INTERGENERATIONAL TRANSMISSION OF CHILDHOOD MALTREATMENT: CHARACTERIZING POTENTIAL MECHANISMS AND OFFSPRING NEUROBEHAVIORAL OUTCOMES

By

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ABBREVIATIONS

11ß-HSD – 11ß-Hydroxysteroid-Dehydrogenase

ABCD – Adolescent Brain Cognitive

ACC – anterior cingulate cortex

ACE – Adverse Childhood Experiences

AC-PC – anterior commissure - posterior commissure

ACTH – adrenocorticotropic hormone

aI – anterior insula

AIC – Akaike Information Criterion

Am-aI – amygdala to anterior insula

Am-vmPFC – amygdala to ventromedial prefrontal cortex

ANCOVA – analysis of covariance

ANOVA – analysis of variance

ANTs – Advanced Normalization Tools Approximation

BOLD – blood oxygen level dependent

CESD – Center for Epidemiological Studies Depression Scale

CFI – Comparative Fit Index

CI – confidence interval

CM – childhood maltreatment

CRH – corticotropin releasing hormone

CTQ – Childhood Trauma Questionnaire

dACC – dorsal anterior cingulate cortex Development

df – degrees of freedom

DMN – default mode network

DSM – Diagnostic and Statistical Manual of Mental Disorders

DTI – diffusion tensor imaging

ECBQ – Early Childhood Behavior Questionnaire-Short Form

ELISA – enzyme-linked immunosorbent assay

EPDS – Edinburgh Postnatal Depression Scale

EPI – echoplanar imaging

FD – frame-wise displacement

FDA – Functional Data Analysis

FIML – Full Information Maximum Likelihood

FIRMM – Frame-wise Integrated Real-time MRI Monitor

fMRI – functional magnetic resonance imaging

FOV – field of view

FRF – Functional Random Forest

GA – gestational age

GAP-43 – Growth Associated Protein 43

GM/WM – gray matter/white matter

HCP – Human Connectome Project

HPA – hypothalamic-pituitary-adrenal

IBQ – Infant Behavior Questionnaire-Revised

IL-6 – Interleukin-6

LA-dACC – left amygdala to dorsal anterior cingulate cortex

LGM – latent growth model

M – mean

mHz – millihertz

MNI – Montreal Neurological Institute

MP-RAGE – Magnetization Prepared Rapid Acquisition Gradient Echo

MPS – maternal perinatal stress

MRI – magnetic resonance imaging

MTL – medial temporal lobe

N – number

NA – negative affect

NIH – National Institutes of Health

ns – non-significant

PALM – Permutation Analysis of Linear Models

pCRH – placental corticotropin releasing hormone

PSS – Perceived Stress Scale

PTSD – Post-Traumatic Stress Disorder

RF – Random Forest

RMSEA – Root Mean Square Error of

ROI – region of interest

RSA – respiratory sinus arrhythmia

rs-fcMRI – Resting-state functional connectivity magnetic resonance imaging

SCL-90 **–** Symptom Checklist

SD – standard deviation

SE – standard error

Sig – Significance

SSP – Strange Situation Paradigm

STAI – State-Trait Anxiety Inventory

t0 – early pregnancy time point

t1 – mid pregnancy time point

T1w – T1-weighted

t2 – late pregnancy time point

T2w – T2-weighted

TE – echo time

TLI – Tucker-Lewis index

TR – repetition time

UCI – University of California, Irvine

USD – United States dollar

vmPFC – ventromedial prefrontal cortex

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ABSTRACT

Childhood maltreatment, such as abuse or neglect, is a pervasive public health problem with lasting consequences for psychological well-being and overall health across the lifespan. There is evidence that the negative effects of childhood maltreatment are not limited to a single individual and may be transmitted across generations, increasing the risk for behavioral and psychiatric disorders in the offspring. The existing paradigm posits that the intergenerational transmission of childhood maltreatment primarily occurs in the context of postnatal maternal mood and maternal-infant attachment; however, there is growing evidence that the intergenerational transmission of childhood maltreatment may also occur during the prenatal period.

The goal of the present work is to increase our understanding of the intergenerational transmission of maternal childhood maltreatment by characterizing potential mechanisms, such as maternal psychological stress during pregnancy, and offspring neurobiological and socioemotional outcomes. Maternal childhood maltreatment history may influence offspring development in utero via stress-sensitive aspects of gestational biology, representing a potential pathway for the intergenerational transmission of childhood maltreatment. Systems undergoing rapid development are particularly susceptible to the influence of environmental factors such as stress; therefore, we examined the developing limbic system shortly after birth to distinguish between the influences of prenatal versus postnatal factors. Maternal psychological stress during pregnancy is potentially a key mechanism for the intergenerational transmission of childhood maltreatment; thus, Study 1 characterized the longitudinal trajectories of maternal stress during pregnancy using a novel approach, the Functional Random Forest,

in two independent mother-infant cohorts. The resulting clusters, characterized by differences in patterns of maternal stress, were examined in relation to neonatal amygdala functional connectivity, infant negative affect development, and maternal childhood maltreatment history. Study 2 examined the association between maternal childhood maltreatment history and neonatal amygdala functional connectivity, infant attachment security, and infant cortisol reactivity. Study 3 expanded on the investigation of the limbic system by examining the association between neonatal hippocampal functional connectivity and maternal childhood maltreatment history. Recognizing the heterogeneity of the hippocampus, a template matching approach with a large adolescent cohort was used to empirically segment the hippocampus.

The results of these studies demonstrate the importance of characterizing the longitudinal heterogeneity of maternal psychological stress during pregnancy and its association with infant brain and negative affect development. They also suggest a neural phenotype related to the limbic system observable in offspring of mothers with a greater history of exposure to maltreatment during childhood. In the present work, stronger amygdala to dorsal anterior cingulate cortex functional connectivity was associated with insecure attachment in the offspring of mothers with a history of exposure to maltreatment during childhood. This association suggests a potential prenatal, instead of postnatal, role for maternal childhood maltreatment in infant attachment security. Finally, the findings suggest that the intrauterine period is important for the intergenerational transmission of the effects of maternal childhood maltreatment. Understanding the heterogeneity of maternal psychological stress, the influence of preconceptional factors such as exposure to maltreatment during childhood, and their effect on infant

neurobiological and socioemotional development is critical to targeting screening and interventions.

CHAPTER 1. INTRODUCTION

1.1 Childhood Maltreatment

Childhood maltreatment, resulting from experiences such as abuse and neglect, is a pervasive public health problem with devastating and lasting consequences for psychological and physical well-being (D 'andrea, Ford, Stolbach, Spinazzola, & Van Der Kolk, 2012; Felitti et al., 1998; Grant, Cannistraci, Hollon, Gore, & Shelton, 2011; Marusak, Martin, Etkin, & Thomason, 2015; van Nierop et al., 2018). Beyond the personal costs, the economic costs of childhood maltreatment are substantial. Child Protective Services direct expenditures are over $30 billion annually (Doyle & Aizer, 2018). Peterson and colleagues (2018) estimated the per-victim lifetime cost and economic burden of childhood maltreatment per year in the United States, which included all measurable morbidity/mortality and intangible costs (grief, suffering). They estimated $830,928 (2015 USD) for the per-victim lifetime cost for nonfatal child maltreatment and an annual United States economic burden of $428 billion to $2.0 trillion for nonfatal child maltreatment, depending on the source used to estimate the incidence (Peterson, Florence, & Klevens, 2018). Van der Kolk describes child abuse as the "gravest and most costly public health issue in the United States" (Van der Kolk, 2015). He goes on to highlight the fact that the daily reality of children experiencing maltreatment has not changed significantly despite the 1998 Adverse Childhood Experiences (ACE) study, which raised public awareness of both the lasting effects of maltreatment and its prevalence (Van der Kolk, 2015). Despite the extensive evidence of lasting personal and economic effects, childhood maltreatment remains a public health challenge that needs to be addressed.

While the problem of childhood maltreatment is not new, it is often unacknowledged and tends to shift in and out of public awareness. The first case in the United States to receive national, and even international, attention was that of Mary Ellen Wilson in 1874. Prior to her case, there were no laws in place to protect children, and limited precedent for government interference in family matters. Since there were no laws protecting children at the time, Etta Wheeler, a social worker, appealed to the founder of the American Society for the Prevention of Cruelty to Animals asking if the provisions that protected animals from mistreatment might be extended to children. Mary Ellen Wilson's case increased national awareness about child abuse, led to the founding of the Society for the Prevention of Cruelty to Children, and started the movement for children's rights in the United States (Shelman & Lazoritz, 2005).

Despite this early recognition of child maltreatment as an important problem requiring advocacy and external, non-familial intervention; it was not until the 1960s, and the publication of the article "The Battered Child Syndrome" by Henry Kempe and colleagues, which described abuse cases based on a nationwide survey of hospitals, that childhood abuse gained widespread and consistent awareness (Oates, 2015). The legislation that followed as a direct result of this paper led to mandated reporting of child abuse in all 50 states (Howard Dubowitz & Newberger, 1989). During this time, the diagnosis of battered-child syndrome was associated with a perpetrator-victim view of the etiology of child abuse, blaming disturbed parents and initially focusing treatment efforts on the parents instead of the child (Howard Dubowitz & Newberger, 1989). The experiences recognized as childhood maltreatment have continued to evolve. During the

1970s, the definition of abuse was expanded to include emotional injury and neglect (Howard Dubowitz & Newberger, 1989).

More recently, as the immediate and long-term negative consequences of child maltreatment have been better characterized and understood, some clinicians and researchers have advocated for the inclusion of developmental trauma disorder as a formal diagnosis in the Diagnostic and Statistical Manual (DSM) (Schmid, Petermann, & Fegert, 2013; Van Der Kolk, 2017). Although the diagnosis of developmental trauma disorder was ultimately not included in the most recent revision of the DSM, the consideration of a diagnosis based on childhood maltreatment is a considerable step forward in the field.

Despite being a widely recognized public health problem with substantial and lasting individual effects, the prevalence of childhood maltreatment is difficult to determine accurately. Childhood maltreatment is notoriously under-reported (Giovannoni, 1989). Even when given the opportunity to disclose a history of childhood maltreatment in a clinical or research setting, individuals may not report their experiences. The Adverse Childhood Experiences (ACE) study reported that 7.9% of respondents to the ACE questionnaire did not complete the question about childhood sexual abuse (Felitti et al., 1998). Lack of routine screening and under-reporting make it difficult to estimate the true prevalence of childhood maltreatment.

Despite these difficulties, attempts have been made to estimate the prevalence of childhood maltreatment. A recent systematic review of self-reported lifetime childhood maltreatment prevalence in North America reported the following median rates: (1) physical abuse (males: 24.3%, females: 21.7%); (2) sexual abuse (males: 14.1%; females:

20.4%); (3) emotional abuse (males: 13.8%, females: 28.4%); and (4) neglect (males: 16.6%, females: 40.5%). Within this review, the authors combined emotional and physical neglect (Moody, Cannings-John, Hood, Kemp, & Robling, 2018). Importantly, they also found that the lifetime prevalence rates of sexual abuse, emotional abuse, and neglect were all higher in women. In the United States, approximately 7.8 million cases of alleged childhood maltreatment are reported to Child Protective Services annually. Of the cases investigated in 2018, 678,000 children were found to be experiencing abuse or neglect, and girls were found to have higher rates of victimization compared to boys (9.6 per 1,000 girls vs. 8.7 per 1,000 boys) (Department of Health, Services Administration for Children, Administration on Children Youth, & Children, 2018). The elevated rates of several types of childhood maltreatment observed in women is important as we consider the potential for intergenerational effects based on the maternal history of exposure to maltreatment during childhood.

Another key factor making it difficult to estimate the prevalence of childhood maltreatment is the fact that the definitions of maltreatment vary widely depending on the setting or context; for example, the medical definition of maltreatment differs from the legal definition (Giovannoni, 1989). There is also considerable variability in how childhood maltreatment is defined and operationalized in the literature (Humphreys et al., 2020). Within this dissertation, childhood maltreatment will include physical abuse, sexual abuse, emotional abuse, physical neglect, and emotional neglect. In order to maintain consistency, the definitions of these maltreatment types will reflect how they are operationalized by the measure used to assess them in the present work, the Childhood Trauma Questionnaire. The Childhood Trauma Questionnaire (CTQ) is a validated,

reliable, and widely used measure (Humphreys et al., 2020). The CTQ includes five domains of childhood maltreatment: (1) Physical abuse: “bodily assaults on a child by an adult or older person that posed a risk of or resulted in injury;” (2) Sexual abuse: “sexual contact or conduct between a child younger than 18 years of age and an adult or older person;” (3) Emotional abuse: “verbal assaults on a child’s sense of worth or well-being or any humiliating or demeaning behavior directed toward a child by an adult or older person;” (4) Physical neglect: “the failure of caretakers to provide for a child’s basic physical needs, including food, shelter, clothing, safety, and health care,” and poor parental supervision in those cases where it jeopardized the child’s safety; and (5) Emotional neglect: “the failure of caretakers to meet children’s basic emotional and psychological needs, including love, belonging, nurturance, and support.” (David P. Bernstein et al., 2003). These domains were selected for inclusion in the present work because there is substantial evidence that they are associated with negative physical and mental health outcomes across the lifespan and across generations (D ’andrea et al., 2012; Felitti et al., 1998; Grant et al., 2011; Marusak et al., 2015; Noll, Trickett, Harris, & Putnam, 2009; van Nierop et al., 2018).

Previous work in the area of childhood maltreatment has often focused on the distinct contributions of a specific type of maltreatment on outcomes, failing to consider that abuse and neglect do not occur in isolation (Higgins & McCabe, 2001; Humphreys et al., 2020). In a review of studies considering multiple types of childhood maltreatment, Higgins and McCabe (2001) found that maltreatment types frequently co-occur (Higgins & McCabe, 2001). They also found that multi-type maltreatment was associated with greater impairment than a single maltreatment type (Higgins & McCabe, 2001). The

cumulative effects of a mother's preconceptional exposures have the potential to affect her child; therefore, the combination of maltreatment exposures, and not the specific type of exposure, will be considered in this dissertation.

Long-term Consequences of Childhood Maltreatment

Childhood maltreatment has long-lasting effects on overall health across the lifespan. Broadly, these effects include alterations in affective and cognitive processing, changes in physiological and behavioral states, heightened stress responsivity (Grant et al., 2011; Marusak et al., 2015; van Nierop et al., 2018), increased psychological stress (D 'andrea et al., 2012; Felitti et al., 1998), poorer health outcomes (Anda et al., 2006; Felitti et al., 1998; Min, Minnes, Kim, & Singer, 2013; Springer, Sheridan, Kuo, & Carnes, 2003), increased risk for psychopathology (Afifi, Boman, Fleisher, & Sareen, 2009; Duncan, Saunders, Kilpatrick, Hanson, & Resnick, 1996; Edwards, Holden, Felitti, & Anda, 2003; Felitti et al., 1998; C. Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; C. Heim, Shugart, Craighead, & Nemeroff, 2010; Min, Minnes, et al., 2013; Navalta, Polcari, Webster, Boghossian, & Teicher, 2006; Shonk & Cicchetti, 2001; Springer et al., 2003; Teicher & Samson, 2013), and increased risk for perinatal psychopathology (Barrios et al., 2015; Bouvette-Turcot et al., 2017; Choi et al., 2015; Gartland et al., 2016; Lara, Navarrete, Nieto, & Le, 2015; Mcdonnell & Valentino, 2016; Mezey, Bacchus, Bewley, & White, 2005; Robertson-Blackmore et al., 2013). The long-term effects are thought to be the result of maltreatment-related alterations to neurobiology, stress physiology, and immunity (Buss et al., 2017). There is extensive evidence that the brain, and more specifically, the limbic system and prefrontal cortex, is

altered in the setting of exposure to maltreatment during childhood (Gerritsen et al., 2017; Hodel, 2018; Teicher & Samson, 2016; Moriah E. Thomason et al., 2014). Previous studies have found associations between stronger amygdala connectivity (Jedd et al., 2015), greater amygdala responsiveness (Dannlowski et al., 2012), and exposure to childhood maltreatment. Alterations to the limbic system and prefrontal cortex related to early environmental exposures have been observed in childhood and adolescence, and have been shown to persist into adulthood (Hodel, 2018).

Importantly, one of the areas altered with exposure to childhood maltreatment is the hypothalamic-pituitary-adrenal (HPA) axis, which is integral to the regulation of stress responses (Gerritsen et al., 2017; C. Heim et al., 2008, 2010). The alterations to the HPA axis vary, depending on the type and timing of maltreatment (C. Heim et al., 2008, 2010; Tarullo & Gunnar, 2006; Van Voorhees & Scarpa, 2004). Maltreatment-related alterations to the HPA axis may result in hyper or hypo-responsivity to stress (C. Heim et al., 2008, 2010; Tarullo & Gunnar, 2006; Van Voorhees & Scarpa, 2004). These alterations potentially play a role in the increased risk for psychopathology (Buss et al., 2017; C. Heim et al., 2008). Physiologically, a history of childhood maltreatment is associated with altered basal cortisol levels (Tarullo & Gunnar, 2006), decreased glucocorticoid receptor sensitivity (Buss et al., 2017), and altered adrenocorticotropic hormone (ACTH) responsivity to psychological stress (Tarullo & Gunnar, 2006). Dysregulation of the HPA axis ultimately affects how an individual reacts and responds to stressful situations throughout their life.

1.2 Intergenerational Transmission of Childhood Maltreatment

There is growing evidence that the negative effects of childhood maltreatment are not limited to a single individual and may be transmitted across generations, increasing the risk for behavioral and psychiatric disorders in the offspring (Bosquet Enlow et al., 2017; Collishaw, Dunn, O'Connor, Golding, & Avon Longitudinal Study of Parents and Children Study Team, 2007; H Dubowitz et al., 2001; Folger et al., 2017; Mcdonnell & Valentino, 2016; Min, Singer, Minnes, Kim, & Short, 2013; Miranda, de la Osa, Granero, & Ezpeleta, 2011; Moog et al., 2018; Noll et al., 2009; Dominic T Plant, Pawlby, Pariante, & Jones, 2017; Sun et al., 2017; Thompson, 2007). Gray and colleagues (2017) found that respiratory sinus arrhythmia (RSA), a marker for self-regulation linked to mental health outcomes, is affected by both maternal childhood adverse experiences and psychological stress during pregnancy. They found that maternal childhood adversity was associated with a lower infant RSA set point, while psychological stress during pregnancy was associated with failure to recover following a stressor (Gray, Jones, Theall, Glackin, & Drury, 2017). Their study suggests distinct intergenerational effects related to a maternal history of childhood adversity that are relevant to offspring biobehavioral outcomes.

Children of maltreated mothers demonstrate behavioral and psychiatric disorders at all ages from early childhood through adolescence even when controlling for potential maternal, familial, and child confounding factors (Dominic T Plant et al., 2017). The timing of abuse matters as well; specifically, there is evidence that the association between a maternal history of physical victimization and offspring behavioral outcomes

is more pronounced when the victimization occurred during the mothers' childhood compared with victimization experienced in adulthood (Thompson, 2007).

There are numerous theoretical frameworks describing the intergenerational transmission of childhood maltreatment. These frameworks include transmission via negative environmental factors, increased offspring exposure to stress and adversity, perpetuation of maltreatment by a maltreated parent, inheritance of genomic/epigenomic alterations, influence of maternal-placental-fetal gestational biology, and the interaction of all of these factors (Dominic T Plant et al., 2017; Su, D'Arcy, & Meng, 2020). The majority of theoretical frameworks focus on the role of the postnatal environment, which is the prevailing paradigm, and an important and relevant pathway for transmission. Given the susceptibility of the developing fetus to environmental cues such as stress, the prenatal period also plays an important role in the intergenerational transmission of childhood maltreatment (see **Figure 1.1**).

There is growing evidence demonstrating that the effects of maternal exposure to maltreatment during childhood are already present at the time of offspring birth, highlighting the importance of considering how the environment during pregnancy may affect the developing fetus and serve as an important route of intergenerational transmission. A maternal history of maltreatment during childhood is associated with adverse birth outcomes such as low birthweight (Blackmore et al., 2016; J. Seng, Low, Sperlich, Ronis, & Liberzon, 2011; M. V. Smith, Gotman, & Yonkers, 2016) and preterm birth (Noll et al., 2009; J. Seng et al., 2011; M. V. Smith et al., 2016). A recent study by Moog and colleagues (2018) showed that maternal childhood maltreatment was associated with global differences in offspring cortical gray matter and reduced

intracranial volume that was independent of numerous potential confounding variables (Moog et al., 2018). Hendrix and colleagues (2020) found that a maternal history of emotional neglect during childhood was associated with stronger offspring amygdala functional connectivity to the dorsal anterior cingulate cortex (dACC) and ventromedial prefrontal cortex (vmPFC) after controlling for potential confounds including maternal stress during pregnancy (Hendrix et al., 2020). Alterations in infant neurodevelopment may eventually explain the observed relationship between maternal maltreatment during childhood and increased developmental risk (Folger et al., 2017; Sun et al., 2017), emotional and behavioral dysregulation (Mcdonnell & Valentino, 2016; Dominic T Plant et al., 2017), and negative emotionality (Bosquet Enlow et al., 2017) in offspring.

A few studies have attempted to examine the interaction between maternal maltreatment during childhood and maternal stress during pregnancy. Enlow and colleagues (2017) looked at the relationship between maternal history of exposure to trauma and domains of infant negative affect. They found that the relationship between maternal history of exposure to trauma and infant sadness was independent of maternal exposure to stress during pregnancy; however, the level of cortisol exposure during the third trimester modified the relationship between maternal exposure to trauma and infant reactivity suggesting an interaction between maternal stress during pregnancy and exposure to maltreatment during childhood (Bosquet Enlow et al., 2017). Hendrix and colleagues (2020) found that the relationship between a maternal history of emotional neglect during childhood and stronger offspring amygdala to dorsal anterior cingulate cortex and ventromedial prefrontal cortex functional connectivity was only significant after controlling for maternal stress during pregnancy (Hendrix et al., 2020).

Taken together, these studies suggest that the maternal environment during pregnancy, as influenced by preconceptional exposure to childhood maltreatment, directly affects the health and development of the fetus. The existing paradigm posits that the intergenerational transmission of childhood maltreatment occurs during the postnatal period in the context of maternal-infant attachment and maternal mood. These studies provide support for the intergenerational transmission of childhood maltreatment during pregnancy.

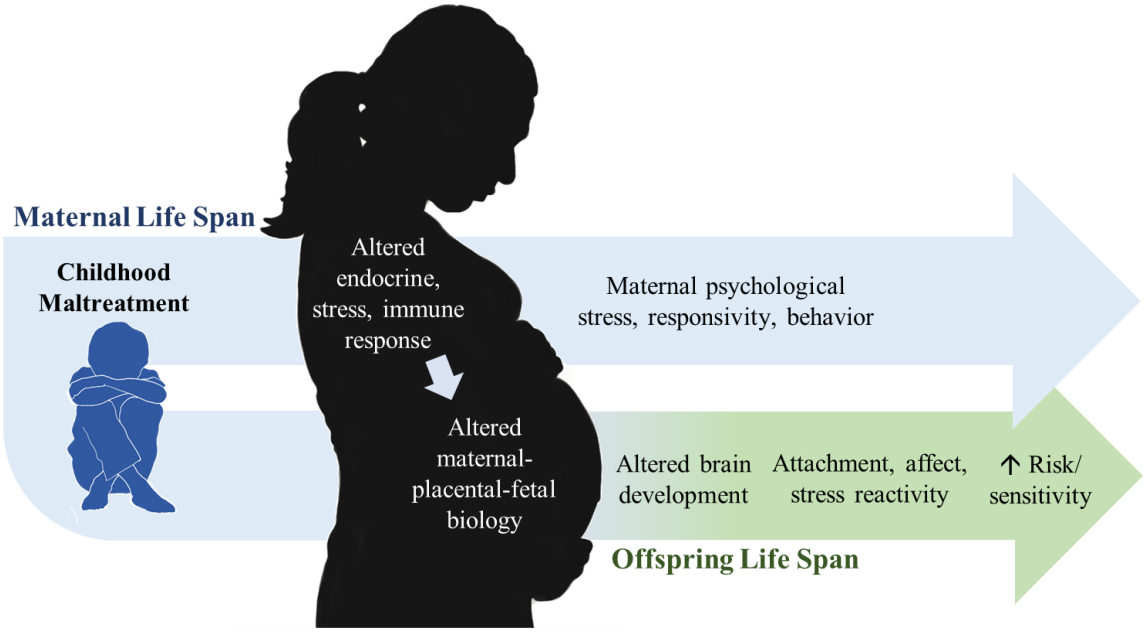

Figure 1.1. Intergenerational transmission of childhood maltreatment. The transmission of a maternal history of exposure to maltreatment during childhood may occur during the prenatal or postnatal periods of offspring development. The long-term physical and mental health consequences of maltreatment will likely persist through pregnancy, altering maternal-placental-fetal biology. Increased maternal psychological stress associated with pregnancy and potential reminders of past abuse may exacerbate existing alterations to endocrine, stress, and immune responses further influencing fetal development. The developing fetal brain is especially sensitive to mediators of stress such as cortisol. Maternal maltreatment history has been associated with increased risk of anxiety, stress, and depression; reduced sensitivity and responsivity to the infant; and attachment insecurity during the postnatal period. The combination of prenatal and postnatal factors play a role in offspring neurobiological and socioemotional development potentially increasing offspring risk or sensitivity for adverse outcomes.

Maternal Exposure to Childhood Maltreatment and Stress During Pregnancy

Maternal psychological stress during pregnancy, and its associated biological effects, is likely a key mechanism for the intergenerational transmission of childhood maltreatment. A history of childhood maltreatment has been shown to increase the odds of antenatal depression (Barrios et al., 2015; Bouvette-Turcot et al., 2017; Choi et al., 2015; Gartland et al., 2016; Lara et al., 2015; Mcdonnell & Valentino, 2016; Mezey et al., 2005; D. T. Plant, Barker, Waters, Pawlby, & Pariante, 2013; Robertson-Blackmore et al., 2013) in a dose-dependent manner (Blackmore et al., 2016), even when accounting for sociodemographic and psychosocial factors (Choi & Sikkema, 2016). Perinatal anxiety (Gartland et al., 2016; Lara et al., 2015), poor mental health, and intimate partner violence during pregnancy (Gartland et al., 2016; Huth-Bocks, Krause, Ahlfs-Dunn, Gallagher, & Scott, 2013) are also associated with a maternal history of childhood maltreatment. Several studies suggest that pregnancy itself may trigger reminders of relational trauma (Huth-Bocks et al., 2013), be re-traumatizing (Lev-Wiesel, Daphna-Tekoah, & Hallak, 2009; Mezey et al., 2005; Montgomery, 2013), and increase symptoms of post-traumatic stress disorder (PTSD) (Choi et al., 2015; Lev-Wiesel et al., 2009; Mezey et al., 2005). Maternal childhood maltreatment is also related to sleep disturbances (Gelaye et al., 2015; Gustafsson, Doyle, Gilchrist, Werner, & Monk, 2017), poor maternal health (Barrios et al., 2015), and obstetric risk behaviors (J. S. Seng, Low, Sperlich, Ronis, & Liberzon, 2009); which may contribute to maternal psychological stress during pregnancy.

1.3 Developmental Programming

The maternal preconceptional state represents the influences of environmental and genetic/epigenetic interactions on psychological, biological, and biophysical systems, and behavior. In the present work, we will focus on the lasting effects of exposure to childhood maltreatment on the maternal preconceptional state. The preconceptional state influences the maternal compartment during pregnancy, which includes the interaction between maternal psychological and biological states. Importantly, the maternal compartment in pregnancy also includes the fetal compartment, where biological signals are exchanged via the placenta. The fetus receives cues about the extrauterine environment via stress-sensitive aspects of maternal-placental-fetal gestational biology (Buss et al., 2017). It is through these biological signals within the fetal compartment that the maternal history of exposure to maltreatment during childhood, and maternal psychological stress during pregnancy potentially influence brain systems sensitive to stress and commonly implicated in neuropsychiatric disorders (Buss et al., 2017).

Developmental programming posits that genetic and environmental factors interact during the prenatal or early postnatal period, a time of rapid development, to cause lasting biophysiological and epigenomic changes affecting health and disease risk (Entringer, Buss, & Wadhwa, 2015; Sutton et al., 2016). One of the core concepts of developmental programming is that systems undergoing rapid development are particularly susceptible to the influence of environmental factors (C. M. Heim, Entringer, & Buss, 2019). There are several ways in which a history of maternal childhood maltreatment might be transmitted to a developing fetus including via epigenomic alterations within the germ line, cellular and molecular alterations to the oocyte, and

gestational biology (Buss et al., 2017). Each of these paths has the potential to influence gestational biology, and ultimately fetal development. In the present work, we will examine alterations to the prenatal environment with a focus on maternal psychological stress during pregnancy. We will briefly discuss potential maltreatment and stress-related alterations to endocrine, stress, and immune/inflammatory responses; which may play a role in the biological transmission of maternal preconceptional and prenatal influences to the developing fetus.

Maternal Psychological Stress During Pregnancy

Psychological stress during pregnancy is associated with heightened offspring stress responses, emotional dysregulation, and behavioral problems in infancy and childhood (Bergman, Sarkar, O'Connor, Modi, & Glover, 2007; Buss, Entringer, Swanson, & Wadhwa, 2012; Buss, Entringer, & Wadhwa, 2012; Davis et al., 2004a; Glynn et al., 2018; Graignic-Philippe, Dayan, Chokron, Jacquet, & Tordjman, 2014; Kingston et al., 2018; Lahti et al., 2017; Sandman, Davis, Buss, & Glynn, 2012; Van den Bergh et al., 2017; van der Waerden et al., 2015; Weinstock, 2008). Maternal stress, anxiety, and depression during pregnancy have been shown to affect offspring limbic system development (Bock, Wainstock, Braun, & Segal, 2015; Buss, Davis, et al., 2012; Davis, Sandman, Buss, Wing, & Head, 2013; Pallarés & Antonelli, 2017; A Qiu et al., 2013; Anqi Qiu et al., 2017; Rifkin-Graboi et al., 2013; Scheinost et al., 2016; Van den Bergh et al., 2017; Wen et al., 2017), which is particularly vulnerable during fetal periods of rapid growth (Buss, Entringer, Swanson, et al., 2012). Specifically, maternal psychological stress during pregnancy has been associated with increased amygdala

volume (Buss, Davis, et al., 2012; Graham et al., 2018; Rifkin-Graboi et al., 2013; Wen et al., 2017), altered amygdala connectivity (Graham et al., 2016; Scheinost et al., 2016), and decreased hippocampal volumes (A Qiu et al., 2013; Anqi Qiu et al., 2017). Increased amygdala volume and connectivity have been associated with increased fear (Graham et al., 2016; Thomas et al., 2019) and affective problems in children (Buss, Davis, et al., 2012), while decreased hippocampal volumes have been associated with behavioral problems in children (Hanson et al., 2015).

Maternal psychological stress during the prenatal period is potentially a key mechanism for the intergenerational transmission of childhood maltreatment. The majority of studies examining maternal stress during pregnancy consider the magnitude or severity of stress as the 'risk factor'; however, psychological stress, particularly during the prenatal period, is dynamic and variable (Ahmed, Bowen, Feng, & Muhajarine, 2019; Baron, Bass, Murray, Schneider, & Lund, 2017; Fredriksen, von Soest, Smith, & Moe, 2017; Mora et al., 2009; H. Santos, Tan, & Salomon, 2017). Brain development occurs sequentially and is sensitive to environmental influences, meaning that the effect of any insult is likely as much about the timing as it is severity.

Maternal stress and emotional complaints during the first trimester have been linked to internalizing problems (Graignic-Philippe et al., 2014; Van den Bergh et al., 2017), behavioral problems, alterations in attention, and difficult temperament in offspring (Van den Bergh et al., 2017). Additionally, Buss and colleagues found that higher concentrations of maternal cortisol in early gestation were associated with larger right amygdala volume in girls at 7 years of age (Buss, Davis, et al., 2012). Maternal prenatal stress during the first and second trimesters are associated with alterations in

cognitive development (Van den Bergh et al., 2017). In the Project Ice Storm study, poorer outcomes and more difficult temperament at 6 months of age were associated with stress exposure during the first or second trimester of pregnancy (Charil, Laplante, Vaillancourt, & King, 2010; King, Dancause, Turcotte-Tremblay, Veru, & Laplante, 2012; Laplante, Brunet, Schmitz, Ciampi, & King, 2008). Elevated levels of maternal anxiety during the early second trimester have been associated with region-specific reductions in gray matter volume and executive function impairments at 6 to 9 years of age (Buss, Davis, Muftuler, Head, & Sandman, 2010). Maternal emotional complaints and stress during the third trimester are associated with autism (Charil et al., 2010; Graignic-Philippe et al., 2014), greater total emotional and behavioral dysregulation (Charil et al., 2010; O'Connor, Heron, Golding, Beveridge, & Glover, 2002; O'Connor, Heron, Golding, & Glover, 2003), and schizophrenia (Graignic-Philippe et al., 2014). Bereavement during the third trimester is associated with an increased risk of attention deficit hyperactivity disorder (Van den Bergh et al., 2017) and autism spectrum disorder (Class et al., 2014). Maternal stress, anxiety, and depression during pregnancy are further associated with an increased risk of heightened stress responsivity, increased behavioral reactivity and irritability, and delayed behavioral recovery in offspring (Davis, Glynn, Waffarn, & Sandman, 2011; Davis et al., 2004b; Martini et al., 2017; Rieger et al., 2004; Van den Bergh et al., 2017; Yong Ping et al., 2015), all of which influence the expression and regulation of negative emotionality in infancy.

Stress-Sensitive Mechanistic Pathways

Endocrine and Stress Response

We will not be examining the role of maternal endocrine and stress responses experimentally as part of the dissertation studies. A brief overview of the HPA axis is provided, due to its role in the biological response to stress, including psychological stress; its relevance to fetal brain development and stress reactivity; and its sensitivity to environmental stressors as evidenced by HPA axis alterations following exposure to childhood maltreatment. The endocrine and stress response represents one of the pathways through which maternal exposure to maltreatment during childhood and psychological stress during pregnancy influence fetal development.

Regulation of the HPA axis changes dramatically during pregnancy. With pregnancy, circulating cortisol levels increase two to four times non-gravid levels (Guardino et al., 2016) due to stimulation of corticosteroid-binding globulin by estrogen (Duthie & Reynolds, 2013). The placenta expresses and secretes corticotropin releasing hormone (CRH), which increases across pregnancy, and stimulates maternal secretion of ACTH and, in turn, cortisol (Aboustate & Baune, 2020; Duthie & Reynolds, 2013). The increase in maternal cortisol stimulates the synthesis of placental CRH in a positive feedback loop that increases levels of cortisol (Duthie & Reynolds, 2013). The elevated levels of bioavailable cortisol are necessary to meet the increased maternal metabolism and energy demands associated with pregnancy (Duthie & Reynolds, 2013; Schepanski, Buss, Hanganu-Opatz, & Arck, 2018). Elevated levels of cortisol, which increase across pregnancy (Duthie & Reynolds, 2013), are also necessary for fetal organ maturation (Aboustate & Baune, 2020; Moisiadis & Matthews, 2014; Schepanski et al., 2018). Given

the importance of cortisol in fetal development, it is further regulated by the placenta through high enzyme expression levels of 11ß-Hydroxysteroid-Dehydrogenase (11ß-HSD)-1 and -2 (Aboustate & Baune, 2020; Schepanski et al., 2018), see **Figure 1.2**. During the third trimester, the high levels of cortisol downregulate maternal CRH production, dampening the maternal physiological and psychological stress response (Buss, Entringer, Swanson, et al., 2012; Duthie & Reynolds, 2013).

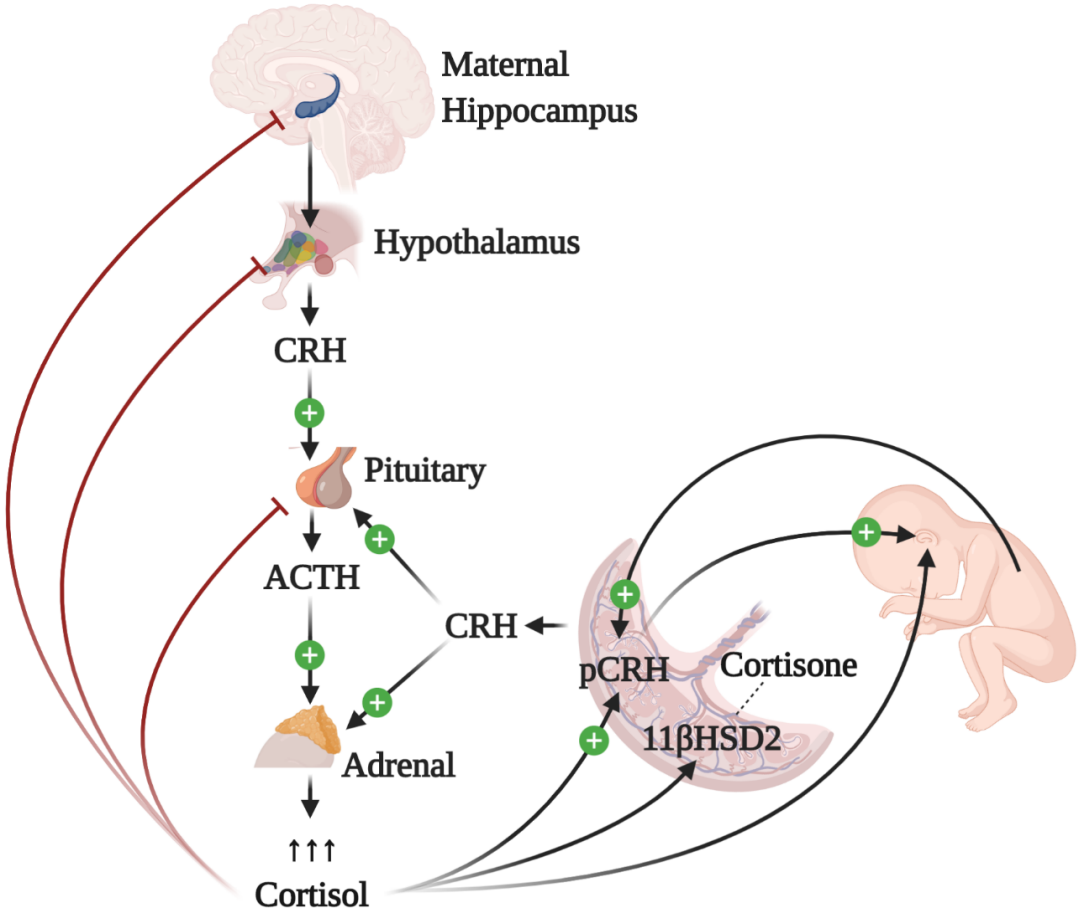

Figure 1.2. HPA axis regulation in pregnancy. Regulation of the HPA axis changes dramatically during pregnancy. The placenta has significant endocrine properties and plays a role in HPA axis regulation. The placenta expresses and secretes corticotropin-releasing hormone (CRH), which increases through pregnancy, and stimulates maternal secretion of ACTH and, in turn, cortisol. The increase in maternal cortisol stimulates the synthesis of placental CRH (pCRH) in a positive feedback loop that increases levels of cortisol. Maternal cortisol also passes through the placenta where some of it is inhibited by placental 11ß-HSD. Placental 11ß-HSD converts cortisol into its inactive form, cortisone. Fetal cortisol also stimulates pCRH creating an additional positive feedback loop. Adapted from (Duthie & Reynolds, 2013; Held, Bird, & Heather, 2020; Sandman et al., 2012). Created with BioRender.com.

HPA axis dysregulation is one of the long-lasting effects of childhood adversity and maltreatment (Buss et al., 2017; Gerritsen et al., 2017; C. Heim et al., 2008, 2010; Tarullo & Gunnar, 2006; Van Voorhees & Scarpa, 2004). There is evidence that maternal adversity is associated with decreased expression of 11ß-HSD-2, potentially leading to offspring exposure to higher levels of cortisol in utero (Bierer et al., 2014). The association between adversity and decreased expression of 11ß-HSD-2 is strongest with early adversity compared to later adversity (Bierer et al., 2014). In a study comparing pregnant women with and without a history of sexual abuse, sexual abuse history was associated with increasing waking cortisol across pregnancy and the absence of a dampening response in late pregnancy (Bublitz & Stroud, 2012). Maternal exposure to maltreatment during childhood has also been associated with an increase in placental CRH production during the second half of pregnancy, again reflecting HPA axis dysregulation during late pregnancy (Moog et al., 2016).

Maternal psychological and biological stress during pregnancy have been shown to disrupt endocrine function and increase levels of bioavailable glucocorticoids via sympathetic activation of the HPA axis (O'Connor, Bergman, Sarkar, & Glover, 2013; Schepanski et al., 2018; Weinstock, 2008). Elevated cortisol in the setting of maternal psychological stress has been associated with alterations to infant amygdala structure and connectivity (Schepanski et al., 2018), and risk for offspring psychopathology (Graham et al., 2019; Schepanski et al., 2018; Weinstock, 2008). Maternal psychosocial stress has also been associated with increased amniotic cortisol levels and downregulation of 11ß-HSD-2, both of which increase fetal cortisol exposure (Aboustate & Baune, 2020; O'Connor et al., 2013). O'Connor and colleagues found that higher levels of cortisol in

the amniotic fluid at 17 weeks gestation were associated with higher baseline cortisol levels in infants at 17 months of age as well as a blunted response to the Strange Situation Paradigm (O'Connor et al., 2013). Fetal exposure to elevated levels of cortisol may dysregulate the fetal HPA axis, which is sensitive to fluctuations in glucocorticoids (Aboustate & Baune, 2020; Charil et al., 2010; Weinstock, 2008), by altering glucocorticoid receptor density within the brain (Yehuda & Seckl, 2011). During infancy, the developing HPA axis depends on external social regulation, making it especially vulnerable to environmental influences (Tarullo & Gunnar, 2006; Van Voorhees & Scarpa, 2004).

The nature of fetal exposure to cortisol varies depending on maternal preconceptional and conceptional states. Some mothers with a history of PTSD demonstrate HPA axis underactivity and low cortisol levels (Yehuda & Seckl, 2011). Conversely, elevated cortisol levels during pregnancy have been reported in women with a history of exposure to childhood maltreatment (Bublitz & Stroud, 2012; Moog et al., 2016), suggesting greater HPA axis activity. Early maltreatment has also been associated with HPA axis hypersensitivity in women (Van Voorhees & Scarpa, 2004). Importantly, both high and low levels of cortisol can potentially influence fetal development and stress responsivity in infants (O'Connor et al., 2013; Yehuda & Seckl, 2011). Enlow and colleagues found that both higher and lower levels of cortisol exposure during fetal development modified the association between a maternal history of traumatic exposures, including childhood maltreatment, and infant stress reactivity. Maternal history of exposure to trauma was positively associated with infant reactivity in the setting of lower levels of cortisol during the third trimester; whereas, in the setting of higher levels of

cortisol, maternal history of trauma exposure was negatively related to infant reactivity (Bosquet Enlow et al., 2017). It is likely that the sensitivity of the offspring's HPA axis to environmental influences begins before birth. During this period, the developing HPA axis is responding and adapting to mediators of maternal psychological and biological stress (see **Figure 1.3**).

Inflammatory and Immune Response

HPA axis dysregulation resulting from psychological stress is related to increased inflammation and altered immune responses (see **Figure 1.3**). Depression and PTSD are both associated with HPA axis dysregulation and inflammatory states (Silverman, 2012). Increased psychological stress is associated with increasing levels of inflammatory markers such as IL-6 and other cytokines that activate inflammatory processes in the fetal brain through both direct and indirect pathways (Graham et al., 2018). Importantly, maternal immune cells and cytokines can cross the placental barrier (Schepanski et al., 2018). Similar to cortisol, IL-6 and other cytokines are important for fetal brain development, but can disrupt cellular survival and proliferation, and synaptogenesis if levels are too high (Graham et al., 2019). Spann and colleagues (2018) found that higher levels of immune activation during the third trimester were positively associated with the strength of neonatal functional connectivity within the salience network including the medial prefrontal cortex (Spann, Monk, Scheinost, & Peterson, 2018). Similarly, Rudolph and colleagues (2018) showed that elevated maternal IL-6 concentrations during the third trimester were the most strongly associated with reduced infant working memory at two years of age (Rudolph et al., 2018).

