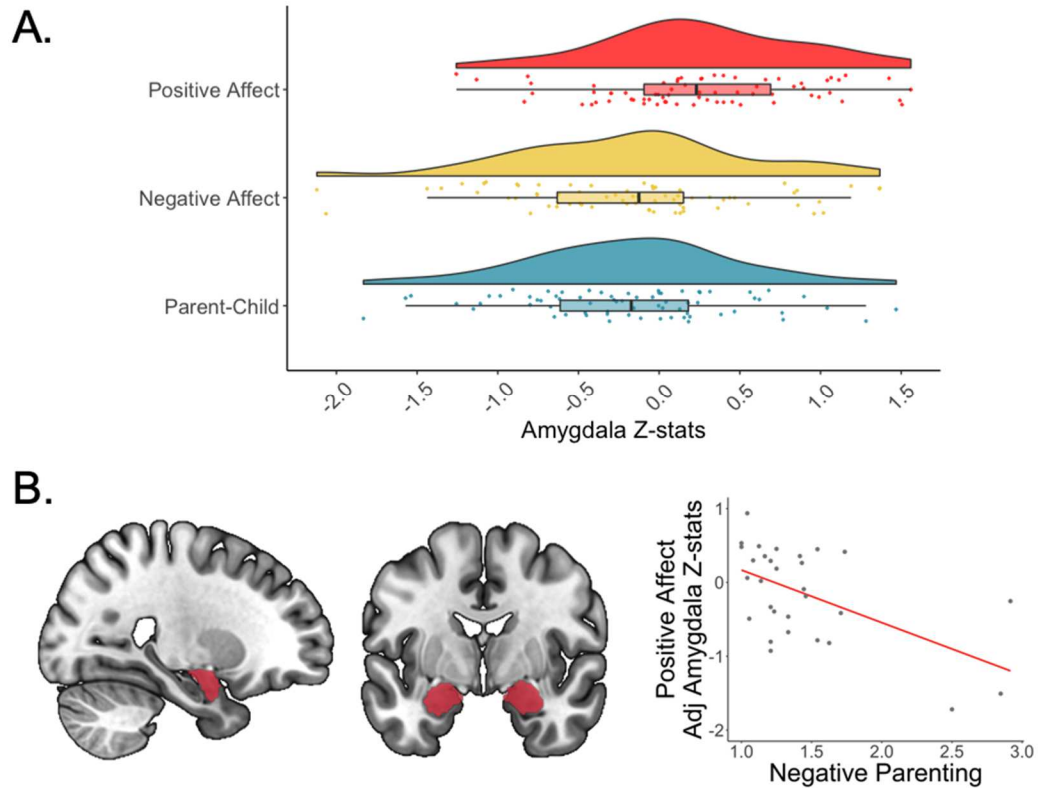
Figure 3.5. Region-of-interest analysis for amygdala activation during the movie. A. Average amygdala activation to positive affect events, negative affect events, and parent-child interaction events during the movie. B. Negative relationship between amygdala activation during the positive affect events and negative parenting behaviors (adjusted for covariates: age, gender, number of outlier volumes).

Associations with demographics and stressful life events

During parent-child interaction events in the movie, higher socioeconomic status (SES) was

related to greater activity in medial orbitofrontal cortex (OFC) (Figure 3.6; peak voxel coordinates

(MNI): -4, 32, -22, maximum z-statistic = 4.23, cluster volume = 316 voxels). Higher SES was not

related to reduced activity in any brain regions, nor were there any significant relationships during

positive affect or negative affect events. No significant positive or negative relationships with age

or stressful life events (LES-C) were found for positive affect, negative affect, or parent-child

interaction events, nor were any relationships found with gender.
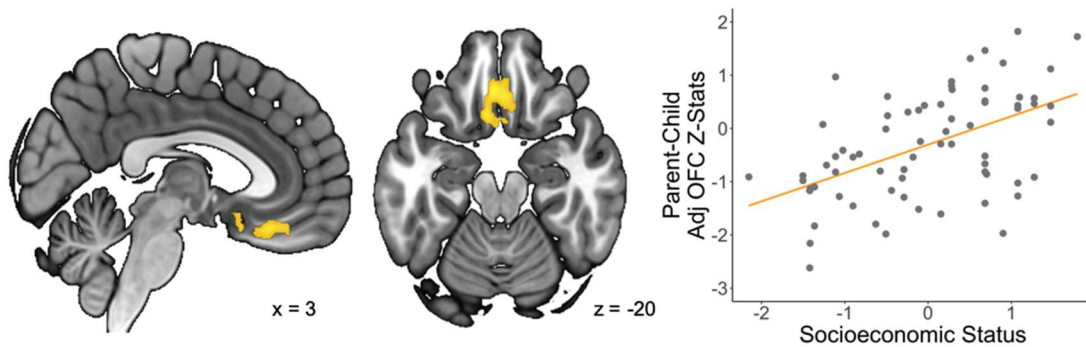
Figure 3.6. Higher socioeconomic status (SES) is associated with greater activity in medial orbitofrontal cortex (OFC) during parent-child interaction events of the movie. SES is defined as the average of Z-scored income and Z-scored parent education. Scatterplot shows the relationship between SES and extracted Z-statistic values within the OFC result (adjusted for covariates: age, gender, number of outlier volumes, dataset). Results were corrected for multiple comparisons at $z = 3.1$, $p < 0.05$, $n = 70$.

Discussion

Children with greater exposure to negative parenting behaviors showed lower activity in the

ventral tegmental area (VTA) and cerebellum while processing naturalistic positive emotional

content. This pattern was specific to positive affect events, and not to negative affect events or

parent-child interaction events. We did not find evidence for a relationship between positive

parenting behaviors and neural activity to events. Our results suggest that negative parenting

may confer risk for children's blunted response to emotionally rewarding experiences.

Our findings are consistent with a prior study in adolescents showing that negative parenting behaviors observed during a parent-child interaction task related to blunted response to positive rewards in regions that track salience (Tan et al., 2014), and also to evidence that early life stress more broadly may disrupt positive valence systems (Kujawa et al., 2020). We found that the relationship between negative parenting and VTA activity remained even after controlling for additional environmental factors, including socioeconomic status (SES) and negative life events (LES-C), as well as other characteristics like parental history of depression and the child's affective expression. It may be that parenting behaviors, particularly those observed during a real-world parent-child interaction, have a specific effect on children's responses to positive emotional content. However, we note that the current, limited literature on parenting and children's neural processing of positive and negative stimuli is mixed, perhaps due to study differences in age range and methods for characterizing parenting, as well as the moderating effects of different risk factors (Farber et al., 2020; Kujawa et al., 2020; Tan et al., 2020). It is also unclear whether *absence* of positive parenting behaviors would show distinct effects from explicitly harsh parenting. In our study, we did not find that positive parenting behaviors related to any differences in neural activity. It could be that negative parenting has a larger disruptive effect on brain activity and we were underpowered to find an effect of positive parenting, or that our measure of positive parenting did not capture the most relevant parent characteristics, or that positive parenting would show more of an impact for specific behaviors, like emotion regulation during negative parts of a movie.

Early alterations in the VTA may have a potent impact on children's socioemotional and motivational development, as the VTA is the origin of major dopaminergic projections innervating large swaths of the brain. Studies in humans (Park et al., 2021) and rodents (Peña et al., 2017; Rincón-Cortés & Grace, 2021) have suggested that early life stress may lead to functional alterations in the VTA. It has been argued that the dopamine system plays a crucial role in supporting the ability to appropriately cope with challenges (Ironside et al., 2018), and to flexibly

adapt to ever-changing environmental priorities (Douma & de Kloet, 2019)—this would help explain why adversity-related disruptions of the dopamine system often lead to difficulties with nuanced behaviors like effortful reward seeking and social exploration. In a region-of-interest analysis, we additionally found that negative parenting was related to lower amygdala activity during positive affect movie events. The amygdala is also part of an integrated network of regions responsible for complex processing of emotion, reward, and social experience (Cromwell et al., 2020). Although prior work has traditionally associated the amygdala with negative emotion and fear learning, the amygdala is involved with both positive and negative valence (Smith & Torregrossa, 2021). One study with adults found that greater cumulative activity in the amygdala during *negative* movie clips predicted heightened sensitivity to subsequently shown fearful faces, while greater cumulative activity in the amygdala during *positive* movie clips predicted a lower amygdala response to the fearful faces (Pichon et al., 2015). In other words, at least in the short-term, responsiveness of the amygdala to positive emotion may help buffer against fear-related stimuli, and suggests a potential mechanism by which persistent blunted activity to positive emotional experiences may worsen responses to negative stimuli and alter future affective functioning.

In addition to blunted VTA activation, we also found that negative parenting was associated with reduced activity in the cerebellum to positive affect movie events. Beyond coordinating motor behaviors, the cerebellum also plays a powerful role in modulating higher-order cognitive, affective, and social functions (Van Overwalle et al., 2014), and may drive the maturation of cognitive and affective cortical areas early in development (Wang et al., 2014). A study in mice found that excitatory projections from the cerebellum to the VTA robustly modulated reward circuitry, and were more active during social exploration (Carta et al., 2019). Early blunting of both the cerebellum and VTA to positive stimuli may point to a broader pattern of early vulnerability with implications for disrupted social behavior, and suggests that the cerebellum is an important target region for future study in early childhood. Finally, we observed a main effect of SES during

the parent-child interaction events of the movie: higher SES was related to greater activity in medial orbitofrontal cortex (OFC). The medial OFC has been proposed to play a role in the affective and goal-oriented evaluation of internally-generated events, like episodic memories and imagining the future (Dixon et al., 2017). Although speculative, one possibility is that higher SES fosters an enhanced ability to introspect about self- and other-related representations, or that children from higher SES backgrounds were interpreting ambiguous parent-child interactions more positively.

To our knowledge, this study is one of the first to relate parenting behaviors observed during a parent-child interaction task to children's affective neural responses elicited during a short film. The use of naturalistic movie fMRI with developmental populations is increasing in popularity (Vanderwal et al., 2019), due to its utility for encouraging compliance in young participants, and its promise for yielding novel insights into the brain's response to more ecologically valid stimuli (Finn et al., 2020; Simony & Chang, 2019; Sonkusare et al., 2019). For example, in the current study, our positive and negative affect movie events captured not only the main character's emotional facial expressions, but also more nuanced narrative-level emotional components (e.g., the main character dealing with jarring physical or social surprises, experiencing the joy of overcoming their fears, etc.). Recent studies have used multivariate techniques to test for differences between children and adults in processing positive and negative movie clips (Camacho et al., 2019; Mitchell et al., 2021). Another study found no main effects of age in relation to valenced movie clips across 4- to 12-year-olds (Karim & Perlman, 2017), but did find an age x irritable temperament interaction on neural responses. This is consistent with the current study, where we also found no effects of age. It could be that there are other moderating factors obscuring age effects, or that the kind of emotional processing elicited by our short film does not show much developmental change in our age range. Indeed, prior work that teased apart emotion reactivity and emotion regulation only found age-related changes in emotion regulation (in ages 10 and up; Silvers et al., 2012).

