AMYGDALA CONNECTIVITY AT REST FOLLOWING TWO FORMS OF EARLY LIFE STRESS

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Dedication

To my family:

To my mom, whose love and support has been the foundation of everything.

To my brother, for his friendship and comradery.

To my husband, the best partner I could ever wish for, who brings joy and adventure to my life.

Finally, in memory of my dad, whose love for learning was contagious and who believed in me from the very beginning.

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CHAPTER 3: Study 2

Individual differences in experiences of childhood maltreatment and resilience to adversity predict resting state amygdala connectivity

CHAPTER 1: General Introduction

Early life stress (ELS), including experiences of abuse and neglect, poses a threat to the typical trajectory of development. Early adversity has been linked to long-term perturbations to both mental and physical health (Anda et al., 2006), with a heightened risk for psychopathology across the lifespan (Cicchetti & Toth, 1995; Kim & Cicchetti, 2010). The societal and economic costs of childhood adversity are great. For instance, the total lifetime financial burden of a single year of new child maltreatment cases in the United States is estimated to be approximately $124 billion, with costs of health care, social services, and productivity losses (Fang, Brown, Florence, & Mercy, 2012). However, the mechanisms through which ELS leads to poor outcomes remain poorly defined.

In infancy, the presence of a caregiver is a species-expected environmental input that is critical for normative development (Tottenham, 2012). Parents provide safety and security to the developing infant, as well as external regulation and buffering from potential environmental stressors (Callaghan, Sullivan, Howell, & Tottenham, 2014; Hostinar, Sullivan, & Gunnar, 2014; Sullivan & Perry, 2015). Interactions between the parent-child dyad are critically important to socioemotional development across the lifespan (Ainsworth, 1979; Bowlby, Ainsworth, & Bretherton, 1992). Disruption to the caregiving relationship is therefore one of the most potent forms of ELS, as it compromises a fundamental component of early development. In cases where the caregiving relationship is absent or even directly harmful to the infant, the developing

system is vulnerable to a host of disturbances both behaviorally and biologically (Cicchetti & Toth, 2005; Esposito & Gunnar, 2014; Tottenham, 2014).

Behaviorally, ELS and disruption to the caregiver relationship is associated with altered emotion processing, perception, and regulation (Kim & Cicchetti, 2010; Pollak, Cicchetti, Hornung, & Reed, 2000; Tottenham et al., 2010). Children who have experienced maltreatment or deprivation are significantly less accurate than typically developing children in the recognition of emotions (Camras et al., 1988; Camras, Grow, & Ribordy, 1983; Tarullo, Bruce, & Gunnar, 2007) and limited evidence indicates that this deficit in persists into adulthood (Young & Widom, 2014). Children who have experienced neglect also show broad deficits in recognizing emotions in facial stimuli, perhaps due to the limited social information available in the home environment (Pollak et al., 2000). In contrast, children who have been physically abused have a response bias towards identifying expressions as angry, and are faster to detect anger in subtle stimuli (Pollak et al., 2000; Pollak, Messner, Kistler, & Cohn, 2009; Pollak & Sinha, 2002). As a whole, the extant body of literature suggests that disruption in emotion processing is prevalent following ELS, and that these disruptions may be associated with heightened risk for psychopathology (Kim & Cicchetti, 2010).

Animal models have been especially informative to our understanding of the biology of the caregiver relationship (Callaghan et al., 2014). Sullivan and colleagues have probed the influence of caregivers on amygdala development in rodents and found that mothers buffer their pup's fear response (Moriceau & Sullivan, 2006). In typical development, rat pups have a stress-hyporesponsive period during which the pups have

blunted hormonal responses to stress (Rincón-Cortés & Sullivan, 2014). However, in the absence of the mother, rat pups show a mature pattern of fear conditioning and disruption to attachment learning. When rat pups are raised by stressed mothers they also show an atypically early pattern of amygdala-dependent fear learning, which has been linked to later behavioral deficits (Moriceau, Shionoya, Jakubs, & Sullivan, 2009). When raised by neglectful mothers, adult offspring are more fearful, low in dominance, and have heightened stress reactivity (Rincón-Cortés & Sullivan, 2014). These data from animal models show the vital importance of the caregiver relationship in fostering neural circuitry underlying emotion, and highlight developmental vulnerability when the caregiver is absent or harmful.

The behavioral disruptions to emotion and fear processing that have been observed in both humans and animal models following ELS point to vulnerable networks in the brain. One region that has been identified as particularly sensitive to ELS is the amygdala, which is associated with emotion processing and in learning about emotionally relevant stimuli (Davis & Whalen, 2001; LeDoux, 2000; Phelps & LeDoux, 2005). Relative to other regions, the amygdala has early structural maturation (Giedd et al., 1996; Ulfig, Setzer, & Bohl, 2003) and the most rapid period of postnatal growth occurs during the first year of life, although changes continue into late adolescence (Gilmore et al., 2012). Across development the amygdala is responsive to emotional stimuli, particularly in the form of facial expressions (Guyer et al., 2008; Hariri, Mattay, et al., 2002; Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002; Thomas et al., 2001; Whalen

et al., 2004), and is involved in the detection of threat (Bach, Hurlemann, & Dolan, 2015; Öhman, 2005).

During emotion processing, the amygdala does not operate in isolation; the prefrontal cortex (PFC) also plays a critical role in the brain's emotional response. The PFC is a large, highly connected region in the frontal lobe that is involved in complex cognitive processes, including attention, executive function, inhibitory control, memory, and emotion regulation (Miller & Cohen, 2001). The PFC shows protracted development, and is among the last areas of the brain to mature, with both gray and white matter continuing to develop into adolescence and adulthood (Giedd et al., 1999; Gogtay et al., 2004; Sowell et al., 2003). Together, these regions interact to produce and regulate emotional responses. In general, the PFC is thought to exert a regulatory influence over the amygdala, although there are reciprocal communications between the regions. Disruption of this frontolimbic circuitry has been implicated in a number of anxiety and mood disorders (Kim, Gee, Loucks, Davis, & Whalen, 2011). As such, it is an important target in identifying mechanisms through which early adversity is associated with later psychopathology.

Animal models have convincingly demonstrated structural alterations in response to ELS in both the amygdala (Mitra, Jadhav, McEwen, Vyas, & Chattarji, 2005; Vyas, Mitra, Shankaranarayana Rao, & Chattarji, 2002) and PFC (Cook & Wellman, 2004; Pascual & Zamora-León, 2007; Radley, 2005; Radley et al., 2008). Research on the effects of ELS on amygdala structure in humans has revealed mixed results, with some evidence for larger volumes (Mehta et al., 2009; Pechtel, Lyons-Ruth, Anderson, &

Teicher, 2014; Tottenham et al., 2010), but many studies finding no difference in relation to ELS (Chaney et al., 2014; De Bellis et al., 2002; De Brito et al., 2013; Hodel et al., 2015; Liao et al., 2013; Sheridan, Fox, Zeanah, McLaughlin, & Nelson, 2012). On the other hand, structural studies of the PFC have more consensus, with generally smaller prefrontal volumes following ELS (De Bellis et al., 2002; Edmiston et al., 2011; Hanson et al., 2010; Hodel et al., 2015; Tomoda et al., 2009).

Functionally, both the amygdala and PFC have shown altered activation following ELS. Convergent data suggest a hyperactive amygdala response associated with childhood maltreatment and deprivation (Dannlowski et al., 2012; Grant, Cannistraci, Hollon, Gore, & Shelton, 2011; McCrory et al., 2011, 2013; McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015; Tottenham et al., 2011; van Harmelen et al., 2013; White et al., 2012). Although subcortical amygdala activation has been the primary focus of the functional neuroimaging literature on ELS, a handful of studies have reported functional differences in PFC activation in relation to childhood maltreatment (Fonzo et al., 2013; Lim et al., 2015; McLaughlin et al., 2015).

Taken individually, the structure and function of the amygdala and PFC are informative in understanding the effects of early life stress. However, more can be learned from exploring the *interactions* between the amygdala and PFC. The need to understand the relationship between ELS and the development of frontolimbic connectivity is bolstered by evidence of structural alterations to the white matter tracts linking amygdala with the PFC following maltreatment (Hanson, Knodt, Brigidi, & Hariri, 2015) and deprivation (Eluvathingal et al., 2006; Govindan, Behen, Helder,

Makki, & Chugani, 2010; Kumar et al., 2014). These findings, which are derived from diffusion tensor imaging, provide helpful information about the properties of the white matter structure. However, they tell us nothing about the functional interactions between regions or how the regions communicate with each other. Recently, methods of assessing functional connectivity have gained traction as a means to understand how functional brain networks interact and co-activate in real time. Resting state fMRI (rsfMRI), has been used to characterize the strength of neural network cohesion when the brain is not engaged in a specific task. The small extant literature on rsfMRI in the context of ELS suggests that frontolimbic circuitry is indeed among the neural systems impacted by stress, including childhood maltreatment and stressful life events (Herringa et al., 2013; Pagliaccio et al., 2015; Thomason et al., 2015; Van der Werff et al., 2013). However, the extent of disruption to the function of these circuits remains poorly understood.

Outline of Dissertation

The goals of this dissertation are to better understand the impact of ELS on resting state amygdala connectivity which underlies emotion processing and regulation. Data on this topic remain sparse, and to date there is not enough research to evaluate the influence of early life stress on limbic circuitry at different stages of development. The dissertation will examine two forms of ELS (institutional rearing and childhood maltreatment) at different points in development (adolescence and adulthood) to attempt to fill in the current gaps in our knowledge. In addition to probing the main effects of ELS on amygdala circuitry, this dissertation will also explore the effects of individual differences in the experience of adversity and in adaptation following stress.

Study 1: Youth exposed to early deprivation.

One extreme form of ELS can be seen in the case of children internationally adopted from orphanage care. In orphanage settings, the dyadic relationship and species-expected environmental input of attentive caregiving is compromised. The chronic stress and impoverished social experiences of post-institutionalized (PI) children are associated with socioemotional disruption, even after adoption to positive family environments (Colvert et al., 2008). The experience of children adopted from institutional care provides a unique example of ELS. Whereas children who experience chronic poverty or maltreatment are likely to experience stress throughout development, the intense stress experienced by post-institutionalized (PI) children is typically circumscribed to experiences prior to adoption. Following adoption, children are often placed into enriched adoptive homes, with ample resources and personalized attention. Therefore, research on PI children can inform our understanding of early stress, without the added confounds of later adversity. While there is rapid developmental catch-up following adoption (van Ijzendoorn & Juffer, 2006), some domains, including emotion processing, show long-term impairment (Esposito & Gunnar, 2014). In this study, the resting state amygdala connectivity of PI youth (ages 12-14) will be compared to that of children raised with their biological families. Previous studies have shown increased deficits in PI children who experience longer periods of deprivation (Julian, 2013). In our study, the adoptive age (and therefore duration of deprivation) varied within the PI group and will be used as a predictor of individual differences in connectivity. Additionally, differences associated

with anxiety will be explored to identify links between amygdala connectivity and psychopathology.

Study 2: Adults with a history of childhood maltreatment.

Childhood maltreatment is known to exert lasting impacts on mental and physical health outcomes (Dante Cicchetti & Toth, 2005). However, the long term impact of childhood maltreatment on neural circuitry remains poorly understood. To date, only a handful of studies have examined resting state connectivity of the amygdala in adults with a history of childhood maltreatment (Birn, Patriat, Phillips, Germain, & Herringa, 2014; Van der Werff et al., 2013). There has been little work comparing multiple forms of maltreatment (physical abuse, sexual abuse, neglect) to a control group that is well-matched on other potential risk factors, such as socioeconomic status. In the current study, all participants come from a longitudinal study of children from high-risk backgrounds and are well matched on demographic variables, including race and childhood socioeconomic status. Although childhood maltreatment confers greater risk for psychopathology, not all children who are maltreated go on to experience negative outcomes in adulthood. Rather, many individuals are resilient in spite of ELS (Cicchetti, 2013; Luthar, Cicchetti, & Becker, 2015). Therefore, in addition to testing main effects of maltreatment, this dissertation will also explore the neural correlates of resilience. Individuals who are resilient despite early adversity may have unique profiles of neural circuitry that differentiate them from more vulnerable individuals. Understanding how resilient individuals adapt will be an important step in developing targeted interventions that foster resilience in children and adults who have experienced maltreatment.

CHAPTER 2: Study 1

Functional connectivity at rest in post-institutionalized youth: Altered amygdala connectivity with the prefrontal cortex and insula[1]

[1]Ruskin H. Hunt, Amanda S. Hodel, Megan R. Gunnar, Kathleen M. Thomas are listed as coauthors on this publication.

Synopsis

Post-institutionalized (PI) youth experience social deprivation in orphanage care, followed by an enriched post-adoption environment. While PI children show developmental catch-up in many domains affected by orphanage rearing, problems in socioemotional functioning persist, with higher rates of internalizing disorders emerging in adolescence (Hawk & McCall, 2010). The neural structures underlying emotion processing and regulation, namely the amygdala and prefrontal cortex (PFC), show both structural and functional differences following early life stress. However, there is little understanding of how baseline intrinsic connectivity between the amygdala and PFC is impacted by orphanage rearing, because amygdala connectivity at rest has yet to be explored in PI samples. The current study used seed-based amygdala resting state connectivity to evaluate group differences between PI youth and their non-adopted (NA) peers. Compared to the NA group, PI youth had more positive connectivity with two regions in the medial PFC. In contrast, the NA group had greater connectivity between the amygdala and the left insula. Few differences were observed in relation to the duration of deprivation within the PI group, and self-reported anxiety was not significantly associated with resting state connectivity. More longitudinal research is necessary to understand the developmental trajectory of these connections following early life stress.

Introduction

Institutional rearing is an extreme form of early life stress that has the potential to alter a child's developmental trajectory. Children raised in institutional care experience a deviation from typical, species-expected, caregiving (Tottenham, 2012). While orphanages vary widely in quality of care, all are characterized by low caregiver to infant ratios, typically with high instability of care and/or poorly trained staff members (Groze & Ileana, 1996; Gunnar, Bruce, & Grotevant, 2000; Johnson, 2000; Rutter and the ERA Team, 1998). The behavioral sequelae of institutionalization have been well-documented (Gunnar & van Dulmen, 2007), with atypical patterns of physical, cognitive and emotional development across childhood (Camras, 2006; Colvert et al., 2008; Ellis, Fisher, & Zaharie, 2004; Fisher, Ames, Chisholm, & Savoie, 1997; Fries & Pollak, 2004; Hawk & McCall, 2010; Merz, Harlé, Noble, & Mccall, 2016; Merz, McCall, Wright, & Luna, 2013). For many of these domains, longer duration of institutionalization is related to greater disruption (Julian, 2013). Importantly, adoption into families is an effective intervention, mitigating many of the adverse effects of institutional rearing, with developmental catch-up in physical growth, attachment, and school achievement (van Ijzendoorn & Juffer, 2006). However, persistent effects remain, with some sleeper effects emerging over time, including a higher risk for internalizing disorders that are more likely to arise in adolescence (Hawk & McCall, 2010).