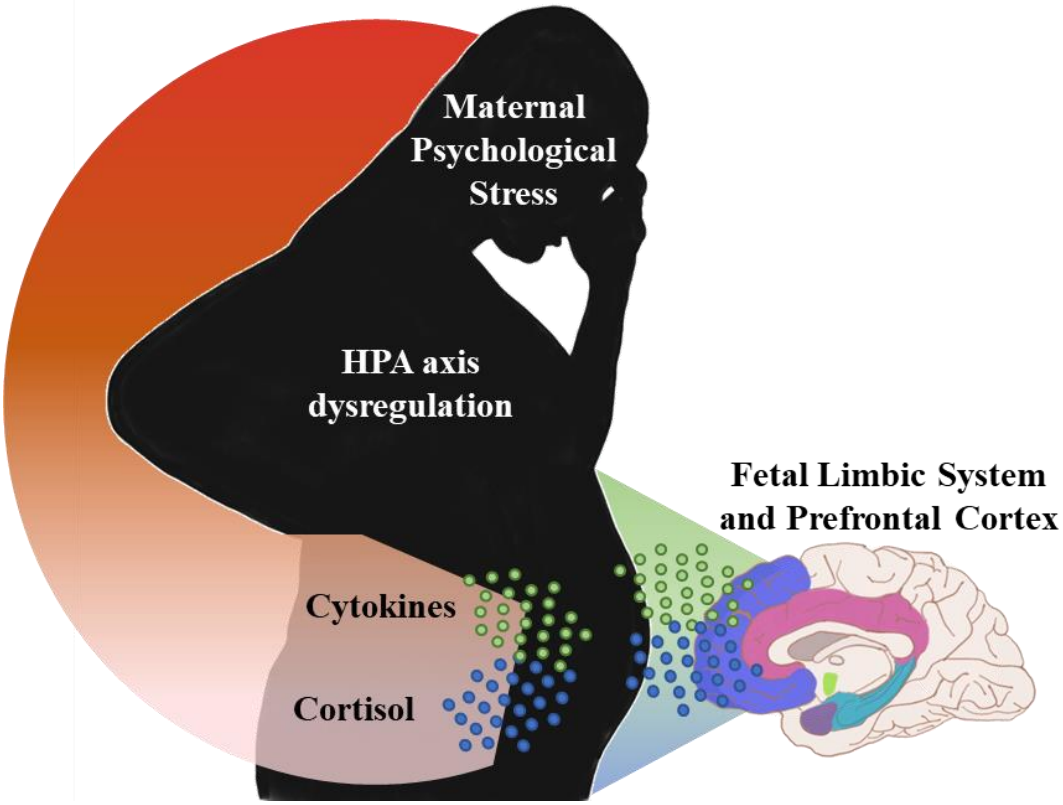

Figure 1.3. Maternal psychological stress during pregnancy can affect fetal limbic system development. Maternal psychological and biological stress during pregnancy have been shown to disrupt endocrine function and increase levels of bioavailable glucocorticoids via sympathetic activation of the HPA axis. HPA axis dysregulation is related to increased inflammation and altered immune responses. Importantly, maternal immune cells, cytokines, and cortisol can cross the placental barrier. While cortisol and markers of immunity are important for fetal brain development, they can disrupt cellular survival and proliferation, and synaptogenesis if the levels are too high. The general architecture and connectivity of the limbic system and prefrontal cortex are largely established before birth, providing a window for maternal psychological and biological stress to influence its development. Studies have shown an association between maternal psychological and biological stress during pregnancy and altered offspring limbic system and prefrontal cortex development in infancy.

1.4 Early Brain Development

During the prenatal period, the nervous system develops from a single cell into a functioning and interconnected system capable of responding to a dynamic environment. Brain growth and development occurs at an increasingly rapid pace and is susceptible to environmental influences (see **Figure 1.4**). The prenatal period represents a key time when the past and present experiences and health of the mother exert a direct influence on the developing fetus (Buss et al., 2017; Buss, Entringer, & Wadhwa, 2012; C. M. Heim et al., 2019; Sandman et al., 2012). The ordered process of neurodevelopment suggests that brain structures may be differentially vulnerable to the effects of stress at different stages of development. It is therefore critical to characterize the effects related to the timing of maternal biological and psychological stress mediators on offspring development.

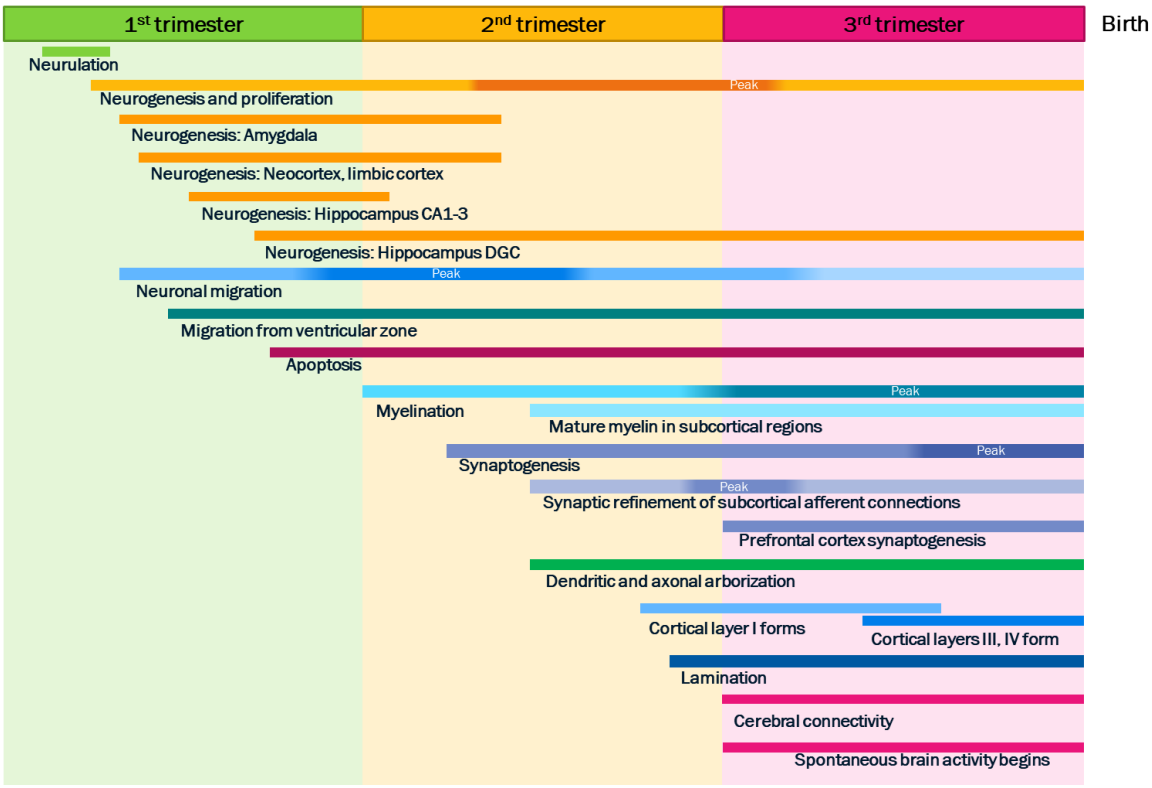

Figure 1.4. Neurodevelopment during the prenatal period. Brain development is rapid during the embryonic and fetal period. Stress-sensitive aspects of maternal-placental-fetal biology provide a mechanism for environmental conditions to influence the trajectory of neurodevelopment. Brain regions with high concentrations of glucocorticoid receptors and known roles in susceptibility for psychiatric disorders, including the amygdala and hippocampus, begin to develop during the first trimester of pregnancy. The rapid sequence of neurodevelopment during this period creates potential for the effects of stress exposure to have significantly different impacts depending on timing. Adapted from (Clancy, Darlington, & Finlay, 2001; Lenroot & Giedd, 2006; Workman, Charvet, Clancy, Darlington, & Finlay, 2013) for full list of figure references see (Marr, 2020).

First Trimester

Brain development is rapid during the embryonic and fetal period. Stress-sensitive aspects of maternal-placental-fetal biology provide a mechanism for environmental conditions to influence the trajectory of neurodevelopment. Maternal psychological stress likely has a differential influence on the developing brain depending on the timing of stress exposure. During the first trimester, neuroepithelial cells differentiate into neural progenitors (Tau & Peterson, 2010). Neurulation starts at around 2 to 3 weeks gestational age (GA), followed by neurogenesis and neuronal proliferation (Tau & Peterson, 2010). Beginning at 8 weeks GA, neuronal migration results in the formation of the subplate zone, which plays a critical role in guiding the development of the cortex (Buss, Entringer, Swanson, et al., 2012). Amygdala and hippocampal development also begins during the first trimester. At around 6 weeks GA, the amygdaloid complex appears, differentiating sequentially over subsequent weeks into the basolateral complex, central nucleus, and lateral amygdaloid nucleus (Humphrey, 1968). Stress-related changes during the first trimester are likely to have a more global effect given that this period is essential for the early establishment of key structures.

Second Trimester

The second trimester is defined by the development of pathways and connections. The process of myelination, synaptogenesis, and dendritic and axonal arborization begins during the second trimester (Tau & Peterson, 2010). Neuronal migration peaks during the first half of the second trimester and is largely complete by the first few weeks of the third trimester (Tau & Peterson, 2010). Between the 8th and 24th week of gestation, the

cortical circuits are organized (Graignic-Philippe et al., 2014) and by ~17 weeks the cingulum bundle connecting the frontal and parietal regions is visible (Ball et al., 2014). Fetal white matter, deep subcortical structures, and the cerebellum have their greatest growth trajectories during the second trimester (Andescavage et al., 2017). The rapid growth trajectories and developing cortical circuits during the second trimester make this a period of heightened vulnerability for the developing brain (Graignic-Philippe et al., 2014). Appreciable levels of fetal adrenal cortisol are produced around 22 weeks GA (Buss, Davis, et al., 2012), leading to functional feedback within the HPA axis (Van den Bergh et al., 2017).

The transition from the second trimester to the third trimester is a time of rapid and substantial changes in the developing brain that are characterized by prolific cortical maturation, circuit formation, synaptogenesis and refinement, peak myelination, axonal outgrowth, and increasing neuronal connectivity (Andescavage et al., 2017; Jakab et al., 2014; Tau & Peterson, 2010). From 24 to 31 weeks GA, there is an increase in synaptogenesis within the cortical plate, maximal growth of the subplate, and a significant increase in neuronal connectivity (Andescavage et al., 2017; Jakab et al., 2014). The cerebral volume begins to increase in a linear manner at 25 weeks GA and continues on this trajectory through 36 weeks (Andescavage et al., 2017). Jakeb and colleagues (2014) referred to the time from ~ 25 weeks to 29 weeks GA as an "expansion period" of total functional connectivity, noting that the increase in the rate of signal synchronicity peaked around 26 weeks GA (Jakab et al., 2014). By the end of the second trimester, the architecture of the brain is established (Vasung et al., 2019). The genetic influences that guided brain development during the first two trimesters are silenced

during the third trimester, allowing for environmental influences to play a greater role in the ongoing process of neurodevelopment (Vasung et al., 2019).

Third Trimester

The third trimester is a period of expansive growth. The developing cortex thickens due to accelerating dendritic arborization and synaptogenesis (Tau & Peterson, 2010). At 28 weeks GA, the total number of neurons in the developing brain peak before undergoing loss through apoptosis (Tau & Peterson, 2010). Long-distance cortico-cortical connections are also developing with maximal axonal growth and elongation, as measured by Growth Associated Protein 43 (GAP-43) expression, evident from 21 to 43 weeks GA (Ball et al., 2014). Cerebral gray matter also demonstrates a rapid increase during the 3rd trimester, especially in cortical regions (Andescavage et al., 2017). The peak growth of fetal white matter occurs between 29 and 30 weeks GA, and the trajectory of cortical gray matter growth is exponential during the 3rd trimester (Andescavage et al., 2017). The peak period of fetal synaptogenesis (Tau & Peterson, 2010) and synaptogenesis of the prefrontal cortex occurs in the third trimester (Huttenlocher & Dabholkar, 1997). Fetal myelination also peaks during the 3rd trimester (Tau & Peterson, 2010), and spontaneous brain activity begins (Moriah E. Thomason et al., 2015).

The third trimester is also a time of growing connectivity within the fetal brain. During the second and third trimester, long-distance cortico-cortical connections are established (Ball et al., 2014). Functional connections are strengthened during this time, with increased connections between the parietal and frontal lobes and increased long-range correlations between the frontal and temporal lobes (Jakab et al., 2014). By 30

weeks GA, the major pathways associated with rich club organization can be observed using diffusion tensor imaging (DTI) (Ball et al., 2014). From 30 to 40 weeks GA, DTI indicates the existence of emerging structural connectivity between hub regions and the rest of the cortex, significantly increasing white matter connectivity across the cortex (Ball et al., 2014). The growing connectome stabilizes after 31 weeks GA in coordination with the dissolution of the subplate and the consolidation of existing networks (Jakab et al., 2014).

During the last few weeks of pregnancy, there is a five-fold increase in white matter myelination (Hüppi et al., 1998). The period right before birth is characterized by a rapid and dramatic increase in synaptic connections and cortical growth, and is considered a critical period for the development of the cortical connectome (Collin, Sporns, Mandl, & Van Den Heuvel, 2014; Garcia et al., 2018; van den Heuvel et al., 2014). Stress-related alterations during this time will likely affect cortical development and the formation and strengthening of cortical connections.

Infant Postnatal Brain Development

The rapid brain growth and complex array of neurodevelopmental processes that started during the prenatal period continue during infancy. During the first year, the brain reaches approximately 70% of its adult size (Knickmeyer et al., 2008). Cortical gray matter growth is greatest during the first year and is visible in MRI studies of development (Tau & Peterson, 2010). Synaptogenesis, which begins later in the prefrontal cortex, peaks in this region around 8 months of age (Tau & Peterson, 2010). Myelination of fiber tracts progresses rapidly during infancy, peaking during the first

year (Anqi Qiu, Mori, & Miller, 2015), followed by a less pronounced increase over the second year of life (W. Gao et al., 2009). White matter maturation and short-range cortico-cortical connections also continue to develop during the postnatal period (Keunen, Counsell, & Benders, 2017). Nearly all white matter tracts and major bundles, such as the limbic and associative bundles, are observable using DTI by two years of age (Dubois et al., 2014). Pruning increases during the postnatal period, refining the neural circuitry (Tau & Peterson, 2010). The period between birth and two years of life represents a time of increasing integration between regions and decreasing functional segregation (Dubois et al., 2014). In the present work, we will not be examining brain development outside of the neonatal period since we are focusing on the role of prenatal, not postnatal influences.

Limbic System and Prefrontal Cortex Development

The limbic system and prefrontal cortex are highly interconnected both structurally and functionally (Kalin, 2019; Maclean, 1985). They play an interactive role in the interpretation and response to stress and emotion, and are associated with psychopathology (Kalin, 2019). Within the literature, there are some differences in opinion as to what structures constitute the limbic system (Kalin, 2019). In the present work, we will define the limbic system as including the amygdala, hippocampus, and cingulate cortex (Kalin, 2019; Maclean, 1985). The prefrontal cortex includes the dorsolateral, ventrolateral, ventromedial, medial, and orbitofrontal regions of the frontal lobe (Kalin, 2019).

Studies have demonstrated that the limbic system is highly responsive to biological and psychological stress (Bock et al., 2015; Callaghan, Sullivan, Howell, & Tottenham, 2014; Charil et al., 2010; Bruce S. McEwen & Gianaros, 2011), including both acute (Y. Li et al., 2017) and chronic stress (Felmingham et al., 2009; Gianaros et al., 2007; B S McEwen, 2000; Smith, 2005). This stress response results in alterations to limbic and prefrontal structures (Bock et al., 2015; Buss, Davis, et al., 2012; Callaghan et al., 2014; Charil et al., 2010; Felmingham et al., 2009; Gianaros et al., 2007; Y. Li et al., 2017; B S McEwen, 2000; Papagni et al., 2011; Sekiguchi et al., 2013; M. E. Smith, 2005) and function (Scheinost et al., 2016; Sripada et al., 2012; L. Wang, Su, Shen, & Hu, 2012; Wolf & Herringa, 2016; Xiaoyu Zhang, Zhang, Wang, Li, & Zhang, 2016) that are observable over periods as brief as 3 months (Papagni et al., 2011). Recently, studies have shown similar alterations to the structure and functional connectivity of the limbic system in infancy (Graham et al., 2016, 2019, 2018; Hendrix et al., 2020; Moog et al., 2018; A Qiu et al., 2015, 2013; Anqi Qiu et al., 2017; Rifkin-Graboi et al., 2013, 2015; Scheinost et al., 2016; Soe et al., 2018, 2016; Wen et al., 2017) suggesting that these changes may be present early in development and not exclusively associated with exposure to the postnatal environment.

The limbic system may be particularly vulnerable to stress during periods of rapid growth (Buss, Entringer, Swanson, et al., 2012) such as fetal development and early childhood. Rapid development is associated with increased metabolic requirements, making the developing region more sensitive to environmental and biological influences (Hodel, 2018). The general architecture and connectivity of the limbic system is largely established before birth (Hodel, 2018), providing a window for mediators of maternal

psychological and biological stress to influence its development. Several studies have shown an association between maternal psychological and biological stress mediators during pregnancy and altered offspring limbic system development in infancy (Graham et al., 2018; Hendrix et al., 2020; A Qiu et al., 2015; Rifkin-Graboi et al., 2015; Scheinost et al., 2016). Additionally, stress during pregnancy may exert a stronger influence on the limbic system than postnatally because dendritic growth and synpatic formation of the underlying neural networks are still increasing (Hodel, 2018). The vulnerability of the frontal lobe during the prenatal period is also due to the protracted nature of white matter development and the persistence of pre-myelinating oligodendrocytes, which are more susceptiable to insult (Hodel, 2018). Because the limbic system and prefrontal cortex play a central role in the regulation of stress and negative emotions, these stress-induced alterations may increase the risk for emotional and behavioral dysregulation (Bhat et al., 2015; Buss, Entringer, Swanson, et al., 2012; Lundy et al., 1999), stress reactivity (Davis et al., 2011, 2004b; Yong Ping et al., 2015), and psychopathology (Buss, Entringer, Swanson, et al., 2012; Buss, Entringer, & Wadhwa, 2012; Glynn et al., 2018), independent of the postnatal environment (Barker, Jaffee, Uher, & Maughan, 2011; Davis et al., 2004b; Korhonen, Luoma, Salmelin, & Tamminen, 2012; Lebel et al., 2016; Sandman et al., 2012; Wen et al., 2017) and genetic inheritance (Rice et al., 2010).

1.5 Resting-state Functional Connectivity MRI in Developmental Research

Resting-state functional connectivity magnetic resonance imaging (rs-fcMRI) is a non-invasive method of examining the brain's functional organization. This technique

measures spontaneous fluctuations in brain blood flow referred to as the Blood Oxygen Level Dependent (BOLD) signal (Fox & Raichle, 2007; Logothetis & Wandell, 2004; Raichle & Mintun, 2006) and identifies spatially distinct brain regions that demonstrate repeated patterns of activity in the absence of a task or external stimulus (Fox & Raichle, 2007; Graham, Pfeifer, Fisher, Lin, et al., 2015; Logothetis & Wandell, 2004). The observed patterns of activity reflect shared functional properties, connectivity between regions, and information on the intrinsic functional organization of the brain (Fox & Raichle, 2007; Fox et al., 2005; W. Gao, Lin, Grewen, & Gilmore, 2017; Wei Gao, Alcauter, Elton, et al., 2015; Graham, Pfeifer, Fisher, Lin, et al., 2015; H. Zhang, Shen, & Lin, 2019).

Resting-state functional connectivity MRI is an especially promising tool for understanding early neurodevelopment because MRI scans can be acquired during the fetal period or shortly after birth during infant natural sleep. During the fetal period, rs-fcMRI provides insight into network formation, while rs-fcMRI scans shortly after birth allow for the characterization of network development and completion (H. Zhang et al., 2019). By assessing infants shortly after birth, it is possible to begin to distinguish between the potential influences of prenatal and postnatal effects. The efforts to better characterize the role of gestational biology on neurodevelopment by examining the brain's functional organization during fetal development or shortly after birth, in order to isolate the effects of prenatal influences, are ongoing (Buss, Entringer, & Wadhwa, 2012; Emerson, Gao, & Lin, 2016; W. Gao et al., 2017; Wei Gao, Alcauter, Smith, Gilmore, & Lin, 2015; Graham, Pfeifer, Fisher, Lin, et al., 2015; M. E. Thomason et al., 2013; Moriah E. Thomason et al., 2015, 2018; H. Zhang et al., 2019).

Resting-state functional connectivity MRI is also an important tool in studies of neurodevelopment because it has high temporal and spatial resolution that allow for the examination of systems of interest, such as the limbic system, that are related to outcomes of interest (H. Zhang et al., 2019). The organization of functional brain networks can be observed during the fetal and neonatal period, before behavioral outcomes of interest are observable, and may represent early markers of risk or resilience (Graham, Pfeifer, Fisher, Lin, et al., 2015). In the present study, we focus on the functional connectivity of the neonatal amygdala and hippocampus, two key structures in the limbic system that are relevant to the negative valence system, stress responsivity, and attachment.

1.6 Associated Developmental Outcomes

Negative Affect Development

A maternal history of exposure to maltreatment during childhood is related to alterations in offspring neurobiological and socioemotional development, including increased stress reactivity and negative emotionality, emotional and behavioral dysregulation, and increased risk of neurodevelopmental and psychiatric disorders (Bosquet Enlow et al., 2017; Burghy et al., 2012; Buss, Davis, et al., 2012; Collishaw et al., 2007; Davis et al., 2011; Etkin & Wager, 2007; Folger et al., 2017; Mcdonnell & Valentino, 2016; Dominic T. Plant, Jones, Pariante, & Pawlby, 2017; Yong Ping et al., 2015). Most of these neurobiological alterations relate directly to the negative valence system, which is responsible for our responses to aversive situations and includes fear and anxiety (Carcone & Ruocco, 2017; T. R. Insel, 2014). Enlow and colleagues (2017) found that a maternal history of exposure to trauma was related to several domains of

infant negative affect (Bosquet Enlow et al., 2017), providing further support for the consideration of the negative valence system when examining the intergenerational transmission of childhood maltreatment.

The development of fear and anxiety in infancy and early childhood follows a distinct trajectory (Braungart-Rieker, Hill-Soderlund, & Karrass, 2010; Brooker et al., 2013; Garstein & Rothbart, 2003; Graham et al., 2016; Partridge & Lerner, 2007; Thomas et al., 2019). Fear and anxiety increase over the first year as infants begin to explore their environments. Fear of strangers and attention to human facial expressions emerges at approximately 6 months of age, which contributes to the increasing levels of fear (Braungart-Rieker et al., 2010; Brooker et al., 2013; Graham et al., 2016; Peltola, Leppänen, Mäki, & Hietanen, 2009). Around 12 months of infant age, fear of strangers peaks (Brooker et al., 2013; Gartstein et al., 2010; Gullone, 2000), separation anxiety emerges, and fear of strange objects and heights increases (Gullone, 2000). Fear and anxiety appear to stabilize by 24 months of age as infants begin to develop regulatory skills (Gartstein et al., 2010; Lemery, Goldsmith, Klinnert, & Mrazek, 1999; Thomas et al., 2019). Fear and anxiety play an important developmental role and are thought to facilitate caregiver attachment (Ainsworth & Bell, 1970; Landers & Sullivan, 2012), support (Lemery et al., 1999), and prosocial behaviors (Graham et al., 2016). Higher levels of negative affect in infancy are associated with an increased risk of affective and behavioral disturbances later in life (Abulizi et al., 2017), highlighting the importance of this early behavioral attribute to outcomes throughout the lifespan.

Attachment

Attachment is an important part of infant development and is crucial to the acquisition of self-regulatory skills. At birth, infants lack self-awareness as well as the capacity to discriminate between needs and wants (Blaustein, Margaret Ekinninburgh, 2018). Infants develop an awareness about bodily cues and learn to communicate their needs in the context of relationships (Blaustein, Margaret Ekinninburgh, 2018). Attachment with a caretaker not only provides training on the expression and regulation of emotions, but also serves as a model for relationships (Blaustein, Margaret Ekinninburgh, 2018). Bowlby refers to this mental representation of the self and the expected reactions from others and the environment formed through early attachment patterns as the *internal working model* (Bowlby, 1982). This internal working model informs adult relationships despite its early formation.

Attachment, like exposure to childhood maltreatment, can be transmitted across generations (Chamberlain et al., 2019; Levy & Orlans, 1998). Childhood maltreatment is intentional and interpersonal; disrupting the child's relationship with the caretaker, systems of attachment, and a sense of the self (J. Herman, 2015). Children exposed to maltreatment are less likely to form a secure attachment with their caretaker (Cyr, Euser, Bakermans-Kranenburg, & Van Ijzendoorn, 2010; Khan & Renk, 2018) and, in turn, are less likely to form a secure attachment with their own children (Khan & Renk, 2018; Levy & Orlans, 1998; Savage, Tarabulsy, Pearson, Collin-Vézina, & Gagné, 2019).

The type of maltreatment experienced by the mother has also been shown to affect the nature of her attachment with her child. Emotional neglect and physical abuse have been associated with reduced maternal sensitivity (Pereira et al., 2012). Physical

abuse has also been associated with more intrusive mothers (Lyons-Ruth & Block, 1996; Riva Crugnola, Ierardi, Bottini, Verganti, & Albizzati, 2019), and sexual abuse has been associated with higher levels of parental withdrawal (Lyons-Ruth & Block, 1996) and insecure attachment (Erozkan, 2016). A maternal history of neglect is associated with infant display of avoidant strategies (Lyons-Ruth & Block, 1996). Mothers with greater PTSD symptoms (Enlow, Egeland, Carlson, Blood, & Wright, 2014) during the early postnatal period, a history of PTSD (Chamberlain et al., 2019; Enlow et al., 2014; J. S. Seng et al., 2013; Soe et al., 2018), or psychological distress, including depression (Chamberlain et al., 2019; J. S. Seng et al., 2013), were more likely to have an insecure attachment with their child.

A maternal history of exposure to maltreatment is also associated with increased infant negative affect (Lyons-Ruth & Block, 1996). Increased infant negative affect, in turn, further influences attachment security. Elevated infant negative affect has been associated with reduced maternal responsivity and sensitivity (Chamberlain et al., 2019; Haltigan, Leerkes, Supple, & Calkins, 2014). Environmental factors like socio-economic deprivation can increase parenting stress and negatively affect attachment security (Chamberlain et al., 2019). Ultimately, attachment represents a synthesis of the interaction between maternal, infant, and environmental factors.

Within this dissertation, attachment will be classified using the Strange Situation Paradigm (Ainsworth, Blehar, Waters, & Wall, 1978), a validated, reliable, and widely used measure. The Strange Situation Paradigm assesses attachment security based on infant behavior during separations and reunions with their caretaker. In the present work, attachment security is classified into one of four groups: Secure, Avoidant, Ambivalent,

or Disorganized. Avoidant infants do not demonstrate distress with caretaker departure, engage in exploration and play in the presence of a stranger, and show little interest when the caretaker returns. Ambivalent infants show intense distress with the departure of the caretaker, avoid the stranger and disengage from play and exploration, and demonstrate both approach and resistant behavior when the caretaker returns. Disorganized or disoriented infants, a classification added later (Mary & Solomon, 1990), demonstrate fear or apprehension of the caretaker, freezing behavior, and contradictory behaviors. Disorganized/disoriented attachment has been associated with a maternal history of unresolved trauma or loss (Main & Hesse, 1990) and depression (Levy & Orlans, 1998). Insecure attachment includes the avoidant, ambivalent, and disorganized classifications.

Stress Reactivity

Infant stress reactivity has been associated with maternal psychological stress during pregnancy (Davis et al., 2011, 2004b; Galbally, van Rossum, Watson, de Kloet, & Lewis, 2019; Leung et al., 2010; Nazzari et al., 2019; O'Connor et al., 2013; Rash et al., 2016; Swales et al., 2018; Tollenaar, Beijers, Jansen, Riksen-Walraven, & De Weerth, 2011; Van den Bergh et al., 2017; Zietlow, Nonnenmacher, Reck, Ditzen, & Müller, 2019) and a history of maternal exposure to trauma (Bosquet Enlow et al., 2017; Brand et al., 2010). As previously described, one potential pathway for this observed association could be the role of maltreatment-associated HPA axis alterations on gestational biology. Moog and colleagues found that maternal exposure to maltreatment during childhood was associated with increased placental CRH production (Moog et al., 2016), potentially influencing the developing fetal HPA axis. Brand and colleagues found that a history of

maternal childhood abuse was associated with lower baseline cortisol in their infants at six months of age (Brand et al., 2010). They also found that a maternal history of childhood abuse in the presence of a lifetime history of PTSD was associated with greater infant cortisol reactivity (Brand et al., 2010). Enlow and colleagues (2017) found that the level of cortisol exposure during the third trimester, high or low, modified the relationship between maternal exposure to trauma and infant reactivity (Bosquet Enlow et al., 2017). In the context of attachment, greater infant cortisol stress reactivity has been associated with disruptive maternal interacting quality (Köhler-Dauner et al., 2019). Although salivary cortisol is a non-invasive and accessible measure of cortisol stress reactivity, there is evidence that cortisol reactivity in infants is most responsive to physical and not psychological stressors (Jansen, Beijers, Riksen-Walraven, & de Weerth, 2010). In the setting of physical stressors, effect sizes have been shown to decrease with infant age, potentially due to the buffering role of attachment (Jansen et al., 2010).

1.7 Goals of the Dissertation

The goal of this dissertation is to increase our understanding of the intergenerational transmission of maternal exposure to maltreatment during childhood by characterizing potential mechanisms, such as maternal psychological stress during pregnancy, and offspring neurobiological and socioemotional outcomes (see **Figure 1.5**). The present work used neonatal rs-fcMRI to examine the influence of maternal psychological stress and maternal exposure to maltreatment during childhood on the offspring brain shortly after birth in order to distinguish these

preconceptional and prenatal factors from postnatal factors. We focused on the limbic system because it is especially vulnerable to stress including early childhood. The general architecture and connectivity of the limbic system is largely established before birth (Hodel, 2018), suggesting potential malleability to mediators of maternal psychological and biological stress. The limbic system plays an important role in the regulation of stress; thus, stress-induced alterations may increase the risk for emotional dysregulation (Burghy et al., 2012; Buss, Davis, et al., 2012), heightened negative affect and stress reactivity (Davis et al., 2011; Yong Ping et al., 2015), and subsequent psychopathology (Etkin & Wager, 2007) in offspring. Given the susceptibility of the developing brain to environmental cues such as stress, the prenatal period likely plays an important role in the intergenerational transmission of childhood maltreatment.

Study 1 (Chapter 2) examines how trajectories of maternal psychological stress during pregnancy affect neonatal amygdala functional connectivity and negative affect development. Maternal psychological stress during pregnancy is potentially a key mechanism for the intergenerational transmission of childhood maltreatment. The majority of studies examining maternal psychological stress during pregnancy consider the magnitude of stress as the 'risk factor;' however, psychological stress, particularly during the prenatal period, is dynamic and variable (Buss, Entringer, Swanson, et al., 2012). Fetal neurodevelopment follows a rapid and sequential progression; therefore, characterizing the timing and variability of maternal stress across pregnancy is a critical step in advancing our understanding of stress as an early influencer of offspring brain and behavioral development. The present study employs a novel, flexible, and data-driven approach to characterize individual longitudinal trajectories of maternal stress across

pregnancy and the early postpartum period. Maternal psychological stress was assessed in two independent mother-infant dyad cohorts (Total N=2,271). Maternal perinatal stress trajectories were characterized and grouped into clusters using a novel machine learning algorithm, the Functional Random Forest. Across both cohorts, the association between maternal stress trajectories and infant negative affect was examined. The relationship between neonatal amygdala functional connectivity and maternal perinatal stress trajectories was examined in the cohort with neuroimaging data. Finally, we examined the association between maternal perinatal stress clusters and maternal exposure to maltreatment during childhood.

Study 2 (Chapter 3) examines the association between maternal exposure to maltreatment during childhood and neonatal amygdala functional connectivity, mother-infant attachment security, and infant cortisol reactivity. Numerous studies have focused on the role of attachment and bonding during the postnatal period as a potential mechanism for the intergenerational transmission of childhood maltreatment, but it is possible that prenatal influences also play a role. First, we examined the association between maternal exposure to maltreatment during childhood and offspring neonatal amygdala functional connectivity. Next, we examined the association between neonatal amygdala functional connectivity and attachment security at 12 months of infant age. Given the relationship between maternal exposure to maltreatment during childhood and infant reactivity, we further considered the association between offspring neonatal amygdala functional connectivity and cortisol reactivity in infants at 12 months of age. Focusing on the neonatal brain and its associations with attachment and cortisol reactivity increases our ability to differentiate between prenatal and postnatal influences, and helps

us to elucidate potential prenatal mechanisms for the intergenerational transmission of childhood maltreatment.

Study 3 (Chapter 4) examines the association between maternal exposure to maltreatment during childhood and neonatal hippocampal functional connectivity. The hippocampus is highly sensitive to stress such as early adversity and childhood maltreatment. It also plays a regulatory role in HPA axis responsivity, which is known to be altered during pregnancy and following exposure to early adversity. In the present study, we examine neonatal hippocampal functional connectivity in relation to a history of maternal childhood maltreatment. There is evidence that the major adult network functional components are present during childhood (Damaraju, Caprihan, & Lowe, 2014; De Asis-Cruz, Bouyssi-Kobar, Evangelou, Vezina, & Limperopoulos, 2015; Emerson et al., 2016; Fransson, Aden, Blennow, & Lagercrantz, 2011; Fransson et al., 2009, 2007; W. Gao et al., 2017; Wei Gao, Alcauter, Elton, et al., 2015; Wei Gao, Alcauter, Smith, et al., 2015; Grayson & Fair, 2017; Grayson et al., 2014; Jakab et al., 2014; Keunen et al., 2017; Scheinost et al., 2017; H. Zhang et al., 2019); therefore, we leverage a template matching approach, based on a large adolescent cohort, to empirically segment the hippocampus. Finally, we examine the resulting segments from the template matching approach in relation to a maternal history of childhood maltreatment. Investigating the functional connectivity of hippocampal subregions in infants will allow us to better characterize their potential role in risk or sensitivity to future psychopathology.

The results of these studies will characterize the longitudinal heterogeneity of maternal psychological stress during pregnancy and will examine the influence of

maternal exposure to maltreatment during childhood on offspring neurobiological and socioemotional outcomes. Understanding the heterogeneity of maternal psychological stress, the influence of preconceptional factors such as exposure to childhood maltreatment, and their effect on infant neurobiological and socioemotional development is critical to targeting screening and interventions.

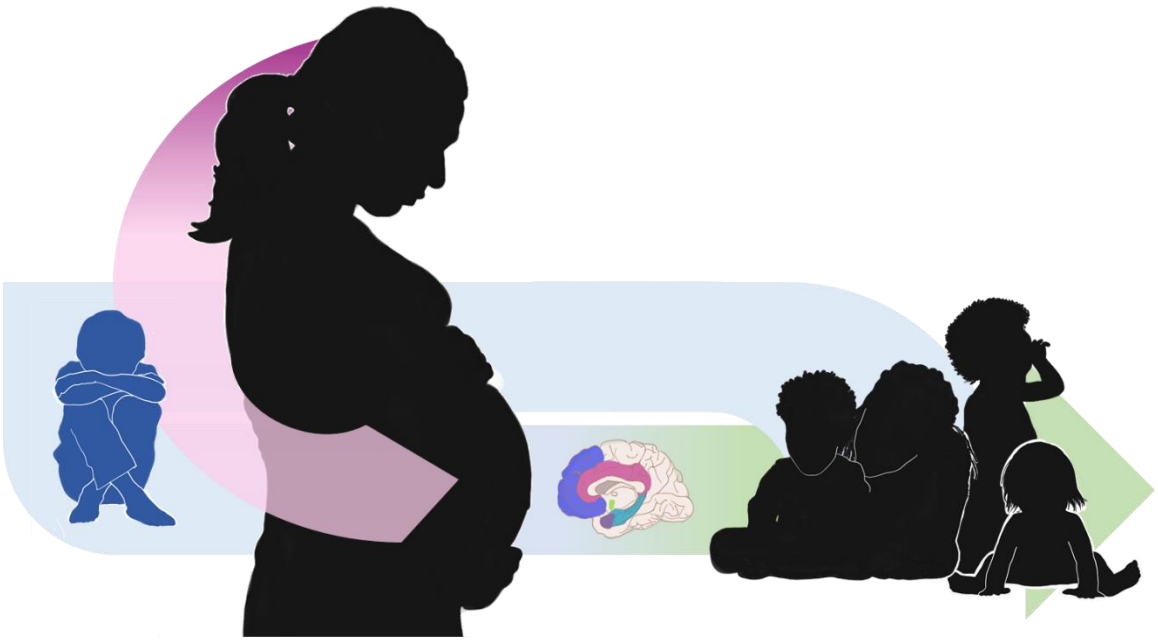

Figure 1.5. Overview of dissertation studies. The intergenerational transmission of maternal exposure to maltreatment during childhood was explored by characterizing potential mechanisms and outcomes. Study 1 examined the association of maternal psychological stress trajectories during pregnancy with neonatal amygdala functional connectivity, infant negative affect development, and a maternal history of exposure to childhood maltreatment. Study 2 examined the association between maternal exposure to maltreatment during childhood and neonatal amygdala functional connectivity, attachment security, and cortisol reactivity. Study 3 examined the association between maternal exposure to maltreatment during childhood and neonatal hippocampal functional connectivity in both the whole hippocampus and hippocampal subregions identified through a template matching approach.

CHAPTER 2. MATERNAL PERINATAL STRESS AND OFFSPRING AMYGDALA CONNECTIVITY AND NEGATIVE AFFECT DEVELOPMENT

This chapter has been reformatted for inclusion in this dissertation from:

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2.1. Abstract

Background: Maternal psychological stress during pregnancy is a common and potentially modifiable risk factor for offspring psychiatric disorders. Here we employ novel methods to investigate heterogeneity in maternal psychological stress and associations with infant brain and behavioral development.

Methods: Maternal psychological stress was assessed across pregnancy and early postpartum in two independent mother-infant dyad cohorts (Total N=2,271). Maternal perinatal stress trajectories were characterized and grouped into clusters using a novel machine learning algorithm, the Functional Random Forest. Across both cohorts, maternal stress trajectories were examined in relation to infant negative affect. Neonatal amygdala resting-state functional connectivity MRI was examined in the cohort with neuroimaging data.

Outcomes: In the original sample, four distinct clusters characterized by differences in the pattern of change over time (trajectory), and two characterized by overall magnitude of stress (higher versus lower) were identified. The magnitude clusters were not associated with infant brain or behavioral outcomes, but were associated with a history of maternal exposure to maltreatment during childhood. In contrast, the trajectory cluster characterized by increasing stress in late pregnancy was associated with altered infant negative affect development. The trajectory clusters and the association with infant negative affect were replicated in the independent cohort. In the original cohort, trajectories with increasing or peak maternal stress in late pregnancy were additionally associated with stronger offspring neonatal amygdala functional connectivity to the anterior insula and ventromedial prefrontal cortex.

Interpretation: The current report makes clear that the trajectory of perinatal stress, as opposed to purely the severity, is important for offspring brain and behavioral development. Stress late in pregnancy appears to be a highly sensitive time with effects on increased neonatal amygdala functional connectivity and negative affect development lasting over the first two years of life. Understanding the heterogeneity of perinatal stress trajectories and their influence on infant brain and behavioral development is critical to targeting future interventions.

2.2. Introduction

Maternal psychological stress during pregnancy (e.g., anxiety, depression, and perceived stress) has implications for maternal health and is a common and potentially modifiable risk factor for offspring psychiatric and other health disorders.

Previous studies of maternal psychological stress during pregnancy primarily consider stress in terms of its magnitude (i.e., high, medium, or low). However, several lines of evidence highlight how the dynamic nature of psychosocial stress over the course of pregnancy might be an equally important indicator of long-term offspring health (C. M. Heim et al., 2019; Mora et al., 2009). Despite such evidence, there is a limited understanding of how individual differences or heterogeneity in maternal psychological stress across pregnancy relate to offspring neurodevelopment. Fetal neurodevelopment is a dynamic process that is differentially sensitive to environmental influences during distinct phases. Thus, it is likely that the effect of any insult, such as maternal stress, may depend just as much on the timing and rate of change of the stressor as it does on the severity.

The fetus receives cues about the extrauterine environment via stress-sensitive aspects of maternal-placental-fetal biology (Buss et al., 2017; C. M. Heim et al., 2019), potentially influencing brain systems sensitive to stress and commonly implicated in neuropsychiatric disorders. For example, maternal psychological and biological stress mediators during pregnancy have been associated with altered offspring limbic system development in infancy (Graham et al., 2018; A Qiu et al., 2015; Rifkin-Graboi et al., 2015). Because the limbic system plays an important role in the regulation of stress and negative affect, these stress-induced alterations may increase the risk for emotional dysregulation (Burghy et al., 2012; Buss, Davis, et al., 2012), heightened negative affect and stress reactivity (Davis et al., 2011; Yong Ping et al., 2015), and subsequent psychopathology in offspring (Etkin & Wager, 2007). Offspring development of negative emotionality is of particular interest as a transdiagnostic endophenotype of susceptibility for subsequent psychiatric disorders (Damme et al., 2020; T. Insel et al., 2010).

Fetal neurodevelopment follows a rapid and sequential progression; therefore, characterizing the timing and variability of maternal stress across pregnancy is a critical step in advancing our understanding of stress as an early influencer of offspring brain and behavioral development. The present study employs a novel, flexible, and data-driven approach to characterize individual longitudinal trajectories of maternal stress across pregnancy and the early postpartum period. We characterize specified clusters of stress trajectories and then test the associations between these clusters and offspring affective development and relevant patterns of amygdala connectivity.

2.3. Methods and Materials

Participants

Two datasets were employed to examine maternal stress trajectories and offspring outcomes. The primary cohort included mother-infant dyads enrolled as part of a prospective longitudinal cohort study conducted at the University of California, Irvine (UCI) from February 2011 to November 2018, for details see (Moog et al., 2018). Mothers were recruited through prenatal clinics during early pregnancy. A subset of mothers (n=115) was selected based on the completion of maternal stress measures in early pregnancy and at one month postpartum. A cohort diagram indicating the number of mothers and infants participating at each stage of analysis is presented in **Figure 2.7** in the Supplemental Materials at the end of this chapter. Demographic data for participants are presented in **Table 2.1**. All procedures were approved by the Institutional Review Board at the UCI.

Table 2.1. Demographic data for University of California, Irvine cohort.

	Mean (SD)
Maternal age in first trimester, Years (n=115)	28.07 (4.88)
Infant Age	
Gestational age at birth, Weeks (n=110)	39.24 (1.53)
Age at functional MRI data collection, Days (n=60)	26.22 (11.45)
Infant Sex (n=110)	**No. (%)**
Male	59 (54)
Female	51 (46)
Race/Ethnicity (n=105)	
Caucasian non-Hispanic	42 (40)
African American non-Hispanic	1 (1)
Asian non-Hispanic	8 (8)
Multi-racial non-Hispanic	8 (8)
Caucasian Hispanic	40 (38)
Asian Hispanic	1 (1)
Multi-racial Hispanic	5 (5)
Highest Level of Maternal Education (n=106)	
Primary, elementary, or middle school	4 (4)
High school or test equivalent	19 (18)
Vocational school or some college	44 (43)
Associates degree	6 (6)
Bachelors or graduate level degree	32 (30)
Gross Annual Household Income (n=111)	
< $15,000	13 (12)
$15,000 - 29,999	15 (14)
$30,000 - 49,999	29 (26)
$50,000 - 100,000	43 (39)
> $100,000	11 (10)

The second, replication cohort of mother-infant dyads was part of a prospective longitudinal cohort study conducted at the University of Turku as part of the FinnBrain Birth Cohort Study from December 2011 to April 2015, for details see (Karlsson et al., 2018). Briefly, mothers were recruited for the study during their first trimester of pregnancy. A subset of mother-infant dyads (n=2,156) was selected for this study based on completion of maternal prenatal depression and anxiety measures and at least one infant negative affect measure (6, 12 or 24 months). Demographic data for participants are presented in **Table 2.2**. Study protocols were approved by the Ethics Committee of the Hospital District of Southwest Finland.

Table 2.2. Demographic data for FinnBrain data, replication cohort.

	Mean (SD)
Maternal age in the due date, Years (n=2156)	31.24 (4.41)
Gestational age at birth, Weeks (n=2156)	39.77 (1.71)
Infant Sex (n=2156)	**No. (%)**
Male	1146 (53)
Female	1010 (47)
Race/Ethnicity (n=2156)	
Caucasian	2153 (99.9)
Highest Level of Maternal Education (n=2049)	
Primary, elementary, or middle school	37 (2)
High school or test equivalent	257 (12)
Vocational school or some college	364 (18)
Vocational tertiary/applied university	614 (30)
Bachelors or graduate level degree in university	777 (38)
Maternal Monthly Income in Pregnancy (n=2046)	
< €1000	425 (21)
€1000 - 2000	998 (49)
€2000 - 3000	530 (25)
€3000 - 4000	80 (4)
> €4000	13 (1)
Economic satisfaction in the first trimester (N = 2044), range 0-10	5.85 (2.45)

Maternal Psychological Stress Measures

Maternal Psychological Stress Measures in the UCI Cohort

Participants in the UCI cohort completed the Center for Epidemiological Studies Depression Scale (CESD) (Radloff, 1977), Perceived Stress Scale (PSS) (Cohen, Kamarck, & Mermelstein, 1983), and State-Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch, & Lushene, 1970) in early (M: 12.84, SD: 1.83 weeks), mid (M: 20.50, SD: 1.44 weeks) and late (M: 30.48, SD: 1.39 weeks) pregnancy and at one, three, six, nine, twelve, and twenty-four months postpartum. Stress measure scores were only calculated if three or fewer items were missing. Mean scores were calculated for each scale to reduce the effect of missing items. The mean scores of the three scales were z-

transformed and then combined to generate composite stress scores creating an overall indicator of maternal psychological stress at each time point from early pregnancy through early postpartum. All measures were weighted equally. Composite stress scores were created only if two out of the three scales were available. Measures at each time point were highly correlated (r: 0.331 to 0.705, all $p \leq 0.001$), supporting the creation of a composite indicator, see **Table 2.3**. We will refer to maternal stress from pregnancy through one month postpartum as perinatal stress. Postnatal maternal composite stress scores at three, six, nine, twelve, and twenty-four months were included as time-varying covariates in analyses examining infant behavior in order to adjust for the potential influence of the postnatal environment.