Although in the current study we found effects that were specific to negative parenting, positive parenting can also serve as a protective factor in environments that are associated with greater stress exposure, like low SES (Brody et al., 2019). A recent study examined impacts of a parenting intervention designed to increase secure attachment in high-risk children, by training parents to increase nurturance and sensitivity to their child, and decrease negative parent behaviors (Valadez et al., 2020). Across all children, viewing maternal cues (picture of one's own mother) resulted in greater activation in regions like the amygdala, hippocampus, thalamus, and orbitofrontal cortex (OFC), relative to viewing a stranger. Children in the parenting intervention group showed greater activation in regions including the precuneus and cuneus, angular gyrus, hippocampus, and cerebellum. One possible interpretation is that early positive dyadic experiences resulted in enhanced activity in regions that are important for social cognition and self-other representations (and perhaps, the underlying architecture for healthy attachment).

This study has a number of limitations. First, our data are cross-sectional and the sample size is limited, meaning that longitudinal work should be pursued in order to more closely assess the directionality between negative parenting behaviors and blunted VTA activity. Second, although our use of a naturalistic parent-child interaction task provides rich and nuanced data on parenting behaviors, this is also a one-time snapshot into the parent-child dynamic, which could be influenced by social desirability concerns or transient stressors. In particular, the frequency of negative parenting behaviors in this study tended to be low, and it is possible that the laboratory context made it less likely that more extreme negative behaviors would be observed. It may be useful to consider administering parent-child interaction tasks at multiple time points, using ecological momentary assessment methods to sample parent and child behaviors over many days (Leonard et al., 2020), or combining parent-child observational data with questionnaire data from multiple informants (Farber et al., 2020). Relatedly, we did not have data on how much time the child generally spends at home with the participating parent. It would be useful to have greater insight into the longer-term relationship beyond what we observed in the lab. Third, our

measures of positive and negative parenting were averaged across multiple types of parenting behaviors, meaning that while we can broadly interpret differences between harsh and supportive parenting on the development of affective circuitry, we cannot isolate specific parenting behaviors that might serve as promising targets for intervention. Examples of more specific parent behaviors that have been studied in the literature include parent criticism, emotion coaching, modeling of appropriate emotion regulation, etc. (Tan et al., 2020). Fourth, one challenge of using naturalistic movie fMRI is the difficulty of teasing apart emotion reactivity and emotion regulation, i.e., it is difficult to interpret whether an attenuated response to negative stimuli is due to overall blunted emotional responsiveness, or to more effective use of top-down emotion regulation. Finally, due to the diversity of our participant sample, we acknowledge that there are cultural differences in parenting practices that have not historically been well accounted for in developmental research, and that warrant more sensitive, nuanced exploration in future work (Nielsen et al., 2017).

In sum, our findings suggest that early exposure to negative parenting may shape how children experience rewarding positive information, above and beyond other kinds of stressors. Future work should examine how children's positive emotional responses can be supported, even in harsh circumstances—perhaps through parenting interventions that teach parents to be more sensitive to their child's emotional needs (Valadez et al., 2020).

CHAPTER 4: Neural correlates of curiosity in childhood, and environmental predictors of curiosity

Introduction

As early as infancy, children begin to engage curiously with their environment, actively gathering information and testing hypotheses, in order to build internal representations of the world (Schulz, 2012). Epistemic curiosity—broadly defined as the intrinsic motivation to seek knowledge— supports learning in young children and has been linked to positive academic outcomes (Gottfried et al., 2016), especially for children from low socioeconomic backgrounds (Shah et al., 2018). It is possible that by fostering curiosity early in development, parents and educators can encourage the cultivation of long-term interests and deeper learning (Hidi & Renninger, 2020). Indeed, curiosity has been associated with early precursors for STEM engagement, like greater interest in science topics (Williams et al., 2021) and success with solving novel science-relevant problems (Fusaro & Smith, 2018). However, much is still unknown about individual differences in curiosity in early childhood, due in part to the wide variety of approaches to defining and measuring curiosity (Jirout & Klahr, 2012; Kidd & Hayden, 2015). For example, parents and teachers can report on children's stable ("trait") levels of scientific curiosity, or lab tasks can capture momentary ("state") curiosity in response to specific environmental stimuli (e.g., a child's spontaneous behaviors when interacting with toys, such as attention to novelty, complexity, or ambiguity).

One prominent theory, known as Loewenstein's "information-gap theory," argues that curiosity arises when you encounter a gap in your knowledge, thus motivating you to reduce this unpleasant "deprivation" state of uncertainty by seeking out information (Loewenstein, 1994). Indeed, studies have found that adults show an inverted-U shape relationship between knowledge and curiosity: curiosity is highest when an individual is moderately confident in their knowledge (presence of a gap), and curiosity is lower when their confidence is either very high

(boring) or very low (too much unknown) (Kang et al., 2009). Thus, one important component of curiosity is the perception of being able to expand upon an existing knowledge base, or region of proximal learning (Metcalfe et al., 2020). Another notable component, one that is often anecdotally associated with children, is the joy that comes with discovery. In other words, children's trait-level curiosity can be operationalized along dimensions of "deprivation" (D-type curiosity) and "interest" (I-type curiosity; Litman, 2005; Piotrowski et al., 2014), where D-type curiosity is linked more with negative feelings of frustration and uncertainty, and may trigger persistent information search, while I-type curiosity is linked more with positive feelings of the intrinsic excitement to learn (Vogl et al., 2020).

One behavior that children frequently employ to satisfy both I- and D-type curiosity is asking questions. Children actively seek out explanations—the "how" and the "why"—in order to make sense of the underlying structure of the world, especially when faced with novel or surprising information (Liquin & Lombrozo, 2020). Explanation-seeking questions emerge early in development (Chouinard, 2007), and even at a young age, children are beginning to develop a sophisticated understanding of what and who to ask, based on factors like expertise (Aguiar et al., 2012; Jirout & Klahr, 2020; Mills et al., 2011). Understanding the underlying neural states that give rise to effective question asking may help inform the design of educational practices that foster curiosity. However, little is known about how curiosity is represented in the brain in childhood.

Dopaminergic circuitry is thought to contribute to curious behavior (van Lieshout et al., 2020). When encountering novel information, the hippocampus communicates in a functional loop with the ventral tegmental area (VTA) in the midbrain, as well as with regions like the nucleus accumbens (NAcc), allowing novel information to be encoded into memory (Adcock et al., 2006; Lisman & Grace, 2005). Curiosity increases activity in memory-related brain regions when subjects guess incorrectly, suggesting that curiosity plays a role in learning from surprising new

information (Kang et al., 2009). When participants anticipate the answers to trivia questions, activity in the midbrain and NAcc increases with curiosity, and activity in the hippocampus and NAcc to high-curiosity questions predicts later memory (Gruber et al., 2014). Gruber and Ranganath have proposed a framework, known as the Prediction, Appraisal, Curiosity, and Exploration (PACE) framework (Gruber & Ranganath, 2019), suggesting that curiosity is triggered by prediction errors in the hippocampus or anterior cingulate cortex (ACC), resulting in a cycle of increased exploration, information gathering, and hippocampus-dependent memory formation. The ACC in particular may play a role in detecting information gaps, while lateral prefrontal cortex appraises those information gaps and directs behavior accordingly. It is also possible that processing in the amygdala could trigger anxiety in response to uncertainty, rather than curious approach behaviors. Since the connectivity between subcortical regions like the amygdala and hippocampus with prefrontal cortex has a protracted developmental trajectory, one hypothesis is that curiosity in early childhood might be more automatic, as more complex appraisal processes have not yet come online (Gruber & Fandakova, 2021). This would be consistent with the idea that young children might show a greater bias towards curiosity in the face of uncertainty (rather than anxiety), and thus engage in more exploratory behavior.

Finally, in addition to better understanding the underlying neural correlates of curiosity, it will be critical to identify factors that can encourage or harm the development of curious behavior. Parents are particularly well-positioned to play an active role in fostering and supporting effective question-asking behavior in children. Prior work found that children explored more when an adult experimenter was accepting and supportive, rather than aloof and critical (Moore & Bulbulian, 1976). A positive caregiving dynamic that supports healthy attachment may allow children to explore more freely (Bosmans & Kerns, 2015; Engel, 2011). On the flip side, stressful and unpredictable environments have deleterious effects on exploratory behavior, shifting strategy choice towards exploitation of safe but limited outcomes (Humphreys et al., 2015). Thus, stress exposure may make a child less likely to engage curiously with the world.

In the current study, we examined the environmental predictors and neural correlates of curiosity in children, by measuring parent-report of child epistemic curiosity, as well as real-world child question-asking behavior. We examined whether there are environmental experiences that predict individual differences in child curiosity, at multiple levels: socioeconomic status (SES) and adverse childhood experiences (ACEs), which broadly capture stress exposure; positive and negative parenting observed during a parent-child interaction task, to tap into real-world parent-child relationship dynamics; and unpredictability of nurturance, a parent-report measure of the degree to which the child can seek out the parent for dependable and nurturing care. We additionally explored whether individual differences in curiosity was related to the functional connectivity of mesocorticolimbic areas, including the VTA, hippocampus, nucleus accumbens, and medial prefrontal cortex.

Methods

Participants

The Institutional Review Board at the University of Pennsylvania approved this study. All parents provided informed, written consent. Children younger than age 8 provided verbal assent, and children ages 8 and older provided written assent. Participants were recruited from Philadelphia and the surrounding regions through advertisements on public transportation, partnerships with local schools, outreach programs, community family events, and social media ads. Data were collected from April 2018 to March 2020.

Resting-state fMRI data were acquired for 130 participants. Ninety participants were included in the final sample for resting-state fMRI analyses (see exclusion criteria below). Children were

between the ages of 4 and 9 (*M* = 6.95, *SD* = 1.41, range = 4.11 to 9.93). The racial and ethnic makeup of the sample was as follows: 56% Black, 41% White, 12% Asian, 10% Other, and 9% Hispanic/Latino. Percentages sum to greater than 100% because parents could endorse multiple races. Participants were excluded for: missing data on the I- and D- Type Epistemic Curiosity Scale (*n* = 5); not completing the resting-state scan (e.g., due to falling asleep or wanting to end the scan early, *n* = 20); incorrect registration of the participant at the scanner (*n* = 1); or a parent-reported psychiatric diagnosis (*n* = 4). Participants were also excluded for having no usable resting-state data due to average head displacement (3 translations, 3 rotations) of greater than 1.2 mm (*n* = 9; see Chapter 2 for further details on the choice of motion threshold), as well as for having an unusable structural scan (*n* = 1).

Analyses of the environmental measures included all participants with available questionnaire and parent-child interaction data, regardless of having MRI data. Parent-child interaction data were available in 111 participants. Participants were excluded for: missing data from the I- and D-type curiosity questionnaire (*n* = 3), speaking a language other than English during the parent-child interaction task (*n* = 1), or a parent-reported psychiatric diagnosis (*n* = 5). The final sample for analyses of environmental measures included 102 participants.

