Emotion Regulation: Neural correlates soon after birth and Implications for future behavior

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CERTIFICATE OF APPROVAL

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Abbreviations

ER – emotion regulation

RDoC – research domain criteria

HPA – hypothalamic pituitary adrenal

CRH – cortisol-releasing hormone

ACTH – adrenocorticotrophic hormone

EEG – electroencephalogram

mPFC – medial prefrontal cortex

vmPFC – ventromedial prefrontal cortex

Am-mPFC – amygdala medial prefrontal cortex

Am-Ins – amygdala insula

Am-aI – amygdala anterior insula

MRI – magnetic resonance imaging

rs-fcMRI – resting state functional connectivity magnetic resonance imaging

BOLD – blood oxygen level dependent

fMRI – functional magnetic resonance imaging

amygdala-aI – amygdala bilateral anterior insula

NE – negative emotionality

T1w – T_1 weighted

T2w – T_2 weighted

TR – time to repeat

EPI – echoplanar imaging

FOV – field of view

FD – frame displacement

CSF – cerebrospinal fluid

ROIs – regions of interest

IBQ-R – Infant Behavior Questionnaire-Revised

ECBQ – Early Childhood Behavior Questionnaire-Short

HOME – Home Observation for Measurement of the Environment

CESD – Center for Epidemiological Studies of Depression Scale

LGM – latent growth models

GA – gestational age

FIML – full-information maximum likelihood

MAR – missing-at-random

CFI – comparative fit index

TLI – Tucker-Lewis index

RMSEA – root mean square error approximation

HCP – Human Connectome Project

Bayley-III – Bayley Scales of Infant and Toddler Development, third edition

CBCL – Child Behavior Check List

V1 – primary visual cortex

Ram – right amygdala

ANOVA – analysis of variance

ANCOVA – analysis of covariance

EF – executive function

SES – socioeconomic status

WM – working memory

ADHD – attention deficit hyperactivity disorder

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Abstract

Emotion regulatory ability (ER) is the capacity to independently modify the duration or intensity of an affective response. The ability to regulate negative affect is particularly important; heightened and poorly regulated negative affect is considered a transdiagnostic risk factor for psychopathology. While it is known that the early development of negative affect and accompanying emotion regulation skills are related to subsequent mental health, the neural correlates of these processes remain poorly understood. The current studies aimed to increase understanding in these areas. They comprise secondary analysis of an existing longitudinal data set from University of California at Irvine directed by Dr. Claudia Buss. Participants were 71 women recruited during early pregnancy and their infants born after 34 weeks gestation. This data set included measures of neonatal rs-fcMRI, infant behavioral observations at 6 and 24 months-of-age, maternal ratings of infant behavior at 6, 9, 12 and 24 months-of-age. Mothers also rated aspects of the home and caregiving environment at 6-months-of-age. Toddler executive function was assessed by standardized laboratory observations.

Three studies were conducted. As the ability to regulate negative emotionality is of particular importance to future mental health, study 1 examined the neural correlates of fear and sadness development over the first two years of life, using resting state functional connectivity MRI (rs-fcMRI). Results revealed average developmental patterns of change in fear and sadness involved an increase through the first year of life followed by a decline through the second year of life. Interestingly, amygdala coordinated functioning with the anterior insula (Am-Ins) related to fear development,

while amygdala connectivity to the ventromedial prefrontal cortex (Am-vmPFC) was associated with sadness development.

Study 2 evaluated the neural correlates of the emotional reactivity component of emotion regulation in infancy, and how it related to emerging internalizing symptoms (fear, sadness) in toddlerhood. Results indicated neonatal Am-mPFC connectivity was associated with toddler emotion regulation (measured by coding of latency to distress during the still-face paradigm), while Am-Ins connectivity failed to reach the threshold for significance. Additionally, regional specificity was observed, such that stronger amygdala connectivity to the ventral mPFC and primary sensory systems was associated with weaker emotion regulation, while stronger amygdala connectivity to the more dorsal mPFC and higher order systems was associated with greater emotion regulation. Results also indicated greater emotion regulation in infancy was associated with less internalizing symptomatology at 2-years-of-age. Moreover, emotion regulation in infancy also statistically mediated a relationship between amygdala functional connectivity at birth and future internalizing symptomatology.

Study 3 examined how emotion regulation in infancy may relate to regulatory ability in toddlerhood, more broadly, beyond negative affect, by examining executive functioning (measured by observation during the Minnesota Executive function scale, spin-the-pots task and snack delay task) at 24-months-of-age. Results indicated that high-reactivity (coded from the still-face paradigm) paired with high-regulation and low-reactivity paired with low-regulation (coded from the still-face paradigm) at 6-months of age predicted better executive function at 24-months-of-age. Moderating influences of parental behavior and socioeconomic status on associations between infant emotional

reactivity and toddler executive function did not meet the threshold for statistical significance.

Together these three studies showcase the extent to which infants brain functioning soon after birth and early emerging emotion regulation interact with hypothesized environmental influences in predicting subsequent behavior and executive functioning.

Chapter 1: Introduction

1.1. What is Emotion regulation and why does it matter?

Emotion regulation (ER) is defined herein the ability to modify the intensity or duration of an affective response (Gyurak et al., 2011). Typically there is an emotion evoking stimulus, which is followed by some level of emotional arousal, which is then emotionally regulated, see **Figure 1a** (Townsend et al., 2013). The level of emotionality experienced paired with an individual's ability to engage in effective regulatory behaviors determines their emotion regulatory ability, see **Figure 1b** (Frick et al., 2017).

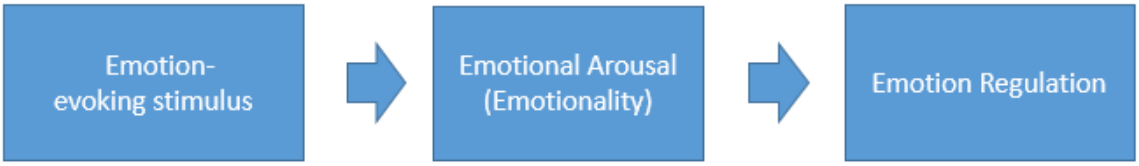

Figure 1a. Emotion regulation follows a sequence of events. Typically there is an emotion evoking stimulus, which is followed by some level of emotional arousal, whicih is then emotionally regulated.

Figure 1b. The level of emotionality experienced paired with an individual's ability to engage in effective regulatory behaviors determines their ability to modify their emotional response.