Table 2.3. Correlations for stress, anxiety, and depression measures at each time point.

	Early pregnancy		**Mid pregnancy**		**Late pregnancy**		**Early postpartum**	
CESD	**PSS (r)**	**STAI (r)**	**PSS (r)**	**STAI (r)**	**PSS (r)**	**STAI (r)**	**PSS (r)**	**STAI (r)**
Early pregnancy	0.528	0.536						
Mid pregnancy			0.331	0.432				
Late pregnancy					0.701	0.636		
Early postpartum							0.705	0.661

Maternal childhood maltreatment history was assessed in mid-pregnancy using the Childhood Trauma Questionnaire (CTQ) (D P Bernstein et al., 1994). The CTQ is a standardized, retrospective self-report tool that assesses five domains of childhood maltreatment: physical, sexual, and emotional abuse; and physical and emotional neglect.

It is a 28-item questionnaire with 3 items making up an additional Minimization/Denial scale designed to capture potential under-reporting (Villano et al., 2004). Each item within the five maltreatment domains is scored on a 5 point scale where 1 = never and 5 = very often. The total CTQ score is a sum score of all maltreatment domains.

Maternal Psychological Stress Measures in FinnBrain Cohort

Participants in the FinnBrain cohort completed the Edinburgh Postnatal Depression Scale (EPDS) (Cox, Holdenand, & Sagovsky, 1987) and the Symptom Checklist (SCL-90) (Derogatis, Lipman, & Covi, 1973) in early (M: 15.2, SD: 2.7), mid (M: 25.3, SD: 1.5 weeks) and late (M: 35.1, SD: 1.8 weeks) pregnancy, and at six, twelve, and twenty-four months postpartum. Only the anxiety subscale of the SCL-90 was examined to parallel the anxiety measure in the UCI cohort. Early-, mid-, and late-pregnancy principal component scores based on these two scales were calculated to create an overall indicator of maternal psychological stress at each time point. This resulted in one component at each time point with high factor loadings (T1= 0.91, T2 = 0.91, T3= 0.90), providing support for a single composite measure of maternal psychological stress at each time point. Missing time point data (<6.8%) were handled through the default missing values replacement procedure as part of the principal component analysis in SPSS 25 (IBM Corp., 2017).

Infant Negative Affect

In the UCI cohort, mothers completed the Infant Behavior Questionnaire-Revised (IBQ) (Parade & Leerkes, 2008) to assess infant negative affect at three, six, nine, and

twelve months of infant age and The Early Childhood Behavior Questionnaire-Short Form (ECBQ) (Putnam, Gartstein, & Rothbart, 2006) at twenty-four months of age. The negative affect composite was created by computing the mean scores of completed items for each of the relevant subscales and averaging them together. A latent growth model (LGM; (Muthén & Muthén, 2017)) was used to define infant negative affect development from three to 24 months of age. Only subjects with identified maternal perinatal clusters (Model- and Correlation-based) and IBQ/ECBQ scores with a minimum of one time point were included in the LGM (n=110). The parameter estimates for the unconditional model are listed in the supplement (**Table 2.21**). The intercept and growth terms from these models were used as outcome variables in analyses examining infant behavior.

In the FinnBrain cohort, mothers completed the Infant Behavior Questionnaire-Revised (IBQ-R) (Parade & Leerkes, 2008) to assess infant negative affect at six and twelve months of infant age and The Early Childhood Behavior Questionnaire-Short Form (ECBQ) (Putnam et al., 2006) at twenty-four months age (n with complete data from all time points=1,062).

Resting-state Functional Connectivity MRI

Brain imaging was only available for the UCI cohort. Data were acquired at approximately one month of age (28.42 ± 13.31 days) during natural sleep. Data acquisition and preprocessing procedures were previously described (Graham et al., 2016, 2018; Moog et al., 2018). We previously identified patterns of increased neonatal amygdala functional connectivity with the ventromedial prefrontal cortex (vmPFC) and anterior insula (aI) that predicted infant negative affect development (Graham et al.,

2016; Thomas et al., 2019). In the current study, we focused on these predefined amygdala connections due to prior work indicating the vulnerability of the amygdala to early life stress exposure, beginning in the antenatal period (Buss, Davis, et al., 2012; Graham et al., 2016, 2018; A Qiu et al., 2015; Thomas et al., 2019).

Data Acquisition

A TIM Trio, Siemens Medical System 3.0T scanner was used to obtain high-resolution T1-weighted (MP-RAGE TR = 2400 ms, inversion time = 1200 ms, echo time = 3.16 ms, flip angle = 8°, resolution = 1 x 1 x 1 mm, 6 min 18 secs) and T2-weighted (TR = 3200 ms, echo time = 255ms, resolution = 1 x 1 x 1 mm, 4 min 18 secs) images. Resting-state functional connectivity MRI images were obtained using a gradient-echo, echoplanar imaging (EPI) sequence sensitive to BOLD contrast (TR = 2000 ms; TE = 30 ms; FOV = 220 x 220 x 160 mm; flip angle = 77°).

fMRI Data Preprocessing

Pre-processing followed established procedures for neonatal neuroimaging (Graham et al., 2016). Briefly, brain images were isolated from surrounding head tissue and functional images were pre-processed to reduce artifacts. Atlas transformation involved calculation of a single matrix to facilitate registration to a standard infant template (0- to 2-month age range; National Institutes of Health MRI Study of Normal Brain Development) (Vladimir Fonov et al., 2011; VS Fonov, Evans, McKinstry, Almli, & Collins, 2009) and to the Talairach coordinate system (Talairach & Tournoux, 1988).

rs-fcMRI Preprocessing

Additional preprocessing steps were conducted to address potential signal stemming from non-neuronal processes including temporal low-pass filtering (0 f < 0.1 Hz) (Fair et al., 2012; Fox & Raichle, 2007). These included regression of rigid body head motion parameters in 6 directions, regression of whole brain signal, regression of average ventricular signal, regression of white matter signal, and regression of first order derivative terms for the whole brain, ventricular, and white matter signals (Graham et al., 2016; Rudolph et al., 2018). To correct for motion, an examination of frame-wise displacement (FD) was conducted and volumes with greater than 0.3 mm FD plus the preceding volume and subsequent 3 volumes were removed (J. D. Power et al., 2011). Following volume removal for motion, scan length for the remaining infants (n=60) was about five and half minutes (M: 5.66 minutes, range: 4.27 - 6.37 minutes) with a remaining FD of 0.085 (M: 0.085, range: 0.048 – 0.135).

Amygdala Connections

Automatic amygdala segmentation was performed using a multi-template, multi-modality-based method that combined T1 and T2 weighted high-resolution images (J. Wang et al., 2014). Following anterior-posterior realignment, amygdala segmentations were manually corrected using ITK-Snap (Yushkevich et al., 2006). For rs-fcMRI analyses, amygdalae were transformed to atlas space based on the previously computed atlas transformation (Graham et al., 2018).

Analytic Approach

The Functional Random Forest

The Functional Random Forest is a novel approach designed to capture unknown heterogeneity in samples (Feczko et al., 2017, 2019), and is extended here to characterize the heterogeneity of maternal perinatal stress trajectories. The approach integrates three validated techniques, Functional Data Analysis, Random Forest, and community detection (i.e., Infomap). Community detection is applied in two ways to identify (1) "Model-based clusters" or (2) "Correlation-based clusters." Both approaches capture longitudinal symptom heterogeneity in a flexible and data-driven manner, see **Figure 2.1**. Mothers from the UCI cohort were included in the model if they had data for at least three of the four assessments, including the first and the last time point.

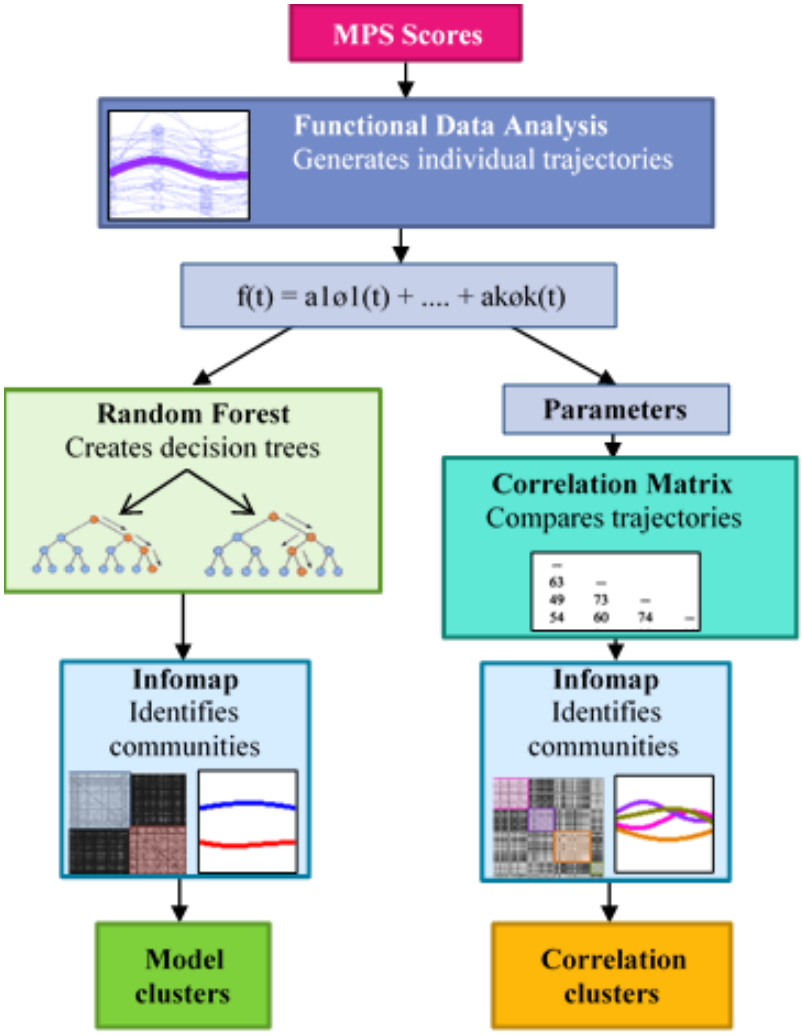

Figure 2.1. Functional Random Forest. The FRF combines Functional Data Analysis, the Random Forest, and Infomap to characterize subgroups within populations. Self-report measures of maternal perinatal stress (MPS) were used to create Model and Correlation clusters.

Post-hoc analyses (see Supplement) were conducted to examine the validity of identified clusters and further characterize differences in clusters (chi-square and ANOVAs). Modularity permutation tests (see Supplemental Materials **Tables 2.5 – 2.7**) show that all clusters had significantly greater modularity than random assignments, suggesting that the clusters represent stable subgroups. The modularity associated with the lowest edge density is reported below. Modularity values at each edge density and by community are reported in the Supplemental Materials at the end of the chapter.

Association between Maternal Clusters and Brain and Behavioral Outcomes

A simple multiple regression approach was used to examine maternal stress clusters in relation to infant amygdala connections and negative affect development. Covariates for gestational age (GA) at birth and infant age at scan were included in all analyses to account for neonatal brain maturity at the time of MRI scan acquisition. Additional covariates were also tested to ensure that model results remained consistent, including infant sex, maternal annual income, and maternal obstetric risk factors.

A latent growth model (LGM) in MPlus 8 (Muthén & Muthén, 2017) was used to define infant negative affect development from three to twenty-four-months-of-age. Only subjects with identified maternal perinatal clusters (Model- and Correlation-based) and IBQ/ECBQ scores with a minimum of one time point were included in the LGM (n=110). The intercept and growth terms from these models were used as outcome variables in analyses examining infant behavior.

Replication in FinnBrain Cohort

For the replication study in the FinnBrain cohort, we first extracted trajectory model parameters for clusters based on the "Correlation-based clusters" using multinomial logistic regression on the UCI maternal composite stress scores. Specifically, the maternal stress cluster classification served as the dependent variable, and the maternal stress composite scores for each of the three time points served as independent variables in the logistic regression. The intercept and parameters for the early, mid, and late pregnancy composite scores were extracted from this model. The UCI early, mid, and late pregnancy composite score parameters were then mapped onto the early, mid, and late antenatal FinnBrain principal component scores. To assign FinnBrain subjects to UCI maternal stress clusters, a multinomial logistic regression was performed with the UCI maternal stress cluster classification again serving as the dependent variable and the mapped FinnBrain stress scores serving as independent variables. Classification of FinnBrain subjects was based on the fit of the FinnBrain early, mid, and late antenatal stress scores with the maternal stress trajectories identified in the UCI cohort.

A repeated measures ANCOVA was used to examine infant negative affect growth over time accounting for infant sex, gestational age, and maternal postnatal depression. An ANCOVA was used to model negative affect growth because there were not enough time points in the FinnBrain cohort to include a quadratic term in the LGM, which we have found to be necessary to capture the trajectory of infant negative affect development across the first two-years of life (Partridge & Lerner, 2007). Infant negative affect scores were residualized for postnatal depression at each time point to more closely

match the time-varying covariate approach used in the LGM model as described in the supplement.

2.4. Results

Maternal Trajectories of Perinatal Stress

Approach 1. Model-based Clustering Captures Magnitude

Maternal perinatal composite stress scores in the UCI cohort were entered into the FRF algorithm. The Model-based approach identified two clusters, divided nearly evenly, with a third cluster containing only one subject who was excluded from analysis. The two remaining clusters had significantly greater modularity than random assignments ($Q=0.729$, $p<0.001$, see Supplement) and captured magnitude differences in maternal perinatal stress ($t(1998)=113.47$, $p<0.001$, CI 0.414, 0.429), see **Figure 2.2A**. These clusters differed significantly at every time point in a two-way ANOVA (all $p<0.001$), and reflected mothers with high and low mean composite scores. We refer to these clusters, hereafter as "*magnitude clusters*." We next plotted the associated trajectories of the magnitude clusters, which clearly reflected the high/low split, in **Figure 2.2B**. The mean velocities of the two clusters were similar and mostly flat because they encompassed participants with varying trajectories (see Approach 2 below).

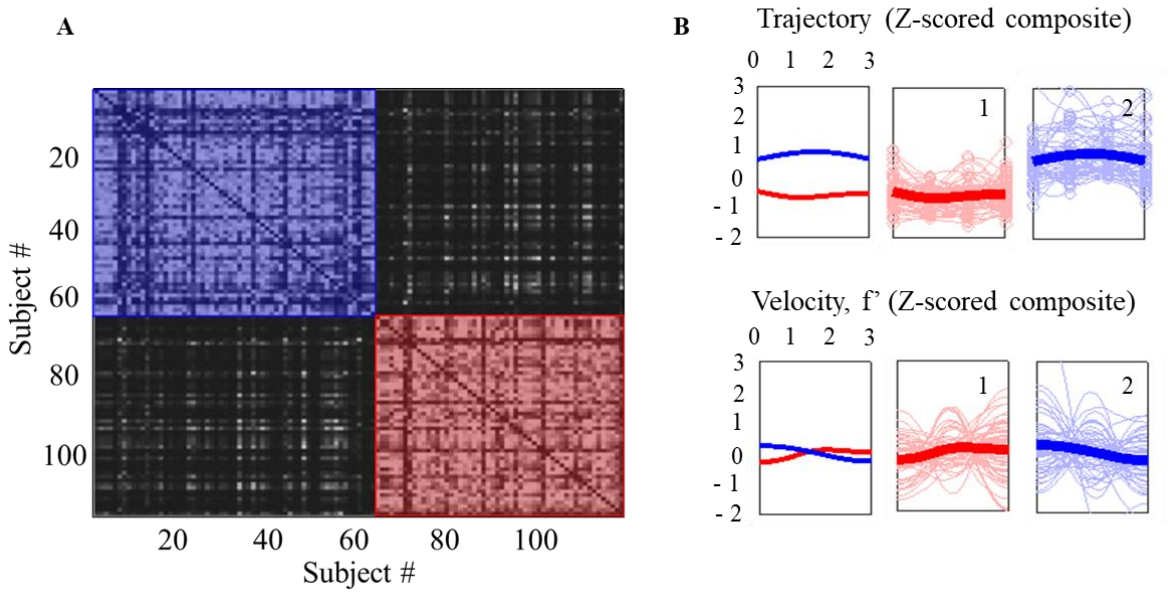

Figure 2.2. Functional Random Forest identified distinct subgroups related to the magnitude of maternal stress. Maternal perinatal stress measures were completed during early (0), mid (1), and late (2) pregnancy, and 1 month postnatal (3). **(A) Sorted proximity matrix for model-based approach.** Two distinct clusters were identified. **(B) Two distinct trajectories reflecting high/low maternal perinatal stress from model-based approach.** Top row shows individual stress trajectories with central tendency of each cluster in bold. Group 1 (red) had lower maternal perinatal stress scores. Group 2 (blue) had higher scores and greater variability. Bottom row shows the velocity of perinatal stress (rate of change in maternal stress) with central tendency of each cluster in bold. The clusters did not show clearly divergent patterns in terms of velocity. Clusters are labeled in the upper right hand corner (1, 2). Far left column of both rows shows the central tendency of all clusters.

Although our primary analysis focuses on overall maternal psychological stress, we also examined the mean and standard deviation for each individual measure (CESD, PSS and STAI), see **Tables 2.9 - 2.12** in Supplemental Materials. We additionally plotted these results by magnitude cluster assignment to examine whether the overall trends were the same for each contributing measure (see **Figure 2.8** in Supplemental Materials).

Approach 2. Correlation-based Clustering Captures Shape and Velocity of Maternal Perinatal Stress

This analysis utilized the same participants as above and identified four Correlation-based clusters ($Q=0.811$, $p<0.001$, see **Figure 2.3A**) with distinct trajectories defined by the shape and velocity of changes in maternal perinatal stress, see **Figure 2.3B**. We hereafter refer to these clusters as "*trajectory clusters.*" Clusters with less than 10 subjects were not considered reliable and were excluded from further analyses. The final trajectory clusters accounted for 102 mothers. The 13 mother-infant dyads that belonged to clusters excluded from the analyses did not differ significantly from those included, see missing data analysis section in supplement.

Trajectory 1 (late gestation peak) demonstrated a horizontal s-shape with lower stress at second trimester and a peak stress at the third trimester, see **Figure 2B**. The velocity for Trajectory 1 was highest between the second and third trimester indicating the greatest change in stress level across this period. The opposite pattern was present in Trajectory 2 (midgestation peak), which showed an early peak in stress at the second trimester followed by a decrease in stress in the third trimester. This trajectory also

showed the greatest change between the second and third trimester, but in a direction opposite to Trajectory 1, indicating a decrease in stress. Trajectory 3 (late gestation increase) was u-shaped with a trough at the second trimester increasing across the third trimester. The velocity of Trajectory 3 demonstrated increasing stress across the third trimester to the first postnatal month. Finally, the shape and velocity of Trajectory 4 (postnatal decline) reflected a shallow initial rise followed by a drop-off in stress from the third trimester to the first postnatal month.

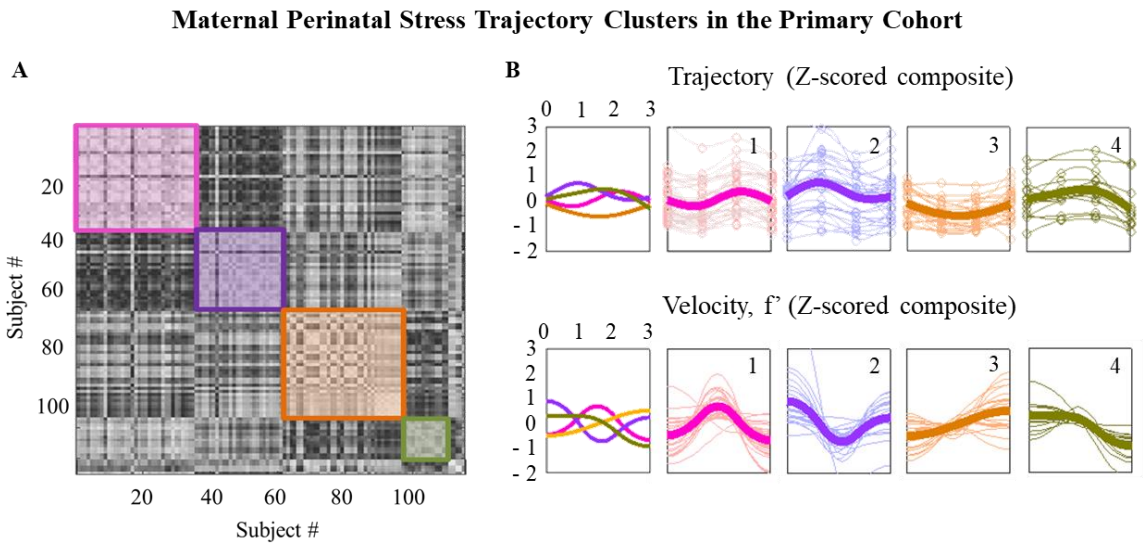

Figure 2.3. Functional Random Forest identified distinct subgroups. Maternal perinatal stress measures were completed during early (0), mid (1), and late (2) pregnancy, and 1 month postnatal (3). **(A) Sorted proximity matrix for correlation-based approach.** Four clusters were identified. **(B) Four distinct trajectories reflecting differences in peak stress and velocity of stress over time from correlation-based approach.** Top row shows individual stress trajectories with central tendency of each cluster in bold. Bottom row shows the velocity (rate of change in maternal stress) of perinatal stress with central tendency of each cluster in bold. Clusters are labeled in the upper right hand corner (1-4). Far left column shows central tendency of all clusters.

As with the magnitude clusters, we examined mean total scores and standard deviations on the three measures at each perinatal time point (see **Tables 2.13 – 2.16** in Supplemental Materials). We also plotted scores for individual measures by trajectory cluster assignment to examine whether trends remain consistent for each contributing measure (see **Figure 2.9** in Supplemental Materials).

Maternal Perinatal Stress Clusters are Associated with Infant Negative Affect Development

We next examined the association between maternal clusters and infant negative affect development by adding dummy-coded magnitude and trajectory clusters as predictors, along with relevant covariates, to the LGM model of negative affect from three to 24 months ofage, see Supplemental Materials for analytic approach. The magnitude and trajectory clusters were included in the same model to evaluate their independent contributions to infant negative affect development.

Magnitude clusters. The magnitude clusters predicted the intercept term (*B*=0.339, p=0.008) suggesting that higher maternal perinatal stress throughout pregnancy is related to elevated infant negative affect at 3 months of age, **Table 2.21** in Supplemental Materials. However, when adjusting the models for maternal postnatal stress scores using time varying covariates, the magnitude clusters no longer predicted the intercept, suggesting that postnatal maternal stress explains the association between maternal perinatal stress and infant negative affect.

Trajectory clusters. Maternal trajectory clusters did not predict intercept. However, Trajectory 3 (late gestation increase) predicted less linear growth (*B*=-0.918,

p=0.032) of infant negative affect (**Table 2.21** in Supplement; **Figure 2.4A**, bottom left). When adjusting for maternal postnatal stress scores, Trajectory 3 continued to significantly predict the linear term of infant negative affect development (*B*=-0.921, p=0.031). The plot of infant negative affect development (**Figure 2.4a**, bottom left) suggests that infants of mothers in the Trajectory 3 (late gestation increase) show an overall divergent pattern of negative affect development, beginning at approximately 12 months of age. The level of negative affect was found to be significantly different between Trajectory 3 and the others clusters at 12 months (t=2.841, df=69, p=0.01).

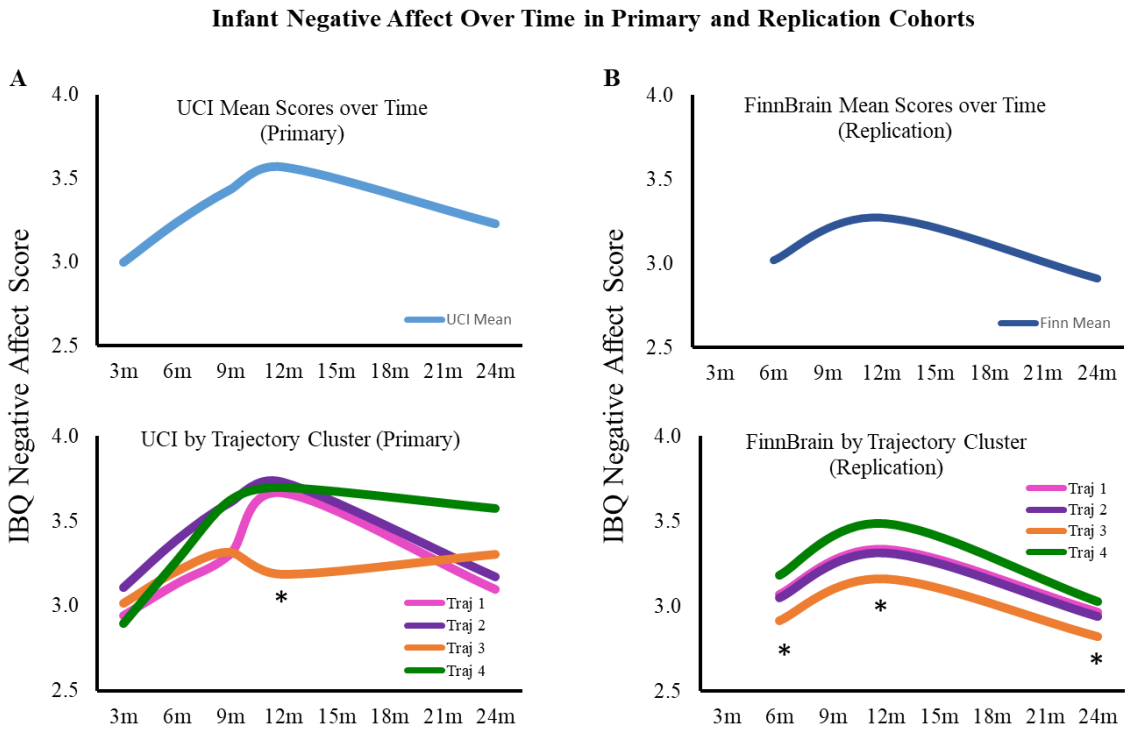

Figure 2.4. Infant negative affect growth has an inverted u-shaped trajectory. A. *Top*. Negative affect growth in the UCI cohort (Primary). The quadratic shape in this model reflects an increase in negative affect mean scores until 12 months of age with scores then decreasing through 24 months of age. ***Bottom.* Trajectory 3 independently predicts slope of infant negative affect growth in the UCI cohort (Primary).** Trajectory 3 (orange) differs significantly (*) from the other clusters at 12 months of age (t=-2.841, p=0.01). **B. *Top*. Negative affect growth in the FinnBrain cohort (Replication).** Mean scores show negative affect increasing through 12 months of age then decreasing through 24 months of age. ***Bottom.* Trajectory clusters are associated with infant negative affect growth in the FinnBrain cohort (Replication).** Trajectory clusters significantly predicted infant negative affect scores at different time points (F=3.04, p=0.028). Trajectory 3 (orange) differed significantly from all other clusters (*) and has lower negative affect mean scores compared to the other clusters.

We also examined the association between composite stress scores at each perinatal time point and infant negative affect development (See Supplemental Materials, **Tables 2.22-2.25**).

Replication in FinnBrain Cohort

Maternal Trajectory Clusters

To examine whether the maternal clusters could be replicated in an independent sample, we applied the parameters for the UCI trajectory clusters to maternal antenatal stress principal component scores from the FinnBrain cohort (**Figure 2.5**). FinnBrain Trajectory 1 showed the same decreasing then increasing stress found in the original sample Trajectory 1. Trajectory 2 similarly mimicked the increasing then decreasing stress observed in the original sample Trajectory 2. Trajectory 3 also showed an overall decline in stress followed by a flattening similar to the original Trajectory 3. In contrast, Trajectory 4 diverged from the original sample Trajectory 4 showing increasing then flattening stress. The antenatal FinnBrain trajectories are shown beside UCI trajectories in **Figure 2.5**.

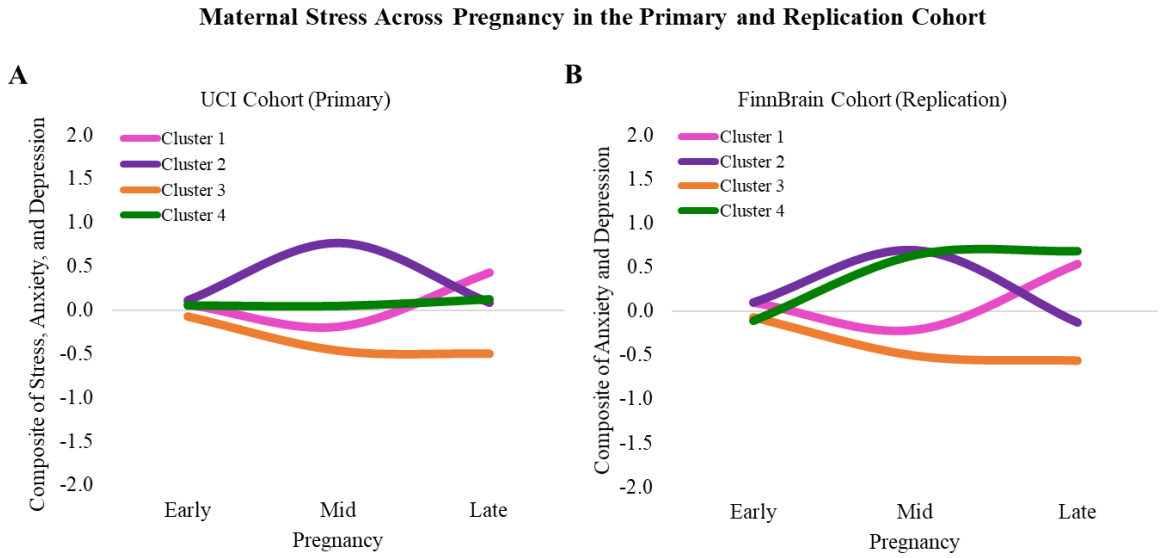

Figure 2.5. Maternal stress correlation-based trajectories are similar between primary and replication cohorts. Maternal stress measures were completed during early, mid, and late pregnancy in both cohorts. **(A)** Four distinct trajectories reflecting differences in antenatal stress from the correlation-based approach in the UCI cohort (Primary). **(B)** Four similar trajectories reflecting differences in antenatal stress were identified in the FinnBrain cohort (Replication) using the model parameters from the UCI cohort.

FinnBrain Cohort Maternal Antenatal Stress Clusters are Associated with Infant Negative Affect Trajectories

We next modeled infant negative affect development over the first two years of life. Consistent with the UCI cohort, a repeated measures ANOVA suggested that there was a statistically significant change in negative affect between 6 and 24 months ($F = 111.319$, $p < 0.001$). Bonferroni-corrected post-hoc tests revealed that negative affect increased from six ($M = 3.02$, $SD = 0.75$) to 12 months ($M = 3.28$, $SD = 0.73$) and decreased from 12 to 24 months ($M = 2.91$, $SD = 0.55$). This mimics the quadratic pattern of change identified with the LGM in the original sample, representing increasing negative affect, which peaked at 12 months of infant age, before decreasing (see **Figure 2.4B**).

We then examined the association between FinnBrain maternal antenatal stress clusters and infant negative affect development using a repeated measures ANCOVA with relevant covariates. Consistent with the results from the UCI cohort, maternal trajectory clusters showed a significant main effect of group on infant negative affect over time ($F=3.04$, $p=0.028$). This effect remained significant after adjusting for infant sex, length of gestation, and postnatal depression ($F=3.23$, $p=0.022$). Post-hoc analyses examining the contribution of specific trajectories also demonstrated a similar pattern to that identified in the original cohort. Specifically, there was a significant difference between Trajectory 3 and all other clusters for infant negative affect at 6 months ($F=4.423$, $p=0.004$), 12 months ($F=6.674$, $p<0.001$), and 24 months ($F=6.011$, $p<0.001$). The difference between Trajectories 3 and 4 remained significant when controlling for maternal postnatal depression, infant sex, and gestational age (12m: $B= -0.202$, $p=0.020$;

24m: B= -0.151, p=0.018). This suggests that, as in the UCI cohort, infants of mothers in the Trajectory 3 cluster show a divergent pattern of negative affect development beginning at approximately 12 months of age.

Maternal Perinatal Stress Clusters are Associated with Neonatal Functional Connectivity

To examine the effects of the maternal magnitude and trajectory clusters on the infant brain, we evaluated neonatal offspring functional connectivity in the UCI cohort. Maternal trajectory clusters were dummy coded and included as predictors in all analyses.

The **magnitude clusters**, capturing symptom severity, were not associated with neonatal Am-vmPFC (*B*=0.015, p=0.746) or Am-aI (*B*=0.008, p=0.841) functional connectivity; however, the **trajectory clusters** showed significant associations with amygdala connectivity. Trajectory 1 (late gestation peak), was significantly associated with stronger Am-vmPFC (*B*=0.173, p=0.011) and Am-aI (*B*=0.166, p=0.006) connectivity (see **Figure 2.6**). Trajectory 3 (late gestation increase in stress) also significantly predicted stronger Am-vmPFC connectivity (*B*=0.172, p=0.011). Trajectory 2 (midgestation peak) and 4 (postnatal decline) were not associated with alterations in Am-vmPFC or Am-aI connectivity.

We also examined the association between composite stress scores at each perinatal time point and neonatal functional connectivity (See Supplemental Materials, **Table 2.26**).

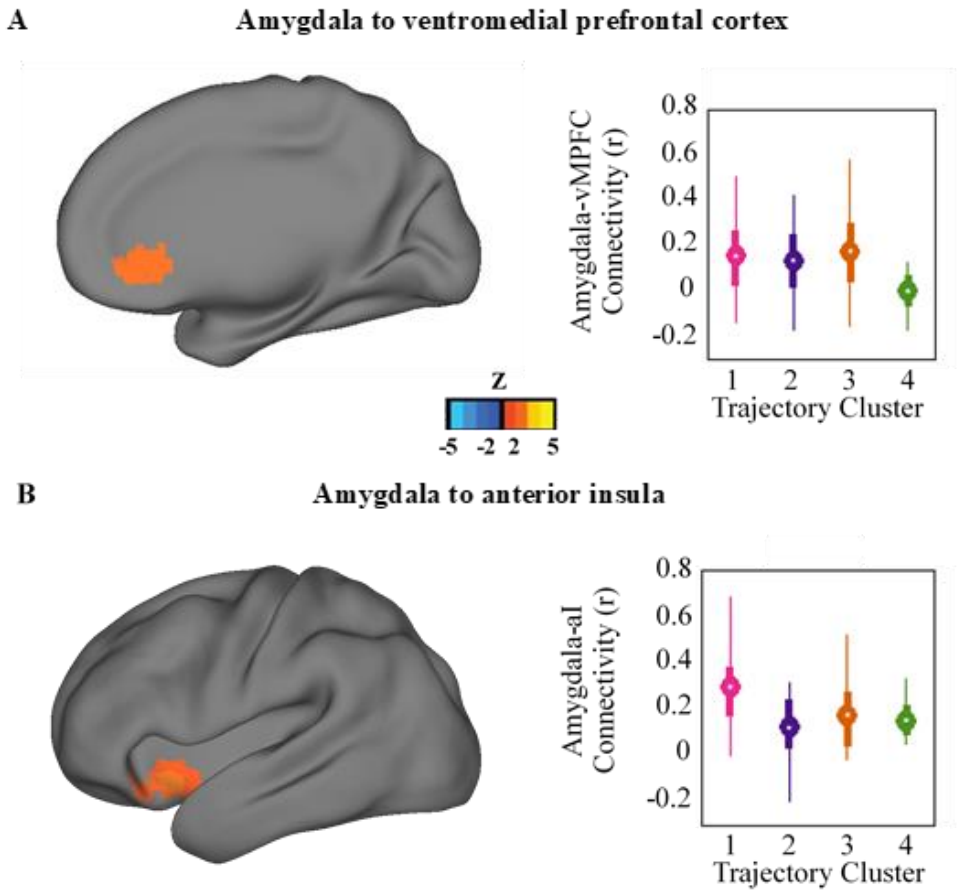

Figure 2.6. Maternal perinatal stress trajectory clusters are associated with neonatal infant amygdala connectivity. Both panels show results for the left amygdala using regions of interest (ROIs) identified in a prior study (Graham et al., 2016) and displayed here. Covariates for gestational age at birth and infant age at scan were included to account for neonatal brain maturity at the time of MRI scan acquisition. Correlation values are reported for amygdala functional connectivity (r). Circles represent cluster means. Bolded color bars represent interquartile range (25th to 75th percentile) and thin lines represent data from the 2.5th to 97.5th percentile. **(A)** Maternal trajectory clusters 1 and 3 were associated with stronger infant amygdala connectivity to the ventromedial prefrontal cortex (vmPFC). Infant amygdala-vmPFC connectivity for mothers in the

Trajectory 2 cluster appeared to be stronger compared to cluster 4, but did not reach statistical significance (*B*=0.127, p=0.069). **(B)** Maternal trajectory cluster 1 was associated with increased infant amygdala connectivity to the bilateral anterior insula (aI).

Maternal Perinatal Stress Clusters are Associated with Maternal History of Childhood Maltreatment

Finally, we examined the relationship between a history of maternal exposure to maltreatment during childhood and maternal perinatal stress clusters in the UCI cohort. Total scores for each maltreatment subscale and the overall CTQ score were examined by maternal stress clusters using an ANOVA. The **magnitude clusters**, capturing symptom severity, were significantly associated with a history of maternal childhood maltreatment (see **Table 2.4**). The **trajectory clusters** did not show a significant association with a history of maternal childhood maltreatment (see **Table 2.27** in Supplemental Materials).

Table 2.4. Magnitude clusters are significantly associated with a history of maternal childhood maltreatment.

	Group 1 (Low)		Group 2 (High)			
	N	**Mean (SD)**	**N**	**Mean (SD)**	**F**	**Sig***
Emotional Abuse	56	6.68 (3.05)	57	8.58 (4.52)	6.829	0.010
Physical Abuse	56	5.55 (0.89)	57	7.28 (4.22)	8.965	**0.003**
Sexual Abuse	56	5.38 (1.32)	57	7.61 (5.29)	9.466	**0.003**
Emotional Neglect	56	7.91 (3.52)	57	10.82 (4.33)	15.364	< **0.001**
Physical Neglect	56	5.80 (1.33)	57	7.82 (3.30)	18.163	< **0.001**
Overall CTQ score	56	31.32 (7.39)	57	42.12 (18.18)	17.007	< **0.001**

*Bolded font indicates significant after Bonferroni correction

2.5. Discussion

In the current report, we found that trajectories of maternal perinatal stress were related to infant brain phenotypes and negative affect development over the first two years of life. Offspring of mothers with increasing or peak stress late in pregnancy showed increased amygdala functional connectivity at one month of age and altered negative affect development over the first two years of life. Interestingly, the overall magnitude of perinatal stress was not associated with offspring brain or behavioral development when considered in the same models with information about the trajectory of stress. The relationship between the trajectory of maternal stress during pregnancy and infant negative affect development was replicated in an independent cohort comprising more than 2,000 mother-infant dyads. Overall, the data highlight that the trajectory of maternal perinatal stress may contribute to both offspring brain and affective development in a manner that is independent of overall stress magnitude. We also found

that the magnitude of maternal stress during pregnancy was significantly related to a maternal history of exposure to maltreatment during childhood.

To many in the field, the finding that maternal psychological stress during pregnancy is related to infant emotional development, especially negative emotionality, is not surprising given the extant literature in this area. However, the large majority of these prior studies only consider the magnitude of stress. In the current report, we show that heterogeneity exists in maternal stress trajectories during pregnancy with regard to timing and rate of change, and this variance in trajectories is an important characteristic affecting offspring brain and behavioral outcomes. When grouping women by overall magnitude of stress versus the timing and rate of change in stress (trajectory), the trajectory appears to be more important for offspring brain and behavioral development.

Sampling Maternal Stress in Mid or Late Pregnancy may be Important to Reveal Associations with Infant Negative Affect Development

Our overall findings can be considered in two ways in the context of the current literature: (1) that the entire trajectory is an important parameter for offspring development that needs to be considered, and (2) in the absence of the trajectory (i.e. when studies only sample one time point), the time when that sample was taken is also critically important. To highlight this point, we followed our trajectory analyses by examining each antenatal time point separately (see **Tables 2.18 – 2.20**). Maternal stress, examined at single time points, during pregnancy and does not predict neonatal amygdala functional connectivity suggesting that the entire trajectory is an important parameter with regard to the observed brain outcomes. Maternal stress during mid and late

pregnancy was associated with infant negative affect growth over the first two years of life indicating that sampling in mid or late pregnancy may be more likely to reveal associations between antenatal stress and infant negative affect development.

Maternal Stress Trajectories, as Opposed to Stress Magnitudes, are Related to Neonatal Amygdala Connectivity

In the UCI cohort, trajectories with either peaks or increases in maternal stress in late pregnancy, such as Trajectories 1 (late gestation peak) and 3 (late gestation increase), related strongly to offspring amygdala connectivity and negative affect development in offspring, even when accounting for the overall magnitude of maternal stress. The distinct effects of maternal psychological stress during late pregnancy on offspring limbic system development is in line with previous findings on maternal anxiety and infant hippocampal development, suggesting that the timing of stress may play a role in infant developmental outcomes (A Qiu et al., 2013; Rifkin-Graboi et al., 2018). It is worth noting that Trajectory 3 (late gestation increase) was associated with distinct patterns of both offspring amygdala connectivity and infant negative affect development despite a pattern of lower magnitude of stress during pregnancy, further highlighting the importance of considering changes in stress across pregnancy and not the magnitude of maternal stress alone. The lower levels of maternal stress seen in Trajectory 3 were also found in the FinnBrain cohort. In both cohorts, Trajectory 3 was associated with an altered trajectory of infant negative affect, indicating the robustness of this finding.

Maternal-Placental-Fetal Biology During Mid to Late Pregnancy may Explain the Importance of Maternal Psychological Stress for Offspring Brain Outcomes

There is growing evidence to suggest that the fetus may be especially sensitive to extrauterine cues transmitted via stress-sensitive aspects of maternal-placental-fetal biology during late pregnancy. Cortisol bioavailability, which is altered during increased psychological stress, plays a key role in fetal maturation and is associated with risk for offspring psychopathology (Graham et al., 2019). Cortisol is involved in fetal brain neurogenesis, synaptogenesis, and axonal growth through glucocorticoid receptors (Graham et al., 2019). Although maternal cortisol levels vary across pregnancy, there is a surge during late pregnancy (Stoye et al., 2020). Several studies have shown that maternal cortisol during late pregnancy is associated with infant reactivity and negative emotionality (Braithwaite et al., 2017), a finding potentially explained by the high concentration of glucocorticoid receptors present in the amygdala (Graham et al., 2019). Increased psychological stress is also associated with increasing levels of inflammatory markers such as IL-6 and other cytokines that activate inflammatory processes in the fetal brain through both direct and indirect pathways (Graham et al., 2018). Like cortisol, IL-6 and other cytokines are important for fetal brain development, but can disrupt cellular survival and proliferation, and synaptogenesis if the levels are too high (Graham et al., 2019). Spann and colleagues (2018) found that higher levels of immune activation during the third trimester were associated with the strength of neonatal functional connectivity within the salience network including the medial prefrontal cortex (Spann et al., 2018). Similarly, Rudolph and colleagues (2018) showed that elevated maternal IL-6

concentrations during the third trimester were the most strongly associated with reduced infant working memory at two years of age (Rudolph et al., 2018). The period right before birth is characterized by a rapid and dramatic increase in total physical connections between neurons of the cerebral cortex and is therefore considered a critical period for development of the cortical connectome (van den Heuvel et al., 2014). Rapid cortical maturation, circuit formation, and increased neuronal connectivity are hallmarks of third trimester neurodevelopment, and may explain why this period is particularly sensitive to increases in maternal stress (Andescavage et al., 2017; Tau & Peterson, 2010; Moriah E. Thomason et al., 2015).

Maternal Stress Magnitudes, as Opposed to Stress Trajectories, are Related to Maternal Exposure to Childhood Maltreatment

In the UCI cohort, magnitude clusters representing greater stress severity across the perinatal period were significantly associated with a history of maternal exposure to maltreatment during childhood. Several studies have reported on the association between childhood maltreatment and greater psychological stress during pregnancy (Lara et al., 2015; River, Narayan, Atzl, Rivera, & Lieberman, 2019; J. S. Seng et al., 2009, 2013). Greater levels of depression and PTSD symptoms during pregnancy have been associated with higher levels of reported maternal exposure to maltreatment during childhood (River et al., 2019), which is consistent with the present findings. Maternal exposure to maltreatment during childhood is a chronic and distal stressor, and may affect stress levels more consistently across pregnancy instead of during a specific trimester. Given the known association between stress severity during pregnancy and maternal childhood

maltreatment history, it is not surprising that maltreatment history was associated with magnitude and not trajectory clusters.