Measures of curiosity

Children's curiosity was captured in two different ways (Figure 4.1): a "trait" measure, i.e., child's epistemic curiosity with parent-report, and a "state" measure, i.e., child's question-asking during a laboratory parent-child interaction task.
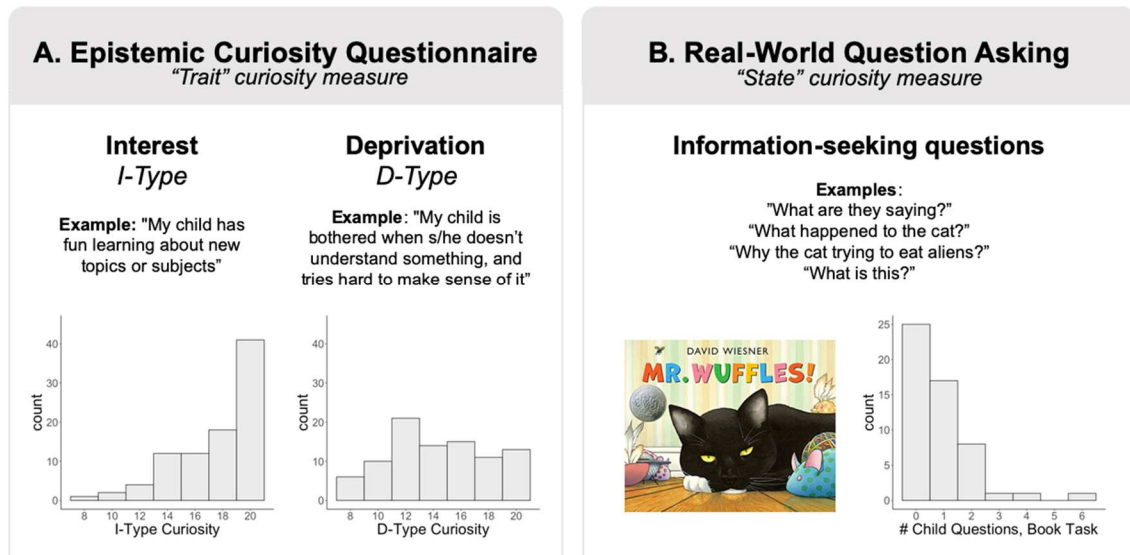
Figure 4.1. Two methods for quantifying curiosity in children: A) parent-report questionnaire of epistemic curiosity, and B) spontaneous child question-asking during a parent-child interaction task (reading a picture book). Example items and distributions of the measures are pictured.

Questionnaire measure: Parent-reported curiosity. Parents completed the I- and D- Type Epistemic Curiosity Scale (Piotrowski et al., 2014), which captures children's curiosity along two dimensions: Interest-type curiosity and Deprivation-type curiosity (Figure 4.1A). The I-type subscale consists of questions about children's positive intellectual interest when learning new things, e.g., "When my child learns something new, s/he asks many questions about it," and "My child has fun learning about new topics or subjects." The D-type subscale consists of questions about children's negative feelings when feeling uncertain about a lack of information, e.g., "My child is bothered when s/he doesn't understand something, and tries hard to make sense of it." I-type and D-type scores were calculated by summing Likert-scale ratings (from 1 = Almost Never to 4 = Almost Always), such that a higher score indicates a higher frequency of curious behavior.

Parent-child interaction task: Child question-asking. We measured question-asking behavior in a subset of children (*n* = 74). The task consisted of the parent and child reading a wordless

picture book together ("Mr. Wuffles", by David Wiesner) (Figure 4.1B). At the beginning of the

session, the parent and child were instructed to play as they normally would at home, and no

further directions were given for the picture book (meaning that child questions were

spontaneously generated, in an effort to capture a relatively naturalistic measure of the child's

parent-directed questions). Trained research assistants watched the video recording of the

parent-child interaction, and transcribed the child's questions. Another researcher arbitrated any

discrepancies in question transcriptions, and labeled whether questions were information-seeking

questions. Questions were limited to information-seeking questions made specifically about the

contents of the story (e.g., "Why is the cat trying to eat the aliens?"). We excluded information-

seeking questions that were off-task (e.g., "How much longer until we're done?"), as well as

questions that served a social or pragmatic function in the parent-child interaction (e.g., asking

the parent to repeat themselves).

We created a question-asking score by summing the total number of questions asked. In

question-asking analyses, we controlled for the total duration of time spent on the task (to

account for cases where the task ended early, due to reasons like logistical issues, the dyad

choosing to stop early on their own, etc.). We also controlled for the child's overall frequency of

making verbalizations during the parent-child interaction task, which was measured using the

PARCHISY coding scheme's Likert-style ratings (described further below).

Environmental predictors: Observational

Positive and negative parenting. The parent-child interaction task, as well as the coding

scheme used to quantify parenting behaviors, is explained in detail in Chapter 3, and briefly

summarized here. We collected a 15-minute parent-child interaction task, with 3 sub-tasks: a

wordless picture book (the same task was used for quantifying child question-asking behavior), a

challenging block puzzle task, and a free-play collection of novel toys. Observer ratings of parent

behaviors were captured using the PARCHISY coding scheme (Deater-Deckard et al., 1997). Positive parenting was defined as the average between parent positive content and parent positive affect. Negative parenting was defined as the average between parent negative content and parent negative affect. Ratings were averaged across the three sub-tasks. Six pairs of coders watched video recordings of the parent-child interaction task and provided PARCHISY ratings (note that the PARCHISY coders were different from the research assistants who transcribed child questions during the book portion). Ratings were averaged across coding pairs. Positive parenting and negative parenting did not differ by child's age or gender. Reliability between coding pairs was high (Cronbach's alpha > 0.90 for all parenting behaviors examined).

Environmental predictors: Questionnaires

Socioeconomic status (SES). Parents reported their total annual income and highest education level, as well as the highest education level of their partner if applicable (85% of parents reported the education level of their partner). Average parental education ranged from 11 to 20 years (*Mdn* = 13, *SD* = 2.30, *n* = 101). Thirty-nine percent had a high school diploma or less education. Annual family income ranged from $2,500/year to $200,000/year (*Mdn* = $42.5K, *SD* = $66K, *n* = 98, parents could report up to $200,000). SES was defined as the average of Z-scored income and Z-scored years of parental education (parental education was averaged across parents if available for both parents).

Adverse childhood experiences (ACEs). Parents completed the child version of the Adverse Childhood Experiences (ACEs) questionnaire (Murphy et al., 2016), which asked parents about their child's lifetime experiences with parent separation, abuse, and neglect, as well as with experiences like witnessing interpersonal violence, or living with a person who abuses substances or has a mental illness. An ACEs score was calculated by summing the binary ratings for ten types of experiences. ACEs sum ranged from 0 to 7 (*Mdn* = 1, *SD* = 1.68, *n* = 98).

Experiences of unpredictability (FUS). The Family Unpredictability Scale (FUS; Ross & Hill, 2000) focuses on four subscales of unpredictability in the home, in the domains of discipline, nurturance, meals, and money. Here we focused on the subscale of nurturance. Example items include: "I let my children know on a regular basis that they're important to me" and "When our children get their feelings hurt, they come to me for comfort." An FUS nurturance score was calculated by averaging all items. FUS nurturance ranged from 1.00 to 3.57 (Mdn = 1.42, SD = 0.68, n = 97). A higher FUS score indicates more unpredictable behavior.

History of parental depression. Parents were asked to self-report on whether any family members have difficulties with depression (binary yes/no response). Twelve out of the 90 parents (13%) who participated in the parent-child interaction task indicated a past history with depression.

Analyses of environmental predictors

We ran the following models: we tested the relationships between curiosity (I-type curiosity, D-type curiosity, and question-asking) with 1) the positive parenting composite, 2) the negative parenting composite, 3) SES, 4) ACEs, and 5) the FUS nurturance subscale. Each model included child age and gender as covariates. We also ran all analyses with and without controlling for parental history of depression. For any analyses that included child question-asking, we additionally controlled for the PARCHISY variable of child verbalizations (frequency of the child speaking throughout the interaction), as well as the length of time spent on the book task.

Neuroimaging data acquisition

Resting-state neuroimaging data acquisition and preprocessing are described in detail in Chapter 2. Briefly, 5-10 minutes of functional data were acquired for each child. Data were excluded from

analysis if average head motion exceeded 1.2 mm. Preprocessing included simultaneous

realignment and slice timing correction, bandpass filtering (0.01-0.1 Hz), spatial smoothing

(isotropic 6 mm Gaussian kernel FWHM), and normalization to the OASIS-30 Atropos template

(in MNI152 2 mm space). The following confounds were regressed out of the functional data: 6

realignment parameters (3 translations, 3 rotations) and their first-order derivatives, outlier

volumes flagged by Artifact Detection Tools (ART; one nuisance regressor per outlier), composite

motion, and linear and quadratic polynomials to detrend the data. Five principal components were

also derived from segmentations of both cerebrospinal fluid (CSF) and white matter (WM), and

regressed from the data, to correct for physiological noise like heart rate and respiration

(aCompCor; Behzadi et al., 2007).

ROI-to-ROI analyses

Based on the PACE framework (Gruber & Ranganath, 2019), we examined the resting-state

functional connectivity (rs-FC) of the ventral tegmental area (VTA) with three other regions:

nucleus accumbens (NAcc), anterior hippocampus (aHipp), and medial prefrontal cortex (mPFC)

(Figure 4.2). The VTA was defined from a probabilistic atlas created from hand-drawn ROIs

(Murty et al., 2014). Bilateral nucleus accumbens (NAcc) was defined using the Harvard-Oxford

subcortical atlas provided through FSL. Bilateral anterior hippocampus was defined from a

probabilistic atlas of the medial temporal lobe (Hindy & Turk-Browne, 2016), divided into anterior

and posterior sections at Y = -21, and masked by the Harvard-Oxford hippocampus to prevent

the seed from extending into the white matter. Medial prefrontal cortex was defined as

FreeSurfer's parcellation of bilateral rostral anterior cingulate cortex (rACC) (Desikan-Killiany

atlas; Desikan et al., 2006). We extracted the average time series within each ROI from

unsmoothed data, to ensure that signal was not blurred outside of the ROI. ROI-to-ROI

connectivity values were generated by calculating the Pearson's correlation coefficient for each

pair of ROIs (Fisher Z-transformed). We tested the relationship between our child curiosity

measures and VTA-NAcc rs-FC, VTA-aHipp rs-FC, and VTA-rACC rs-FC. All models controlled

for age, gender, average head motion, and number of resting-state volumes. Models examining

question-asking additionally controlled for duration of time spent on the book task (in minutes; M

= 4.77 min, SD = 0.52 min), and frequency of the child's verbalizations, as measured by

PARCHISY (Likert, on a scale of 1 to 7, M = 4.96, SD = 0.80).
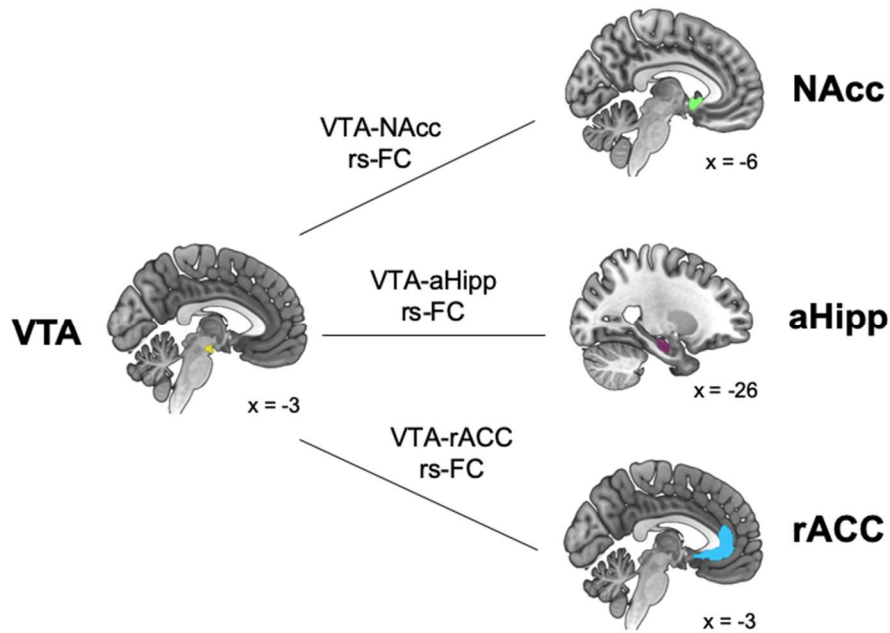
Figure 4.2. Region-of-interest analyses (ROI-to-ROI) with the ventral tegmental area (VTA).
NAcc: nucleus accumbens; aHipp: anterior hippocampus; rACC: rostral anterior cingulate cortex;
rs-FC: resting-state functional connectivity.