While ER applies to both positive and negative affect, it is particularly important for psychopathology development in the context of managing negative emotionality. This

is in part because the ability to down regulate negative emotionality is tied to our ability to cope with everyday distress (Riediger et al., 2011). Furthermore, difficulties regulating negative emotionality comprise an important feature across many mental health disorders including substance abuse (Weiss et al., 2015), eating disorders (Svaldi et al., 2012), internalizing behaviors (Buehler et al., 2007) like anxiety (Cisler et al., 2010) and depression (Berking & Wupperman, 2012), psychotic disorders (Kring & Caponigro, 2010), as well as ADHD (Nigg et al., 2020) and oppositional defiant disorder. Because of its importance as a transdiagnostic risk factor for psychopathology, negative emotionality is a research domain criteria (RDoC) domain (Gore & Widiger, 2018). Moreover, signs of dysregulated negative affect in early childhood are a risk factor for future psychopathology (Wakschlag et al., 2007).

Thus, improving ER skills is a target for interventions aimed at prevention and symptom improvement for children and adolescents at-risk for (Cameron et al., 2018; Houck et al., 2016), and those already diagnosed with mental illnesses (Thomson et al., 2015). Already in infancy, regulatory difficulties are associated with emerging maladaptive behaviors in childhood (Dale et al., 2011; Gustafsson et al., 2020). Though this evidence needs further specification, childhood behavioral problems are costly (Kohlboeck et al., 2014) and can lead to problems later in life (Jamnik & DiLalla, 2019; Kassing et al., 2019; Narusyte et al., 2017). Thus understanding the early development of negative emotionality and ER is of significant importance for supporting mental health and improving prospects for early intervention and prevention.

1.2. The development and measurement of emotion regulation behavior

The emergence of ER occurs over the first year of life when infants go through rapid cognitive and neural development (Gao et al., 2015). The ability to regulate emotions initially emerges in the context of the caregiving relationship. This is a form of *extrinsic* regulation, in which infants rely heavily on their caregivers to regulate their emotional distress for them (Spanglar et al., 1994). Specifically, extrinsic regulation, which occurs primarily in early life and also throughout development and adulthood, refers to the intentional or automatic, yet effective support of regulation of one's emotions by another (Nozaki & Mikolajczak, 2020). This is in contrast to *intrinsic* emotion regulation in which one regulates ones emotions alone, which emerges increasingly with development (Gross, 2015; Nigg, 2017). By 9-weeks-of-age, infants can communicate their emotional state to their caregiver through behavioral cues such as gestures, facial expressions, crying and tone of voice (Legerstee et al., 1990). Given these cues, a caregiver can act to accurately identify and respond to the infant's needs (Weinberg & Tronick, 1994) once again engaging in extrinsic regulation. During development, emotion regulation gradually progresses from mostly extrinsic to increasingly intrinsic.

Thus, over the first 6 months of life, infants may begin to rapidly develop their own cognitive and behavioral strategies for intrinsic ER (Cole et al., 2004; Fox & Calkins, 2003; Kopp, 1989; Poehlmann et al., 2011). This represents the early precursors of intrinsic emotion regulation. In particular, attentional orienting, may emerge by 6-months of age, allowing infants to orient and sustain their attention in a way that appears strategic (Reynolds & Romano, 2016; Rothbart, 2011). This ability allows infants to

disengage from stressful stimuli and orient to more neutral or positive stimuli, thus reducing their own levels of distress (Crockenberg & Leerkes, 2004). Infants may also avert gaze when over or under-stimulated during face-to-face interactions to adjust autonomic arousal (Field, 1981) and negative affect (Harman et al., 1997; Stifter & Braungart, 1995). In addition to attentional orienting, infants can learn to employ other emotion regulatory strategies including: self-soothing behaviors such as hand and foot clasping, self-manipulation, non-nutritive-sucking and avoidance behaviors (Derryberry & Rothbart, 1981; Thomas et al., 2017). These regulatory behaviors have also been shown to cause reductions in negative affect (Stifter & Braungart, 1995). and can be reliably measured through the use of observational coding systems and through parent report measures (Garstein et al., 2003; Kostyrka-Allchorne et al., 2020; Leerkes et al., 2012; Sullivan et al., 2015).

1.3. Neural connections support emotion regulation ability

With regard to neurobiology, the hypolathalamic-pituitary adrenal (HPA-axis) plays an important role in the early development of emotional reactivity and regulation (Gunnar & Quevedo, 2007). Infants are born with a functioning stress response system, which allows them to react to changes in their internal or external environment already at birth (Jansen et al., 2010). The HPA axis is first activated by the hypothalamus, which receives input from higher order brain regions and the amygdala. The hypothalamus produces cortisol-releasing hormone (CRH) which stimulates production of adrenocorticotrophic (ACTH) hormone from the anterior pituitary. ACTH is then released into general circulation where it stimulates cells in the adrenal cortex to produce

cortisol (Stansbury & Gunnar, 1994). The final product of the HPA axis, the release of cortisol into the blood stream, exerts a wide array of endocrine, immune and metabolic effects on most cells in the infant's body, and results in the increased availability of glucose (Chrousos & Gold, 1992; Chrousos & Kino, 2009).

Changes in salivary cortisol in response to a stressor are often used as a measure of cortisol reactivity (Stansbury & Gunnar, 1994). Following the onset of a stressor, it takes 10-15 minutes to produce a rise in circulating cortisol levels and 20-30 minutes for peak stress concentrations to be reached in the plasma (Stansbury & Gunnar, 1994). During the first 5-10 minutes after exposure to a stressor, the infant must appraise the stressor and engage in emotion regulation as needed, which may increase or decrease the cortisol response. Typically a greater increase in cortisol release following a stressor is interpreted as a sign of increased reactivity (Laurent et al., 2016). Alternatively, an increase following stress and a subsequent return to baseline is viewed as a sign of overall regulation (Jansen et al., 2010; Stansbury & Gunnar, 1994; Ursache et al., 2014). Thus measurement of salivary cortisol changes during ER in infancy may provide a window into how physiological systems support emerging ER already in the newborn period.

For infants 0-2 months-of-age salivary cortisol increases can be reliably seen in response to noxious stimulation or handling (Gunnar, 1992). From 2-6 months of age, noxious stimuli still reliably cause increases in cortisol, however psychosocial stressors do not reliably result in a cortisol response (Gunnar, 1992). Consistent cortisol reactivity to psychosocial stress decreases even more when infants are 12-24 months-of-age (Jansen et al., 2010). By the end of the first year of life, the infant's attachment quality to its

caregiver appears to buffer HPA axis activity, such that infants with insecure attachments are more likely to experience increases in cortisol than their securely attached counterparts (Gunnar & Quevedo, 2007; Gunnar et al., 1996, 2009). These findings suggest that from infancy through early childhood HPA activity in response to negative stress is dampened due to the protective role of caregivers (Gunnar & Quevedo, 2007; Gunnar et al., 2009). Though it is difficult to assess HPA activity as an indicator of stress reactivity and regulation in infants, at 6-months-of-age observational tasks can be used in an attempt to elicit negative emotional challenge and concomitant increases in cortisol (Gunnar et al., 2009; Provenzi et al., 2016).