One possible explanation for the emergence of psychopathology in early adolescence is stress-induced alterations to brain circuitry underlying cognitive and emotional processing. In particular, the amygdala and the prefrontal cortex are two brain

regions that may be sensitive to effects of early life stress (Tottenham, 2014). The amygdala, a subcortical region involved in the processing of emotions and fear learning (Davis & Whalen, 2001; LeDoux, 2000; Phelps & LeDoux, 2005) develops relatively early, and has a diverse range of cortical and subcortical connections (Saygin et al., 2015). The prefrontal cortex (PFC), a large heterogeneous region, is associated with a wide range of executive functions (Miller & Cohen, 2001). In relation to the amygdala, the PFC serves a regulatory function (Etkin, Egner, & Kalisch, 2011). Amygdala-PFC communication is often thought to be top-down (from the PFC to amygdala), though bottom-up (amygdala to PFC) signaling also occurs (Amaral & Price, 1984; Carmichael & Price, 1995; Ghashghaei, Hilgetag, & Barbas, 2007). Disruptions to frontolimbic circuitry between the amygdala and prefrontal cortex have been implicated in a range of psychiatric and mood disorders, including schizophrenia, depression, bipolar disorder, and anxiety disorders (Bjorkquist, Olsen, Nelson, & Herbener, 2016; Connolly et al., 2017; Hamm et al., 2014; Kim, Gee, et al., 2011; Liu et al., 2014).

Frontolimbic alterations in PI youth

In PI youth, there is evidence of both structural and functional alterations to the frontolimbic system following early life stress. A number of studies have revealed reduced prefrontal volumes in PI children compared to non-adopted peers (Hodel et al., 2015; Mehta et al., 2009; Sheridan, Fox, Zeanah, McLaughlin, & Nelson, 2012). Findings have been more discrepant for the amygdala, with some studies showing increased amygdala volumes (Mehta et al., 2009; Tottenham et al., 2010), and others showing no difference (Sheridan et al., 2012) or even smaller volumes (Hodel et al., 2015). In

addition, there is evidence of disruption to white matter tracts between the amygdala and prefrontal cortex (Eluvathingal et al., 2006; Govindan et al., 2010; Hanson, Adluru, et al., 2013; Kumar et al., 2014), providing further evidence that the connectivity between the two regions is sensitive to stress.

Functional neuroimaging studies have shown increased amygdala activation in PI children, suggesting a heightened sensitivity to threatening stimuli (Maheu et al., 2010; Tottenham et al., 2011). Task-based connectivity studies have reported altered amygdala-PFC connectivity in PI youth during emotion processing (Gee, Gabard-Durnam, et al., 2013; Jedd McKenzie et al., under review) and aversive learning (Silvers et al., 2016) tasks. In comparison to typically developing control children, PI children have been argued to show a more developmentally mature profile of connectivity during an emotional face processing task (Gee, Gabard-Durnam, et al., 2013). Specifically, Gee and colleagues (2013) observed negative mPFC-amygdala task-based connectivity in PI children that was similar to a more mature profile of connectivity previously identified by their group (Gee, Humphreys, et al., 2013). This finding is consistent with the stress acceleration hypothesis (Callaghan & Tottenham, 2016), which posits premature maturation of emotional behaviors and brain circuitry following early stress. Our own research using an emotional face matching task also found altered task-related amygdala-mPFC connectivity (Jedd McKenzie et al., under review). However, in this study, the PI group showed altered connectivity during the non-emotional component of the task, suggesting that differences in connectivity following institutionalization are not limited to emotion processing.

rsfMRI measures of amygdala connectivity

While task-based studies are useful in understanding connectivity in context, they are difficult to compare, since task-demands differ by study and are not necessarily generalizable. One method of avoiding this problem is the use of resting state functional MRI (rsfMRI). Resting state connectivity allows for the investigation of connectivity in the absence of task-demands. Networks identified through rsfMRI are thought to represent intrinsic connectivity at baseline (or crosstalk between regions) and can help to characterize interactions in the absence of an explicit task (Deco, Jirsa, & McIntosh, 2011). Functional connectivity of brain regions at rest can therefore be an important marker of the overall strength or cohesion of a network.

Normative studies of amygdala connectivity using rsfMRI with adults show patterns of both positive and negative connectivity (Roy et al., 2009). Specifically, amygdala signal positively correlates with activity in mPFC (including dorsal and rostral ACC, vmPFC), hippocampus, insula, thalamus, and striatum. In a review of functional amygdala connectivity in adulthood, Kim and colleagues (2011) suggest that the strength of amygdala-mPFC connectivity at rest is indicative of efficient signaling between the two regions. Individual differences in the strength of positive amygdala-PFC connectivity at rest are predictive of adaptive functioning, including decreased anxiety symptoms in adults (Kim, Loucks, et al., 2011). In addition to prefrontal regulation, other regions that positively correlate with amygdala activity at rest may also contribute to the processing of emotion. For instance, the hippocampus is related to emotional memory encoding (Murty, Ritchey, Adcock, & Labar, 2010), and the insula is involved in emotion

perception, interoception, and emotional salience detection (Cauda et al., 2011, 2012; Singer, Critchley, & Preuschoff, 2009). Negative connectivity has been observed between the amygdala and more dorsal and posterior regions of the brain (including dmPFC, superior frontal gyrus, middle frontal gyrus, posterior cingulate cortex and parietal and occipital corticies; Roy et al., 2009). Many of these regions are involved in more cognitive strategies for emotion regulation, such as emotional reappraisal (Buhle et al., 2014; Etkin et al., 2011; Ochsner & Gross, 2005). It is worth noting, however, that there is some disagreement about whether negative connectivity in resting state reflects true anticorrelations in activity between regions or may instead be an artifact of including global signal in the model (Fox, Zhang, Snyder, & Raichle, 2009; Murphy, Birn, Handwerker, Jones, & Bandettini, 2009; Saad et al., 2012). For this reason, valence of connectivity across studies may not be generalizable, depending on the statistical models used in the analysis.

Development of resting state connectivity and early life stress

While developmental studies of resting state connectivity remain sparse, there is evidence of normative developmental change in amygdala connectivity. When compared to adults, children have shown weaker connectivity between the amygdala and both cortical and subcortical regions, including, importantly, the vmPFC (Qin, Young, Supekar, Uddin, & Menon, 2012). In a recent study examining connectivity in participants aged 4-23 (Gabard-Durnam et al., 2014), amygdala connectivity was found to be largely stable across development with the primary network already established by age 4. However, age related changes were observed, whereby amygdala-mPFC

connectivity became more positive with age. Young participants initially showed no significant coupling between the amygdala and mPFC, and positive coupling first emerged after 10 years of age. In contrast, connectivity with parts of the insula and the posterior cingulate became more negative across age. These findings suggest that while much of the amygdala's circuitry shows early maturation, developmental changes continue across the transition from childhood to adolescence, and beyond.

Although task-based data suggest deprivation-related disruption of emotion circuitry, to date, there are no studies of resting-state amygdala connectivity in PI youth. However, resting-state data from youth who experienced other forms of childhood adversity have provided support for the hypothesis of stress-induced changes to amygdala-PFC circuitry. Altered amygdala-PFC connectivity was observed in a sample of urban youth, aged 9-15, exposed to childhood trauma (Thomason et al., 2015). Specifically, trauma-exposed youth showed more positive amygdala-subgenual ACC (sgACC) connectivity than youth without histories of trauma. A similar result was found in a sample of 9-14 year olds who had experienced early trauma (including stressful life events, medical trauma, and maltreatment): adolescents with a history of trauma showed weakened negative (i.e. more positive) connectivity between the amygdala and ACC (Pagliaccio et al., 2015). Interestingly, in both of these studies the typically developing adolescents showed negative amygdala-ACC connectivity, while trauma was related to more positive connectivity, suggesting qualitatively different patterns of cross-talk between the amygdala and PFC.

Current study

As previously discussed, the extant literature is missing an exploration of resting state connectivity in PI samples. Previous findings from our group (Jedd McKenzie et al., under review) have shown altered task-related limbic connectivity in PI children during non-emotional, or baseline, components of a task, indicating that altered connectivity is not limited to explicitly emotional contexts. It remains to be seen whether amygdala connectivity is also related to the experience of institutionalization under resting conditions, when there is no external task. The current study seeks to fill this gap in the literature to better characterize differences associated with early deprivation. PI youth (ages 12-14 years old) adopted internationally from orphanage care (prior to age 5) were compared to youth who had been raised in their biological families. We utilized a seed-based approach to characterize amygdala connectivity at rest. Although we had *a priori* interest in the mPFC, we also explored differential connectivity across the whole brain. In accordance with the small existing literature on trauma exposed youth, we predicted more positive amygdala-mPFC connectivity in the PI group. Since positive amygdala-mPFC connectivity is typically observed in adults, this pattern would also be indicative of a more mature profile of connectivity, and would be consistent with the early maturation of task-based functional connectivity observed by Gee and colleagues (2013). Because amygdala connectivity at rest has been linked to anxiety (Kim, Loucks, et al., 2011) and PI children have shown higher rates of anxiety (Ellis et al., 2004) we examined the association between connectivity and child- and parent-reported anxiety symptoms. In addition, we examined individual differences in duration of deprivation within the PI

group, since more time in institutional care has been linked to more severe behavioral disruption across multiple domains (Julian, 2013).

Methods

Participants

Participants were part of a larger study on neurobehavioral development in children internationally adopted following institutional rearing. The final sample included 41 PI youth (PI group; 26 female, 15 male, M_{age} = 13 years, SD = 0.62, range = 12.18-14.09 years). PI youth were internationally adopted between 4-58 months of age (M = 15.82 mos, SD = 12.84 mos) and spent a mean of 92 percent of their pre-adoptive lives in institutional care. In this sample, age at adoption was used as a proxy measure for duration of deprivation. To evaluate differential connectivity related to duration of early life stress, age at adoption was used both continuously and categorically. The PI group was split into two groups: an earlier-adopted group (adopted by 12 months of age, n = 22), and a later-adopted group (adopted after 12 months of age, n = 19). PI youth were adopted from diverse countries of origin, including Russia (n = 14), China (n = 8), India (n = 4), Romania (n = 4), Ukraine (n = 3), Vietnam (n = 3), Ecuador (n = 1), Ethiopia (n = 1), Guatemala (n = 1), Mexico (n = 1), and Slovakia (n = 1). Participants also included 42 non-adopted comparison participants raised in the United States with their biological families (NA group; 28 female, 14 male, M_{age} = 12.81 years, SD = 0.52, range = 12.04-13.96 years). The NA group was selected to be well-matched to the PI group on post-adoptive familial environment, including family income.

All participants were prescreened for: developmental disorders (e.g. Autism, genetic disorders), known neurological disorders, symptoms of Fetal Alcohol Spectrum Disorders, serious medical conditions, known low IQ (<80), or contraindications for MRI scanning (e.g. braces, claustrophobia, or metal in the body). In addition, the NA group was screened for prematurity, birth complications, and diagnosed psychiatric disorders or learning disabilities. Psychiatric or psychological disorders were not an exclusion factor for the PI group. PI and NA groups did not differ in sex distribution, χ^2 (1, N = 83) = .097, p = .756, or age at test, t(81)=1.533, p=.129.

An additional 43 participants completed the resting state scan, but were excluded primarily due to head motion within the scanner that exceeded our stringent criterion (See Resting State Analysis). Twenty-eight PI participants were excluded: 23 for motion, 2 for missing IQ data, 1 for scanner error, 1 for a brain anomaly, and 1 who stopped the scan early. Fifteen NA participants were excluded: 9 for motion, 2 for missing IQ data, 1 for scanner error, and 3 for brain anomalies. PI participants and NA participants were equally likely to be excluded, χ^2 (1, N = 126) = 2.825, p = .093. Excluded participants did not differ from included participants in sex, χ^2 (1, N = 126) = 2.58, p = .611, IQ scores, t(118) = -0.03, p = .976, age at test, t(124) = -1.066, p = .289, or presence of psychiatric diagnosis χ^2 (1, N = 126) = .177, p = .674. Within the PI group, age at adoption did not differ for included versus excluded participants, t(67) = -.71, p = .48.

Self & Caregiver Report Measures

Primary caregivers were interviewed by a clinically trained researcher. Ten PI youth (24%) met DSM-IV diagnostic criteria on the S (K-SADS-PL; Kaufman et al.,

1997). Diagnoses included Attention Deficit Hyperactivity Disorder (n=3), Oppositional Defiant Disorder (n = 3), anxiety disorders (n = 3), depression (n = 2), Post-Traumatic Stress Disorder (n = 1) and Tics (n = 1), with 3 participants meeting diagnostic criteria for more than one disorder. In the NA group, participants met criteria for Oppositional Defiant disorder (n = 1) and Enuresis (n = 1).

Both caregivers and youth completed the Screen for Child Anxiety Related Disorders (SCARED, child and parent forms; Birmaher et al., 1997). There were no group differences between NA and PI groups on either parent $t(81) = -.249, p = .804$ or child $t(81) = .65, p = .518$ reported anxiety. Parent and child reported anxiety were only weakly correlated, $r = .33, p<.05$. IQ data were collected using the Weschler Abbreviated Scales of Intelligence (WASI; Weschler, 1999). NA youth had significantly higher IQ scores than the PI group $t(81) = -4.039, p<.001$; however, for both groups IQ was in the normal or above-average range, with similar variance within groups [$M_{PI} = 106.83, SD_{PI} = 12.86; M_{NA} = 118.07, SD_{NA} = 12.50$].

MRI Data Acquisition

Participants were scanned with a Siemens 3T TIM Trio whole-body scanner using a 12-channel head coil. A T1-weighted anatomical volume was acquired using an MPRAGE sequence (TR = 2530 ms, TE = 3.65 ms, Flip = 7°, 240 slices, matrix = 256x256, 1 mm thick sagittal slices; 10 min, 49 sec). Whole brain EPI BOLD images were acquired during eyes open rest (TR = 2500 ms, TE = 30 ms, Flip = 80°, FOV = 240, matrix = 64x64, 40 interleaved AC-PC aligned axial slices, 3.5 mm slice thickness with no gap, 140 TRs; 5 min, 57 sec). A field map with identical slice prescription was

acquired immediately prior to the resting state scan for the purpose of correcting geometric distortions in the EPI data (TR = 400 ms, TE1 = 2.71 ms, TE2 = 5.71 ms, Flip = 50°, FOV = 240, matrix = 64x64, 40 interleaved AC-PC aligned axial slices, 3.5mm slice thickness with no gap; 54 sec).

