Dimensions of Early Adversity as Distinct Predictors of Adolescent Brain Development

by

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Dedication

To the families that shared their experiences with me – our time together inspires my dedication to use research to improve policy and practice.

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Abstract

Understanding the development of neural circuitry underlying socioemotional function, as well as how this development may be altered by early adversity, is essential for informing prevention and intervention approaches that can be used to improve outcomes for children and families. The aim of this dissertation is to explore the relations between brain structure and function across levels of socioemotional function, as well as the distinct effects of childhood violence exposure and social deprivation on adolescent brain function and internalizing psychopathology. The first chapter reviews what is currently known about the development of neural circuitry underlying socioemotional function in adolescence, as well potential neural mechanisms linking early adversity to later mental health and the contributions of this work to policy and practice. The following two chapters provide original research examining how brain structure and function are related and how this brain function is impacted by qualitatively different early adverse experiences. The second chapter characterizes how structural connectivity of the uncinate fasciculus is related to amygdala habituation. The third chapter explores the unique effects of childhood violence exposure and victimization on adolescent threat-related brain function and childhood social deprivation on adolescent reward-related brain function. Importantly, both studies use data from a large, socioeconomically diverse sample of youth. In the fourth chapter, I discuss how this original research informs our understanding of the impacts of early adversity on socioemotional and neural development in adolescence and what this suggests for policy and practice.

Chapter 1 : General Introduction

Poverty is associated with a set of circumstances that put children at increased risk for later anxiety and depression (Grant et al., 2003; McLaughlin et al., 2011) – disorders that contribute to multi-generational perpetuation of poverty (Wickrama, Conger, & Abraham, 2005). Given the tremendous personal and societal costs of these circumstances, understanding the mechanisms that link childhood poverty and mental disorders is a public health imperative. Children growing up in poverty often face multiple adversities (McLoyd, 1998), which may differentially alter brain development and increase risk of later psychopathology (Miller et al., 2018). However, little is known about how exposure to poverty impacts brain development and gives rise to anxiety and depression (Liberzon et al., 2015). Previous neuroimaging work has often used income as the sole index of poverty; these investigations cannot disentangle the potential contributions of different poverty-related adversities. Further, in order to gain insight as to how brain development may be associated with the etiology of mental disorders, it is important to understand brain development across a full range of socioemotional function. Although the development of brain structure and function have been studied separately in previous work, this approach is limited in that it cannot investigate bidirectional influences between the two (Cicchetti & Dawson, 2002). In this dissertation, I aim to assess neural mechanisms that may link early poverty-related adversities to later internalizing disorders. The next two chapters consist of studies that investigate the neural bases of socioemotional development, as well as how these neural mechanisms may link childhood poverty-related adversity to internalizing disorders in adolescence. The first study evaluates the relation between amygdala habituation and uncinate fasciculus integrity in a diverse adolescent sample. The

second study investigates whether childhood exposure to poverty-related adversities that fall under categories of violence exposure and social deprivation differentially predict anxiety and depression symptoms in adolescence and whether these relations are mediated by alterations in threat- and reward-related brain function in adolescence. In the final chapter, I will explore future directions of research linking childhood adversity to later mental health.

Theoretical Frameworks

Several theoretical frameworks underscore the value of assessing neural mechanisms linking childhood poverty-related adversity to later mental health. The first of these frameworks, developmental psychopathology, aims to elucidate the origins and time courses of mental disorders (Sroufe & Rutter,1984). The developmental psychopathology perspective also emphasizes the importance of studying developmental processes across a full range of functioning, from typically developing individuals to those with mental disorders (Cicchetti & Rogosch, 2002). Instead of identifying group differences in neural structure and function between groups, neuroscience using a developmental psychopathology perspective seeks to understand how group differences emerge (Hyde, 2015). This dissertation investigates potential neural mechanisms linking childhood poverty-related adversity to adolescent mental health in samples that contain a full range of socioemotional function.

A second theoretical framework utilized by this dissertation is the social causation perspective for studying the effects of poverty on development, which posits that poverty and conditions that are linked to poverty cause variations in child development (e.g., Conger et al., 2002; Conger & Donnellan, 2007). This is in opposition to the social selection perspective, which proposes that parental traits influence their social status as well as the development of their children (e.g., Mayer 1997; Conger & Donnellan, 2007). This dissertation aims to parse different aspects of poverty-related adversity in order to better understand the mechanisms

through which poverty gives rise to later mental disorders. Importantly, although this dissertation utilizes the social causation perspective, this dissertation cannot determine causation. I acknowledge the utility of the interactionist approach, which integrates the social causation perspective with the social selection perspective and argues that individual differences can produce variation both in family income as well as child development (Conger & Donnellan, 2007). However, this dissertation does not focus on social selection processes.

A third theoretical framework is cumulative risk, which is derived from clinician observations that while a single risk factor can impact development, children who experience multiple risk factors are more likely to experience psychological disorders (Evans, Li, & Whipple, 2013; Rutter 1979; Rutter 1981). These observations led to a large body of work (e.g., Rutter's Isle of Wight Studies, Sameroff's Rochester Longitudinal Study) that investigated multiple risk factors in children. Across these efforts, it was found that accumulating risk factors have worse developmental consequences than single risk exposures (Evans, Li, & Whipple, 2013; Rutter 1979; Rutter 1981; Sameroff, 2006; Sameroff, Seifer, & McDonough, 2004). There are several advantages to a cumulative risk approach. One advantage is improved statistical modeling (Evans, Li, & Whipple, 2013); utilizing multiple risk factors in a single metric improves validity (Brinberg & Kidder, 1982; Ghiselli et al., 1981) and improves statistical power by removing the need for multiple collinear predictors in a single model (Cohen, West, & Aiken, 2014; Well & Myers, 2003). A second advantage is that cumulative risk more accurately reflects the reality of many children, particularly those living in impoverished contexts. Children are often exposed to multiple co-occurring risks, such as simultaneously living in a high crime neighborhood and attending a school with few resources (McLoyd, 1998), as opposed to being exposed to a single risk factor. If a single indicator of risk is used, its importance may be overestimated due to its association with other confounding risk factors (Evans, Li, & Whipple,

2013). A third advantage is that cumulative risk is a potent predictor of later outcomes; when it comes to predicting later problems, any specific risk factor is secondary to the quantity of risk factors or cumulative risk (Sameroff, Seifer, & McDonough, 2004). This suggests a less intuitive point: that experiencing two risk factors, such as a parent with a mental disorder and low family income, is more predictive of negative outcomes than experiencing a single more severe risk factor, such as childhood physical abuse. Despite these advantages, there are some limitations of the cumulative risk approach. Although it is incredibly helpful for identifying who is at most risk of worse developmental outcomes, cumulative risk models aggregate qualitatively different adversities that are likely to have unique effects on development. On an applied and policy level, this is problematic for a few reasons. First, it limits the ability to develop effective intervention strategies for children who have already experienced multiple qualitatively different risk factors that are likely exerting unique effects on development. Second, in the case of childhood poverty exposure, one of the policy solutions derived from cumulative risk work is to reduce poverty and thereby reduce exposure to multiple risk factors. Unfortunately, such policy solutions are often not politically feasible in the United States.

A fourth theoretical framework is the dimensional model of adversity and psychopathology (DMAP), which argues that early adversity can be studied along two dimensions in order to better understand how early adversity is related to later outcomes with greater specificity (McLaughlin, Sheridan, & Lambert, 2014). This model provides a compromise for studying the effects of early adversity on neural development. Prior work has taken one of two approaches. One focused on a single type of adversity, which does not reflect the reality of many children growing up in poverty, specifically that adversities are often co-occurring. A second approach has been to focus on cumulative risk, which, as previously discussed, has been helpful for identifying individuals who are in greatest need of intervention

but aggregates qualitatively different forms of adversity that are likely to exert unique influences on development and later mental health. Two dimensions that the model proposes are threat (to one's physical integrity) and deprivation (of biologically-expected input) (Figure 1.1). Experiences of threat are hypothesized to relate to alterations in fear-related circuitry and anxiety (McLaughlin et al., 2014). Deprivation is conceptualized by McLaughlin and colleagues to include both material deprivation (e.g., lack of cognitive stimulation), as well as more social deprivation (e.g., emotional neglect), and is hypothesized to relate primarily to alterations in cortical thickness and cognitive outcomes in addition to alterations in reward circuitry and depression (McLaughlin et al., 2014).

These dimensions have been studied extensively in animal literature, providing a strong neuroscience basis for their predicted impacts on brain development and well-being. McLaughlin, Sheridan, and Lambert (2014) draw on the extensive fear learning research in rodents to make predictions about the neural consequences of their proposed threat dimension. Specifically, findings from the rodent literature suggest that threatening experiences are associated with changes in amygdala and hippocampal structure and function, as well as poor performance on learning and memory tasks and increased anxiety and depression behaviors mediated by amygdala reactivity (McLaughlin, Sheridan, & Lambert, 2014). They also draw support from existing work in humans, which finds that early threat exposure is associated with reduced hippocampal volume in adults (Andersen & Teicher, 2008; Hart & Rubia, 2012; Teicher et al., 2012) and increased amygdala reactivity in children (McCrory et al., 2011; McCrory et al., 2013; McLaughlin, Sheridan, & Lambert, 2014). Sensory deprivation research, particularly work which found that sensory deprivation during development shapes neural structure and function by pruning overproduced synaptic connections (Huttenlocher et al., 1982), serves as the basis for McLaughlin, Sheridan, and Lambert's (2014) proposed mechanisms through which deprivation

in humans results in altered neural development. Specifically, they suggest that early cognitive and social deprivation predict reductions in association cortex thickness and volume, due to early or over-pruning of synaptic connections and reductions in performance on tasks that depend on these areas, such as complex cognitive tasks (McLaughlin, Sheridan, & Lambert, 2014). Research with individuals with congenital blindness lends additional support; these individuals have reduced thickness of primary visual cortex compared to sighted or late-blind individuals (Collignon et al., 2013; Leporé et al., 2010, McLaughlin, Sheridan, & Lambert, 2014). By conceptualizing early adversity along these specific dimensions of threat and deprivation, which each have a strong animal literature precedent, the DMAP can make mechanistic predictions about the impacts of qualitatively different forms of early adversity.

In the DMAP, deprivation is the less well-specified dimension; it contains multiple forms of deprivation that are qualitatively different from one another. As a result, previous animal work is usually applicable to only one form of deprivation; prior work exploring the role of environmental complexity in neural development may be relevant for material deprivation but is less relevant for social deprivation. Likewise, animal models of social deprivation, such as maternal separation, would be relevant for social deprivation but less relevant for material deprivation. Further, maternal separation is conceptualized as containing high threat and deprivation components (McLaughlin, Sheridan, & Lambert, 2014). Therefore, it is more difficult to hypothesize the developmental consequences of a broader deprivation dimension. Additionally, the human research used to support the DMAP deprivation dimension has either used very extreme measures of deprivation, such as institutional rearing, or poverty, which has been identified as an exposure containing both the threat and deprivation dimensions (McLaughlin, Sheridan, & Lambert, 2014).

Because my interest in this model is in its utility to explore neural mechanisms that link early poverty-related adversity to later anxiety and depression, I focused on social deprivation, or absence of positive social interactions. Deprivation is hypothesized to be associated with alterations in brain regions implicated in executive function and reward processing, as well as leading to cognitive deficits and increased depression (McLaughlin et al., 2014; McLaughlin & Sheridan, 2016). This hypothesis is motivated by prior work finding that more social forms of deprivation (e.g., institutional rearing, emotional neglect) have been linked to alterations in reward-related brain function (Hanson, Hariri, & Williamson, 2015; Mehta et al., 2010) and that these alterations partially explain the association between deprivation and depression (Hanson et al., 2015). Based this prior work, I hypothesize that social deprivation is related to alterations in reward-related brain function and depression. The second study of this dissertation tests this modified model in a sample at increased odds of experiencing early adversity.

Internalizing Disorders in Adolescence

Adolescence can be defined as beginning with the onset of puberty (9-12 years) and ending with adulthood (Crone & Dahl, 2012). Studies 1 and 2 of this dissertation include participants who are between 15 and 17 years of age and therefore will be referred to as adolescents.

Adolescence is a major transition period in development marked by significant change in socioemotional and reward function. Socioemotional function involves self-regulation of behavior to facilitate social relationships or opportunities in the social world (Challis & Berton, 2015). Reward is a multidimensional concept that conveys the positive value an organism assigns to an object, act, or internal physical state (Schultz, Dayan, & Montague, 1997). Previous work has established that negative emotional states peak in adolescence (Compas, Hinden, & Gearhardt 1995; Petersen et al. 1993; Rutter et al. 1976). Additionally, emotional responses in

adolescence are marked by increased intensity and variability of emotions compared to emotional responses in adults (Arnett 1999; Buchanan, Eccles, & Becker 1992; Eccles et al. 1989; Simmons & Blyth 1987). Adolescence is also a time of changes in reward-seeking; it increases between preadolescence and mid-adolescence and then declines after mid-adolescence (Steinberg, 2010). Furthermore, rewarding stimuli, such as winning a gambling task or interacting with a high interest peer, are more salient for adolescents relative to both children and adults (Somerville, Jones, & Casey, 2010). Significant changes in socioemotional and reward function may alter one's ability to self-regulate behavior as it relates to interacting with others or rewards. For example, increased emotional intensity may result in heightened sensitivity to negative interpersonal events, such as rejection by a romantic partner or peer. In adolescence, these types of negative interpersonal events are strong predictors of initial depressive episodes (Hecht, Inderbitzen, & Bukowski, 1998; Monroe, Rhode, Seeley, & Lewinsohn, 1999; Nelson, Leibenluft, McClure, & Pine, 2005). Because adolescence is a developmental stage when many changes in socioemotional and reward function occur, it is also a time of increased risk for anxiety and depression.

Adolescence is the developmental stage when the first onset of anxiety is most likely to occur and is also a period of significantly increased risk for depression (Burke, Burke, Regier, & Rae, 1990; Hasin, Goodwin, Stinson, & Grant, 2005; Kessler et al., 2005; Andren, Gabel, Stelmokas, Rich, & Bieliauskas, 2017). The median age of onset for any anxiety disorder is 11 years (Kessler et al., 2005). Multiple epidemiological studies have found that risk of depression increases significantly from childhood to adolescence (Andrade et al., 2003; Kessler et al., 2003). Further, in one large representative study, 11% of adolescents aged 13 to 18 had a lifetime history of depression (Avenevoli, Swendsen, He, Burstein, Merikangas, 2015). Therefore, it is

important to study emotion processing and reward function in adolescence in order to better understand the development of anxiety and depression.

Overlap of Emotion and Reward Processing

Emotion and reward processing are both associated with internalizing disorders, and the neural circuitry underlying these mechanisms overlap. Reward processing is not a unitary construct; it contains sensory, motivational, and affective components that each have associated neural circuitry (Murray, 2007). For example, the amygdala modulates responses to rewarding stimuli as part of circuity with the subiculum, bed nucleus of the stria terminalis, nucleus accumbens, and medial prefrontal cortex (Charney, 2004). This enables establishment of emotional value of a reward. However, the emotional component is just one part of reward processing and is tightly connected to other components such as motivation (Chiew & Braver, 2011). Although emotion and reward processing both relate to affect, the circuitry that support them vary in important ways.

Neural Circuitry of Emotion Processing

Despite substantial evidence that the environment influences the development of internalizing disorders in adolescence, little is known about the mechanisms through which this influence occurs. One potential mechanism is brain development; the environment may alter brain maturation and increase risk of later anxiety and depression. Two prominent techniques for studying brain development are functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI). fMRI assesses activation, or changes in blood flow associated with activity, as well as functional connectivity, or changes in the contribution of activation in one area to activation in another across different conditions (Friston et al., 1997). DTI indexes structural connectivity between regions; it evaluates white matter, or myelinated tracts that connect various regions of the brain. Specifically, DTI can measure multiple indicators of white

matter connectivity including: fractional anisotropy (FA), or how much water molecules diffuse along one direction; mean diffusivity (MD), or the extent to which water molecules diffuse; radial diffusivity (RD), or how much water molecules diffuse perpendicular to the axis of the fiber; and axial diffusivity (AD), or how much water molecules diffuse along the axis of the fiber (Feldman et al., 2010; Jones, Knösche, & Turner, 2013).

fMRI and DTI have been utilized to explore the components of emotion and reward processing systems in the brain. Emotion processing involves several brain regions that interact to enable processing of emotional stimuli. One key region is the amygdala, which is activated in response to emotional stimuli and is involved regulating emotion (Phelps & LeDoux, 2005). Amygdala reactivity demonstrates significant individual variability, which may contribute to the development of maladaptive emotion regulation seen in internalizing disorders (Adolphs, 2010). A second region involved in emotion processing is the prefrontal cortex. The prefrontal cortex, and in particular the ventral prefrontal cortex, which has been implicated in punishment and reward learning (Clark, Cools, & Robbins, 2004), has bidirectional communication with the amygdala; the amygdala drives prefrontal cortical activity and the prefrontal cortex downregulates amygdala activity. This enables successful socioemotional function; increased amygdala-driven prefrontal cortical activity in combination with decreased prefrontal cortex downregulation of the amygdala is believed to underlie anxiety (Bishop, 2007). Bidirectional communication between the amygdala and prefrontal cortex is facilitated by the uncinate fasciculus, a white matter tract connecting the frontal lobe to limbic structures (Petrides & Pandya, 2002). Increased uncinate fasciculus structural connectivity is hypothesized to facilitate prefrontal cortical regulation of the amygdala (Swartz et al., 2014; Tromp et al., 2012), thereby facilitating socioemotional function.

Changes in Emotion Processing Neural Circuitry in Adolescence

During adolescence, the neural networks involved in emotion processing undergo substantial structural and functional change. The amygdala experiences most structural development in childhood (Giedd et al., 1996; Mosconi et al., 2009; Schumann et al., 2004), whereas the prefrontal cortex experiences a protracted development, continuing to mature throughout adolescence (Casey, Jones, & Hare, 2008; Gogtay et al., 2004; Paus, 2005; Sowell et al., 1999; Sowell et al., 2013). Most previous fMRI investigations found that amygdala reactivity to socioemotional stimuli, such as emotional faces, decreases from adolescence to adulthood (Guyer, Monk et al., 2008; Hare et al., 2008; Monk et al., 2003; Nelson et al., 2015; Scherf, Smyth, & Delgado, 2013; Somerville, Fani, & McClure-Tone, 2011; Somerville, Jones, & Casey, 2010), but a few studies have failed to replicate this finding (McRae et al., 2012; Vasa et al., 2011). Prefrontal cortical regions that are involved in socioemotional function consistently demonstrate reduced reactivity during the transition from adolescence to adulthood (Blakemore 2008; Blakemore 2012; Burnett et al., 2009; Burnett, Sebastian et al., 2011; Gunther Moor et al., 2011; Pfeifer & Blakemore, 2012; Pfeifer, Lieberman, & Dapretto, 2007; Monk et al., 2003; Nelson et al., 2015). Functional connectivity between the amygdala and prefrontal cortex during social tasks increases in adolescence (Pfeifer, Masten et al., 2011; Spielberg, Jarcho et al., 2014; Nelson et al., 2015). This increased functional connectivity is hypothesized to reflect increased top-down prefrontal cortical inhibitory control of amygdala reactivity (Gee et al., 2013), helping to regulate the increased amygdala reactivity that is observed in adolescence.