Limitations and Additional Considerations

There are several limitations to consider. First, maternal stress was characterized using self-report measures. Although not a diagnostic interview, the use of self-report measures to characterize stress is clinically relevant given that this is how depression and anxiety are typically monitored during routine antenatal care. Similarly, infant behavior was based on maternal-report measures. Infant emotions are difficult to assess and could reflect maternal mood, expectations, or recall. We addressed this limitation by including maternal stress at each infant behavior time point as a covariate. In addition, the replication of findings across two independent cohorts increases our level of confidence in the capacity of these measures to detect meaningful variation in the constructs of interest.

The FRF requires the user to specify the set and number of basis functions used to measure trajectories. In this study, such functions were chosen *a priori* based on the number of time points per participant. Such an approach limits the potential for overfitting the trajectories. While our selection is consistent with prior literature in Functional Data Analysis, tweaking these parameters may alter the trajectories and uncover different clusters. A future study of the FRF approach may seek to identify the best practices and standards for basis function selection. Second, while a supervised FRF can identify subtypes tied to a specific question (e.g. maternal health outcomes), an unsupervised RF was used to generate proximity matrices here (which was subsequently

used to identify subtypes). As a result, identified clusters are not tied to a specific question. This limitation is mitigated by the fact that the clusters themselves appeared biologically relevant. Nevertheless, future studies may want to use a supervised RF to better tie clusters to a specific or alternative clinical outcome.

The neuroimaging component of this study focused on the resting state functional connectivity between the amygdala and two regions of interest. The processing, interpretation, and expression of negative affect involves multiple brain regions and networks beyond those explored in the present study. Future work will be required to explore the full extent of how maternal perinatal stress trajectories relate to the structure and function of the neonatal brain. Future studies are also needed to explore the role of maternal stress in the postnatal environment. We were not powered to test the role of functional connectivity as a mediator in our model of maternal perinatal stress on the growth of infant negative affect. However, based on the current literature it is likely that alterations in the limbic system associated with stress exposure during pregnancy might explain some of the observed differences in the growth of infant negative affect over the first two years of life observed here.

The prevalence of maternal exposure to childhood maltreatment in the UCI cohort was low. Mothers with a history of childhood maltreatment were distributed across all of the perinatal stress clusters, making it difficult to probe the potential interaction between stress during pregnancy and maltreatment history. To better understand the interaction between stress during pregnancy and childhood maltreatment history, future work will need a larger cohort or a cohort enriched for a history of childhood maltreatment.

2.6. Conclusions

The identified trajectories provide information on the timing and variability of stress during pregnancy. Importantly, the trajectory clusters identified by the FRF differed in terms of the timing of peak stress and changes in the rate of stress across pregnancy. Recognizing the sequential process of neurodevelopment, it is likely that alterations in psychological stress have a differential impact on brain development depending on the timing of peak stress or change. Consistent with this conceptualization, we found that maternal perinatal stress trajectories were related to both infant neurodevelopment and psychosocial development in a manner independent of the overall magnitude of stress exposure. This work highlights the importance of considering variability in maternal perinatal stress over time, as opposed to focusing predominantly on stress severity. Advancing understanding of heterogeneity in perinatal psychological stress represents an important step towards identifying contributing factors to the experience of stress and the implications for offspring development. Finally, gaining a more nuanced understanding of perinatal stress and its influence on infant neurobiological and psychosocial development is critical for refining and improving preventive interventions designed to support maternal and infant mental health.

2.7. Supplemental Materials

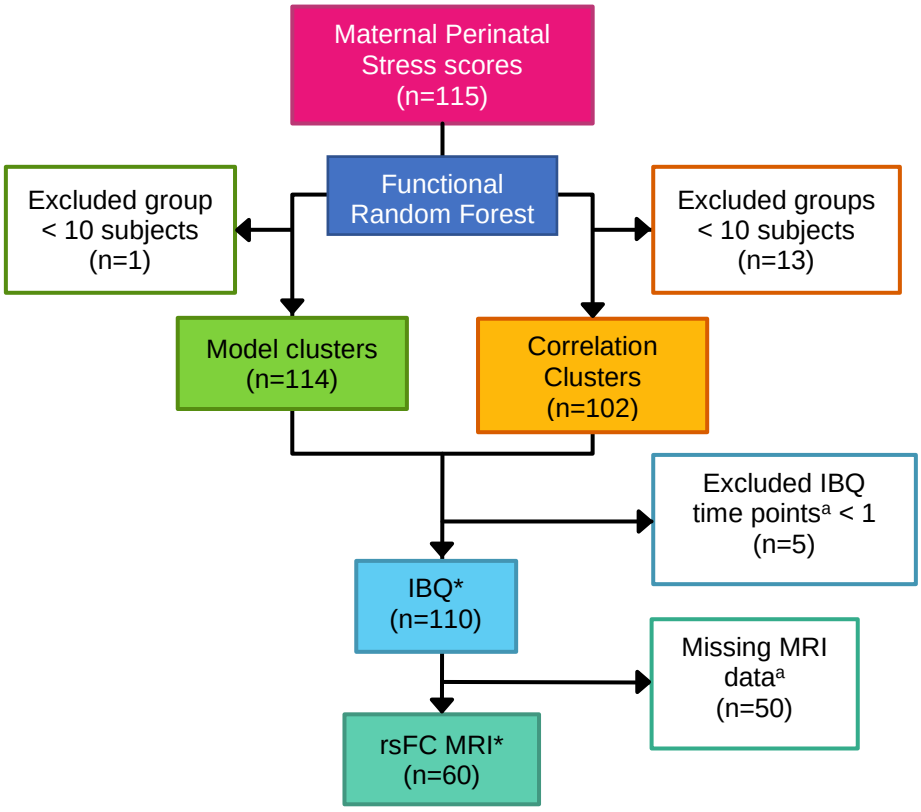

Figure 2.7. UCI study cohort diagram. Boxes with white backgrounds represent excluded subjects. Reason for exclusion is described within each box. Boxes with a colored background represent included subjects and related analyses. IBQ: Infant Behavior Questionnaire-Revised scores, rsFC: resting-state Functional Connectivity, [a] Indicates infant data.

The Functional Random Forest

Using two approaches, the FRF identified different symptom-associated clusters. Because the FRF makes few assumptions about the nature of the data, these clusters represent trajectories that cannot be captured using a single parametric model, such as mixture modelling used in LGMs. LGMs are very powerful approaches to identifying clusters, but require specifying how many clusters to find and the shape of the trajectories. The FRF can identify varying trajectory shapes that are not specified or explored via multiple model comparisons. Though the FRF can be a hybrid approach to identify clusters tied to a developmental or clinical outcome (Feczko et al., 2017, 2019), our study used the FRF in an unsupervised manner to explore several potential outcomes.

Approach 1: Model-Based Clusters

The Model-based approach to identify clusters is a *hybrid approach*, where a Random Forest (RF) model evaluates whether real trajectories based on the symptom data provided to the algorithm can be dissociated from artificially generated trajectories. The approach uses a combination of Functional Data Analysis (FDA), RF, and Infomap. First, FDA is employed to capture underlying trajectories present in the longitudinal data (Brumback & Rice, 1998; Hall & Heckman, 2002; James, Hastie, & Sugar, 2000; Malfait & Ramsay, 2003; Ramsay, 2002). Specifically, 4^{th} order cubic B-splines are fit to each individual's dataset and the coefficients (weights) for each individual are extracted from the best fit solution. Knots, fixed values with respect to time, are set at each of the observed time points. To limit the potential for unrealistic values (e.g. as shown by Runge's phenomenon) 2^{nd} order cubic B-splines form a set of cost functions to penalize

coefficients where limited data may be available. Finally, unrealistic fits are evaluated by generating a dense timeseries from the basis functions per individual. This dense timeseries represents the "trajectory" of a given individual, and timeseries that do not fall within realistic values for the measures (i.e. between X or Y) are rejected and the individual is excluded from subsequent analysis. For each individual with acceptable data, the model's coefficients are passed to the Random Forest (RF) which classifies multiple patterns or pathways in these weights using decision trees (Breiman, 2001). Here, we used an unsupervised approach, meaning that the subject's stress scores were not linked to a specific outcome variable of interest, to classify between fake and real trajectories, using a 10-fold cross validation strategy repeated thrice. Fake trajectories were simulated by randomly shuffling the weights across the subjects, such that fake trajectories show only random fluctuations with time. Null models are generated by randomly permuting the labels between fake and real trajectories and performing the same 10-fold cross-validation. The null model measures performance under the assumption that trajectories are random. If the observed model performs better than expected by the null model, then it is likely that the observed trajectories are non-random. The RF produces a similarity matrix, which represents the number of times pairs of participants traveled the same paths throughout the forest. This proximity matrix is passed into Infomap (Feczko et al., 2017; Rosvall & Bergstrom, 2008) (see **Figure 2.3A**). To generate consensus communities, the proximity matrix was thresholded at multiple edge densities, from 20 to 100 percent in steps of 5 percent. Per threshold, communities were identified and a consensus community matrix was formed, where each cell

represents the proportion of times two participants were in the same community. Consensus communities were identified by running Infomap on this consensus matrix.

Approach 2: Correlation-based Clusters

The Model-based, hybrid approach described above represents one way to identify putative trajectory subtypes. However, it is possible that other, equally valid subtypes may be identified with other approaches. We wanted to contrast the Model-based cluster approach with another approach to examine potential differences in identified subtypes. Therefore, an alternate correlation-based approach was also used and compared with the model-based approach to see whether identified subgroups overlap, or whether it could identify new subtypes that may be important to potentially different outcomes. With the correlation-based approach, the trajectories of participants derived from FDA can be correlated from every participant to every other participant and passed into Infomap instead. From correlation-based clusters the FRF identified distinct trajectory clusters based on changes in maternal stress during the prenatal and perinatal period.

Modularity Analysis

Post-hoc analyses were conducted to examine the validity of identified clusters and further characterize differences in clusters (chi-square and ANOVAs). Modularity (Q) is a measure of clustering stability that can be unrelated to Infomap-identified subtypes. Specifically, modularity measures the proportion of edges within clusters to the total number of edges across all s nodes. Modularity is the difference between this

proportion and the mean proportion found in a series of randomly re-wired graphs, and therefore represents the cluster stability greater than what is observed in similarly structured but random graphs. Modularity was calculated on both of the model-based and correlation-based subtypes and significance was calculated via a permutation test, where 10,000 permutations were run. Per permutation, subtype assignment was shuffled across cases and modularity was calculated as above, forming a null distribution across all 10,000 permutations. The significance of the observed modularity is its proportional rank on the null distribution. Here, we additionally measured modularity for each cluster, by calculating the proportion of edges within each cluster relative to the total possible number of edges across all the given cluster's nodes. Though modularity is typically an overall metric, the per-network metric allows us to assess differences in cluster stability post hoc. Modularity permutation tests show that all clusters had significantly greater modularity than random assignments, suggesting that the clusters represent stable subgroups. The modularity associated with the lowest edge density and modularity values at each edge density and by community are reported in the **Tables 2.5 – 2.7.**

Table 2.5. Overall modularity for magnitude clusters by density.

Edge Density	*Q*	*p value*
0.20	0.729	<0.001
0.25	0.718	<0.001
0.30	0.709	<0.001
0.35	0.696	<0.001
0.40	0.676	<0.001
0.45	0.660	<0.001
0.50	0.639	<0.001
0.55	0.617	<0.001
0.60	0.596	<0.001
0.65	0.572	<0.001
0.70	0.545	<0.001
0.75	0.514	<0.001
0.80	0.481	<0.001
0.85	0.451	<0.001
0.90	0.421	<0.001
0.95	0.385	<0.001
1.00	0.291	<0.001

Table 2.6. Community modularity for magnitude clusters by density.

Edge	**Cluster 1[a]**		**Cluster 2[a]**		**Cluster 3**	
Density	*Q*	*p value*	*Q*	*p value*	*Q*	*p value*
0.20	0.959	<0.001	0.961	<0.001	0.498	0.083
0.25	0.939	<0.001	0.937	<0.001	0.494	0.115
0.30	0.922	<0.001	0.920	<0.001	0.492	0.118
0.35	0.901	<0.001	0.894	<0.001	0.488	0.161
0.40	0.863	<0.001	0.856	<0.001	0.487	0.177
0.45	0.830	<0.001	0.821	<0.001	0.487	0.131
0.50	0.788	<0.001	0.782	<0.001	0.485	0.131
0.55	0.747	<0.001	0.739	<0.001	0.484	0.357
0.60	0.705	<0.001	0.697	<0.001	0.482	0.609
0.65	0.659	<0.001	0.649	<0.001	0.480	0.790
0.70	0.604	<0.001	0.595	<0.001	0.480	0.745
0.75	0.542	<0.001	0.537	<0.001	0.478	0.915
0.80	0.476	<0.001	0.472	<0.001	0.477	0.990
0.85	0.415	<0.001	0.413	<0.001	0.477	0.975
0.90	0.355	<0.001	0.352	<0.001	0.478	0.954
0.95	0.281	<0.001	0.280	<0.001	0.478	0.946
1.00	0.091	<0.001	0.091	<0.001	0.481	0.645

[a] Cluster has greater than 10 subjects and included in analyses

Table 2.7. Overall modularity for trajectory clusters by density.

Edge Density	0.05	0.06	0.07	0.08	0.09	0.10
Q	0.811	0.793	0.774	0.746	0.729	0.704
p value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Table 2.8. Community modularity for trajectory clusters by density.

	Edge Density											
	0.05		0.06		0.07		0.08		0.09		0.10	
Cluster	Q	p	Q	p	Q	p	Q	p	Q	p	Q	p
1[a]	0.949	<0.001	0.916	<0.001	0.897	<0.001	0.863	<0.001	0.850	<0.001	0.818	<0.001
2[a]	0.839	<0.001	0.828	<0.001	0.810	<0.001	0.800	<0.001	0.788	<0.001	0.775	<0.001
3[a]	0.730	<0.001	0.727	<0.001	0.699	<0.001	0.660	<0.001	0.645	<0.001	0.614	<0.001
4	0.574	<0.001	0.563	<0.001	0.561	<0.001	0.545	<0.001	0.535	<0.001	0.528	<0.001
5[ab]	0.629	<0.001	0.630	<0.001	0.621	<0.001	0.615	<0.001	0.606	<0.001	0.590	<0.001
6	0.510	<0.001	0.504	<0.001	0.502	<0.001	0.496	0.004	0.492	0.014	0.491	0.010
7	0.510	<0.001	0.509	<0.001	0.508	<0.001	0.507	<0.001	0.506	<0.001	0.504	<0.001
8	0.500	0.009	0.496	0.085	0.496	0.071	0.495	0.089	0.494	0.080	0.493	0.109

[a] Cluster has greater than 10 subjects and included in analyses
[b] Referred to as cluster 4 in all analyses

Maternal Stress, Anxiety, and Depression by Cluster

Participants in the UCI cohort completed the CESD, PSS, and STAI in early (M: 12.84, SD: 1.83 weeks), mid (M: 20.50, SD: 1.44 weeks) and late (M: 30.48, SD: 1.39 weeks) pregnancy and at one month postpartum. Mean total scores and standard deviations on the three measures at each perinatal time point are provided by cluster in **Tables 2.9-2.12** and plotted in **Figure 2.8**.

Table 2.9. Maternal psychological stress by magnitude clusters in early pregnancy.

	Anxiety Mean (SD)	***Stress Mean (SD)***	***Depression Mean (SD)***
Magnitude Cluster 1	27.75 (7.56)	8.88 (4.35)	8.77 (4.63)
Magnitude Cluster 2	37.96 (8.39)	15.13 (5.89)	18.18 (9.17)

Table 2.10. Maternal psychological stress by magnitude clusters in mid pregnancy.

	Anxiety Mean (SD)	***Stress Mean (SD)***	***Depression Mean (SD)***
Magnitude Cluster 1	25.38 (5.06)	8.65 (4.58)	5.86 (3.54)
Magnitude Cluster 2	39.96 (10.08)	15.06 (5.85)	17.98 (9.11)

Table 2.11. Maternal psychological stress by magnitude clusters in in late pregnancy.

	Anxiety Mean (SD)	***Stress Mean (SD)***	***Depression Mean (SD)***
Magnitude Cluster 1	28.053 (6.05)	9.81 (5.10)	8.40 (5.08)
Magnitude Cluster 2	41.11 (9.24)	16.63 (6.34)	19.98 (8.14)

Table 2.12. Maternal psychological stress by magnitude clusters in early postpartum.

	Anxiety Mean (SD)	***Stress Mean (SD)***	***Depression Mean (SD)***
Magnitude Cluster 1	26.53 (6.35)	11.00 (4.94)	6.84 (4.69)
Magnitude Cluster 2	37.36 (10.23)	18.21 (5.58)	17.05 (9.97)

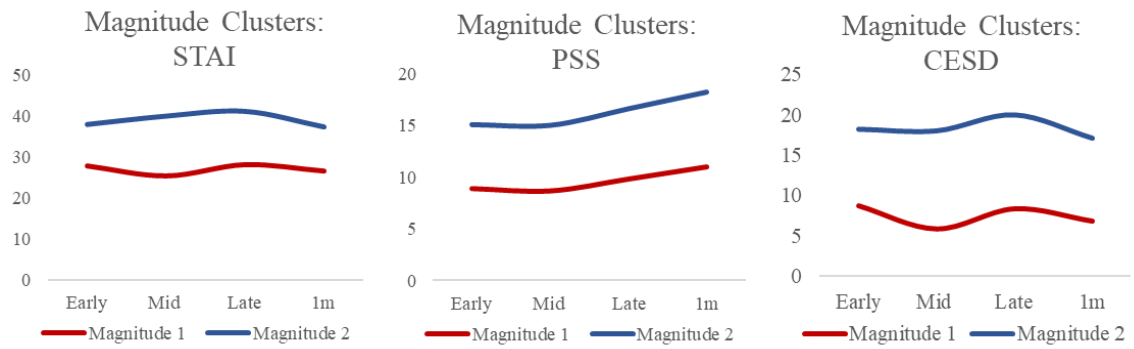

Figure 2.8. Maternal psychological stress mean scores by magnitude clusters across pregnancy.

Table 2.13. Maternal psychological stress by trajectory clusters in early pregnancy.

	Anxiety Mean (SD)	***Stress Mean (SD)***	***Depression Mean (SD)***
Trajectory Cluster 1	32.29 9.64)	11.74 (5.91)	13.94 (9.83)
Trajectory Cluster 2	34.63 (11.33)	14.35 (7.01)	15.15 (10.10)
Trajectory Cluster 3	31.58 (9.22)	9.84 (4.60)	11.64 (5.02)
Trajectory Cluster 4	33.86 (8.67)	10.92 (5.05)	15.79 (8.34)

Table 2.14. Maternal psychological stress by trajectory clusters in mid pregnancy.

	Anxiety Mean (SD)	***Stress Mean (SD)***	***Depression Mean (SD)***
Trajectory Cluster 1	30.03 (7.94)	11.70 (5.54)	10.94 (8.46)
Trajectory Cluster 2	42.28 (13.37)	15.12 (6.94)	18.63 (11.56)
Trajectory Cluster 3	27.30 (5.59)	8.73 (4.41)	7.38 (4.43)
Trajectory Cluster 4	31.36 (8.67)	13.64 (4.78)	13.67 (7.19)

Table 2.15. Maternal psychological stress by trajectory clusters in late pregnancy.

	Anxiety Mean (SD)	*Stress Mean (SD)*	*Depression Mean (SD)*
Trajectory Cluster 1	37.34 (9.98)	14.33 (6.73)	17.86 (9.71)
Trajectory Cluster 2	34.37 (11.47)	15.78 (6.59)	14.93 (8.44)
Trajectory Cluster 3	28.50 (5.49)	10.56 (5.86)	8.92 (4.81)
Trajectory Cluster 4	40.43 (9.42)	13.14 (6.68)	17.29 (8.85)

Table 2.16. Maternal psychological stress by trajectory clusters in early postpartum.

	Anxiety Mean (SD)	*Stress Mean (SD)*	*Depression Mean (SD)*
Trajectory Cluster 1	32.46 (10.99)	14.86 (6.15)	11.60 (7.97)
Trajectory Cluster 2	34.00 (11.81)	15.63 (6.20)	14.04 (10.54)
Trajectory Cluster 3	30.35 (7.36)	14.73 (6.47)	10.46 (6.58)
Trajectory Cluster 4	29.36 (7.87)	12.14 (6.97)	10.07 (8.42)

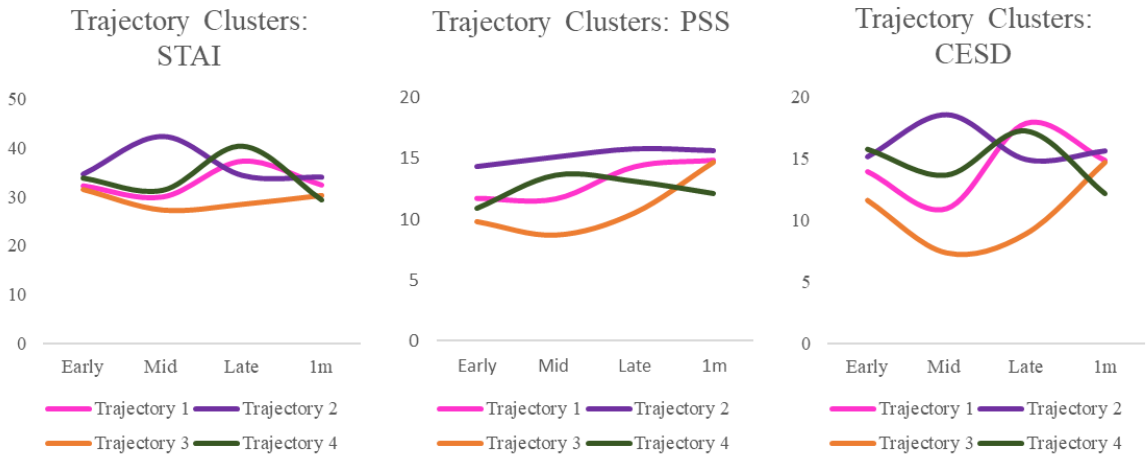

Figure 2.9. Maternal psychological stress mean scores by trajectory clusters across pregnancy.

Maternal Psychological Stress Measures in the Replication Cohort

Participants in the FinnBrain cohort completed the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987) and the Symptom Checklist (SCL-90) (Derogatis et al., 1973) in early (M: 15.2, SD: 2.7 weeks), mid (M: 25.3, SD: 1.5 weeks) and late (M: 35.1, SD: 1.8 weeks) pregnancy, and at six, twelve, and twenty-four months postpartum. Averages of mean total scores and standard deviations on the two measures at each antenatal time point are provided below, see **Tables 2.17 – 2.19**.

Table 2.17. Replication Cohort: Maternal anxiety and depression by trajectory clusters in early pregnancy.

	Anxiety Mean (SD)	***Depression Mean (SD)***
Whole sample	3.21 (3.94)	4.99 (3.94)
Trajectory Cluster 1	3.26 (3.79)	5.05 (3.91)
Trajectory Cluster 2	3.57 (4.30)	5.36 (3.99)
Trajectory Cluster 3	2.96 (3.91)	4.67 (4.09)
Trajectory Cluster 4	2.76 (3.14)	4.62 (3.11)

Table 2.18. Replication Cohort: Maternal anxiety and depression by trajectory clusters in mid pregnancy.

	Anxiety Mean (SD)	***Depression Mean (SD)***
Whole sample	3.81 (4.28)	4.79 (4.04)
Trajectory Cluster 1	3.12 (3.38)	3.84 (3.26)
Trajectory Cluster 2	6.36 (5.11)	7.68 (4.26)
Trajectory Cluster 3	1.84 (2.47)	2.63 (2.57)
Trajectory Cluster 4	6.17 (5.09)	7.88 (3.60)

Table 2.19. Replication Cohort: Maternal anxiety and depression by trajectory clusters in late pregnancy.

	Anxiety Mean (SD)	*Depression Mean (SD)*
Whole sample	3.11 (3.91)	4.74 (4.00)
Trajectory Cluster 1	4.91 (4.67)	7.08 (4.02)
Trajectory Cluster 2	2.70 (3.34)	4.15 (3.54)
Trajectory Cluster 3	1.24 (1.90)	2.27 (2.32)
Trajectory Cluster 4	5.30 (4.57)	7.98 (3.63)

Potential Confounders Relevant for Maternal Clusters and Infant Outcomes

Potential confounders relevant to neonatal brain and negative affect development were examined to determine whether any identified associations between maternal psychological stress during pregnancy and infant brain and behavioral development could be better explained by other aspects of the prenatal or postnatal environment. These included annual household income, obstetric risk, and postnatal maternal psychological stress. Annual income was assessed during the first prenatal visit using standardized structured interviews. Income was captured as a categorical variable: Below $15,000; $15,000-29,999; $30,000-49,999; $50,000-100,000; and over $100,000. Obstetric risk includes the presence of major medical complications during pregnancy such as placenta abruption, preeclampsia, and gestational diabetes. Complications were identified through medical chart review and coded as a binary variable capturing the presence or absence of a risk factor.

We first examined how magnitude and trajectory clusters related to potential confounds using IBM SPSS Statistics 25 (IBM Corp., 2017). The magnitude clusters

differed significantly by annual income with lower annual household income associated with higher perinatal stress ($\chi2(4)=11.975$, p=0.018). Magnitude clusters did not differ significantly by maternal age (F=0.420, p=0.518), infant gestational age at birth (F=0.663, p=0.417), infant sex ($\chi2(1)=0.141$, p=0.707), race/ethnicity ($\chi2(7)=9.443$, p=0.222), obstetric risk ($\chi2(4)=2.763$, p=0.598), or level of maternal education ($\chi2(7)=9.161$, p=0.241). The trajectory clusters did not differ significantly by maternal age (F=0.174, p=0.914), infant gestational age at birth (F=0.987, p=0.402), infant sex ($\chi2(3)=0.341$, p=0.952), race/ethnicity ($\chi2(21)=14.245$, p=0.859), level of maternal education ($\chi2(21)=16.616$, p=0.734), or annual income ($\chi2(12)=16.823$, p=0.156). Trajectory clusters differed by obstetric risk ($\chi2(8)=1.000$, p=0.042).

Given the observed differences in maternal annual income and obstetric risk between clusters, we included them in our initial model to assess their contribution to infant outcome measures. Maternal annual income (Am-vmPFC: *B*=0.018, p=0.811; Am-aI: *B*= -0.001, p=0.184), obstetric risk (Am-vmPFC: *B*= -0.002, p=0.318; Am-aI: *B*=0.020, p=0.616), and infant sex (Am-vmPFC: *B*= -0.044, p=0.369; Am-aI: *B*= -0.070, p=0.098) were not associated with amygdala functional connectivity and were not included in the final model. Although magnitude groups differed significantly by maternal annual income, maternal annual income did not significantly predict the parameters of infant negative affect development (see **Table 2.20**) and therefore was not included in the model. Obstetric risk and infant sex were not associated with infant negative affect development and therefore were not included in the final model (see **Table 2.20**).

Table 2.20. Annual income, obstetric risk, and infant sex do not predict the parameters of infant negative affect development.

	Intercept		Slope		Quadratic	
	Beta	***p-value***	***Beta***	***p-value***	***Beta***	***p-value***
Annual income	-0.002	0.236	0.001	0.236	-0.001	0.693
Obstetric risk	0.107	0.467	-0.172	0.467	0.019	0.895
Infant sex	0.042	0.747	0.039	0.881	-0.081	0.481

Latent Growth Model

Infant negative affect growth from 3 to 24 months of age was defined using a quadratic growth curve model with intercept factor loadings fixed at 0 (3 months) and linear factor loadings fixed at 3, 6, 9, 12, and 24 months. In order to improve the fit of the model, q was restricted due to limited variance, and the means at 9 and 12 months were allowed to covary because they were highly correlated, AIC = 721.553, $\chi 2$ (8) = 13.252, p = 0.104, CFI = 0.966, TLI = 0.957, RMSEA = 0.077. Consistent with our prior work and the literature (Braungart-Rieker et al., 2010; Brooker et al., 2013; Garstein & Rothbart, 2003; Graham et al., 2016; Partridge & Lerner, 2007; Thomas et al., 2019), infant negative affect increases over the first year of life and then decreases to 24 months of age, forming an inverted u-shaped trajectory defined by a quadratic term with a significant negative mean (*M*= - 0.452, p<0.001; **Figure 2.4A**). The slope (*M*=1.061, p<0.001) was positive and significant, reflecting an overall increase in negative affect over time, see **Figure 2.4A**, top left. The mean (*M*=2.990, p<0.001) and variance (σ^2 = 0.304, p<0.001) of the intercept term were also significant indicating large inter-individual differences in infant negative affect at 1 month of age (see **Table 2.21**). The

intercept and growth terms from these models were used as outcome variables in analyses examining infant behavior. Missing data was estimated in MPlus using Full Information Maximum Likelihood (FIML).

For the conditional models, variables describing membership in each Correlation-based cluster were created by dummy coding clusters 1 through 3 (membership=1). Cluster 4 was used as the referent cluster. Maternal perinatal stress clusters were examined with the LGM parameters capturing infant negative affect development as the outcome of interest. The same forward selection approach was used here as described for the linear regression models. Maternal postnatal stress can have an impact on infant negative affect development and may affect maternal report of infant behavior. Therefore, the final model included maternal postnatal stress as a time-varying covariate at each time point when negative affect was assessed to account for its role as a possible contributing factor to infant negative affect growth in subsequent analyses. We were not powered to test the role of functional connectivity as a mediator in our model of maternal perinatal stress on the growth of infant negative affect. Unstandardized estimates (*B*) are reported for all growth models unless otherwise noted.

Table 2.21. Infant negative affect growth reflects significant individual differences and is associated with maternal perinatal stress clusters.

	Unconditional		Perinatal Clusters		Perinatal Clusters and Postnatal Stress	
	Estimate	***SE***	***Estimate***	***SE***	***Estimate***	***SE***
Intercept Mean	2.990***	0.064	2.363***	0.284	2.613***	0.304
Intercept Variance	0.304***	0.056	0.272***	0.052	0.254***	0.051
Slope Mean	1.061***	0.125	1.267*	0.546	0.664	0.620
Slope Variance	0.062	0.035	0.069*	0.034	0.070*	0.033
Quadratic Mean	-0.452***	0.056	-0.434	0.242	-0.256	0.272
Quadratic Variance	*restricted*		*restricted*		*restricted*	
Predictors of intercept						
Magnitude clusters			0.339**	0.127	0.179	0.145
Trajectory group 1			0.043	0.214	0.024	0.207
Trajectory group 2			0.187	0.220	0.177	0.208
Trajectory group 3			0.192	0.229	0.198	0.219
Predictors of slope						
Magnitude clusters			-0.006	0.251	0.369	0.314
Trajectory group 1			0.070	0.408	0.140	0.411
Trajectory group 2			0.067	0.412	0.127	0.410
Trajectory group 3			-0.918*	0.428	-0.921*	0.427
Predictors of quadratic						
Magnitude clusters			-0.023	0.110	-0.132	0.137
Trajectory group 1			-0.115	0.181	-0.137	0.181
Trajectory group 2			-0.134	0.183	-0.156	0.180
Trajectory group 3			0.359	0.190	0.360	0.187

*** p< 0.001 **p<=0.01 *p<0.05

Single Time Point Analysis of Infant Negative Affect Development

Latent growth curve models (LGM) were performed using perinatal composite stress scores at a single time point and infant negative affect growth over the first two years as the outcome. Maternal stress at early, mid, and late pregnancy is associated with the intercept of infant negative affect. In early pregnancy this association disappears when maternal postnatal stress is accounted for within the model (**Table 2.22**). Maternal stress in mid pregnancy is additionally associated with the quadratic term of infant negative affect growth. When maternal postnatal stress is accounted for within the model, mid pregnancy stress is associated with the linear and quadratic terms of infant negative affect growth (**Table 2.23**). Similar results are observed in late pregnancy, late pregnancy stress is associated with the linear and quadratic term of infant negative affect growth when postnatal stress is included in the model (**Table 2.24**). Model fit indices for perinatal composite stress scores at each pregnancy time point and in the presence of time-varying covariates of maternal postnatal stress are shown in **Table 2.25**.

Table 2.22. Infant negative affect growth and maternal psychological stress in early pregnancy.

	Early pregnancy composite		Early pregnancy with postnatal time-varying covariates	
	Estimate	***p-value***	***Estimate***	***p-value***
Intercept Mean	2.980	**0.0001**	2.984	**0.0001**
Intercept Variance	0.257	**0.0001**	0.239	**0.0001**
Slope Mean	1.083	**0.0001**	1.077	**0.0001**
Slope Variance	0.060	0.082	0.069	**0.050**
Quadratic Mean	-0.460	**0.0001**	-0.456	**0.0001**
Quadratic Variance	*restricted*		*restricted*	
Predictors of intercept				
Composite stress score (t0)	0.256	**0.001**	0.161	0.076
Predictors of slope				
Composite stress score (t0)	-0.057	0.716	0.121	0.560
Predictors of quadratic				
Composite stress score (t0)	-0.006	0.929	-0.047	0.609

Table 2.23. Infant negative affect growth and maternal psychological stress in mid pregnancy.

	Mid pregnancy composite		Mid pregnancy with postnatal time-varying covariates	
	Estimate	***p-value***	***Estimate***	***p-value***
Intercept Mean	2.987	**0.0001**	2.992	**0.0001**
Intercept Variance	0.251	**0.0001**	0.228	**0.0001**
Slope Mean	1.103	**0.0001**	1.077	**0.0001**
Slope Variance	0.053	0.114	0.050	0.156
Quadratic Mean	-0.470	**0.0001**	-0.459	**0.0001**
Quadratic Variance	*restricted*		*restricted*	
Predictors of intercept				
Composite stress score (t1)	0.197	**0.003**	0.104	0.182
Predictors of slope				
Composite stress score (t1)	0.224	0.108	0.471	**0.007**
Predictors of quadratic				
Composite stress score (t1)	-0.129	**0.038**	-0.208	**0.009**

Table 2.24. Infant negative affect growth and maternal psychological stress in late pregnancy.

	Late pregnancy composite		Late pregnancy with postnatal time-varying covariates	
	Estimate	***p-value***	***Estimate***	***p-value***
Intercept Mean	2.974	**0.0001**	2.984	**0.0001**
Intercept Variance	0.261	**0.0001**	0.235	**0.0001**
Slope Mean	1.075	**0.0001**	1.056	**0.0001**
Slope Variance	0.056	0.093	0.055	0.105
Quadratic Mean	-0.455	**0.0001**	-0.449	**0.0001**
Quadratic Variance	*restricted*		*restricted*	
Predictors of intercept				
Composite stress score (t2)	0.187	**0.008**	0.064	0.443
Predictors of slope				
Composite stress score (t2)	0.206	0.146	0.535	**0.003**
Predictors of quadratic				
Composite stress score (t2)	-0.122	0.051	-0.236	**0.004**

Table 2.25. Fit indices for maternal prenatal composite stress scores and infant negative affect growth with time-varying covariates of maternal postnatal stress.

	Early pregnancy (n=110)	Mid pregnancy (n=110)	Late pregnancy (n=110)
Maternal composite stress scores			
AIC	985.346	999.058	1001.959
$\chi 2$ (10), pvalue	15.624, 0.111	10.818, 0.372	11.073, 0.352
RMSEA	0.072	0.027	0.031
CFI	0.966	0.995	0.993
TLI	0.948	0.993	0.990
Maternal composite stress scores with time-varying covariates			
AIC	2328.938	2313.920	2319.575
$\chi 2$ (53), pvalue	299.574, 0.0001	284.557, 0.0001	290.211
RMSEA	0.206	0.816	0.202
CFI	0.393	0.422	0.414
TLI	0.278	0.313	0.304

Single Time Point Analysis of Neonatal Functional Connectivity

We also examined the association between composite stress scores at each perinatal time point to neonatal amygdala functional connectivity (see **Table 2.26**). Regression models with perinatal composite stress scores at a single time point and neonatal functional connectivity as the outcome were performed. Each model included one pregnancy time point with infant age at scan and gestational age as covariates. Perinatal composite stress scores at single time points during pregnancy do not predict neonatal functional connectivity (see **Table 2.26**).

Table 2.26. Perinatal composite stress scores at single time points during pregnancy do not predict neonatal functional connectivity.

			Standardized	
	Beta	***p-value***	***Beta***	***p-value***
Amygdala to vmPFC (N=60)				
Early (M: 12.84, SD: 1.83 weeks)	0.006	0.854	0.024	0.854
Mid (M: 20.50, SD: 1.44 weeks)	0.013	0.614	0.066	0.613
Late (M: 30.48, SD: 1.39 weeks)	-0.006	0.816	-0.030	0.816
Amygdala to aI (n=60)				
Early (M: 12.84, SD: 1.83 weeks)	-0.009	0.733	-0.044	0.733
Mid (M: 20.50, SD: 1.44 weeks)	-0.032	0.149	-0.182	0.143
Late (M: 30.48, SD: 1.39 weeks)	0.006	0.802	0.032	0.802

Childhood Maltreatment

We examined the relationship between a history of maternal exposure to maltreatment during childhood and maternal perinatal stress clusters in the UCI cohort. Total scores for the maltreatment subscale and the overall CTQ score were analyzed by

maternal stress clusters using an ANOVA. The **magnitude clusters**, capturing symptom severity, were significantly associated with a history of maternal childhood maltreatment (see **Table 2.4**). The **trajectory clusters** did not show a significant association with a history of maternal childhood maltreatment (see **Table 2.27**).

Table 2.27. Trajectory clusters are not significantly associated with a history of maternal childhood maltreatment.

	Trajectory Group 1		**Trajectory Group 2**		**Trajectory Group 3**		**Trajectory Group 4**			
	N	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**F**	**Sig**
Emotional Abuse	34	8.32 (4.20)	27	8.26 (4.61)	26	6.19 (2.28)	14	8.64 (5.54)	1.79	0.15
Physical Abuse	34	6.12 (2.32)	27	7.33 (4.85)	26	5.58 (0.81)	14	8.14 (5.56)	2.22	0.09
Sexual Abuse	34	6.24 (3.47)	27	8.26 (6.69)	26	5.27 (0.83)	14	7.50 (5.30)	2.25	0.09
Emotional Neglect	34	10.0 (4.07)	27	10.33 (4.54)	26	7.50 (3.49)	14	9.36 (4.36)	2.56	0.06
Physical Neglect	34	6.41 (2.02)	27	7.78 (3.21)	26	6.50 (2.45)	14	7.21 (3.95)	1.47	0.23
Overall CTQ score	34	37.09 (12.76)	27	41.96 (20.59)	26	31.04 (7.29)	14	40.86 (21.90)	2.41	0.07

Missing Data Analysis

All missing data analysis was completed using IBM SPSS Statistics 25 and compared excluded subjects to the full sample (n=115). The Center for Epidemiological Studies Depression Scale (CESD), Perceived Stress Scale (PSS), State-Trait Anxiety

Inventory (STAI) were only calculated if three or fewer items were missing. Mean scores were calculated for each scale to reduce the effect of missing items. Averages across the perinatal time period are reported for each measure below.

Maternal Psychological Stress Measures

The 135 mother-infant dyads excluded from the analyses based on missing early pregnancy or early postpartum maternal psychological stress measures did not differ significantly from those included by maternal age ($F=0.590$, $p=0.443$), infant gestational age at birth ($F=0.662$, $p=0.431$), infant sex ($\chi2(1)<0.001$, $p=0.974$), race/ethnicity ($\chi2(9)=16.699$, $p=0.054$), level of maternal education ($\chi2(7)=7.404$, $p=0.388$), obstetric risk ($\chi2(2)=1.547$, $p=0.461$), maternal stress composite scores (early trimester $F=0.158$, $p=0.692$; mid $F=0.157$, $p=0.692$, late pregnancy $F=0.964$, $p=0.327$; 1 month postnatal $F=0.301$, $p=0.584$) average depression ($F=1.011$, $p=0.316$), average perceived stress ($F=1.715$, $p=0.192$), or average anxiety ($F=0.008$, $p=0.930$), see **Table 2.28**. The excluded mother-infant dyads differed by infant age at MRI scan ($F=4.598$, $p=0.035$), excluded neonates were scanned at a younger age, and by annual income ($\chi2(4)=10.145$, $p=0.038$), a great number of excluded mothers reported income over $100,000 and fewer reported income below $15,000 compared to included mothers. The PSS was added after the CESD and STAI, thus more women are missing that measure during pregnancy.

Table 2.28. Comparison of demographics for full sample versus sample excluded from Functional Random Forest analysis.

	Full Sample (n=115) Mean (SD)	**Excluded Sample (n=135) Mean (SD)**
Maternal age in first trimester, Years	28.07 (4.88)	27.54 (5.85)
Infant Age		
Gestational age at birth, Weeks	39.24 (1.53) (n=110)	39.42 (1.58) (n=97)
Age at functional MRI data collection, Days	26.22 (11.45) (n=60)	19.63 (12.60) (n=16)
Average depression (early pregnancy – early postpartum)	0.65 (0.39)	0.73 (0.44) (n=35)
Average perceived stress (early pregnancy – early postpartum)	1.32 (0.55)	1.22 (0.58) (n=131)
Average anxiety (early pregnancy – early postpartum)	1.64 (0.43)	1.64 (0.29) (n=35)
	No. (%)	**No. (%)**
Infant Sex	(n=110)	(n=95)
Male	59 (54)	51 (54)
Female	51 (46)	44 (46)
Race/Ethnicity	**(n=105)**	**(n=35)**
Caucasian non-Hispanic	42 (40)	15 (43)
African American non-Hispanic	1 (1)	1 (3)
Asian non-Hispanic	8 (8)	0
Multi-racial non-Hispanic	8 (8)	1 (3)
Caucasian Hispanic	40 (38)	11 (31)
Asian Hispanic	1 (1)	1 (3)
Multi-racial Hispanic	5 (5)	1 (3)
Other	0	5 (14)
Highest Level of Maternal Education	**(n=106)**	**(n=35)**
Primary, elementary, or middle school	4 (4)	2 (6)
High school or test equivalent	19 (18)	2 (23)
Vocational school or some college	44 (43)	14 (39)
Associates degree	6 (6)	2 (6)
Bachelors or graduate level degree	32 (30)	9 (26)
Gross Annual Household Income	**(n=111)**	**(n=125)**
< $15,000	13 (12)	7 (6)
$15,000 - 29,999	15 (14)	27 (22)
$30,000 - 49,999	29 (26)	20 (16)
$50,000 - 100,000	43 (39)	49 (39)
> $100,000	11 (10)	22 (18)

Maternal Trajectory Clusters

The 13 mother-infant dyads that belonged to trajectory clusters excluded from the analyses did not differ significantly from those included by maternal age (F=2.320, p=0.131), infant gestational age at birth (F=0.128, p=0.722), infant age at MRI scan (F=0.557, p=0.458), infant sex ($\chi 2(1)<0.001$, p=0.996), race/ethnicity ($\chi 2(7)=7.121$, p=0.416), level of maternal education ($\chi 2(7)=3.440$, p=0.842), annual income ($\chi 2(4)=4.702$, p=0.319), obstetric risk ($\chi 2(2)=0.830$, p=0.660), maternal stress composite scores (early trimester F=2.235, p=0.138; mid F=2.865, p=0.093, late pregnancy F=3.813, p=0.053; 1 month postnatal F=0.117, p=0.732) average depression (F=1.411, p=0.237), average perceived stress (F=0.203, p=0.653), or average anxiety (F=0.511, p=0.476), see **Table 2.29**.

Table 2.29. Comparison of demographics for analytic sample versus sample excluded from trajectory clusters.

	Analytic Sample (N=102) Mean (SD)	**Excluded Sample (N=13) Mean (SD)**
Maternal age in first trimester, Years	27.82 (5.02)	30.00 (3.08)
Infant Age		
Gestational age at birth, Weeks	39.27 (1.51)	39.11 (1.40)
Age at MRI data collection, Days—Functional	26.99 (11.84) (n=73)	24.00 (9.39) (n=10)
Average depression (early pregnancy – early postpartum)	0.57 (0.39)	0.44 (0.34)
Average perceived stress (early pregnancy – early postpartum)	1.11 (0.55)	1.04 (0.70)
Average anxiety (early pregnancy – early postpartum)	1.48 (0.41)	1.40 (0.35)
	No. (%)	**No. (%)**
Infant Sex		
Male	55 (54)	7 (54)
Female	47 (46)	6 (46)
Race/Ethnicity	**(n=94)**	**(n=11)**
Caucasian non-Hispanic	40 (43)	2 (18)
African American non-Hispanic	1 (1)	0
Asian non-Hispanic	7 (7)	1 (9)
Multi-racial non-Hispanic	8 (9)	0
Caucasian Hispanic	32 (34)	8 (73)
Asian Hispanic	1 (1)	0
Multi-racial Hispanic	5 (5)	0
Highest Level of Maternal Education	**(n=94)**	**(n=12)**
Primary, elementary, or middle school	3 (3)	1 (8)
High school or test equivalent	18 (19)	1 (8)
Vocational school or some college	39 (42)	6 (50)
Associates degree	6 (6)	0
Bachelors or graduate level degree	28 (30)	4 (33)
Gross Annual Household Income	**(n=98)**	**(n=13)**
< $15,000	13 (13)	0
$15,000 - 29,999	13 (13)	2 (15)
$30,000 - 49,999	25 (26)	4 (31)
$50,000 – 100,000	39 (40)	4 (31)
> $100,000	8 (8)	3 (23)

MRI Scan

The 55 mother-infant dyads excluded from the MRI scan did not differ significantly from those included by maternal age (F=0.113, p=0.737), infant gestational age at birth (F=1.107, p=0.295), infant sex (p=0.709, Fischer's exact test, 2-sided), race/ethnicity ($\chi 2(7)=11.186$, p=0.131), level of maternal education ($\chi 2(7)=6.347$, p=0.500), annual income ($\chi 2(4)=1.812$, p=0.770), obstetric risk ($\chi 2(2)=1.816$, p=0.403), maternal stress composite scores (early trimester F=0.287, p=0.593; mid F=0.030, p=0. 628, late pregnancy F=0.862, p=0.355; 1 month postnatal F=0.755, p=0.387), average depression (F=0.518, p=0.473), average perceived stress (F=0.740, p=0.392), or average anxiety (F=0.658, p=0.419), see **Table 2.30**.