MRI Resting State Analysis

Data were analyzed using FreeSurfer (v5.3.0; Fischl, 2012), FSL (FMRIB Software Library, v5.0.8; Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012) and AFNI (Analysis of Functional NeuroImages, v16.0.00; Cox, 1996). Individual bilateral amygdala masks were created for each subject from the MPRAGE data using FreeSurfer's default pipeline and were then transformed into the subject's functional space. FreeSurfer output was manually evaluated to ensure accurate segmentation. MPRAGE and fieldmap magnitude images were skull stripped using FSL's BET (Brain Extraction Tool) and then hand edited for accuracy.

Slice time correction was performed on raw EPI data, framewise displacement was estimated using FSL's fsl_motion_outliers tool, and data were then corrected for motion using FSL's mcflirt (6 dof). Twenty-four motion confound predictors were generated: 3 linear translation and 3 rotation estimates (6 predictors), the first temporal derivative of these original motion estimates, the square of the original motion estimates, and the first temporal derivatives of the squares (Satterthwaite et al., 2013). Absolute motion was estimated using the root mean square (RMS) summary of the translation and rotation motion estimates. DVARS (Derivative of rms VARiance over voxelS), which measures frame-to-frame BOLD signal fluctuation across the entire brain (Power, Barnes,

Snyder, Schlaggar, & Petersen, 2012), was estimated using FSL's fsl_motion_outliers. Censoring predictors were generated for each TR that contained absolute motion greater than 3.5 mm (1 voxel) or a framewise displacement greater than 0.5 mm. Framewise displacement censoring was expanded to also include one preceding and one following TR. TRs were additionally censored for DVARS values greater than the 75th percentile plus two times the interquartile range. Participants were excluded if the number of TRs censored exceeded 25% of the resting state scan; as such, all participants in the final sample had at least 105 TRs, or 4 min 22.5 sec of usable data.

EPI data were unwarped, which included the registration of each subject's functional data to their structural (MPRAGE) images using boundary based registration (BBR), registration of the MPRAGE image to the MNI152 standard brain (12 dof), and subsequent registration of the EPI data to the standard space. Unwarped EPI data were then demeaned and detrended (linear and quadratic trends) using AFNI's 3dDetrend (Cox, 1996). The stripped MPRAGE data were parcellated using FSL's fast tool to create masks of grey matter, white matter, and cerebrospinal fluid (CSF), which were then projected into the unwarped EPI space. These masks, which were thresholded at 75% probability and binarized, were then used to generate mean time series estimates for each tissue segmentation.

Linear regressions were then run on the EPI data for each subject for the purpose of removing confound signals. Nuisance predictors included the timeseries estimates from white matter and CSF, as well as the motion confound predictors. Estimates of global signal were not included in the regression, since the inclusion of global signal may

falsely introduce anti-correlations in the data (Birn, 2012; Murphy et al., 2009; Saad et al., 2012). The residuals from the confound regression were band pass filtered (0.009-0.08 Hz) and spatially smoothed (6mm FWHM Gaussian kernel) prior to subsequent processing. After back-projecting the bilateral masks derived from FreeSurfer into the participant's unwarped EPI space, the mean amygdala signal time courses for each participant were extracted from these residual images. Back-projected voxels exhibiting greater than 10% signal loss in the corresponding EPI field map were removed from the individual level amygdala masks in order to obtain more accurate estimates of amygdala signal. The extracted mean amygdala time courses were submitted as predictors for each individual's general linear model (GLM) to identify voxels in the brain that correlated in time with the amygdala.

Higher-level analyses were conducted using a random effects GLM to compare group differences in connectivity during resting state and to assess individual differences in connectivity related to age at adoption and anxiety. All higher level analyses included age at test, sex, and IQ as covariates of non-interest. For the vmPFC, as the *a priori* region of interest, non-parametric permutation tests were conducted using Randomise in FSL, within a vmPFC mask (derived from the combination of bilateral Harvard-Oxford frontal medial cortex, and subcallosal cortex anatomical masks), using 5000 permutations at $p<.05$. Whole brain cluster correction was performed in FSL with a voxel-wise significance threshold of $p<.005$ and a cluster threshold of $p<.05$. For clusters that survived correction, ROIs were back-projected into each individual's unwarped EPI space. Individual z-stat maps were transformed into correlation coefficients using the

inverse Fisher z transform and mean correlation coefficients were extracted for each individual using the back-projected ROI mask. For each individual, this produced a mean correlation with the amygdala across voxels within significant ROIs.

Results

Amygdala resting state connectivity

In the full sample, positive connectivity with the bilateral amygdala was observed in a number of regions, including: vmPFC, rostral ACC, frontal pole, ventral striatum, brain stem, posterior insula, temporal pole, posterior cingulate, and lateral occipital. Additionally, negative connectivity was observed with dmPFC, dlPFC, superior frontal gyrus, supramarginal gyrus, and precuneus (see Figure 2.1 for both negative and positive connectivity). These regions are in line with previous findings of amygdala connectivity (Gabard-Durnam et al., 2014; Roy et al., 2009).

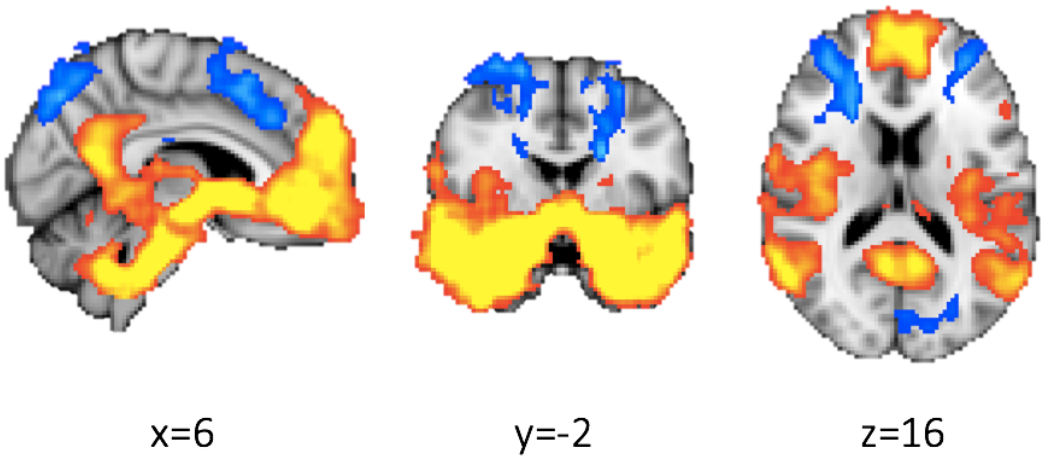

Figure 2.1. Resting state connectivity with bilateral amygdala in the full sample (n = 83). Red/yellow indicates areas with positive correlation with the bilateral amygdala signal and blue indicates negative correlation. Coordinates are in MNI space. Regions survive voxelwise significance threshold of $p<.005$, cluster correction of <.05.

Group differences between PI and NA groups

For positive amygdala connectivity, PIs showed greater connectivity within our *a priori* ROI in two separate clusters: a vmPFC cluster (MNI coordinates, x, y, z = -12, 28, -18) and a sgACC cluster (MNI coordinates, x, y, z = 8, 16, -12). These clusters survived a voxelwise significance threshold of $p<.005$ and region of interest non parametric permutation tests at $p<.05$ (Figure 2.2). Extracted correlation coefficients indicated that for the vmPFC region, NAs had negative, or near zero connectivity, while the PIs exhibited positive connectivity. In the sgACC, both groups showed positive connectivity

with the amygdala, with the PI group showing significantly more positive correlations than the NA group. In the whole brain, PI youth also had greater amygdala connectivity in the OFC (voxelwise $p<.005$), however this region did not survive stringent whole brain cluster correction. The NA group showed significantly greater connectivity than the PI group in the left insula (MNI coordinates, x, y, z = -48, -2, 16; Figure 2.3) which survived whole brain cluster correction. While the PI group showed a slightly negative, near zero correlation, the NA group had positive connectivity with the left insula.

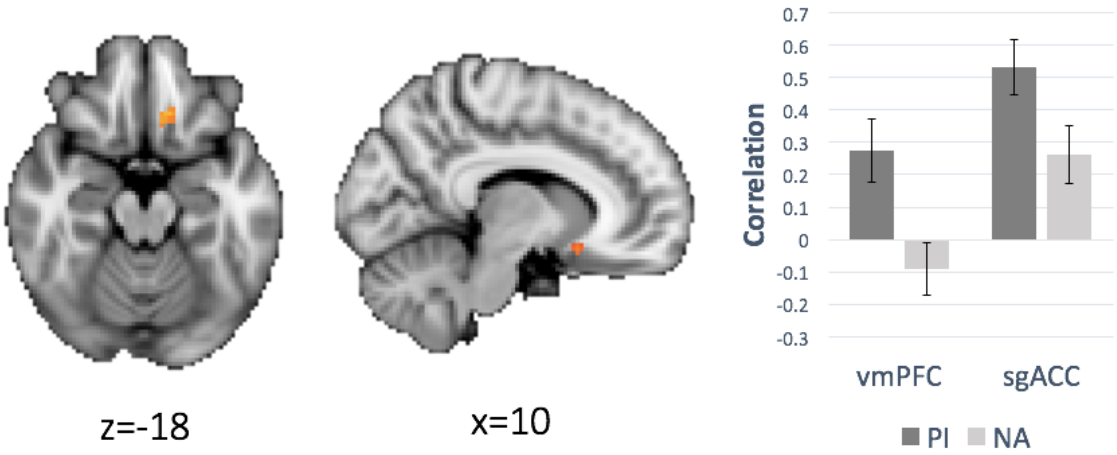

Figure 2.2. Amygdala-mPFC resting state connectivity. Shows significant group differences in vmPFC (left image) and sgACC (right image). The graph shows the correlations between bilateral amygdala and mean connectivity across voxels within each mPFC region by group. In both regions, post-institutionalized (PI) youth had greater positive connectivity than the non-adopted (NA) comparison group. Coordinates are in MNI space. Regions survive voxelwise significance threshold of $p<.005$ and region of interest permutation tests.

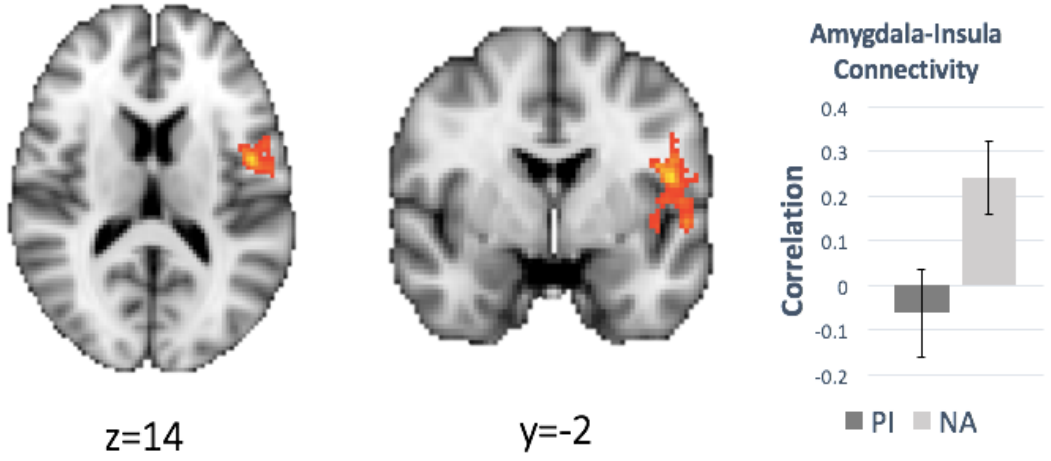

Figure 2.3. Group differences in amygdala-insula resting state connectivity. The post-institutionalized (PI) group showed significantly less connectivity than non-adopted (NA) youth in the left insula. Coordinates are in MNI space. Regions survive voxelwise significance threshold of $p<.005$, cluster correction of $p<.05$.

Age at adoption

Within the PI group, age at adoption was included as a continuous predictor of connectivity. Age at adoption positively predicted amygdala connectivity with a small region of right dlPFC. This region did not survive cluster thresholding. Additionally, when the PI group was split into two groups (earlier-adopted and later-adopted), earlier-adopted youth showed increased positive connectivity compared to later-adopted youth in

right insula and right parahippocampal gyrus, however these regions did not survive our cluster correction thresholds.

Anxiety and diagnoses

Amygdala connectivity across the entire sample was not significantly predicted by parent or child reported anxiety symptoms. Therefore, group differences were not driven by anxiety symptoms. The previously described group analyses were also rerun without the participants who met diagnostic criteria on the K-SADS interview (10 PI, 2 NA) to examine whether PI versus NA differences remained after the removal of youth with psychopathology. The group differences in amygdala-mPFC connectivity were still apparent but became smaller in spatial extent and no longer survived the permutation cluster correction, which is to be expected, given the large reduction in sample size within the PI group. The group difference reported in amygdala-insula connectivity remained significant, which is not surprising, given that the effect was presumably driven by positive amygdala-insula connectivity in the control group, which was minimally impacted by the removal of individuals with diagnoses.

Discussion

In the present study we examined amygdala connectivity at rest in a sample of post-institutionalized youth who experienced early life stress and a non-adopted comparison group. We identified group differences in connectivity, suggesting that the experience of institutional care, regardless of duration, has lasting impacts on the neural circuitry underlying emotion processing and regulation. This difference in brain function was evident in spite of the fact that all PI youth had spent years in enriched adoptive

homes. Our results further support observations of connectivity differences reported by previous studies using different methodologies (e.g. diffusion tensor imaging, task-based connectivity) and show that early life stress affects resting state networks that set the baseline for subsequent brain function.

In comparison to the NA group, PI youth had stronger positive connectivity in two regions of the mPFC (vmPFC and sgACC) and in the OFC. This finding is congruent with studies of resting state amygdala connectivity following early adversity, which have observed more positive amygdala-mPFC connectivity (Pagliaccio et al., 2015; Thomason et al., 2015). In particular, Thomason and colleagues found trauma-associated increases in amygdala connectivity in the same sgACC region in a sample of urban youth. The amygdala-mPFC pathway is critical for efficient emotion regulation, and we observed that, even in the absence of an emotionally engaging task, the PI youth had altered crosstalk between these regions. Our findings point to a neural mechanism through which early deprivation may lead to altered emotion processing and even later psychopathology.