Alterations in Emotion Processing Neural Circuitry in Adolescent Anxiety

Alterations in emotion processing, especially threat-related emotion processing, have been linked to anxiety disorders in adolescence. The amygdala in particular has often been implicated in anxiety symptomatology. Adolescents with anxiety disorders consistently demonstrate increased amygdala reactivity to threatening (e.g., angry faces, fearful faces,

undesirable peers) socioemotional stimuli compared to typically-developing peers (Guyer et al., 2008; McClure et al., 2007; Monk et al., 2008). Further, anxiety severity is often correlated with this increased amygdala reactivity (Killgore & Yurgelun-Todd, 2005; Monk et al., 2008; Swartz et al., 2014; van den Bulk et al., 2014).

In addition to alterations in amygdala reactivity, prefrontal cortical regions also demonstrate differences in function in adolescent anxiety disorders. Adolescents with generalized anxiety disorder (GAD) demonstrate increased activation in ventral prefrontal cortex (vPFC), ventrolateral prefrontal cortex (vlPFC), and anterior cingulate cortex (ACC) (McClure et al., 2007; Monk et al., 2006). Increased amygdala reactivity may drive increased prefrontal cortical activity or increased prefrontal cortical activity may reflect attempts to downregulate increased amygdala reactivity. Monk and colleagues (2006) found that within adolescents with anxiety disorders, increased vlPFC activity was associated with reduced anxiety, so it may be that increased prefrontal cortical activity serves as a compensatory mechanism to downregulate amygdala reactivity.

Investigations of functional connectivity between the amygdala and prefrontal cortical regions in adolescent anxiety have produced conflicting results. Positive correlations in activation between amygdala and vPFC and ACC (McClure et al., 2007), as well as between amygdala and vlPFC (Guyer et al., 2008), have been found in adolescents with anxiety disorders. However, in a sample of youth with generalized anxiety disorder (GAD), Monk and colleagues (2008) found that right amygdala and right vlPFC had both positive and negative coupling, and that negative coupling to masked angry faces was weaker in those with GAD. Further work is needed to clarify how functional connectivity between the amygdala and prefrontal cortex is associated with adolescent anxiety.

Neural Circuitry of Reward Processing

Like emotion processing, reward processing also involves a network of regions that interact to enable handling of rewarding stimuli. Anticipation of rewards has been associated with activation in the striatum, as well as the amygdala and orbitofrontal cortex (OFC), other structures with significant dopaminergic innervation (D'Ardenne, McClure, Nystrom, & Cohen, 2008; O'Doherty, 2004; Ruff & Fehr, 2014). Receiving and consuming rewards has been associated with activation in the OFC (Berridge & Kringelbach, 2008), amygdala (Morrison & Salzman, 2010), and anterior cingulate cortex (ACC) (Rushworth & Behrens, 2008; Ruff & Fehr, 2014). The OFC has been proposed to be a nexus in reward circuitry; in both rat and primate models it receives sensory information from sensory cortices and the amygdala, and then sends both motor and limbic output to the striatum and nucleus accumbens (Berridge & Kringelbach, 2008; Schoenbaum, Roesch, & Stalnaker, 2006).

Changes in Reward Processing Neural Circuitry in Adolescence

During adolescence, brain structures involved in reward processing undergo significant change. Both animal (Andersen et al., 2000; Tarazi & Baldessarini, 2000; Teicher et al., 2003) and human (Seeman et al., 1987; Weickert et al., 2007) studies have found that developmental changes in dopamine receptor density result in dopamine action being stronger in the striatum during early adolescence and being stronger in the PFC in early adulthood. This may be related to increased sensitivity to reward observed in adolescents relative to children and adults (Galván et al., 2006). Specifically, mid-adolescence is when reward processing regions, especially the ventral striatum, exhibit peak reactivity to rewards (Blakemore & Robbins, 2012; Van Leijenhorst et al., 2010). At the same time, adolescents exhibit reduced PFC recruitment when a reward is at stake compared to adults (Geier et al., 2009). In a sample with a wide age range (11-31 years), Christakou and colleagues found that activity in the ventromedial PFC (vmPFC) increases linearly and that this is associated with reduced impulsivity (Christakou et al., 2011).

Finally, activation in response to omitted rewards in the OFC, which is likely a nexus for reward circuitry, does not peak until young adulthood (Van Leijenhorst et al., 2010).

Alterations in Reward Processing Neural Circuitry in Adolescent Depression

Alterations in neural circuitry implicated in reward processing have been linked to depression (Forbes & Dahl, 2012; Hanson, Hariri, & Williamson, 2015; Nestler & Carlezon, 2006). Differences in ventral striatum function in particular have been purported to underlie the anhedonia and apathy that are common in major depressive disorder (MDD) (Nestler & Carlezon, 2006). Support for this theory comes from neuroimaging studies that have found reduced reward-related ventral striatum activity in individuals with MDD (Forbes & Dahl, 2012), including adolescents with MDD (Forbes et al., 2009).

In addition to altered ventral striatum activity, previous work has reported differences in medial PFC (mPFC) and amygdala reactivity to rewarding stimuli in depression, but the nature of these relations is less clear (Forbes & Dahl, 2012). Adolescent depression has been associated with increased (Forbes et al., 2009) and decreased (Forbes et al., 2006) activity in vmPFC areas involved in regulation of reward. Depressed adolescents also demonstrated increased amygdala reactivity to socially rewarding stimuli (Forbes et al., 2006).

The combination of decreased ventral striatum and increased mPFC activation observed in depression may be a function of several alterations in reward circuitry. One possibility is that adolescents with depression have a typical initial response to reward that is overregulated by mPFC (Forbes & Dahl, 2012). A second possibility is that the initial ventral striatum response is blunted and increased mPFC activity reflects efforts to enhance this initial response. A third possibility is that function in both the ventral striatum and mPFC are altered; initial ventral striatum response is blunted and mPFC is extensively recruited (Forbes & Dahl, 2012).

Brain Function as a Mediator for Environmental Influence on Internalizing Disorders in Adolescence

Several large, diverse, representative studies have established that children growing up in poverty face high risk for adolescent anxiety and depression (Gilman et al., 2003; McLaughlin et al., 2012; Wille et al., 2008). However, the mechanisms that link the correlated circumstances of poverty to later mental health are unclear, constituting a barrier to the development of effective prevention and intervention strategies. Neuroscience may provide insight as to how child poverty impacts mental health; one essential principle of the field is that early experiences shape later brain function and structure (McLaughlin, Sheridan, & Lambert, 2014). Children growing up in poverty often face multiple adversities (McLoyd, 1998), which may alter brain development and increase risk of psychopathology. Indeed, recent developments in the fields of neuroscience, psychology, and psychiatry support the role of brain function as a mediator for environmental influence on later internalizing disorders. Fonzo and colleagues (2016) found that increased amygdala and decreased dorsolateral PFC (dlPFC) activity partially mediated a positive relation between child emotional maltreatment (emotional abuse and neglect) and anxiety symptoms in adulthood. In another study, Hanson, Hariri, and Williamson (2015) found that decreased reward-related ventral striatum reactivity partially mediated the association between child emotional neglect and adolescent depressive symptomatology. Brain function as a mediator of environmental influence on later internalizing disorders is a promising avenue of research that may shed light on the mechanisms through which poverty gives rise to later anxiety and depression.

Contributions of Brain Research to Prevention and Intervention Work

This dissertation explores neural mechanisms that may link early adversity with later mental health outcomes. The ultimate goal of this work is to inform prevention and intervention

approaches that may be used to improve outcomes for children and families. Therefore, it is relevant to ask what advantages there are to a neuroscience approach to address questions of early adversity, as well as the utility of brain research in policy and practice discussions. One advantage to a neuroscience approach to studying early adversity is that it can reveal differences between individuals with greater and lesser adversity exposure that may not be apparent with more traditional behavioral measures. For example, several event-related potential (ERP) studies have found that there are socioeconomic disparities in the extent to which children filter out irrelevant sounds when completing an attention task, but none of these studies found socioeconomic disparities in behavioral performance (D'Angiulli, Herdman, Stapells, & Hertzman, 2008; D'Angiulli et al., 2012; Farah, 2018; Stevens, Lauinger, & Neville, 2009). This could be particularly helpful in early identification of individuals needing extra support. Although the second study of this dissertation aims to examine brain function as a mediator between early adversity and internalizing disorders, it is possible that differences in internalizing disorders as a function of early adversity will not emerge. Determining whether there are links between different forms of early adversity and brain function, and the nature of these links, is still helpful for targeting services and support. Further, even if someone does not have a full-blown internalizing disorder, alterations in brain function will impact the way that they interact with the world around them.

A second advantage is that some relations between early adversity and later mental health outcomes may be, at their core, neurobiological. For example, socioeconomic status has been linked to increased risk of depression (Farah, 2018; Grant et al., 2003; McLaughlin et al., 2011). On its own, it may not be clear why early poverty would be linked to depression. However, more recent work suggesting that early adversity is associated with disruptions to the development of prefrontal cortex, amygdala, and reward-related brain structures (Farah, 2018), and that these

associations may explain the link between early poverty and depression, provides a more complete explanation which can be used to guide prevention and intervention work.

Although research exploring the neural mechanisms linking early adversity and later mental health outcomes is relatively new, it has significant potential to contribute to policy and practice in several ways. First, brain research may provide converging evidence in favor of approaches already suggested by behavioral research. Further, different methodologies have their own strengths and weaknesses, so converging evidence across methodologies is particularly meaningful. In policy discussions, additional support for an idea that already exists can play an important role by tipping the balance in decision making (Farah, 2018). There is a concept of weight of evidence (WOE), which involves synthesizing diverse evidence to support decision making, and brain research can contribute to WOE. For example, findings that parenting stress predict parenting behavior, and in turn, predict changes in the development of emotion processing neural circuitry and increase likelihood of mental disorders, would provide additional evidence that screening parenting stress in a pediatric care setting may be worth the costs associated with doing so.

Second, brain research may provide biomarkers that could be used for both identification of those who are in most need of an intervention effort, as well as program evaluation. Neural biomarkers may be particularly beneficial for preverbal infants and young children, who may not be able to complete more traditional behavioral measures (Farah, 2018). For example, it may be possible to use neuroimaging to identify alterations in neural development in young children who have experienced forms of early adversity that are associated with worse mental health outcomes. Given the brain's plasticity, particularly in childhood (Kolb & Gibb, 2011), being able to determine who is in greatest need of additional support earlier provides significant benefits. Additionally, as previously discussed, neuroimaging can sometimes reveal differences that are

not apparent with traditional behavioral measures. Neuroimaging could also be used to assist in evaluations of the efficacy of intervention work aimed towards children and families facing adversity. For example, if the neural mechanisms linking a form of early adversity to a later outcome are known, then repeated neuroimaging measures taken throughout an intervention could be used to see if the intervention is effective, even if the individual receiving the intervention has not yet demonstrated a reduction in the outcome in question or has not even demonstrated the outcome in question at all. In addition to indexing efficacy, these measures could also be used to refine treatments, both at the group and individual levels, improving prevention and intervention work efficacy.

Current Studies

This dissertation seeks to address limitations of previous research by exploring the relations between brain structure and function across levels of socioemotional function, as well as the distinct effects of childhood violence exposure and victimization and social deprivation on adolescent brain function and anxiety and depression. The first study characterizes how structural connectivity of the uncinate fasciculus is related to amygdala function in adolescence (Hein et al., 2018). The second study explores the effects of childhood violence exposure and victimization on adolescent threat-related brain function and anxiety, as well as the effects of childhood social deprivation on adolescent reward-related brain function and depression (Hein et al., in preparation). Both studies use data from a large economically diverse sample of youth, drawn from a population-based sample that provides greater representation of adolescents of color and families from lower socioeconomic contexts, populations often understudied in neuroimaging research (Falk et al., 2013). Thus, the results of the studies in this dissertation will be more generalizable to the broader population than prior neuroimaging work using convenience samples.

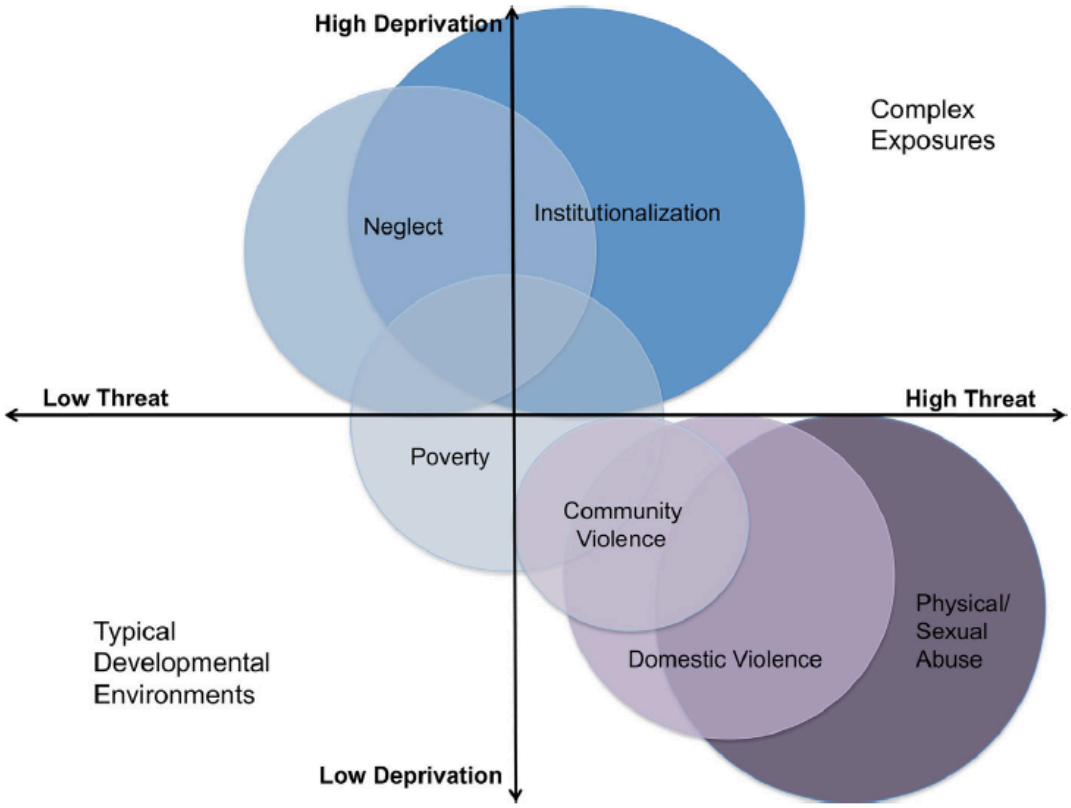

Figure 1.1. Dimensions of threat and deprivation associated with common forms of early adversity as proposed by McLaughlin, Sheridan, & Lambert (2014).

Figure taken from McLaughlin, Sheridan, and Lambert (2014) in Neuroscience and Biobehavioral Reviews.

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Chapter 2 [*]: Amygdala Habituation and Uncinate Fasciculus Connectivity in Adolescence: A Multi-Modal Approach

Introduction

Perceiving, interpreting, and responding appropriately to facial expressions are essential skills for successful socioemotional function across development. Two key regions involved in emotion processing are the amygdala and the prefrontal cortex (Banks, Eddy, Angstadt, Nathan, & Phan, 2007; Davidson 2002; Fusar-Poli et al., 2009; Haxby et al., 2002; Monk et al., 2003; Nelson, Leibenluft, McClure, & Pine, 2005). Heightened activation in the amygdala in response to emotional faces is associated with affect-related disorders (e.g., anxiety, depression) in both adolescents and adults (McClure et al., 2007; Monk, Klein, et al., 2008; Monk, Telzer, et al., 2008; Peluso et al., 2009; Phan, Fitzgerald, Nathan, & Tancer, 2006.; Swartz, Phan, Angstadt, Fitzgerald, & Monk, 2014). The prefrontal cortex (PFC) is well-connected structurally to the amygdala (Barbas, 2000), with the ventral PFC (vPFC) in particular helping to modulate its function (Hariri et al., 2003; Nomura et al., 2004). However, what is less clear is how the amygdala-vPFC circuit functions in adolescence, limiting our ability to understand the etiology of adolescent affect-related disorders.

During adolescence, a developmental period when peer social interactions are highly salient, the neural networks involved in emotion processing undergo significant structural change (Blakemore, 2008; Lenroot & Giedd, 2006). Whereas the amygdala goes through substantial

[*] Chapter 2 corresponds to the publication Hein and colleagues, 2018

development during childhood (Giedd et al., 1996; Mosconi et al., 2009; Schumann et al., 2004; Tottenham & Sheridan, 2009), the prefrontal cortex experiences a protracted development and continues to mature through adolescence (Casey, Jones, & Hare, 2008; Gogtay et al., 2004; Sowell et al., 1999; Sowell et al., 2003). During this time, cortical gray matter volume in the frontal lobe decreases from its peak volume in late childhood (11 years for girls and 12.1 years for boys), reflecting pruning of these regions and myelination of gray matter (Lenroot & Giedd, 2006; Giedd 2008). White matter increases linearly throughout adolescence (Lenroot & Giedd, 2006), improving neuronal communication. Pruning and increased neuronal connectivity help to strengthen information transfer between prefrontal cortical and subcortical regions (Casey, Jones, & Hare, 2008).

The major white matter tract connecting the ventral prefrontal cortex and the amygdala is the uncinate fasciculus (UF), which is the primary conduit of bidirectional communication within amygdala-vPFC circuit (Von Der Heide, Skipper, Klobusicky, & Olson, 2013). The vPFC is hypothesized to modulate amygdala reactivity (Hariri et al., 2003; Monk et al., 2008; Nomura et al., 2004), suggesting that increased structural connectivity of the UF facilitates vPFC regulation of amygdala reactivity. However, little work has examined if UF structural connectivity relates to amygdala reactivity. Further, if the UF is facilitating amygdala downregulation, its structural connectivity should relate to amygdala habituation, defined as a decrement in amygdala reactivity during a task due to repeated stimulus presentation (Plichta et al., 2014; Rankin et al., 2009). Amygdala habituation is hypothesized to result from prefrontal cortical downregulation of amygdala reactivity and facilitate acclimation to our surroundings. Additionally, amygdala habituation is a more reliable indicator of amygdala function (Gee et al., 2015; Plichta et al., 2014). Importantly, no prior work has evaluated the relation between UF structural connectivity and amygdala habituation.