Table 2.30. Comparison of demographics for analytic sample versus sample excluded from MRI scan.

	Analytic Sample (N=60) Mean (SD)	**Excluded Sample (N=55) Mean (SD)**
Maternal age in first trimester, Years	28.22 (4.75)	27.91 (5.06)
Infant Age		
Gestational age at birth, Weeks	39.11 (1.56)	39.40 (1.42)
Age at MRI data collection, Days—Functional	26.22 (11.45) (n=60)	27.70 (13.01) (n=23)
Average depression (early pregnancy – early postpartum)	0.58 (0.39)	0.53 (0.37)
Average perceived stress (early pregnancy – early postpartum)	1.15 (0.57)	1.05 (0.56)
Average anxiety (early pregnancy – early postpartum)	1.50 (0.38)	1.44 (0.43)
	No.(%)	**No.(%)**
Infant Sex		
Male	31 (52)	31 (56)
Female	29 (48)	24 (44)
Race/Ethnicity	**(n=59)**	**(n=46)**
Caucasian non-Hispanic	25 (42)	17 (37)
African American non-Hispanic	1 (2)	0
Asian non-Hispanic	6 (10)	2 (4)
Multi-racial non-Hispanic	5 (9)	3 (7)
Caucasian Hispanic	16 (27)	24 (52)
Asian Hispanic	1 (2)	0
Multi-racial Hispanic	5 (9)	0
Highest Level of Maternal Education	**(n=60)**	**(n=46)**
Primary, elementary, or middle school	2 (3)	2 (4)
High school or test equivalent	12 (20)	7 (15)
Vocational school or some college	24 (40)	21 (46)
Associates degree	2 (3)	4 (9)
Bachelors or graduate level degree	20 (33)	12 (26)
Gross Annual Household Income	**(n=58)**	**(n=53)**
< $15,000	6 (10)	7 (13)
$15,000 - 29,999	8 (14)	7 (13)
$30,000 - 49,999	17 (29)	12 (23)
$50,000 – 100,000	23 (40)	20 (38)
> $100,000	4 (7)	7 (13)

Infant Negative Affect

The 5 mother-infant dyads excluded from the infant negative affect analyses did not differ significantly from those included by maternal age (F=0.386, p=0.535), infant gestational age at birth (F=0.100, p=0.752), infant sex (p=1.000, Fischer's exact test, 2-sided), race/ethnicity ($\chi 2(7)=2.631$, p=0.917), level of maternal education ($\chi 2(7)=6.985$, p=0.430), annual income ($\chi 2(4)=1.066$, p=0.900), obstetric risk ($\chi 2(2)=0.255$, p=0.880), maternal stress composite scores (early trimester F=0.876, p=0.351; mid F=0.295, p=0.588, late pregnancy F=0.067, p=0.796; 1 month postnatal F=0.025, p=0.876), average depression (F=0.105, p=0.746), average perceived stress (F=2.633, p=0.107), or average anxiety (F=0.499, p=0.481), see **Table 2.31**.

Table 2.31. Comparison of demographics for analytic sample versus sample excluded from infant negative affect growth models.

	Analytic Sample (N=110) Mean (SD)	**Excluded Sample (N=5) Mean (SD)**
Maternal age in first trimester, Years	28.01 (4.85)	29.40 (6.03)
Infant Age		
Gestational age at birth, Weeks	39.24 (1.50)	39.46 (0.26)
Age at functional MRI data collection, Days	26.37 (11.87) (n=81)	37.00 (0.00) (n=2)
Average depression (early pregnancy – early postpartum)	0.55 (0.38)	0.61 (0.37)
Average perceived stress (early pregnancy – early postpartum)	1.12 (0.56)	0.71 (0.41)
Average anxiety (early pregnancy – early postpartum)	1.47 (0.40)	1.60 (0.46)
	No.(%)	**No.(%)**
Infant Sex		
Male	59 (54)	3 (60)
Female	51 (46)	2 (40)
Race/Ethnicity	**(n=101)**	**(n=4)**
Caucasian non-Hispanic	41 (41)	1 (25)
African American non-Hispanic	1 (1)	0
Asian non-Hispanic	7 (7)	1 (25)
Multi-racial non-Hispanic	8 (8)	0
Caucasian Hispanic	38 (38)	2 (50)
Asian Hispanic	1 (1)	0
Multi-racial Hispanic	5 (5)	0
Highest Level of Maternal Education	**(n=102)**	**(n=4)**
Primary, elementary, or middle school	3 (3)	1 (25)
High school or test equivalent	19 (19)	0
Vocational school or some college	43 (42)	2 (50)
Associates degree	6 (6)	0
Bachelors or graduate level degree	31 (30)	1 (25)
Gross Annual Household Income	**(n=106)**	**(n=5)**
< $15,000	12 (11)	1 (20)
$15,000 - 29,999	14 (13)	1 (20)
$30,000 - 49,999	28 (26)	1 (20)
$50,000 – 100,000	41 (39)	2 (40)
> $100,000	11 (10)	0

Finn Data, Replication Sample Missing Data Analysis

In comparison with the mothers in the baseline cohort (N = 3,808), mothers who reported infant negative affect (NA) for at least one time point were older (7.34, p <0.001), more highly educated ($\chi 2 = 90.33$, p <0.001) and more satisfied with their economic situation (T = -3.95, p <0.001). They also reported slightly fewer symptoms (Edinburgh Postnatal Depression Scale M = 4.47-4.97, SD = 3.93-4.04, SCL M = 3.10-3.80, SD = 3.81-4.29) than those who did not report infant NA at any postnatal time points (EPDS M = 5.51-5.61, SD = 4.14-4.38, Symptom Checklist M = 3.51-4.27, SD = 3.90-4.4.24), p <0.001).

The sample with complete NA data (N = 1,062) did not differ from the main study sample used in the present study (N = 2,156) in terms of infant NA at any time point (p > 0.20) tested using both raw scores and residualized scores. The complete NA sample also did not differ from the main sample (N = 2,156) in terms of infant gestational age, but the responders reported less depressive symptoms at 1st (T = 2.025, p = 0.043) and 3rd trimester (T = 2.45, p = 0.014). There were no differences regarding the symptoms at any other time point or regarding anxiety symptoms. There was no significant difference in the prenatal trajectory group distributions between those who reported the complete NA data and those who did not ($\chi 2 = 4.56$, p = 0.217).

CHAPTER 3. INTERGENERATIONAL EFFECT OF MATERNAL EXPOSURE TO CHILDHOOD MALTREATMENT AND ASSOCIATIONS WITH NEONATAL AMYGDALA FUNCTIONAL CONNECTIVITY AND INFANT BIOBEHAVIORAL OUTCOMES

3.1 Abstract

Background: Childhood maltreatment, such as abuse or neglect, is a pervasive public health problem with devastating and lasting consequences for psychological well-being and overall health across the lifespan. Although previously thought to be limited to a single individual, the negative effects of childhood maltreatment may be transmitted across generations, increasing the risk for behavioral and psychiatric disorders in the offspring. An increased understanding of the mechanisms underlying intergenerational effects is important for the development of preventive interventions. The present study, therefore, aims to examine the associations between maternal childhood maltreatment and offspring brain and biobehavioral outcomes employing a study design that increases the capacity to disentangle the effects of the pre- versus postnatal environment. We employ a prospective study design examining maternal reports of childhood maltreatment history in relation to offspring neonatal amygdala functional connectivity. We further examine whether alterations in neonatal amygdala connectivity may serve as a potential pathway through which maternal childhood maltreatment history relates to maternal-infant attachment style and infant cortisol reactivity at 12 months of infant age.

Methods: Maternal childhood maltreatment history was assessed during pregnancy using the Childhood Trauma Questionnaire (CTQ) in 64 women. Shortly after birth (M=26.48 ± 11.43 days), their offspring underwent a resting state functional connectivity (rsFC) MRI scan during natural sleep. A whole-brain voxel-wise regression model was performed with the log of the total CTQ score predicting offspring amygdala functional connectivity. Neonatal amygdala connections that remained significantly associated with maternal childhood maltreatment after adjusting for potential confounds were considered as potential candidate neural phenotypes to examine in relation to infant attachment classification and cortisol reactivity. A structural equation model was used to test for mediation by examining the indirect path from maternal childhood maltreatment history to infant biobehavioral outcomes via the selected newborn neural phenotype.

Results: Neonates of mothers with a history of childhood maltreatment showed altered amygdala functional connectivity to several brain regions including the pars opercularis, parahippocampus, temporal pole, dorsal anterior cingulate cortex (dACC), occipital cortex, fusiform, precentral gyrus, and cuneus. Follow up analyses focused on amygdala-dACC functional connectivity, due to its role in stress reactivity and regulation. Stronger amygdala-dACC functional connectivity related to increased likelihood of infants developing an insecure attachment at 12 months of age after adjusting for key potential confounds in the postnatal environment. Interestingly, stronger neonatal amygdala-dACC connectivity also mediated the association between maternal history of childhood maltreatment and increased risk of insecure attachment. Infant cortisol reactivity at twelve months of age was not related to neonatal amygdala-dACC functional connectivity.

Conclusion: The results of this study suggest a neural phenotype related to a maternal history of childhood maltreatment. The findings further suggest that the intrauterine period is important for the intergenerational transmission of the effects of maternal childhood maltreatment, even in a cohort with relatively low rates of reported childhood maltreatment. Given the role of the anterior cingulate cortex as a potential biomarker for both risk and resilience, and its clear sensitivity to environmental influences, it is imperative to explore how prenatal and preconceptional interventions can best support maternal and infant mental health.

3.2 Introduction

Childhood maltreatment, such as abuse or neglect, is a pervasive public health problem with devastating and lasting consequences for psychological well-being and overall health across the lifespan. These effects include alterations in affective and cognitive processing, changes in physiological and behavioral states, heightened stress responsivity (Grant et al., 2011; Marusak et al., 2015; van Nierop et al., 2018), and an increased risk for psychopathology (Afifi et al., 2009; Duncan et al., 1996; Edwards et al., 2003; Felitti et al., 1998; C. Heim et al., 2008; Min, Minnes, et al., 2013; Navalta et al., 2006; Shonk & Cicchetti, 2001; Teicher & Samson, 2013). Additionally, there is growing evidence demonstrating the distinct impact of childhood maltreatment on maternal health during pregnancy. A history of childhood maltreatment has been shown to increase the odds of antenatal depression (Barrios et al., 2015; Bouvette-Turcot et al., 2017; Choi et al., 2015; Gartland et al., 2016; Lara et al., 2015; Mcdonnell & Valentino, 2016; Mezey et al., 2005; Robertson-Blackmore et al., 2013) in a dose-dependent manner

(Blackmore et al., 2016), even when accounting for sociodemographic and psychosocial factors (Choi & Sikkema, 2016). Anxiety (Gartland et al., 2016; Lara et al., 2015), poor mental health, and intimate partner violence during pregnancy (Gartland et al., 2016; Huth-Bocks et al., 2013) are also associated with a maternal history of childhood maltreatment. Several studies suggest that pregnancy itself may trigger reminders of relational trauma (Huth-Bocks et al., 2013), be re-traumatizing (Lev-Wiesel et al., 2009; Mezey et al., 2005; Montgomery, 2013), and increase symptoms of post-traumatic stress disorder (PTSD) (Choi et al., 2015; Lev-Wiesel et al., 2009; Mezey et al., 2005).

Although previously thought to be limited to a single individual, the negative effects of childhood maltreatment may be transmitted across generations, increasing the risk for behavioral and psychiatric disorders in the offspring (Bosquet Enlow et al., 2017; Collishaw et al., 2007; H Dubowitz et al., 2001; Folger et al., 2017; Mcdonnell & Valentino, 2016; Min, Singer, et al., 2013; Miranda et al., 2011; Moog et al., 2018; Dominic T Plant et al., 2017; Sun et al., 2017; Thompson, 2007). Recently, Hendrix and colleagues (2020) found that maternal exposure to maltreatment during childhood was associated with stronger offspring amygdala functional connectivity to the dACC and ventromedial prefrontal cortex at one month of age (Hendrix et al., 2020). Alterations in infant neurobiological and psychosocial development may eventually explain the observed relationship between a history of maternal childhood maltreatment and increased developmental risk (Folger et al., 2017; Sun et al., 2017), altered cortisol levels and stress reactivity (Brand et al., 2010), emotional and behavioral dysregulation (Mcdonnell & Valentino, 2016; Min, Singer, et al., 2013; Miranda et al., 2011; Thompson, 2007), negative emotionality (Bosquet Enlow et al., 2017), and altered

attachment security in offspring (Khan & Renk, 2018; Levy & Orlans, 1998; Savage et al., 2019).

The existing paradigm posits that the intergenerational transmission of childhood maltreatment primarily occurs in the context of postnatal maternal-infant attachment and maternal mood; however, there is growing evidence that the intergenerational transmission of maltreatment may also occur during the prenatal period. Maternal-placental-fetal biology likely plays a key role in the intergenerational transmission of childhood maltreatment through alterations in maternal stress biology resulting from a history of maltreatment (Buss et al., 2017). Hypothalamic-pituitary-adrenal (HPA) axis dysregulation is one of the long-lasting effects of childhood maltreatment (Buss, Entringer, & Wadhwa, 2012; Tarullo & Gunnar, 2006; Van Voorhees & Scarpa, 2004). In a study comparing pregnant women with and without a history of sexual abuse, sexual abuse history was associated with increasing waking cortisol across pregnancy and the absence of a dampening response in late pregnancy (Bublitz & Stroud, 2012). Maternal exposure to maltreatment during childhood has also been associated with an increase in placental CRH production during the second half of pregnancy, again reflecting HPA dysregulation during late pregnancy (Moog et al., 2016).

However, many study designs make it difficult to disentangle the effects of maternal childhood maltreatment history on offspring development that is transmitted during pregnancy from effects due to postnatal exposure to maternal mood and parenting. A recent study by Moog and colleagues made some headway in this regard by examining infant brain structure shortly after birth in relation to maternal childhood maltreatment history. They showed that maternal childhood maltreatment was associated with global

differences in infants' cortical gray matter and reduced intracranial volume at one month of age (Moog et al., 2018). Similarly, Hendrix and colleagues found that a maternal history of maltreatment during childhood was associated with stronger neonatal amygdala functional connectivity to regions associated with fear and stress processing (Hendrix et al., 2020). The results of these studies provide support for an intergenerational effect of maternal exposure to maltreatment during childhood on offspring neurodevelopment prior to exposure to the postnatal environment.

We are seeking to build on these findings by examining maternal exposure to maltreatment during childhood in relation to the neonatal amygdala with a focus on functional connectivity. Studies have shown an association between maternal psychological and biological stress mediators during pregnancy and altered offspring limbic system development in infancy (Graham et al., 2018; A Qiu et al., 2015; Rifkin-Graboi et al., 2015). It is currently hypothesized that the vulnerability of this system is due to its rapid growth during the fetal period. The amygdala contains a high density of glucocorticoid receptors that detect and respond to stress hormones (Herzog et al., 2020) making it susceptible to stress mediators associated with maternal-placental-fetal gestational biology (Buss, Entringer, Swanson, et al., 2012). The amygdala also plays an important role in emotional responses and stress-induced alterations may increase the risk for altered stress reactivity and attachment insecurity in offspring. Therefore, we will examine how potential amygdala alterations, already evident in the neonatal brain, relate to the subsequent formation of maternal-infant attachment and infant stress reactivity.

Childhood maltreatment is pervasive, and an increased understanding of the mechanisms underlying intergenerational effects is important for the development and

implementation of preventive interventions. The present study, therefore, aims to examine the associations between maternal childhood maltreatment and offspring brain and behavioral outcomes employing a study design that increases capacity to disentangle effects of the pre-versus postnatal environment. We specifically employ a prospective study design examining maternal report of childhood maltreatment history, from prior to the birth of their infant, in relation to offspring neonatal amygdala functional connectivity. We further examine whether alterations in neonatal amygdala functional connectivity may serve as a potential pathway through which maternal childhood maltreatment history relates to maternal-infant attachment style and infant cortisol reactivity at 12 months of infant age. Focusing on the neonatal brain and its associations with attachment and cortisol reactivity increases our ability to differentiate between prenatal and postnatal influences and helps us to elucidate potential prenatal mechanisms for the intergenerational transmission of childhood maltreatment.

3.3 Methods and Materials

Participants

Mother-infant dyads (n=64) enrolled as part of a prospective longitudinal cohort conducted at the University of California, Irvine (UCI) were recruited through prenatal clinics during early pregnancy from February 2011 to November 2018, for details see (Moog et al., 2018). Exclusionary criteria included use of psychotropic medications or systemic corticosteroids during pregnancy, premature birth (before 34 weeks' gestation), and infant genetic, congenital, or neurological disorder (Graham et al., 2018). For detailed demographic data; see **Table 3.1**. Biobehavioral data was obtained from infants

at 12 months of age (attachment: mean = 11.33, SD = 3.35; cortisol: M: 11.76, SD=2.61 months). All procedures were approved by the Institutional Review Board at the University of California, Irvine.

Table 3.1. Demographics for study cohort.

	Mean (SD) (n=64)
Maternal age in first trimester, Years	28.53 (5.23)
Infant Age	
Gestational age at birth, Weeks	39.19 (1.50)
Age at functional MRI data collection, Days	26.48 (11.43)
Infant Sex	**No. (%)**
Male	34 (53)
Female	30 (47)
Race/Ethnicity	**(n=60)**
Caucasian non-Hispanic	27 (45)
African American non-Hispanic	1 (2)
Asian non-Hispanic	5 (8)
Multi-racial non-Hispanic	5 (8)
Caucasian Hispanic	17 (28)
Asian Hispanic	1 (2)
Multi-racial Hispanic	4 (7)
Highest Level of Maternal Education	**(n=60)**
Primary, elementary, or middle school	1 (2)
High school or test equivalent	9 (15)
Vocational school or some college	30 (50)
Associates degree	2 (3)
Bachelors or graduate level degree	18 (30)
Gross Annual Household Income	**(n=60)**
< $15,000	6 (10)
$15,000 - 29,999	13 (21)
$30,000 - 49,999	15 (24)
$50,000 - 100,000	23 (37)
> $100,000	5 (8)

Maternal Measures

Maternal childhood maltreatment history was assessed in mid-pregnancy using the Childhood Trauma Questionnaire (CTQ) (D P Bernstein et al., 1994). The CTQ is a standardized, retrospective self-report tool that assesses five domains of childhood maltreatment: physical, sexual, and emotional abuse; and physical and emotional neglect. It is a 28-item questionnaire with 3 items making up an additional Minimization/Denial scale designed to capture potential under-reporting (Villano et al., 2004). Each item within the five maltreatment domains is scored on a 5 point scale where 1 = never and 5 = very often. The total CTQ score is a sum score of all maltreatment domains (range 25 – 125), see **Table 3.2**. In the present study, the total CTQ score was log-transformed to normalize the distribution of the data and used as the principal predictor in statistical analyses.

Table 3.2. Mean (SD) scores on the CTQ scales and number (%) of women meeting cut-off for maltreatment classification.

	Mean (SD)	Moderate N (%)	Severe N (%)
Emotional Abuse Subscale (range= 1-5)	1.52 (0.80)	8 (15.4)	3 (5.3)
Physical Abuse Subscale (range= 1-5)	1.29 (0.68)	5 (10.2)	4 (6.9)
Sexual Abuse Subscale (range= 1-5)	1.21 (0.64)	8 (15.4)	3 (5.3)
Emotional Neglect Subscale (range= 1-5)	1.86 (0.86)	8 (15.4)	5 (8.5)
Physical Neglect Subscale (range= 1-5)	1.39 (0.60)	11 (20.0)	4 (6.6)
CTQ Total Score (range = 25-125)	36.31 (14.52)		

Mothers completed the Center for Epidemiological Studies Depression Scale (CESD) (Radloff, 1977) in early, mid, and late pregnancy and at one, three, six, nine, twelve, and twenty-four months postpartum. During pregnancy, 37 (57.8%) of the women reported at least one clinically elevated mean CESD score (CESD≥0.8). Maternal postnatal depression was included in analyses examining infant attachment in order to adjust for the potential influence of the postnatal environment.

MRI and fMRI Data Acquisition and Processing

Data Acquisition

Data were acquired at approximately one month of age (26.48 ± 11.43 days) during natural sleep. High-resolution T1-weighted (MP-RAGE TR = 2400 ms, inversion time = 1200 ms, echo time = 3.16 ms, flip angle = 8°, resolution = 1 x 1 x 1 mm, 6 min 18 secs) and T2-weighted (TR = 3200 ms, echo time = 255ms, resolution = 1 x 1 x 1 mm, 4 min 18 secs) images were obtained using a TIM Trio, Siemens Medical System 3.0T scanner. Resting-state functional connectivity (rs-FC) magnetic resonance images (MRI) were obtained using a gradient-echo, echoplanar imaging (EPI) sequence sensitive to blood oxygen level-dependent (BOLD) contrast (TR = 2000 ms; TE = 30 ms; FOV = 220 x 220 x 160 mm; flip angle = 77°). Steady-state magnetization was assumed after 4 frames (8 ~ s).

fMRI Data Preprocessing

All functional MRIs were processed using a modified version of the Human Connectome Project (HCP) processing pipeline (DCAN-Labs, 2020b; Glasser et al.,

2013). Several modifications were made to improve the segmentation and parcellation of neonatal images. ANTs DenoiseImage (Manjón, Coupé, Martí-Bonmatí, Collins, & Robles, 2010) and N4BiasFieldCorrection (Tustison et al., 2010) were applied to model Rician scanner noise and bias field inhomogeneities respectively. Next, we performed a rigid body transform to anterior commissure - posterior commissure (AC-PC)-align both T1w and T2w structural images to the neonate template from the National Institutes of Health (NIH) pediatric template (0- to 2-month age range; National Institutes of Health MRI Study of Normal Brain Development) (Almli, Rivkin, & McKinstry, 2007). For brain extraction, a T2w nonlinear warp from atlas-space to native space was performed to the binarized the NIH age-specific atlas in MNI space. A rigid body registration of the T2w to T1w image was used to convert the resulting T2w brain mask to a T1w brain mask. Following T1w masking, we have the initial skull-stripped T1w and T2w infant brain in native volume space. Extracted brains are refined by computing tissue classes in the T2w brain using the ANTs Atropos (Avants, Tustison, Wu, Cook, & Gee, 2011; Avants, Tustison, & Song, 2009) algorithm and applying the gray matter/white matter (GM/WM) masks to the T1w brain. The masked T1w and T2w are then nonlinearly registered to the MNI infant atlas. Segmentation was completed based on the T1 with ANTS Joint Label Fusion (H. Wang et al., 2013) and employing 10 infant atlases with labeled brain regions, which had been refined through manual correction. Finally, the mean intensity of the resulting cortical white and grey matter labels were shifted to match the FreeSurfer adult atlas. This hyper-normalization procedure facilitates the use of HCP's FreeSurfer recon-all to generate white and pial surfaces necessary for surface-based analyses.

rs-fcMRI Preprocessing

DCAN-BOLDproc (DCAN-Labs, 2020a) was used to correct time courses. These steps included resting state time course detrending and processing with mean whole brain, ventricle, and white matter signal as well as displacement on the 6 degrees of freedom, rigid body registration, and their derivatives (Ciric et al., 2017; Friston, Mechelli, Turner, & Price, 2000; Hermosillo et al., 2020; J. D. J. D. Power et al., 2014). Time courses were then filtered using a first order Butterworth band pass filter between 9 and 80 mHz backwards and forwards using MATLAB's *filtfilt* function (MathWorks, n.d.). To correct for motion, an examination of frame-wise displacement (FD) was conducted and volumes with greater than 0.3 mm FD plus the preceding volume and subsequent 3 volumes were removed. Following frame removal for motion, scan length was about 5.80 minutes (range: 4.23 – 6.40 minutes) with a remaining FD of 0.089 (range: 0.056-0.127).

Amygdala Connections

We focused on amygdala connectivity due to prior work indicating the vulnerability of the amygdala to maternal-placental-fetal gestational biology and its role in emotion regulation (Buss, Davis, et al., 2012; Graham et al., 2018; Thomas et al., 2019). Individual amygdalae segmentation was performed using a multi-template, multi-modality based method that combined T1 and T2 weighted high-resolution images (J. Wang et al., 2014). Following anterior-posterior realignment, amygdala segmentations were manually corrected using ITK-Snap (Yushkevich et al., 2006) as described in

(Graham et al., 2019). For rs-fcMRI analyses, amygdalae were transformed to atlas space based on the previously computed atlas transformation (Graham et al., 2018).

Attachment at 12 months of age

The well-established Strange Situation Paradigm (SSP) was used to assess attachment at 12 months of age (Ainsworth et al., 1978). The administration of the SSP followed established procedures, including two episodes of separation and reunion with mothers and an interaction with a stranger (Ainsworth et al., 1978). SSP coding of videotapes followed established procedures for classifying mother-infant dyads as Secure, Insecure-Avoidant, Insecure-Ambivalent/Resistant, and Insecure-Disorganized (Ainsworth et al., 1978). Coding was conducted by V. Alhusen, who underwent extensive training with L.A. Sroufe and E. Carlson at the Institute of Child Development, University of Minnesota and attachment classification of the study cohort is presented in the supplement Table 5. A dichotomous variable indicating secure (51.9%) versus insecure (48.1%) attachment classification was used for analyses in the present study. Secure attachment was coded as 1 and insecure attachment was coded as 0. Within the insecure group, the majority of infants were classified as anxious-avoidant and no infants were coded as disorganized, see **Table 3.3**.

Table 3.3. Attachment classification on the Strange Situation Paradigm for mother-infant dyads at 12 months of infant age.

		N (%) (n=52)
Insecure Avoidant	A1	4 (7.69)
	A2	16 (30.77)
Secure	B1	8 (15.38)
	B2	11 (21.15)
	B3	5 (9.62)
	B4	3 (5.77)
Insecure Resistant	C1	3 (5.77)
	C2	2 (3.85)

Infant Cortisol Reactivity

Cortisol reactivity was assessed by examining the change in salivary cortisol concentrations in response to a potential stressor, the SSP. At 12 months of age (M: 11.76, SD=2.61), three saliva samples were collected from infants by lab assistants on arrival to the lab (baseline), immediately after finishing the SSP (sample 1), and 10 minutes after the SSP (sample 2). Research assistants placed a Salivette (Sarstedt, Newton, NC) directly from a plastic vial into the children's mouths. Once saturated, the Salivette was returned to the vial. The samples were stored at −20 °C until being mailed to the laboratory for assay. Salivary cortisol concentrations were measured using a commercial enzyme-linked immunosorbent assay (ELISA) from Salimetrics (Carlsbad, CA, USA). Ten percent of the samples were assayed in duplicate. The lower limit of sensitivity of the assay was 0.007 μg/dl with a standard curve range from 0.012 μg/dl to 3.0 μg/dl. The assay had an average intra-assay coefficient of variation of 5.42% and an

average inter-assay coefficient of variation of <10%. Outliers were winsorized at +/-3 SD. Many infants had peak cortisol levels at baseline, likely as a result of coming to the laboratory setting (see **Figure 3.1**). Cortisol Samples 1 and 2 were averaged because 37.5% of infants had a cortisol increase immediately after the SSP (Sample 1) and 50% had their peak 10 minutes after (Sample 2). The remaining 12.5% of infants had no change in cortisol between sample 1 and 2. Cortisol percent increase was calculated by subtracting the baseline sample from this mean, dividing that value by the baseline sample and multiplying the resulting value by 100.

Table 3.4. Mean (SD) of infant cortisol levels and age at collection.

	M (SD) (n=48)
Cortisol measures	
Pre-stressor	0.1377 (0.1049)
Post-stressor (Sample 1)	0.1233 (0.0951)
Post-stressor (Sample 2)	0.1406 (0.1097)
Reactivity ([((Avg post1 and post2) – pre) ÷ pre])	0.4154 (1.1353)
Age at Collection	11.76 (2.61)

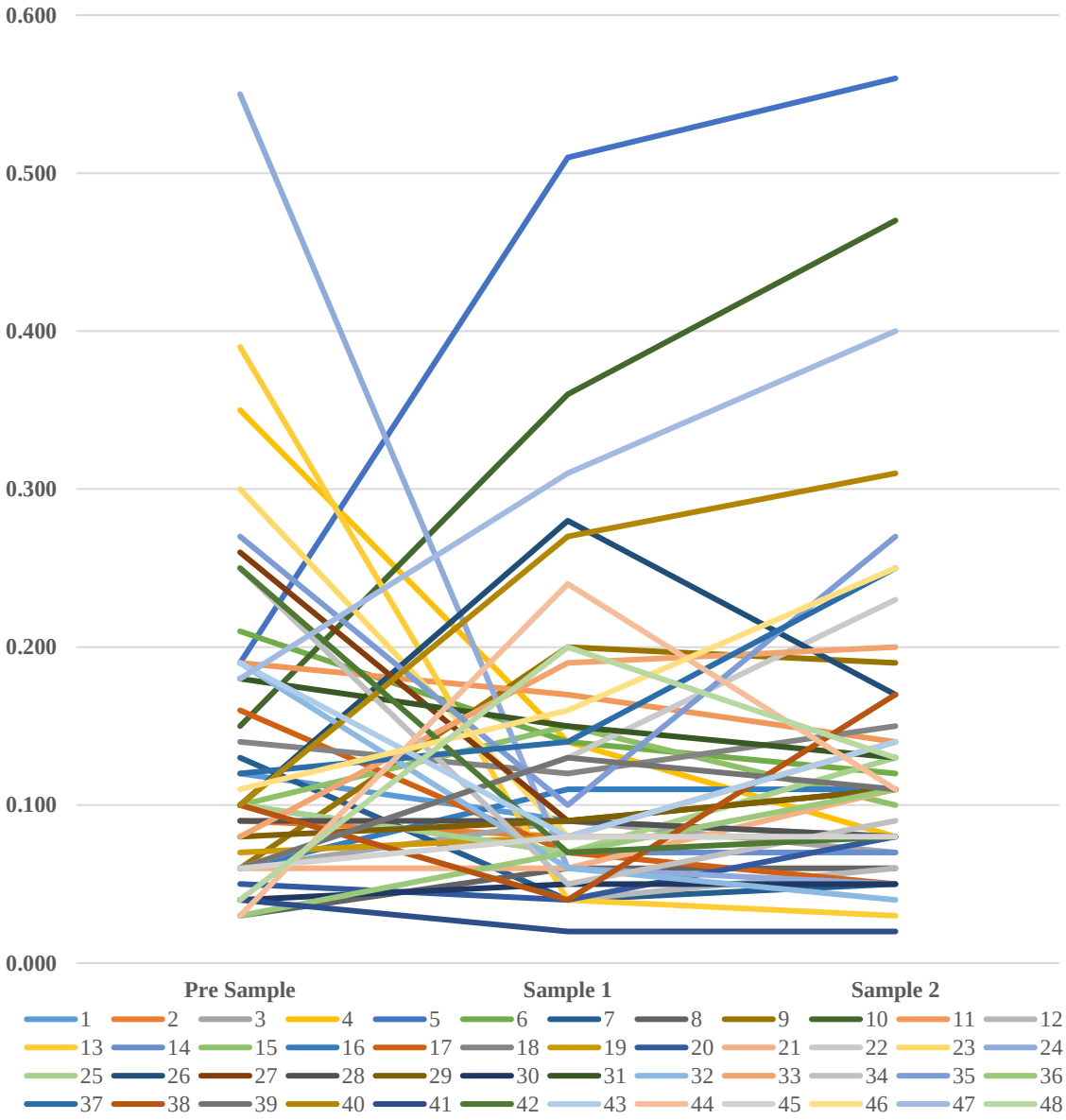

Figure 3.1. Infant cortisol reactivity during the Strange Situation Paradigm. Many infants had peak cortisol levels at baseline. Of those infants who showed an increase in cortisol during the post-stressor assessment times, 37.5% showed an increase immediately after the Strange Situation Paradigm (SSP) and 50% had their peak 10 minutes after (Sample 2). The remaining 12.5% of infants had no change in cortisol between sample 1 and 2.

Potential confounds relevant for neonatal brain and infant biobehavioral outcomes

Potential confounds relevant to neonatal brain development, infant attachment and cortisol reactivity were examined to determine whether any identified associations between a history of maternal childhood maltreatment and neonatal brain and biobehavioral outcomes could be better explained by other aspects of the prenatal or postnatal environment. These included annual household income, obstetric risk, infant sex, and maternal depression. Annual income was assessed during the first prenatal visit using standardized structured interviews. Income was initially captured as a categorical variable: Below $15,000; $15,000-29,999; $30,000-49,999; $50,000-100,000; and over $100,000. Obstetric risk includes the presence of major medical complications during pregnancy such as placenta abruption, preeclampsia, and gestational diabetes. Complications were identified through medical chart review and coded as a binary variable capturing the presence or absence of a risk factor. Maternal depression was assessed using the Center for Epidemiological Studies Depression Scale (CESD) (Radloff, 1977), which was completed at early, mid, and late pregnancy; and at 1, 3, 6, 9, and 12 months of infant age.

Analytic Approach

Left and right amygdalae were examined separately because of the evidence for sexual dimorphism in the neonatal brain (Gilmore et al., 2007). The log-transformed total CTQ score served as the independent variable, infant gestational age at birth (GA), infant sex, and age at scan as covariates, and left and right amygdala whole-brain voxelwise

connectivity as the dependent variable in regression models using MPlus (Muthén & Muthén, 2017). The test statistic was spatially normalized across the brain using a z score-transformation. The estimates from the regression models were the inputs for a cluster-extent based thresholding procedure using PALM ("PALM/UserGuide - FslWiki," n.d.). A threshold value of 3.1 was applied to the z-score statistic image. The extent of the cluster was used as the test statistic. Clusters of contiguous supra-threshold voxels were identified from the thresholded image and ordered by size. A permutation test was conducted under the assumptions of Gaussian random field theory, where the z-score statistical map was shuffled and the largest identified cluster size was stored. A p-value was calculated for each cluster based on size using 1000 permutations as the null distribution. A threshold of 3.1 has been shown to be conservative enough to avoid excessive false positive rates (Eklund, Nichols, & Knutsson, 2016). Post hoc analyses were conducted with the correlation coefficients (r) representing the strength of amygdala connection to clusters identified in the whole-brain analyses.

Post hoc regressions examined the role of potential confounders including maternal depression during pregnancy, income, obstetric risk, and infant sex. Neonatal amygdala connections that remained significantly associated with maternal childhood maltreatment after adjusting for potential confounds were considered as potential candidate neural phenotypes, representing distinct patterns of functional connectivity, to examine in relation to infant attachment classification and cortisol reactivity. A structural equation model was used to test for mediation by examining the indirect path from maternal childhood maltreatment history to infant outcomes via the selected newborn neural phenotype (Hayes, 2017).

3.4 Results

Amygdala Connectivity

Maternal childhood maltreatment was significantly associated with neonatal amygdala connectivity, with different patterns of connectivity present for the left and right amygdalae. For the left amygdala, higher CTQ scores were associated with stronger positive connectivity to the pars opercularis, left parahippocampus, temporal pole, and dorsal anterior cingulate cortex (dACC); and negative connectivity to occipital cortex, fusiform, left parahippocampus, and cuneus (see **Table 3.5, Figure 3.2A**). For the right amygdala, higher CTQ scores were associated with stronger positive connectivity to the precentral gyrus (see **Table 3.5, Figure 3.2B**).

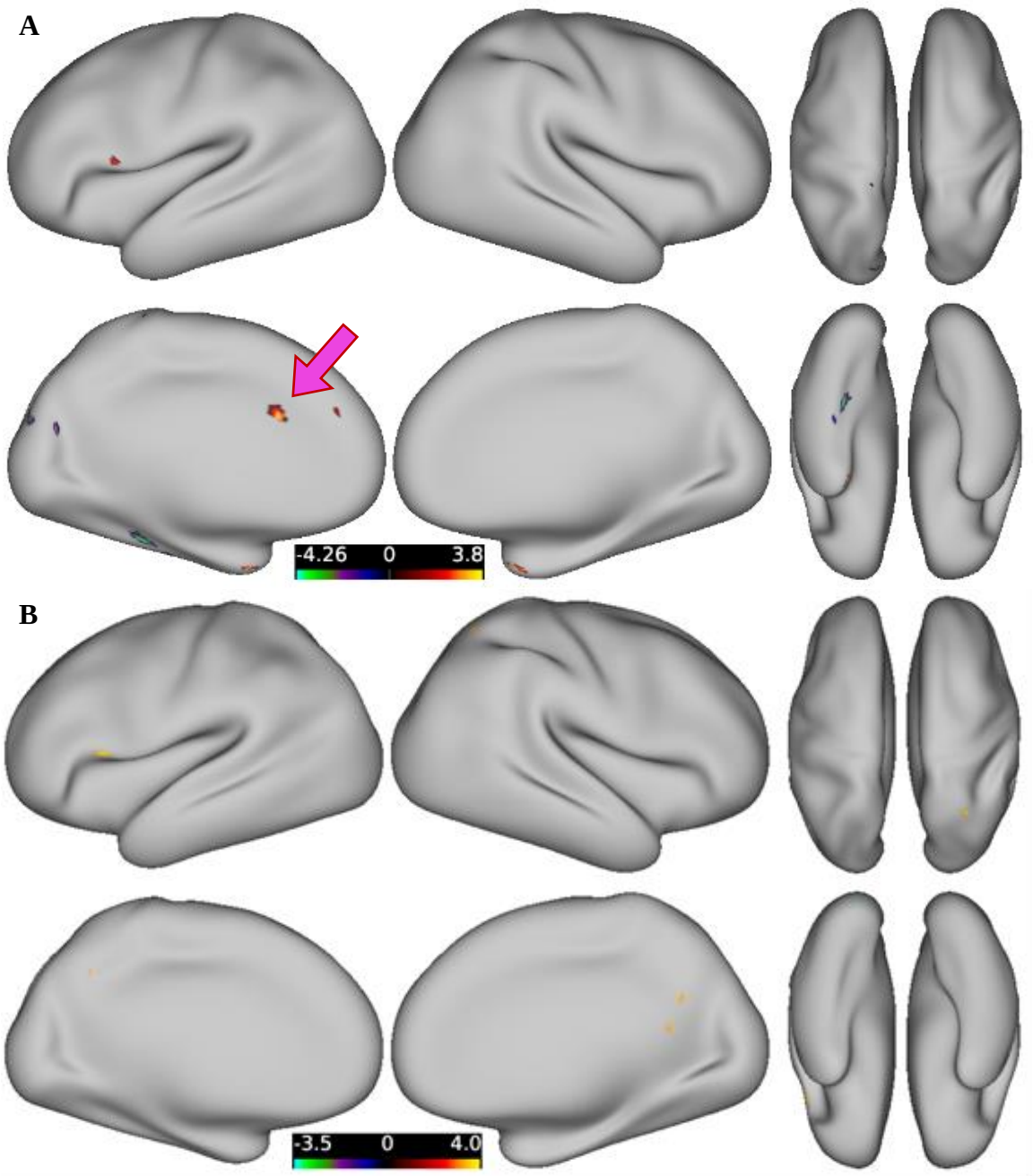

Figure 3.2. Left and right neonatal amygdala functional connectivity. Results for left (A) and right (B) amygdala whole-brain regressions. The log of the total CTQ score was the independent variable and covariates for sex, gestational age at birth, and infant age at scan were included to account for neonatal brain maturity at the time of MRI scan acquisition. Z score-transformed estimates above a threshold of z= ± 3.1 are shown.

Table 3.5. Maternal childhood maltreatment history is associated with neonatal amygdala connectivity. Regions are in ascending order based on cluster extent size. The Pearson correlation between the maternal log-transformed total CTQ score and the extracted connection between the amygdala and each identified region was examined. The direction (positive or negative) is indicated for childhood maltreatment (CM) in the last column. All associations reached statistical significance.

Region	Hem	x	y	z	Cluster size	CM*
Left Amygdala						
Frontal inferior gyrus, opercular	L	-53	11	6	50	+
Calcarine	L	-15	-72	18	54	-
Fusiform	L	-34	-31	-27	66	-
Parahippocampal, uncus	L	-22	0	-31	77	+
Dorsal anterior cingulate cortex	L	-3	13	28	81	+
Parahippocampal gyrus	L	-34	-38	-13	87	-
Parahippocampal, uncus	R	24	7	-34	109	+
Cuneus	L	-9	-91	27	133	-
Right Amygdala						
Precentral gyrus	L	-52	16	8	53	+

* $p<0.01$ for all associations

The effect of maternal childhood maltreatment remained significant for all identified amygdala connections, except the left parahippocampus ($\beta= 0.270$, $p=0.057$), after adjusting for potential confounds.

Neonatal Amygdala Connectivity is Associated with Attachment

Alterations to the anterior cingulate cortex in the context of maltreatment is one of the most consistently reported findings (Teicher & Samson, 2016) suggesting a sensitivity to mediators of psychological stress; therefore, we focused on this region for

our post hoc analyses. Employing a logistic regression model, neonatal left amygdala-dorsal anterior cingulate cortex functional connectivity was significantly associated with infant security (β= -0.316, p=0.026) at 12 months of age in the model including covariates for sex (β= 0.136, p=0.324) and prenatal depression (β= 0.105, p=0.451). Specifically, stronger functional connectivity was associated with increased likelihood of having an insecure attachment. Due to the limited sample size, we did not examine potential interactions between sex or CTQ subscales. The association between neonatal left amygdala-dorsal anterior cingulate cortex functional connectivity and infant attachment security remained significant when controlling for mean maternal postnatal depression over the first 12 months of infant life, maternal responsivity, and household income using a stepwise logistic regression (β= -0.291, p=0.042). Stronger neonatal left amygdala-dorsal anterior cingulate cortex functional connectivity mediated an association between maternal history of childhood maltreatment and attachment security (indirect effect= -1.314 [95% confidence interval (CI) = - 3.971 to -0.673] based on 10,000 bootstrap samples) (see **Figure 3.3**). These analyses identified another pathway from maternal childhood maltreatment to attachment security via stronger neonatal left amygdala-dorsal anterior cingulate cortex connectivity.

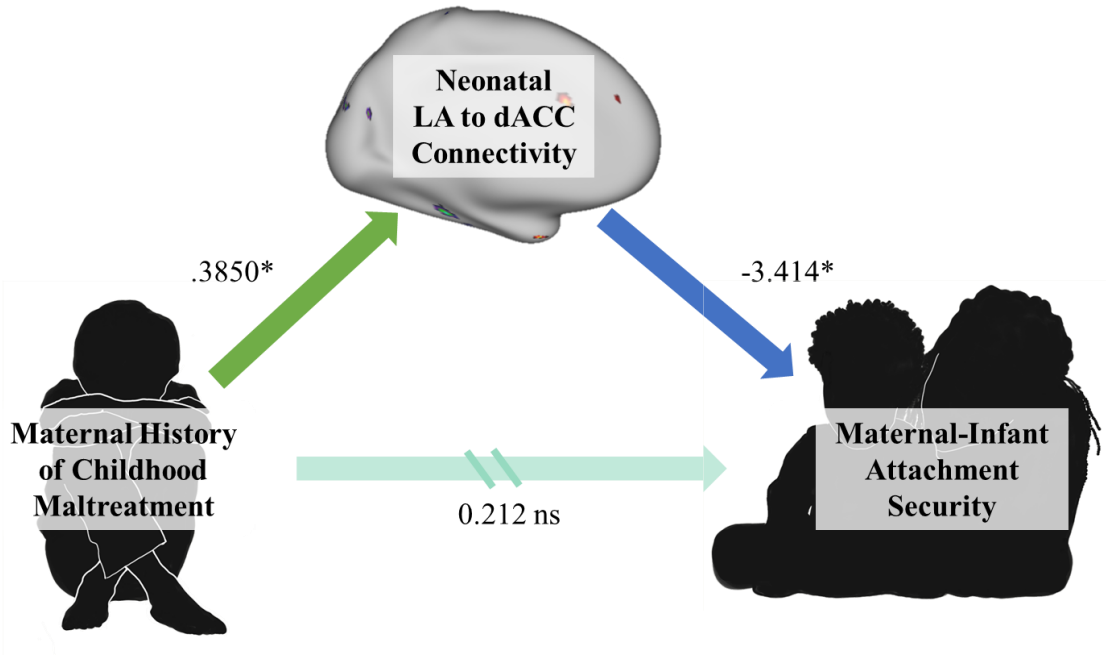

Figure 3.3. Neonatal left amygdala to dorsal anterior cingulate cortex (LA-dACC) mediates between maternal exposure to maltreatment during childhood and mother-infant attachment security. Coefficients are unstandardized and derived from the full mediation model. The indirect effect of maternal exposure to maltreatment during childhood on maternal-infant attachment security through LA-dACC functional connectivity was -1.314, and mediation was supported based on 10,000 bootstrap samples (95% CI: - 3.971, -0.673). *= $p \leq 0.05$, ns=non-significant. Arrows indicate hypothesized direction of effects.