One commonly used observational task is the still-face paradigm (Gunnar et al., 2009). During this paradigm mother and infant first engage in a face to face play interaction, next mothers are asked to face the infant with a blank face for a 2-minute interval; this is followed by a recovery period (Adamson & Frick, 2003). The still face paradigm has been associated with an increase in cortisol magnitude in a subset of studies (Crockett et al., 2013; Feldman, 2003; Haley & Stansbury, 2003; Provenzi et al., 2016). Thus, though difficult, increases in cortisol in response to certain psychosocial stressors are possible.

Little is known about the specific brain regions and systems which support very early emerging ER in humans. EEG studies conducted in the first year of life reveal right frontal asymmetry, greater activity in the right frontal hemisphere than the left, is linked to greater negative emotion reactivity (Calkins et al., 2002), and lower ability to regulate negative affect (Fox, 1991; Smith et al., 2016). However, these studies do not speak to whether specific brain regions and patterns of connectivity, which have been shown to

play a critical role in ER from childhood to adulthood, such as the amygdala (Banks et al., 2007; Erk et al., 2010; Phillips et al., 2003b; Taylor & Liberzon, 2007; Townsend et al., 2013) play a similar role in early emerging ER.

During adulthood, amygdala functional connectivity, in particular, plays a central role in moderating negative emotionality (Bebko et al., 2015; Denny et al., 2015; Mulej Bratec et al., 2015). Thus examining amygdala functional connectivity soon after birth in relation to emerging negative emotionality and emotion regulation represents a natural starting point for the current studies. Some studies indicate that the down regulation of negative emotional experiences occurs through the recruitment of specific frontal regions, such as the medial prefrontal cortex (mPFC), which is associated with reduced amygdala reactivity (Frank et al., 2014; Gyurak et al., 2011). This is known as top-down processing (Rauss & Pourtois, 2013). Moreover, greater amygdala-mPFC (Am-mPFC) functional connectivity has been associated with increased ER skills in children (Pitskel et al., 2011) and adults (Phillips et al., 2003a). In contrast, stronger functional connectivity between the amygdala and the insula (Am-Ins), has been associated with poor ER skills, which manifest as normative and pathological anxiety (Bebko et al., 2015; Roy et al., 2013a; Stein et al., 2007) and other disorders characterized by emotion dysregulation (e.g. bipolar disorder, substance use disorders) (Townsend et al., 2013; Wilcox et al., 2016). It is likely that Am-Ins connectivity plays a role in identifying salient stimuli and interacting with other brain systems to facilitate flexible responding (Menon & Uddin, 2010; Seeley et al., 2007).

However, there are exceptions where recruitment of frontal regions is associated with maladaptive outcomes in adolescents (Forbes et al., 2009, 2010) and amygdala

reactivity is associated with adaptive outcomes in adults (Taylor et al., 2006; Yamamoto et al., 2017). For example, in some instances, increased amygdala engagement has been associated with increased emotion regulation in adults (McRae et al., 2012; Nelson et al., 2015). In infancy, research suggests increased Am-Ins connectivity plays a role in the normative development of negative emotionality, a dispositional tendency to react to events with negative affect (Patrick 1994), as assessed by parental self-report (Graham et al., 2016). While these findings in older human samples and animal models are a potentially useful reference point there is a large developmental gap between this age group and infancy and how amygdala connectivity at birth in relates to a behavioral indicator of emerging emotion regulation in infancy remains unknown.

Previous work suggests potential developmental continuity in neural circuitry associated with ER, as soon after birth stronger Am-Ins and Am-mPFC functional connectivity are already associated with greater fear and fear balanced by cognitive capacity at 6-months-of-age (Graham et al., 2016). Additionally, another study suggests that increased white matter structural integrity between the amygdala and orbital frontal cortex at 3-months-of-age may allow for greater emotion regulation capacity at 9-months-of-age (Banihashemi et al., 2020). Similarly in children, bilateral activity in the orbital frontal cortex has been associated with increased emotion regulation behavior (Lévesque et al., 2004). This pattern of connectivity related to greater ER has also been shown in adults (Ochsner et al., 2004), once again suggesting potential continuity in the neural circuitry support ER.

Multiple higher order brain systems also work together to facilitate ER (Rey et al., 2016). Specifically, functioning within the default mode network (Rey et al., 2016; Tozzi

et al., 2017; Xie et al., 2016), salience (McLaughlin et al., 2015; X. Wu et al., 2016) and dorsal attention networks (Viviani, 2013) support ER skills in adults. Similarly in adolescence, connectivity within the salience network supports ER (McLaughlin et al., 2015). Because immature forms of these large scale brain systems exist already in the newborn period (Gao, Alcauter, Elton, et al., 2015; Gao, Alcauter, Smith, et al., 2015), it may be that coordinated functioning within and between brain regions in these networks contributes to emerging ER skills. In fact, recent work already shows connectivity between default mode network regions in infancy are associated with increased negative emotionality (Graham et al., 2015), and decreased regulatory behavior (Kelsey et al., 2020). These findings interestingly mirror findings in children and adults implicating the involvement of the default mode network in emotional reactivity and regulation (Pan et al., 2018; van der Horn et al., 2016; Xie et al., 2016) once again suggesting potential continuity in neural circuitry support emotion regulation from infancy to adulthood. While the studies cited above have used diffusor tensor imaging, and resting state functional connectivity magnetic resonance imaging (rs-fcMRI) to examined specific brain connections and networks, respectively, in relation to emotion regulation, rs-fcMRI has yet to be used to examine amygdala connectivity soon after birth in relation to an observational measure of emotion regulation in infancy. Given the central role of amygdala functional connectivity in moderating negative emotionality in adulthood (Bebko et al., 2015; Denny et al., 2015; Mulej Bratec et al., 2015) and given the potentially continuity in neural circuitry supporting emotion regulation from infancy to adulthood, examining amygdala connectivity soon after birth in relation to emerging emotion regulation represents a natural starting point for the current studies.

While continuity in emotion regulation neural circuitry between infancy and adulthood appears at least partially to be the case, there are also likely systems involved in emotion regulation that are unique to infancy. Given the emergence of adult-like visual and sensorimotor functional networks early in infancy (Gao et al., 2015), and given that emotion regulatory behavior involves rudimentary processes like shifting visual attention and thumb sucking (Braungart-Rieker & Stifter, 1996), it is possible that amygdala connectivity to sensory processing and integration regions plays a key role in emotion regulation in infancy. It is also likely that specific sensorimotor responses play a lesser role in adulthood, for example, non-nutritive sucking, which is an adaptive mechanism in infancy that does not normatively persist into adulthood (Feştilă et al., 2014; Field & Goldson, 1984). However, attentional control (orienting and executive attention in particular) appears to play a key role in emotion regulation in both infancy and adulthood (Crockenberg & Leerkes, 2004; Posner et al., 2012; Posner & Rothbart, 1998; Viviani, 2013). The anterior-insula-centered-salience functional network emerges in early infancy and supports executive attention (Gao et al., 2017; Posner et al., 2012). Moreover, the ability to anticipate the location of a stimulus is linked to emotion regulation from 6-7 months-of-age, showcasing the importance of orienting as a control system in infancy (Posner et al., 2012).