Further, UF structural connectivity increases throughout childhood, adolescence, and early adulthood (Hasan et al., 2009; Swartz et al., 2014). As a result, adolescence poses a unique challenge to this system. Namely, the UF is in flux, while at the same time the socioemotional environment is rapidly changing. The underlying neurobiology is not yet stabilized, possibly remaining flexible in the face of a changing environmental and hormonal landscape. Despite the potential importance of this developmental phenomenon, surprisingly, little is known about how connectivity between crucial regions develops.

Beyond structural changes, the neural networks involved in emotion processing also experience significant functional development during adolescence. Amygdala responsivity to socioemotional stimuli decreases from adolescence to adulthood (Guyer, Monk et al., 2008; Hare et al., 2008; Nelson et al., 2015; Scherf, Smyth, & Delgado, 2013; Somerville, Fani, & McClure-Tone, 2011; Somerville, Jones, & Casey, 2010), but this finding is not consistent (McRae et al., 2012; Pfeifer & Allen 2012; Vasa et al., 2011). Prefrontal cortical regions involved in socioemotional function (e.g., face processing) consistently demonstrate reduced reactivity from adolescence into adulthood (Blakemore 2008; Blakemore 2012; Burnett et al., 2009; Burnett, Sebastian et al., 2011; Gunther Moor et al., 2011; Pfeifer & Blakemore, 2012; Pfeifer, Lieberman, & Dapretto, 2007; Monk et al., 2003; Nelson et al., 2015). Additionally, functional connectivity between the amygdala and prefrontal cortex in response to social contexts increases in adolescence (Pfeifer, Masten et al., 2011; Spielberg, Jarcho et al., 2014; Nelson et al., 2015). As with structural development, reactivity of neural regions essential to emotion processing change significantly during adolescence, a period of substantial alterations in the socioemotional environment. Although studying structural and functional development separately has yielded important insights, this approach is limited in that it cannot address bidirectional influences between structural and functional development (Cicchetti & Dawson, 2002). For example,

changes in brain structure may facilitate or inhibit changes in brain function or vice versa. It is particularly important to study neural structure and function simultaneously in adolescence, as this is a developmental stage marked by significant changes in both neural structure and function and is also a time of potential flexibility in response to changing environments, hormones, and neural development. In order to attain a more comprehensive understanding of the neural bases of socioemotional development during adolescence, it is essential to utilize and integrate multiple modalities.

To date, only a small number of studies have explored the relation between UF structural connectivity and amygdala reactivity to emotional stimuli. Increased structural connectivity of the UF is thought to facilitate prefrontal cortical regulation of the amygdala (Swartz et al., 2014; Tromp et al., 2012). Consistent with this premise, diffusion tensor imaging (DTI) has shown that fractional anisotropy (FA) values, which reflect the extent to which diffusion is constrained in a single direction and index the connectivity of a fiber tract (Jones, Knösche, & Turner, 2013; Thomason & Thompson, 2011), in the UF are inversely related to amplitude of amygdala response to sad and happy faces in youth (9.6 – 19.2 years of age) recruited from a college town (Swartz et al., 2014). Increased structural connectivity in childhood and adolescence may facilitate decreases in amygdala reactivity that are often observed across development (Swartz et al., 2014), suggesting that increased structural connectivity would be associated with decreased amygdala reactivity in youth. However, in a study of older adolescents and young adults (16.95 – 25.25 years of age) recruited from a college town, UF FA positively correlated with amygdala reactivity to fearful faces (compared to neutral faces; Kim & Whalen, 2009). The inconsistency in findings between these two studies highlights the need for further work to clarify the relation between UF FA and amygdala regulation, particularly during development. Indeed, both Kim & Whalen (2009) and Swartz et al. (2014) relied on relatively small ($N < 40$) convenience samples

recruited from college towns (Kim & Whalen, 2009; Swartz et al., 2014), limiting their applicability to the general population.

Previous work evaluating the relation between UF structural connectivity, amygdala reactivity, and development focused on age, so the role of puberty is less clear. Specifically, the one developmental study to examine UF FA and amygdala activation found that the relation is moderated by age in a child and adolescent sample (9– 19 years old), such that younger participants demonstrate a stronger relation between UF FA and amygdala activation (Swartz et al., 2014). However, the influence of puberty was not examined. Pubertal hormonal changes have been shown to relate to distinct aspects of neural maturation (Spear, 2000; Sisk & Foster, 2004; Blakemore, Burnett, & Dahl, 2010; Galván, Van Leijenhorst, & McGlennen, 2012), so pubertal stage is an important consideration when conducting neuroimaging studies of adolescence. Previous work exploring the relation between pubertal stage and socioemotional processing has been mixed; advancing pubertal stage has been both positively (Moore et al., 2012) and negatively (Forbes et al., 2012) associated with amygdala activation to emotional faces (Galván, Van Leijenhorst, & McGlennen, 2012). The divergence of these findings highlights the importance of further work exploring the role of pubertal stage in socioemotional processing. In addition, there are sex differences in adolescent structural (Schmithorst & Yuan, 2010) and functional (Tahmasebi et al., 2012) neural development. Therefore, sex should be an important consideration when studying puberty and adolescent neural development. However, whether sex influences the relation between neural structure and function is unclear. Despite these intriguing findings, prior studies have not examined the effects of puberty and sex on the relation between UF connectivity and amygdala reactivity.

The primary objective of the current study was to further characterize how UF structural connectivity is related to amygdala function in adolescents. We improved upon previous work in

three ways: 1) we examined amygdala habituation, a more reliable indicator of amygdala function (Gee et al., 2015; Plichta et al., 2014); 2) we used DTI acquisition methods that improved image quality; and 3) we recruited a large sample of adolescents drawn from a population-based sample that provides greater representation of adolescents of color and families from lower SES contexts, populations often understudied in neuroimaging research (Falk et al., 2013). Since our participants were closer in age to the participants in Swartz et al. 2014 than those in Kim & Whalen 2009, we hypothesized that greater UF structural connectivity would predict greater amygdala habituation to emotional faces. In light of findings indicating that age moderates the relation between UF FA and activation (Swartz et al., 2014), our second objective was to assess the potential moderation of the relation between UF structural connectivity and amygdala habituation by age, pubertal status, and gender. We hypothesized that age and pubertal status would moderate the relation between UF structural connectivity and amygdala habituation. Finally, given that demographic variables (puberty, age, and sex) have been linked to alterations in socioemotional and neural development, but their influences on the relations between structure and function are unclear, our third objective was to examine the relations between demographic variables, UF structural connectivity, and amygdala habituation. We hypothesized that age and pubertal status would be positively associated with UF FA and amygdala habituation.

Methods

Participants

The University of Michigan Medical School Institutional Review Board approved this study. All adolescent participants provided written informed assent and their primary caregivers provided written consent for both themselves and their adolescent children, after the study was explained and questions were answered. 106 adolescents from the Detroit or Toledo subsamples of the Fragile Families and Child Wellbeing Study (FFCWS) (Reichman, Teitler, Garfinkel, &

McLanahan, 2001) successfully completed both fMRI and DTI scanning. The FFCWS is a population-based sample of children born in large US cities, with an oversample of non-marital births (Table 2.1). At the beginning of the national FFCWS study, 42.16% of mothers indicated that their household income in the last 12 months was $25,000 or less; 60.51% indicated that their household income in the last 12 months was $50,000 or less. FFCWS families were interviewed at the birth of the focal child and when the child was 1, 3, 5, 9, and 15 years of age. The population of the city of Detroit at the time of the FFCWS baseline was predominantly African American (Brookings Institute, 2003), and the Detroit sample was significantly larger than the Toledo sample (Reichman et al., 2001), so our sample has substantial (73.6%) representation of African American families. One hundred eighty-seven adolescents participated in the current study at the time of analysis, but 16 were unable to be scanned (e.g., due to braces) and 6 declined to participate in scanning. An additional 44 participants were removed from analyses for several other reasons including: not completing the fMRI task (N = 5); fMRI scan quality issues (e.g., significant portions of the brain not covered, N = 8); low coverage of the left or right amygdala (N = 13); low accuracy (<70%) on the task faces (N = 15); outliers on habituation (extracted amygdala habituation was less than (Q1 (lower quartile)-3*IQR (interquartile range)) or greater than (Q3 (upper quartile) +3*IQR) ; (N = 2)); and ASD diagnosis (N = 1). For DTI analyses, an additional 15 participants were removed due to incomplete DTI data acquisition (N = 4) and/or DTI image artifacts (N = 11; Table 2.2). Additionally, comparison was not possible in a small number of participants for which DTI measures from the UF could not be extracted due to inability of tractography to trace the UF, because the FA fell below 0.15 or the minimum angle between current and previous path segments exceeded 30 degrees (Thomason et al., 2010) (N = 8 for the left and 2 for the right). The participants who had useable fMRI and DTI data did not differ on age, $t(163.04) = -0.12266$, $p = 0.9025$, pubertal

status, $t(151.68) = -0.97555$, $p = 0.3308$, or gender, $\chi 2\ (22) = 25.134$, $p = 0.2907$, from participants who did not. Of the adolescents who were included in the present analyses, 73.6% were Black / African American, 14.2% were White/ Caucasian, and 47.2% of families reported annual income below $25,000.

Procedures

Gender identification task

Participants completed an implicit emotion face processing task during continuous fMRI acquisition. In this task, participants were asked to identify the gender of the actor by pressing their thumb for male or their index finger for female on a button box. Faces from the NimStim set (Tottenham et al., 2009) were used and were counter balanced for gender and race (European American and African American). There were 100 pseudo-randomized trials, 20 trials each of the following emotions: fearful, happy, sad, neutral, and angry. Each trial consisted of a fixation cross (500 ms), followed by a face (250 ms), then a black screen (1500 ms) during which participants responded to the face, and finally a second black screen (jittered inter-trial interval: 2, 4, or 6 s). This task is particularly well-suited for studying emotion processing, as the quick presentation time of the face stimuli does not provide opportunity for participants to saccade away from the stimuli (Mattson et al., under review). Accuracy and response times were recorded.

fMRI data acquisition

fMRI data was collected with a GE Discovery MR750 3T MRI scanner with an 8-channel head coil. We collected functional T2*-weighted BOLD images with a gradient echo spiral sequence (TR = 2000ms, TE = 30ms, contiguous 3 mm axial slices, flip angle = 90°, FOV = 22cm, voxel size = 3.44mm x 3.44 mm x 3mm) aligned with the AC-PC plane.

DTI data acquisition

We collected DTI data after fMRI scanning using a spin echo diffusion sequence (TR = 7250ms, TE = minimum, FOV = 22cm, thickness = 3mm, 40 slices, with b = 1000 s/mm^2, and 64 non-linear directions). To transform the diffusion-weighted images to a MNI template, one non-diffusion weighted image (b = 0 s/mm^2) was also collected.

Puberty

Pubertal development was measured using adolescent self-report on the Pubertal Development Scale (Petersen, Crockett, Richards, & Boxer, 1988), which has had high correlations (0.61 – 0.67) with physician ratings (Brooks-Gunn, Warren, Rosso, & Gargiulo, 1987). Total scores range from 1 to 4.

Gender

Adolescent self-report of gender was determined using the Pubertal Development Scale; specifically, if they answered female- or male-specific questions on the scale.

Age

Date of birth was collected using adolescent self-report and parent confirmation on an fMRI safety screener and then the date of the visit and date of birth were used to calculate age in months.

Psychopathology

Current psychopathology was determined with the K-SADS-PL (Kaufman et al., 1997). A trained clinical interviewer (e.g., psychology doctoral student, post-baccalaureate staff) administered the semi-structured interview to the target child and primary caregiver individually. Assessors were trained by two licensed clinical psychologists with 25+ years combined experience with the K-SADS. Training included practice interviews and live supervision of interviews with families. The interviewer arrived at initial DSM-V diagnoses and symptom

counts, which were then reviewed in case conferences with two licensed clinical psychologists (authors LWH and NLD).

Analyses

fMRI data analysis

Anatomical images were homogeneity-corrected using SPM, then skull-stripped using the Brain Extraction Tool in FSL (version 5.0.7) (Smith, 2002; Jenkinson, Pechaud, & Smith, 2005). The functional imaging data then had the following preprocessing steps applied: removal of large temporal spikes in k-space data (> 2 std dev), field map correction and image reconstruction using custom code in MATLAB; and slice-timing correction using SPM8.6313 (http://www.fil.ion.ucl.ac.uk/spm/). The rest of preprocessing was also done in SPM8, including: gray matter segmenting anatomical images; realigning segmented anatomical and functional images to the AC-PC plane; coregistering anatomical and functional images; spatially normalizing functional images into MNI space; and smoothing functional images with a Gaussian filter set to 8 mm FWHM. We conducted image analyses using the general linear model of SPM8. After preprocessing, Artifact Detection Tools (ART) software (http://www.nitrc.org/projects/artifact_detect) identified motion outliers (>2mm movement or 3.5° rotation). Outliers were censored from individual participant models using a single regressor for each outlier volume. Given susceptibility of the amygdala to signal loss, only those participants with a minimum of 70% coverage in the left and right amygdala at a threshold of $p <$ 1, as defined by Automated Anatomical Labeling atlas regions of interest (ROIs; Maldjian, Laurienti, Burdette, & Kraft, 2003; Maldjian, Laurienti, & Burdette, 2004; Tzourio-Mazoyer et al., 2002), were included in group-level analyses. To ensure that participants were engaged in the task, only those with accuracy of 70% or greater were included in group analyses. Condition effects were modeled at the individual level, with incorrect trials modeled as a separate condition

and excluded from subsequent analyses. To assess habituation, we divided the task in half and a separate regressor for each emotion (fearful, happy, sad, neutral, and angry) and half of the task (1st half, 2nd half) was created, yielding 10 regressors of interest (e.g., early and late fearful).

DTI data analysis

We conducted preprocessing and analysis of diffusion weighted images using MrDiffusion, part of the mrVista package (https://white.stanford.edu/software/). Preprocessing involved head motion correction using eddy current correction and linear registration to the non-diffusion weighted image (b=0 image). Based on concerns about DTI artifacts (Soares, Marques, Alves, & Sousa, 2013), three independent raters checked each volume for white pixel or other forms of artifact. If any individual rater considered an artifact to be present in a volume, that volume was marked as having an artifact. We removed participants with artifacts in 8 or more directional volumes from analyses. To ensure equal statistical support of DTI metrics, participants included in the analyses each had a total of 7 volumes removed. These 7 volumes included any volumes with artifacts and then volumes selected by a random number generator. Using regions of interest included in the Johns Hopkins University White Matter Tractography Atlas (Mori et al., 2005), we extracted multiple white matter tracts using the same methodology described in detail in our prior works (Swartz et al., 2014; Thomason et al., 2010).

Group analyses

Amygdala habituation to faces

We tested amygdala habituation in SPM8 by subtracting activation to the second half of the task from activation to the first half of the task (Swartz et al., 2013; Wiggins, Swartz, Martin, Lord, & Monk, 2013). This and all subsequent analyses were small volume corrected (SVC) using anatomically defined (Automated Anatomical Labeling atlas) left and right amygdala masks created with the Wake Forest University PickAtlas (Maldjian et al., 2003; Maldjian et al.,

2004; Tzourio-Mazoyer et al., 2002) to maintain a voxelwise family-wise error of $p < 0.05$. The effects of each emotion (fearful, happy, sad, neutral, and angry) were tested separately, as we wanted to explore the specificity of any effect. We corrected for multiple comparisons in subsequent regression analyses by setting Bonferroni correction to $p < 0.004$ in addition to the voxelwise family-wise error of $p < .05$. This correction was determined by dividing 0.05 by twelve; we tested 6 emotions (all, fear, happy, sad, neutral, and angry) in both the left and right sides of the amygdala. Using structural regions of interest from the Wake Forest University PickAtlas, we extracted individual parameter estimates for the change in amygdala reactivity during the task to use in confirmatory analyses.

Objective 1: Relation between UF FA and amygdala habituation

To assess the relation between UF FA and amygdala habituation, multiple regression analysis in SPM8 was conducted in which UF FA was regressed onto amygdala habituation. In separate analyses, we regressed extracted mean FA values from the left and right UF onto the contrasts of each emotion (all faces, fearful, happy, sad, neutral, angry) versus baseline. Significance was evaluated for the regression of left FA values for the left amygdala ROI and right FA values for the right amygdala ROI. Again, we corrected for multiple comparisons (left and right side as well as six emotions) by setting Bonferroni correction to $p < 0.004$.

We also conducted control analyses in RStudio to determine whether the relation between amygdala habituation and FA values was specific to the UF. This allowed us to determine whether global differences in white matter maturation contributed to DTI effects or if effects were isolated to UF circuitry. To do this, we selected the superior longitudinal fasciculus (SLF) and inferior longitudinal fasciculus (ILF), two of the control tracts used by Swartz et al. (2014). We examined correlations between amygdala habituation (extracted from the structural

amygdala ROI from WFU Pickatlas) and mean FA from the UF, SLF and ILF in RStudio 1.0.136 (RStudio Team).

Objective 2: Moderation of relations between amygdala habituation and UF by age, pubertal status, and gender

We assessed age, pubertal status, and gender as potential moderators of any significant relations between amygdala habituation and UF FA. To examine moderation, we tested whether the interaction between the predictor variable (UF FA) and the moderator variable (age, pubertal status, or gender) significantly predicted the outcome variable (amygdala habituation) in RStudio. If the interaction was significant, then the effect of UF FA on amygdala habituation differed depending on the moderator. We visualized significant moderation using the rockchalk package (Johnson, 2017) in RStudio.

Objective 3: Relations between demographic variables, UF, and amygdala habituation

We evaluated whether amygdala habituation varied by age, pubertal status, and gender. To assess the influences of age and pubertal status on amygdala habituation, we conducted multiple regression analyses in SPM8. We evaluated the role of gender in amygdala habituation by conducting an ANOVA in SPM8. For each demographic variable assessed, we corrected for multiple comparisons (left and right side and six emotions) by setting Bonferroni correction to $p < 0.004$.

We also evaluated whether UF FA varied by age, pubertal status, and gender. We ran Pearson's correlations in RStudio to test whether mean UF FA varied with age or pubertal status and then conducted a t-test in RStudio to determine whether mean UF FA differed by gender.

Task performance

To ensure that amygdala habituation was not a result of changes in accuracy or reaction time, we compared accuracy and reaction time in the first and second halves of the task using

paired t-tests in RStudio. If there was a significant difference, we then evaluated whether the change in accuracy or reaction time between the two halves of the task was related to extracted amygdala habituation.