Whole-brain analyses

We further examined the relationship between child curiosity and whole-brain functional

connectivity, using the same four ROIs as seeds: VTA, NAcc, aHipp, and rACC. We used the

average time series within each seed to generate whole-brain subject-level functional connectivity

maps for the VTA, NAcc, aHipp, and rACC, using FSL's *fsl_glm* tool. Because motion and

physiological noise were already filtered out of the functional data during earlier preprocessing steps, subject-level GLMs only contained the seed time series as a regressor. For participants with two resting-state runs, seed connectivity maps were generated separately for each run, and then the runs were averaged together using a Nipype implementation of a fixed-effects model (using FSL's *flameo*), producing a single connectivity map per participant to be entered into group-level analyses.

Whole-brain group-level analyses were performed with FMRIB's Local Analysis of Mixed Effects tool (FSL's FLAME 1). Only voxels that had unanimous coverage across subjects were tested, resulting in a mask that covered the entire brain. We ran the following GLMs (testing for both positive and negative associations): main effects of 1) I-type curiosity, 2) D-type curiosity, and 3) question-asking (number of questions asked). All group GLMs included the following covariates: age, gender, average head motion, and number of resting-state volumes. The question-asking GLM additionally controlled for duration of time spent on the book task and frequency of the child's verbalizations.

Z-statistic maps were corrected for multiple comparisons with parametric clusterwise inference using FSL's cluster tool (relies on Gaussian Random Field Theory) at a cluster-defining threshold of $z = 3.1$ ($p < .001$), neighborhood size of 26, and an FWE-corrected threshold of $p < .05$. All statistical analyses were conducted in R.

Results

Curiosity characterization

The relationships between the curiosity measures are shown in Figure 4.3. All three measures were significantly skewed, as assessed by the Shapiro-Wilk Test (I-type: W = 0.82, p < .001; D-type: W = 0.97, p = .01; question-asking: W = 0.72, p < .001). I-type curiosity and D-type curiosity were significantly positively correlated (r_s(100) = 0.61, p < .001; Figure 4.3A). However, question-asking was not related to either I-type curiosity or D-type curiosity (Figure 4.3B).
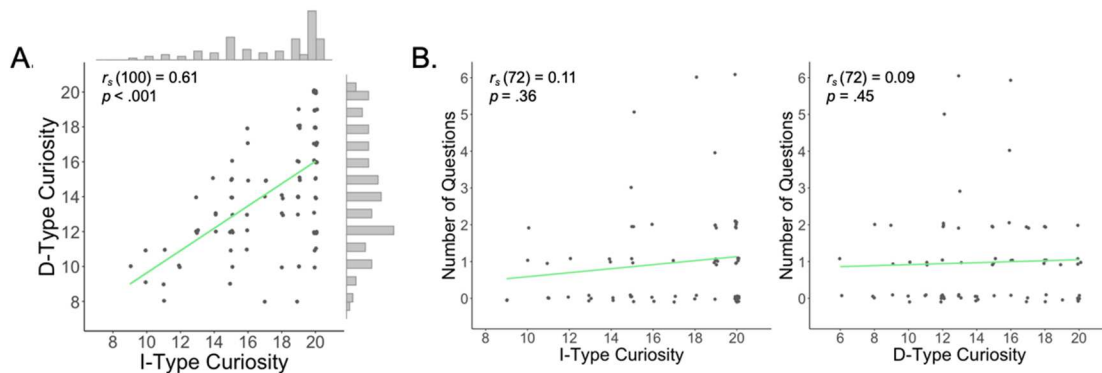
Figure 4.3. Scatterplots of the curiosity measures. A. Scatterplot between I-type and D-type curiosity, with histograms. B. Scatterplots with question-asking. I-type: Interest-type curiosity; D-type: Deprivation-type curiosity. Number of questions asked by the child was captured during a parent-child book reading task.
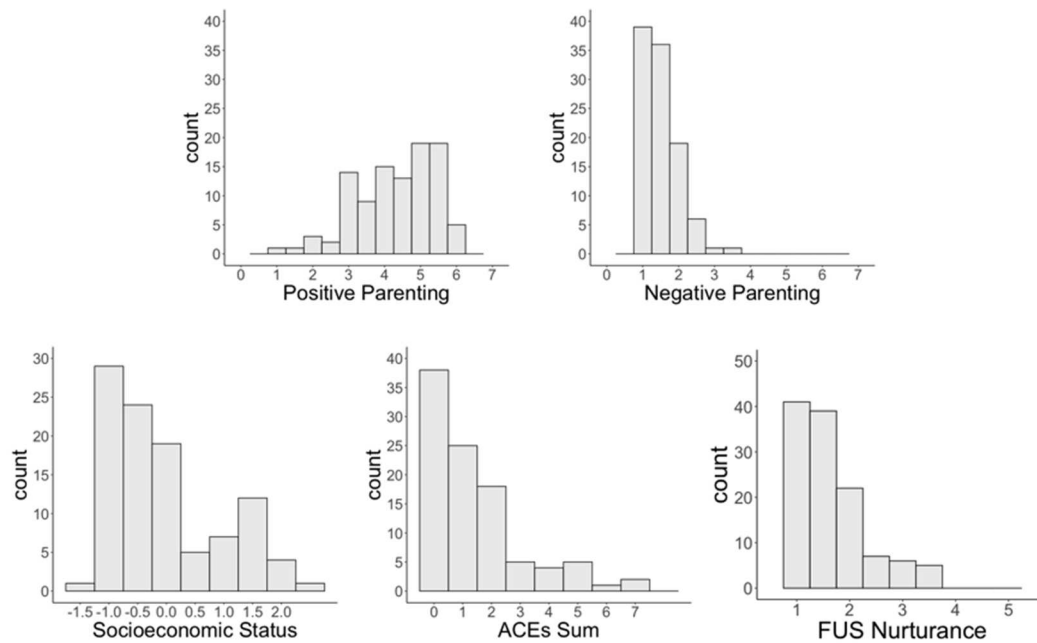
Figure 4.4. Histograms of environmental predictors. Positive parenting and negative parenting are Likert ratings from an observed parent-child interaction task. Socioeconomic status is a Z-scored composite measure of family income and parent education level. ACEs: Adverse Childhood Experiences. FUS: Family Unpredictability Scale.

Distributions for all environmental predictors are shown in Figure 4.4. Associations among environmental measures and curiosity measures are shown in Figure 4.5. The only measure that showed any associations with curiosity was unpredictability. Unpredictability in nurturance (FUS nurturance) had a significant negative association with both I-type curiosity (t(98) = -3.38, p = .001) and D-type curiosity (t(98) = -2.40, p = .02) (Figure 4.6), but no association with question-asking. In other words, greater experience of unpredictability in the domain of nurturance (warm and dependable parenting) was related to lower parent-reported child curiosity.
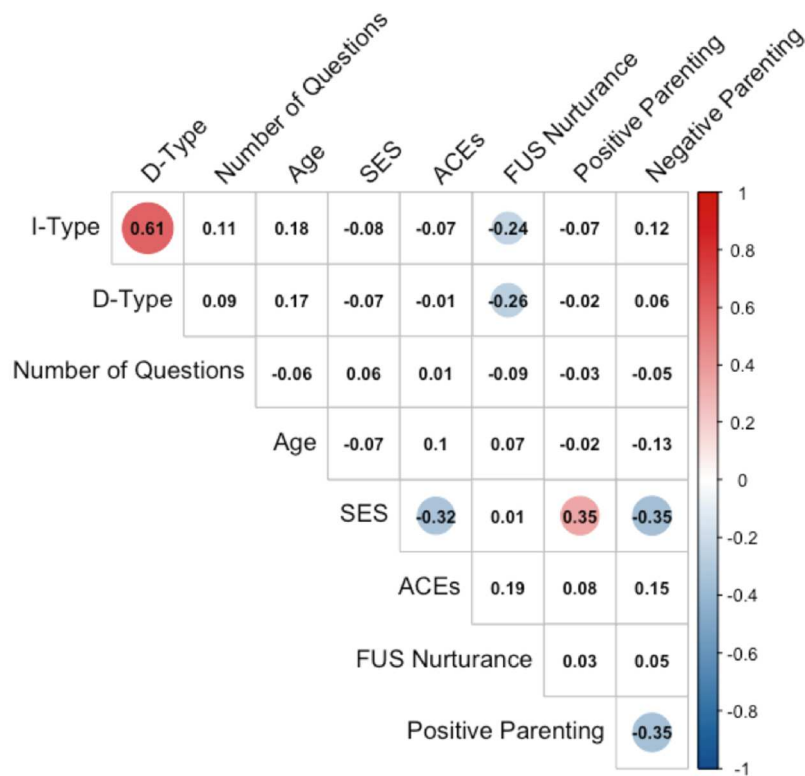
Figure 4.5. Spearman correlations between curiosity measures (I-type, D-type, and question-asking), and environmental predictors (SES: socioeconomic status; ACEs: Adverse Childhood Experiences; FUS: Family Unpredictability Scale nurturance; and positive and negative parenting observed during a parent-child interaction task). Circles indicate a correlation that is significant at $p < .05$ (red = positive correlation, blue = negative correlation, size of the circle is proportional to effect size).
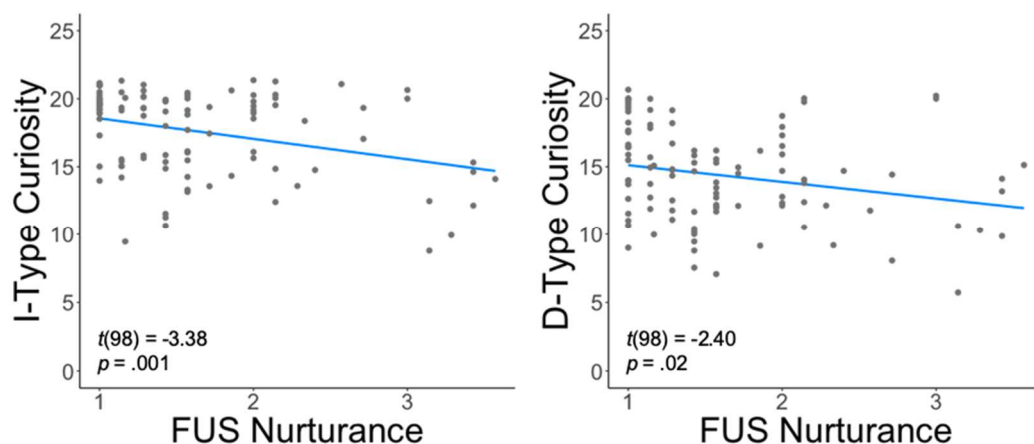
Figure 4.6. Scatterplots showing the relationship between I-type and D-type curiosity and the nurturance subscale of the Family Unpredictability Scale (FUS). Adjusted for age and gender covariates.