Previous research suggests a developmental shift towards positive amygdala-mPFC resting state connectivity (Gabard-Durnam et al., 2014), that can be seen in adults (Roy et al., 2009). Therefore, more positive amygdala connectivity with the mPFC following orphanage care in our adolescent sample may be consistent with the stress-acceleration hypothesis (Callaghan & Tottenham, 2016). Much of the support for the stress-acceleration hypothesis comes from animal models, which have been informative to our understanding of the biology of the caregiver relationship. For instance, in the absence of the mother, rat pups show a mature pattern of fear learning, suggesting that

normally, the mother's presence buffers the fear response during this sensitive period of development (Moriceau & Sullivan, 2006). In addition to animal models, there is evidence of stress-accelerated development in children with a history of early deprivation (Gee, Gabard-Durnam, et al., 2013). Consequently, our results may support the early maturation of frontolimbic circuitry reported by Gee and colleagues (2013) using task-based connectivity. Gee and colleagues found differences (the more mature profile of circuitry) in PI children below 10 years of age, but not in PI adolescents. Our findings were observed slightly later in development, with participants aged 12-14. It may be that accelerated maturation of emotion circuitry following early life stress serves an adaptive function that then becomes maladaptive in other contexts or developmental periods (Tottenham, 2013). Although our findings may support the stress-accelerated hypothesis, we were unable to directly test this question because of the restricted age range of our participants. Therefore, more longitudinal research is necessary to evaluate the effects of early life stress on resting state connectivity and to determine if there may be stress-related acceleration of frontolimbic brain networks.

In addition to the group differences in amygdala-PFC connectivity, we also observed novel group differences in amygdala connectivity with a large region of the left insula. The NA group showed positive coupling between the amygdala and insula, while the PI group had near-zero, or slightly negative correlations. Broadly, the insula has been related to a wide range of cognitive, emotional, and physiological functions (Craig, 2009; Menon & Uddin, 2010; Singer, Critchley, & Preuschoff, 2009). The anterior insula has been shown to be involved in emotional salience detection, while the posterior insula is

more involved in regulating physiological reactivity (Menon & Uddin, 2010). Recent research suggests that amygdala-insula circuitry is implicated in psychopathology, though the direction of effects is not uniform across studies (Baur, Hänggi, Langer, & Jäncke, 2013; Bebko et al., 2015; Roy et al., 2013). In one study of adults, resting state connectivity between the amygdala and anterior insula positively predicted anxiety (Baur et al., 2013). Similarly, another study observed increased amygdala-insula connectivity in adolescents with generalized anxiety disorder (Roy et al., 2013). In contrast, decreased amygdala-insula connectivity has been found in adolescents with more depression symptoms and more behavioral and emotional dysregulation (Bebko et al., 2015). However, this result was observed in posterior portions of the insula, while our finding was more anterior. Since we did not observe any associations with anxiety, and the result remained even after the removal of participants who met diagnostic criteria for Axis I disorders, it appears that our finding is not related to psychopathology. Rather, it may be that early life stress impacts similar neural circuits as those affected in individuals with mood and anxiety disorders.

As with the prefrontal connectivity, the pattern of insula connectivity observed may reflect a more mature phenotype in the PI youth. If true, this would suggest that the stress-acceleration of amygdala circuitry extends beyond the frontal lobe, and that other regions of the brain may show similarly mature relationships with the amygdala following early life stress. At present there is still limited data on the normative development of amygdala-insula circuitry. One recent study suggests that amygdala connectivity with parts of the insula becomes more negatively coupled across

development (Gabard-Durnam et al., 2014), although this effect was lateralized to the opposite side of the brain from the results reported here. Additional research in both normative and at risk populations across development is needed to understand how amygdala-insula connectivity changes over time.

Contrary to our expectations, age at adoption (our proxy measure for duration of deprivation) did not play an important role in predicting individual differences in amygdala connectivity in PI youth. Although there was some evidence of age at adoption effects in the dlPFC, parahippocampal gyrus, and insula, they did not survive our stringent significance threshold. It is possible that our sample size was not large enough to detect subtle differences related to duration of deprivation. However, our results suggest that it is more important whether an individual has ever experienced deprivation rather than how long the individual spent in institutional care. This lack of duration effect was similarly observed previously by our group when examining structural differences in the PFC (Hodel et al., 2015). Additionally, similar results were observed in the English and Romanian Adoptees Study, which found cognitive impairment in children adopted after 6 months of age, that did not vary by duration of deprivation within the 6-42 month range (Beckett et al., 2016). The authors suggested that by 6 months, deprivation is sufficient to produce long-term changes, regardless of whether or not the stress of institutional care continues past 6 months. In our sample, the minimum age at adoption was 4 months, which may be enough time to produce disruption to the early foundations of frontolimbic communication.

Additionally, we did not observe connectivity differences related to either child or parent reported anxiety. This was somewhat unexpected, since prior studies have demonstrated links between anxiety and amygdala connectivity (see Kim, Loucks, et al., 2011 for review). Interestingly, child and parent self-reported anxiety were only weakly correlated with each other in our adolescent sample, suggesting that there was a mismatch in the perceptions of anxiety between youth and their parents. A more fine-tuned measure of psychosocial stress or anxiety may have been a better predictor of amygdala connectivity.

Although this study provides novel evidence of the disruption to neural circuitry following early life stress, it has a number of limitations. We chose to test participants at ages 12-14 due in part to the important developmental changes occurring during this transition to adolescence and because adolescence is marked by increased emergence of psychopathology in PI youth (Hawk & McCall, 2010). This approach allowed us to highlight differences in connectivity specific to the early adolescent years. However, given our restricted age range, we were unable to test developmental differences in the changes in connectivity between the two groups. As with all studies of PI children, we could not rule out preexisting differences in children who were institutionalized. We do not have data on the prenatal environments of our sample, nor can we characterize individual differences in the quality of orphanage care. Our study also had limited behavioral and self-report measures. This restricted our ability to relate connectivity to actual socioemotional functioning. Future studies on the links between resting state

connectivity and behavior in PI samples are needed to understand the real-world impact of the differences we reported.

An additional 32 participants were tested, but excluded for head motion within the scanner. Given the substantive concerns regarding the effects of head motion in skewing results (Power et al., 2012) and the short duration of our resting-state scan, we erred on the side of excluding participants in favor of retaining clean data. While this bolsters our confidence in the veracity of our findings, it means we excluded participants who may have contributed to group effects and individual differences. Given our interest in regulatory regions, it is certainly possible that we excluded participants who had greater regulatory issues and could not stay still in the scanner. Our final sample therefore, may represent higher functioning PI youth. The use of longer resting state scans may have circumvented this issue by providing more opportunities to gather clean data.

Overall, our findings suggest that resting state functional connectivity of the amygdala is altered, even years after the experience of institutional rearing. While group differences in connectivity were observed in the hypothesized regions (mPFC), the largest regional difference associated with early life stress was in the insula. This finding underscores the need to understand how early life stress impacts multiple brain networks and to probe differences outside of the amygdala-PFC pathway. Given the risk for psychopathology in individuals who have experienced early life stress, altered trajectories of amygdala-PFC and amygdala-insula circuitry may be explanatory mechanisms through which stress leads to long-term socioemotional problems.

CHAPTER 3: Study 2

Individual differences in experiences of childhood maltreatment and resilience to adversity predict resting state amygdala connectivity[2]

[2]Ruskin H. Hunt, Dante Cicchetti, Lauren Demers, Fred A Rogosch, Sheree L. Toth, and Kathleen M. Thomas are listed as coauthors on this publication.

Synopsis

Childhood maltreatment is an extreme form of childhood adversity that can compromise typical development and lead to lasting alterations in emotional behavior and reactivity. Maltreatment is associated with heightened risk for psychopathology throughout development, however some individuals are resilient in spite of early life stress. This study evaluated the circuitry underlying emotion processing and regulation in a high-risk sample of adults (n = 67), roughly half of whom experienced maltreatment in childhood. fMRI resting state connectivity analyses used the bilateral amygdala as a seed region. Maltreatment history (including subtype and chronicity of maltreatment), depression, and resilience were all examined as predictors of amygdala connectivity at rest. There were no differences between maltreated and non-maltreated individuals in connectivity. Participants who experienced physically violent forms of abuse had more amygdala-parahippocampal connectivity than comparison participants, and an association with depression was observed in the same region. Differences were observed in relation to chronicity, with individuals who experienced maltreatment across more periods of childhood showing less amygdala connectivity with dorsal medial prefrontal cortex and caudate. An interaction effect was observed between self-reported resilience and maltreatment history in the caudate, with higher amygdala-caudate connectivity in resilient, comparison participants, and lower amygdala-caudate connectivity in resilient, maltreated participants. Together the findings from this study emphasize the need to explore individual differences in maltreatment experiences and adaptation to stress.

Introduction

Childhood maltreatment is a severe environmental threat that can alter the typical trajectory of brain and behavioral development. Over the past few decades, extensive research on the behavioral sequelae of childhood maltreatment has consistently identified maltreatment-related disruption to socioemotional functioning (Aber & Cicchetti, 1984; Pechtel & Pizzagalli, 2011). Individuals who experience childhood maltreatment are also at greater risk for developing psychopathology across the lifespan (Cicchetti & Toth, 1995; Kim & Cicchetti, 2010). In particular, childhood maltreatment confers increased risk of mood and anxiety disorders (Bernet & Stein, 1999; Chapman et al., 2004; Green et al., 2010; Toth, Manly, & Cicchetti, 1992).

Children who have experienced maltreatment show deficits in emotion processing and recognition (Camras et al., 1988, 1983; Pollak, Cicchetti, Hornung, & Reed, 2000; Pollak & Sinha, 2002), including attentional biases towards threatening stimuli (Pollak et al., 2009; Pollak & Tolley-Schell, 2003). While these behavioral responses may be adaptive in the context of an abusive household, heightened sensitivity to threat in other contexts may be maladaptive and lead to psychosocial problems later in life (Cicchetti, Toth, & Maughan, 2000). Indeed, adults with a history of childhood maltreatment show long-term differences in emotion recognition and attentional biases (Günther, Dannlowski, Kersting, & Suslow, 2015; Young & Widom, 2014).

In addition to behavioral sequelae, recent neuroimaging research has identified alterations to brain structure and function following maltreatment (Hart & Rubia, 2012). These findings point to potential neurobiological mechanisms through which

maltreatment leads to altered behavior. Neural structures involved in emotion processing and regulation are of particular interest given behavioral disruption in these domains. The amygdala, a subcortical region of the brain located in the temporal lobe, is implicated in the processing of emotions and in learning about emotionally relevant stimuli (Davis & Whalen, 2001; LeDoux, 2000; Phelps & LeDoux, 2005). Across development, the amygdala is responsive to emotional stimuli (Guyer et al., 2008; Hariri, Mattay, et al., 2002; Hariri, Tessitore, et al., 2002; Thomas et al., 2001; Whalen et al., 2004), and is involved in the detection of threat (Bach et al., 2015; Öhman, 2005). The amygdala has been implicated in a range of psychopathology, including mood and anxiety disorders. The amygdala is also vulnerable to the effects of stress; in rat models, stress is associated with increased dendritic arborization and spine density of neurons in the amygdala (Mitra et al., 2005; Vyas et al., 2002).

Due to its role in emotion processing, vulnerability to stress, and its association with psychopathology, the amygdala has been a key target for research on neural outcomes associated with childhood maltreatment. Convergent data suggest a hyperactive amygdala response to emotionally salient stimuli following childhood maltreatment. This association has been observed in both children/adolescents (McCrory et al., 2011, 2013; McLaughlin et al., 2015; White et al., 2012) and adults (Dannlowski et al., 2012, 2013; Grant, Cannistraci, Hollon, Gore, & Shelton, 2011; van Harmelen et al., 2013).

In addition to activation of the amygdala, more recent research has focused on the connectivity of the amygdala with other brain regions, especially regions involved in behavioral and emotional regulation. Broadly, the prefrontal cortex (PFC), a large region

important for higher-order cognition and executive functions, has been shown to be involved in regulation of amygdala activity. Fiber tracing in rodent models has suggested that the medial PFC (mPFC) in particular has direct anatomical connections to the amygdala (Mcdonald, Mascagni, & Guo, 1996). Generally, the more ventral portions of the mPFC (vmPFC) are thought to be involved in emotion regulation, while dorsal regions (dmPFC) have been associated with cognitive control, as well as the appraisal and evaluation of emotions (Etkin et al., 2011). One increasingly used method of assessing communication of the amygdala with other regions is to evaluate the functional connectivity, or temporal correlation between regions. In resting state functional connectivity, more ventral regions of the PFC, including vmPFC and rostral ACC tend to show positive connectivity with the amygdala, whereas more dorsal regions of the PFC, including dmPFC and dlPFC show negative correlations with amygdala signal (Roy et al., 2009). The strength of amygdala-PFC connectivity at rest has been related to a number of psychological outcomes, including anxiety (Hahn et al., 2011; Kim, Loucks, et al., 2011; Kim, Gee, Loucks, Davis, & Whalen, 2011) and depression (Connolly et al., 2017; Cullen et al., 2014), suggesting that disruption to this circuitry may be an important target for understanding psychopathology.

There is evidence that adults with a history of childhood maltreatment exhibit altered functional connectivity between the amygdala and PFC during performance of emotion related tasks (Fonzo et al., 2013; Jedd et al., 2015). While these task-based approaches are useful in characterizing connectivity during specific activities, it is difficult to generalize findings across studies that use different tasks, and findings cannot

be used to exemplify baseline connectivity states in the brain. Resting state studies are therefore needed to better define the roll of childhood maltreatment in the development of intrinsic connectivity networks. To date, a small number of studies have observed correlations between childhood maltreatment and altered amygdala-prefrontal resting state functional connectivity in children and adolescents (Herringa et al., 2013; Pagliaccio et al., 2015; Thomason et al., 2015). The resting state literature in *adults* who experienced childhood maltreatment is particularly sparse, but provides further evidence for long-term disruptions in amygdala-prefrontal circuitry. For instance, in a study of military veterans, childhood maltreatment was associated with decreased positive amygdala connectivity with both the medial and lateral PFC (Birn et al., 2014). Similarly, in a separate study, childhood emotional maltreatment was related to decreased positive connectivity between the amygdala and a large a prefrontal region including the orbital frontal cortex (OFC; van der Werff et al., 2013).

In addition to amygdala-prefrontal connectivity, there is a small body of evidence implicating disruption of other amygdala circuits following childhood maltreatment. For example, van der Werff and colleagues (2013) observed decreased amygdala-insula connectivity in adults with exposure to childhood emotional maltreatment. The insula has been implicated in a wide range of cognitive and affective functions, including empathy, self-awareness, interoception and sensory integration, and salience detection (Craig, 2009; Menon & Uddin, 2010; Singer, Critchley, & Preuschoff, 2009). The insula may be an important network hub following early life stress, as increased general network

centrality (or connectedness) of the insula has been observed in adults with a history of maltreatment (Teicher, Anderson, Ohashi, & Polcari, 2014).