Motion outliers

We evaluated whether the number of motion outliers detected by ART throughout the scan related to our demographic variables of interest (age, gender, pubertal status) and compared the number of motion outliers in the first and second halves of the scan in RStudio in order to ensure that any results were not driven changes in motion. If there was a significant relation between motion outliers and demographic variables or difference in motion outliers between the two halves of the scan, we then evaluated whether this was related to amygdala habituation.

Current psychopathology

To ensure that our findings were not solely due to current psychopathology, we removed all participants with a current DSM-V disorder diagnosis and re-ran main analyses with the smaller sample (albeit with reduced power).

Results

Amygdala habituation to faces

We observed significant habituation in the right, but not left, amygdala at the group level mean (see Table 2.3). Specifically, the right amygdala demonstrated significant habituation to the contrasts all faces versus baseline and neutral faces versus baseline. Though the left amygdala did not show significant habituation at the group level (i.e., the group mean of T2-T1 was not significantly different from 0), there was substantial individual variability (left amygdala habituation to fear mean = 0.0002; SD = 0.614; range = -2.023 – 1.331) in habituation scores and thus these scores were examined in relation to UF FA.

UF FA

The mean extracted left UF FA value was 0.304 (SD = 0.024, range = 0.261-0.390) and the mean extracted right UF FA value was 0.300 (SD = 0.021, range = 0.233-0.359).

Objective 1: Relation between UF FA and amygdala habituation

Multiple regression analyses in SPM8 examining the relation between left UF FA and left amygdala habituation revealed a positive relation, such that higher FA values were associated with more amygdala habituation to fearful faces, t (96) = 3.76, p = .003, XYZ = -26, -2, -18; see Table 2.4 and Figure 2.1. This was also found in confirmatory correlation analyses in RStudio, r (96) = 0.314, p = 0.002; see Figure 2.2. In addition, we evaluated the influence of one extreme score on left UF FA by removing it and re-running the correlation analyses, which yielded similar results.

There were no significant relations between right UF FA and right amygdala habituation. Control analyses assessing the relations between SLF and ILF FA and amygdala habituation found no significant relations for either side.

Objective 2: Moderation of relation between amygdala habituation and UF FA by age, pubertal status, and gender

We tested whether age or pubertal status moderated the association between left UF FA and left amygdala habituation to fearful faces. The regression including the moderation effect of puberty was significant, R^2 = 0.18, F(3,92) = 6.786, p = 0.0003, and the interaction of puberty and left UF FA, B = -15.340, SE = 6.464, t (95) = -2.373, p = 0.0197, significantly predicted left amygdala habituation to fearful faces. To ensure that this moderation effect was specific to puberty, we tested whether the interaction of puberty and left UF FA was still significant after including age as a term in the regression. The regression that included age as well as the moderation effect of puberty was still significant, R^2 = 0.18, F(4,91) = 5.063, p = 0.001, indicating that the interaction of puberty and left UF FA, B = -15.256, SE = 6.502, t (95) = -

2.347, $p = 0.02112$, predicted left amygdala habituation to fearful faces even after accounting for age. The relation between left UF FA and left amygdala habituation to fearful faces is stronger for participants who are earlier in pubertal development, see Figure 2.3. Follow-up F tests to compare variances in left UF FA and left amygdala habituation between those above and below the average for puberty revealed variance in left amygdala habituation to fearful faces was trending towards being greater for participants who were earlier in pubertal development, $F(37,57) = 1.7061$, $p = 0.06809$. Neither the interaction of age and left UF FA, B = 0.7902, SE = 0.5134, $p = 0.127$, nor the interaction of gender and left UF FA, B = 8.275, SE = 4.973, $p = 0.0994$, predicted left amygdala habituation to fearful faces. Finally, we evaluated the influence of one extreme score on left UF FA by removing it and re-running the analyses, which gave similar results.

Objective 3: Relations between demographic variables, UF FA, and amygdala habituation

We assessed whether age, pubertal status, or gender related to either amygdala habituation or UF FA. We did not find significant relations between age and amygdala habituation (see Table 2.5). Further, we did not find significant relations between pubertal status and amygdala habituation (see Table 2.6). Amygdala habituation and UF FA did not differ by gender. Neither age nor puberty were significantly related to UF FA.

Task performance

After removing participants with below 70% accuracy, the average accuracy across the task was 94.68% (SD = 5.97% , range = 72.00-100.00%) and the average reaction time (RT) was 709.74 ms (SD = 126.99 ms, range = 501.76 – 998.21 ms). Accuracy did not significantly differ between the first and second halves of the task $t(105) = 1.7037$, $p = 0.091$, but reaction time did, $t(105) = 2.528$, $p = 0.013$. Average RT was slower in the first half of the task (mean = 718.43 ms, SD = 137.26 ms, range = 475.10 – 1072.88 ms) than in the second half of the task (mean =

701.05 ms, SD = 126.17 ms, range = 495.43 – 1007.50 ms). The change in accuracy between the first and second halves of the task was not significantly related to amygdala habituation to any emotion on either hemisphere of the brain (all $p > 0.17$). The change in reaction time between the first and second halves of the task was also not significantly related to amygdala habituation to any emotion on either hemisphere of the brain (all $p > 0.094$).

Motion outliers

The total number of motion outliers detected by ART throughout the fMRI scan did not relate to age, gender, or pubertal status (all $p > 0.50$). However, the number of motion outliers detected by ART did differ between the first and second halves of the scan, $t(105) = -2.0561$, $p = 0.04$. The change in number of motion outliers from the first half to the second half of the scan was related to left amygdala habituation to angry faces, $t(96) = -3.1336$, $p = 0.002$, right amygdala habituation to fearful faces, $t(104) = 3.0958$, $p = 0.0025$, and right amygdala habituation to happy faces, $t(104) = 2.3772$, $p = 0.0193$. However, these contrasts are not involved in the significant findings of this paper.

Current psychopathology

When excluding participants with current DSM-V disorder diagnoses (n = 30), left UF FA was still associated with left amygdala habituation to fearful faces, but the finding became a trend, likely due to reduced statistical power associated with a reduced sample size, $r(67) = 0.23$, $p = 0.055$. Even with reduced power, the regression including the moderation effect of puberty was still significant, $R^2 = 0.15$, $F(3,63) = 3.593$, $p = 0.01834$, and the interaction of puberty and left UF FA, B = -22.617, SE = 9.860, t (66) = -2.294, $p = 0.0251$, significantly predicted left amygdala habituation to fearful faces. We still found no significant relations between gender, age, puberty, and left UF FA or left amygdala habituation to fearful faces in the sample that excluded participants with current psychopathology diagnoses.

Discussion

The present study characterized the relation between UF structural connectivity and amygdala function in a large sample drawn from a population-based sample and with substantial representation of understudied youth – African American adolescents and adolescents from lower SES families. We found a significant positive relation between left UF FA and left amygdala habituation to fearful faces. Further, we found that pubertal status moderated the relation between left UF FA and left amygdala habituation, such that this relation was stronger for participants who were earlier in pubertal development.

As hypothesized, greater UF structural connectivity predicted larger amygdala habituation to emotional faces. That is, increased UF FA was associated with a greater reduction in amygdala response to fearful faces over the course of the task. Although prior work has not examined the relation between UF connectivity and amygdala habituation, our results were more consistent with Swartz and colleagues' finding that UF FA structural connectivity predicted reduced amygdala activation, than Kim and Whalen's finding that UF FA structural connectivity predicted increased amygdala activation (Kim & Whalen, 2009; Swartz et al., 2014). Further, the relation between UF FA and amygdala habituation that we found supports the hypothesis that the UF facilitates amygdala downregulation. Importantly, this relation between UF FA and amygdala habituation was specific to the left hemisphere of the brain. The laterality of this finding was consistent with previous work examining the relation between UF FA and amygdala activity in youth; Swartz et al. (2014) found significant relations in the left hemisphere only. Results of a meta-analysis suggested that the right amygdala is involved in a more short-term response to emotional stimuli, whereas the left amygdala engages in more sustained responses (Sergerie, Chochol, & Armony, 2008). Bidirectional communication between the amygdala and prefrontal cortex may be more influential on the sustained responses of the left amygdala,

whereas the temporal dynamics of the right amygdala may result in effective habituation with less prefrontal cortical input. This research may also explain our finding of group-level habituation in the right amygdala only; it is possible that the temporal dynamics of the right amygdala are such that there is less individual difference in habituation, whereas individual differences in bidirectional communication between the amygdala and prefrontal cortex are more significant for left amygdala habituation, even when the group mean is 0. The role of amygdala-prefrontal cortex circuitry may differ by hemisphere, but further work is warranted to clarify potential differences by hemisphere.

The positive relation between UF FA and amygdala habituation suggested that increased structural connectivity of the UF facilitates prefrontal cortical regulation of the amygdala in adolescence. However, theoretical accounts of adolescent development posit that a dual-systems model where limbic reactivity is increased and prefrontal cortical activity is immature in adolescence may be overly simplistic (Crone & Dahl, 2012; Pfeifer & Allen, 2012). Therefore, further empirical work is needed in order to better understand the nuances of affective neural development in adolescence; Pfeifer and Allen (2012) suggested that research combining neuroimaging modalities may be particularly helpful. Our study is the first to combine fMRI and DTI to explore the relations between amygdala habituation and UF structural connectivity. Our finding that increased structural connectivity was related to increased amygdala downregulation helped to clarify the previous literature by utilizing habituation instead of activation, which is thought to index emotion regulation. Future work should integrate structural and functional connectivity of limbic circuitry in adolescence in order to determine whether the UF facilitation of amygdala habituation is due to PFC downregulation, which would be reflected as increased UF structural connectivity and increased amygdala-PFC functional connectivity both relating to amygdala habituation. Further, Gee and colleagues (2013) found that previously

institutionalized youths exhibited more mature bilateral amygdala-medial PFC connectivity and that this was associated with reduced anxiety (Gee et al., 2013). Increased habituation has also been linked to reduced anxiety; individuals with higher trait anxiety demonstrated reduced amygdala habituation in the left amygdala (Hare et al., 2008). It may be that altered amygdala-PFC connectivity and amygdala habituation in the left hemisphere may contribute to anxiety, but further work is warranted. A prior quantitative meta-analysis (Wager, Phan, Liberzon, & Taylor, 2003) found no support for a hypothesis of overall lateralization of emotional function. In a systematic review, Baas, Aleman, & Kahn (2004) found that the left amygdala is more often activated than the right amygdala, and this predominant left amygdala activation is not due to stimulus type, task instructions, different habituation rates between left and right amygdala, and elaborate processing. A recent review suggests that functional lateralization of emotion in the amygdala is modulated by sex, with the greatest impairments being associated with right-hemisphere lesions in men and left-hemisphere lesions in women (Reber & Tranel, 2017). Nevertheless, Hare and colleagues did not find an effect of gender on habituation (Hare et al., 2008). Similarly, in the present study, we did not find an effect of gender. As discussed in Reber & Tranel (2017), there is much work that needs to be done in order to understand how sex differences and neurological organization interact with other factors to influence emotion. Further, to truly evaluate the role of laterality, one needs to directly compare left and right amygdala function, to ensure that the two sides differ significantly as opposed to one side being under threshold and the other being above threshold. Future work should evaluate the extent to which UF facilitation of amygdala habituation is influenced by early life stress and impacts anxiety, whether there are unique effects by hemisphere of the brain, and whether any hemispheric effects differ by sex.

Beyond the primary hypothesis, a second objective of our study was to assess the potential moderation of the relation between UF structural connectivity and amygdala habituation by age, pubertal status, and gender. We found that pubertal status, but not age, moderated the association between left UF FA and left amygdala habituation to fearful faces. This finding held even when accounting for age. UF FA was more predictive of amygdala habituation in participants who were earlier in pubertal development relative to participants who were later in pubertal development. Increased strength of the relation between UF FA and amygdala habituation in participants who were earlier in pubertal development may be explained by slightly greater variability in amygdala habituation in participants who were earlier in pubertal development or may also be a function of hormonal changes that take place earlier in pubertal development. Early puberty may be a developmental period where structural connectivity of the UF is particularly important for emotion processing. However, we did not find that age moderated the association between limbic structure and function, as previous work has (Swartz et al., 2014). The age range of our sample was narrow (15-17 years); this enabled us to better evaluate the relation between UF structural connectivity and amygdala habituation in mid-adolescence, as well as the influence of puberty on this relation, but it did limit our ability to explore the influence of age. Another possibility supported by our findings is that pubertal status, not age, drives the age moderation of the relation between UF FA and amygdala activation found in prior work (Swartz et al., 2014). Further work is needed to parse the influences of age and pubertal status on brain structure and function development.

Finally, a third objective of our study was to better understand how age, gender, and pubertal status are related to amygdala habituation and UF structural connectivity. Inconsistent with our predictions, we did not find statistically significant relations between age, gender, pubertal status, and amygdala habituation, but this may be due to our conservative correction for

multiple comparisons. Age was positively associated with right amygdala habituation and pubertal status was positively associated with left amygdala habituation, but these findings did not survive comparison for multiple corrections. Similarly, as discussed above for our second objective, it is possible that this may be a function of the relatively narrow age range of our sample; perhaps we did not have enough variability in age to find an effect of age. It is possible that future work with greater variability in age and pubertal status may find statistically significant relations between these demographic variables and amygdala habituation, clarifying inconsistencies between our work and previous research. Age has been negatively associated with amygdala activation (Swartz et al., 2014), and pubertal status has been both positively (Moore et al., 2012) and negatively (Forbes et al., 2012) linked to amygdala activation. A second possibility is that differences in amygdala activation by age or pubertal status found in previous work were not necessarily a function of amygdala habituation; differences in mean amygdala activation over an entire task may be due to differences in amygdala habituation or differences in initial amygdala responsivity (Plichta et al., 2014). Future work examining the relations between age, pubertal status, and amygdala habituation may resolve differences between our work and previous research.

We also found that age, pubertal status, and gender did not relate to UF FA. These findings were inconsistent with our hypotheses and with previous work supporting a positive relation between age and UF FA (Hasan et al., 2009; Swartz et al., 2014). However, these findings may be a function of the relatively narrow age range of our sample (15-16.8 years) compared to Hasan et al. (2009) (7-68 years) and Swartz et al. (2014) (9.6-19.2 years). Future work utilizing a sample with a larger age range could clarify the inconsistencies between our current findings and previous work.

There were a number of limitations with the current study. One limitation is that due to the population-based sampling methodology used in the original FFCWS, a significant portion of our participants were not eligible to participate in MRI scanning. For example, 9 subjects had braces and 4 subjects were unable to fit in the scanner. Moreover, because we did not use weighting in our analyses, our findings cannot be seen as city, nor nationally representative. Second, due to the multi-modal neuroimaging approach, a greater number of participants had to be removed due to unusable DTI or fMRI data than if a single neuroimaging modality had been used. Despite these limitations, our sample size was more than double previous work exploring the relation between UF structural connectivity and amygdala reactivity. Further, our sample contained substantial representation of African American youth and families living in low SES contexts, populations often missing in neuroimaging research. A third limitation is that we failed to find statistically significant habituation in the left amygdala (the right amygdala did habituate). This null finding may be due to a relatively small number of trials (20) of each of the five emotions; a longer task or fewer emotions may yield better habituation results. Another possibility is that subgroups may habituate, sensitize, or experience no change in reactivity during the task; this will be examined in future work with this sample. Although habituation itself was not statistically significant, the degree to which a participant habituated was still predicted by left UF FA, meaning that although the sample did not demonstrate left amygdala habituation on the whole, individual differences in left UF FA predicted decreases in left amygdala responsivity during the course of the task. Despite these limitations, our work contributes to the field by improving upon prior work in three ways: 1) we examined amygdala habituation, a more reliable measure than amygdala activation (Gee et al. 2015) that is thought to index emotion regulation; 2) we used more advanced DTI methods; and 3) we recruited a large

adolescent sample that was drawn from a population-based sample and included greater representation of understudied adolescents and families.

In conclusion, the current study identified a positive relation between UF FA and amygdala habituation in a large, well-sampled cohort of adolescents. Adolescents with greater UF white matter structural connectivity had more amygdala habituation, whereas adolescents with less UF white matter structural connectivity had less amygdala habituation. Additionally, pubertal status moderated this relation, such that the relation was stronger earlier in pubertal development. Only a few studies have linked structural and functional aspects of limbic circuitry and this is the *first* to do so with habituation as well as specific demographic variables (puberty, age, and gender). By combining structural and functional neuroimaging, this study marks a key step toward a more comprehensive understanding of neural bases of socioemotional development.

Measure	**Count (%)**
Gender	
Female	61(57.5%)
Male	45(42.5%)
Race	
Black / African-American	78(73.6%)
White / Caucasian	15(14.2%)
Asian	1(0.9%)
Other	1(0.9%)
Multiracial	6(5.7%)
Missing	5(4.7%)
Ethnicity	
Hispanic	6(5.7%)
Not Hispanic	98(92.5%)
Missing	2(1.9%)
Measure	**Mean(SD), Range**
Age (months)	188.12(5.04), 180-202
Puberty	2.94(0.44), 1.8 - 4.0

Table 2.1. Participant demographics.

	Number of Subjects
Original Sample	187
fMRI analyses attrition	
Did not attempt MRI scan	22
Incomplete fMRI scan	5
fMRI scan quality issues (e.g., image distortion)	8
(<70%) amygdala coverage (left or right)	13
(<70%) accuracy on faces task	15
Habituation outlier	2
ASD	1
Total included in habituation analyses	121
DTI analyses attrition	
Incomplete DTI scan	4
DTI scan quality (>7 artifacts)	11
Unable to extract L UF measures	8
Unable to extract R UF measures	2
Total included in habituation & L UF analyses	**98**
Total included in habituation & R UF analyses	**104**

Table 2.2. Sample attrition.

Contrast	Side	t(120)	p-value(FWE)	X	Y	Z
All1>All2	L	2.74	0.051	-30	-6	-14
Fear1>Fear2	L		> 0.100			
Happy1>Happy2	L		> 0.100			
Sad1>Sad2	L		> 0.100			
Neutral1>Neutral2	L	2.82	0.044	-18	-2	-14
Angry1>Angry2	L	2.67	0.053	-28	-8	-12
All1>All2	**R**	**4.71**	**< 0.001**	**32**	**-8**	**-12**
Fear1>Fear2	R	2.17	0.162	32	-8	-12
Happy1>Happy2	R	2.42	0.099	28	-8	-14
Sad1>Sad2	R	3.17	0.018	32	-8	-12
Neutral1>Neutral2	**R**	**4.17**	**0.001**	**32**	**-2**	**-12**
Angry1>Angry2	R	3.43	0.008	32	-8	-12

Table 2.3. Amygdala habituation to faces.