Neuroimaging results

There were no significant effects of VTA-NAcc, VTA-aHipp, or VTA-rACC functional connectivity on I-type curiosity, D-type curiosity, or question-asking. At the whole-brain level, question-asking was positively related to VTA functional connectivity with regions in right inferior frontal gyrus (Figure 4.7; peak voxel coordinates (MNI): 50, 6, 20, maximum z-statistic = 4.22, cluster volume = 290 voxels) and right parietal cortex (peak voxel coordinates (MNI): 48, -22, 18, maximum z-statistic = 4.15, cluster volume = 226 voxels).
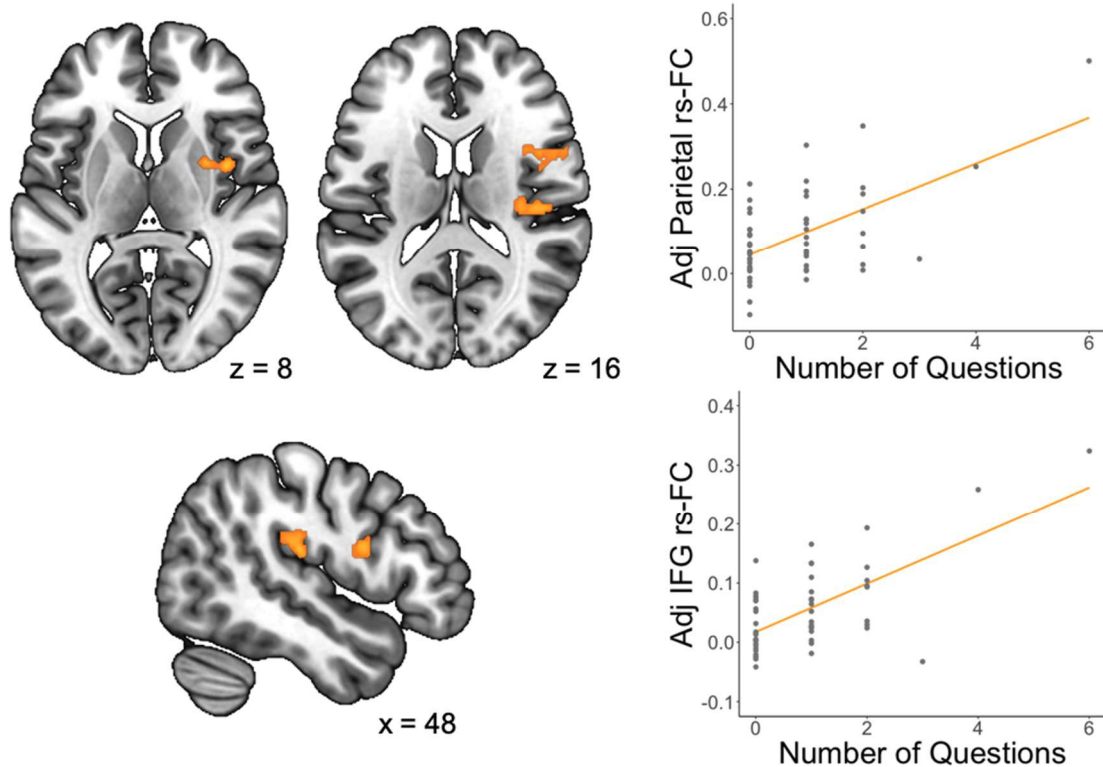
Figure 4.7. Positive association between question-asking and ventral tegmental area (VTA) functional connectivity. Model controlled for age, gender, average head motion, number of resting-state volumes, duration of time spent on the book reading task, and frequency of child verbalizations. Results were corrected for multiple comparisons at $z = 3.1$, $p < 0.05$, $n = 53$. Scatterplots show the relationship between question-asking and extracted parameter estimates (adjusted for covariates). IFG: inferior frontal gyrus; rs-FC: resting-state functional connectivity.

Discussion

We tested for environmental predictors and neural correlates of trait and state measures of curiosity in childhood, but found limited results. We expected higher stress exposure to be associated with lower curiosity. We found only an association between parent-reported unpredictability of nurturance and lower epistemic curiosity. No stress measures were associated with the observational measure of curiosity (question-asking behavior). Based on a recent framework suggesting that dopaminergic circuitry drives curious behavior through dynamic cycles of appraising unexpected novel situations or information gaps (Gruber & Ranganath, 2019), we hypothesized that curiosity would be related to resting-state functional coupling of the dopaminergic ventral tegmental area (VTA) with regions like the nucleus accumbens, anterior hippocampus, and medial prefrontal cortex. However, we only found a positive relationship between question-asking behavior and functional connectivity of the VTA with the right inferior frontal gyrus, as well as parts of parietal cortex. Given the limitations of the question-asking measure (discussed below), we are cautious in the interpretation of this unanticipated finding.

This study operationalized child curiosity in two different ways: parent-reported curiosity along dimensions of I-type and D-type curiosity; and question-asking behavior during a parent-child interaction task. The parent-report questionnaire measure was intended to capture "trait"-based curiosity, i.e., a reflection of the child's curiosity-related behaviors combined across a variety of experiences and contexts (as observed by the parent). On the other hand, the question-asking measure was selected to capture "state" curiosity in a more naturalistic setting (given that parents are likely a major resource for answering their child's questions in real life). This in theory would provide greater ecological validity, since one overarching goal is to better understand real curiosity-related behaviors that could be effectively targeted through interventions. However, one possible interpretation for the limited results in this study is that we ultimately were not able to meaningfully capture child curiosity. Challenges with the I-type and D-type curiosity questionnaire

79

include potential biases in parent-report. I-type curiosity was highly skewed, such that most parents indicated that their child enjoyed learning new things. Parents could also potentially be biased in terms of having differing beliefs about the value of fostering curiosity. It is also very possible that the association between greater unpredictability of nurturance and lower epistemic curiosity is driven primarily by the fact that both measures are parent-report questionnaires, perhaps merely reflecting the parent's appraisal style more generally. Future work might consider ecological momentary assessment (EMA) as a way to capture more objective parent and child curiosity-related behaviors over a longer time scale, or perhaps asking additional sources for input, like teachers.

The major difficulty with the question-asking measure was that children overall asked much fewer questions than expected during the book-reading task (most children asked 0 questions or only 1 question, with 6 being the maximum number of questions asked by any participant, across a 5 minute open-ended task). One possibility is that the nature of the task—a videotaped laboratory task—may have primed certain unintended expectations about the goals of the parent-child interaction. We observed that a number of parents used a heavily pedagogical approach, i.e., asking the child questions about the book's narrative or prompting the child to explain what was happening, perhaps preempting spontaneous questions from the child. On the other hand, we also know that children are already developing a sophisticated understanding of how to ask effective questions and receive informative answers, and are attuned to expertise when deciding whether to ask (Mills et al., 2011). Thus, it is possible that children would have asked more questions if the task had been designed such that the parent was clearly more knowledgeable about the book contents than the child (rather than it being a book that both were seeing for the first time), or if the book focused more on real-world science-related topics (related to hypothesis testing or cause-and-effect) rather than on fantasy. Finally, another challenge to note with the question-asking measure was that children's quality of questions also varies with age and perhaps with language and other abilities (Ronfard et al., 2018; Ruggeri & Lombrozo, 2015)—it is

unclear whether a lack of questions reflects a genuine lack of curiosity, or is merely due to language limitations. In the future, it may be useful to develop a task that purposefully enriches for questions (although this may come at some costs to ecological validity), or that captures multiple state-based measures of curiosity (some verbal, some non-verbal).

We explored whether there are environmental experiences that predict individual differences in child curiosity. We found that experiencing unpredictable nurturance was associated with lower trait curiosity. One possible interpretation is that unpredictable nurturance may disrupt attachment processes, increasing distress in the parent-child relationship, and reducing opportunities for the child to freely engage in exploration. Chronically stressful experiences, like growing up with negative, unreliable parenting, may lead children to develop greater reliance on habitual behavior patterns (e.g., a passive coping style that prioritizes maintaining low risk). Although this behavioral strategy may be initially adaptive, it can lead to difficulties when environments fluctuate. Harsh and unpredictable parenting could cause a prioritization of inflexible behavioral strategies, with potentially damaging implications for children's curious exploration and motivation to learn (Humphreys et al., 2015), although further research is needed. There has been increasing interest in understanding how an unpredictable environment might negatively shape child development (Glynn & Baram, 2019; Young et al., 2020). Thus, future work could examine the extent to which unreliable caregiving specifically relates to curiosity and exploratory behavior, compared to other more general forms of environmental predictability.

We did not find that curiosity related to stress exposure (SES, ACEs), or to parenting behaviors observed during a parent-child interaction task. One possible reason is that these measures capture broad exposures that may impact the development of dopaminergic circuitry generally, but not necessarily curiosity specifically. It may be fruitful to target a more narrowly defined, curiosity-specific experience, like the degree to which parents ask their child pedagogical questions (Birbili & Karagiorgou, 2009; Yu et al., 2019), or explicitly encourage or value curious

behaviors. For example, one study found that parent stimulation of child curiosity, through acts like exposure to novel experiences and encouraging question-asking, was related to science intrinsic motivation and achievement (Gottfried et al., 2016). Others have suggested explicitly building comfort with uncertainty in learning situations to help encourage curious behavior (Jirout et al., 2018; Lamnina & Chase, 2019). Nevertheless, it will likely still be important to study curiosity with the environmental context in mind (i.e., chronic stress exposure, or the general warmth of the parent-child relationship), because a safe and encouraging environment may still be necessary, if not sufficient, to foster curious behavior. Indeed, it is thought that certain initial intervention successes may show fade out effects over the long-term, due to a broader environment that was unlikely to support intervention gains (Bailey et al., 2020).

We expected to see relationships between curiosity and VTA resting-state functional coupling with regions like the nucleus accumbens, hippocampus, and prefrontal cortex. Resting-state fMRI is thought to capture previous history of co-activation between brain regions (Gabard-Durnam et al., 2016), so one might expect that frequent engagement of curiosity-related dopaminergic circuitry would be reflected even during resting-state. However, it could be that certain VTA connectivity relationships only emerge in task-dependent or motivation-related contexts (Murty et al., 2018). In other words, since curiosity is often a context-dependent and dynamic phenomenon, we may need to turn to task-based methods in order to reveal brain differences. Previous studies have used tasks like trivia (Gruber et al., 2014; Kang et al., 2009) or ambiguous perceptual stimuli (Jepma et al., 2012) to assess curiosity (Gruber & Fandakova, 2021). However, traditional task fMRI is likely to be challenging for young children, especially if it requires responses during the scan. Another possibility might be to take advantage of movie fMRI to elicit curious states (perhaps by using films that emphasize mystery, or by using science-related educational video clips that are designed to reveal "how stuff works" in an engaging way). It might also be possible to have children watch a movie twice, to see whether curiosity-related processing is reduced the second time around.