There remains much to be learned about the general impact of maltreatment on amygdala connectivity. Even less is known about variation in the nature of the maltreatment experience (e.g. type and timing) or the individual response to maltreatment (e.g. adaptation). Given well documented differences in emotion processing and regulation following distinct subtypes of maltreatment (e.g. physical abuse vs. neglect; Pollak, Cicchetti, Hornung, & Reed, 2000), it is probable that these differences reflect unique patterns of connectivity in the brain. While there is likely to be considerable variability in relation to maltreatment type and severity, we also know that not all individuals who experience maltreatment go on to develop psychopathology (Cicchetti, 2013). In fact, many display resilient functioning that allows them to function well despite early trauma (Cicchetti & Garmezy, 1993; Cicchetti, Rogosch, Lynch, & Holt, 1993; Luthar, Cicchetti, & Becker, 2015). Resilience is not a static, immutable trait, but rather a dynamic process of positive adaptation in spite of adversity (Masten, 2001, 2007). The extant literature on resilience to childhood maltreatment and resting-state connectivity is extremely limited. One small study compared maltreated participants with and without a psychiatric diagnosis as a proxy for low and high resilience, and observed altered frontal connectivity in the resilient group (Van der Werff et al., 2013). In work from our own group, we observed task-based amygdala-PFC connectivity that was predicted by resilience over and above any maltreatment related effects (Demers et al., under review). Because the literature is so sparse, the links between resilience and

functional connectivity in the context of childhood maltreatment remain largely unknown.

In the current study, we utilized resting state functional connectivity as a means of assessing the strength of associations between the amygdala and related regions at baseline. The goals of the current study were threefold: the first goal was to evaluate long-term alterations in amygdala connectivity in individuals with substantiated histories of childhood maltreatment, using a well matched comparison group. In this study, we use extensive documentation of maltreatment, with substantiated reports and a prospective longitudinal design. This is particularly important, since research shows that retrospective self-reported experiences of maltreatment may contain significant measurement error, with inaccurate reporting (Hardt & Rutter, 2004). Maltreatment commonly occurs within the context of poverty; therefore, to isolate the unique contribution of maltreatment it is vital to include a comparison group that is well matched on socioeconomic risk variables, since socioeconomic status is also associated with changes to both brain structure and function (Hanson et al., 2013; Kim et al., 2013). In our study, all participants (both maltreated and comparison) were recruited during childhood from the same high-risk, low socioeconomic neighborhoods. This means that all participants experienced early adversity in the form of low socioeconomic status, with one group additionally experiencing the early life stress of childhood maltreatment. In line with previous research, we anticipated altered amygdala-PFC, and amygdala-insula connectivity in relation to childhood maltreatment.

A second goal of our study was to probe variation in connectivity as a function of individual differences in type and severity of maltreatment. Little is known about the unique contributions of physical versus non-physical forms of maltreatment. In our study, we divided the maltreated sample into two subgroups: one group who experienced physically violent maltreatment (physical and sexual abuse) and one group who experienced non-physically violent forms of abuse (emotional maltreatment, and neglect) only. We also created a proxy measure for chronicity of maltreatment experiences by measuring the number of developmental periods in which each participant experienced maltreatment. We predicted that chronic maltreatment (i.e. maltreatment across multiple periods of childhood and/or adolescence) would be associated with greater disruption to intrinsic amygdala-PFC network connectivity.

Finally, since little is currently known about brain outcomes associated with adaptation, we wanted to evaluate neural correlates of resilience in the context of childhood maltreatment. Since there are many different methods used to measure resilience, we conceptualized resilience in two different ways: first using a more subjective self-report of self-efficacy, and second, using a more objective composite measure of success on a range of developmentally appropriate tasks. We also examined associations with depression, since maltreated individuals are at greater risk for psychopathology. Given the limited prior research on this topic, we did not have specific hypotheses about the nature of the relationship between resilience and amygdala functional connectivity, but predicted that metrics of resilience may interact with the experience of childhood maltreatment to impact resting state functional brain networks.

Methods

Participants

Participants included 67 adults (M_{age} = 30.1 years, SD_{age} = 3.41 years, range 23-37 years, 34 female, 33 male, see Table 3.1 for participant demographics). All participants had been studied longitudinally since childhood, when they were recruited to participate in a summer camp for low-income families. Thirty-five participants had a history of childhood maltreatment as documented through Department of Human Services records. Thirty-two participants had no history of maltreatment, as confirmed through search of Department of Human Services records. Additionally, the Maternal Maltreatment Classification Interview (Cicchetti, Toth, & Manly, 2003) was used to rule out the possibility of unreported maltreatment. Type and timing of maltreatment were determined using the Maltreatment Classification System (Barnett, Manly, & Cicchetti, 1993). Maltreatment experiences included physical abuse, sexual abuse, physical neglect, and emotional maltreatment (See Table 3.2 for maltreatment characteristics). Sixty percent of the maltreated participants experienced more than one form of childhood maltreatment, with physical neglect being the most commonly occurring form. For purposes of evaluating type of maltreatment, the maltreatment group was further divided into two groups: one group who had only experienced physically violent forms of abuse (sexual and physical abuse, Mal-PASA group, n = 16) in addition to potential neglect or emotional maltreatment, and another group who had experienced only non-physically violent forms of abuse (neglect, emotional maltreatment, Mal-NEM group, n = 16). Additionally, to quantify the chronicity of maltreatment, the number of developmental

periods in which maltreatment occurred were used (defined as: infancy, toddler, preschool, early school, later school, and adolescence). Sufficiently detailed maltreatment information was missing from three subjects who were excluded from analyses related to type and timing of maltreatment.

Exclusion criteria included contraindications for MRI (claustrophobia, metal in the body, or extreme obesity), neurological disorders or trauma, known intellectual impairment, and uncorrected visual or auditory impairments. An additional 35 participants (20 maltreated, 15 comparison) completed the resting state procedure but were excluded from the final analyses. The majority (33 participants) were excluded due to excess head motion during the scan (see Resting State Analyses), 1 due to scanner error, and 1 due to serious mental illness (schizophrenia). Maltreated participants were not more likely to be excluded than comparison participants [χ^2 (1, N=122) = 1.128, p = .288].

Measures

Participants completed a number of self-report measures, including a demographics questionnaire with information about income, occupation, relationships, and education. The Adult Self-Report questionnaire (Achenbach & Rescorla, 2003) provided normed scales of adaptive functioning, substance use, internalizing and externalizing. Additionally participants completed the Beck Depression Inventory–II (BDI-II; Beck, Steer, Ball, & Ranieri, 1996) to assess existence and severity of depression. The groups were not significantly different in income levels, educational attainment, or depression ratings (See Table 3.1).

Resilience: Self-report

Self-reported resilience was measured using the Connor-Davidson Resilience Scale (CDRISC; Connor & Davidson, 2003), a 25 item questionnaire with questions related to perceived success in coping with stress. Each item was measured on a 5-point scale scoring 0-4. Total scores therefore could range from 0-100, with higher numbers indicating higher levels of resilience.

Resilience: Developmental Tasks

Success on developmental tasks was evaluated using a composite of ranked scores on seven domains: education, work, financial autonomy, romantic involvement, peer involvement, family involvement, and substance abuse. This approach has been reported by our group previously (Demers et al., under review) and followed the example of Schulenberg et al (2004). Information for each domain was extracted from the demographics questionnaire and the Adult Self-Report questionnaire (Achenbach & Rescorla, 2003). Participants were ranked into three categories for each domain: stalling, maintaining, and succeeding, with scores of 0-2 respectively. Scores were relative to other participants in the study, all of whom came from similar low-socioeconomic backgrounds. Consequently, for the composite developmental tasks score, scores a ranged from 0-14, with higher numbers indexing greater resilience and success on developmental tasks.

The education domain used self-reported measures of educational attainment. In our sample, stalling individuals included 21 participants those who did not finish high school or received a GED. Sixteen were classified as maintaining, having completed high

school. Succeeding participants (n = 30) completed a vocational technical diploma or some college (n = 18), an associate's degree (n = 8), bachelor's degree (n = 2), or master's degree (n = 2).

For the work domain, occupational standing was evaluated using two measures. First, using Hauser & Waren's (1997) Socioeconomic Index (SEI) score, occupations were ranked according to the earnings, educational requirements, and prestige traditionally associated with such occupations. Second, the job score on the ASR was averaged for current and usual job score. Individuals were considered stalling if unemployed or disabled (n = 13). Maintaining individuals (n = 37) included those who reported keeping house, attending school, working a job with a low-level standing, or showing an adaptive functioning job score on the ASR of <1.5 (low job satisfaction and confidence). Succeeding individuals (n = 17) had high SEI scores and adaptive functioning job scores greater than 1.5 (indicative of medium to high satisfaction and confidence).

The financial autonomy domain was ranked using self-reported family income. Stalling (n = 18) was defined as a family income of less than $20K per year, maintaining (n = 31) as $20-40K per year, and succeeding (n = 18) as greater than $40K per year.

The romantic involvement domain used self-reported relationship quality as well as marital status. Here, Schulenberg et al.'s (2004) standard for average age of marriage was changed from 26 to 28 years of age to reflect the average age of marriage in New York state. Consequently, unmarried and non-cohabitating participants less than 28 years of age were classified as maintaining. Otherwise rankings used the ASR measures of

relationship status and quality. Stalling individuals (n = 21) included those with more than 2 divorces, those who were single/non-cohabitating (and over 28 years of age), or in a low quality marriage (ASR adaptive functioning spouse/partner score <1). Maintaining individuals (n = 31) were either divorced but remarried, cohabitating, or married but unsatisfied (ASR adaptive functioning spouse/partner score = 1-1.5). Individuals classified as succeeding in the romantic involvement domain (n = 15) had no history of divorce, and were in high quality marriages (ASR adaptive functioning spouse/partner score > 1.5).

The peer involvement domain used the ASR adaptive functioning, friends score to evaluate both the quality of friendships, and the quantity of friendships/contact with friends. Stalling individuals (n = 23) scored <1.75 on the ASR. Maintaining individuals (n = 24) had scores of 1.75-2.25. Finally, participants classified as succeeding (n = 20) had ASR scores higher than 2.25.

Similarly, the family involvement domain used the ASR adaptive functioning, family score to describe how well participants got along with family members. Scores on the ASR were averaged across family members with which the participant was still in contact, since, particularly in the context of maltreatment, there may have been adaptive reasons to be out of touch with some family members. Individuals were classified according to the ASR family score: stalling (n= 27), ASR score <1.25; maintaining (n = 17), ASR score 1.25-1.75; and succeeding (n = 23), ASR score >1.75.

Finally, the substance abuse domain used self-reported information from the ASR substance use scale. Rankings were based on the average of three scores (tobacco,

alcohol, and drug use) with potential scores from 50-100. Stalling participants (n = 22) had substance use scores >66.67, maintaining (n=24) with scores between 50-66.67, and succeeding (n=21) with scores of 50.

MRI Data Acquisition

Participants were scanned with a Siemens 3T TIM Trio whole-body scanner using a 32-channel head coil. A T1-weighted anatomical volume as acquired using an MPRAGE sequence (TR = 2530 ms, TE = 3.44 ms, Flip = 7º, 192 slices, matrix = 256x256, 1 mm thick sagittal slices; 5min, 52sec). Whole brain EPI BOLD images were acquired during eyes-open rest (TR = 2000, TE = 30, Flip = 90º, FOV = 224 matrix = 64x64, 30 interleaved AC-PC aligned axial slices, 3.5 mm slice thickness with no gap, 180 TRs; 6min, 4sec). A fieldmap with identical slice prescription was acquired immediately prior to the resting state scan for the purpose of correcting geometric distortions in the EPI data (TR = 400, TE1 = 5.19, TE2 = 7.65, Flip = 60 º, FOV = 224, matrix=64x64, 30 interleaved AC-PC aligned axial slices, 3.5mm slice thickness with no gap; 54sec).

MRI Resting State Analysis

Data were analyzed using FreeSurfer (v5.3.0; Fischl, 2012), FSL (FMRIB Software Library, v5.0.8; Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012) and AFNI (Analysis of Functional NeuroImages, v16.0.00; Cox, 1996). Individual bilateral amygdala masks were created from the MPRAGE data using FreeSurfer's default pipeline. Bilateral amygdala masks were produced for each subject using FreeSurfer segmentations that were then transformed into the subject's functional space. MPRAGE

and fieldmap magnitude images were skull stripped using FSL's BET (Brain Extraction Tool) and then hand edited for accuracy. Slice time correction was performed on raw EPI data, framewise displacement was estimated using FSL's fsl_motion_outliers tool, and data were then corrected for motion using FSL's mcflirt (6 dof). Twenty-four motion confound predictors were generated: 3 linear translation and 3 rotation estimates (6 predictors), the first temporal derivative of these original motion estimates, the square of the original motion estimates, and the first temporal derivatives of the squares (Satterthwaite et al., 2013). Absolute motion was estimated using the RMS summary of the translation and rotation motion estimates. DVARS (Derivative of rms VARiance over voxelS), which measure frame to frame BOLD signal fluctuation across the entire brain (Power et al., 2012), were estimated using FSL's fsl_motion_outliers. Censoring predictors were generated for each TR that contained absolute motion greater than 3.5mm (1 voxel) or a framewise displacement greater than 0.5 mm. Framewise displacement censoring was expanded to include one preceding and one following TR. TRs were additionally censored for DVARS values greater than the 75th percentile plus two times the interquartile range. Participants were excluded if the number of TRs censored exceeded 25% of the resting state scan, meaning that all participants had at least 135 TRs, or 4 min 30 sec of usable data. EPI data were unwarped, which included the registration of each subject's functional data to their structural (MPRAGE) images using BBR, registration of the MPRAGE image to the MNI152 standard brain, (12 dof), and subsequently registration of the EPI data to the standard space. Unwarped EPI data were then demeaned and detrended (linear and quadratic trends) using AFNI's 3dDetrend

(Cox, 1996). The stripped MPRAGE data were parcellated using FSL's fast tool to create masks of grey matter, white matter, and cerebrospinal fluid (CSF), that were then projected into the unwarped EPI space. These masks, which were thresholded at 75% probability and binarized, were then used to generate mean timeseries estimates for each tissue segmentation. Linear regressions were then run on the EPI data for each subject for the purpose of removing confound signals. Nuisance predictors included the timeseries estimates from white matter and CSF, as well as the motion confound predictors. Estimates of global signal were not included in the regression, since the inclusion of global signal may falsely introduce anti-correlations in the data (Birn, 2012; Murphy et al., 2009; Saad et al., 2012). The residuals from the confound regression were bandpass filtered (0.009-0.08 Hz) and spatially smoothed (6mm FWHM Gaussian kernel) prior to subsequent processing. From these residual images, the mean amygdala signal timecourses for each participant were extracted after back-projecting the bilateral masks derived from FreeSurfer into that participant's unwarped EPI space. Back-projected voxels exhibiting greater than 10% signal loss in the corresponding EPI fieldmap were removed from the individual level amygdala masks in order to obtain more accurate estimates of amygdala signal. The extracted mean amygdala timecourses were submitted as predictors for each individual's general linear model (GLM) to identify voxels that correlated in time with the amygdala.