1.4. Using Rs-fcMRI to study the brain soon after birth

Resting state-functional magnetic resonance imaging (Rs-fcMRI) is a powerful tool that allows for the non-invasive study of functional and structural infant brain characteristics during natural sleep. Rs-fcMRI provides information about how the brain

is intrinsically functionally organized. Structurally, subcortical structures of the brain can be measured in three-dimensional voxel space, which allows for the characterization of the volumetric size of different subcortical brain structures. Additionally grey matter and white cortical brain matter can be delineated, allowing for the characterization of amount of myelination, cortical thickness or sulci depth (Glasser et al., 2013).

Rs-fcMRI allows the measurement patterns of connectivity across the brain, allowing us to see individual connections between brain regions as well as large-scale network connections in the brain at rest. With this information we are able to determine how brain functional connectivity is associated with infant behavior and other aspects of infant physiology. Rs-fcMRI is measured based on correlations between spontaneous fluctuations in the blood oxygen level dependent (BOLD) signal between different brain regions (Biswal et al., 1995). The BOLD signal indirectly measures activity in the brain and relies on the magnetic properties of hemoglobin in the blood (Ogawa et al., 1990).

For infant studies in particular, rs-fcMRI offers several advantages over other forms of neuroimaging. First and foremost, rs-fcMRI, based on low-frequency fluctuations in the BOLD signal across the brain, can measure activity across the brain in the absence of any task (Murayama et al., 2010). This allows for the measurement of resting state functional connectivity during natural sleep. Rs-fcMRI also allows for a more complete representation of brain regions involved (Fox & Raichle, 2007) while task-based fMRI may only activate a limited number of connectivity patterns in a particular domain, with each task activating specific brain regions. Moreover, because scans are conducted during natural sleep, there are even more limitations on the types of tasks that can be given to the infant during the scan, which limits the number of regions

that can be activated in a particular behavioral domain. Furthermore, rs-fcMRI allows for the comparison of functional neural connections across development (Dosenbach et al., 2007; Fair, 2010; Fair et al., 2012). Moreover, rs-fcMRI allows for the measurement of brain connections and systems associated with complex behaviors later in life, which may provide a window already in the neonatal period to patterns of brain organization later relevant for psychiatric disorders (Graham, Pfeifer, Fisher, Lin, et al., 2015).

1.5. Influence of the caregiving environment on the development of emotion regulation

A caregiver's ability to accurately identify and respond to the infant's needs, known as caregiver responsivity, is particularly important for the development of ER (Crockenberg & Leerkes, 2004; Leerkes & Crockenberg, 2003; Morris et al., 2017; Thomas et al., 2017). This form of extrinsic regulation presumably must be present if intrinsic regulation is ever to develop. In early infancy, infants are almost completely reliant on their caregivers for the regulation of their emotions. During this time, infants can use behavioral cues such as tone of voice, gestures, facial expressions and vocalizations to express their emotional state to their caregiver, who then, through timely and accurate responses to the infant's needs, can regulate the infant's emotions (Weinberg & Tronick, 1994). Caregivers can aid in the regulation of infant emotion by encouraging infants to redirect attention from distressing or novel stimuli, by responding accurately to the infants expressed need, or by motivating a positive interaction (Crockenberg & Leerkes, 2004). Responsive caregivers can effectively reduce infant distress in emotion-filled contexts; these interactions may teach infants strategies for

reducing their own emotional arousal in future situations, (previously noted as intrinsic regulation (Leerkes et al., 2009; Nigg, 2017). As a result, infants of relatively more responsive mothers may show more regulatory behaviors, in the absence of maternal input, than infants of relatively less responsive mothers (Frick et al., 2017a; Haley & Stansbury, 2003; Leerkes & Crockenberg, 2003).

In addition to influencing infant behavior, the caregiving environment influences infant physiology. Specifically, the caregiving environment can influence associations between infant positive emotionality and prefrontal and occipital cortical networks, such that more maternal mental state-talk is associated with greater infant positive emotionality and greater resilience of prefrontal and occipital cortical networks (Hanford et al., 2018). Additionally, differences in amount of maternal care in early life in rodent models have been shown to alter gene expression, particularly impacting the transcription of proteins regulating brain formation and function in the hippocampus (Weaver et al., 2006). Moreover, recurrent maternal care in early life may support the expression of genes involved in later attenuation of the stress-response (Fenoglio et al., 2006). Lastly, infants of more responsive caregivers may be better able to regulate their physiological response to stress, in the form of heart rate, when exposed to stressors (Haley & Stansbury, 2003). Thus the caregiving environment appears to play a key role in the emergence of infant emotion regulation behavior and underlying physiology.

Maternal depressive symptomatology, primarily through its effects on maternal responsivity, also appears to be important for the development of emotion regulation partly due to interfering with her responsivity. Depressed mothers are more likely to express lower sensitivity, inconsistent support of infant engagement, and a restricted

range of affective expression (Weinberg & Tronick, 1998). These qualities can create difficultly for development of adequate regulatory behaviors. Thus, infants of depressed mothers may express higher negative emotionality and less mature regulatory strategies (Feldman et al., 2009). Depressed mothers may also rate their infants as more difficult than non-depressed mothers in self-report questionnaires (Leerkes & Crockenberg, 2003; McGrath et al., 2008), thus maternal depressive symptomatology is an important covariate in studies with self-report measures. Maternal depressive symptoms may also impact physiology underlying infant emotion regulation. Findings from an EEG study, indicate that infants of depressed mothers show significantly lower frontal asymmetry scores than infants of non-depressed mothers, potentially indicative of early patterns of depressive symptoms (Dawson et al., 1997). Similarly, in a more recent EEG study, maternal depressive symptomatology was specifically associated with greater relative right-frontal alpha asymmetry in newborns (Gustafsson et al., 2018) and maternal depression predicted infant behavior. Additionally, maternal prenatal depression has been associated with infant negative affect (Gustafsson et al., 2018). Therefore infants of depressed mothers may have neural connectivity patterns potentially indicative of risk for future depression, and lower emotion regulation ability.

1.6. Executive function as a marker for future mental health and academic success

Executive function and its precursors constitute an important early emerging indicator of capacity for successfully engaging in academics and social functioning (Blair & Razza, 2007; Carlson et al., 2004; Mulder et al., 2017). As expressed by adulthood, executive function can be defined as a set of cognitive abilities involved in purposeful,

flexible, goal-directed behavior (Miyake et al., 2000). One model of executive function by adulthood is composed of three closely related, but distinct factors: inhibitory control (the ability to inhibit a prepotent response), working memory (the ability to retain and manipulate relevant information for the task at hand), and shifting (the ability to disengage from irrelevant tasks and reengage in relevant tasks) (Diamond, 2013; Miyake et al., 2000). Poor executive function abilities, like negative emotionality, can be an indicator of risk for mental health problems (Bettis et al., 2017; Pennington & Ozonoff, 1996; Zelazo, 2020).