In conclusion, while findings in the current study were limited, and developing improved methods for measuring curiosity-related brain function in children will undoubtedly be challenging, there is nonetheless great potential to build upon this work. And the translational goal of fostering intrinsic curiosity early in life, in order to improve learning and encourage finding lifelong interests, is certainly worthy of future research.

CHAPTER 5: GENERAL DISCUSSION

Summary

Children are remarkably open to experience. Development is a period when neural architecture is being built and sculpted, in direct response to environmental inputs, through synaptic growth and pruning. During this time of protracted plasticity, children explore and learn about the characteristics of their own unique environments. They have the opportunity to play, ask questions, exercise creativity, and build up a repertoire of behavioral strategies for successfully navigating life's challenges. Indeed, it has been argued that childhood is, by design, a period uniquely dedicated to intensive exploration, allowing the brain to become tuned to a complex world, in preparation for the stable, goal-directed priorities of adulthood (Gopnik, 2020). However, this malleability is a double-edged sword, also leaving children vulnerable to negative influences. Thus, early exposure to harm has the potential to substantially impact the overall developmental trajectory of reward circuitry, with downstream effects on health and well-being (Hanson et al., n.d.). This dissertation sought to examine whether biomarkers for early disruptions to dopaminergic neurocircuitry can be identified in children (ages 4 to 10), in order to inform efforts to better protect children from long-term negative impacts. In the first study (Chapter 2), we demonstrated that, in contrast to children with lower stress exposure, children with higher stress exposure did not show a positive relationship between age and functional coupling of the ventral tegmental area (VTA) and medial prefrontal cortex (mPFC). In the second study (Chapter 3), we further found that children who experienced negative parenting showed reduced activity in the VTA while viewing movie events characterized by positive emotion. These two studies suggest that early negative experiences may have a blunting effect on VTA function, which may increase the risk for maladaptive outcomes later in life. Finally, in the third study (Chapter 4), we explored whether VTA connectivity predicted individual differences in children's curiosity—a reward-related behavior that is critical for children's learning. However, findings were limited, and future work will

need to investigate alternative ways of measuring curiosity. Taken together, this work highlights the VTA as a promising region for future study of both positive and negative environmental influences on early child development.

This research is consistent with a number of recent animal studies that provide causal, mechanistic explanations for the effects of early life stress on the programming of VTA function. Early life stress in mice encodes long-term vulnerability in the VTA via changes in the developmental transcription factor *Otx2*, causing them to be less resilient to stress experienced in adulthood (Peña et al., 2017). Importantly, experimental *knockdown* of *Otx2* in the VTA in juvenile mice induced the same kind of stress susceptibility, while *Otx2 overexpression* reversed the effects of early life stress, providing powerful causal evidence that the VTA is a key mediator for long-term vulnerability. Similarly, another study induced adverse maternal behaviors by depriving the dam of adequate nesting materials, and found that her offspring showed attenuated VTA activity even well into adulthood (Rincón-Cortés & Grace, 2021). Disrupting attachment bond formation also results in VTA-related depression-like symptoms in mice, specifically in female offspring (Lo Iacono et al., 2021). I highlight several important points emerging from this work. First, the "two-hit" model of stress demonstrates that early stress-induced disruptions to dopaminergic circuitry may not become visible as problematic behaviors until triggered by later stressors. Thus, neuroimaging techniques could be useful for assessing early vulnerability, long before behavioral symptoms start to emerge. Second, these studies offer some evidence of sensitive periods for stress effects on VTA development early in life (Gomes et al., 2019; Lo Iacono et al., 2021; Peña et al., 2017). Third, experimental methods with animal models are critical for reaching a more mechanistic understanding of the impacts of stress, and may inspire new directions for studying how poverty in humans "gets under the skin." For example, depriving animals of adequate resources (as in the limited bedding paradigm) may serve as an interesting model for the intergenerational transmission of stress through adverse parental care.

In addition to this compelling work in mice models, a number of studies have also begun to examine the VTA in humans. One study in youth (ages 7 to 17) found that trauma exposure (abuse and/or neglect) was related to lower functional connectivity between the VTA and hippocampus (Marusak et al., 2017), and another study found that young adults with childhood trauma showed reduced reward-related activation in the VTA and hippocampus (Richter et al., 2019). Thus, evidence is starting to accumulate that stress-related alterations in the VTA (as well as in other important hubs of corticolimbic circuitry) are detectable in humans. My dissertation builds on this work in humans by studying normative variations in VTA development earlier in life, when interventions may be even more effective.

Future Directions

One strength of this dissertation is its use of more ecologically valid methods: Chapter 3 extended beyond parent-report questionnaires by observing parent behavior during a laboratory task, and also examined children's brain responses to naturalistic emotional movie stimuli. Chapter 4 sought to capture children's curiosity by assessing question-asking, a behavior that has real-world relevance. While data collected using naturalistic measures can be noisy, they also have the potential to more directly inform intervention work. In an effort to obtain a more representative assessment of observed parenting behavior, future studies could collect multiple parent-child interactions, spread out over time, in order to get several snapshots of the parent-child dynamic, and also to potentially study the effects of greater variability or inconsistency in the relationship. However, it is also the case that longitudinal lab-based parent-child interaction tasks are time-intensive and challenging to collect, so another possibility would be to leverage methods like ecological momentary assessment (EMA). In our lab, we have demonstrated the power of collecting EMA data on parent and child behaviors over the span of many days (Leonard et al., 2020). This approach can yield individualized insight into moment-to-moment influences on child

behavior, in their home context. It may be possible to collect daily videos of parents and children performing brief tasks that are designed to tap into specific processes of interest (e.g., question-asking, coping with frustration, etc.), as well as responses to questions on recent positive or negative experiences.

Use of naturalistic fMRI stimuli (i.e., movie fMRI) also has great potential to more richly assess how the brain responds to life-like experiences. In Chapter 3, we collected fMRI data while children watched a movie (the Pixar short film, Piper) that was selected for its relevance to many of our themes of interest: parent-child interactions, happiness and joy, overcoming fear, theory of mind, etc. We can take advantage of complex movie narratives to study cognitive processes that may be difficult to capture with more controlled and simplified fMRI experiments. For example, movies can be used to study how humans encode and predict complex narrative schemas (Baldassano et al., 2018; Richardson & Saxe, 2020). With a movie like Piper, it might be possible to examine whether children with different parenting experiences show differences in the dynamic processing of the parent-child relationship depicted in the movie. Also, in Chapter 3, we found that parenting behavior related to brain activity during positive emotional events, but not negative emotional events. This could be consistent with prior work showing that children show a bias for processing positive events, relative to adults (Garcia & Tully, 2020; Picardo et al., 2016), or could mean that this particular movie had more intense positive emotion compared to negative emotion. In the future, it could be useful to measure brain responses to a variety of movie clips that vary in their emotional intensity. Thus, movie fMRI is a promising future direction for capturing complex functional processes, with the added benefit of increasing compliance in young children (Vanderwal et al., 2019). Movie fMRI has also shown promise for enhancing prediction of individual differences, perhaps even above and beyond traditional task fMRI and resting-state fMRI (Finn et al., 2020). Indeed, in Chapter 4, we were not able to demonstrate a clear relationship between VTA resting-state functional connectivity and children's trait-level curiosity. One possible explanation is that a motivational context may need to be provided (Murty et al.,

2018) that engages curiosity-related processes. Movie fMRI could potentially be leveraged to study state-level curiosity, especially since even passive-viewing traditional task fMRI would likely be challenging to collect with young children.

Although this dissertation has emphasized the possible long-lasting implications of early adverse programming of VTA function, there is still also promise for positive buffering effects. For example, one study found evidence for resilience: young adults with childhood trauma showed reduced reward-related activation in VTA and hippocampus, but resilience-related traits (i.e., self-reported competence and acceptance) related to increased activity in these regions (Richter et al., 2019). In addition to resilience that emerges from internally motivated cognitions, studies have also found that positive parenting can buffer against the negative effects of growing up in poverty (Brody et al., 2019; Brown et al., 2020; Stevens et al., 2021). Finally, one study from the Bucharest Early Intervention Project, a randomized controlled trial of foster care for institutionalized children, found heightened sensitivity to quality caregiving during the adolescent time period (Colich, Sheridan, et al., 2020). It has been argued that adolescence may constitute another sensitive period in development, with a particular role for social experience (Blakemore & Mills, 2014; Fuhrmann et al., 2015). Thus, future work should use longitudinal designs to map out the timing of when specific kinds of interventions are most likely to have a buffering effect.

Open Questions

This dissertation raises additional broader questions, which I discuss below in the context of current theories in the field, and have organized into sections on 1) early experience, 2) brain activity, and 3) child behavior:

How do specific dimensions of early experience impact VTA circuitry?

Cumulative vs. dimensional approaches to studying adversity

Much of the work to-date has taken a broad approach to studying adversity, operationalizing stress as measures like chronic "wear-and-tear" of the body (McEwen & Seeman, 1999), cumulative risk exposure (i.e., the sum of dichotomous risk factors; Evans et al., 2013), or living in poverty (Farah, 2017), which is correlated with, but not equivalent to, experiencing a wide range of negative life experiences. In Chapter 2, I focused on socioeconomic status (SES), using a composite measure of parental income and education, and adverse childhood experiences (ACEs), which sums across lifetime exposure to abuse, neglect, and household dysfunction. Both constructs are relatively simple to measure via questionnaires, capture a swath of experiences that robustly predict negative mental health outcomes (Green et al., 2010; Hughes et al., 2017; Reiss, 2013), and have played an important role in motivating discussions on policies to support child development (Farah, 2018; Larkin et al., 2014; Weems et al., 2021). However, with SES and ACEs alone, it is difficult to draw conclusions about whether our findings on VTA differences are primarily due to the *accumulation* of stressors, or due to a specific *type* (or combination) of stressor (Lanier et al., 2018). Researchers in the field are advocating for a dimensional approach to measuring adversity (McLaughlin et al., 2021), since different types of experiences likely impact brain development through dissociable mechanisms. For example, studies can be more explicit about important features of stressful experiences, like timing, severity, and type (e.g., threat, deprivation, controllability, predictability, caregiver involvement, etc.; Cohodes et al., 2021). In Chapter 3, I narrowed in on parenting behaviors specifically, and found that negative parenting related to blunted activity in the VTA, even after additionally controlling for SES and stressful life events. Thus, it may be that caregiving-specific stressors are a promising mechanism for impacts on the VTA. Indeed, the VTA-related rodent work described above largely delivered stress exposure via the mother (i.e., maternal separation, Peña et al., 2017; maternal fragmented care, Rincón-Cortés & Grace, 2021; attachment bond interference, Lo Iacono et al.,

2021). Future work on the development of the VTA in humans could more directly compare the effects of caregiver-mediated stress with other kinds of negative experiences, like cognitive deprivation or neighborhood violence (although I acknowledge that this is often a major challenge in human studies, where different types of stressors commonly coexist). Finally, I note that while much of the work described here assumes a deficit model of adversity, it may also be possible to take a "hidden talents" approach: understanding what social and cognitive abilities may be *enhanced* by experience with adversity, like finding creative solutions to problems or better understanding other people (Frankenhuis et al., 2020).