Higher level analyses were conducted using a random effects GLM to compare group differences in connectivity during resting state and to assess individual differences related to maltreatment subtype, chronicity, depression, and resilience in separate GLMs.

All higher level analyses included age and sex as covariates of non-interest. Whole brain cluster correction was performed in FSL with a voxelwise significance threshold of $p<.005$ and a cluster threshold of $p<.05$. For clusters that survived correction, ROIs were back-projected into each individual's unwarped EPI space. Individual zstat maps were transformed to correlation coefficients using the inverse Fisher z transform and mean correlation coefficients were extracted for each individual using the backprojected ROI mask. For each individual, this produced a mean correlation with the amygdala across voxels within significant ROIs.

Results

Resilience and self-report measures

The maltreatment and comparison groups were not significantly different on either the CDRISC [$t(65) = -.711, p = .479$] or success on developmental tasks [$t(65) = -.838, p = .405$] measures (See Table 3.1 for means and standard deviations). Additionally, depression, as measured by the BDI, was not significantly different between groups [$t(65) = -.141, p = .888$]. The CDRISC and success on developmental tasks were not significantly correlated ($p = .214$)

When divided by maltreatment subtype, the Mal-PASA and Mal-NEM groups were not different on the self-reported CDRISC [$t(30) = .825, p = .416$]. The Mal-PASA group had significantly lower scores than the Mal-NEM group on the success on developmental tasks measure [$M_{PASA} = 5.62, SD_{PASA} = 1.96; M_{NEM} = 7.44, SD_{NEM} = 2.90; t(30) = 2.072, p = .047$]. Additionally, the Mal-PASA group had higher levels of depression on the BDI [$M_{PASA} = 14, SD_{PASA} = 12.66; M_{NEM} = 7.75, SD_{NEM} = 5.42$; $t(30) = -$

2.106, p = .044]. The number of developmental periods in which maltreatment occurred was not significantly associated with either measure of resilience or with depression.

Full sample connectivity

The full sample showed positive connectivity of the amygdala with the vmPFC, bilateral insula, bilateral putamen, bilateral hippocampus/parahippocampal gyrus, and superior temporal gyrus (see Figure 3.3). Negative connectivity was observed in the posterior cingulate gyrus. These patterns of connectivity are in line with previous reports of amygdala resting state connectivity (Roy et al., 2009).

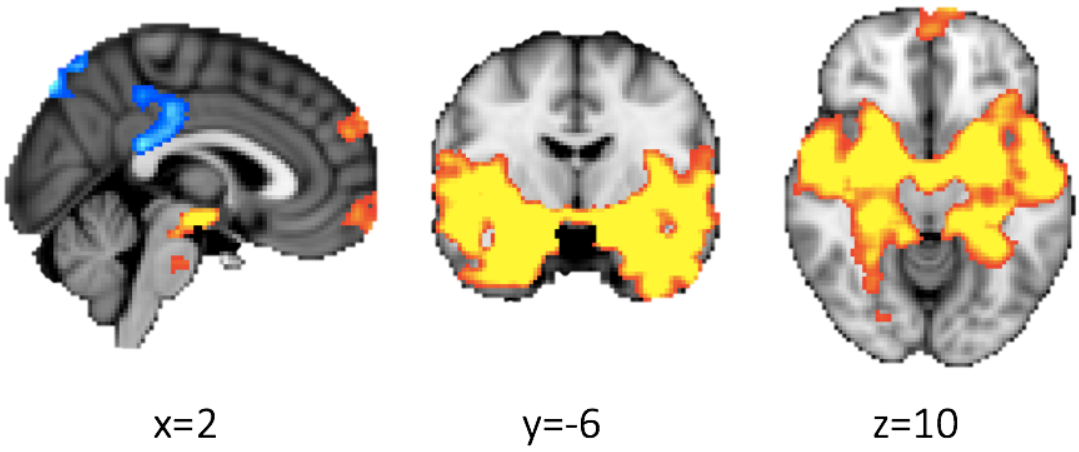

Figure 3.1. Resting state connectivity with bilateral amygdala in the full sample (n = 67). Red/yellow indicates areas with positive correlation with the bilateral amygdala and blue indicates negative correlation. Coordinates are in MNI space. Regions survive voxelwise significance threshold of p<.005, cluster correction of <.05.

Maltreatment and comparison groups

There were no significant differences in amygdala functional connectivity between the maltreatment and comparison groups.

Sex & age effects

The main effects of the covariates of sex and age were evaluated while controlling for maltreatment status. There were no significant main effects of age. For sex, there was an effect in the right insula, bilateral inferior/middle temporal, and precuneus (See Table 3.3). In each of these regions, males had more positive connectivity with the amygdala than females.

Depression

For the BDI-II measure of depression, there was a significant positive correlation between depression and connectivity of the amygdala with the right parahippocampal gyrus (See Table 3.3). There were no significant interaction effects between maltreatment and depression.

Maltreatment subtype

The Mal-PASA and Mal-NEM groups were compared to each other, and to the comparison group individually. Compared to the Mal-PASA group, the Mal-NEM group had more connectivity of the amygdala with the vmPFC, however this region did not survive cluster correction. Compared to the comparison group, the Mal-PASA group had significantly more connectivity with the right parahippocampal gyrus (See Table 3.3; Figure 3.2). This was the same region where a correlation with depression was observed. Once depression was included in the model, the group difference was still present, but the

region became smaller and was no longer large enough to survive cluster correction. The association with depression was also reduced in this model.

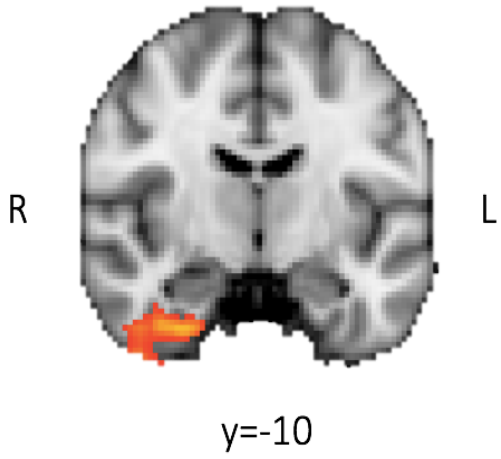

Figure 3.2. Greater amygdala-parahippocampal gyrus connectivity in the Mal-PASA group compared to the non-maltreated group. Coordinates are in MNI space. Regions survive voxelwise significance threshold of $p<.005$, cluster correction of $<.05$.

Chronicity

Chronicity of maltreatment across childhood was evaluated using the number of developmental periods in which maltreatment occurred. Within the maltreated group, the number of developmental periods was positively associated with amygdala-occipital connectivity. There was also a negative correlation between number of developmental periods and positive amygdala connectivity with the dmPFC, bilateral caudate, inferior frontal gyrus, and frontal pole (See Table 3.3, Figure 3.3).

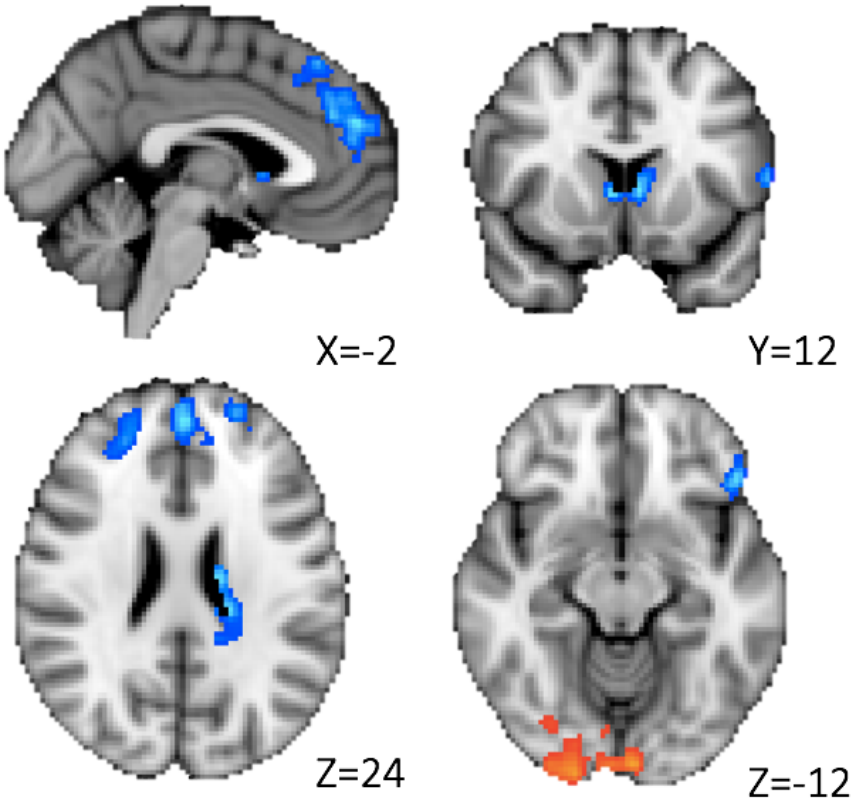

Figure 3.3. Correlations between amygdala connectivity and number of developmental periods (chronicity) of maltreatment. Regions in red-yellow represent positive correlations with number of developmental periods, while regions in blue represent negative correlations. Coordinates are in MNI space. Regions survive voxelwise significance threshold of $p<.005$, cluster correction of $<.05$.

Resilience: Self-report

For the CDRISC self-report measure of resilience, there were no main effects of resilience (while controlling for maltreatment status, sex, and age). There was a

significant interaction between CDRISC scores and maltreatment status in the left caudate (Figure 3.4). For comparison participants, there was a positive relationship between amygdala-caudate connectivity and resilience. In the maltreated group, there was a negative correlation between amygdala-caudate connectivity and resilience.

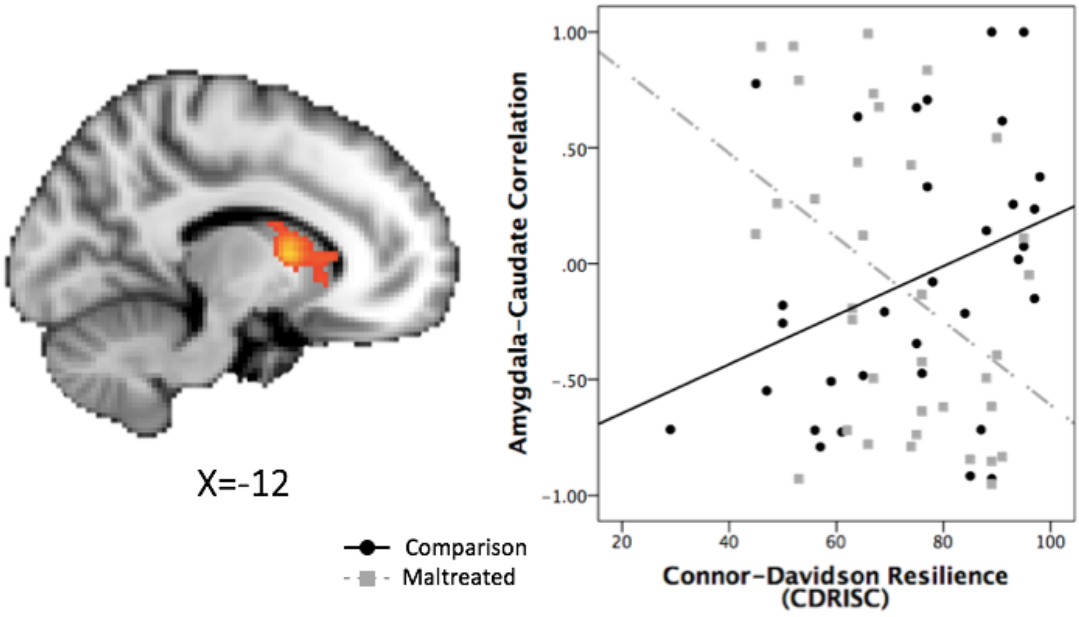

Figure 3.4. Interaction between self-reported resilience (CDRISC) and maltreatment in amygdala connectivity with the left caudate. Graph shows comparison group exhibited positive relationship between resilience and amygdala-caudate connectivity, while the maltreated group showed a negative relationship. Coordinates are in MNI space. Regions survive voxelwise significance threshold of $p<.005$, cluster correction of $<.05$.

Resilience: Developmental tasks

There were no significant correlations between the Developmental Tasks measure of resilience and connectivity that survived once controlling for sex and age. Although the interaction of maltreatments status and Developmental Tasks revealed clusters in the rostral mPFC, and right insula, these regions did not survive cluster thresholding.

Discussion

In this study we evaluated the long-term neural correlates of childhood maltreatment with resting state functional connectivity. Due to our interest in emotion processing and regulation, we used the bilateral amygdala as the seed region to evaluate differences in limbic connectivity. We predicted effects related to maltreatment history, maltreatment subtype and chronicity, and individual differences in resilience following adversity. Overall our results suggest that variations in the experience of maltreatment and in an individual's adaptation are both critical variables to consider when evaluating the long-term impact of maltreatment on neural circuitry.

Contrary to our expectations, we did not observe differences in amygdala resting state connectivity as a function of childhood maltreatment history. In our sample, there were no significant differences between the adults who had experienced childhood maltreatment and those who had not. This lack of expected finding may be due to the fact that all participants came from high-risk, low socioeconomic backgrounds. We know that poverty is a stressful early experience that has lasting impacts on brain development (Farah et al., 2006; Hanson, Hair, et al., 2013; Luby et al., 2013; Miller & Chen, 2013).

Therefore, it is possible that with our well matched control group we were unable to separate the effects of maltreatment from the other chronic stressors experienced by our sample. Given the many years that have passed in our sample since the adults experienced childhood maltreatment, it may be difficult to disentangle the stress of maltreatment from many other life stressors over the course of development. Previous work from our group has observed maltreatment related differences *task-based* amygdala connectivity (Jedd et al., 2015). Given those findings, it may be that frontolimbic circuitry differences are only apparent when the system is sufficiently challenged by an emotional stressor. At rest the circuitry may function similarly, with differences only observable once the system has been engaged.

While not part of our original hypotheses, we observed sex differences in amygdala connectivity, whereby males had more connectivity with the right insula, bilateral inferior temporal cortex, and precuneus. This was observed while controlling for maltreatment, and strengthened our justification for using sex as a covariate in subsequent analyses. We did not observe an interaction between maltreatment and sex. While not widely studied, there is prior evidence of sex differences in amygdala connectivity, with sex specific lateralization of left and right amygdala connectivity (Kilpatrick, Zald, Pardo, & Cahill, 2006). In our case, we observed differences in bilateral amygdala connectivity. Although the sex differences observed did not interact with maltreatment status, there may be more to learn about the development of sex differences in limbic connectivity in high-risk environments.