Note: FWE-corrected is based on structurally-defined amygdala regions of interest. FWE = family-wise error; coordinates are in Montreal Neurological Institute (MNI) space. Bolded type indicates that finding survives Bonferroni correction for 12 comparisons.

Contrast	Side	Positive effect of UF FA, t(96)	p-value(FWE)	X	Y	Z
All1>All2	L	2.48	0.091	-24	0	-16
Fear1>Fear2	**L**	**3.76**	**0.003**	**-26**	**-2**	**-18**
Happy1>Happy2	L		> 0.100			
Sad1>Sad2	L	2.97	0.03	-20	0	-12
Neutral1>Neutral2	L		> 0.100			
Angry1>Angry2	L	2.37	0.107	-24	4	-18
Contrast	Side	Positive effect of UF FA, t(102)	p-value(FWE)	X	Y	Z
All1>All2	R	2.57	0.086	28	-8	-14
Fear1>Fear2	R	2.28	0.143	26	-6	-16
Happy1>Happy2	R	1.93	0.255	24	0	-18
Sad1>Sad2	R		> 0.100			
Neutral1>Neutral2	R		> 0.100			
Angry1>Angry2	R	1.87	0.271	28	-8	-14

Table 2.4. Relation between uncinate fasciculus FA and amygdala habituation to faces.

Note: FWE-corrected is based on structurally-defined amygdala regions of interest. FWE = family-wise error; coordinates are in Montreal Neurological Institute (MNI) space. Bolded type indicates that finding survives Bonferroni correction for 12 comparisons.

Contrast	Side	Positive effect of age, t(104)	p-value(FWE)	X	Y	Z
All1>All2	L		> 0.100			
Fear1>Fear2	L		> 0.100			
Happy1>Happy2	L		> 0.100			
Sad1>Sad2	L		> 0.100			
Neutral1>Neutral2	L		> 0.100			
Angry1>Angry2	L	2.70	0.054	-20	-6	-16
Contrast	Side	Positive effect of age , t(104)	p-value(FWE)	X	Y	Z
All1>All2	R	2.84	0.047	22	2	-16
Fear1>Fear2	R		> 0.100			
Happy1>Happy2	R	2.79	0.048	22	2	-16
Sad1>Sad2	R		> 0.100			
Neutral1>Neutral2	R	2.52	0.097	24	0	-12
Angry1>Angry2	R	3.53	0.007	22	-4	-16

Table 2.5. Relation between age and amygdala habituation to faces.

FWE = family-wise error; coordinates are in Montreal Neurological Institute (MNI) space.
Bolded type indicates that finding survives Bonferroni correction for 12 comparisons.

Contrast	Side	Positive effect of pubertal status, t(102)	p-value(FWE)	X	Y	Z
All1>All2	L	1.73	0.323	-18	-4	-12
Fear1>Fear2	L	3.33	0.012	-22	-6	-16
Happy1>Happy2	L		> 0.100			
Sad1>Sad2	L		> 0.100			
Neutral1>Neutral2	L		> 0.100			
Angry1>Angry2	L		> 0.100			
Contrast	Side	Positive effect of pubertal status , t(102)	p-value(FWE)	X	Y	Z
All1>All2	R		> 0.100			
Fear1>Fear2	R		> 0.100			
Happy1>Happy2	R		> 0.100			
Sad1>Sad2	R		> 0.100			
Neutral1>Neutral2	R		> 0.100			
Angry1>Angry2	R		> 0.100			
Contrast	Side	Negative effect of pubertal status, t(102)	p-value(FWE)	X	Y	Z
All1>All2	L		> 0.100			
Fear1>Fear2	L		> 0.100			
Happy1>Happy2	L	2.35	0.115	-30	-4	-14
Sad1>Sad2	L		> 0.100			
Neutral1>Neutral2	L		> 0.100			
Angry1>Angry2	L		> 0.100			
Contrast	Side	Negative effect of pubertal status , t(102)	p-value(FWE)	X	Y	Z
All1>All2	R		> 0.100			
Fear1>Fear2	R		> 0.100			
Happy1>Happy2	R	2.31	0.136	32	-8	-12
Sad1>Sad2	R		> 0.100			
Neutral1>Neutral2	R		> 0.100			
Angry1>Angry2	R		> 0.100			

Table 2.6. Relation between pubertal status and amygdala habituation to faces.

Note: FWE-corrected is based on structurally-defined amygdala regions of interest. FWE = family-wise error; coordinates are in Montreal Neurological Institute (MNI) space. Bolded type indicates that finding survives Bonferroni correction for 12 comparisons.

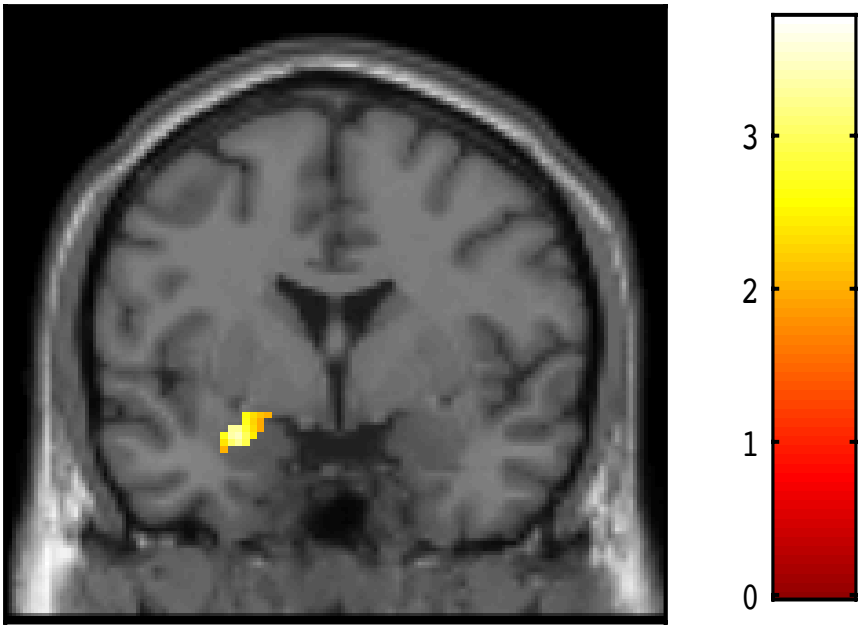

Figure 2.1. Positive relation between left UF FA and left amygdala habituation to fearful faces.

t(96) = 3.76, *p* = .003, XYZ = -26, -2, -18. Left UF FA estimates were extracted from a structural left UF ROI and entered as regressors in a multiple regression analysis in SPM8.

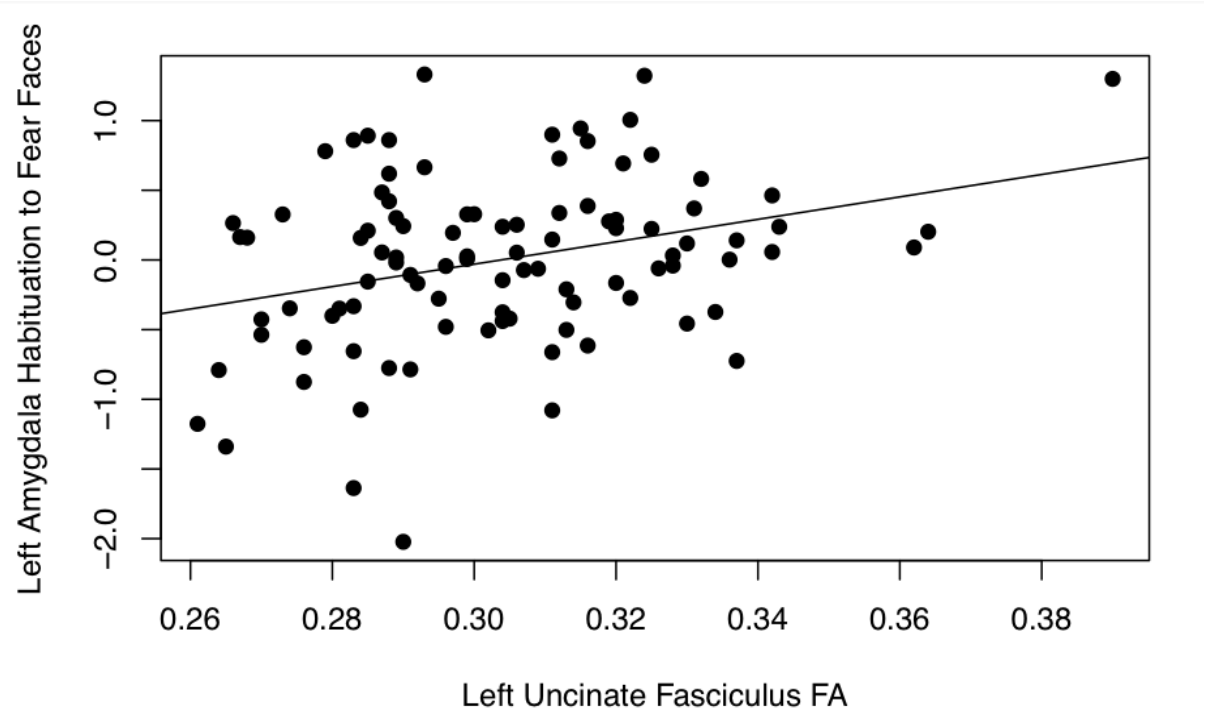

Figure 2.2. Correlation between left UF FA and left amygdala habituation to fearful faces.

In a confirmatory analysis in RStudio, left amygdala habituation to fearful faces is positively correlated with mean FA values extracted from the left UF, $r = 0.314$, $p = 0.002$. Left amygdala habituation parameter estimates were extracted from a structural left amygdala ROI from WFU PickAtlas and left UF FA estimates were extracted from a structural left UF ROI.

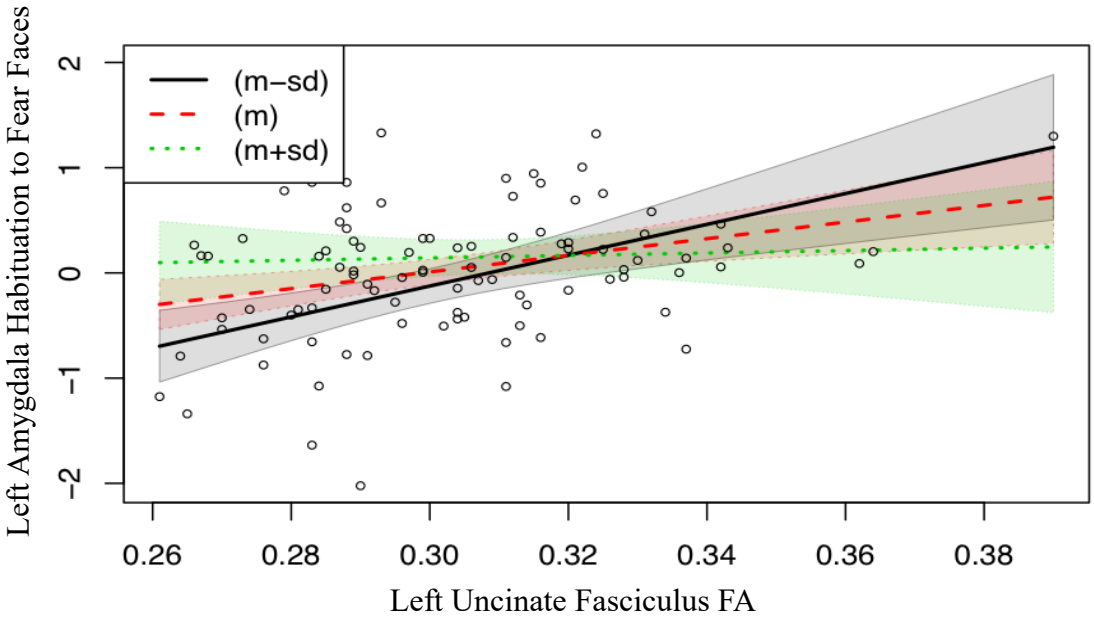

Figure 2.3. Puberty moderates association between left UF FA and left amygdala habituation to fearful faces.

The association between left UF FA and left amygdala habituation to fearful faces is moderated by puberty, B = -15.340, SE = 6.464, t (95) = -2.373, p = 0.0197, such that left UF FA was more predictive of left amygdala habituation to fearful faces in participants who were earlier in pubertal development relative to participants who were later in pubertal development. The coloring in the figure represents pubertal status; the dotted green line and green shading represents participants who are later in pubertal development (at the mean plus the standard deviation of pubertal development for this sample or greater), the dashed red line and red shading represents participants who are average in their pubertal development, and the black solid line and black shading represent participants who are earlier in pubertal development (at the mean minus the standard deviation of pubertal development for this sample or less).

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Chapter 3 [†]: Childhood Violence Exposure and Social Deprivation Predict Threat and Reward Neural Function in Adolescents

Introduction

Forty-five percent of children in the United States experience at least one adverse childhood experience (ACE) (Sacks & Murphey, 2018) and these experiences are potent contributors to multiple mental disorders, such as depression and anxiety (CDC, 2016; Sacks & Murphey, 2018). The high prevalence and deleterious effects of adversity have fueled investigations into brain mechanisms linking ACEs to negative outcomes. Many studies focused on a single category of adversity, such as previous institutionalization (e.g., Maheu et al., 2010) or child maltreatment (e.g., DeBellis & Hooper, 2012), and how these experiences predict brain function and structure. However, adverse experiences often co-occur, meaning that many children are exposed to an array of correlated experiences. This observation led to a focus on cumulative risk, in which the number of exposures is the focus, rather than the specific type (e.g., Sameroff, Seifer, & McDonough, 2004; note, however, that this has rarely been applied to neuroimaging studies). This approach yielded numerous findings linking childhood adversities to internalizing and externalizing problems later in development (e.g., Appleyard, Egeland, van Dulmen, & Sroufe, 2005). Though this research demonstrated that the number of exposures predicts outcome, it aggregates qualitatively different adversities together; thereby obfuscating potential links from specific forms of adversity to brain development and symptomatology.

[†] Chapter 3 corresponds to the publication Hein and colleagues, in preparation

To improve specificity, two alternatives emerged. One strategy was to create cumulative risk indices within specific domains (e.g., Deater-Deckard, Dodge, Bates, & Petit, 1998; Trentacosta, Hyde, Goodlett, & Shaw, 2013). Unfortunately, little of this work has been guided by neurobiology, particularly animal models that identify how specific types of adversities may have differential impacts on brain circuits. The second approach is the Dimensional Model of Adversity and Psychopathology (DMAP) (McLaughlin, Sheridan, & Lambert, 2014; Sheridan & McLaughlin 2014). DMAP posits that many early adverse experiences are captured by dimensions of threat and deprivation, which include experiences across domains that are qualitatively similar. These dimensions are expected to differentially predict specific types of alterations in brain development. Threat is conceptualized as actual or perceived threat of harm to one's physical integrity and includes experiences such as physical abuse and intimate partner violence. Based on human and animal models, threat experiences are hypothesized to affect the development of neural structures involved in fear conditioning in the limbic system (e.g., the amygdala) (McLaughlin et al., 2014; McLaughlin & Sheridan, 2016). In support of this hypothesis, experiences with a high threat component (child maltreatment, family violence) relate to increased amygdala reactivity (Hein & Monk, 2017; McCrory et al., 2011). Deprivation is the absence of biologically-expected input (cognitive or social) and includes experiences such as institutionalization and emotional neglect. Deprivation is hypothesized to be associated with alterations in brain regions implicated in executive function and reward processing, such as the striatum (specifically the ventral striatum which contains the nucleus accumbens, a key center for reward processing) (McLaughlin et al., 2014; McLaughlin & Sheridan, 2016). In line with this hypothesis, more social forms of deprivation (e.g., institutional rearing, emotional neglect) were linked to alterations in neural circuitry associated reward processing, particularly blunted ventral striatum reactivity (Hanson, Hariri, & Williamson, 2015; Mehta et al., 2010).

Previous neuroscience work on the impact of early adversity on socioemotional outcomes often focus on two neural circuits: one that is involved in processing threat; the other in processing reward. Perceiving and responding correctly to stimuli that signal risk of harm, such as an angry face or a fearful face, gives an individual a survival advantage (Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002). These abilities arise from the interaction of several brain regions, one key region being the amygdala, which is activated in response to emotional stimuli more broadly and is involved in emotion regulation (Phelps & LeDoux, 2005). Amygdala reactivity demonstrates significant individual variability, which may contribute to the development of maladaptive emotion regulation (Adolphs, 2010). In addition to measuring amygdala reactivity, assessing amygdala habituation, or decrease in amygdala reactivity during a task due to repeated stimulus presentation (Plichta et al., 2014; Rankin et al., 2009), provides insight into the time course of threat processing. Further, it is a more reliable indicator of amygdala function (Gee et al., 2015; Plitchta et al., 2014). Like threat processing, reward processing provides a survival advantage. It does so by facilitating reward seeking, whether that be food, money, or social approval indicated by a happy face (Izuma, Saito, & Sadato, 2008; McClure, York, & Montague, 2004). One key region in this circuit is the nucleus accumbens, which is part of the ventral striatum and receives dopaminergic projections from the ventral tegmental area (Russo & Nestler, 2013). The nucleus accumbens, as well as the ventral striatum more broadly, serve as a node for reward-driven behaviors (Schultz, Apicella, Scarnati, & Ljungberg, 1992; Telzer, 2016). Processing of both threat and reward in the social environment is essential to successful socioemotional function and are both hypothesized to be disrupted by different dimensions of early adversity; nevertheless, they have not been examined simultaneously.

We evaluated whether dimensions of early adversity have unique associations with the development of threat- and reward-related neural regions by integrating longitudinal and neuroimaging data in a sample of adolescents drawn from a nationally representative sample. Our conceptualization of violence exposure and victimization (violence exposure, henceforth) included child abuse, intimate partner violence, and community violence. This dimension is similar to DMAP's threat dimension but is isolated to experiences of violence as opposed to other experiences that may also fall in the threat dimension, such as natural disasters. Based on prior work linking exposure to violence and alterations in threat processing (McCrory et al., 2011), we examined amygdala habituation and activation to angry and fearful faces, which signal threat in the environment. Social deprivation included neglect from a caregiver, absence of supportive romantic relationships, and absence of supportive community relationships. We focused on social deprivation, or absence of positive social interactions, as opposed to DMAP's deprivation which includes both material and social deprivation. Based on work that found that deprivation that is social in nature is related to altered reward processing (Hanson et al., 2015), we examined neural response to happy faces, inherently socially rewarding stimuli. Our focus on the nucleus accumbens is based on previous work showing blunted activation in the nucleus accumbens to happy emotional faces in youth at familial risk of depression (Monk et al., 2008).