Mechanisms leading from adverse caregiving to negative child development

Why is the caregiving relationship thought to be of such singular importance for early child development? It has been proposed that there may be an early sensitive period for amygdala-prefrontal connectivity, during which parents externally modulate their child's emotional reactivity until the child's emotional circuitry matures enough to independently self-regulate (Tottenham, 2020a). One study found that viewing photos of one's own mother resulted in reduced amygdala reactivity relative to viewing a stranger, as well as greater amygdala-mPFC functional connectivity, and greater attachment security (specifically in childhood, not in adolescence; Gee et al., 2014). Thus, it may be that this early emotional scaffolding plays a hugely consequential role in the development of secure attachment and appropriate emotion regulation processes. Experiences like maternal separation and negative parenting may lead to more "mature" patterns of connectivity between the amygdala and prefrontal cortex (Kopala-Sibley et al., 2018; Thijssen et al., 2017). It could be that this reflects accelerated development (Callaghan & Tottenham, 2016a), which may have the short-term benefit of improved, more adult-like coping (Gee et al., 2013) but perhaps confers later risk for poor emotion regulation. However, we also note that recent work has found that findings of age-related changes in amygdala-mPFC connectivity are not consistently robust to different fMRI processing pipelines (Bloom et al., 2021). In Chapter 3,

we found that negative parenting related to reduced amygdala activity to positive emotional events. Although the amygdala has been traditionally associated with fear processing, the amygdala encodes both positive and negative valence, and plays an important role in influencing motivated behavior (Smith & Torregrossa, 2021). Blunted amygdala activity to positive emotion (together with blunted VTA activity) may reflect an overall stress-related reduction in responsiveness to rewarding stimuli. It could also be that negative parenting prompted faster maturation of top-down control over the amygdala, resulting in lower amygdala reactivity. However, we cannot tease apart these two possibilities with our current data.

Another mechanism has been proposed for how negative caregiving results in child behavioral problems: *unpredictable* parenting (Gee & Cohodes, 2021). Unpredictable maternal mood and behavior is associated with internalizing problems during childhood, and anxiety and depression symptoms in adolescence (Glynn & Baram, 2019), as well as poor cognitive function (Davis et al., 2017). These effects persist even after controlling for alternate factors like the mother's overall mood level and socioeconomic status, suggesting that there is something important about the *pattern* of unpredictable maternal input, though other explanations, including shared genetics, are also possible. We know that children are attuned to the statistics of their environment (Schulz, 2012), behave rationally when encountering unreliable others (Kidd et al., 2013; McGuire & Kable, 2013; Michaelson & Munakata, 2016), and show trauma-related differences in beliefs about the likelihood of receiving rewards (Hanson, van den Bos, et al., 2017). Thus, it is possible that early exposure to unpredictability in the parent-child relationship may result in biases in *a priori* expectations about the underlying reward structure of the environment. This could have an impact on how children approach learning during development (i.e., is it safe to freely explore, or is it better just to exploit current resources), or on behaviors like risk-taking and self-control.

How do early changes in VTA circuitry impact brain function?

Medial prefrontal cortex as a top-down regulator

Chapter 2 raises important questions about the role of medial prefrontal cortex (mPFC) during childhood. In this study, only children with lower stress exposure showed a positive relationship between age and the functional coupling between VTA and dorsal mPFC. Based on rodent models, we know that dopamine projections continue to develop even into adolescence, and drive maturation of the prefrontal cortex (Reynolds et al., 2018), which is highly susceptible to environmental experience (Kolb et al., 2012; McEwen & Morrison, 2013). mPFC is important for behaviors like decision making and affective appraisal, and acts as a top-down regulator over emotion and reward processing via its connections with subcortical structures like the amygdala (Klune et al., 2021; Milad et al., 2006), as well as the midbrain and striatum (Ferenczi et al., 2016). It will be important for future work to map out how the role of mPFC changes over the course of early development, especially since one hypothesis is that mPFC-subcortical connections are important for forming affective and attachment-related schemas that inform later social relationships (Tottenham, 2020b).

What are behavioral consequences of disrupted dopaminergic circuitry?

Although this dissertation brings attention to the possible role of the VTA as a biomarker for long-term vulnerability in dopaminergic circuitry, I did not find robust relationships with child behavior (specifically, curiosity, which depends on reward processing and intrinsic motivation). It could be that behavioral differences have not yet emerged in the age range we are studying (4- to 10-year-olds), and would become visible later in adolescence or adulthood. Indeed, many psychiatric disorders that involve dysregulation of the dopamine system tend to emerge in adolescence (Paus et al., 2008). Some of the behaviors and skills supported by the dopamine system (Salamone & Correa, 2012) that have important potential ramifications in childhood and

adolescence include: reinforcement learning, i.e., learning from rewards to inform future behavior (Nussenbaum & Hartley, 2019); making decisions about effort (Hauser et al., 2017); flexibly coping with changing environmental demands (Lloyd & Dayan, 2016); navigating the explore-exploit tradeoff (Daw et al., 2006; Humphreys et al., 2015); and self-control (Casey, 2015). Alterations in VTA function may also have consequences for learning. Indeed, VTA stimulation in animal models leads to increased plasticity (Bao et al., 2001). In our lab, we have found that adults with stronger connectivity between the VTA and lateral prefrontal cortex are better able to learn a working memory task (Boroshok et al., submitted). Further research is needed on biomarkers of learning and plasticity in childhood. Lastly, clinical symptoms related to dopamine dysregulation include: depression, anhedonia (reduced ability to feel pleasure), reduced social exploration, impulsivity, addiction, etc. (Birnie et al., 2020; Chong, 2018; Kaufling, 2019). Taken together, all of these examples demonstrate the powerful role that dopamine plays in behaviors that involve appraising salient environmental information and directing appropriate behavioral responses (Douma & de Kloet, 2019). When chronic stress causes the deterioration of the dopamine system, this is thought to result in the reduced ability to cope flexibly with changing environments, instead biasing towards more habitual, "locked in", responses—this may help explain the symptoms of various reward-related disorders (e.g., more habitual addictive behavior, selection of a passive learned helplessness coping strategy, as in depression, etc.). In response to chronic stress, in childhood we might expect to see outcomes like reduced exploration and less effortful behavior.

Looking Ahead

There is still much unknown about when specific cognitive and socioemotional skills are most malleable (Hensch & Bilimoria, 2012; Park & Mackey, 2021). Mapping out sensitive periods in development would be useful for making decisions about what kinds of interventions and