Neonatal Amygdala Connectivity is Not Associated with Infant Cortisol Reactivity

Cortisol samples were taken before and after the strange situation to measure infant cortisol reactivity to a psychological stressor. Neonatal left amygdala-anterior cingulate cortex functional was significantly associated with blunted infant cortisol reactivity (β= -0.314, p=0.021). However, the association did not remain significant when covariates for time of sample collection and sex were included in the model (β= -0.228, p=0.111). Due to the limited sample size, we did not examine potential interactions based on sex.

3.5 Discussion

In the current study, we found that maternal childhood maltreatment was related to neonatal amygdala functional connectivity. Neonates of mothers with a history of childhood maltreatment showed altered amygdala functional connectivity to several brain regions including the pars opercularis, parahippocampus, temporal pole, dorsal anterior cingulate cortex, occipital cortex, fusiform, precentral gyrus, and cuneus. Follow up analyses focused on amygdala-dACC connectivity, due to the involvement of the dACC in effects of maltreatment in older samples and its role in stress reactivity and regulation. Stronger amygdala-dACC related to increased likelihood of infants developing an insecure attachment at 12 months of age after adjusting for key potential confounds in the postnatal environment. Interestingly, stronger neonatal amygdala-dACC connectivity also mediated an association between maternal history of childhood maltreatment and

increased risk of insecure attachment. Infant cortisol reactivity at twelve months of age was also inversely related to neonatal amygdala-dACC connectivity.

Brain Regions and Networks Involved and Relation to Childhood Maltreatment

The results of this study reveal a pattern of altered neonatal amygdala functional connectivity in association with a history of maternal childhood maltreatment potentially representing a neural phenotype related to intergenerational exposure to maltreatment. The majority of the regions associated with stronger amygdala functional connectivity in the present study are part of the limbic system including the parahippocampus, temporal pole, and dorsal anterior cingulate cortex. Importantly, the association between stronger neonatal amygdala-dACC functional connectivity and maternal history of exposure to childhood maltreatment supports the findings of a recent study by Hendrix and colleagues (Hendrix et al., 2020). Alterations to the cuneus, fusiform, and occipital cortex; areas involved in the visual processing of faces, have also been previously associated with maltreatment (Cassiers et al., 2018; Edmiston & Blackford, 2013; Neukel et al., 2019; Puetz et al., 2016). The fact that these regions have been previously associated with exposure to childhood maltreatment suggests that they may be sensitive to environment influences such as stress. There is evidence that the fetal limbic system is responsive to physiological and biological stress mediators in utero (Graham et al., 2018; A Qiu et al., 2015; Rifkin-Graboi et al., 2015), representing a potential pathway for the intergenerational transmission of maternal childhood maltreatment.

Anterior Cingulate Cortex may Represent a Key Brain Region

The anterior cingulate cortex has been identified as a key region in studies of childhood maltreatment, early life stress, child and adult PTSD, and PTSD recovery and treatment responsiveness (Demers et al., 2015; Hamner, Lorberbaum, & George, 1999; Hart et al., 2018; Stevens et al., 2016; Teicher, Anderson, Ohashi, & Polcari, 2014; Teicher & Samson, 2016) suggesting that this region may be especially sensitive to biological mediators of psychological stress. The anterior cingulate cortex (ACC) is involved in emotional learning and regulation, expression of internal states, and the assignment of emotional valence to stimuli including fear acquisition and inhibition (Jovanovic et al., 2011; Palomero-Gallagher, Mohlberg, Zilles, & Vogt, 2008). In a review of 41 published studies on childhood maltreatment with brain morphological data, alterations to the ACC were the most consistently reported finding (Teicher & Samson, 2016). The most commonly observed alteration to this region is attenuated development and volume reduction potentially due to neuronal loss (Teicher & Samson, 2016; Thomaes et al., 2010). Previous studies further suggest that alterations to the structure and function of the anterior cingulate cortex are enduring and may reflect the additive effects of child maltreatment and adult trauma (Stevens et al., 2016). The ACC has also been identified as a potential biomarker for PTSD as well as a marker of resilience and PTSD treatment responsiveness (Stevens et al., 2016).

Additionally, there is also evidence that the developing ACC is sensitive to environmental stressors. Graham and colleagues found that higher inter-parental, non-physical conflict during pregnancy was associated with increased activation of the ACC in infants between 6 and 12 months of age when listening to angry vs. neutral voices

(Graham, Fisher, & Pfeifer, 2013). Similar to the present study, Hendrix and colleagues found that stronger amygdala-dACC functional connectivity in offspring at one month of age was related to a maternal history of emotional neglect during childhood after accounting for maternal stress during pregnancy, highlighting the importance of this region and its sensitivity to prenatal and preconceptional influences (Hendrix et al., 2020). Although we were not powered to examine the distinct contributions of different types of maltreatment exposure, the emotional neglect subscale had the highest mean score of all of the CTQ subscales within our sample, potentially influencing our findings. The long-lasting nature of alterations to the ACC, its role in HPA axis regulation (James P. Herman, Ostrander, Mueller, & Figueiredo, 2005), and its responsiveness to environmental influences make it a key region for consideration when evaluating the question of intergenerational transmission of maltreatment. Given the ACC's potential as a risk and resiliency marker for trauma-related psychopathology, it is especially important to consider how alterations to this brain region beginning during the fetal period may affect an infant's sensitivity and responsiveness to early life stress.

Maternal Childhood Maltreatment Exposure, Attachment Security, and the Anterior Cingulate Cortex

Mothers with a history of childhood maltreatment are at a greater risk of having difficulties forming secure attachments with their infants (Khan & Renk, 2018). Maternal-infant interactions and attachment security have also been shown to differ by maltreatment type. Emotional neglect and physical abuse have been associated with reduced maternal sensitivity (Pereira et al., 2012). Physical abuse has also been

associated with more intrusive mothers (Riva Crugnola et al., 2019), and sexual abuse has been associated with higher levels of parental withdrawal (Lyons-Ruth & Block, 1996) and insecure attachment (Erozkan, 2016). Like many studies in this area, we did not find a direct association between maternal childhood maltreatment and infant attachment security (Vaillancourt, Pawlby, & Fearon, 2017). Studies on maternal childhood maltreatment, caregiving behavior, and infant attachment often report indirect or partial associations with maltreatment history highlighting the complexity of the factors involved in maternal and infant attachment behaviors (Vaillancourt et al., 2017).

The majority of studies focus on the effect of maternal maltreatment history on parenting behaviors and how the quality of parenting and associated behaviors influence maternal-infant attachment (Vaillancourt et al., 2017). We found that alterations to offspring amygdala-dACC functional connectivity mediated the association between maternal childhood maltreatment history and attachment security. The role of the anterior cingulate cortex as a neural correlate of attachment has been previously reported. Zhang and colleagues (2018) found that attachment anxiety was associated with decreased regional ACC volume (Xing Zhang et al., 2018) and functional connectivity studies in women have demonstrated an association between stronger ACC activation and avoidant attachment styles (Vrtička, Bondolfi, Sander, & Vuilleumier, 2012; Vrtička et al., 2014). In the present study, we found that stronger amygdala-dACC functional connectivity in offspring was associated with insecure attachment, which includes avoidant attachment styles. Given that attachment is by nature dyadic, it is likely that the brain regions associated with attachment in adults are also reflected in infants.

In the present study, stronger amygdala to dACC functional connectivity was associated with insecure attachment in the offspring of mothers with a history childhood maltreatment. This association suggests a potential prenatal, instead of postnatal, role for maternal childhood maltreatment in infant attachment security and adds to the growing literature demonstrating prenatal influences on offspring behavior. It also suggests the need to consider how earlier, prenatal influences, might affect later attachment security through the developmental programming of brain function in regions relevant to social development and attachment.

One potential mechanism for the intergenerational transmission of childhood maltreatment is via stress-sensitive aspects of maternal-placental-fetal biology. Like other regions that make up the limbic system, the ACC is sensitive to stress, particularly given its role in the regulation of autonomic and endocrine function (Palomero-Gallagher et al., 2008). Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is an enduring effect of childhood maltreatment (Gonzalez, 2013). Additionally, the HPA axis changes dramatically during pregnancy resulting in elevated levels of circulating cortisol that can overcome the placenta's protective barrier and influence fetal development (Duthie & Reynolds, 2013). Evidence suggests that maternal HPA axis dysregulation alters the fetal HPA axis (Duthie & Reynolds, 2013), which may explain the observed alterations to amygdala-dACC functional connectivity.

While cortisol response is known to be altered in the setting of childhood maltreatment (Buss et al., 2017; Gerritsen et al., 2017; Tarullo & Gunnar, 2006; Van Voorhees & Scarpa, 2004; Yehuda & Meaney, 2018; Yehuda & Seckl, 2011) and has been shown to be altered in the setting of maternal stress during pregnancy (Schepanski

et al., 2018), the influence of maternal exposure to maltreatment during childhood on offspring cortisol response is less clear. Previous studies have identified both the presence (Ben-Dat Fisher et al., 2007; Brand et al., 2010) and lack (Köhler-Dauner et al., 2019; Martinez-Torteya et al., 2014) of an association between maternal history of childhood maltreatment and infant cortisol response. O'Connor and colleagues found that higher levels of cortisol in the amniotic fluid at 17 weeks gestation were associated with higher baseline cortisol levels in infants and a blunted response to the Strange Situation Paradigm (O'Connor, 2013). It is possible that the severity of maternal childhood maltreatment, which is related to maternal HPA axis dysregulation (Alink, Cicchetti, Kim, & Rogosch, 2012) influences whether there is intergenerational effect. Another possibility is that the quality of maternal interactions in response to infant stress, which is more proximal than the history of maternal childhood maltreatment, plays a stronger role in infant cortisol reactivity. This is supported by the work of Kohler-Dauner et al (2019), which found that maternal interacting quality, and not maternal history of childhood maltreatment, better predicted infant cortisol reactivity in response to the SSP (Köhler-Dauner et al., 2019).

Limitations and additional considerations

There are several limitations to consider. First, maternal childhood maltreatment was assessed retrospectively using a self-report measure, which could be influenced by event recall and reporting as well as a desire for non-disclosure. Previous studies suggest that mood at the time of assessment and awareness or denial of the events can also affect reporting (Hardt & Rutter, 2004). Self-reported rates of childhood maltreatment are

generally lower than research-defined rates of maltreatment (Silvern, Waelde, Baughan, Karyl, & Kaersvang, 2000) suggesting that the results presented here would most likely reflect under-reporting. Similarly, depression was assessed by self-report and not by a diagnostic interview, which is in line with how it is assessed in clinical settings during routine antenatal and postnatal care. Second, our sample size is small which limits our ability to test the role of specific types of childhood maltreatment on offspring brain and biobehavioral outcomes. The type, timing, chronicity, and allostatic load of childhood maltreatment is associated with differential alterations to brain structure (Herzog et al., 2020; Teicher et al., 2018) and function (Teicher, Samson, Anderson, & Ohashi, 2016), and divergent behavioral outcomes (Hahm, Lee, Ozonoff, & van Wert, 2010; Savage et al., 2019). As described above, different types of maternal childhood maltreatment have been associated with specific attachment styles. Future studies are needed to better characterize the distinct contributions of different types of maternal childhood maltreatment on infant attachment security. Additionally, our cohort was not enriched for a history of maternal exposure to maltreatment during childhood, which must be considered when comparing to other studies. Although the rates of childhood maltreatment were low, the prevalence in our cohort is similar to that of several large, population-based samples suggesting that the results may generalize to community samples (Gerdner & Allgulander, 2009; Walker et al., 1999).

The follow-up behavioral analyses in the present study focused on resting state functional connectivity between the amygdala and a single region of interest, the dACC. Attachment and cortisol reactivity involve multiple brain regions and networks beyond those explored in the present study. Additionally, amygdala functional connectivity

clusters identified in the whole-brain analysis as being associated with a maternal history of childhood maltreatment were not fully explored in the present study to reduce multiple comparisons. Future work is needed to gain a more comprehensive understanding of how maternal childhood maltreatment relates to the functional organization of the neonatal brain. The amygdala and ACC are comprised of multiple subregions that were not examined in the present study (G. Bush, Luu, & Posner, 2000; LeDoux, 2007; Rosell & Siever, 2015; Sah, Faber, De Armentia, & Power, 2003; Shenhav, Cohen, & Botvinick, 2016). These subregions are functionally and structurally heterogeneous and demonstrate differential responsivity to stress (Nogovitsyn et al., 2020; Oshri et al., 2019; Veer et al., 2015). Thus, it is likely that specific subregions will have distinct associations with a history of maternal childhood maltreatment and offspring behavioral outcomes. Rs-fcMRI reference atlases that define amygdala subregions have been used in studies of infants and children. However, they are currently based on adult cytoarchitectural patterns (K. Amunts et al., 2005; Katrin Amunts, Mohlberg, Bludau, & Zilles, 2020) and may not accurately reflect the relative proportion of amygdala subregions in children and neonates (Kim et al., 2010). Future work is needed to elucidate the association between alterations to amygdala and ACC subregions associated with a history of childhood maltreatment and the potential relevance for neonatal functional connectivity and child behavioral outcomes. Finally, future studies with larger study cohorts should explore the potential role of sex in mediating infant cortisol reactivity and amygdala-dACC functional connectivity.

3.6 Conclusions

The results of this study suggest a neural phenotype related to a maternal history of childhood maltreatment. The findings further suggest that the intrauterine period is important for the intergenerational transmission of the effects of maternal childhood maltreatment, even in a cohort with relatively low rates of reported childhood maltreatment. Given the role of the ACC as a potential biomarker for both risk and resilience and its clear sensitivity to environmental influences, it is imperative to explore how prenatal interventions can best support maternal and infant mental health.

3.7 Supplemental Materials

Missing data analysis

All missing data analysis was completed using IBM SPSS Statistics 25 (IBM Corp., 2017) and compared excluded subjects to subjects included in the imaging cohort (n=64).

Full Sample

The 67 mother-infant dyads not included in the imaging cohort data did not differ significantly from those included by maternal age (F=1.742, p=0.189), infant gestational age at birth (F=0.228, p=0.634), infant age at MRI scan (F=1.949, p=0.167), infant sex (p=1.000, Fischer's exact test, 2-sided), race/ethnicity ($\chi 2(8)=5.715$, p=0.679), level of maternal education ($\chi 2(7)=7.200$, p=0.408), annual income ($\chi 2(4)=1.080$, p=0.897), obstetric risk ($\chi 2(2)=2.171$, p=0.338), total CTQ score (F=0.739, p=0.392), mean maternal depression during pregnancy (F=2.327, p=0.130), or mean postnatal depression through 12 months of infant age (F=0.306, p=0.392), see **Table 3.6.**

Table 3.6. Demographic data for mother-infant dyads included and excluded from the imaging sample.

	Full Sample (n=67) Mean (SD)	**Imaging Sample (n=64) Mean (SD)**
Maternal age in first trimester, Years	27.28 (5.35) n=67	28.53 (5.23)
Infant Age		
Gestational age at birth, Weeks	39.19 (1.41) n=66	39.19 (1.50)
Age at functional MRI data collection, Days	23.71 (12.13) n=31	26.48 (11.43)
Infant Sex	**No. (%)**	**No. (%)**
Male	37 (56)	34 (53)
Female	29 (44)	30 (47)
Race/Ethnicity	**(N=66)**	**(n=60)**
Caucasian non-Hispanic	24 (36)	27 (45)
African American non-Hispanic	1 (2)	1 (2)
Asian non-Hispanic	3 (5)	5 (8)
Multi-racial non-Hispanic	5 (7)	5 (8)
Caucasian Hispanic	30 (45)	17 (28)
Asian Hispanic	1 (2)	1 (2)
Multi-racial Hispanic	2 (3)	4 (7)
Highest Level of Maternal Education	**(n=67)**	**(n=60)**
Primary, elementary, or middle school	4 (6)	1 (2)
High school or test equivalent	9 (13)	9 (15)
Vocational school or some college	31 (46)	30 (50)
Associates degree	4 (6)	2 (3)
Bachelors or graduate level degree	19 (28)	18 (30)
Gross Annual Household Income	**(n=63)**	**(n=60)**
< $15,000	7 (11)	6 (10)
$15,000 - 29,999	11 (18)	13 (21)
$30,000 - 49,999	14 (22)	15 (24)
$50,000 - 100,000	22 (35)	23 (37)
> $100,000	9 (14)	5 (8)

Attachment

The 12 mother-infant dyads without attachment classification did not differ significantly from those included by maternal age (F=0.021, p=0.886), infant gestational age at birth (F=2.150, p=0.148), infant age at MRI scan (F=2.234, p=0.140), infant sex (p=1.000, Fischer's exact test, 2-sided), race/ethnicity ($\chi 2(7)=3.860$, p=0.696), level of maternal education ($\chi 2(7)=9.760$, p=0.203), annual income ($\chi 2(4)=4.667$, p=0.323), obstetric risk ($\chi 2(2)=2.615$, p=0.270), total CTQ score (F=0.097, p=0.756), mean maternal depression during pregnancy (F=0.333, p=0.566), or mean postnatal depression through 12 months of infant age (F=0.282, p=0.597), see **Table 3.7**.

Table 3.7. Comparison of demographics for sample with and without attachment classification.

	With Attachment Data (n=52) Mean (SD)	Without Attachment Data (n=12) Mean (SD)
Maternal age in first trimester, Years	28.58 (5.23)	28.33 (5.42)
Infant Age		
Gestational age at birth, Weeks	39.32 (1.45)	38.62 (1.67)
Age at functional MRI data collection, Days	27.50 (11.25)	22.08 (11.63)
Infant Sex	**No. (%)**	**No. (%)**
Male	28 (53)	6 (50)
Female	24 (47)	6 (50)
Race/Ethnicity (n=60)		
Caucasian non-Hispanic	21 (41)	6 (67)
African American non-Hispanic	1 (2)	0
Asian non-Hispanic	5 (10)	0
Multi-racial non-Hispanic	4 (8)	1 (11)
Caucasian Hispanic	16 (31)	1 (11)
Asian Hispanic	1 (2)	0
Multi-racial Hispanic	3 (6)	1 (11)
Highest Level of Maternal Education (n=60)		
Primary, elementary, or middle school	0	1 (11)
High school or test equivalent	9 (18)	0
Vocational school or some college	25 (48)	5 (56)
Associates degree	2 (4)	0
Bachelors or graduate level degree	15 (30)	3 (33)
Gross Annual Household Income (n=60)		
< $15,000	4 (8)	2 (17)
$15,000 - 29,999	9 (18)	4 (33)
$30,000 - 49,999	14 (28)	1 (8)
$50,000 - 100,000	18 (36)	5 (42)
> $100,000	5 (10)	0

Cortisol Reactivity

The 16 mother-infant dyads with missing cortisol reactivity data did not differ significantly from those included by maternal age (F=0.272, p=0.604), infant gestational age at birth (F=0.360, p=0.550), infant age at MRI scan (F=4.045, p=0.049), infant sex (p=0.405, Fischer's exact test, 2-sided), race/ethnicity ($\chi 2(7)=2.885$, p=0.823), level of maternal education ($\chi 2(7)=4.293$, p=0.745), annual income ($\chi 2(4)=5.584$, p=0.232), obstetric risk ($\chi 2(2)=0.756$, p=0.685), total CTQ score (F=0.047, p=0.829), mean maternal depression during pregnancy (F=3.343, p=0.072), or mean postnatal depression through 12 months of infant age (F=3.539, p=0.065). Infant age at MRI scan (F=4.045, p=0.049) differed significantly between groups. Infants with cortisol reactivity data were significantly older compared to those without reactivity data, see **Table 3.8**.

Table 3.8. Comparison of demographics for sample with and without cortisol reactivity data.

	With Cortisol Data (n=48) Mean (SD)	Without Cortisol Data (n=16) Mean (SD)
Maternal age in first trimester, Years	28.73 (5.04)	27.94 (5.87)
Infant Age		
Gestational age at birth, Weeks	39.25 (1.47)	38.99 (1.64)
Age at functional MRI data collection, Days	28.10 (11.61)	21.63 (9.62)
Infant Sex	**No. (%)**	**No. (%)**
Male	27 (56)	7 (44)
Female	21 (44)	9 (56)
Race/Ethnicity (n=60)		
Caucasian non-Hispanic	19 (42)	8 (53)
African American non-Hispanic	1 (2)	0
Asian non-Hispanic	5 (11)	0
Multi-racial non-Hispanic	4 (8)	1 (7)
Caucasian Hispanic	12 (27)	5 (33)
Asian Hispanic	1 (2)	0
Multi-racial Hispanic	3(7)	1 (7)
Highest Level of Maternal Education (n=60)		
Primary, elementary, or middle school	0	1 (7)
High school or test equivalent	7 (16)	2 (14)
Vocational school or some college	23 (51)	7 (45)
Associates degree	1 (2)	1 (7)
Bachelors or graduate level degree	14 (31)	4 (27)
Gross Annual Household Income (n=60)		
< $15,000	4 (8)	2 (17)
$15,000 - 29,999	9 (18)	4 (33)
$30,000 - 49,999	14 (28)	1 (8)
$50,000 - 100,000	18 (36)	5 (42)
> $100,000	5 (10)	0

Potential confounds relevant for neonatal brain and infant biobehavioral outcomes

Potential confounds relevant to neonatal brain development, infant attachment and cortisol reactivity were examined to determine whether any identified associations between a history of maternal childhood maltreatment and neonatal brain and biobehavioral outcomes could be better explained by other aspects of the prenatal or postnatal environment. These included annual household income, obstetric risk, infant sex, and maternal depression. Annual income was assessed during the first prenatal visit using standardized structured interviews. Income was initially captured as a categorical variable: Below $15,000; $15,000-29,999; $30,000-49,999; $50,000-100,000; and over $100,000. Obstetric risk includes the presence of major medical complications during pregnancy such as placenta abruption, preeclampsia, and gestational diabetes. Complications were identified through medical chart review and coded as a binary variable capturing the presence or absence of a risk factor. Maternal depression was assessed using the CESD, which was completed at early, mid, and late pregnancy; and at 1, 3, 6, 9, and 12 months of infant age.

Post hoc analyses were conducted with the correlation coefficients (r) representing the strength of amygdala connection to clusters identified in the whole-brain analyses. We first examined how LA-dACC functional connectivity (r) related to potential confounds using IBM SPSS Statistics 25.[26] Annual income (β= -0.047, p=0.720), obstetric risk (β= 0.053, p=0.680), infant sex (β= 0.022, p=0.860), and maternal depression during pregnancy (β= 0.004, p=0.975) were not significantly related to LA-dACC functional connectivity.

We examined the relationship between potential confounds and infant security at 12 months of age. Annual income (β= 0.025, p=0.861), infant sex (β= 0.106, p=0.453), maternal depression during pregnancy (β= 0.163, p=0.253), maternal postnatal depression over the first 12 months (β= 0.021, p=0.886), and maternal responsivity (β= 0.147, p=0.314) were not significantly related to infant attachment security at 12 months using a stepwise logistic regression model.

We examined the relationship between potential confounds and infant cortisol reactivity. Annual income (β= -0.191, p=0.198), obstetric risk (β= 0.139, p=0.340), infant sex (β= 0.161, p=0.246), and maternal depression during pregnancy (β= -0.117, p=0.442) were not significantly related to infant cortisol reactivity at 12 months.

CHAPTER 4. INTERGENERATIONAL EFFECT OF MATERNAL EXPOSURE TO CHILDHOOD MALTREATMENT AND ASSOCIATIONS WITH NEONATAL HIPPOCAMPAL FUNCTIONAL CONNECTIVITY

4.1 Abstract

Background: Childhood maltreatment, such as abuse or neglect, is a pervasive public health problem with devastating and lasting consequences for psychological well-being and overall health across the lifespan. Although previously thought to be limited to a single individual, the negative effects of childhood maltreatment may be transmitted across generations, increasing the risk for behavioral and psychiatric disorders in the offspring. An increased understanding of the mechanisms underlying intergenerational effects is important for the development of preventive interventions. The present study, therefore, aims to examine the associations between maternal childhood maltreatment and offspring hippocampal functional connectivity employing a study design that attempts to disentangle effects of the pre-versus postnatal environment. We employ a prospective study design examining maternal report of childhood maltreatment history in relation to offspring neonatal hippocampal functional connectivity.

Methods: Maternal CM history was assessed during pregnancy using the Childhood Trauma Questionnaire (CTQ) in 64 women. Shortly after birth (M=26.48 ± 11.43 days), their offspring underwent a resting state functional connectivity (rsFC) MRI scan during natural sleep. A whole-brain voxel-wise regression model was performed with the log of

the total CTQ score predicting offspring hippocampal functional connectivity. The template matching approach was used to empirically segment the hippocampus in a large adolescent cohort and the resulting subregions were applied to infant hippocampi. The resulting hippocampal subregions in infants and their association with a maternal history of childhood maltreatment were examined.

Results: Neonates of mothers with a history of childhood maltreatment showed stronger hippocampal functional connectivity to the primary visual cortex, dorsomedial prefrontal cortex, and multiple regions associated with the default mode network; and weaker connectivity to the orbitofrontal cortex, ventromedial prefrontal cortex, parahippocampus, cuneus, and insula. Using the template matching approach to empirically segment the hippocampus in a large adolescent sample, we identified a bilateral posterior hippocampal cluster. We applied this posterior hippocampal cluster to our infant cohort as a seed region and examined the association between maternal exposure to maltreatment during childhood and neonatal posterior hippocampal functional connectivity. There was no association between maternal history of childhood maltreatment and neonatal posterior hippocampal functional connectivity.

Conclusion: The results of this study suggest a neural phenotype related to a maternal history of childhood maltreatment. The findings further suggest that the intrauterine period is important for the intergenerational transmission of the effects of maternal childhood maltreatment, even in a cohort with relatively low rates of reported childhood maltreatment.

4.2 Introduction

Maternal exposure to maltreatment during childhood is associated with psychopathology during pregnancy (Barrios et al., 2015; Bouvette-Turcot et al., 2017; Choi et al., 2015; Gartland et al., 2016; Lang & Gartstein, 2018; Lara et al., 2015; Mcdonnell & Valentino, 2016; Mezey et al., 2005; River et al., 2019; Robertson-Blackmore et al., 2013; J. S. Seng et al., 2009, 2013), and increased severity of PTSD and depression symptoms (River et al., 2019). Although the existing paradigm posits that maternal exposure to maltreatment during childhood is transmitted to the next generation through the postnatal environment, there is growing evidence that the negative effects of maternal childhood maltreatment may be transmitted during pregnancy through maternal-placental-fetal biology (Buss et al., 2017). One of the long-lasting effects of childhood maltreatment is hypothalamic-pituitary-adrenal (HPA) axis dysregulation (Buss et al., 2017; Tarullo & Gunnar, 2006; Van Voorhees & Scarpa, 2004), which may be transmitted through gestational biology affecting stress-sensitive structures of the fetal brain. Moog and colleagues found that maternal exposure to maltreatment during childhood was associated with an increase in placental cortiocotropin-release hormone (CRH) production demonstrating HPA axis dysregulation during pregnancy (Moog et al., 2016).

The sensitivity of the hippocampus to stress exposure has been well established in animal models (Tottenham & Sheridan, 2009). Human studies also demonstrate consistent associations between early life adversity, particularly childhood maltreatment, and the hippocampus (Dahmen et al., 2018; Riem, Alink, Out, Van Ijzendoorn, & Bakermans-Kranenburg, 2015). Decreased hippocampal volumes have been associated

with early life stress (Dahmen et al., 2018), childhood maltreatment (Riem et al., 2015), and psychiatric disorders such as depression (Barch et al., 2019; McKinnon, Yucel, Nazarov, & MacQueen, 2009; M. A. O. Santos, Bezerra, Carvalho, & Brainer-Lima, 2018; Schmaal et al., 2016), and post-traumatic stress disorder (PTSD) (Bromis, Calem, Reinders, Williams, & Kempton, 2018; O'Doherty, Chitty, Saddiqui, Bennett, & Lagopoulos, 2015; Szeszko, Lehrner, & Yehuda, 2018). The vulnerability of the hippocampus to stress is expected given the high density of glucocorticoid receptors (Herzog et al., 2020), and its role in HPA axis regulation (Jankord & Herman, 2008). There is growing evidence that prenatal, and even preconceptional, events can affect the development of stress-sensitive regions of the developing fetal brain (Buss, Davis, et al., 2012; Davis et al., 2013; Pallarés & Antonelli, 2017; A Qiu et al., 2013; Anqi Qiu et al., 2017; Rifkin-Graboi et al., 2013; Wen et al., 2017). Hippocampal neurogenesis begins during the first trimester of pregnancy and continues through birth (Hodel, 2018), which means that the developing fetal hippocampi are exposed to potential mediators of maternal stress for most of the prenatal period. Several studies have shown that maternal stress during pregnancy is associated with decreased offspring hippocampal volumes (A Qiu et al., 2013; Anqi Qiu et al., 2017; Wu et al., 2020) and altered functional connectivity (Scheinost, Spann, McDonough, Peterson, & Monk, 2020). Given that alterations in hippocampal volume and connectivity can be observed shortly after birth, this effect may originate during fetal development, reflecting a potential pathway for the intergenerational transmission of childhood maltreatment.

In addition to being highly responsive to stress, there is a wealth of evidence from both animal and human studies demonstrating that the hippocampus is functionally and

structurally heterogeneous. The posterior hippocampus is connected to the neocortex and is associated with cognitive functions, spatial learning and memory, and reward processing (Chase et al., 2015; Goosens, 2011; Sheldon, McAndrews, Pruessner, & Moscovitch, 2016). Gene expression in this region is associated with information processing in cortical regions (Fanselow & Dong, 2010). The anterior hippocampus is directly connected to subcortical structures, including the amygdala, and is associated with regulating, processing, and responding to emotions and stress, context coding, and autobiographical memory representations (Chase et al., 2015; Decker, Duncan, Finn, & Mabbott, 2020; Goosens, 2011; Nadel, Hoscheidt, & Ryan, 2013; Sheldon et al., 2016). Lesions to the anterior hippocampus have been shown to decrease social anxiety, impair fear, and reduce freezing after fear conditioning (Goosens, 2011). In resting-state functional connectivity studies, the anterior hippocampus demonstrates stronger connectivity to the orbitofrontal and temporal cortex (Goosens, 2011), as well as a stronger association with the default mode network (Chase et al., 2015). The differential functional connectivity patterns of the anterior and posterior hippocampus are especially evident in studies of anxiety. Using the State Trait Anxiety Inventory, Satpute and colleagues (2012) found that state anxiety was more strongly associated with the anterior hippocampus, while trait anxiety was more strongly associated with the posterior hippocampus (Satpute, Mumford, Naliboff, & Poldrack, 2012). Studies of individuals with post-traumatic stress disorder (PTSD) also demonstrate differences in posterior hippocampal functional connectivity (Lazarov, Zhu, Suarez-Jimenez, Rutherford, & Neria, 2017; Malivoire, Girard, Patel, & Monson, 2018). The clear evidence of structural and functional differences between the anterior and posterior hippocampus supports the

need for a more specialized approach when examining the role of the hippocampus in studies of functional connectivity.

Emerging evidence indicates the importance of considering these distinct subregions in order to better understand the effects of early adversity and childhood maltreatment. In a recent study by Wang and colleagues (2019) looking at the functional connectivity of both the anterior and posterior hippocampus, maternal sensitivity at 6 months of infant age was associated with anterior hippocampus functional connectivity at 4 and 6 years of age, and there was no association with posterior hippocampal functional connectivity (Q. Wang et al., 2019). The heterogeneity of the hippocampus as evidenced by the structural and functional diversity of the subregions may explain why many studies have reported null effects when looking at the hippocampus as a whole (Buss, Davis, et al., 2012). It is possible that the effects of maternal stress during pregnancy on the developing hippocampus are partially masked in studies looking at the hippocampus as a whole. Failure to capture the distinct effects of maternal stress or exposure to childhood maltreatment on hippocampal subregions will make it difficult to truly characterize their unique associations with offspring biobehavioral outcomes and subsequent psychopathology.

Advances in neuroimaging techniques are increasing the capacity to differentiate hippocampal subregions empirically. There is evidence that the major adult network functional components are already present during infancy (Blankenship, Redcay, Dougherty, & Riggins, 2017; Damaraju et al., 2014; De Asis-Cruz et al., 2015; Emerson et al., 2016; Fransson et al., 2011, 2009, 2007; W. Gao et al., 2017; Wei Gao, Alcauter, Elton, et al., 2015; Wei Gao, Alcauter, Smith, et al., 2015; Grayson & Fair, 2017;

Grayson et al., 2014; Jakab et al., 2014; Keunen et al., 2017; Scheinost et al., 2017; H. Zhang et al., 2019). Therefore, it is possible to apply advanced neuroimaging techniques based on functional networks from adolescents and adults populations to infants. This creates a unique opportunity to leverage large existing datasets available for older populations and to employ advanced brain mapping methods to understand the functional organization of the brain. One exciting advanced method is template matching developed by Gordon and colleagues (Gordon et al., 2016). Template matching compares the whole-brain connectivity of each grayordinate to a series of group network templates in order to assign that grayordinate to a network (Gordon et al., 2016). Importantly, this method provides an empirical approach for the identification of subregions based on their participation in large scale brain systems based on a large adolescent cohort.

In the present study, we examine neonatal hippocampal functional connectivity in relation to a history of maternal exposure to maltreatment during childhood. Next, we leverage the template matching approach to empirically segment the hippocampus in a large adolescent cohort. Finally, we examine the resulting hippocampal subregions in infants and their association with a maternal history of childhood maltreatment. Examining the functional connectivity of hippocampal subregions in infants will allow us to better investigate the granular mechanistic role of these subregions and their potential role in risk or sensitivity to future psychopathology.

4.3 Methods and Materials

Participants

Infant Cohort

Mother-infant dyads (n=64) enrolled as part of a prospective longitudinal cohort conducted at the University of California, Irvine (UCI) were recruited through prenatal clinics during early pregnancy from February 2011 to November 2018; for details see (Moog et al., 2018). Exclusionary criteria included use of psychotropic medications or systemic corticosteroids during pregnancy, premature birth (before 34 weeks' gestation), and infant genetic, congenital, or neurological disorder (Graham et al., 2018). All procedures were approved by the Institutional Review Board at the University of California, Irvine. For detailed demographic data, see **Table 4.1.**

Table 4.1. Demographic data for University of California, Irvine cohort (n=64).

	Mean (SD) (n=64)
Maternal age in first trimester, Years	28.53 (5.23)
Infant Age	
Gestational age at birth, Weeks	39.19 (1.50)
Age at functional MRI data collection, Days	26.48 (11.43)
Infant Sex	**No. (%)**
Male	34 (53)
Female	30 (47)
Race/Ethnicity	**(n=60)**
Caucasian non-Hispanic	27 (45)
African American non-Hispanic	1 (2)
Asian non-Hispanic	5 (8)
Multi-racial non-Hispanic	5 (8)
Caucasian Hispanic	17 (28)
Asian Hispanic	1 (2)
Multi-racial Hispanic	4 (7)
Highest Level of Maternal Education	**(n=60)**
Primary, elementary, or middle school	1 (2)
High school or test equivalent	9 (15)
Vocational school or some college	30 (50)
Associates degree	2 (3)
Bachelors or graduate level degree	18 (30)
Gross Annual Household Income	**(n=60)**
< $15,000	6 (10)
$15,000 - 29,999	13 (21)
$30,000 - 49,999	15 (24)
$50,000 - 100,000	23 (37)
> $100,000	5 (8)

Maternal Psychological Measures

Maternal childhood maltreatment history was assessed in mid-pregnancy using the Childhood Trauma Questionnaire (CTQ) (D P Bernstein et al., 1994). The CTQ is a standardized, retrospective self-report tool that assesses five domains of childhood maltreatment: physical, sexual, and emotional abuse; and physical and emotional neglect. It is a 28-item questionnaire with 3 items making up an additional Minimization/Denial

scale designed to capture potential under-reporting (Villano et al., 2004). Each item within the five maltreatment domains is scored on a 5 point scale where 1 = never and 5 = very often. The total CTQ score is a sum score of all maltreatment domains (range 25 – 125). In the present study, the total CTQ score was log-transformed to normalize the distribution of the data and used as the principal predictor in statistical analyses. Mothers completed the Center for Epidemiological Studies Depression Scale (CESD) (Radloff, 1977) in early, mid, and late pregnancy.

Adolescent Cohort

Children from 9 to 10 years of age through adolescence were recruited as part of the Adolescent Brain Cognitive Development (ABCD) study, a longitudinal on brain development; for details see (Casey et al., 2018). Demographic data are presented in **Table 4.2**.

Table 4.2. Demographic data for Adolescent Cohort.

	Group 1 Mean (SD) (N=2995)	**Template Group Mean (SD) (N=161)**
Age (in months)	119.64 (7.48)	118.37 (7.73)
Grade level	4.27 (0.78)	4.20 (0.76)
Highest parent education	17.38 (2.85)	16.83 (2.90)
Combined income (in thousands).	7.51 (2.24)	7.08 (2.35)

	Group 1 (N=2995) N (%)	**Template Group (N=161) N (%)**
# Female*	1411 (47.10)	78 (48.45)
Anesthesia exposure	966 (32.2)	42 (26.1)
Right handed	2401 (80.2)	136 (84.5)
Race/Ethnicity		
White	2399 (80.10)	106 (65.84)
Black	539 (18.00)	30 (18.63)
American Indian/Alaska Native	94 (3.14)	4 (2.48)
Native Hawaiian/Pacific Islander	19 (0.63)	4 (2.48)
Asian	173 (5.78)	9 (5.59)
Other	143 (4.77)	21 (13.04)
Unknown	23 (0.77)	4 (2.48)
Latino/Latina	544 (18.16)	28 (17.39)

* Self-identified non-binary gender

MRI and fMRI Data Acquisition and Processing

Adolescent Cohort

The MRI data acquisition and processing are extensively described in (Casey et al., 2018). Methods will be briefly described here.

Data acquisition

Three-dimensional T1-weighted MRI (1mm isotropic, TR=(either 2500 or 6100 ms, TE=2-2.9 ms, 8^{o} flip angle, 256 x 256 FOV), T2-weighted MRI (1mm isotropic, TR=2500 or 3200ms, TE=60–565ms, variable flip angle, 256 x 256 FOV), and 1-2 runs of rs-fMRI (1mm isotropic, TR=800ms, TE=30, variable flip angle= 52^{o}, 216 x 216 FOV) , and a randomized order of Monetary inceptive delay, Stop Signal task, and emotional n-back tasks were obtained using Siemens, Philips, and GE 3T scanners. Sequences were harmonized across scanners. Resting-state functional connectivity magnetic resonance images (MRI) were obtained using a gradient-echo, echoplanar imaging sequence sensitive to blood oxygen level-dependent contrast (TR =800 ms, TE =30 ms, flip angle = 90°, voxel size = 2.4 mm3, 60 slices). Head motion was monitored in real time using Framewise Integrated Real-time MRI Monitor (FIRMM) software at Siemens sites (Dosenbach et al., 2017). Participants were instructed to lie still and focus on a crosshair at the center of their visual field for the resting state scans.

fMRI Data Processing

All functional MRIs were processed using a modified version of the HCP processing pipeline that is publicly available ABCD-HCP pipeline (DCAN-Labs, 2020a). Following denoising and bias field correction of the anatomical T1 and/or T2 weighted images, brain extraction was performed by PreFreesurfer. ANTs DenoiseImage and ANTs N4BiasFeildCorrection (Advanced Normalization Tools) (Avants et al., 2009; Tustison et al., 2010) were applied to improve structural clarity and reduce field bias (Marek et al., 2019).

rs-fcMRI Processing

DCAN-BOLDproc (DCAN-Labs, 2020a) was used to correct time courses. These steps included resting state time course detrending and processing with mean whole brain, ventricle, and white matter signal as well as displacement on the 6 degrees of freedom, rigid body registration, and their derivatives (Ciric et al., 2017; Friston et al., 2000; Hermosillo et al., 2020; J. D. J. D. Power et al., 2014). Time courses were then filtered using a first order Butterworth band pass filter between 9 and 80 mHz backwards and forwards using MATLAB's *filtfilt* function (v2016-2018x The MathWorks, Cambridge, UK). To correct for motion, an examination of frame-wise displacement (FD) was conducted and volumes with greater than 0.2 mm FD plus the 5 contiguous volumes were removed. Only subjects with greater than 10 minutes of data post-motion correction were included.

Hippocampal Segmentation and Region of Interest

The hippocampi were segmented using FreeSurfer automated subcortical segmentation, which uses atlas-based probabilistic information on structure location (Filipek, Richelme, Kennedy, & Caviness, 1994; Glasser et al., 2013). The hippocampal segmentations derived from the Template Matching procedure in the adolescent cohort, described below, were extracted as a label and applied to each infant subject using cifti-parcellate. The resulting hippocampal segmentations, now applied to the infant cohort, were used as seed regions. These seed regions and the resting-state time series scans were used to calculate Pearson's correlation for all 91,282 grayordinates; for details see (Hermosillo et al., 2020).

Infant Cohort

Data Acquisition

Data were acquired at approximately one month of age (26.48 ± 11.43 days) during natural sleep. High-resolution T1-weighted (MP-RAGE TR = 2400 ms, inversion time = 1200 ms, echo time = 3.16 ms, flip angle = 8°, resolution = 1 x 1 x 1 mm, 6 min 18 secs) and T2-weighted (TR = 3200 ms, echo time = 255ms, resolution = 1 x 1 x 1 mm, 4 min 18 secs) images were obtained using a TIM Trio, Siemens medical System 3.0T scanner. Resting-state functional connectivity (rs-FC) magnetic resonance images (MRI) were obtained using a gradient-echo, echoplanar imaging (EPI) sequence sensitive to blood oxygen level-dependent (BOLD) contrast (TR = 2000 ms; TE = 30 ms; FOV = 220 x 220 x 160 mm; flip angle = 77°). Steady-state magnetization was assumed after 4 frames (8 ~ s).

fMRI Data Preprocessing

All functional MRIs were processed using a modified version of the HCP processing pipeline (DCAN-Labs, 2020b; Glasser et al., 2013). Several modifications were made to improve the segmentation and parcellation of neonatal images. ANTs DenoiseImage (Manjón et al., 2010) and N4BiasFieldCorrection (Tustison et al., 2010) were applied to model Rician scanner noise and bias field inhomogeneities respectively. Next, we performed a rigid body transform to AC-PC-align both T1w and T2w structural images to the neonate template from the NIH pediatric template (0- to 2-month age range; National Institutes of Health MRI Study of Normal Brain Development) (Almli et al., 2007). For brain extraction, a T2w nonlinear warp from atlas-space to native space was

performed to the binarized the NIH age-specific atlas in MNI space. A rigid body registration of the T2w to T1w image was used to convert the resulting T2w brain mask to a T1w brain mask. Following T1w masking, we have the initial skull-stripped T1w and T2w infant brain in native volume space. Extracted brains are refined by computing tissue classes in the T2w brain using the ANTs Atropos (Avants et al., 2011, 2009) algorithm and applying the GM/WM masks to the T1w brain. The masked T1w and T2w are then nonlinearly registered to the MNI infant atlas. Segmentation was completed based on the T1 with ANTS Joint Label Fusion (H. Wang et al., 2013) and employing 10 infant atlases with labeled brain regions, which had been refined through manual correction. Finally, the mean intensity of the resulting cortical white and grey matter labels were shifted to match the FreeSurfer adult atlas. This hyper-normalization procedure facilitates the use of HCP's FreeSurfer recon-all to generate white and pial surfaces necessary for surface-based analyses.

rs-fcMRI Preprocessing

DCAN-BOLDproc (DCAN-Labs, 2020a) was used to correct time courses. These steps included resting state time course detrending and processing with mean whole brain, ventricle, and white matter signal as well as displacement on the 6 degrees of freedom, rigid body registration, and their derivatives (Ciric et al., 2017; Friston et al., 2000; Hermosillo et al., 2020; J. D. J. D. Power et al., 2014). Time courses were then filtered using a first order Butterworth band pass filter between 9 and 80 mHz backwards and forwards using MATLAB's *filtfilt* function (MathWorks, n.d.). To correct for motion, an examination of frame-wise displacement (FD) was conducted and volumes with

greater than 0.3 mm FD plus the preceding volume and subsequent 3 volumes were removed. Following frame removal for motion, scan length was about 5.80 minutes (range: 4.23 – 6.40 minutes) with a remaining FD of 0.089 (range: 0.056-0.127).

Whole Hippocampus Segmentation

We focused on hippocampal connectivity due to prior work indicating the vulnerability of the hippocampus to early life stress exposure, beginning in the antenatal period (A Qiu et al., 2013; Anqi Qiu et al., 2017). In the infant cohort, individual hippocampal segmentation was performed using a multi-template, multi-modality based method that combined T1 and T2 weighted high-resolution images (J. Wang et al., 2014). Following anterior-posterior realignment, hippocampal segmentations were manually corrected using ITK-Snap (Yushkevich et al., 2006) as described in (Graham et al., 2019). For rs-fcMRI analyses, hippocampi were transformed to atlas space based on the previously computed atlas transformation (Graham et al., 2018).