1.6.1. The development of executive function

The foundations of executive function begin to develop in early life, with the support of attentional, cognitive, sensory motor skills, and neurobiology (Garon et al., 2008; Gottwald et al., 2016; Wu et al., 2017). For example, strategies to maintain or redirect attentional focus and general cognitive capacity in toddlerhood have been associated with executive function performance in childhood (Conway & Stifter, 2012; Eigsti et al., 2006; Wu et al., 2017). Moreover, prospective motor control supports precursors of executive functions at 18-months-of-age (Gottwald et al., 2016). The neurobiological correlates of executive function have also been hypothesized and include the dorsolateral and ventrolateral prefrontal cortex, which develop rapidly across the first two years of life (Diamond, 2002, 2013; Garon et al., 2008).

Multiple terms are used to refer to regulation of cognitive and emotional processes, effortful control is one such term, defined as an innate aspect of temperament reflecting propensity to self-regulate emotion and cognition with ease (Diamond et al., 2013). In toddlerhood executive function is in a primitive form and is not well

differentiated (Espy et al., 1999). During this time, effortful control, attention development and the ability to hold information in mind facilitates the development of early precursive executive functions (Michael I Posner & Rothbart, 1998).

Emerging effortful control, attention and short term memory support the development of early precursive executive functions. The ability to hold information in mind (short term memory) develops in infancy and supports the development of working memory and impulse control (Diamond et al., 2013). While impulse control is not yet present in toddlerhood, attention shifting ability and effortful control are present as precursors (Diamond et al., 2013). These precursors likely impact the inhibitory control of attention which allows for the ability to selectively attend to specific information and ignore information that is not relevant (Eigsti et al., 2006). Cognitive flexibility builds on working memory and impulse control and begins to emerge much later in development. Advanced skills, like planning, are not yet present in toddlerhood except in a very rudimentary form (Diamond et al., 2013).

The developmental course of early precursive executive functions relates to subsequent development across domains. Early precursive executive function skills have been associated with future internalizing and externalizing symptomatology in childhood (Murray & Kochanska, 2002) and executive function in late adolescence (Eigsti et al., 2006) Moreover, early precursive executive function skills may provide a foundation for healthy development (Blair & Razza, 2007; Mulder et al., 2017), with implications for academic and social functioning (Carlson et al., 2004; Hughes & Ensor, 2005).

1.6.2. The interplay of negative affect, emotion regulation, and executive function

Both executive function and ER, while conceptually independent constructs, are closely related and share conceptual space. For example, both concepts involve top down aspects of self-regulation (Nigg, 2017). However, ER and executive function are not the same as self-regulation, rather executive function can enable self-regulation and emotion regulation, but top down ER can be extended to multiple strategies in adulthood (Gross 2015; Nigg, 2017). Developmentally, the relationship between emotion regulation and executive function may also be bi-directional. Research indicates children ages 8-12, with better emotion regulation skills may have greater proficiency on precursive executive function measures (Sudikoff et al., 2015). Moreover, individuals with greater executive function may be better able to use emotion regulation strategies to decrease negative affect (Pe et al., 2013). Effortful control in infancy, which impacts both executive function and ER, can serve to increase or decrease the onset, duration or intensity of temperament reactions (Rothbart 2011). In turn, infants and toddlers who have higher negative emotional reactivity paired with low effortful control are more likely to develop ADHD (Willcutt et al., 2005).

Early skills like redirecting attention and effortful control are simultaneously the precursors of executive function and the precursors of intrinsic ER (Feldman, 2009). Greater intrinsic emotion regulatory skills in infancy, which are the same as top-down executive function, have been associated with greater executive function skills at 5-years-of-age (Feldman, 2009). Furthermore, unregulated negative emotionality has been associated with worse executive function in preschoolers (Ferrier et al., 2014). Thus, development of executive function abilities may therefore rely on the earlier effective

regulation of negative emotionality (Zelazo & Cunningham 2007). However, it may not be emotion regulation or negative emotionality alone that support emerging executive function; it may be the specific match between levels of negative emotionality and emotion regulation that is relevant for executive function. Importantly this is recursive. Effortful control and attention development, the precursors of executive function, support the development of ER, and in turn the consolidation of ER facilitates the development of executive function (Posner & Rothbart, 1998).

Specifically, in one study the interaction between emotion regulation and reactivity at 15-months-of-age predicted executive function at 48-months-of-age (Ursache et al., 2012). These findings indicate that high reactivity paired with high regulation is associated with greater executive function, while high reactivity paired with low regulation is associated with worse executive function. This suggests that reactivity must be balanced by regulation for the development of executive function skills. Thus it appears important to assess both levels of emotion regulation and negative emotionality in relation to executive function see **Figure 2**. While this interaction has already been examined in relation to executive function in early life, associations between emotion regulation and negative emotionality in the first year of life and specific domains of executive function in toddlerhood remain unknown.

Figure 2. High reactivity paired with high regulation is associated with greater executive function, while high reactivity paired with low regulation is associated with worse executive function. This suggests that reactivity must be balanced by regulation for the development of executive function skills. Thus negative emotionality paired with the ability to regulate emotions may predict future executive functions.

1.6.3. Psychosocial moderators may influence associations between negative emotionality and emerging executive function

Associations between negative emotionality and emerging executive function may also be influenced by variation in the caregiving environment and socioeconomic status (SES). SES may influence development of executive function through availability of learning resources, opportunities in the home environment, as well as the time and guidance provided by caregivers (Hackman et al., 2015). For example, variation in access to computers and home literacy activities has been shown to mediate a relationship between low SES and executive function (Lipina et al., 2013). Moreover, SES likely influences development through the quality, sensitivity, and responsivity of caregiving (Hackman et al., 2015). The caregiving environment, particularly maternal responsivity, may exert a strong impact on emerging executive function (Fay-Stammbach et al., 2014). Specifically, sensitive caregiving can promote the infants internalization of regulatory strategies (Bernier et al., 2012). As such, sensitive, engaging interactions with caregivers may be associated with decreased negative emotionality and increased executive function

competence (Rhoades et al., 2011). Moreover, negative emotionality at 9-months-of-age, moderated by maternal caregiving at 9-months-of-age, has been associated with executive function at 5-years-of-age (Miller et al., 2019). Early maternal caregiving has also been shown to influence infant temperament reactivity (Miller et al., 2019a) and associations between negative emotional reactivity in infancy and executive function in childhood (Miller et al., 2019b). Thus it appears important to consider the postnatal environment when evaluating associations between negative emotionality and executive function.