programs to invest in, and when to implement them. Neuroimaging of proxy measures of plasticity, including VTA connectivity and myelination, may lead to important insights on intervention efficacy (Cooper & Mackey, 2016). The mechanistic study of childhood adversity will undoubtedly inform improvements to educational and parenting programs, and shed light on specific ways we can support positive development. However, in addition to important basic science, there is also an urgent need for systems-level change, to broadly support families today. We know that growing up in poverty tends to result in major disruptions to achievement and health, and that opportunities for parent-child bonding early in development are critical for positively shaping psychosocial processes. The COVID-19 pandemic has made even more starkly clear the current problems in these areas, and has also highlighted their historical roots in systemic racism and inequality. Ultimately, society-wide disparities in access to such needs are a policy choice. Policies like the Child Tax Credit (part of the American Rescue Plan Act of 2021, which is projected to reduce child poverty by more than 50%; Parolin et al., 2021) and paid parental leave (Kozak et al., 2021) have enormous potential to level the playing field and provide a safety net for millions of children in the U.S. Understandably, there is thus some tension in deciding what to prioritize in terms of research. Returning to Bronfenbrenner: at which level should we be investing the most resources to have the most impact? Is it a parenting intervention to improve nurturance and sensitivity to a child's needs, or is it paid parental leave to give parents dedicated time to spend with their children, or is it cash transfer? Ultimately, we will likely need basic science research in tandem with strong pushes for near-term policy changes (Gee, 2021; Pollak & Wolfe, 2020; Shonkoff & Levitt, 2010) that value and prioritize the well-being of children living with adversity today.
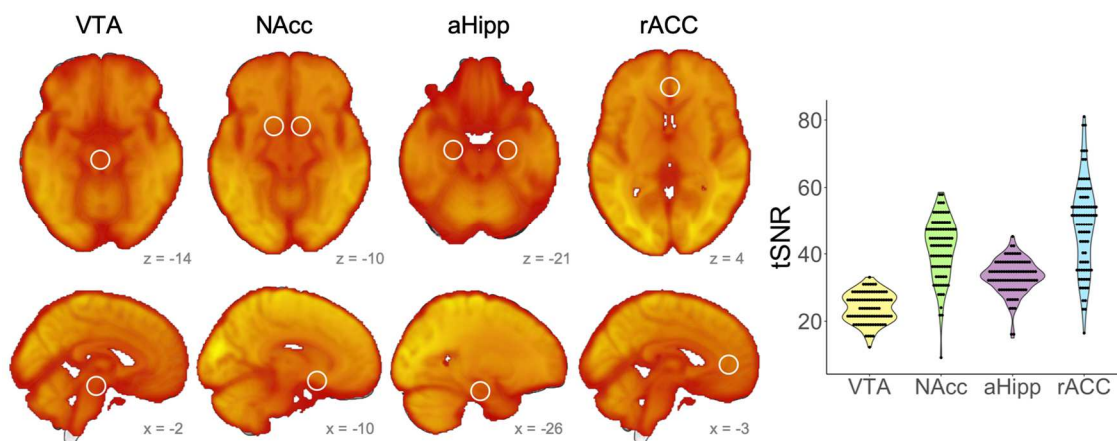
SM Figure S1. Temporal Signal-to-Noise Ratio (tSNR) in seed regions: ventral tegmental area (VTA), nucleus accumbens (NAcc), anterior hippocampus (aHipp), and rostral anterior cingulate cortex (rACC). White circles show the approximate location of the seed regions, for visualization purposes. Violin plots show the distribution of average tSNR values within each region.
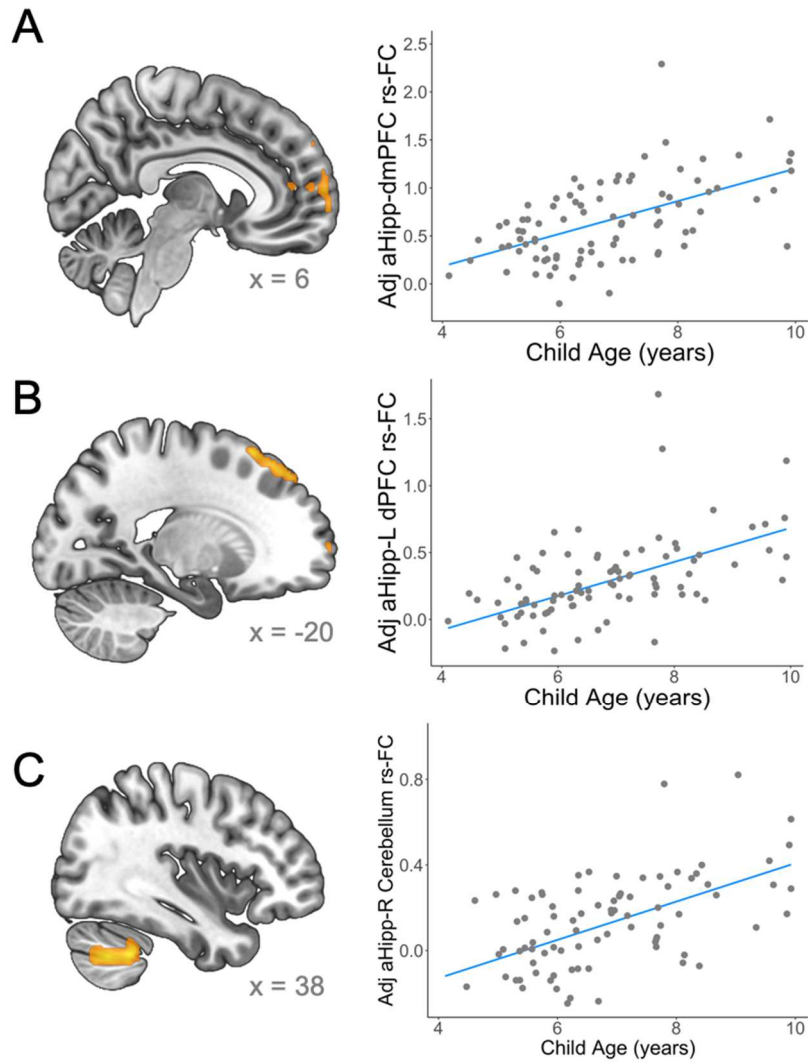
SM Figure S2. Positive relationships between age and anterior hippocampus (aHipp) functional connectivity in 3 clusters: dorsal medial prefrontal cortex (dmPFC), left dorsal PFC, and right cerebellum. Models control for gender, average head motion, number of resting-state volumes, and race/ethnicity, and are corrected for multiple comparisons at $z = 3.1$, $p < 0.05$, $N = 88$. Scatterplots show the relationship between age and extracted parameter estimates (adjusted for covariates).
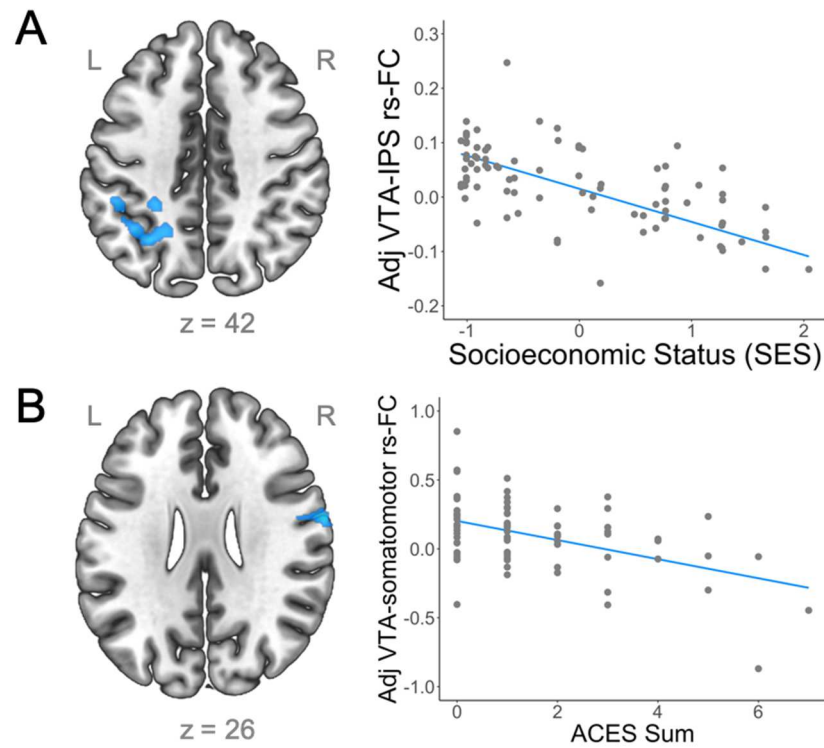
SM Figure S3. (A) Main effect of socioeconomic status (SES_ on ventral tegmental area (VTA) functional connectivity, *additionally controlling for main effect of ACEs*. (B) Main effect of ACEs on VTA functional connectivity, *additionally controlling for main effect of SES*. Results are corrected for multiple comparisons at z = 3.1, p < 0.05. Scatterplots show the relationship between the independent variables (SES, ACEs) and extracted parameter estimates (adjusted for covariates). All models control for gender, average head motion, number of resting-state volumes, and race/ethnicity.
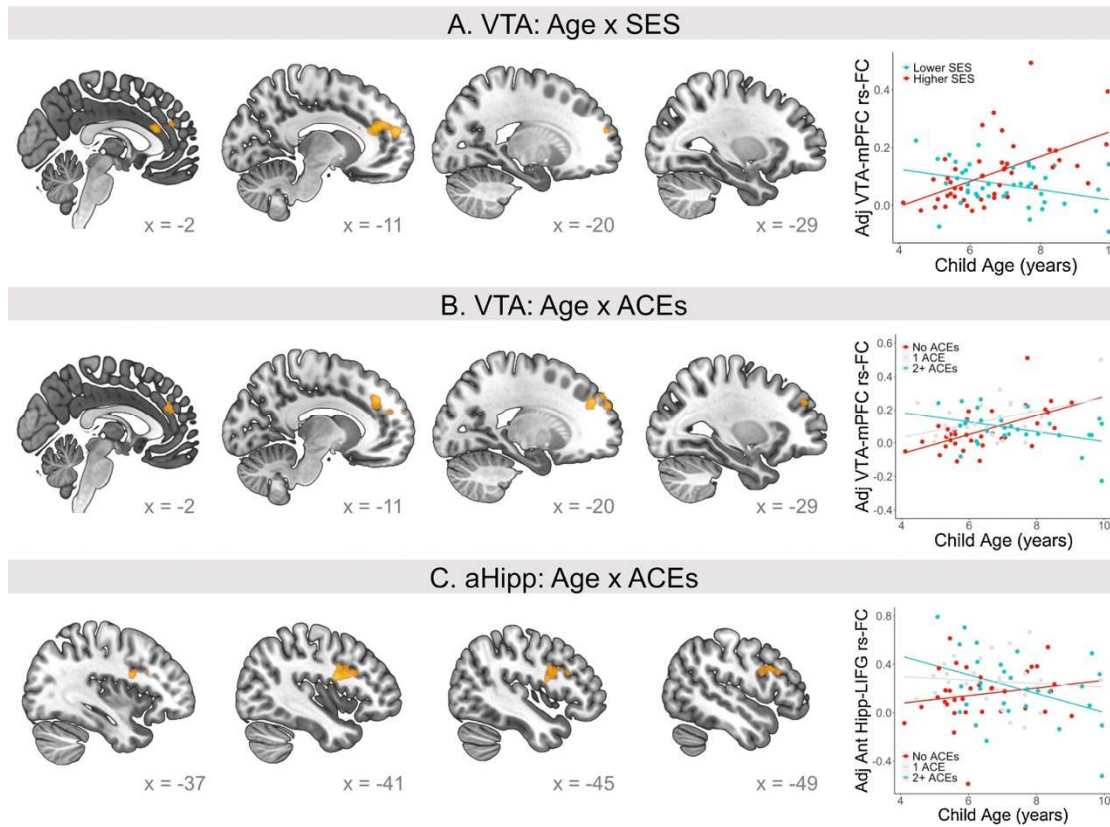
SM Figure S4. (A) Age x Socioeconomic Status (SES) interaction on ventral tegmental area (VTA) functional connectivity, *additionally controlling for main effect of ACEs*. Scatterplot shows the relationship between child age and extracted parameter estimates, plotted by median split on SES for visualization purposes. (B) Age x Adverse Childhood Experiences (ACEs) interaction on VTA functional connectivity, *additionally controlling for main effect of SES*. For visualization purposes, participants were grouped by having exposure to 0, 1, or 2+ ACEs. (C) Age x ACEs interaction on anterior hippocampus (aHipp) functional connectivity, *additionally controlling for main effect of SES*. Results are corrected for multiple comparisons at z = 3.1, p < 0.05. All models control for gender, average head motion, number of resting-state volumes, and race/ethnicity.
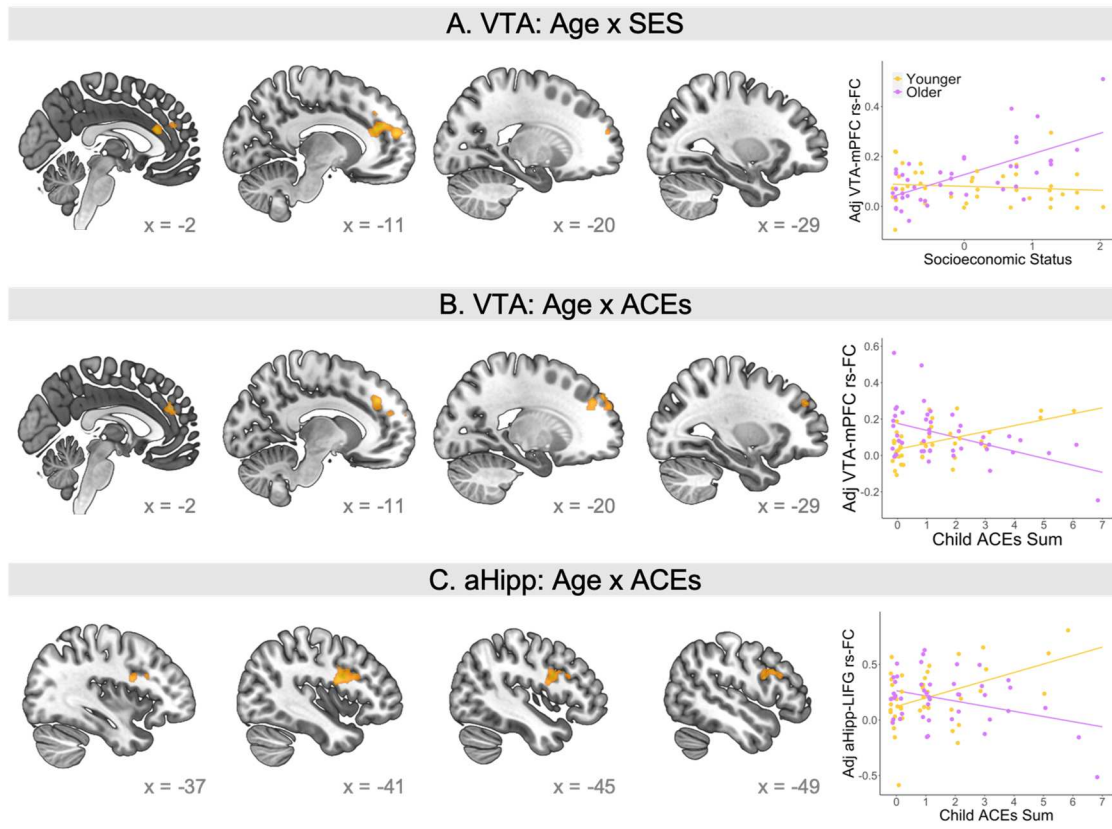
SM Figure S5. Visualizing the interaction plots with stress measures on the X-axis, grouped by age (Younger and Older groups were created by median split, at age 6.6 years). SES = Socioeconomic Status, ACEs = Adverse Childhood Experiences (ACEs), VTA = ventral tegmental area, aHipp = anterior hippocampus.

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106

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