To better understand the many variables at play in our sample, we also investigated whether depression symptoms were associated with amygdala connectivity. We observed a correlation between depression and connectivity of the amygdala with the right parahippocampal gyrus. The parahippocampal gyrus is involved in a range of cognitive and emotional functions, including memory and contextual processing (Aminoff, Kveraga, & Bar, 2013; van Strien, Cappaert, & Witter, 2009). There is evidence that the amygdala interacts with the parahippocampus to modulate the storage of emotional memories (Kilpatrick & Cahill, 2003) Interestingly, we observed differences in this same region when we divided the maltreated group into subtypes, with participants who experienced physical abuse and/or sexual abuse (Mal-PASA group) and those who experienced only non-physically violent forms of maltreatment (neglect and emotional maltreatment, Mal-NEM group). In comparison to the non-maltreated participants, the group exposed to physical violence had greater connectivity between amygdala and right parahippocampal gyrus. The overlap between this finding and the correlation with depression is perhaps unsurprising, given the higher depression ratings in the group exposed to physical violence compared to the neglected and/or emotionally maltreated group. Once we included both maltreatment subtype and depression in the model, both effects became smaller, but were still present, in slightly different areas of the parahippocampal gyrus. In other words, maltreatment subtype and depression exerted both unique and overlapping influence on connectivity between the amygdala and the right parahippocampal gyrus.

Our results suggest that the type of maltreatment matters for understanding alterations to limbic circuitry. Although it was not large enough to survive our stringent cluster correction, the observation of increased amygdala-vmPFC connectivity in the physically/sexually abused group compared to the neglect/emotional maltreatment group is of interest, since amygdala-vmPFC connectivity is critical to emotion regulation (Kim, Loucks, et al., 2011). This, together with the difference observed in the parahippocampal gyrus, suggests that there are different effects of physically violent forms of abuse versus non-violent abuse/neglect. This observation fits well with the framework put forward by McLaughlin, Sheridan, and Lambert (2014), which proposes unique neural effects of threat versus deprivation. Once we divided our maltreatment group into subtypes we may have had insufficient power to detect differences that would survive cluster correction. Extension of this work is necessary to determine whether different maltreatment subtypes are reliably associated with alterations to frontolimbic circuitry.

We also observed differences in connectivity related to the chronicity of maltreatment experience. There was a negative correlation between the number of developmental periods in which maltreatment occurred and amygdala connectivity with large regions in dmPFC and bilateral caudate. In other words, individuals with more maltreatment experiences across development had less connectivity with these regions. Altered connectivity between the amygdala and dmPFC during performance of an emotional task has been observed previously by our group in a subset of these same individuals (Jedd et al., 2015). Generally, the dmPFC is thought to help regulate emotion through cognitive processes, such as reappraisal, and in the expression of fear (Banks,

Eddy, Angstadt, Nathan, & Luan Phan, 2007; Etkin et al., 2011; Ochsner & Gross, 2005). Less connectivity between the amygdala and dmPFC in adults who had longer extent of maltreatment experiences may mean that the baseline circuitry underlying cognitive strategies for emotion regulation is negatively impacted. The bilateral caudate was not a region that we hypothesized would vary in connectivity. While often associated with motor control, the caudate, a region rich in dopamine, is also involved in reward processing, decision making, and cognitive control (Balleine, Delgado, & Hikosaka, 2007). Altered connectivity of the caudate with the amygdala may be indicative of changes to the reward system, however more research is needed to assess this possibility.

The final goal of our study was to examine whether individual differences in resilience or adaption were associated with differential connectivity. Because there are multiple ways to conceptualize resilience, we used two different approaches to characterize positive adaptation. The first, the CDRISC measure, was a self-report questionnaire that probed the individual's perception of their own ability to cope with and bounce back from adversity. The second method used a more objective approach to evaluate success on developmental tasks in a number of domains, from relationships to employment, to substance use. These two measures captured unique aspects of the larger construct of resilience, and were not significantly correlated with one another.

In previous work from our group, we observed associations between the success on developmental tasks measure and task-based frontolimbic connectivity (Demers et al., under review). However, in this examination of resting state functional connectivity, success on developmental tasks was not a strong predictor of connectivity. Rather,

perceived self-efficacy, as measured by the CDRISC, was associated with differential connectivity, depending on maltreatment history. In the left caudate, we found a positive relationship between resilience and amygdala-caudate connectivity in the comparison group, but a negative association in the maltreated group. Therefore, high resilience in the maltreated group was linked to *lower* amygdala-caudate connectivity, while resilience in the comparison group involved *higher* amygdala-caudate connectivity. Interestingly, in a study of children, Pagliaccio and colleagues (2015) found an interaction effect in amygdala-caudate connectivity whereby increased genetic risk was associated with lower connectivity in individuals who had experienced more stressful life events, and higher connectivity in children with low incidence of stressful life events. This finding does not map neatly on to our own since the interaction was observed with increasing genetic risk, not increasing resilience to stress. However, it does suggest that the caudate may be an important region that has differential communication with the amygdala depending on early life experience. Since amygdala-caudate connectivity is not widely studied, particularly following early life stress, our study highlights the need to better understand the role of this circuit and its response to experience. Generally, in our sample, the role of amygdala-caudate connectivity, and its association with adaptation, varied by maltreatment history.

This study is not without limitations. Since we have imaging data from only one time-point in adulthood, we cannot say whether there were pre-existing differences in brain function that preceded maltreatment or resilient functioning. Little is known about the neural correlates of resilience, and it is not clear whether altered limbic circuitry is a

protective factor, an outcome of resilience, or if there are unmeasured additional variables at play. One strength of the study was the well-matched control group, who came from similarly high-risk, low socioeconomic backgrounds. We intentionally included well-matched comparison participants to assess the specific effects of maltreatment, without the added contrast of unequal socioeconomic status. However, as demonstrated by our results, in a sample who have all experienced early life stress, the separable effects of maltreatment may not be detectable in amygdala functional connectivity into adulthood. This work highlights the need to understand the impact of poverty on the developing brain, since low socioeconomic status is a potent stressor. A third comparison group of low-risk adults from middle to higher socioeconomic backgrounds would have been helpful in defining a more typical pattern of limbic connectivity in a similar age group, without the added risk of poverty. Additionally, while we were able to separate out physically violent experiences of maltreatment from non-violent experiences, there is still much to be learned about the effects of unique maltreatment subtypes. Since overlap in the types of maltreatment experienced is very common, we were not able to isolate the effects of each kind of experience.

A large proportion of our original sample (33 participants) was excluded from the final analyses due to head-motion within the scanner. Our scan was relatively short, and therefore, we were concerned about retaining enough clean data to be able to reliably characterize patterns of resting-state correlations. Additionally, head motion has been shown to be associated with spurious correlations in resting-state connectivity analyses (Power et al., 2012). We therefore erred on the side of excluding participants in favor of

retaining clean data. While we believe this strengthens the validity of the remaining data, we recognize that we excluded a large proportion of our sample, potentially restricting the variability within our data. The high rates of motion are atypical for adult studies, however, given the high-risk nature of our sample, it is perhaps less surprising that many individuals were unable to stay still during the scan. The final sample of included participants therefore likely reflects higher functioning individuals who were better able to regulate their behavior in a potentially stressful scanning environment.

Overall, our findings highlight individual differences in maltreated individuals and show the need to move beyond evaluating simple group differences. Within a sample who all came from high-stress environments, maltreatment status was not a significant predictor of amygdala resting state connectivity. However, we did observe significant differences in relation to the type of maltreatment and the chronicity of maltreatment experiences across childhood. The relationship between depression and connectivity as well as the interaction observed between resilience and maltreatment, all indicate that understanding effects of early adversity is a complicated story, with many variables at play. The type and timing of maltreatment, sex, mental health, and adaptive functioning in adulthood, all contribute in complex ways to the connectivity of the limbic system.

Table 3.1. Demographics and sample characteristics.

Sample Characteristics	**Maltreated Group *N*=35**	**Comparison Group *N*=32**	*p*-value
Age, *M*(*SD*)	30.89 (3.06)	29.22 (3.62)	**.045**
Male, *n*(%)	17 (48.6)	16 (50)	.907
Race, *n*(%)			.313
Black	24 (68.6)	25 (78.1)	
White	9 (25.7)	3 (9.4)	
Other/Multiracial	2 (5.7)	4 (12.5)	
Total Family Income, *M*(*SD*); Range	$32.9K (23.3K); 2.3K- 103K	$30.3K (20.9K); 5.2K- 100.1K	.629
Marital Status *n*(%)			.530
Not married	17 (48.6)	18 (56.2)	
Married or cohabitating	18 (51.4)	14 (43.8)	
Education *n*(%)			.360
Some high school	7 (20)	4 (12.5)	
High school diploma or GED	16 (45.7)	10 (31.3)	
Technical degree, Associate's degree, or some college	9 (25.7)	17 (53.1)	
Bachelor's or Master's degree	3 (8.6)	1 (3.1)	
Depression- BDI scores *M(SD)*	10.14 (9.90)	10.47 (8.97)	.888
Resilience			
CDRISC, *M(SD)*	71.86 (14.74	74.75 (18.48)	.479
Success on Developmental Tasks, *M(SD)*	6.71 (.47)	7.28 (.49)	.405

Table 3.2. Characteristics of childhood maltreatment.

Maltreatment Characteristics	***N (%)***		***N (%)***
Maltreatment Subtype		**Number of Subtypes**	
Emotional Maltreatment	19 (59.4)	1 subtype	10 (31.2)
Physical Neglect	25 (78.1)	2 subtypes	14 (43.8)
Physical Abuse	13 (40.6)	3 subtypes	7 (21.9)
Sexual Abuse	4 (12.5)	4 subtypes	1 (3.1)
Mal-PASA	16 (50)		
Physical abuse and sexual abuse			
Mal-NEM	16 (50)		
Neglect and emotional maltreatment only			

Note: Due to a few cases of poor specificity in maltreatment records, 3 cases were missing clear subtype classifications and sufficient information on timing.

Table 3.3: Amygdala resting state connectivity coordinates in regions showing significant associations with individual differences. Whole brain cluster correction was performed in FSL with a voxelwise significance threshold of $p<.005$ and a cluster threshold of $p<.05$.

Region	Side	Volume (mm^3)	Z-mean	MNI Coordinates		
				x	y	z
Sex						
Male > Female						
Middle/Inferior temporal gyrus	L	6200	2.943	-50	-60	6
Inferior temporal gyrus	R	3680	2.956	42	-58	0
Insula/Operculum	R	3240	2.955	46	-4	14
Precuneus	B	2352	2.764	0	-52	42
Depression						
Positive correlation						
Parahippocampal gyrus	R	4176	3.169	34	-6	-42
Number of Developmental Periods (Chronicity)						
Positive correlation						
Lateral occipital cortex	R	23016	3.117	16	-60	72
Lingual gyrus/occipital pole	R	8224	2.814	6	-78	-8
Negative correlation						
Dorsal medial PFC	B	12400	2.99	0	52	26
Frontal pole	R	4368	2.916	24	44	20
Thalamus	L	3784	2.942	-18	-26	22
Caudate	B	3768	2.976	-6	10	2
Orbital frontal cortex	L	3128	3.031	-44	40	-18
CDRISC (Resilience)						
Interaction with maltreatment						
Caudate	L	3024	2.948	-10	4	8

CHAPTER 4: General Discussion

This dissertation explored the relationship between early life stress (ELS) and resting state functional connectivity of the amygdala in two samples: adolescents adopted from orphanage care as young children and adults with a history of childhood poverty and maltreatment. The goals of the dissertation were to characterize patterns of amygdala connectivity following ELS and to relate individual differences in connectivity to aspects of the experience of and response to stress. We used resting state functional connectivity to understand patterns of amygdala intrinsic connectivity that were not specific to a particular task or psychological state. This analysis allowed us to move beyond traditional regional activation approaches towards understanding networks within the brain and the crosstalk between regions. Each of these studies makes a unique contribution to the existing literature by providing novel information on the neural sequelae of ELS.

In Study 1, resting state connectivity of the amygdala was explored in a sample of youth who had experienced early deprivation in the form of institutional rearing. Post-institutionalized (PI) youth were compared to non-adopted peers who were raised by their biological families. We observed greater amygdala-ventral medial prefrontal cortex (vmPFC) and reduced amygdala-insula connectivity in PI youth. However, individual differences in connectivity were not related to current anxiety symptoms or duration of deprivation.

In Study 2, we characterized resting state amygdala connectivity in an adult sample, all of whom came from high-risk, low socioeconomic backgrounds, and half of

whom additionally experienced childhood maltreatment. Contrary to expectations we did not observe group differences in connectivity related to childhood maltreatment, but rather found altered amygdala connectivity throughout the brain in relation to the type and chronicity of childhood maltreatment experiences. Additionally, we observed an interaction between self-reported resilience and maltreatment in amygdala-caudate connectivity.

Impact of ELS on amygdala-PFC circuitry

Amygdala connectivity with the prefrontal cortex (PFC) was of special interest in this dissertation given the PFC's role in emotion regulation and its demonstrated sensitivity to stress (Etkin et al., 2011; Tottenham, 2014). In each study, we observed alterations to amygdala-PFC connectivity, although the nature of the effects varied. In Study 1, the ELS group (PI youth) had greater connectivity between the amygdala and vmPFC, a region associated with emotion regulation and fear extinction (Kim, Loucks, et al., 2011; Phelps, Delgado, Nearing, & Ledoux, 2004). In Study 2, greater chronicity of maltreatment across development was associated with reduced connectivity between the amygdala and dorsal medial PFC (dmPFC), a region involved in the cognitive control of emotion and also fear expression (Etkin et al., 2011). The regions of significant effects in the PFC were therefore different between the two studies.

Given that both the age ranges and types of early adverse experiences are different across the two studies, it is impossible to directly compare the effects. It may be the case that the effects of early adversity change across development, with initial adolescent differences in ventral portions of the PFC and differences in dorsal PFC not

emerging until adulthood. However, we cannot test this possibility given the current data because we did not have longitudinal data within this age range. It is also very possible that the different types of ELS have unique regional effects. In one case, PI children were deprived of cognitive and social stimulation, and in particular, did not get the species-expected input from a dyadic caregiving relationship. In the case of adults who experienced childhood maltreatment, children did experience an early caregiving relationship; however, the relationship was either neglectful, or actively harmful to the child. McLaughlin, Sheridan, and Lambert (2014) have proposed differential effects on brain development following threat versus deprivation. Our findings provide some support for this; in the adult sample we observed differences related to maltreatment subtype with distinctions between physically threatening and non-physically threatening maltreatment. Therefore, it seems likely that the experience of orphanage rearing, with global deprivation, would also produce differential effects on connectivity when compared to abuse. In addition to differences in the type of experience, the temporal profile of ELS was very different across the two groups. For PI children, ELS was limited to infancy and early childhood, whereas it was more persistent across development in adults who came from high-risk backgrounds and experienced maltreatment within the family. Therefore, there are many potential factors contributing to the unique effects observed across the two studies and more research is needed to tease apart the unique effects of type and timing of adversity.