1.7. The current studies

The current studies aimed to identify the earliest neural precursors of intrinsic emotion regulation through the examination of coordinated functioning of the newborn brain in relation to emerging negative emotionality and emotion regulation behavior and physiology at 6-months-of-age with consideration of selected aspects of the caregiving environment. In addition, toddler outcomes associated with infant emotion regulation are examined. Specifically, Study 1 examined if a-priori neonatal amygdala functional connectivity to regions of interest for emotional reactivity and regulation are associated with infant negative emotionality development across the first two years of life. Study 2 examined potential pathways from neonatal amygdala functional connectivity to emerging emotion regulation/ reactivity behavior and physiology during infancy, and subsequent internalizing and externalizing symptomatology in toddlerhood. Lastly, Study 3 examined how emerging emotional reactivity, emotion regulation, and two environmental measures, SES status and caregiver behavior during infancy, relate to subsequent executive function skills during toddlerhood.

Chapter 2: Amygdala Connectivity soon after birth supports early emerging Fear

2.1. Introduction

2.1.1. The importance of examining early neural correlates of fear

Fear is an emotion essential for adaptive functioning expressed when an animal perceives potential danger (Milad & Quirk, 2012; Phelps & LeDoux, 2005). While fear expression is essential for adaptation, heightened levels of fear are associated with psychopathology (Engle & Mcelwain, 2011; Gjone et al., 1997). Limbic-prefrontal brain systems play a critical role in normative and pathological variability in fear in children and adults (Etkin et al.,2011, 2007; Milad & Quirk, 2012; Qin et al., 2014; Ruocco et al., 2013); however, how these brain systems in the newborn period contribute to the early development of fear is poorly understood.

2.1.2. Typical development of fear

Fear expression typically increases over the first year of life as increasing mobility facilitates increasingly complex interactions with the environment, and increasing exposure to threatening stimuli (Shaw et al., 2000). It is likely that fear expression rises during the first year of life as it becomes ecologically significant for the infant's survival (Callaghan et al., 2014). By the second year of life, the infant's expression of fear stabilizes (Garstein & Rothbart, 2003; Partridge & Lerner, 2007). This is likely due to the infant's increasing ability to regulate emotions both independently, and through use of caregiver support (Gartstein et al., 2012; Lemery et al., 1999). Due to

changes in fear expression over time (Gartstein et al., 2010; Lipscomb et al., 2012; Partridge et al., 2007), it is critical to examine fear at multiple time points to capture it's full early developmental trajectory.

2.1.3. Early brain connectivity as a predictor of fear

We have previously shown that newborn amygdala functional connections predict early fear expression (Graham et al., 2016). Specifically, stronger connectivity between the amygdala and bilateral anterior insula (amygdala-aI) was associated with higher fear at 6-months-of-age. This finding is in line with adult literature suggesting an important role for amygdala-aI connectivity in normative (Baur et al., 2013), and pathological fear (Etkin et al., 2007; Rabinak et al., 2011; Sripada et al., 2012). This suggests potential continuity in the neural circuitry underlying the early emergence of fear. Furthermore, we have previously shown that stronger connectivity between the amygdalae and ventral medial prefrontal cortex (amygdala-vMPFC) at birth is associated with a phenotype characterized by higher fear and more advanced cognitive development at 6-months-of-age potentially suggesting that a balance between negative affect and cognitive skills is relevant for effectively regulating negative affect (Degnan & Fox, 2007; Gartstein et al., 2012; Nigg, 2006). In line with this interpretation, amygdala-vMPFC connectivity plays an important role in emotion regulation in children and adults (Gee, Gabard-Durnam, et al., 2013; Milad et al., 2007; Schiller & Delgado, 2010; Silvers et al., 2017), and has been frequently implicated in conditions involving poor regulation of negative affect, including anxiety (Casey & Lee, 2015; Loucks, et al., 2011; Roy et al., 2013a) and depression (Burghy et al., 2012; Connolly et al., 2017; Wang et al., 2013). However, the

role of amygdala-vMPFC connectivity in the development of fear and other aspects of negative emotionality (NE) during infancy and toddlerhood has not been examined.

2.1.4. Key influences on the development of fear

During infancy, caregivers serve an important role in influencing infants emotion reactivity and regulation (Bernier et al., 2016). Infants use behavioral cues to communicate their emotional state to caregivers who aid in emotion regulation through quick and accurate responses to the infant's expressed needs (Thomas et al., 2017). Responsive caregivers can effectively reduce infant distress, decreasing infants' expression of fear and other aspects of NE over time (Leerkes et al., 2009). Moreover, neural phenotypes may increase or decrease the influence of maternal responsivity on emerging fear (Ellis et al., 2011). It is therefore important to consider the caregiving environment as well as interactive effects of maternal responsivity and newborn brain phenotypes in relation to emerging fear.

Maternal depressive symptomology influences maternal reporting and observation of infant NE. Mothers with greater depressive symptoms are more likely to rate their infants as more difficult than parents who are not depressed (Parade & Leerkes, 2008). Additionally, more severe maternal depressive symptoms have been associated with greater increases in infant fear from 8-12 months of age (Gartstein et al., 2010). Research to date also suggests some specificity, such that the association between maternal symptomatology in the postpartum period and infant NE is specific to maternal depression versus anxiety (Feldman, et al., 2009). These results highlight the importance of considering maternal depressive symptoms in examining infant fear development.

2.1.5 Present study

In the current study we examine how newborn amygdala-vMPFC and amygdala-aI connectivity relate to the developmental trajectory of fear over the first two years of life. Further, to see if these connections are specific to emerging fear or more generalizable to other aspects of NE, we also examine them in relation to emerging sadness. Finally, we consider how maternal responsivity and depressive symptomology may moderate associations between these newborn amygdala connections and subsequent development of NE.

Based on previous work (Etkin & Wager, 2007; Graham et al., 2016; Rabinak et al., 2011; Sripada et al., 2012), we hypothesize stronger amygdala-aI connectivity will be associated with higher fear at 6-months-of-age and greater increase in fear over the first two years of life. Due to the role of amygdala-vMPFC connectivity in depression and anxiety in adolescents and adults (Casey & Lee, 2015; Wang et al., 2013), we anticipate this connection will demonstrate associations with both fear and sadness development. While stronger amygdala-vMPFC connectivity is associated with greater emotion regulatory ability in adolescents and adults (Silvers et al., 2017), due to the developmental switch in how amygdala activity relates to vMPFC activity while viewing negatively valenced stimuli (Gee et al., 2013), we anticipate stronger amygdala-vMPFC connectivity will be associated with higher levels of NE at 6-months and greater increase in NE from 12-24 months-of-age. Finally, we anticipate associations between newborn amygdala connectivity and NE development will be moderated by levels of maternal responsivity.