The current study had three objectives: (1) establish the associations of childhood violence exposure on adolescent amygdala habituation to threat; (2) assess the relation between childhood violence exposure and adolescent amygdala activation to threat; (3) relate childhood social deprivation to adolescent nucleus accumbens activation to social reward. These objectives and the associated variables and analyses were pre-registered with the open science framework (https://osf.io/qgupf/). Data from the SAND study is publicly available through the National Institute of Mental Health's RDoCdb (https://data-archive.nimh.nih.gov/rdocdb/).

We hypothesized the following: (1) greater childhood violence exposure would predict decreased amygdala habituation to threat; (2) greater childhood violence exposure would predict increased amygdala activation to threat; and (3) greater childhood social deprivation would predict decreased nucleus accumbens reactivity to social reward.

Methods

Participants

The Fragile Families and Child Wellbeing Study (FFCWS) (Reichman, Teitler, Garfinkel, & McLanahan, 2001) comprises a population-based sample of children born in large US cities, with an oversample of non-marital births. FFCWS families were interviewed at the birth of the focal child, and when the child was 1, 3, 5, 9, and 15 years of age. At age 15, 237 adolescents from the FFCWS (born in Detroit, Toledo, or Chicago) and their caregivers participated in the Study of Adolescent Neural Development (SAND), a neuroimaging follow-up study of the core FFCWS (Appendix S1). Importantly, this sample contains substantial representation of African American youth, as well as adolescents from families living in low-income contexts (Appendix S1). 167 adolescents successfully completed fMRI scanning (Appendix S1). Adolescents provided written informed assent, and their caregivers provided written consent for both themselves and their adolescent children, after the study was explained and questions were answered. The University of Michigan Medical School Institutional Review Board approved this study (UM IRBMED: HUM00074392).

Procedures

Emotional faces task

Participants completed an event related emotional faces task during fMRI acquisition (Hein et al., 2018). Participants were asked to identify the gender of actors displaying one of five emotions: fearful, happy, sad, neutral, and angry. Faces were presented for 250ms.

Violence Exposure and Social Deprivation Composite Scores

Composite scores indexing violence exposure and social deprivation in childhood were created using data collected at ages 3, 5, and 9 years from the FFCWS (Appendix S2). Violence exposure included abuse from a caregiver, intimate partner violence in the home, and violence within the community. Social deprivation included neglect from a caregiver, absence of supportive relationships within the home, and absence of supportive relationships within the community. A primary caregiver in the household reported on child abuse, community violence, child neglect, and absence of supportive relationships within the community. The focal child's mother reported on intimate partner violence and absence of romantic partner support, from either the focal child's father or a current romantic partner. However, if the focal child did not live with their mother at least half of the time for a given wave, data on intimate partner violence and absence of romantic partner support was coded as missing.

Analyses

fMRI data analysis

fMRI data were collected, preprocessed, and activation was analyzed using methodology detailed in our prior work (Goetschius et al., in press; Appendix S3). Habituation was analyzed using methodology described in our prior work (Hein et al., 2018; Appendix S3).

Group analyses

Objectives 1 and 2: Childhood violence exposure, adolescent amygdala habituation to threat, and adolescent amygdala activation to threat

The relations between childhood violence exposure and both adolescent amygdala habituation and activation to threatening (angry and fearful) faces were evaluated using multiple regression analysis in SPM12. For habituation, we regressed the violence exposure composite score onto the contrasts of early > late angry and early > late fearful, while controlling for social

deprivation, the interaction of violence exposure and social deprivation, and gender. We adjusted for the interaction of violence exposure and social deprivation to better isolate the main effects of each dimension. For activation, we ran similar analyses, but regressed the violence exposure composite score onto the contrasts of angry > baseline and fearful > baseline. Significance was evaluated for structural left and right amygdala regions of interest (ROIs) created with Pickatlas (Maldjian, Laurienti, Kraft & Burdette, 2003; Tzourio-Mazoyer et al., 2002) at a threshold of voxelwise family-wise error of $p<0.05$. Additionally, we corrected for multiple comparisons for both habituation and activation analyses using a Holm-Bonferroni correction for 4 comparisons: 2 emotions (angry, fearful) in both amygdalae. Individual parameter estimates for amygdala habituation were extracted by averaging across voxels.

Objective 3: Childhood social deprivation and adolescent nucleus accumbens activation to social reward

The relation between childhood social deprivation and adolescent nucleus accumbens reactivity to socially rewarding (happy) faces was evaluated using SPM12 multiple regression analyses. We regressed the social deprivation composite score onto the contrast of happy > baseline, while adjusting for violence exposure, the interaction of violence exposure and social deprivation, and gender. Significance was evaluated for structural left and right nucleus accumbens ROIs created from Pickatlas. We corrected for multiple comparisons by using the same correction described above. This corrected for two comparisons: one emotion (happy) in left and right nucleus accumbens. Individual parameter estimates for both nucleus accumbens activation were extracted by averaging across voxels.

Adolescent Internalizing Psychopathology

Our preregistration proposed structural equation modeling (SEM) analyses that tested whether alterations in threat- and social reward-related brain function mediated associations

between violence exposure, social deprivation, and adolescent anxiety and depression. To create multi-informant, multi-method measures of anxiety and depression, we ran confirmatory factor analysis (CFA) in the Lavaan package (version 0.5-23.1097) (Rosseel, 2012) in RStudio (version 1.1.463) (RStudio Team, 2015). We also evaluated whether a single factor (internalizing psychopathology) would fit our data better than a two-factor model of anxiety and depression. Indicators in the confirmatory factor analysis included: DSM-V current symptom counts for major depressive disorder (MDD), persistent depressive disorder (PDD), generalized anxiety disorder (GAD), specific phobia, and social anxiety disorder (social phobia) from a structured clinical interview (Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime (K-SADS-PL), Kaufman et al., 1997); adolescent self-report on depression and anxiety symptoms (Children's Depression Inventory (CDI), Kovacs & Beck, 1977; Mood and Feelings Questionnaire (MFQ), Angold & Costello, 1987; Screen for Child Anxiety Related Emotional Disorders (SCARED), Birmaher et al., 1997); and caregiver report on adolescent depression and anxiety symptoms (MFQ and SCARED; Appendix S4). In the event of nonsignificant mediation analyses, we planned to re-run our SPM analyses with our internalizing psychopathology measure(s) as a covariate, to evaluate whether our SPM findings were being driven by internalizing psychopathology.

Adolescent Stress

To control for current stress, we re-ran our SPM analyses with adolescent life stress as a covariate. Adolescent life stress was measured using a modified Adolescent Life Events Scales (ALES) (adapted (Shaw, Gilliom, Ingoldsby, & Nagin, 2003) from Masten, Neemannn, & Adenas, 1994). A z-scored total score representing the number of stressful life events the participant experienced in the 6 months prior to the visit was used.

Results

Violence exposure and social deprivation composite scores

Violence exposure and social deprivation composite scores were correlated, $r(235)=0.45$, $p<0.001$, but their VIF was 1.24, indicating multicollinearity was low (Sheather, 2009).

Objective 1

Higher levels of violence exposure predicted reduced right amygdala habituation to angry faces (Table 3.1,Figure 3.1). This effect was specific to angry faces; violence exposure was not related to other expressions. Using individual parameter estimates extracted from the significant clusters from this analysis, we visualized activation in the first and second halves of the faces task, separating participants into groups based on above or below mean levels of violence exposure (Figure 3.2). Individuals low on violence exposure demonstrate a typical amygdala habituation, with significantly less activation to angry faces in the second half of the task. In contrast, individuals high on violence exposure fail to demonstrate amygdala habituation. Further, individuals high on violence exposure are trending towards having less amygdala activation to angry faces in the first half of the task compared to individuals low on violence exposure.

Objective 2

Higher levels of violence exposure predicted reduced left amygdala activation to angry faces specifically (Table 3.2).

Objective 3

Higher levels of social deprivation predicted reduced left and right nucleus accumbens activation to happy faces (Table 3.3,Figure 3.3), but only findings for the right side remained significant with control for multiple comparisons. Social deprivation did not relate to other emotions.

Adolescent internalizing psychopathology

17.7% met criteria for current depressive and/or anxiety disorders (Appendix S5). Factor analysis indicated that a one factor model of internalizing psychopathology in adolescence fit the data best: χ^2=38.558 (p=0.011), CFI=0.936, TLI=0.862, and RMSEA=0.059 (Appendix S6).

Mediation analyses

We evaluated the relations between violence exposure, social deprivation, and adolescent internalizing psychopathology. Neither were associated with our adolescent internalizing psychopathology latent factor. Therefore, proceeding with mediation analyses with violence exposure and social deprivation was not warranted.

Adjusting for adolescent internalizing psychopathology and stress

Since we did not find support for mediation models, we re-ran our SPM analyses adjusting for both adolescent internalizing psychopathology and adolescent stress and found that all SPM findings held.

Discussion

The present study evaluated whether two dimensions of early adversity, violence exposure and social deprivation, separately predicted activity in specific neural circuits. Utilizing an open science framework, we tested three pre-registered hypotheses. Consistent with our hypothesis, childhood violence exposure uniquely predicted decreased right amygdala habituation (i.e., more sustained amygdala activation) to angry faces in adolescence. Also, in line with our hypothesis, childhood social deprivation uniquely predicted decreased right nucleus accumbens activation to socially rewarding stimuli in adolescence. These associations held when adjusting for internalizing psychopathology and adolescent current life stress. Opposite to our hypothesis, childhood violence exposure uniquely predicted *decreased* left amygdala reactivity to angry faces in adolescence. Importantly, this study used a well-sampled cohort with

substantial representation of understudied youth – African American adolescents and adolescents from lower SES families.

To better understand the potentially discrepant amygdala findings, we examined extracted habituation data (Figure 3.2) and found that those with greater violence exposure both start out with lower levels of activation to threatening stimuli and then do not experience a change in reactivity during the task. High violence environments may lead to an adaptive response of lower initial reactivity and therefore habituation does not occur or it occurs rapidly. Further work, particularly research evaluating connectivity between the prefrontal cortex and amygdala in those who have experienced violence, will be important for understanding the pattern of amygdala activation.

The influence of early adversity on amygdala habituation has not been studied directly; existing work is in the context of post-traumatic stress disorder (PTSD), which aims to predict who develops PTSD after exposure to trauma, as opposed to the effect of early adversity specifically. Adult men with PSTD evidenced reduced right amygdala habituation relative to controls, but both groups experienced trauma (Shin et al., 2005). In adolescents, childhood sexual abuse-related PTSD predicted rapid amygdala habituation compared to those with internalizing disorders, but adolescents in the internalizing group could have experienced other early adversities (van den Bulk, 2016). In both studies, a main effect of adversity was not reported, so it is impossible to disentangle the effects of adversity and psychopathology. We demonstrated a main effect of violence exposure on amygdala habituation when controlling for internalizing psychopathology, suggesting a unique association with threatening early experiences.

The finding that greater violence exposure was associated with *less* amygdala activation is inconsistent with a meta-analysis of maltreatment (Hein & Monk, 2017). Nevertheless, recent

work with a somewhat comparable sample found that multiple adversities in early childhood, including parental harshness, related to lower amygdala reactivity to threatening faces in adulthood (Gard et al., 2017). Similarly, a broad index of childhood family adversity was associated with reduced amygdala reactivity to faces in adults (Holz et al., 2017). Given findings of both hypo- and hyperactivation of the amygdala following early adversity, it is possible that moderate amygdala reactivity may be optimal. Additionally, our sample, as well as those studied by Gard and colleagues (2017) and Holz and colleagues (2017) were all at higher risk of experiencing chronic forms of early adversity. As with literature examining the influence of early adversity on cortisol reactivity, it is possible that exposure to more short-term or isolated forms of childhood stress may be associated with increased stress reactivity, whereas sustained early adversity may be associated with blunted stress response (Fries, Hesse, Hellhammer & Hellhammer, 2005; Hannibal & Bishop, 2014). In order to determine whether divergent findings on the associations of early adversity and amygdala reactivity are due to timing or chronicity of adversity, further work in diverse samples is necessary.

The finding that social deprivation predicted reduced right nucleus accumbens to happy faces is consistent with work showing that emotional neglect was linked to decreased ventral striatum activation to monetary rewards (Hanson et al., 2015). Hanson and colleagues also found that greater decreases in ventral striatum reactivity across two time points predicted greater depression at the second timepoint (Hanson et al., 2015). We did not find an association with concurrent internalizing psychopathology; further, our finding that social deprivation predicted reduced nucleus accumbens activation held after adjusting for internalizing psychopathology. It will be important to follow our sample longitudinally to see if nucleus accumbens reactivity at this wave, or changes between this wave and a future wave, predict internalizing psychopathology. Another possibility is that reduced nucleus accumbens reactivity is associated

with social deprivation, but this reduced reactivity is inconsistently related to internalizing disorders. Research evaluating the influence of social deprivation on connectivity with prefrontal cortical areas may be particularly helpful in understanding the links between social deprivation and reward reactivity.

Despite some prior work (e.g., Hanson et al., 2015; Gard et al., 2017), we did not find evidence that alterations in threat- and social-reward brain function mediate associations between violence exposure, social deprivation, and adolescent internalizing psychopathology. Further, adjusting for internalizing psychopathology did not impact the associations of violence exposure and social deprivation with brain reactivity. This may be for a number of reasons. Psychopathology rates are relatively low in this sample; 16.1% of U.S. adolescents ages 15-17 had a major depressive episode in the last year (NIMH, 2016), whereas 8.3% of our sample had a major depressive episode in the last six months and 12.2% had a major depressive episode in their lifetimes. Many in our sample are from low-income families, which is associated with a number of stressors that are in turn associated with psychopathology, so a low internalizing psychopathology rate for this sample is surprising. Our sample may be resilient in the domain of mental health; further work will evaluate whether there are markers of resilience to dimensions of early adversity. Additionally, psychopathology rates may change as participants enter adulthood; continuing to follow them during this developmental stage is important.

The current study had the following limitations. Due to the population-based sampling methodology used, as opposed to using convenience samples selected for their ability to participate in neuroimaging data collection, a significant portion of our participants were ineligible to participate in fMRI scanning for reasons such as having braces and being too large to comfortably fit in an fMRI scanner (Hein et al., 2018). Despite this, our sample size was significantly greater than many neuroimaging studies and had substantial representation of

African-American adolescents and adolescents from families living in low-income contexts, portions of the population that are often underrepresented in neuroimaging research (Falk et al., 2013). A second limitation is that our study is correlational, and therefore, unlike randomized control trials (e.g., Bucharest Early Intervention Project), it is not possible to identify causal variables. Importantly, the present study improved upon previous research using dimensional approaches to study early adversity in several ways: (1) we used propsective longitudinal measures of exposure to specific forms of adversity; (2) as stated above, we used a well-sampled group of participants; and (3) we used multi-method, multi-informant measures of adolescent depression and anxiety. Additionally, by controlling for adolescent life events, we demonstrated that adversities in childhood exert influence on adolescent threat- and social reward-related brain function that are separate from associations with continued life stress.

In conclusion, two dimensions of early adversity – violence exposure and social deprivation – predicted adolescent amygdala and nucleus accumbens reactivity, respectively, in a large, well-sampled cohort of adolescents. That dimensions of adversity were parseable and predicted different alterations in brain reactivity suggests that qualitatively different forms of early adversity impact different regions of the brain and should be considered separately when evaluating the mechanisms linking early adversity to later mental health outcomes. By evaluating dimensions of early adversity using prospective longitudinal data with a well-sampled cohort, this study provides a key step towards understanding the neural mechanisms linking early adversity to later socioemotional function.

Contrast	Side	Negative effect of violence exposure, t(160)	p-value (FWE)	X	Y	Z
Fear1 > Fear2	L					
Fear1 > Fear2	R					
Angry1 > Angry2	L					
Angry1 > Angry2	R	3.36	0.012	34	4	-20
		3.09	0.024	34	0	-20
		2.88	0.043	34	4	-26

Table 3.1. Increased violence exposure predicts right amygdala habituation to angry faces.

Note: FWE correction is based on structurally-defined regions of interest. Fear 1 > Fear 2 refers to contrasting neural response to fearful faces in the first and second halves of the task; FWE = family-wise error; coordinates are in MNI space.

Contrast	Side	Negative effect of violence exposure, t(161)	p-value (FWE)	X	Y	Z
Fear > Baseline	L					
Fear > Baseline	R					
Angry > Baseline	L	2.90	0.04	-22	2	-18
Angry > Baseline	R					

Table 3.2. Increased violence exposure predicts reduced left amygdala activation to angry faces.

Note: FWE correction is based on structurally-defined amygdala regions of interest. FWE = family-wise error; coordinates are in MNI space.

Contrast	Side	Negative effect of social deprivation, t(161)	p-value (FWE)	X	Y	Z
Happy > Baseline	L	2.52	0.037	-14	2	-12
Happy > Baseline	R	2.97	0.016	16	6	-14

Table 3.3. Social deprivation predicts reduced left and right nucleus accumbens activation to happy faces.

Note: FWE correction is based on structurally-defined nucleus accumbens regions of interest. FWE = family-wise error; coordinates are in MNI space. Only right side survives correction for multiple comparisons.

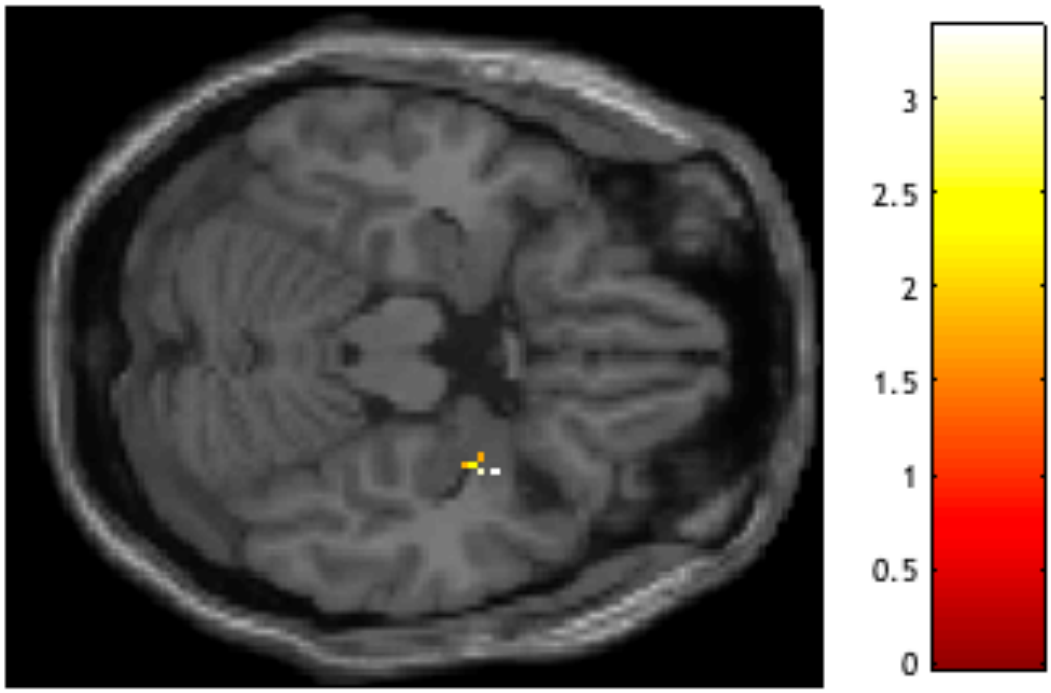

Figure 3.1. Negative relation between violence exposure and right amygdala habituation to angry faces.