Hippocampus Subregion Identification

The adolescent template was generated using a set of network parcellations that assigns each grayordinate to one of 14 functional networks based on the similarity of whole-brain connectivity the networks (Gordon et al., 2017). A seed reflecting each network was created by averaging the resting state data for all greyordinates contained within a given network. These network seed regions were next compared to the resting-state time series data and used to calculate Pearson's correlation for all 91,282 grayordinates; for details see (Hermosillo et al., 2020). The seed –based correlation

values were then averaged across subjects, for each network, resulting in a network vector that was averaged independently across subjects to generate seed-based network templates. The network templates were z-score transformed and thresholded at $Z \geq 1$.

Precision brain mapping was then implemented on all the subjects in group1 using the following technique. For each subject in the group1, a whole brain connectivity matrix was generated using the motion-censoring described above. The correlation matrix was then Z-scored within each cortical hemisphere and subcortex to normalize the signal-noise bias in connectivity between regions. Then for each greyordinate, whole-brain connectivity was examined, and each grayordinate was assigned to the network which it most strongly resembled (using the maximum η^2). Regions of networks that were smaller than 30 contiguous greyordinates were incorporated into neighboring networks starting with the largest networks first. After all adolescent subjects underwent this mapping procedure, probabilistic maps were generated for subjects in group1 by calculating the probability of observing a given network at each greyordinate. A minimal region size of 30 and a probability threshold of 80% was used for the probabilistic regions of interest. Within the hippocampus, only the posterior aspect showed consistent network concordance (>80%) and it was within the medial temporal network.

Potential confounders relevant for neonatal brain outcomes

Potential confounders relevant to neonatal brain development were examined to determine whether any identified associations between a history of maternal childhood maltreatment and neonatal brain outcomes could be better explained by other aspects of the prenatal environment. These included annual household income, obstetric risk, infant

sex, and maternal depression. Annual income was assessed during the first prenatal visit using standardized structured interviews. Income was initially captured as a categorical variable: Below $15,000; $15,000-29,999; $30,000-49,999; $50,000-100,000; and over $100,000. Obstetric risk includes the presence of major medical complications during pregnancy such as placenta abruption, preeclampsia, and gestational diabetes. Complications were identified through medical chart review and coded as a binary variable capturing the presence or absence of a risk factor. Maternal depression was assessed using the Center for Epidemiological Studies Depression (CESD), which was completed at early, mid, and late pregnancy.

Analyses

In all analyses, left and right hippocampi were examined separately because of the evidence for sexual dimorphism in the neonatal brain (Gilmore et al., 2007)and differences in the volume and structure of the hippocampus (Persson et al., 2014). The log-transformed total CTQ score served as the independent variable, infant gestational age at birth (GA), infant sex, and age at scan as covariates, and left and right hippocampal whole-brain voxelwise connectivity as the dependent variable in regression models using MPlus (Muthén & Muthén, 2017). The test statistic was spatially normalized across the brain using a z score-transformation. The estimates from the regression models were the inputs for a cluster-extent based thresholding procedure using PALM (“PALM/UserGuide - FslWiki,” n.d.). A threshold value of 3.1 was applied to the z-score statistic image. The extent of the cluster was used as the test statistic. Clusters of contiguous supra-threshold voxels were identified from the thresholded image and

ordered by size. A permutation test was conducted under the assumptions of Gaussian random field theory, where the z-score statistical map was shuffled and the largest identified cluster size was stored. A p-value was calculated for each cluster based on size using 1000 permutations as the null distribution. A threshold of 3.1 has been shown to be conservative enough to avoid excessive false positive rates (Eklund et al., 2016). Post hoc analyses were conducted with the correlation coefficients (r) representing the strength of hippocampal connection to clusters identified in the whole-brain analyses.

4.4 Results

Whole Hippocampal Connectivity is associated with a History of Maternal Childhood Maltreatment

Maternal childhood maltreatment was significantly associated with neonatal hippocampal connectivity, with different patterns of connectivity present for the left and right hippocampus. For the left hippocampus, higher CTQ scores were associated with stronger positive connectivity to the primary visual cortex and dorsal medial prefrontal cortex; and negative connectivity to the orbitofrontal cortex, parahippocampus, and cuneus (see **Table 4.3, Figure 4.1A**). For the right hippocampus, higher CTQ scores were associated with stronger positive connectivity to the lateral parietal cortex, posterior cingulate cortex and temporoparietal junction; and weaker connectivity to the insula and ventromedial prefrontal cortex (see **Table 4.3, Figure 4.1B**).

Table 4.3. Maternal childhood maltreatment history is associated with neonatal hippocampal connectivity. Regions are in ascending order based on cluster extent size. The Pearson correlation between the maternal log-transformed total CTQ score and the extracted connection between the hippocampus and each identified region was examined. The direction (positive or negative) is indicated for childhood maltreatment (CM) in the last column. All associations reached statistical significance.

Region	Hem	x	y	z	Cluster size	CM*
Left Hippocampus						
Primary visual cortex (V1)	L	-9	-80	-8	78	+
Parahippocampus	R	20	-14	-24	87	-
Orbitofrontal cortex	R	8	66	-8	113	-
Dorsal medial prefrontal cortex	R	6	26	40	154	+
Cuneus	R	7	-88	26	324	-
Right Hippocampus						
Lateral parietal cortex	R	47	-61	38	88	+
Insula	L	-34	-25	18	101	-
Ventromedial prefrontal cortex	R	5	63	-3	126	-
Temporoparietal junction	L	-51	-58	21	179	+
Posterior cingulate cortex	R	7	-53	28	190	+

* $p<0.01$ for all associations

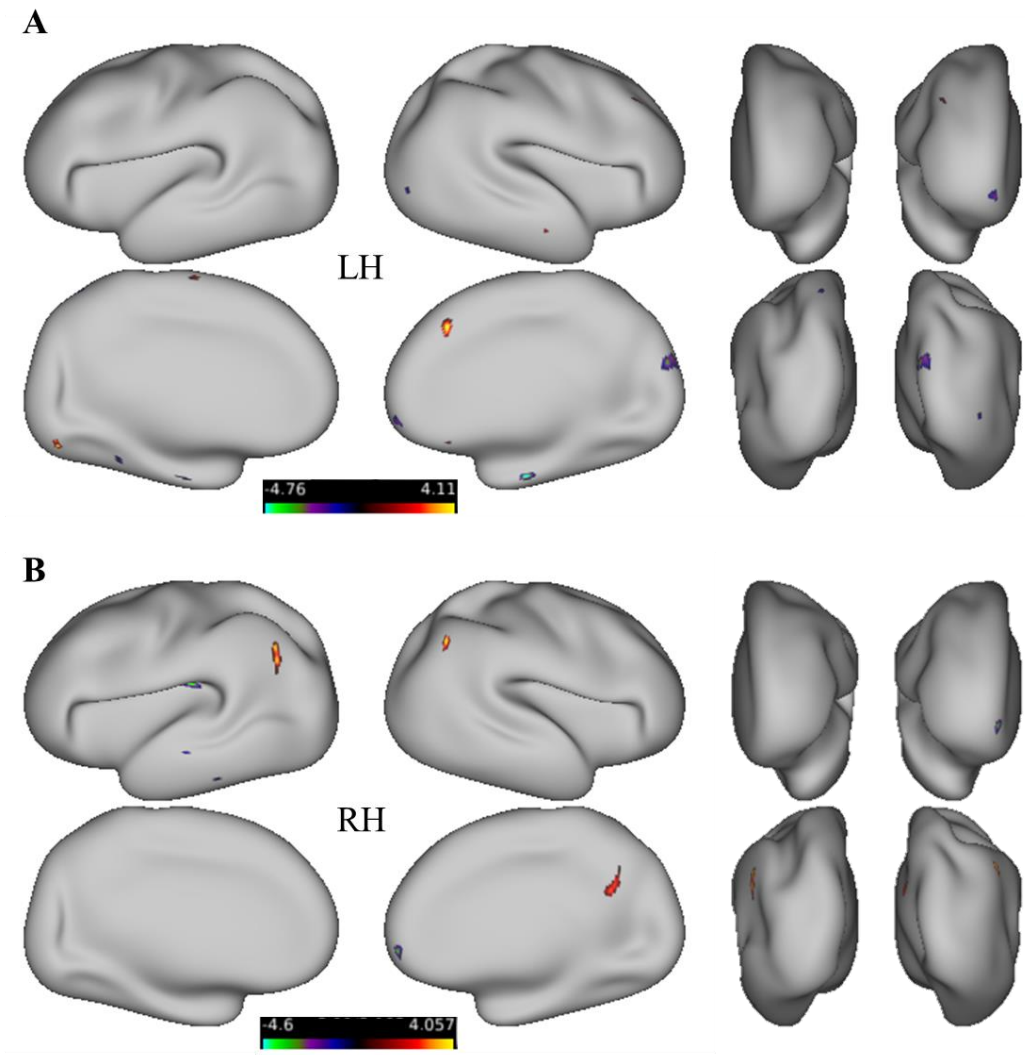

Figure 4.1. Left and right neonatal hippocampal functional connectivity. Results for left (A) and right (B) hippocampal whole-brain regressions are displayed here. The log of the total CTQ score was the independent variable and covariates for sex, gestational age at birth, and infant age at scan were included to account for neonatal brain maturity at the time of MRI scan acquisition. Z score-transformed estimates above a threshold of z= ± 3.1 are shown.

The effect of maternal childhood maltreatment remained significant for all identified hippocampal connections after adjusting for potential confounding covariates including maternal depression during pregnancy, annual income, and obstetric risk.

Template matching identified a posterior hippocampal subregion only

The template matching procedure resulted in a posterior hippocampal cluster (see **Figure 4.2**) at a probability mapping threshold of 80% across all participants in group 1 (n=2,995). This posterior cluster was associated with the medial temporal lobe (MTL) functional network (see **Figures 4.3 & 4.4**). The posterior hippocampal cluster was bilateral and the only hippocampal cluster identified (see **Figure 4.5**).

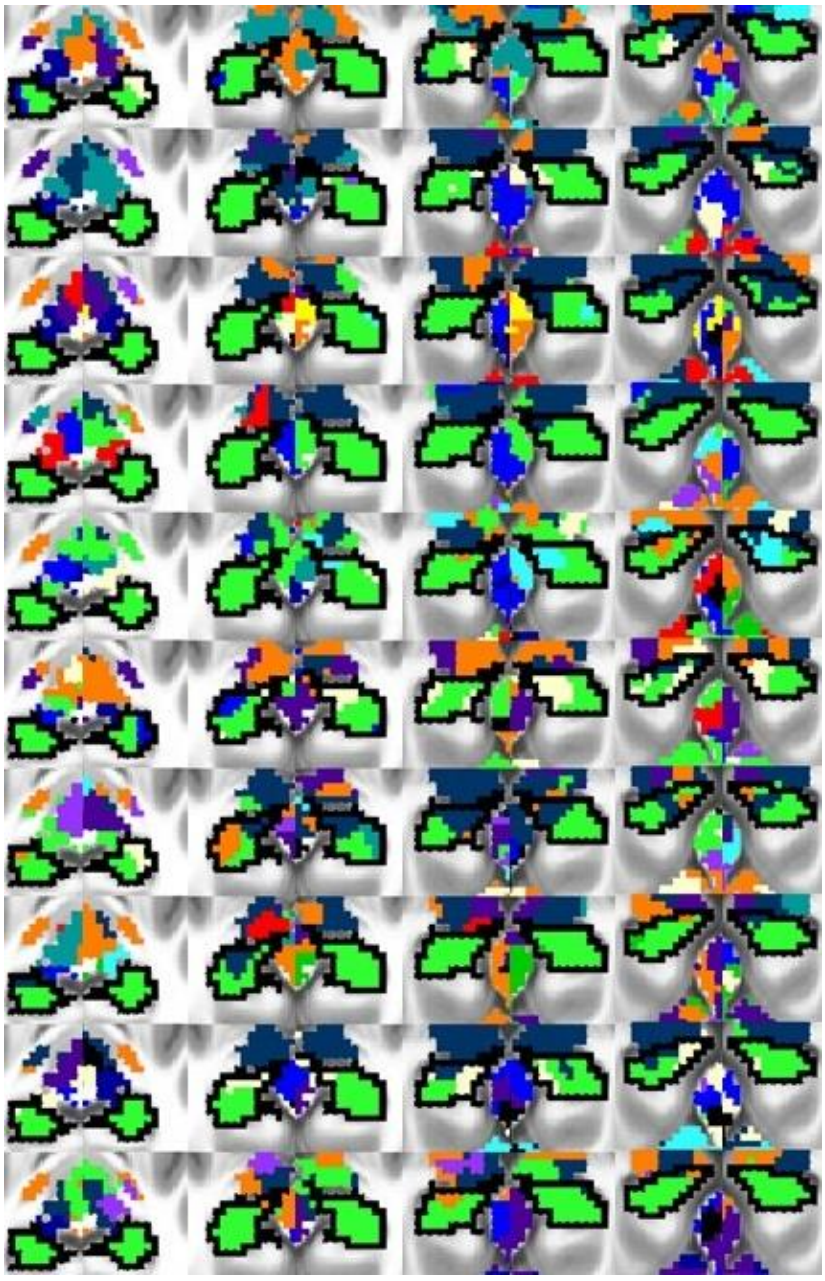

Figure 4.2. Individual hippocampi reflecting functional network participation. Individual hippocampi for subjects in the ABCD cohort are outlined in black. The colors represent the association of a given grayordinate with a functional network. The anterior hippocampus has several different associated colors representing heterogeneous network participation. The posterior hippocampus is consistently bright green, which is associated with the medial temporal network, reflecting functional homogeneity.

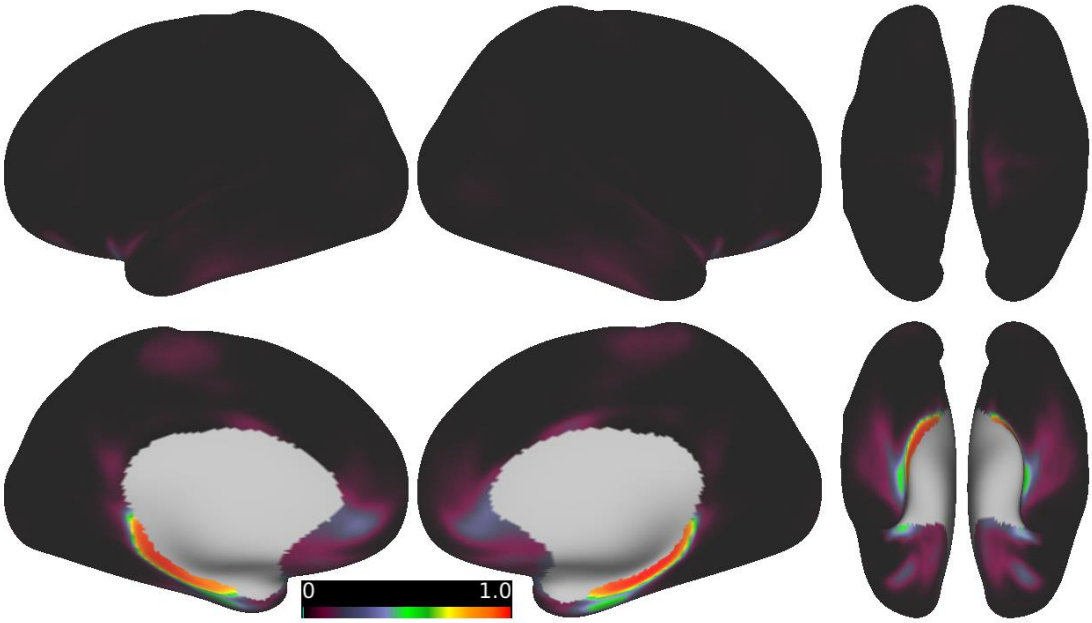

Figure 4.3. Medial temporal lobe surface probabilistic map. The probabilistic map for the medial temporal lobe (n=2,995) is shown on the surface of the brain. The colors represent probability values. Brighter colors reflect higher probability.

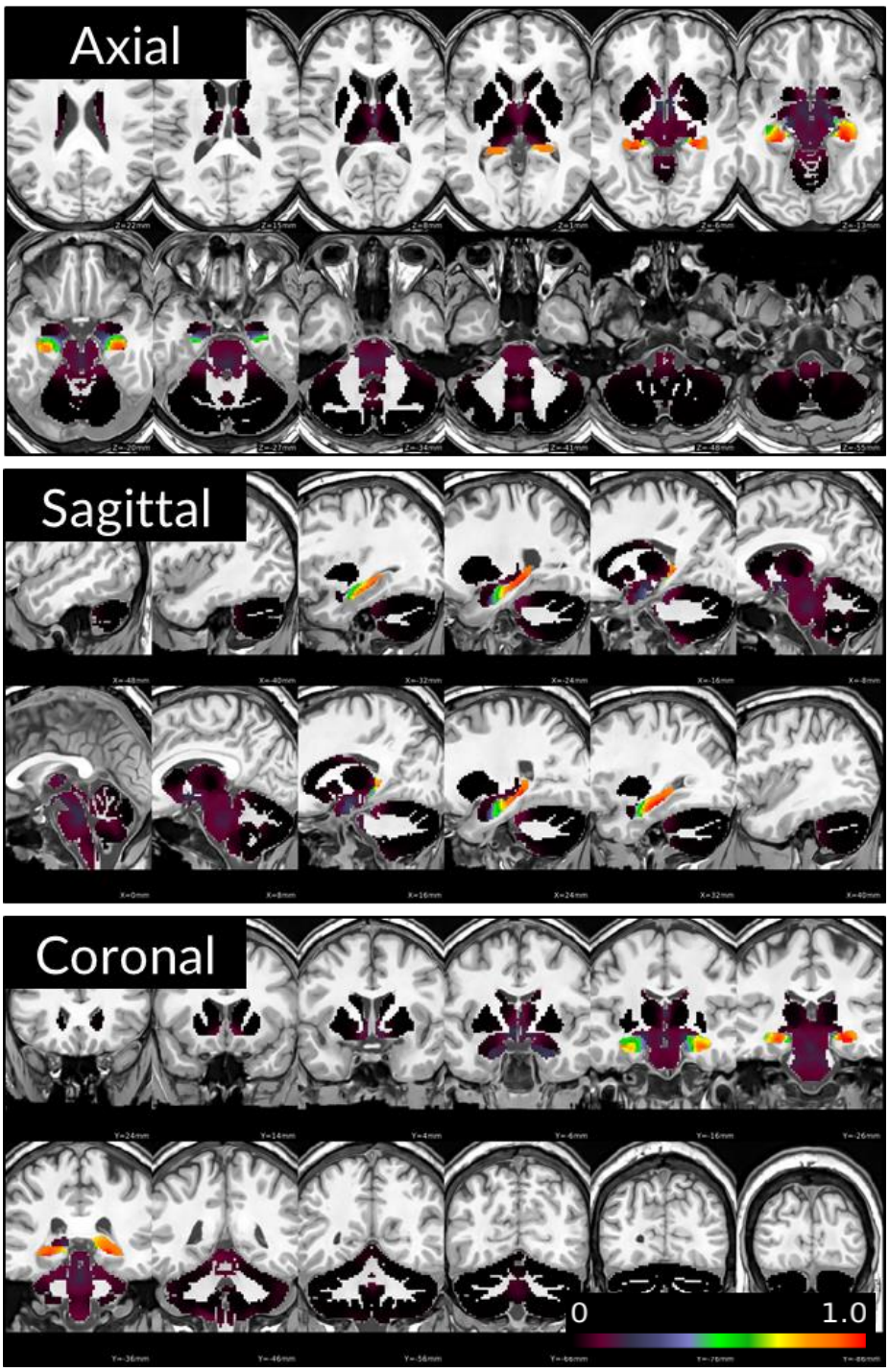

Figure 4.4. Medial temporal lobe volume probabilistic maps. The probabilistic map for the medial temporal lobe showing subcortical structures in three planes. The colors represent probability values. Brighter colors reflect higher probability.

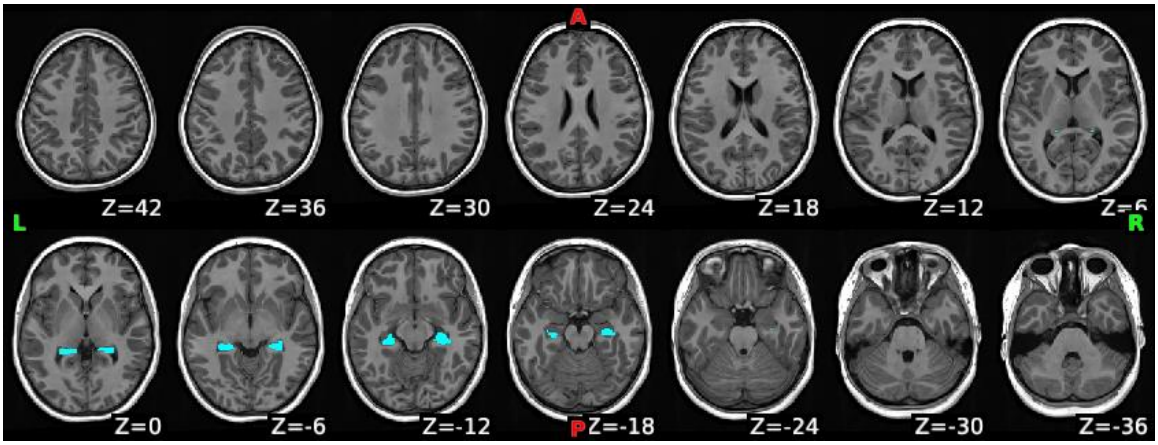

Figure 4.5. Posterior hippocampal cluster identified with template matching approach. The posterior hippocampus (shown in aqua) is based on the 80% probability map of Group 1 (n=2,995) compared to ABCD template group (n=161) and was the only cluster present in the hippocampus.

Posterior hippocampal Connectivity is not associated with a History of Maternal Childhood Maltreatment

Maternal childhood maltreatment was not significantly associated with neonatal posterior hippocampal connectivity. No significant brain associations were identified using the left and right posterior hippocampal clusters identified through the template matching procedure.

4.5 Discussion

In the current study, we found that maternal exposure to maltreatment during childhood was related to neonatal whole-brain hippocampal functional connectivity. Children of mothers with a history of childhood maltreatment showed stronger neonatal

hippocampal functional connectivity to the primary visual cortex, dorsomedial prefrontal cortex, and multiple regions associated with the default mode network; and weaker connectivity to the orbitofrontal cortex, ventromedial prefrontal cortex, parahippocampus, cuneus, and insula. Using the template matching approach to empirically segment the hippocampus in a large adolescent sample, we identified a bilateral posterior hippocampal cluster. We applied this posterior hippocampal cluster to our infant cohort as a seed region and examined the association between maternal exposure to maltreatment during childhood and neonatal posterior hippocampal functional connectivity. There was no association between maternal history of childhood maltreatment and neonatal posterior hippocampal functional connectivity.

Brain Regions and Networks Involved and Relation to Childhood Maltreatment

The results of this study reveal a pattern of altered hippocampal functional connectivity in association with a history of maternal exposure to maltreatment during childhood potentially representing an early neural phenotype. These finding are consistent with previous studies demonstrating an association between hippocampal connectivity and childhood maltreatment (Birn et al., 2013; Herringa et al., 2013; McLaughlin, Weissman, & Bitrán, 2019). More specifically, alterations to the cuneus, primary visual cortex, and occipital cortex; areas involved in the processing of visual information, have been associated with maltreatment (Aas et al., 2017; Teicher & Samson, 2016).

The posterior cingulate cortex, lateral parietal cortex, and temporoparietal junction are part of the default mode network (DMN) (Raichle et al., 2001; Rebello, Moura, Pinaya, Rohde, & Sato, 2018). A "proto-default network," which includes the lateral parietal cortex and posterior cingulate cortex, is observable in infancy (Fransson et al., 2011, 2009, 2007; Wei Gao, Alcauter, Elton, et al., 2015; Wei Gao, Alcauter, Smith, et al., 2015, 2015; Wei Gao et al., 2014, 2009; Graham, Pfeifer, Fisher, Carpenter, et al., 2015; Smyser et al., 2010). The DMN is also altered in the setting of childhood maltreatment (Philip et al., 2013; Teicher & Samson, 2016) and early life stress (Graham, Pfeifer, Fisher, Carpenter, et al., 2015). Graham and colleagues found that non-physical, interparental conflict during pregnancy was associated with stronger DMN functional connectivity during the first year of infant life (Graham, Pfeifer, Fisher, Carpenter, et al., 2015). These studies suggest that DMN is sensitive to environmental influences, including stress experienced by the mother during the prenatal period. In the present study, we found that a maternal history of exposure to childhood maltreatment was associated with increased offspring hippocampal integration into the DMN.

Many of the regions associated with altered hippocampal functional connectivity in the present study are part of the limbic system and prefrontal cortex, highly interconnected structures that include the orbitofrontal cortex, ventromedial prefrontal cortex, dorsomedial prefrontal cortex, parahippocampus, posterior cingulate cortex, and insula. The limbic system is not only important for emotion processing and memory, but is highly responsive to stress hormones due to the high concentration of glucocorticoid receptors in the hippocampus, amygdala, and prefrontal region (Graham et al., 2019; Herzog et al., 2020). Importantly, there is evidence that the fetal limbic system is

responsive to physiological and biological stress mediators in utero (Graham et al., 2018; A Qiu et al., 2015; Rifkin-Graboi et al., 2015) and that stress-related alterations to the developing brain are long-lasting (Blankenship, Botdorf, Riggins, & Dougherty, 2019), representing a potential pathway for the intergenerational transmission of maternal childhood maltreatment.

Anterior and Posterior Hippocampal are Heterogeneous

The template matching procedure only identified a posterior hippocampal cluster. Past studies segmenting the hippocampus in adults found that the anterior portion of the hippocampus was associated with weaker connectivity across multiple regions of interest and greater differences in signal and shape (Frank, Bowman, & Zeithamova, 2019), which might explain why a probability-based cluster was not identified in anterior hippocampus in the present study. While the anterior and posterior segmentation approach makes sense for infant studies, where brain regions are still growing rapidly and may be harder to segment more finely, adult studies of hippocampal segmentation using functional topography suggest three to six functional subregions (Robinson et al., 2015; Zhong et al., 2019). There is also evidence of variation in hippocampal anterior and posterior connectivity by age in adolescents. One study found that younger boys demonstrated greater posterior connections, while older boys and younger girls demonstrated greater anterior connections (Riley et al., 2018). Girls over 11 years of age showed weaker and widely distributed connectivity (Riley et al., 2018). Another study looking at changes in the hippocampus associated with development in preadolescent children found that the age-associated changes were strongest in girls (Lin et al., 2013).

In the present study, we performed the template matching procedures using resting-state functional connectivity scans from preadolescents and adolescents. The age-associated changes in the distribution of hippocampal connections during this age range may also explain why we were only able to identify a posterior cluster. Future studies should attempt the template matching approach using infant data given that the cortical connectivity of neonates is still highly variable at this age. Convolutional neural networks is another potential approach that has already been used to segment infant cortical and subcortical structures (Ding et al., 2020; G. G. Li, Chen, Li, Wu, Lian, et al., 2019). Convolutional neural networks can overcome some of the issues associated with the heterogeneity of the hippocampal functional subregions by building on both local and contextual information to segment structures (G. G. Li, Chen, Li, Wu, Lian, et al., 2019; G. G. Li, Chen, Li, Wu, Sun, et al., 2019; Zhu et al., 2019).

Anterior, not Posterior Hippocampus, is Usually Associated with Stress-Related Changes and Childhood Maltreatment

The identified posterior hippocampal cluster was not associated with maternal exposure to maltreatment during childhood. The posterior hippocampus is associated with cognitive functions, and spatial learning and memory; and may be less effected by stress. In fact, both animal and human studies suggest that the anterior hippocampus is more sensitive to stress than the posterior hippocampus. Studies of chronic stress in rodents demonstrate decreased neurogenesis resulting in reduced anterior hippocampal volume (Hawley, Morch, Christie, & Leasure, 2012; Szeszko et al., 2006), while studies of acute stress show distinct stress-related response patterns at the molecular level

(Floriou-Servou et al., 2018). Stress-associated volume reduction in the anterior hippocampus has also been demonstrated in human studies of stress and PTSD (Szeszko et al., 2006; Vythilingam et al., 2005) and early life stress has been associated with reduced anterior hippocampal to entorhinal cortex functional connectivity (Xu, Guan, Li, Zhang, & Xu, 2020). The anterior hippocampus is associated with regulating, processing, and responding to emotions and stress; has greater subcortical connectivity; and plays a role in HPA axis regulation (Chase et al., 2015; Goosens, 2011; Sheldon et al., 2016). It is possible that the alterations associated with a maternal history of exposure to childhood maltreatment identified in relation to neonatal functional connectivity in the full hippocampus were driven by alterations to the anterior hippocampus. The stress susceptibility of this subregion, and its association with the HPA axis, potentially make it vulnerable to altered cortisol levels associated with a maternal history of childhood maltreatment during the gestational period. Indeed, the anterior hippocampus's heterogeneous network participation (relative to the posterior hippocampus), suggests that stress-related responses have the potential have to cause widespread alterations in connectivity (as was observed in whole-hippocampus findings).

Limitations and Additional Considerations

There are several limitations to consider. First, maternal childhood maltreatment was assessed retrospectively using a self-report measure, which could be influenced by event recall and reporting as well as a desire for non-disclosure. Previous studies suggest that mood at the time of assessment and awareness or denial of the events can also affect reporting (Hardt & Rutter, 2004). Self-reported rates of childhood maltreatment are

generally lower than research-defined rates of maltreatment (Silvern et al., 2000) suggesting that the results presented here would most likely reflect under-reporting. Second, our sample size is small which limits our ability to test the role of specific types of childhood maltreatment on offspring brain development. The type, timing, chronicity, and allostatic load of childhood maltreatment is associated with differential alterations to brain structure (Herzog et al., 2020; Teicher et al., 2018) and function (Teicher et al., 2016), which we were not able to explore here. Additionally, our cohort was not enriched for a history of childhood maltreatment and the rates of childhood maltreatment were low, which must be considered when comparing to other studies. The identified clusters associated with a maternal history of childhood maltreatment were not fully explored in the present study to reduce multiple comparisons. Future work is needed to examine the full extent to which maternal childhood maltreatment is related to the structure and function of the neonatal brain. While a promising approach, applying a label derived from adolescent hippocampal segmentation to infants may not be the best way to capture the functional differences of the hippocampus in infancy. Future work should explore the template matching approach using an infant template. Finally, future studies are needed to elucidate the association between alterations to hippocampal subfields associated with a history of childhood maltreatment and the potential relevance for the functional organization of the neonatal brain and child behavioral outcomes.

Conclusion

The results of this study suggest a neural phenotype related to a maternal history of childhood maltreatment. The findings further suggest that the intrauterine period is

important for the intergenerational transmission of the effects of maternal childhood maltreatment. Given the centrality of the hippocampus in memory and emotional processing and its clear sensitivity to environmental influences, it is imperative to explore how prenatal interventions can best support maternal and infant mental health.

CHAPTER 5. DISCUSSION

5.1 Summary of Findings

The goal of this dissertation was to characterize mechanisms and outcomes relevant to the intergenerational transmission of maternal exposure to maltreatment during childhood. We started by considering a potential mechanism. We characterized the longitudinal of heterogeneity of maternal psychological stress during pregnancy and examined its relationship to a maternal history of exposure to childhood maltreatment as well as infant brain and behavioral outcomes. Recognizing that many study designs make it difficult to disentangle the effects of maternal childhood maltreatment history on offspring development transmitted during pregnancy versus effects due to the postnatal environment, we examined neonatal functional connectivity within one month of birth.

Alterations in maternal psychological stress during pregnancy is potentially a key mechanism for the intergenerational transmission of childhood maltreatment. In Study 1, we characterized the longitudinal trajectories of maternal psychological stress during pregnancy using a novel, flexible, and data-driven approach, the Functional Random Forest, in two independent mother-infant dyad cohorts (Total N=2,271). We identified four distinct clusters characterized by differences in the pattern of change over time (trajectory), and two characterized by overall magnitude of stress (higher versus lower). The magnitude clusters were not associated with infant neonatal amygdala functional connectivity or negative affect development, but were associated with a history of maternal exposure to maltreatment during childhood. Offspring of mothers with increasing or peak stress late in pregnancy showed increased amygdala functional connectivity at one month of age and altered negative affect development over the first

two years of life. The trajectory clusters were replicated in an independent cohort. Importantly, the association between trajectory cluster 3 and altered negative affect development was also replicated in the independent cohort. This study is unique due to the replication sample. Overall, the data highlight that the trajectory of maternal perinatal stress may contribute to both offspring brain and affective development in a manner that is independent of overall stress magnitude.

The amygdala plays an important role emotional responses, and stress-induced alterations may increase the risk for increased stress reactivity and attachment insecurity in offspring. Therefore, in Study 2, we examined how potential amygdala alterations, already evident in the neonatal brain, relate to the subsequent formation of maternal-infant attachment and infant stress reactivity. We found that neonates of mothers with a history of childhood maltreatment showed distinct patterns of amygdala functional connectivity to several brain regions including the pars opercularis, parahippocampus, temporal pole, dorsal anterior cingulate cortex, occipital cortex, fusiform, precentral gyrus, and cuneus. Follow up analyses focused on amygdala-dACC functional connectivity, due to its role in stress reactivity and regulation. Since numerous studies have focused on the role of attachment and bonding during the postnatal period as a potential mechanism for the intergenerational transmission of maternal childhood maltreatment, we examined the relationship between neonatal amygdala-dACC functional connectivity and mother-infant attachment security. Stronger amygdala-dACC functional connectivity related to increased likelihood of infants developing an insecure attachment at 12 months of age after adjusting for key potential confounds in the postnatal environment. Interestingly, stronger neonatal amygdala-dACC connectivity also

mediated the association between maternal history of childhood maltreatment and increased risk of insecure attachment. Given the involvement of the dACC in stress reactivity, we examined infant cortisol reactivity during the Strange Situation Paradigm. Infant cortisol reactivity at twelve months of age was not related to neonatal amygdala-dACC connectivity. The results of this study suggest a potential neural phenotype related to a maternal history of childhood maltreatment. The findings further suggest that the intrauterine period is important for the intergenerational transmission of the effects of maternal childhood maltreatment, even in a cohort with relatively low rates of reported childhood maltreatment. Finally, the findings suggest that in utero alterations to offspring functional connectivity potentially influence later patterns of attachment.

The hippocampus is highly sensitive to stress such as childhood maltreatment and plays a regulatory role in HPA axis responsivity, which is known to be altered during pregnancy. In study 3, we found that neonates of mothers with a history of exposure to childhood maltreatment showed stronger neonatal hippocampal functional connectivity to the primary visual cortex, dorsomedial prefrontal cortex, and multiple regions associated with the default mode network; and weaker connectivity to the orbitofrontal cortex, ventromedial prefrontal cortex, parahippocampus, cuneus, and insula. The hippocampus is composed of subregions, which are functionally distinct and differentially responsive to stress. Recognizing that these subregions may differ in their response to in utero stress exposure, we next examined hippocampal subregions. Using the template matching approach to empirically segment the hippocampus in a large adolescent sample, we identified a bilateral posterior hippocampal cluster. We applied this posterior hippocampal cluster to our infant cohort as a seed region and examined the association

between maternal exposure to maltreatment during childhood and neonatal posterior hippocampal functional connectivity. There was no association between maternal history of childhood maltreatment and neonatal posterior hippocampal functional connectivity. The results of this study support potential hippocampal neural phenotype related to a maternal history of childhood maltreatment.

These studies provide evidence of the intergenerational effects of childhood maltreatment. The findings support the hypothesis that the intrauterine period is important for the intergenerational transmission of the effects of maternal exposure to maltreatment during childhood. They suggest a neural phenotype involving alterations in amygdala and hippocampal functional connectivity that is observable in offspring as early as one month of age and related to a maternal history of exposure to maltreatment during childhood. The results highlight the importance of considering both preconceptional and prenatal influences on fetal neurodevelopment. Finally, the results of these studies also demonstrate the importance of characterizing the longitudinal heterogeneity of maternal psychological stress during pregnancy and its association with a maternal history of exposure to childhood maltreatment and infant brain and negative affect development. .

5.2 Characterizing Maternal Psychological Stress During Pregnancy

Psychological stress is a complex construct encompassing stress severity, chronicity, and variability. However, maternal psychological stress during pregnancy has frequently been examined as a static construct. While a handful of studies have examined

the trajectories of maternal psychological stress during the prenatal and postnatal periods (Ahmed et al., 2019; Baron et al., 2017; Fredriksen et al., 2017; Kingston et al., 2018; Lahti et al., 2017; Mora et al., 2009; Mughal et al., 2018; H. Santos et al., 2017; van der Waerden et al., 2015), few studies have focused on the prenatal period. Those studies that have examined maternal stress during pregnancy primarily consider the magnitude of stress (i.e., high, medium, or low). However, there are several lines of evidence that highlight how psychosocial stress is dynamic and heterogeneous over the course of pregnancy (Ahmed et al., 2019; Buss, Entringer, Swanson, et al., 2012; Mora et al., 2009). Despite the evidence suggesting considerable within-person variability over the course of pregnancy and the early postpartum period, there is limited understanding of how trajectories, as opposed to magnitudes, of maternal psychological stress relate to offspring neurobiological and socioemotional development. New methods are needed to truly capture the longitudinal heterogeneity of maternal psychological stress during the prenatal and postnatal periods. Because pre- and postnatal neurodevelopment occurs sequentially, is dynamic, and is differentially sensitive to environmental influences at various periods; the effect of any insult, such as maternal psychological stress, depends just as much on timing and rate of change as it does on severity.

The existing literature is limited in four ways. First, sampling often includes only one or two time points, limiting our ability to examine stress trajectories. Second, even when multiple time points are available, prior work has primarily focused on the severity or magnitude of stress, as opposed to patterns of change over time. Third, previous studies have not replicated their findings in an independent sample, especially one with a very large sample size. Finally, prior work has not taken a data driven approach to

identifying potential heterogeneity with regard to both magnitude and patterns of change over time. No study to date has empirically tested and characterized the heterogeneity or patterns of individual maternal stress trajectories and examined their association with both infant brain and behavioral outcomes.

Maternal psychological health during pregnancy and postpartum has been increasingly recognized as a public health priority and represents a potential mechanism for the intergenerational transmission of childhood maltreatment. Decades of research have made clear that early prevention and intervention efforts related to maternal stress and its effects of offspring mental health outcomes will not be one size fits all. It is therefore critical to advance the understanding of heterogeneity in maternal psychological stress and the implications of individual differences for offspring development in order to maximize these efforts. In this prospective longitudinal cohort study of mothers and their infants, we found associations between the trajectory of maternal psychological stress during the perinatal period and negative affect in offspring out to 2-years of age using a novel machine learning algorithm. The Functional Random Forest, a flexible, data-driven approach, allowed us to characterize the longitudinal heterogeneity in maternal psychological stress during pregnancy. Patterns of offspring amygdala functional connectivity were affected by maternal stress trajectories. In other words, the trajectory, as opposed to the magnitude, of perinatal stress appears to be critical in determining how maternal perinatal stress affects offspring brain and behavioral development. These findings represent an important addition to the literature because they suggest that variability in the trajectory, including the timing of increases and peaks in maternal perinatal stress, influences infant brain and behavioral outcomes.

We found that increasing or peak maternal psychological stress during late pregnancy was associated with offspring brain and behavioral outcomes in the primary cohort. Although maternal cortisol levels vary across pregnancy, there is a surge during late pregnancy (Stoye et al., 2020). Several studies have shown that maternal cortisol during late pregnancy is associated with infant reactivity and negative emotionality (Braithwaite et al., 2017), a finding potentially explained by the high concentration of glucocorticoid receptors present in the amygdala (Matthews, 2000). Cortisol is involved in fetal brain neurogenesis, synaptogenesis, and axonal growth through these glucocorticoid receptors (Matthews, 2000; Moisiadis & Matthews, 2014). The period right before birth is especially important for the developing brain. This period is characterized by a rapid and dramatic increase in total physical connections between neurons of the cerebral cortex and is therefore considered a critical period for development of the cortical connectome (van den Heuvel et al., 2014). Rapid cortical maturation, circuit formation, and increased neuronal connectivity are hallmarks of third trimester neurodevelopment, and may explain why this period is particularly sensitive to alterations in maternal stress (Andescavage et al., 2017; Tau & Peterson, 2010; Moriah E. Thomason et al., 2015).

Given the sequential process of neurodevelopment, it is possible that alterations in maternal psychological stress have a differential impact on brain development depending on the timing of peaks or changes in stress. Screening for psychological stress at a single time point will therefore likely be insufficient for understanding women's risk trajectories and potential impacts on offspring neurodevelopment. Our results suggest that in the context of scarce resources in clinical and research settings, it may be particularly

important to focus on signs of increasing stress in later gestation. There is growing evidence to suggest that the fetus may be especially sensitive to extrauterine cues transmitted via stress-sensitive aspects of maternal-placental-fetal biology during late pregnancy. This research lays a foundation for future work focused on factors contributing to heterogeneity and changes in levels of maternal psychological stress, which will be critical for providing an empirical basis for effectively supporting maternal and infant health.

5.3 Maternal History of Exposure to Maltreatment During Childhood and the Functional Organization of the Offspring's Limbic System

Childhood maltreatment is associated with lasting alterations to neurobiology, stress physiology, and immunity (Buss et al., 2017). Maternal exposure to maltreatment during childhood has been associated with an increase in placental CRH production during the second half of pregnancy, reflecting HPA dysregulation during late pregnancy (Moog et al., 2016). Similarly, pregnant women with a history of sexual abuse had increasing waking cortisol across pregnancy and did not demonstrate a dampening response in late pregnancy (Bublitz & Stroud, 2012). Cortisol bioavailability, which is affected by maltreatment-related HPA axis dysregulation (Gerritsen et al., 2017; Tarullo & Gunnar, 2006; Van Voorhees & Scarpa, 2004), plays a key role in fetal maturation and is associated with risk for offspring psychopathology (Buss et al., 2017; Graham et al., 2019). Several studies have shown that maternal cortisol during late pregnancy is

associated with infant reactivity and negative emotionality (Braithwaite et al., 2017). Additionally, there is evidence that cortisol and other mediators of stress resulting from exposure to childhood maltreatment affect the development of specific brain regions sensitive to stress (Teicher & Samson, 2016). The limbic system is one of these regions and there is extensive evidence that it is altered in the setting of exposure to childhood maltreatment (Gerritsen et al., 2017; Hodel, 2018; Teicher & Samson, 2016). These alterations have been observed in childhood, adolescence, and have been shown to persist into adulthood (Hodel, 2018).

The limbic system is not only important for emotion processing and memory, but is highly responsive to stress hormones due to the high concentration of glucocorticoid receptors in the hippocampus, amygdala, and prefrontal region (Herzog et al., 2020; Matthews, 2000). These stress-induced alterations may increase the risk for emotional dysregulation (Burghy et al., 2012; Buss, Davis, et al., 2012), heightened negative affect and stress reactivity (Davis et al., 2011; Yong Ping et al., 2015), and subsequent psychopathology (Etkin & Wager, 2007) in offspring. Increased amygdala volume and connectivity have been associated with increased fear (Graham et al., 2016; Thomas et al., 2019) and affective problems in children (Buss, Davis, et al., 2012), while decreased hippocampal volumes have been associated with behavioral problems (Hanson et al., 2015) in children.

The general architecture and connectivity of the limbic system is largely established before birth (Hodel, 2018), suggesting potential malleability to mediators of maternal psychological and biological stress. There is evidence that the fetal limbic system is responsive to physiological and biological stress mediators in utero (Graham et

al., 2018; A Qiu et al., 2015; Rifkin-Graboi et al., 2015), representing a potential pathway for the intergenerational transmission of maternal childhood maltreatment. We therefore focused on the functional connectivity of the neonatal limbic system because of its vulnerability to stress and its role in emotion regulation and expression. Additionally, in an effort to link the brain and behavioral outcomes, we examined negative affect development, stress reactivity, and mother-infant attachment security.

Amygdala

In the present work, we found that a maternal history of exposure to maltreatment during childhood was associated with offspring stronger positive amygdala connectivity to the parahippocampus, temporal pole, pars opercularis, precentral gyrus, and dorsal anterior cingulate cortex; and negative functional connectivity to the occipital cortex, fusiform, left parahippocampus, and cuneus. The results of this study reveal a pattern of altered neonatal amygdala functional connectivity in association with a history of maternal childhood maltreatment potentially representing a neural phenotype related to intergenerational exposure to maltreatment.

In examining one of the amygdala connections associated with maternal history of exposure to maltreatment, we found that stronger amygdala to dorsal anterior cortex functional connectivity was related to increased risk of insecure attachment in infants. Previously, studies have focused exclusively on the influence of postnatal factors such as maternal mood, infant temperament, and socio-economic status on attachment security. In the present study, we found that stronger amygdala to dorsal anterior cortex functional connectivity mediated the relationship between maternal exposure to maltreatment during

childhood and infant attachment security. This suggests the need to consider how earlier, prenatal influences might affect later attachment security through the developmental programming of brain function in regions relevant to social development and attachment. The findings further support the importance of the intrauterine period for its role in the intergenerational transmission of the effects of maternal exposure to maltreatment during childhood.