2.2. Methods and materials

2.2.1 Participants

Infants included in this study (N=62) were part of an ongoing longitudinal study of mothers and infants conducted at the University of California Irvine (for details see Moog et al., 2017). Mothers were recruited during their first trimester of pregnancy. Exclusionary criteria included: maternal use of systemic corticosteroids or psychotropic medications during pregnancy, infant birth before 34 weeks' gestation, and infant congenital, genetic, or neurological disorder. An MRI and fMRI scan was completed when infants were approximately 4-weeks-of-age (*M* ± *SD*, 3.7 ± 1.7). Temperament assessments were completed at 6, 9, 12, and 24-months-of-age. Detailed demographic information is provided in **Table 1.**. All procedures were approved by the Institutional Review Board at the University of California, Irvine. The number of subjects with data at each time point is provided in **Table 1.**

Table 1.: Demographics

	Mean (SD)
Age in Weeks	
Gestational age at birth	39.1 (1.5)
Age at fMRI data collection	3.7 (1.7)
Age at 6 moth behavioral assessment	28.0 (2.4)
Age at 9 month behavioral assessment	39.9 (7.4)
Age at 12 month behavioral assessment	55.0 (3.1)
Age at 24 month behavioral assessment	240.0 (35.1)
	Percentage
Sex	
Male	54.8
Female	45.2
Race/ethnicity	
Caucasian non-Hispanic	37.7

African American non-Hispanic	2.6
Asian non-Hispanic	7.8
Multi-racial non-Hispanic	10.4
Caucasian Hispanic	33.8
Asian Hispanic	1.3
Multi-racial Hispanic	5.2
Other Hispanic	1.2
Highest level of maternal education	
Primary, Elementary, or Middle School	1.6
High-school or test equivalent	14.5
Technical or vocational school	12.9
Some college, but no degree	30.6
Associates degree	3.2
Bachelor's degree	19.4
Graduate level degree	12.9
Certificate	4.8
Gross annual household income	
<$15,000	9.6
$15,000- 29,999	19.2
$30,000- 49,999	27.4
$50,000- 100,000	35.6
>$100,000	8.2

2.2.2 MRI and fMRI data acquisition and processing

2.2.2.1 Data acquisition

As described in our previous work (Graham et al., 2016, 2017, 2018; Rudolph et al., 2018) a TIM Trio, Siemens Medical System 3.0T scanner was used to collected neuroimaging data with infants during natural sleep. A T2-weighted scan (TR = 3200 ms, echo time = 255ms, resolution = 1 x 1 x 1 mm, 4.18 min) was used as an anatomical reference for functional images. A T1-weighted scan (MR-RAGE TR = 2400 ms, inversion time = 1200 ms, echo time = 3.16 ms, flip angle = 8°, resolution = 1 x 1 x 1 mm, 6.18 min) was used in conjunction with the T2-weighted scan for amygdala

segmentation. To obtain functional images for rs-fcMRI, 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°) was used. Using 32 ascending-interleaved 4 mm axial slices with a 1 mm skip, full brain coverage was obtained. Steady-state magnetization was assumed after 4 frames (8 ~ s). Functional data was obtained in a single scan consisting of 150 volumes for early participants (N = 8), and increased to 195 volumes for the remaining participants (N = 54) in later stages of the study to increase the likelihood of acquiring a sufficient number of volumes for analysis. Only functional scans with at least 4 minutes of data (after volume removal for motion) were included in the present study.

2.2.2.2 fMRI data preprocessing

The Brain Extraction Tool from the FMRIB Software library (Beckmann et al., 2006; Smith et al., 2001; Smith, 2002) was used as an initial step to separate the brain from the rest of the head tissue in images. Next, an in house tool was used to remove the remaining skull. This tool involved registration of a skull stripped infant atlas (0- to 2-month age range; MRI Study of Normal Brain Development; (Fonov et al., 2011)) to the individual image, which allowed for creation of a refined individual brain mask. Functional images were preprocessed to reduce artifacts (Miezin et al., 2000) as in our prior work (see Graham et al., 2016). Atlas transformation of the functional data was computed for each individual via the high-resolution T2 scan (see Graham et al., 2016). Visual inspection of data resulted in the loss of two subjects for poor quality EPI scans,

and one subject for a structural abnormality identified in the high resolution T2- weighted scan.

2.2.2.3. rs-fcMRI preprocessing

To control for signal from non-neuronal processes additional preprocessing steps were conducted for rs-fcMRI data as in our prior studies (D. Fair et al., 2012; Graham et al., 2016; Rudolph et al., 2018). A volume censoring approach was used to remove volumes associated with greater than 0.3 mm frame-wise displacement (FD) (including 1 preceding and 2 following volumes to account for temporal blurring (Power et al., 2012)). Scans with less than 4 mins of remaining data were removed. This resulted in an additional 3 infants being removed from the analysis. Scan length after volume removal for remaining infants (N = 62) was approximately 5 and a half minutes (M = 5.50, range = 4.14 – 6.30), and the remaining FD was approximately 0.08 (M = 0.081, range = 0.047 – 0.134). To rule out effects of remaining motion on results, post-hoc analysis included adjustment for remaining FD (Fair et al., 2012; Power et al., 2015).

2.2.2.4 Amygdala regions of interest

2.2.2.4.1 Amygdala ROIs

Amygdalae were automatically segmented using a multi-template, multi-modality based method combining T1 and T2 weighted high-resolution images (J. Wang et al., 2014). Data was then realigned such that the anterior-posterior direction was positioned along the hippocampal long axis for manual correction of the amygdala segmentations in ITK-Snap (Yushkevich et al., 2006). Manual correction involved a strict protocol

consisting of shape correction and definition of the boundary between the hippocampus and amygdala defined by CSF contrast in the T2 weighted image. Manual corrections of the automatic segmentations were performed using both the T1- and T2-weighted image (see Graham et al., 2016 for details).

2.2.2.4.2. Amygdala connections to anterior insula and vMPFC

We examined amygdala functional connections identified in a prior study (Graham et al., 2016). Specifically, our prior work employed several whole brain regressions to examine newborn left and right amygdala connectivity in relation to infant fear and a fear and cognition phenotype at 6-months-of-age (Graham et al., 2016). The results of this analyses indicated that newborn functional connectivity between the left amygdala and bilateral anterior insula was related to infant fear, and connectivity between both right and left amygdala and vMPFC was related to a fear-cognition phenotype. Regions of interest (ROIs) for the bilateral anterior insula and vMPFC were extracted from the whole brain maps resulting from these analyses. Specifically, in line with previous research (Fair et al., 2007; Mills et al., 2012), a search algorithm from the 4dfp Suite of Image Processing Programs (ftp://imaging.wustl.edu/pub/raichlab/4dfp_tools/) was used to identify peak voxels within the whole brain map (with z-values greater than or equal to 2.25 for consistency with the Monte Carlo correction for multiple comparisons). Regions were then defined around the peaks beginning with a radius of 10mm, consolidating regions with peaks closer than 10mm, and masking out voxels falling outside of the Monte Carlo corrected whole brain regression. Since there were multiple peaks within the vMPFC and bilateral

anterior insula, the peak with the highest z-value was the basis for each of these ROIs. Coordinates in Talairach space are as follows: vMPFC (8, 27, -1; -2, 20, -20), anterior insula (-38, 13, -8; 36, 12, -5). Due to Type 1 error concerns (Eklund et al., 2016) these regions were further validated with secondary analyses (for details see Graham et al., 2016).