Peak t(160)=3.36, *p*=0.012, XYZ=34, 4, -20. Violence exposure, social deprivation, the interaction of violence exposure and social deprivation, and gender were entered as regressors in a multiple regression analysis in SPM12. Finding visualized in SPM with a p <0.05 uncorrected threshold.

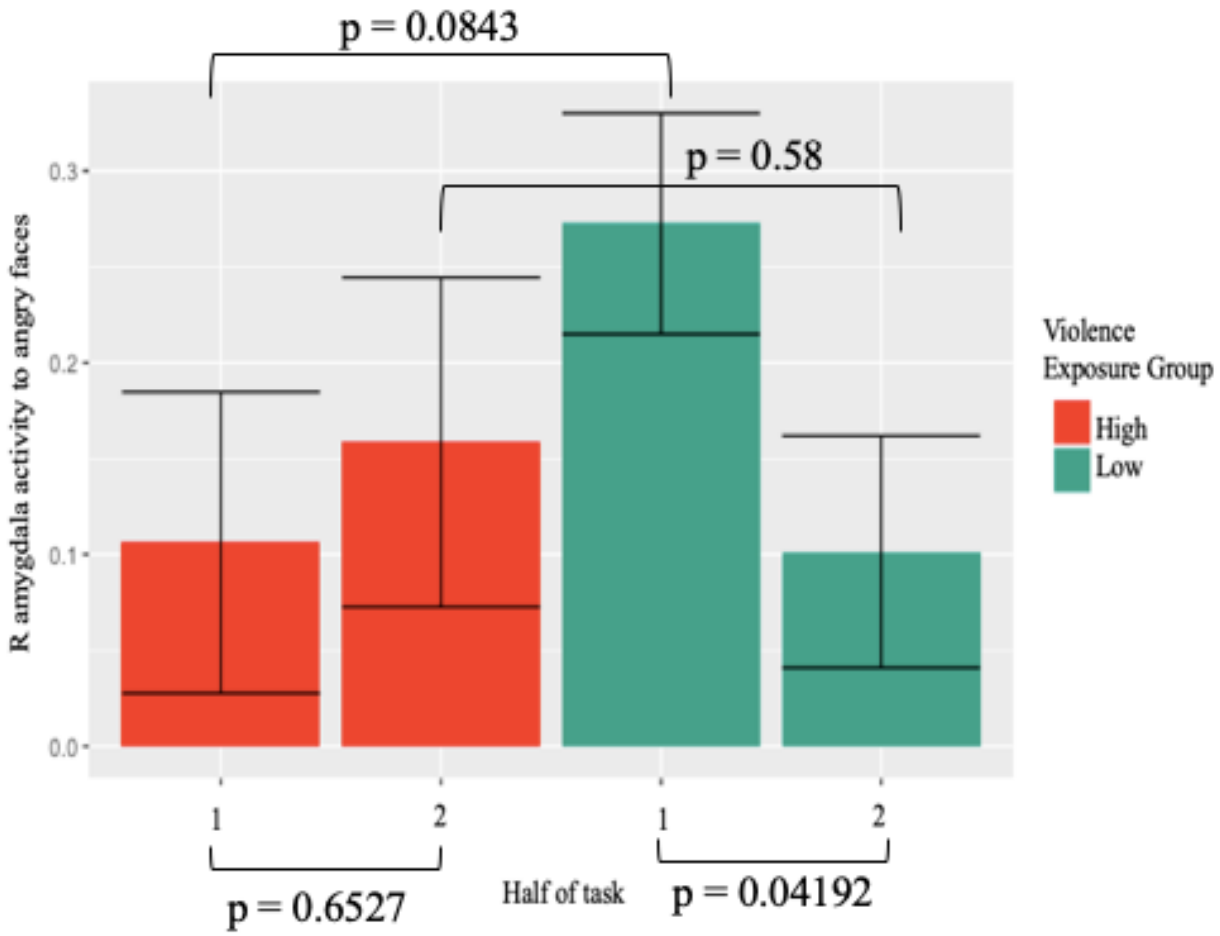

Figure 3.2. Right amygdala habituation to angry faces in individuals with high and low violence exposure.

In a confirmatory data visualization in RStudio, participants high (above the mean) on violence exposure demonstrate less right amygdala habituation to angry faces than participants low (below the mean) on violence exposure. T-tests were used to compare activation between first and second halves of the task within groups, and to compare activation within a half between groups.

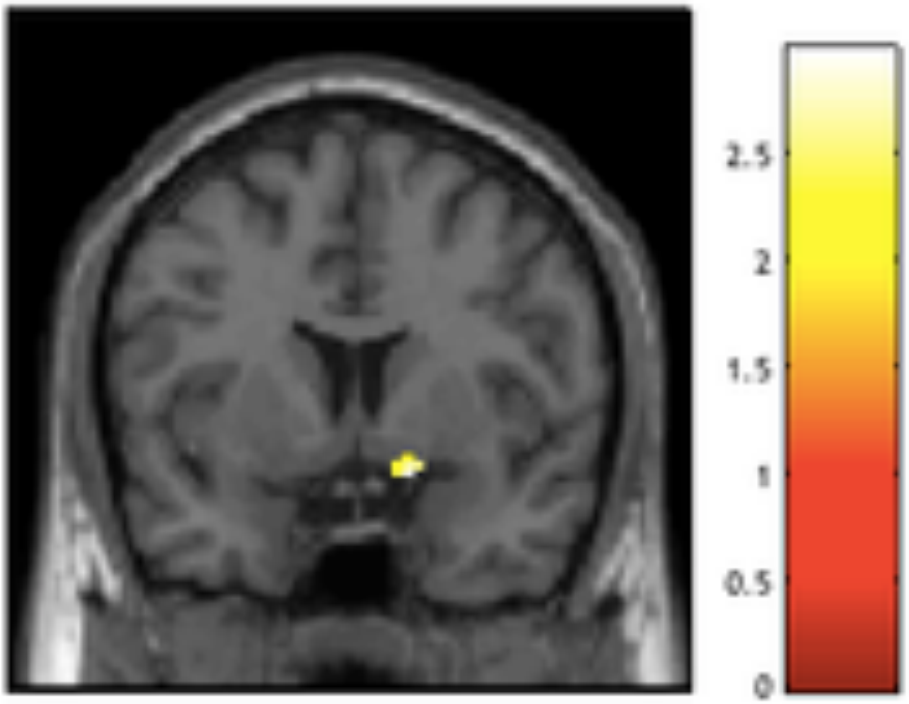

Figure 3.3. Negative relation between social deprivation and right nucleus accumbens activation to happy faces.

Peak t(161)=2.97, *p*=0.016, XYZ=16, 6, -14. Violence exposure, social deprivation, the interaction of violence exposure and social deprivation, and gender were entered as regressors in a multiple regression analysis in SPM12. Finding visualized in SPM with a p <0.05 uncorrected threshold.

Appendix

S1. Participant Recruitment.

Participants in the age 15 wave of the Fragile Families and Child Wellbeing Study (FFCWS) were asked if they were willing to be contacted by members of the Study of Adolescent Neural Development (SAND) team regarding participation in this follow-up study. There were 425 families in the original Detroit and Toledo subsamples of FFCWS; all families from these sites that expressed interest in being contacted by the SAND study were contacted. To increase the number of participants, 34 families from the Chicago subsample were also contacted. In total, 459 FFCWS families were contacted, and 237 of these families participated in SAND data collection.

Of the 237 adolescents who participated in SAND data collection, 167 had useable fMRI faces task data (Table S1.2 and Figure S1.1). Participants with useable fMRI data did not differ on violence exposure, Welch's $t(158.08)=-1.5915$, $p=0.1135$, social deprivation, Welch's $t(135.01)=-0.75298$, $p=0.4528$, latent internalizing factor score, Welch's $t(149.04)=-0.60688$, $p=0.5499$, or gender, $\chi 2(1)=0.55978$, $p=0.4544$, from participants who did not.

Measure	fMRI Sample Count (%), N = 167	Full Sample Count (%), N = 237
Gender		
Female	90(53.9%)	124(52.3%)
Male	77(46.1%)	113(47.7%)
Race		
Black / African-American	117(70.1%)	170(71.7%)
White / Caucasian	24(14.4%)	34(14.3%)
Asian	2(1.2%)	2(0.8%)
Native American	1(0.6%)	1(0.4%)
Multiracial	12(7.2%)	16(6.8%)
Other	1(0.6%)	1(0.4%)
Missing	10(6.0%)	13(5.5%)
Ethnicity		
Hispanic	12(7.2%)	16(6.8%)
Not Hispanic	155(92.8%)	221(93.2%)

Table 3.4. Participant demographics.

	Number of Subjects
Original Sample	237
fMRI analyses attrition	
Did not attempt MRI scan	28
Incomplete fMRI scan	4
fMRI scan quality issues (e.g., image distortion)	11
Low (<70%) amygdala coverage (left or right)	4
Low (<70%) accuracy on faces task	18
Alternate task version	2
Activation outlier	1
Autism spectrum disorder	2
Total included in activation analyses	167
Habituation analyses attrition	
Habituation outlier	2
Total included in habituation analyses	165

Table 3.5. Sample attrition.

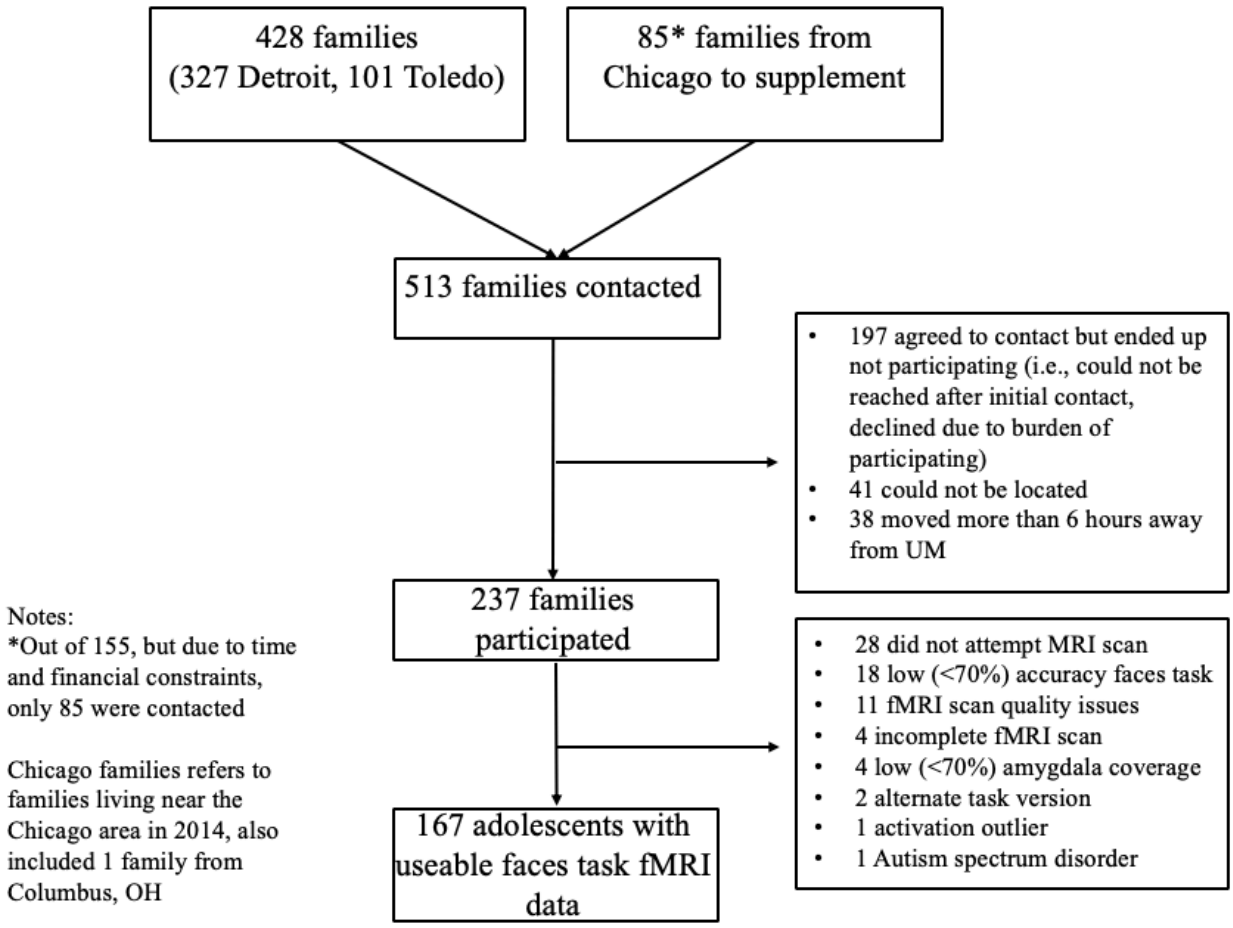

Figure 3.4. Participant recruitment.

S2. Violence Exposure and Social Deprivation Composite Score Measures.

Child Abuse

Child abuse was measured using subscales of the Parent-Child Conflict Tactics Scale (CTS-PC; Straus, Hamby, Finklehor, Moore, & Runyan, 1998). The CTS-PC measured acts of child abuse that occurred in the year prior to the interview. Physical abuse was measured with five items, including whether the parent had "hit him/her on the bottom with something like a belt, hairbrush, or stick, or some other hard object", and "shook him/her". Emotional abuse was measured with five items, including whether the parent had "sworn or cursed at" or "called him/her dumb or lazy or some other name like that". To calculate the degree of abuse, we

summed items that comprised the physical and emotional abuse subscales. Previous studies have used similar items to approximate child abuse in this sample; while they do not reflect legal thresholds for child maltreatment, they conceptually align with maltreatment subtypes (Font & Berger, 2015; Hunt, Slack, & Berger, 2017).

Intimate Partner Violence

Items for intimate partner violence were selected based on a prior study of early adverse childhood experiences (ACEs) in this sample (Hunt et al., 2017). Mothers were asked to report on any physical, emotional, or sexual intimate partner violence inflicted by the target child's biological father or a current romantic partner. Physical violence was measured with two items: "he slapped or kicked you" and "he hit you with his fist or a dangerous object". Emotional violence was measured with three items, including "he tried to isolate you from family and friends" and "he tried to prevent you from going to work and /or school". Sexual violence was measured with one item: "he tried to make you have sex or do sexual things you didn't want to do". To calculate the degree of intimate partner violence, we summed items that comprised the physical, emotional and sexual intimate partner violence subscales. If the target child did not live with the mother at least half of the time for a given wave, intimate partner violence data for this wave was coded as missing.

Community Violence

Items for community violence were selected based on a prior study of community violence exposure in this sample (Zhang & Anderson, 2010) and measured exposure to community violence in the year prior to the interview. These items asked respondents about experiencing or witness or being victims of out-of-family violence in the past year. To calculate the degree of community violence exposure, we summed items that indexed witnessing or being a victim of the following types of violence: beatings; attacks with a weapon; shootings; and

killings (for killings only witnessing was asked). For age 9, the FFCWS did not include victimization or witnessing killing items, so only non-killing witnessing items were included.

Child Neglect

Child neglect was measured subscales of the Parent-Child Conflict Tactics Scale (CTS-PC; Straus et al., 1998). The CTS-PC measured acts of child neglect that occurred in the year prior to the interview. Physical neglect was measured using four items, including asking whether the parent was ever "not able to make sure your child got the food he/she needed" and "so drunk or high that you had a problem taking care of your child". Emotional neglect was measured with a single item, which asked whether the parent had been so caught up with their own problems that they were not able to show love to the child. To calculate the degree of neglect, we summed items that comprised the physical and emotional neglect subscales. Previous studies have used similar items to approximate child neglect in this sample; while they do not reflect legal thresholds for child maltreatment, they conceptually align with maltreatment subtypes (Font & Berger, 2015; Hunt et al., 2017).

Romantic Partner Support

Partner support items were selected based on a prior study of stress, social support, and depression in this sample (Manuel, Martinson, Bledsoe-Mansori, & Bellamy, 2012). Mothers were asked to report on the relationship quality between themselves and the target child's birth father or current partner. If the target child did not live with the mother for at least half the time for a given wave, the romantic partner support data was coded as missing for this wave.

Neighborhood Social Cohesion

Neighborhood social cohesion items were selected based on a prior study of neighborhood cohesion and adolescent mental health (Donnelly et al., 2016), and were adapted from earlier neighborhood research for FFCWS (Morenoff, Sampson, & Raudenbush, 2001).

Calculating Violence Exposure and Social Deprivation Composite Scores

We created composite scores using averaging (Song, Lin, Ward, & Fine, 2013) within a dimension, and then divided by the number of experiences within a dimension each participant had data for, maximizing sample size diversity by minimizing drop out due to missing data at any given wave. We assessed multicollinearity of violence exposure and social deprivation using variance inflation factor (VIF). We centered violence exposure and social deprivation scores and created an interaction term of the two variables.

Appendix S3. Neuroimaging acquisition, preprocessing, and first level analyses.

fMRI data acquisition

fMRI data were collected with a GE Discovery MR750 3T MRI scanner with an 8-channel head coil. We collected functional T2*-weighted BOLD images with a gradient echo spiral sequence (TR=2000ms, TE=30ms, contiguous 3 mm axial slices, flip angle=90°, FOV=22cm, voxel size=3.44mm x 3.44 mm x 3mm) aligned with the AC-PC plane.

fMRI preprocessing

Anatomical images were homogeneity-corrected using SPM2, then skull-stripped using the Brain Extraction Tool in FSL (version 5.0.7) (Smith, 2002; Jenkinson, Pechaud, & Smith, 2005). The functional imaging data then had the following preprocessing steps applied: removal of large temporal spikes in k-space data (> 2 std dev), field map correction and image reconstruction using custom code in MATLAB; and slice-timing correction using SPM8.6313 (http://www.fil.ion.ucl.ac.uk/spm/). Functional images were realigned to the AC-PC plane in the mean image. The rest of preprocessing was also done in SPM12.6906, including: coregistering anatomical and functional images; spatially normalizing functional images into MNI space using parameters from segmented (gray and white matter, cerebrospinal fluid, bone, soft tissue, and air,

created using a Tissue Probability Map in SPM12) T1 images; and smoothing functional images with a Gaussian filter set to 8mm FWHM.

fMRI first level analyses

After preprocessing, Artifact Detection Tools (ART) software (http://www.nitrc.org/projects/artifact_detect) identified motion outliers (>2mm movement or 3.5° rotation). Outliers were censored from individual participant models using a single regressor for each outlier volume. Given susceptibility of the amygdala to signal loss, only those participants with a minimum of 70% coverage in the left and right amygdala at a threshold of $p < 1$, as defined by Automated Anatomical Labeling atlas regions of interest (ROIs; Maldjian, Laurienti, Burdette, & Kraft, 2003; Maldjian, Laurienti, & Burdette, 2004; Tzourio-Mazoyer et al., 2002), were included in group-level analyses. To ensure that participants were engaged in the task, only those with accuracy of 70% or greater were included in group analyses. Condition effects were modeled at the individual level, with incorrect trials modeled as a separate condition and excluded from subsequent analyses. To assess habituation, we divided the task in half and a separate regressor for each emotion (fearful, happy, sad, neutral, and angry) and half of the task (1^{st} half, 2^{nd} half) was created, yielding 10 regressors of interest (e.g., early and late fearful).