Hippocampus

The sensitivity of the hippocampus to stress exposure has been well established in animal models (Bruce S. McEwen, 1999; Tottenham & Sheridan, 2009). Human studies also demonstrate consistent associations between early life adversity, particularly childhood maltreatment, and the hippocampus (Dahmen et al., 2018; Riem et al., 2015). Decreased hippocampal volumes have been associated early life stress (Dahmen et al., 2018), childhood maltreatment (Riem et al., 2015), and psychiatric disorders such as depression (Barch et al., 2019; McKinnon et al., 2009; M. A. O. Santos et al., 2018; Schmaal et al., 2016), and post-traumatic stress disorder (PTSD) (Bromis et al., 2018; O'Doherty et al., 2015; Szeszko et al., 2018). The vulnerability of the hippocampus to stress is expected given the high density of glucocorticoid receptors (Herzog et al., 2020), and its role in HPA axis regulation (Jankord & Herman, 2008). Several studies have shown that maternal stress during pregnancy is associated with decreased offspring hippocampal volumes (A Qiu et al., 2013; Anqi Qiu et al., 2017; Wu et al., 2020) and altered functional connectivity (Scheinost et al., 2020). Given that alterations in hippocampal volume and connectivity can be observed shortly after birth, this effect may

originate during fetal development, reflecting a potential pathway for the intergenerational transmission of childhood maltreatment that begins before birth.

In the present study, we found that a maternal history of exposure to maltreatment during childhood was associated with altered hippocampal functional connectivity to the orbitofrontal cortex, ventromedial prefrontal cortex, dorsomedial prefrontal cortex, parahippocampus, posterior cingulate cortex, and insula; all of which are part of the limbic system or prefrontal cortex. We also found a number of regions association with the default mode network, including the posterior cingulate cortex, lateral parietal cortex, and temporoparietal junction. There is evidence that a "proto-default network," which includes the lateral parietal cortex and posterior cingulate cortex, is observable in infancy (Fransson et al., 2011, 2009, 2007; Wei Gao, Alcauter, Elton, et al., 2015; Wei Gao, Alcauter, Smith, et al., 2015, 2015; Wei Gao et al., 2014, 2009; Graham, Pfeifer, Fisher, Carpenter, et al., 2015; Smyser et al., 2010). Importantly, the DMN is known to be altered in the setting of childhood maltreatment (Philip et al., 2013; Teicher & Samson, 2016) and early life stress (Graham, Pfeifer, Fisher, Carpenter, et al., 2015). Graham and colleagues found that non-physical, interparental conflict during pregnancy was associated with stronger DMN functional connectivity during the first year of infant life (Graham, Pfeifer, Fisher, Carpenter, et al., 2015) suggesting that this functional network may be susceptible to prenatal influences. Similar to the study of interparental conflict during the prenatal period, we found that a maternal history of exposure to maltreatment during childhood was associated with increased offspring hippocampal integration into the DMN. These results suggest that the influence of the early environment on the organization of the DMN may begin before birth. This finding has important implications

for how we interpret prior results focused on the role of the postnatal environment because it shows that the functional organization of the brain is established during the prenatal period. This functional organization likely influences infant responses to the postnatal environment as well as behavioral development.

5.4 Leveraging MRI to Examine Functional Heterogeneity

Resting-state functional connectivity MRI is an especially promising tool for understanding early neurodevelopment because MRI scans can be acquired shortly after birth during infant natural sleep (Graham et al., 2013; H. Zhang et al., 2019). By assessing infants shortly after birth, it is possible to begin to distinguish between the potential influences of prenatal and postnatal effects. Resting-state functional connectivity MRI is an especially important tool because it has high temporal and spatial resolution that allow for the examination of systems of interest, such as the limbic system, that are related to outcomes of interest (H. Zhang et al., 2019). Advances in neuroimaging techniques are improving spatial resolution and increasing the capacity to differentiate stress-sensitive subregions. In the present study, we leveraged a large existing dataset to empirically segment the hippocampus and examine the relationship between subregions and associations of interest.

Extending the capacity for infant neuroimaging is of considerable importance because it allows us to observe the organization of functional brain networks, before behavioral outcomes of interest are observable (Graham, Pfeifer, Fisher, Lin, et al., 2015). Increasing our understanding of the developing brain and its relationship to stress and other environmental factors could help us to identify early markers of risk or

resilience. These early markers will allow for early intervention with mothers during pregnancy as well as their infants. The timing of early interventions are especially important given of the plastic nature of the brain during the fetal period and early childhood. The sensitivity of the brain during this period will likely make it more responsive to therapeutic interventions and protective factors.

Advances in neuroimaging methods and the increasing number of consortium studies with large sample sizes are creating exciting opportunities to understand the functional organization of the brain. The template matching approach, which was used in the present study, can empirically segment structures such as the hippocampus based on their affiliation with different large scale networks. We leveraged the large ABCD dataset to segment the hippocampus and identified a posterior hippocampal cluster, which we then applied to an infant cohort. Although the identified posterior hippocampal cluster was not related to a maternal history of exposure to maltreatment during childhood, template matching remains an important avenue to pursue. Future studies should attempt the template matching approach using infant data given that the cortical connectivity of neonates is still highly variable at this age.

In addition to being highly responsive to stress, there is a wealth of evidence from both animal and human studies demonstrating that the hippocampus is functionally and structurally heterogeneous. The heterogeneity of the hippocampus as evidenced by the structural and functional diversity of the subregions may explain why many studies have reported null effects when looking at the hippocampus as a whole (Buss, Davis, et al., 2012). It is possible that the alterations associated with a maternal history of exposure to maltreatment during childhood identified in relation to neonatal functional connectivity in

the full hippocampus were driven by alterations to the anterior hippocampus. Indeed, the anterior hippocampus's heterogeneous network participation (relative to the posterior hippocampus), suggests that stress-related responses have the potential have to cause widespread alterations in connectivity (as was observed in whole-hippocampus findings). Failure to capture the distinct effects of maternal stress or exposure to maltreatment during childhood on hippocampal subregions will make it difficult to truly characterize their unique associations with offspring biobehavioral outcomes and subsequent psychopathology. Emerging evidence indicates the potential importance of considering these distinct subregions in order to better understand the effects of early adversity and childhood maltreatment.

5.5 Additional Consideration

The Timing of Maltreatment and Intergenerational Transmission

There is a wealth of evidence that the timing of maltreatment is important (Caldji et al., 1998; J. Herman, 2015; Teicher et al., 2018, 2016; Teicher & Samson, 2016). Early life stress and maltreatment during sensitive windows of development seem to have a greater impact (Teicher et al., 2018; Teicher & Samson, 2016) than stress that occurs later in life. Similarly, chronic maltreatment, especially at the hands of a caretaker, has a different effect than a single acute trauma that is impersonal and unintentional (J. Herman, 2015). It is likely that the timing and chronicity of childhood maltreatment will also prove relevant in whether or not transmission to the next generation occurs. There is already evidence that the association between a maternal history of physical victimization and offspring behavioral outcomes is more pronounced when the victimization occurred

during the mothers' childhood compared with victimization experienced in adulthood (Thompson, 2007). As studies seek to better understand and characterize the intergenerational transmission of childhood maltreatment, the timing and chronicity of maltreatment needs to be considered.

Trauma-Related Symptoms and Symptom Burden

A history of exposure to childhood maltreatment has been shown to increase the odds of perinatal depression (Barrios et al., 2015; Bouvette-Turcot et al., 2017; Choi et al., 2015; Gartland et al., 2016; Lara et al., 2015; Mcdonnell & Valentino, 2016; Mezey et al., 2005; Robertson-Blackmore et al., 2013), anxiety (Gartland et al., 2016; Lara et al., 2015), and intimate partner violence during pregnancy (Gartland et al., 2016; Huth-Bocks et al., 2013). Several studies suggest that pregnancy itself may trigger reminders of relational trauma (Huth-Bocks et al., 2013), be re-traumatizing (Lev-Wiesel et al., 2009; Mezey et al., 2005; Montgomery, 2013), and increase symptoms of PTSD (Choi et al., 2015; Lev-Wiesel et al., 2009; Mezey et al., 2005).

The present study considered maternal anxiety, depression, and perceived stress; but did not consider maltreatment-related or PTSD symptoms. It is likely that the trajectory of maltreatment-related symptoms will show heterogeneity as was observed in the patterns of depression, anxiety, and stress symptoms in the present cohort. These maltreatment-related symptoms will likely interact with symptoms of depression, anxiety, and stress in important ways that are relevant for both maternal and fetal health. The present cohort demonstrated lower levels of depression, anxiety, and stress symptom severity compared to clinical cohorts. It is telling that infant neurobehavioral outcomes

were observed in association with a maternal history of exposure to childhood maltreatment in a cohort with low levels of maltreatment exposure and lower depression, anxiety, and stress symptom severity. It is possible that women with a greater symptom burden, including maltreatment-related symptoms, will experience the stress of pregnancy differently in ways that distinctly affect infant development.

Heterogeneity of Maltreatment Response and Stress

There is considerable variability in how people respond to childhood maltreatment both physiologically and psychologically. For example, HPA axis alterations have been shown to vary, depending on the type and timing of maltreatment (Tarullo & Gunnar, 2006; Van Voorhees & Scarpa, 2004). The current version of the DSM recognized the heterogeneity of trauma-related responses in the most recent revisions by removing PTSD from Anxiety Disorders and creating a new category "Trauma and Stress-Related Disorders" (American Psychiatric Association, 2013) that included a range of potential stress responses including, but not limited to, PTSD. In an attempt the address the variability within the PTSD diagnosis itself, they added a dissociative and preschool subtype to the existing diagnostic criteria (American Psychiatric Association, 2013).

Consideration of the heterogeneity of neurobiological and physiological responses is imperative when examining the intergenerational transmission of childhood maltreatment. At the individual level, there is substantial evidence that the response to maltreatment and the resulting symptoms are more important than the exposure itself (Yehuda & Meaney, 2018). This suggests that the mother's response to maltreatment,

more than the exposure itself, is likely to be relevant when considering the potential for intergenerational effects. In the present work, our cohort was not enriched for a history of exposure to maltreatment during childhood; therefore, we were not able to fully explore the individual variation in responses and symptom trajectories. It is possible that maltreatment-related trajectories will demonstrate distinct patterns. Women with more avoidance and numbing symptoms or a history of past or current dissociation may have blunted stress trajectories; while women with greater trauma-related arousal and reactivity or intrusion symptoms may demonstrate greater magnitude and variability over time. Future work with cohorts enriched for maltreatment exposure will need to examine the role of maltreatment-related symptom heterogeneity in maternal and infant outcomes.

There is also variability in fetal outcomes related to maternal mediators of biological and psychological stress. Exposure to cytokines during the prenatal period, which are associated with stress-and inflammatory states, have been shown to decrease (Schepanski et al., 2018) and increase amygdala volume (Graham et al., 2018); while exposure to higher levels of cortisol, also associated with stress, are related to an increase in total neurons within the amygdala (Schepanski et al., 2018). There is also variability in how the hippocampus responds to stress. In animal models, short-term, mild stress during the prenatal period enhanced hippocampal neurogenesis and maturation; whereas, severe, long-lasting stress suppressed the morphology of hippocampal neurons (Fujioka, Fujioka, Ishida, Maekawa, & Nakamura, 2006). Higher levels of cortisol during pregnancy are necessary to meet increased maternal metabolic demands (Duthie & Reynolds, 2013; Schepanski et al., 2018) and for fetal organ maturation (Aboustate & Baune, 2020; Moisiadis & Matthews, 2014; Schepanski et al., 2018). Alterations in cortisol levels,

either too high or too low, may distinctly affect infant brain development. The differential impact of stress mediators on fetal brain development highlight the importance of characterizing maternal stress heterogeneity during the prenatal period.

Framing Conversations about Maltreatment-Related Outcomes

There is a long-standing history of blaming survivors of childhood maltreatment, including mothers (Breckenridge, 2006), who experienced maltreatment during childhood. Judith Herman discusses how it is easier for society to blame the survivor than wrestle with what it means for society to allow childhood maltreatment and violence to occur unchecked (J. Herman, 2015). She describes society's dissociative amnesia around trauma and how there are periods of awareness and activism followed by periods of denial and shifting the blame to survivors (J. Herman, 2015). As we consider the findings of any study related to childhood maltreatment, we must be thoughtful in our interpretation. Yehuda and Meaney discuss the importance of distinguishing the consequences of maltreatment from the consequences of maltreatment-related symptoms in studies of intergenerational transmission (Yehuda & Meaney, 2018). They highlight how physiological responses to maltreatment may be adaptive in adverse environments. They further discuss how childhood adversity may be protective from later psychopathology in stress-filled environments (Yehuda & Meaney, 2018). This reasoning is supported by studies in animal models and humans examining differential susceptibility and differential sensitivity to context (Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007; Belsky & Pluess, 2009, 2013; N. R. Bush & Boyce, 2016; N. R.

Bush et al., 2017; Hartman, Freeman, Bales, & Belsky, 2018; Pluess & Belsky, 2011; Pluess, Bolten, Pirke, & Hellhammer, 2010).

In the present study, we found that a maternal history of exposure to maltreatment during childhood was associated with distinct offspring neonatal neural phenotypes related to the amygdala and hippocampus. The presence of this phenotype could be considered in the context of transmission of risk based on maternal history of exposure to maltreatment during childhood, as it is often framed in the literature. Another way of thinking about this finding is that prenatal influences, such as maternal stress, program postnatal developmental plasticity making infants more sensitive and responsive to later environmental influences both positive and negative (Belsky et al., 2007; Belsky & Pluess, 2009, 2013; N. R. Bush & Boyce, 2016; N. R. Bush et al., 2017; Hartman et al., 2018; Pluess & Belsky, 2011; Pluess et al., 2010). Given the rapid brain development that occurs during early childhood, this increased developmental plasticity may enhance infant sensitivity and responsiveness to positive environmental factors. It further suggests the potential for increased responsivity to therapeutic interventions delivered during early childhood (Belsky et al., 2007). The present work only identified potential neural phenotypes associated with limbic functional connectivity without evaluating their responsivity or sensitivity to postnatal influences. Future studies should follow children during early development and investigate whether these neural phenotypes are associated with enhanced sensitivity and responsivity to the postnatal environment.

Therapeutic Potential of Considering the Intergenerational Transmission of Childhood Maltreatment

Screening for anxiety and depression is common in clinical settings, but there is often resistance to screening for childhood maltreatment or PTSD because of a fear of opening "Pandora's Box" (Havens, Ford, Grasso, & Marr, 2012). The failure to assess for maltreatment history in clinical practice may also reflect a lack of awareness of the relevance of childhood maltreatment for current, reproductive, and offspring health. Survivors are unlikely to report a history of exposure to childhood maltreatment unless asked and most physicians do not ask (Springer et al., 2003). Importantly, studies suggest that women with a history of childhood maltreatment want their physicians to ask about this history (Springer et al., 2003). The present work highlights the importance of screening for childhood maltreatment and trauma-related symptoms before or during pregnancy. If we do not ask about maltreatment history, we cannot provide support or address its lasting effects when it is present; and more importantly, we continue to perpetuate the blame and stigma associated with abuse and neglect by being silent (Havens et al., 2012; J. Herman, 2015; Springer et al., 2003). The present work also demonstrates the importance of screening for maternal psychological stress across pregnancy and attending to changes in symptoms, not symptom severity alone.

Identifying a history of childhood maltreatment and changes in symptom severity during pregnancy through screening provides opportunities for timely, evidence-based therapeutic interventions. For example, maternal interventions could be delivered during pregnancy such as Mindfulness-Based Cognitive Therapy for Perinatal Depression, which has been shown to be reduce distress and depressive symptoms in pregnant women

(Dimidjian et al., 2016; Tomfohr-Madsen et al., 2016); or even preconception to reduce symptoms and health outcomes related to exposure to maltreatment during childhood. Given the plasticity of the infant brain and its potential responsivity to positive environmental factors, therapeutic interventions could also be delivered after birth. Attachment and Biobehavioral Catch-Up is designed for families with a history of childhood maltreatment, and has been shown to improve attachment security and alter neural processing in regions associated with social cognition (Valadez, Tottenham, Tabachnick, & Dozier, 2020; Zajac, Lee Raby, & Dozier, 2019). The Attachment and Biobehavioral Catch-Up intervention is especially promising since there is evidence that it affects patterns of hippocampal activation and attachment security in children, both offspring outcomes identified as related to the intergenerational transmission of childhood maltreatment in the present work. Clinicians should screen for a history of childhood maltreatment and trauma-related symptoms as a routine part of prenatal care. An awareness of maternal childhood maltreatment history and current symptom severity will help clinicians identify which interventions will best support maternal and infant health.

5.6 Limitations and Future Work

There are several limitations, beyond the additional considerations described above, to consider. We will discuss these limitations, their relevance to future studies, and potential future work below.

Self-Report Measures

A history of maternal exposure to childhood maltreatment was assessed retrospectively using a self-report measure, which could be influenced by event recall and reporting as well as a desire for non-disclosure. Previous studies suggest that mood at the time of assessment and awareness or denial of the events can also affect reporting (Hardt & Rutter, 2004). Self-reported rates of childhood maltreatment are generally lower than research-defined rates of maltreatment (Silvern et al., 2000) suggesting that the results presented here would most likely reflect under-reporting. Similarly, depression and anxiety were assessed by self-report and not by a diagnostic interview, which is in line with how it is assessed in clinical settings during routine antenatal and postnatal care. Finally, we did not ask about maltreatment-related symptoms or history of past or present PTSD, which is an important consideration in distinguishing between the influence of exposure versus symptomology resulting from that exposure. Future work should explore the influence of maltreatment-related symptoms and a diagnosis of past or present PTSD on offspring biobehavioral outcomes and subsequent psychopathology. Additionally, understanding the interaction between maltreatment-related symptoms and maternal stress during pregnancy, and how this interaction relates to offspring brain and behavioral outcomes, is also an important future direction.

Sample Size and Maltreatment Prevalence

Our sample size is small, which limits our ability to test specific aspects of childhood maltreatment exposure on child brain and biobehavioral outcomes. The type, timing, chronicity, and allostatic load of childhood maltreatment is associated with

differential alterations to brain structure (Herzog et al., 2020; Teicher et al., 2018), function (Teicher et al., 2016), and divergent behavioral outcomes (Hahm et al., 2010; Savage et al., 2019). Future studies are needed to better characterize the distinct contributions of maternal childhood maltreatment history and related symptoms on maternal psychological stress during pregnancy and infant outcomes. Our cohort was not enriched for a history of maternal exposure to maltreatment during childhood, which must be considered when comparing to other studies. Although the rates of childhood maltreatment were low, the prevalence in our cohort is similar to that of several large, population-based samples suggesting that the results may generalize to community samples (Gerdner & Allgulander, 2009; Walker et al., 1999). Future work should examine the associations between maternal history of exposure to childhood maltreatment and offspring brain and behavioral outcomes in a cohort enriched for childhood maltreatment.

Functional Connectivity Clusters

The neuroimaging component of this study focused on the resting state functional connectivity between the amygdala and specific regions of interest. The other amygdala and hippocampal functional connectivity clusters associated with a maternal history of childhood maltreatment were not fully explored in the present study to reduce multiple comparisons. The processing, interpretation, and expression of negative affect, attachment, and reactivity involves multiple brain regions and networks beyond those explored in the present study. Future work is needed to explore the full extent to which

maternal childhood maltreatment is related to the structure and function of the neonatal brain.

Subregion Heterogeneity

There is significant structural and functional heterogeneity in the limbic regions examined in the present work. In all of our studies, we averaged across the amygdala and hippocampus when creating regions of interest, potentially obscuring the contributions of subnuclei and subregions. Subregions play a key role in the neurobiology of the amygdala, hippocampus, and anterior cingulate cortex. The functional differences of subregions, as well as their differential susceptibility to stress, are especially relevant to understanding the effects of stress and maltreatment. We averaged across these regions in the present work because we lacked the neonatal rs-fcMRI reference atlases necessary to explore the distinct contributions of specific amygdala, hippocampal, and anterior cingulate cortex subregions. Although we lacked the appropriate methods to examine the role of subregions in rs-fcMRI data in infants, emerging evidence suggests that differential patterns of subregion connectivity are evident as early as the neonatal period (Gabard-Durnam et al., 2018). Significant challenges remain in examining limbic system subregion connectivity in neonates; however, we recognize that understanding the contributions of subregions is an important area of future work. Therefore, we briefly discuss the neurobiology and connectivity of amygdala, hippocampal, and anterior cingulate cortex subregions for context, even though this is not a focus of the present work.

Amygdala Neurobiology and Connectivity

Amygdala subnuclei are a key part of the neurobiology of the amygdala and have differential structural and functional connectivity. Studies of amygdala subnuclei in adolescents and adults demonstate that the subnuclei play distinct roles in emotional and fear responses, memory, learning, and psychiatric disorders (LeDoux, 2007; Rosell & Siever, 2015; Sah et al., 2003). There is also evidence that amygdala subnuclei are differentially responsive to the effects of adversity, maltreatment, and trauma (Nogovitsyn et al., 2020; Oshri et al., 2019; Veer et al., 2015). Given the clear relevance of amygdala subnuclei to our understanding of the effects of stress and maltreatment, and behavioral and psychiatric outcomes; we briefly discuss the neurobiology and connectivity of the subnclei below.

There are several approaches to describing the subregions and nuclei of the amygdala (LeDoux, 2007; Tyszka & Pauli, 2016). For the purposes of this dissertation, three major subdivisions of the amygdala will be described based on subdivisions identifiable using in vivo MRI in humans (Rosell & Siever, 2015). The first subdivision is the basolateral complex, which includes the lateral, basolateral, basomedial (accessory basal), and paralaminar nuclei (Rosell & Siever, 2015; Tyszka & Pauli, 2016). The lateral amygdala primarily receives sensory inputs such as sight, sound, and pain (LeDoux, 2007). Overall, the basolaternal complex projects to the prefrontal cortex, thalamus, memory system of the medial temporal lobe, hippocampus, perirhinal cortex, and nucleus accumbens (Sah et al., 2003). The basolateral complex plays a role in the storage of memories associated with fear and the regulation of fear extinction (Nogovitsyn et al., 2020). The second subdivision is the centromedial complex, which includes the medial

and central nuclei, and the amygdaloid portion of the bed nucleus of strai terminalis (Rosell & Siever, 2015; Sah et al., 2003). The central nucleus is involved in the expression of emotional responses and is primarily involved in output, passing information from the amygdala to nuclei of the midbrain, pons, and medulla oblongata; the hypothalamus; and the bed nucleus of the stria terminalis (Sah et al., 2003). These areas are involved in arousal, reactivity, and autonomic nervous system activation (LeDoux, 2007; Rosell & Siever, 2015; Sah et al., 2003). The third subdivision is the corticomedial (superficial) group, which includes the cortical nuclei, the nucleus of the lateral olfactory tract, the bed nucleus of the accessory olfactory tract, and the periamygdaloid cortex (Sah et al., 2003). The role of the corticomedial group is not fully understood (Rosell & Siever, 2015).

Rs-fcMRI reference atlases that define amygdala subregions have been used in studies of infants and children. However, they are currently based on adult cytoarchitectural patterns (K. Amunts et al., 2005; Katrin Amunts, Mohlberg, Bludau, & Zilles, 2020) and may not accurately reflect the relative proportion of amygdala subregions in children and neonates (Kim et al., 2010). Age-specific reference atlases segmenting the amygdala by subnuclei are not publically available for neonates. Adapting adult amygdala reference atlases to neonates obscures the developmental changes within this region, which are especially important to consider during the neonatal period since this is a time of rapid growth and expansion of structural and functional connectivity.

Even when reference atlases are available, it can be difficult to accurately and consistently segment all of the different amygdala subnuclei (Tyszka & Pauli, 2016).

Thus, the existing studies generally focus on alterations to the volume of larger amygdala subdivisions, which can be delineated more consistently. Nogovitsyn and colleagues (2020) found that greater childhood trauma was associated with smaller bilateral basolateral complex volume in adolescents. Looking at specific types of trauma, they found that physical abuse was associated with significant reduction in the basolateral complex volume bilaterally. A history of sexual abuse was also associated with reduced volumes in the basolateral complex as well as reduced right cortical nucleus volume. Adolescents who reported sexual abuse lasting greater than one year had smaller lateral nuclei bilaterally compared to those who reported sexual abuse lasting less than one year (Nogovitsyn et al., 2020). Although none of the adolescents met the criteria for a clinical diagnosis of depression or anxiety, they found that reduced right basolateral and cortical nuclei volume mediated the association between greater childhood sexual abuse and higher levels of depression and anxiety (Nogovitsyn et al., 2020). Oshri and colleagues (2019) found that adverse childhood experiences were associated with reduced basolateral and centromedial volumes in emerging adults. Like Nogovitsyn and colleagues, they found that reduced right basolateral volumes mediated the association between adverse childhood experiences and greater anxiety and depression symptom severity (Oshri et al., 2019). Veer and colleagues (2015) also found reduced right basolateral and superficial nuclei volumes in adults with PTSD following childhood trauma compared to controls (Veer et al., 2015). In addition, they found the severity of sexual abuse during childhood was inversely associated with right amygdala volume (Veer et al., 2015). The lasting effects of childhood adversity and maltreatment on the

amygdala and specific amygdala subregions highlights the sensitivity of this structure to stress.

Two studies have attempted to examine differences in amygdala subnuclei functional connectivity in infants. Hansen and colleagues (2020) found less differentiated patterns of basolateral amygdala functional connectivity in neonates. While adults showed varying levels of connections between regions associated with face and object processing and primary sensory regions, neonates demonstrated undifferentiated basolateral amygdala connectivity across all functional regions examined (Hansen, Li, & Saygin, 2020). Unlike adults, neonates demonstrated greater amygdala to primary visual and auditory cortex functional connectivity (Hansen et al., 2020). In a sample of children ages 3 months to 5 years of age, Gabard-Durnam and colleagues found that the basolateral amygdala had stronger positive functional connectivity with the frontal, ventral cortical, and subcortical regions; and stronger negative connectivity with the dorsomedial prefrontal cortex, dorsal anterior cingulate cortex, fusiform gyrus, visual cortex, caudate, and pre- and post-central gyri (Gabard-Durnam et al., 2018). The basolateral amygdala demonstrated positive linear changes in sensory and motor cortical regions with increasing age. The superficial subregion had stronger positive connectivity to the thalamus and striatum, and stronger negative connectivity to the rostral ventromedial prefrontal cortex, medial prefrontal cortex, dorsal cingulate, precentral gyrus, precuneus, cuneus, posterior cingulate, fusiform gyrus, hippocampus, parahippocampal gyri, thalamus, as well as several other regions (Gabard-Durnam et al., 2018). The superficial subregion demonstrated negative linear changes in subcortical and cortical sensory and motor region connectivity with increasing age (Gabard-Durnam et

al., 2018). The ongoing development of the amygdala during infancy and early childhood, as evidenced by the changing strength, direction, and specificity of amygdala subregion functional connectivity, suggests that the amygdala likely remains sensitive to environmental influences, such as stress, across early childhood with the potential for long-lasting effects. When developmentally appropriate reference atlases are available, studies should examine the relationship between maternal history of exposure to childhood maltreatment and offspring amygdala subregion functional connectivity. They should further examine how these functional connections relate to offspring biobehavioral development and psychopathology.

Hippocampus Neurobiology and Connectivity

There is a wealth of evidence from animal and human studies demonstrating the functional and structural heterogeneity of the hippocampus. The heterogeneity of the hippocampus, which is due to the structural and functional diversity of the hippocampal subregions, may explain why many studies have reported null effects when looking at the hippocampus as a whole (Buss, Davis, et al., 2012). It is possible that the effects of maternal stress during pregnancy on the developing hippocampus are partially masked in studies looking at the hippocampus as a whole. Failure to capture the distinct effects of maternal stress or exposure to childhood maltreatment on hippocampal subregions will make it difficult to truly characterize their unique associations with offspring biobehavioral outcomes and subsequent psychopathology.

There are multiple ways to divide the hippocampus into regions. Broadly, the hippocampus can be divided along its longitudinal axis into posterior (dorsal), body

(intermediate), and anterior (ventral) regions (Strange, Witter, Lein, & Moser, 2014; Zheng et al., 2020). There is debate about the specificity of these regions functionally and whether they are starkly demarcated or organized along a longitudinal axis gradient (Strange et al., 2014). The differences in how the hippocampus is divided largely depends on the methods with which it is studied. Gene expression studies of the hippocampus demonstrate clear functional boundaries, while electrophysiological and anatomical studies demonstrate a long-axis gradient (Strange et al., 2014).

The anterior hippocampus is directly connected to subcortical structures, including the amygdala, and is associated with regulating, processing, and responding to emotions and stress, context coding, and autobiographical memory representations (Chase et al., 2015; Decker et al., 2020; Goosens, 2011; Nadel et al., 2013; Sheldon et al., 2016). In resting-state functional connectivity studies, the anterior hippocampus demonstrates stronger connectivity to the orbitofrontal and temporal cortex (Goosens, 2011), as well as a stronger association with the default mode network (Chase et al., 2015). Studies of chronic stress in rodents demonstrate decreased neurogenesis resulting in reduced anterior hippocampal volume (Hawley et al., 2012; Szeszko et al., 2006), while studies of acute stress show distinct stress-related response patterns at the molecular level (Floriou-Servou et al., 2018). Stress-associated volume reduction in the anterior hippocampus has also been demonstrated in human studies of stress and PTSD (Szeszko et al., 2006; Vythilingam et al., 2005) and early life stress has been associated with reduced anterior hippocampal to entorhinal cortex functional connectivity (Xu et al., 2020). It is possible that the alterations associated with a maternal history of exposure to childhood maltreatment identified in relation to neonatal functional connectivity in the

full hippocampus in the present work were driven by alterations to the anterior hippocampus. Indeed, the anterior hippocampus's heterogeneous network participation (relative to the posterior hippocampus), suggests that stress-related responses have the potential have to cause widespread alterations in connectivity (as was observed in whole-hippocampus findings). The stress susceptibility of this subregion, and its association with the HPA axis, potentially make it vulnerable to altered cortisol levels associated with a maternal history of childhood maltreatment during the gestational period.

The posterior hippocampus is connected to the neocortex and is associated with cognitive functions, spatial learning and memory, and reward processing (Chase et al., 2015; Goosens, 2011; Sheldon et al., 2016). Gene expression in this region is associated with information processing in cortical regions (Fanselow & Dong, 2010). Studies of individuals with post-traumatic stress disorder (PTSD) demonstrate differences in posterior hippocampal functional connectivity (Lazarov et al., 2017; Malivoire et al., 2018).

Emerging evidence highlights the importance of considering these distinct subregions in order to better understand the effects of early adversity and childhood maltreatment. In a recent study by Wang and colleagues (2019) looking at the functional connectivity of both the anterior and posterior hippocampus, maternal sensitivity at 6 months of infant age was associated with anterior hippocampus functional connectivity at 4 and 6 years of age, and there was no association with posterior hippocampal functional connectivity (Q. Wang et al., 2019). While the anterior and posterior segmentation approach makes sense for infant studies, where brain regions are still growing rapidly and may be harder to segment more finely, adult studies of hippocampal segmentation using

functional topography suggest three to six functional subregions (Robinson et al., 2015; Zhong et al., 2019).

The functional subregions identified in adolescent and adult imaging studies reflect distinct underlying neurobiology, connectivity, and histology. The hippocampus proper can be divided into the cornu ammonis (CA) fields (CA1-CA4) and dentate gyrus (Wible, 2013), which form a trisynaptive loop (Yang & Wang, 2017). The major input to the hippocampus is the dentate gyrus, which receives projections from the entorhinal cortex (Wible, 2013). In turn, the entorhinal cortex receives output from the dorsal CA1, which also projects to the subiculum (Yang & Wang, 2017). The ventral subiculum is involved in HPA axis inhibition following psychological stress and behavioral responses to stress (J. P. Herman, Dolgas, & Carlson, 1998; Teicher, Anderson, & Polcari, 2012). The ventral subiculum is also a primary output of the hippocampus (Teicher et al., 2012). The dorsal CA1 is associated with episodic and spatial learning and memory (Chase et al., 2015; Goosens, 2011; Sheldon et al., 2016). Given its projections to the amygdala, nucleus accumbens, and medical prefrontal cortex; the ventral CA1 is associated with affective behaviors and regulating, processing, and responding to emotions and stress (Chase et al., 2015; Decker et al., 2020; Goosens, 2011; Nadel et al., 2013; Sheldon et al., 2016; Yang & Wang, 2017). The ventral CA1 also receives inputs from the basolateral amygdala and is involved in emotion-associated memory and anxiety (Yang & Wang, 2017).

The lack of age-specific reference atlases make it difficult to accurately segment the hippocampus into subregions in infants. Age-specific reference atlases segmenting the hippocampus by functional subregions are not publically available for neonates.

Adapting adult hippocampal reference atlases to neonates obscures the developmental changes within this region, which is especially important given the existing evidence of age and sex-associated hippocampal variation. Riley and colleagues found that younger boys demonstrated greater posterior connections, while older boys and younger girls demonstrated greater anterior connections (Riley et al., 2018). Girls over 11 years of age showed weaker and widely distributed connectivity (Riley et al., 2018). It is possible that age and sex-related hippocampal subregion variation is also present in infancy, and that hippocampal subregions follow different developmental growth trajectories. Developing age and sex-specific hippocampal reference atlases for infancy and early childhood is an important area of future work.

As with the amygdala, existing studies generally focus on alterations to the volume of larger hippocampal subregions in adolescents and adults, where the subregions can be delineated more consistently. Teicher and colleagues (2012) found that childhood maltreatment was associated with volume reductions in the left CA2-CA3 and CA4, dentate gyrus subfields, and the subiculum, independent of a history of major depressive disorder and PTSD (Teicher et al., 2012). Dahmen and colleagues found reduced CA1, CA3, and dentate gryrus subfield volumes were associated with early life adversity (Dahmen et al., 2018). Aghamohammadi-Sereshki and colleagues found that childhood maltreatment was associated with reductions in volume of CA subregions 1-3 and the anterior hippocampus in patients with major depressive disorder (Aghamohammadi-Sereshki et al., 2021). Future studies should examine the relationship between maternal history of exposure to childhood maltreatment and adversity and offspring hippocampal subregion functional connectivity. Future work should also examine how these functional

connections relate to offspring biobehavioral development and subsequent psychopathology.

Anterior Cingulate Cortex Neurobiology and Connectivity

Like the limbic structures we have discussed previously, there is significant structural and functional heterogeneity in the ACC. In adolescents and adults, the ACC subregions play distinct roles in the processing, control, and regulation of cognitive and emotional information, attention, and response selection (G. Bush et al., 2000; Shenhav et al., 2016). There is also evidence that the ACC subregions are differentially sensitive to the effects of adversity, maltreatment, and trauma (Demers et al., 2015). Therefore, we briefly explore the potential contributions of ACC subregions to offspring behavioral outcomes and their vulnerability to maltreatment and stress below.

There are two major subdivisions of the ACC as well as numerous smaller subregions reflecting structural and functional differences. The first major subdivision is the dorsal ACC (also called the anterior mid-cingulate), which is associated with the processing and control of cognitive information, attention, and response selection (G. Bush et al., 2000; Shenhav et al., 2016). The dorsal ACC is connected to the lateral prefrontal cortex, parietal cortex, and motor cortex (G. Bush et al., 2000; Shenhav et al., 2016). Studies suggest that the dorsal ACC and lateral prefrontal cortex coordinate in situations requiring high mental effort (G. Bush et al., 2000). Importantly, the dorsal ACC has been implicated as a critical region in studies of early adversity and PTSD (Demers et al., 2015; Teicher et al., 2016). This region appears to be uniquely vulnerable

to the effects of childhood trauma, demonstrating reduced neuronal integrity and volume in individuals with a history of childhood maltreatment (Demers et al., 2015).

The rostral ACC is associated with the processing, integration, and regulation of emotional information (G. Bush et al., 2000; Shenhav et al., 2016). The ventral ACC is connected to the amygdala, nucleus accumbens, anterior insula, hypothalamus, periaqueductal gray, and orbitofrontal cortex (G. Bush et al., 2000); and can be further divided into the pregenual and subgenual regions (Stevens et al., 2016). The subgenual region has the most connectivity to the limbic system and areas related to the autonomic nervous system, and plays a role in autonomic control and conditioned learning (Stevens et al., 2016). The pregenual ACC is involved in emotion regulation and emotional responses to pain (Stevens et al., 2016). Neuroimaging studies suggest that activation of the pregenual ACC is associated with the suppression of early limbic system responses (Stevens et al., 2016). In a study of adults with a history of childhood maltreatment, only those adults with current PTSD demonstrated an inhibition deficiency associated with ventral ACC activity (Stevens et al., 2016).

The ACC subregions demonstrate specific responses to stress and maltreatment exposure, as well as distinct associations with outcomes such as psychopathology. Future studies are needed to elucidate the association between alterations to specific ACC subregions associated with a history of exposure to childhood maltreatment and the potential relevance for offspring brain functional organization and behavioral outcomes.

Seed-Based Connectivity and Artifacts

Functional connectivity relies on correlation estimates, which can be sensitive to multiple types of artifacts (Fair et al., 2020; Maknojia, Churchill, Schweizer, & Graham, 2019; J. D. Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; J. D. Power et al., 2018; Satterthwaite et al., 2012). Motion artifacts are commonly addressed during processing through the removal of frames associated with high motion and motion correction algorithms, which were used in the present work (Maknojia et al., 2019; J. D. Power et al., 2018). An important approach to addressing motion during acquisition is by using real-time motion analytics such as Framewise Integrated Real-time MRI Monitoring Attenuation, which allow the operator to track infant head motion and monitor scan quality during the scan (Dosenbach et al., 2017). By tracking motion during scan acquisition, the operator can ensure that an adequate amount of low movement data are collected and adjust infant positioning to reduce motion if necessary. Attenuation artifacts due to magnetic field inhomogeneity are another important consideration in studies using seed-based functional connectivity since attenuated signals may be averaged into a region of interest (Peer, Abboud, Hertz, Amedi, & Arzy, 2016). One approach to deal with attenuated signals is intensity-based masking (Peer et al., 2016). In this approach, maximum BOLD voxel intensity values are modeled as a bimodal Guassian distribution separating low and high intensity voxels. A threshold is applied at the midpoint to create a mask and only high intensity voxels representing white or gray matter with limited signal attenuation are used for future steps in the approach. After the mask is applied, activity is averaged by predefined regions to create regional time-courses. This approach limits the effect of signal from low-intensity voxels from influencing correlation and

improves cluster detection by revealing distant connections that would not be incorporated in the traditional averaging approach (Peer et al., 2016). In the present work, we did not use intensity-based masking. It is possible that using this approach would increase the likelihood of identifying additional clusters associated with the amygdala or hippocampus because of reduced signal inhomogeneity in cortical regions. There is also a possibility that it would not affect the results. One of the primary sources of signal attenuation is air in the sinuses and brain cavities (Peer et al., 2016). The presence of air creates magnetic field inhomogeneity in nearby cortical regions (Peer et al., 2016). Inhomogeneity from this source is less of a concern in neonates where there are fewer air cavities than in adolescents and adults. Additionally, we used subcortical structures for our seed regions in all of the aims. The amygdala and hippocampus do not directly border air cavities and are therefore less likely to be affected by related inhomogeneity.

Reproducibility, Reliability, and Resting-State Functional Connectivity

The present study was conducted with a limited amount of resting state data. The ability to identify functional networks in the context of individual heterogeneity improves with longer scan times. Twelve to twenty minutes of resting-state data are recommended as a minimum (Birn et al., 2013; Gordon et al., 2017). Gordon and colleagues found that 10 to 80 minutes of rs-fcMRI were needed to reliability characterize individual rs-fcMRI correlations and network assignments, and cautioned against using scans with less than 10 minutes of data (Gordon et al., 2017). It is difficult to acquire scans of this length during a single session in infants who may wake up in response to MRI sounds or due to

hunger. Longer scan times and multiple scanning sessions are often required to ensure 10-20 minutes of low-motion rs-fcMRI data.

The present study was also conducted in a small sample. The size of the cohort is an important limitation to consider. A recent paper by Marek and colleagues (2020) suggested that small sample sizes, such as the cohort size in the present study, are underpowered to identify meaningful associated between brain function and behavioral outcomes. They found that smaller samples had inflated effect sizes and were more likely to be irreproducible (Marek et al., 2020). They found that the associations between brain and behavioral outcomes stabilize with sample size of around 2,000 participants or more. They suggest turning to large, consortium-level cohorts to overcome the issue of reproducibility in neuroimaging (Marek et al., 2020). Recognizing this limitation, we leveraged the ABCD dataset in the present study to empirically segment the hippocampus.

While the need for larger cohorts is undisputed, the applicability of large childhood, adolescent, and adult cohorts to early development is less clear. In the present study, it is possible that heterogeneity in the developing hippocampus, specific to adolescence; limited its generalizability to our infant cohort. The difference in brain development over a lifespan will also limit our ability to use large adolescent and adult cohorts for replication studies of developmental findings unique to infancy. In many ways, we have come full circle. Previously, adolescent and adult structural and functional scans were applied to infant datasets and used to make inferences about infant development. As infant scanning became more feasible, there was a push to look at infant brain development directly to avoid potential assumptions that might arise by working

from adolescent and adult brains. In the past several years, image acquisition and processing procedures specific to infants have been developed. These procedures allowed for the characterization of developing structural and functional organization of the infant and even fetal brain. Unfortunately, it is difficult to enroll and retain large cohorts of pregnant women and infants at a single site. As the field turns towards larger datasets, there is a need for consortia that focus on infant MRI.

Leveraging infant data from large consortia is not without its own set of limitations. Infant heart and breathing rates, which are already more rapid than that of adults, change in an age-dependent way (H. Zhang et al., 2019). The changing heart and breathing rates adds an additional level of variability to infant scans. During natural sleep, infants cycle between quiet and active sleep stages, which affects the organization of functional networks (Lee et al., 2020; Tokariev et al., 2019). These stages are associated with further changes in heart rate and breathing, which adds artifacts during the acquisition of resting-state scans (Litscher, Pfurtscheller, Bes, & Poiseau, 1993). Future studies should use physiologic measures during scanning to allow for more precise approaches to the removal of respiratory artifacts during resting-state functional connectivity (Fair et al., 2020). Motion represents another important source of artifacts in infant scans that must be considered during acquisition and addressed during processing and post-processing (H. Zhang et al., 2019). The increased variability inherent in infant scanning due to development and motion, coupled with the variability introduced by the use of different scanners, and potentially scanning protocols, may make it more difficult to combine infant scans across multiple sites in a meaningful way.

The deep, prospective biobehavioral characterization possible in small studies is also an important consideration as the field moves towards large consortia studies. The in-depth collection of prospective, biobehavioral data may not be possible in larger studies across multiple sites because of the time commitment for participants; instead, interviews may be replaced by surveys. Shifting to survey data may also affect outcomes. The recommended administration for many psychological assessments is verbal delivery, not written response or survey, because the method of administration changes how the participant responds (First, Williams, Karg, & Spitzer, n.d.; Steinberg & Beyerlein, 2013). Small studies that are able to characterize biobehavioral phenotypes remain important for hypothesis generation. In the present study, we used a small cohort to characterize potential mechanisms and neurobehavioral outcomes related to the intergenerational transmission of maternal exposure to maltreatment during childhood in a flexible and exploratory way.

5.7 Conclusions

The results of these studies demonstrate the importance of characterizing the longitudinal heterogeneity of maternal psychological stress during pregnancy and its association with a maternal history of exposure to maltreatment during childhood and infant brain and negative affect development. They also suggest a neural phenotype observable in offspring that is related to a maternal history of exposure to maltreatment during childhood. The findings further suggest that the intrauterine period is important for the intergenerational transmission of the effects of maternal childhood maltreatment, even in a cohort with relatively low rates of reported childhood maltreatment.

Understanding the heterogeneity of maternal psychological stress, the influence of preconceptional factors such as exposure to childhood maltreatment, and their effect on infant neurobiological and socioemotional development is critical to targeting screening and interventions.

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Dear Reader,

Thank you for your time and attention, for sticking through to the very end. I wasn't certain anyone would read it all the way through (outside of those who were required to read it all, of course).

Since we've made it this far together, I wanted to share something with you. Graduate school was hard. There were days I thought about giving up and days where finishing seemed impossible. I often felt that I wasn't good enough, smart enough, dedicated enough. I worried about being a disappointment to everyone. I doubted my ability to write this dissertation. I was certain I would not know enough to defend it; how can we ever know enough?

Reading the material for this topic is tough. There is a hopelessness to aspects of this topic. The literature often assumes that adversity equals destiny and conversations on resilience often fall woefully short.

We made it.
We made it all of the way through, so here is what I want to share.

No matter where you are in your journey, there will be tough times and seemingly impossible tasks. There will be hard days and hopelessness. It can be easy to focus on the voices that tear you down, easy to believe them; but I challenge you to *challenge those voices instead*. What you do not generally find in the literature on childhood maltreatment is commentary on the strength of survivors. We are the strongest people out there. We have endured, we have survived, and we will continue to survive. Recognize your strength and give yourself credit for it. You can overcome the obstacles that you will encounter. Look how far you have already come. You can do it, whatever it is, you can do it.
I believe in you and your journey.

If you have the chance, please leave some words of encouragement for future readers. I've created space by adding several blank pages after this one. If you aren't reading a shared copy, consider writing some words of encouragement to yourself somewhere to refer to when you need them or sending some kind words to someone else. We can all use encouragement.

My hope is for the end of this document to be about strength and support and love.