Broadly, disruption to amygdala-prefrontal circuitry at rest may be an underlying mechanism through which diverse forms of ELS lead to psychopathology. Previous

studies have suggested that amygdala-PFC connectivity at rest relates to anxiety (Hahn et al., 2011; Kim, Loucks, et al., 2011; Kim, Gee, Loucks, Davis, & Whalen, 2011) and a growing literature has linked dysfunction of this circuitry to other disorders, such as depression, mania, and schizophrenia (Bebko et al., 2015; Connolly et al., 2017; Cullen et al., 2014; Liu et al., 2014). The baseline crosstalk between the amygdala and PFC seems to be an important marker to consider when evaluating risk for psychopathology, that, as demonstrated in this dissertation, is sensitive to childhood adversity.

Impact of ELS on amygdala connectivity beyond prefrontal circuitry

In addition to differences in amygdala-prefrontal connectivity, both studies demonstrated that stress related alterations extend into other neural pathways. Reduced amygdala-insula connectivity was observed in PI youth in Study 1. In Study 2, we observed differences in amygdala-parahippocampal connectivity in relation to maltreatment subtype. Additionally, we found amygdala-caudate alterations in association with chronicity and this circuitry showed an interaction between resilience and maltreatment. Together these findings suggest that ELS exerts effects that extend beyond frontolimbic circuitry, which is commonly discussed in relation to early adversity (e.g. Callaghan & Tottenham, 2015). While prior research has generally focused on the top-down regulation of the amygdala (from the PFC to the amygdala), our findings suggest that the story may be more complex, with altered communication of the amygdala with regions involved in other aspects of emotion processing/interoception (insula), memory (parahippocampus), and cognition/reward (caudate). Therefore, emotion processing deficits observed in relation to ELS may not be simply due to

impaired regulation. The amygdala also may be differentially involved in other networks related to cognition/emotion. Indeed, links between ELS and other neural networks have been reported, including the default mode network (Bluhm et al., 2009; Philip et al., 2013) and the salience network (Van der Werff et al., 2013). This dissertation further motivates exploration of neural circuits beyond frontolimbic connectivity, that will likely uncover additional networks that are vulnerable to ELS.

Long-term impact of ELS

This dissertation highlights the potential of ELS to exert long lasting impacts on brain circuitry. In both studies, connectivity differences associated with variation in early experience were identified even years after ELS. In Study 1, PI youth were tested at 12-14 years of age, with a mean age of adoption of 16 months of age. At the time of testing, PI youth had therefore spent a minimum of 7 years in their adoptive homes, with many experiencing over 10 years of life in these positive, likely highly enriching, environments. However, a history of early orphanage care was still associated with alterations to the circuitry underlying emotion processing and regulation. In Study 2 we observed connectivity differences in a sample of adults related to type and chronicity of experiences. Together these results are in line with previous findings showing long-term associations between ELS and brain structure and/or function (Hart & Rubia, 2012; Pechtel & Pizzagalli, 2011). This dissertation adds to a growing literature demonstrating that stress during infancy and childhood shapes the way the limbic system communicates across the lifespan.

Although direct comparison of effects is difficult, different profiles of regional effects of ELS in PI youth (Study 1) in comparison to maltreated adults (Study 2) suggest that the nature of the brain's response to ELS is likely not universal across development. More longitudinal research is needed to understand the trajectory of both normative and atypical patterns of connectivity across development. As the field moves away from simple regional activation analyses towards a more complex model of functional connectivity across brain regions, it will be increasingly important to understand how communication between regions changes, both with maturation and/or as a function of experience. The trajectory of connectivity may be perturbed by early adversity, placing the system on a different developmental pathway. What starts out as an adaptive response to an early stressor may have negative long-term impacts over the course of development, particularly in cases where the environmental context changes (as can be seen in the children adopted from orphanage care). Neural circuitry that served an adaptive function in one context may therefore prove maladaptive in other contexts. These effects may manifest differently at different points in development.

One prominent hypothesis about the effects of ELS is the stress-accelerated maturation hypothesis (Callaghan & Tottenham, 2016). While our studies were not designed to test this hypothesis, we did observe amygdala-PFC connectivity differences in PI youth that may be consistent with early maturation. Premature maturation of fear and emotion circuitry could be a necessary or adaptive response to early adverse environments; however this response may come at a cost later in life (Tottenham, 2014). Unfortunately, we do not have longitudinal data to test whether our sample of maltreated

adults might have had similar patterns of advanced connectivity in childhood/early adolescence. Again, longitudinal data are needed to provide further support to the hypothesis of stress-accelerated maturation.

Individual differences in ELS experience and response

One of the primary goals of this dissertation was to identify differences in connectivity related to the type and timing of stressful early experiences. While Study 1 did not observe effects of the duration of deprivation, Study 2 revealed individual differences in connectivity related to the type and chronicity of maltreatment. Physically and sexually abused participants had altered connectivity with the parahippocampal gyrus, a region involved in memory and emotion, when compared to non-maltreated participants. This difference was not observed when comparing participants who only experienced neglect or emotional maltreatment, suggesting a distinction between the experience of threat versus deprivation. Prior research has demonstrated that abused children show different behavioral deficits in the recognition of emotion than those who are neglected (Pollak et al., 2000; Pollak & Sinha, 2002; Pollak & Tolley-Schell, 2003). Our finding further highlights the differences between these types of maltreatment experience and suggests that research examining differential effects in neural networks is necessary to understand the mechanisms underlying behavioral differences.

In Study 1, we did not observe any effects of the duration of deprivation, only group differences. In contrast, in Study 2 there were no group differences in PFC connectivity related to maltreatment history, only effects related to individual differences in the duration/chronicity of maltreatment experiences. While the lack of duration effects

in the PI children is counterintuitive, it may be that the severity of early deprivation prior to adoption was sufficient to exert long lasting influence, even in children adopted by 4 months of age. Similar findings have been observed by the English and Romanian Adoptees Study, which found persistent adverse effects of deprivation in children adopted after 6 months of age, with less differentiation in relation to age at adoption in the 6-42 month range (Beckett et al., 2016). This study suggested that 6 months may represent an important threshold for lasting negative effects. Therefore, adoption in the first year of life may not be early enough to prevent lasting effects of this severe form of early deprivation. The severity of deprivation in infancy may overwhelm effects associated with individual differences in later experience.

Although we did not observe duration effects in the PI sample, in Study 2 the chronicity of childhood maltreatment experiences was predictive of amygdala connectivity in adulthood across a number of regions, suggesting that the duration of stress was a critical factor. In contrast to the comprehensive environmental deprivations experienced by children in orphanage care, childhood maltreatment in the home may be a fundamentally different experience, with the cumulative stress of maltreatment building over time. Therefore, the chronicity of negative experiences across childhood may be more predictive of later outcomes for children raised in the context of a family than for children who experience the wide-spread early deprivation of orphanage rearing. Together, the studies in this dissertation suggest that effects of timing and chronicity may vary depending on the type and severity of adversity.

Individual differences in resilience and adaptive functioning

It is well-known that there are individual differences in adaptation following ELS (Cicchetti, 2013). We did not have direct measures of resilience in Study 1, with adolescents. However, in Study 2 we had measures of everyday adaptive functioning and resilience which we then linked to brain circuitry. Our study makes an important, novel contribution, since the literature on the neural correlates of resilience is especially sparse. In our adult sample, all of whom were raised in low-socioeconomic backgrounds, we observed an interaction between resilience and maltreatment history in amygdala-caudate connectivity. In non-maltreated, comparison adults, resilience was negatively associated with amygdala-caudate connectivity; in other words, individuals who were more resilient had lower connectivity. However, for the maltreated adults, this association was reversed: more positive amygdala-connectivity was linked to higher resilience. Although the caudate serves many purposes (e.g. cognitive control, implicit learning, motor inhibition), it is part of the striatal reward processing system. Therefore, adults with a history of maltreatment may use limbic-reward circuitry differently; amygdala-caudate connectivity may serve a compensatory mechanism that fosters higher perceived self-efficacy.

Broadly, our findings suggest that individual differences in adaptive functioning following adversity are manifest in the brain, and that the neural profiles of resilient individuals differ depending on the kind of stress experienced. Self-reported resilience may therefore be an important measure to add to future studies with early risk samples. In general, much remains to be learned about the neural correlates of resilience to better understand how individuals show positive adaptation in spite of early stress.

Other forms of risk

Although this dissertation focused on characterizing outcomes following two types of ELS, results suggest that other forms of adversity, beyond child abuse and neglect, may also be important in the consideration of network connectivity. Specifically, the lack of observed group differences in connectivity related to childhood maltreatment history in Study 2 was surprising. However, given that all participants in Study 2 were raised in low socioeconomic environments, it is possible that effects specific to maltreatment were washed out by other risk factors, such as poverty and neighborhood risk. There are a number of studies showing both short and long-term structural brain alterations associated with childhood poverty (Hanson, Hair, et al., 2013; Jednoróg et al., 2012; Noble et al., 2015). Our study demonstrates the importance of appropriate control groups when evaluating the effects of ELS. Without a comparison group that is well matched on risk factors like socioeconomic status, we cannot be sure whether effects reflect childhood maltreatment specifically, or risk more generally. When evaluating the outcomes associated with ELS, more precise measures of cumulative risk may be critical to defining the full range of stressors (Evans, Li, & Whipple, 2013).

Policy implications

This work has implications for policies and interventions that aim to help children and adults who have experienced ELS. Our results add to the mounting body of evidence that ELS leads to long-term impacts on the brain. This in itself is a useful contribution, since policymakers should be informed of the full scope of disruption to both brain and behavior following early adversity. To be convinced of the need to invest in intervention and preventative measures, policymakers must have evidence of the gravity of the

problem, including the long-term effects. While behavioral data certainly suggests that early adverse experiences, such as maltreatment, are associated with negative life outcomes, the added dimension of brain science lends support to the seriousness of childhood adversity as an intense stressor that compromises normative development. Although not always warranted, neuroscientific evidence has unique appeal and can be especially persuasive to the public (Weisberg et al., 2008; McCabe & Castel, 2008). Brain data are often given extra weight in decision-making and can help galvanize legislators to enact policy supporting child abuse prevention. Therefore, it is critically important that scientists communicate and leverage this information accurately and responsibly.

Unfortunately, despite the high prevalence of ELS, there is a scarcity of effective prevention and intervention programs that address recovery in individuals with a history of adversity. Incorporating neuroimaging into the existing literature on ELS can help explain the mechanisms through which maltreatment gets "under the skin". Understanding mechanisms is critical to designing interventions that effectively target vulnerable processes. An example of this approach can be seen in applications of attention bias modification for the treatment of anxiety (e.g. Browning, Holmes, Murphy, Goodwin, & Harmer, 2010; Hakamata et al., 2010). By understanding the neural circuitry underlying anxiety in response to threat, researchers were able to design behavioral interventions that in turn altered brain function and reduced anxiety. Critically, our findings suggest potential mechanisms through which ELS leads to psychopathology. Not only is the structure of the brain altered, but also the way that different regions of the

brain interact at rest, even when they not being actively recruited for a task, is fundamentally changed. More research is needed to explore the full implications of altered circuitry, but this research is one important step towards identifying mechanisms.

In both Study 1 and Study 2, disruption to the parent-child care-giving relationship was at the core of the ELS experience. Therefore, interventions targeted towards the parent-child relationship may be most effective at ameliorating the impact of ELS. In fact, the PI youth in our study received an intensive intervention when they were adopted into families. Although, as demonstrated by our results, there are lingering effects, PI youth show great plasticity and developmental catch-up across many domains of functioning (van Ijzendoorn & Juffer, 2006). The Bucharest Early Intervention Program, which randomly assigned children to foster care or continued institutional care, showed the effectiveness of family based interventions on cognitive and emotional outcomes (e.g. Ghera et al., 2009). Therefore, although we observed altered neural development in PI children, there is good evidence showing the effectiveness of adoption as an intervention and the amelioration of negative effects.

There are a wide-range of prevention and intervention programs aimed towards addressing child maltreatment (MacMillan et al., 2009). The most effective, evidence-based programs to date include the Nurse-Family Partnership (Olds, 2006) and the Early Start Program, both home visitation program that provide support for new parents and have been linked to reduced rates of child maltreatment (MacMillan et al., 2009). A core similarity of most evidence-based program is the reduction of parental stress and encouragement of sensitive parent-child interactions and contingent responsiveness (what

have been termed "serve and return" interactions (Shonkoff & Bales, 2011)). This dissertation further strengthens the argument for intervention programs that focus on the parent-child relationship by underscoring disruption to brain circuitry in the absence of healthy parent-child interactions.

The results of Study 2 demonstrated that, in high-risk populations, long-term effects specific to childhood maltreatment may not be detectable in individuals who were all raised in environments of poverty and neighborhood violence. This has both targeted and wide-spread implications for how we think about childhood poverty. Broadly, on a social policy level, more attention should be paid to addressing childhood poverty to combat the long-term negative impacts of this potent stressor. Mounting evidence shows the negative and costly impact of poverty on developmental outcomes (Duncan et al., 1994; Farah et al., 2006; Kim et al., 2013; Miller & Chen, 2013). As well as large scale policy changes, treatment and intervention approaches that use trauma-informed care may need to shift towards a broader focus on *adversity*-informed care, since trauma is not the only form of ELS that has lasting impacts on development.

In addition to understanding the many forms of ELS in childhood, we need better data on the most effective timing for interventions. While there are known periods of rapid changes in brain development, there is much still to be learned about when brains are most sensitive to stress and amenable to intervention. Together, our results show the importance of early experience, during which neural circuits are especially sensitive to environmental input. In the case of international adoptees, deprivation within the first six months of life was enough to produce altered neural circuitry at adolescence. The

relationship between connectivity and chronicity in the sample of maltreated adults showed that the more frequently a child experiences maltreatment across childhood, the greater the disruption to brain function. Therefore, prevention efforts and interventions that minimize both early stress and continued stress across childhood are critical for the promotion of healthy brain development. Indeed, economists have shown greater return on investment for programs that intervene earlier in development (Doyle, Harmon, Heckman, & Tremblay, 2009).

While it is necessary to communicate the critical importance of intervening early, it is also important to emphasize that there is great potential for resilience in the developing system. Our findings suggest that there are neural correlates of resilience and adaptation, and that the brain's response to adversity looks different in resilient individuals. Resilience is not a static, immutable trait, but rather a *dynamic process* of adaptation (Masten, 2001). As such, we have great potential to intervene and foster healthy development. Effective communication of the science behind the brain's response to ELS is necessary to highlight vulnerability of the brain, but by focusing on resilience in conjunction with ELS, we can shift the conversation towards strengthening the brain's capacity for positive adaptation.

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