Appendix S4. Adolescent Internalizing Disorders Latent Variable Measures.

Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime (K-SADS-PL)

Anxiety and depression symptoms were determined with the K-SADS-PL (Kaufman et al., 1997). A trained clinical assessor (psychology doctoral student or post-baccalaureate staff) administered the semi-structured interview to the target child and caregiver individually. Assessors were trained by two licensed clinical psychologists (authors NLD, LWH) with 25+ years combined experience with the K-SADS. Training included practice interviews and live supervision of interviews with families. The interview arrived at initial DSM-V diagnoses and

symptom counts, which were then reviewed in case conference with the assessment team and licensed clinical psychologists. For anxiety disorder symptoms, we combined current symptom counts for generalized anxiety disorder (GAD), specific phobia, and social anxiety disorder (social phobia). For depressive disorder symptoms, we used current symptom counts of major depressive disorder (MDD) or persistent depressive disorder (PDD).

Mood and Feelings Questionnaire (MFQ)

Adolescent depression was also assessed using the MFQ (Angold & Costello, 1987), a 34-item measure that is intended for child and adolescents to self-report depressive symptoms. Both the target child and caregiver reported on the target child's feelings over the two weeks prior to the interview. Separate total MFQ scores were calculated for each reporter.

Screen for Child Anxiety Related Emotional Disorders (SCARED)

Adolescent anxiety was also assessed using SCARED (Birmaher et al., 1997), a 38-item measure that is used for child and parent self-report of child anxiety symptoms. Both the target child and caregiver reported on the target child's behaviors over the three months prior to the interview. Separate total SCARED scores were calculated for each reporter.

Children's Depression Inventory (CDI)

Adolescent depression was also assessed using the Children's Depression Inventory (CDI) (Kovacs & Beck, 1977), a 27-item measure that is used for child self-report of child depression symptoms. The target child reported on their own behaviors over the two weeks prior to the interview, and the items were summed within a reporter to create a total CDI score for the target child.

Appendix S5. Adolescent Internalizing Disorders Rates.

Diagnosis	Past Count (%)	Current Count (%)
MDD	28(12.2%)	19(8.3%)
MDD-NOS	7(3.0%)	2(0.9%)
PDD	7(3.0%)	4(1.7%)
PDD-NOS	1(0.4%)	1(0.4%)
Social Phobia	15(6.5%)	15(6.5%)
Specific Phobia	6(2.6%)	6 (2.6%)
GAD	5(2.2%)	5(2.2%)
GAD-NOS	2(0.9%)	2(0.9%)
Anxiety-NOS	5(2.2%)	3(1.3%)

Table 3.6. Internalizing psychopathology past and current diagnoses in the full sample (N=237). MDD = major depressive disorder; PDD = persistent depressive disorder (dysthymia); GAD = generalized anxiety disorder; NOS = not otherwise specified.

Appendix S6. Adolescent Internalizing Disorders Factor Analysis.

Factor loadings and fit indices were compared to determine the final models of internalizing disorders in adolescence. Good fit indices used for model selection were a nonsignificant χ^2 p-value, comparative fit index (CFI) > 0.95, Tucker-Lewis index (TLI) > 0.95, and root mean square error of approximation (RMSEA) < 0.06 (Hu & Bentler, 1999). Maximum likelihood robust (MLR) estimation was used due to continuous indicators and analyses were carried out under conditions of full information maximum likelihood (FIML). The final two-factor (anxiety and depression) and one-factor (internalizing) solutions were compared by using a Satorra-Bentler χ^2 difference test. For all factor analyses, indicators from the same reporter (e.g., all child report measures) were correlated.

In order to derive the best estimates (using adolescent and parent report on both questionnaires and interviews) of anxiety and depression in adolescence, well-fitting factors were created separately. The best fitting one-factor model of depression had a χ^2 of 7.181 (p = 0.304), a CFI of 0.994, a TLI of 0.984, and a RMSEA of 0.029. The depression factor included K-

SADS-PL current major depressive disorder symptom count, K-SADS-PL current persistent depressive disorder symptom count, child report MFQ total score, caregiver report MFQ total score, child report CDI total score, and caregiver report CDI total score. All factor loadings were significant ($p < 0.05$), except for K-SADS-PL current persistent depressive disorder symptom count, which was trending ($p = 0.081$). The best fitting one-factor model of anxiety had a χ^2 of 0.213 ($p = 0.644$), a CFI of 1.000, a TLI of 1.366, and a RMSEA of 0.000. The anxiety factor included K-SADS-PL current GAD symptom count, K-SADS-PL current social phobia symptom count, child report total SCARED score, and parent report total SCARED score. The factor loadings for K-SADS-PL current GAD and social phobia symptom counts were significant, but the factor loadings for child and parent report total SCARED scores were not. A two-factor model comprised of the best fitting depression and anxiety factors described above, plus K-SADS-PL current specific phobia symptom count added to the anxiety factor, indicated that depression and anxiety were correlated greater than one, and this was driven by a high correlation between child report MFQ total score and child report SCARED total score ($r = 0.995$, $p < 0.001$). When child report MFQ total score was removed, the two-factor model had acceptable fit, with a χ^2 of 317.250 ($p = 0.000$), a CFI of 0.965, a TLI of 0.920, a RMSEA of 0.045. However, the factor loading for K-SADS-PL current persistent depressive disorder symptom count dropped to nonsignificance and the factor loading for parent report CDI total score dropped to trending for the depression factor. Further, the factor loading for K-SADS-PL current social phobia symptom count dropped to trending for the anxiety factor.

The one-factor model of internalizing contained all indicators used in the two-factor model just described. This model also had acceptable fit, with a χ^2 of 38.558 ($p = 0.011$), a CFI of 0.936, a TLI of 0.862, and a RMSEA of 0.059. The factor loadings were significant ($p < 0.05$) for all indicators except for K-SADS-PL current persistent depressive disorder symptom count (p

= 0.140), parent report CDI total score (p = 0.069), K-SADS-PL current GAD symptom count (p = 0.114), K-SADS-PL current social phobia symptom count (p = 0.182), and K-SADS-PL current specific phobia symptom count (p = 0.0598). A Satorra-Bentler χ^2 difference test indicated that the two-factor model was trending (p = 0.07237) towards being a better fit than the one-factor model. Bayesian Information Criterion (BIC) was also used to compare the two-factor (BIC = 11212.670) and one-factor (11215.887) models. Since the Satorra-Bentler χ^2 difference test was trending and the BIC for the two models were within 10 of each other, we concluded that the two-factor model was not a better fit than the one factor model (Kass & Rafferty, 1995), and therefore went with the most parsimonious model to evaluate internalizing psychopathology in subsequent analyses.

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Chapter 4 : Conclusion

Summary

As discussed in the General Introduction (Chapter 1), there is an urgent public health need to better understand the neural mechanisms linking early adversity and adolescent socioemotional function. Two studies evaluating the neural bases of socioemotional development and how these neural mechanisms may link childhood adversity to later internalizing disorders in adolescence were offered as examples of research that may help to fill this important gap. The first study (Chapter 2) characterized how structural connectivity of the uncinate fasciculus was related to amygdala habituation. In this chapter, I showed that left uncinate fasciculus fractional anisotropy was associated with left amygdala habituation to fearful faces, suggesting that increased structural connectivity of the uncinate fasciculus may facilitate amygdala regulation. Further, I showed that pubertal status moderated this relation, such that the association was stronger in those who were less mature. This suggested that uncinate fasciculus integrity may be particularly important for emotion regulation in early puberty.

The second study (Chapter 3) explored the unique effects of childhood violence exposure and victimization on adolescent threat-related brain function and childhood social deprivation on adolescent reward-related brain function. In this chapter, I determined that it is possible to parse two qualitatively different but often co-occurring dimensions of adversity: violence exposure and victimization and social deprivation. Further, I showed that violence exposure and victimization uniquely predicted decreased amygdala habituation and activation to threatening stimuli, whereas social deprivation uniquely predicted decreased nucleus accumbens activation to

socially rewarding stimuli. This suggested that childhood violence exposure and victimization and social deprivation are two separable dimensions of early poverty-related adversity that exert unique effects on adolescent brain function.

Taken together, the two studies illuminate the development of two neural circuits essential for socioemotional function, one involved in threat processing and the other in social reward processing, and how these circuits are altered by early adversity. Study 1 (Chapter 2) highlights the importance of structural connectivity with prefrontal cortical regions for amygdala habituation, which facilitates adaptive levels of arousal to emotional stimuli. Study 2 (Chapter 3) demonstrates that violence exposure predicts blunted amygdala response to threatening stimuli – specifically, it is associated with reduced amygdala habituation and activation. It will be important for future work to evaluate whether violence exposure impacts the structural connectivity with the prefrontal cortex explored in Study 1. Study 2 also found that social deprivation predicts reduced nucleus accumbens reactivity to social rewarding stimuli. Importantly, study 2 did not find evidence that alterations in threat – and social reward-related reactivity associated with violence exposure and social deprivation were also associated with internalizing psychopathology.

Much work remains to be done to fully understand the mechanisms that link early poverty-related adversity to later health and well-being outcomes, as well as sources and markers of resilience in the face of early poverty-related adversity.

Future Directions

Developmental Timing of Environmental Influences

Developmental neuroscience suggests that environmental influences may differ based on the developmental timing of when they occurred. As discussed in study 1 (Chapter 2), the brain undergoes a protracted development; the amygdala experiences most development during

childhood (Giedd et al., 1996; Mosconi et al., 2009; Schumann et al., 2004; Tottenham & Sheridan, 2009), whereas the prefrontal cortex experiences a protracted development, continuing to mature through adolescence and into early adulthood (Casey, Jones, & Hare, 2008; Gogtay et al., 2004; Sowell et al., 1999; Sowell et al., 2003). Therefore, one may hypothesize that the amygdala is most susceptible to the effects of early life adversity, whereas prefrontal cortical regions may continue to be susceptible to adversity into the third decade of life and beyond (Pechtel & Pizzagalli, 2011). An important future direction for research will be to evaluate whether the effects of different forms of early adversity vary by the age at which the adversity was experienced.

Functional Connectivity

As discussed in the General Introduction (Chapter 1), emotion and reward processing are facilitated by networks of brain regions as opposed to single structures such as the amygdala or nucleus accumbens. The prefrontal cortex, especially the ventral prefrontal cortex, experiences bidirectional communication with the amygdala to enable socioemotional function. Connectivity between the amygdala and ventral prefrontal cortex has been implicated in internalizing psychopathology such as anxiety. Study 1 (Chapter 2) found that structural connectivity between the amygdala and ventral prefrontal cortex was associated with amygdala habituation; it will be important to evaluate how dimensions of early adversity such as violence exposure and social deprivation impact this structural connectivity. Study 2 (Chapter 3) revealed that violence exposure uniquely predicted reduced amygdala activation to angry faces, which was inconsistent with my hypotheses. One possibility is that this reduced activation is a function of altered neural function and/or connectivity throughout emotion processing neural circuitry. Future functional connectivity research should evaluate the effects of violence exposure and social deprivation in

order to deepen understanding of how these early adverse experiences impact all aspects of emotion processing neural circuitry.

The prefrontal cortex is also implicated in reward processing. As discussed in the General Introduction (Chapter 1), the orbitofrontal cortex has been purported to be a nexus in reward circuitry, both receiving sensory information and sending out input to motor and limbic areas (Berridge & Kringelbach, 2008; Schoenbaum, Roesch, & Stalnaker, 2006). Study 2 (Chapter 3) found that social deprivation uniquely predicted reduced nucleus accumbens activation to happy faces. Future structural and functional connectivity research evaluating the influence of social deprivation on reward processing circuitry would help illuminate the mechanisms linking this dimension of early adversity with mental health and well-being outcomes.

Larger Sample Sizes

In response to increased awareness of underpowered neuroimaging studies and the reproducibility crisis in psychology, there have been a number of longitudinal neuroimaging samples with increased sample size, such as Pitt Mother and Child Project (N = 310) and the Study of Adolescent Neural Development (N = 237), featured in this dissertation. However, to address sophisticated mechanistic questions about the nature of the association between early adversity and later mental health, even larger sample sizes will be required. In the General Introduction (Chapter 1), I discussed the promise of studying brain function as a mediator for environmental influence on internalizing disorders in adolescence. Although structural equation modeling has been successfully used by some research groups with similar sample sizes to address questions of mediation (e.g., Hanson et al., 2015; Gard et al., 2017), I did not find support for alterations in threat- and social reward-related brain function mediating associations between early adversity and adolescent internalizing psychopathology in study 2 (Chapter 3). One possibility is that I was underpowered to do so. Larger longitudinal neuroimaging studies

such as the Adolescent Brain Cognitive Development (ABCD) Study, which will invite over 10,000 children across 21 research sites from around the country to participate, are better suited to address questions of neural mediation. In order to fully understand the mechanisms that link early adversity to later health and well-being, sophisticated statistical analyses enabled by larger data sets will be essential.

Mechanisms of Resilience

Despite extensive literature linking early adversity, as well as the amygdala and nucleus accumbens function explored in study 2 (Chapter 3), to psychopathology including anxiety and depression, I did not find support for alterations in threat- and social reward-related brain function mediating associations between early adversity and adolescent internalizing psychopathology. Further, adjusting for internalizing psychopathology did not influence my findings. This may be due to relatively low rates of psychopathology in the SAND sample; the rate of depression in our sample was approximately one-half to two-thirds of the rate of depression amongst adolescents in the United States (NIMH, 2016). Given that many of the adolescents in the SAND sample come from low-income contexts, where they are more likely to experience stressors that are associated with psychopathology, these findings were surprising. This cohort of adolescents may be particularly resilient in the domain of mental health. Resilience, conceptualized as positive outcomes in spite of threats to development, is a common phenomenon theorized to arise from normative function of systems that allow for human adaptation to the environment (Masten, 2001). Brain development in humans exhibits a protracted development, from the prenatal period into the third decade of life (Giedd et al., 1999), allowing individuals to adapt to their surrounding environment. Therefore, the brain is one of the central systems for adaptation (McEwen, 2016) and is likely involved in resilience following early adversity. There are several factors believed to contribute to resilience, including

attributes of individuals themselves, aspects of an individual's family, and characteristics of the social environment, and these factors interact with each other (Luthar et al., 2000). Brain development is likely a reflection of the interactions of these factors, as it adapts to the environment to facilitate survival in the context (physical, social, emotional) in which the individual is living. Despite the role of brain development in resilience processes and calls for improving our understanding of neural correlates of resilience, fMRI studies of youth resilience are scarce (Burt et al., 2016). Further work in the SAND sample as well as other samples should evaluate whether there are neural markers of resilience to early adversities such as violence exposure and social deprivation.

Implications for Prevention and Intervention Work

The ultimate goal of work exploring neural mechanisms linking early poverty-related adversity with later health and well-being outcomes is to inform prevention and intervention approaches to help improve outcomes for children and families. As discussed in the General Introduction (Chapter 1), a neuroscience approach can contribute to policy and practice in several ways. First, it can reveal differences between individuals with varying levels of adversity exposure that may not be apparent with more traditional behavioral measures (Farah, 2018). In the second study (Chapter 3), I found that childhood violence exposure and social deprivation exerted unique effects on adolescent brain function. However, when looking only at the behavioral measures in this study, I found that neither social deprivation nor violence exposure predicted increased internalizing psychopathology. Without neuroimaging data, I would not have known about the effects of violence exposure on threat processing and the effects of social deprivation on social reward processing. Given the importance of threat processing to our everyday interactions, it is likely that alterations in threat processing have significant impacts on the lived experiences of individuals with a history of violence exposure, regardless of whether it

manifests in internalizing psychopathology or not. Additionally, these alterations in threat processing in adolescence may predispose an individual to internalizing psychopathology later in life. The results of the second study lend support to the idea that neuroimaging could someday be used in identification of individuals impacted by early adversity or to evaluate programs and policies to aid those impacted by early adversity. However, the high cost of neuroimaging combined with the difficulties of using neural markers discovered on a group level for individual level identification makes this an unlikely possibility in the near future.

A second way that neuroscience can contribute to policy and practice is by contributing converging evidence to complement behavioral research used to support decision making (Farah, 2018). If other studies employing dimensional approaches similar to those used in this dissertation also find that dimensions of early adversity exert unique influences on behavioral, mental health, or well-being outcomes, this provides further support that policies and programs aiming to address consequences of early adversity should consider dimensions of experience. For example, analyses evaluating the effectiveness of a policy or program should consider the specific adversities an individual has experienced and the dimensions that these adversities fall into.

A third policy implication of the neuroimaging research presented in this dissertation is that it highlights the importance of funding neuroimaging work using large, diverse samples. In the second study (Chapter 3), I found that violence exposure predicted decreased amygdala reactivity, contrary to the majority of neuroimaging work looking at the impacts of early adversity on amygdala activation. However, the direction of this finding is consistent with other work in more diverse samples. In order for research findings to be as applicable to the general population as possible, it will be critical for funding agencies to focus on supporting research using well-sampled, diverse cohorts above research utilizing convenience samples.

Outside of the neuroimaging data presented in this dissertation, the development of violence exposure and social deprivation measures for study 2 (Chapter 3) also has implications for applied and policy work. In this study, I was able to create measures of two related but distinct dimensions of early adversity: violence exposure and social deprivation. Further, these measures had unique effects on adolescent brain function. This suggests that further work examining early adversity, particularly research to develop new interventions or evaluations of existing programs and policies, may benefit from considering dimensions similar to violence exposure and social deprivation. Considering these dimensions separately may clarify which programs work for whom, ultimately resulting in better outcomes for children and families facing adversity.

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