Fisher *Z*-transformed (normally distributed) correlation coefficients representing connectivity strength between the bilateral amygdala-vMPFC ROIs and left amygdala-aI ROIs were used in subsequent analyses. These a-priori hypothesized regions are provided in **Figure 1**.

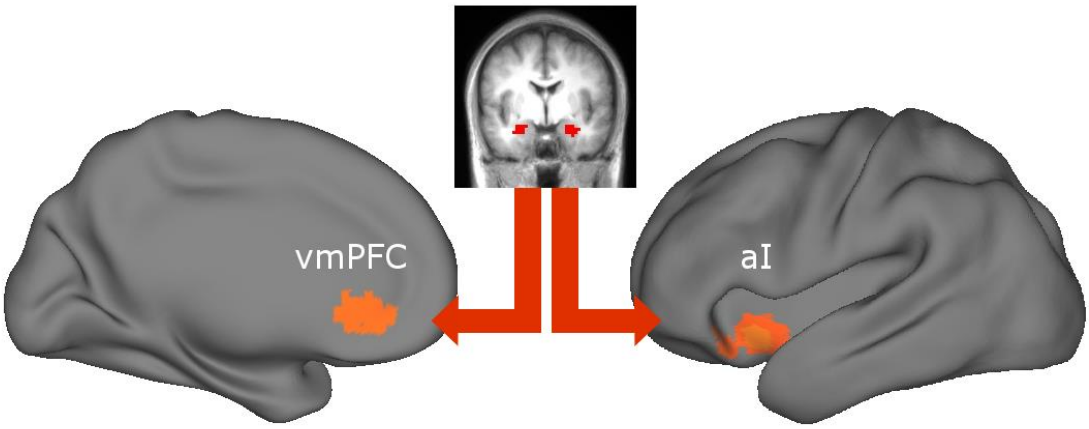

Figure 1. The ventromedial prefrontal cortex (vMPFC) and anterior insula regions (aI) of interest (ROIs) were identified in a prior study examining whole brain voxel-wise connectivity of the neonatal amygdala in relation to fear and a fear-cognition phenotype at 6-months-of-age (Graham et al., 2016). The ROIs from this prior study are displayed here. Based on the results of this prior work, amygdala-aI and amygdala-vMPFC connections were extracted and examined in the current study.

2.2.3. Infant behavioral outcomes

2.2.3.1 Infant fear and sadness

Infant fear and sadness were assessed at 6 months (M6), 9 months (M9) and 12 months (M12) via maternal report on the Infant Behavior Questionnaire-Revised (IBQ-R) (Garstein & Rothbart, 2003) designed for 3-12 month old infants. At 24 months of age (M24), fear and sadness were assessed via maternal report on the Early Childhood Behavior Questionnaire-Short Form (ECBQ) (Putnam et al., 2006) designed for 18-26 month old infants. Importantly, prior research indicates convergent validity between laboratory-based observational measures of fear and maternal-self reported measures of fear on the IBQ-R at 6, 9 and 12 months of age (Gartstein & Marmion, 2008; Parade & Leerkes, 2008), indicating the utility of this measure across the first year of life. Additionally in longitudinal work, convergent validity between IBQ-R and ECBQ subscales of fear and sadness has been demonstrated (Putnam et al., 2008), supporting the idea of consistency in these measurements across time. On both questionnaires mother's rated their infants' engagement in specific fear- and sadness-related behaviors on a Likert-type scale from 1 (never) to 7 (always). Fear was assessed based on the amount of distress the infant experienced to sudden changes in stimulation, exposure to novel physical objects or social stimuli (Garstein & Rothbart, 2003). Sadness ratings reflected activity and lowered mood caused by the infant's personal suffering, physical state, loss of an object, or inability to perform a desired action (Garstein & Rothbart, 2003).

2.2.3.2 Postnatal caregiving environment

When infants were 6-months-of-age, quality of the postnatal caregiving environment was assessed using the Home Observation for Measurement of the Environment (HOME) Inventory (Bradley et al., 2003). Assessments were made by trained observers who had achieved reliability with a certified administrator of the inventory (95% agreement on two consecutive videos). Home visits were done to observe the infant's activities and interactions in their caregiving environment and conduct a semi-formal interview with their mothers. In our analysis, we used the subscale HOME Responsivity to assess the extent of maternal responsiveness to the infant. Responsive mothers respond quickly and appropriately to cues from their infants; in early life this has a strong effect on the development and future expression of NE (Ester M Leerkes et al., 2009).

2.2.3.3 Maternal depressive symptomology

To assess maternal depressive symptomology the 20-item Center for Epidemiological Studies of Depression Scale (CESD) (Radloff, 1977) was administered at M6, M9, M12 and M24.

2.2.4. Analytic approach

We examined longitudinal trajectories of fear and sadness development using latent growth models (LGM) in a structural equation-modeling framework. First, we created an unconditional LGM for each of the developmental trajectories - fear and sadness - to look at the average growth patterns for the sample. This was done using data

from four time points: M6, M9, M12 and M24. The latent intercept was specified at the M6 time point with growth factors representing change from M6-M24.

To assess the association between newborn amygdala connectivity patterns and the development of fear and sadness, for each connection of interest (amygdala-aI and amygdala-vMPFC), we tested a separate model with the connection as a predictor of the latent growth factors. In each model we controlled for gestational age at birth (GA) and age at scan.

Additionally, we considered maternal CESD scores as a covariate for time points with significant correlations between CESD scores and fear and sadness measures to account for potential maternal reporting bias due to depressive symptomology. Lastly, we examined the independent and moderating effects of HOME responsivity scores on emerging fear and sadness trajectories. All models were estimated using full-information maximum likelihood (FIML) under the missing-at-random (MAR) assumption with Mplus Version 7.4 (Muthén & Muthén, 2015). To ensure infants lost to follow- up at 9, 12, or 24 months did not differ from the remainder of the cohort across key clinical variables, we conducted independent sample T-tests to compare sample means of maternal responsivity, average maternal CESD, and connectivity measures across subjects with and without data at each time point. No significant differences between means were found ($p > 0.05$); indicating infants lost to follow-up did not differ from the remainder of the cohort across these measures.

2.3. Results

2.3.1 Descriptive analyses

2.3.1.1 Infant fear and sadness

Means for fear and sadness measures and Cronbach's alpha coefficients at each time point in the current sample are provided in **Table 2**. Fear and sadness were significantly correlated at each time point, but the strength of correlations were moderate (r = .51- .53, $p < 0.01$) providing support for fear and sadness being related, but distinct constructs. With regard to internal reliability, Cronbach's alpha for the fear and sadness scales at each time point exceeded 0.70 (α = .72- .91). There was one exception for sadness at 24-months-of-age (α = .46), which was likely due to the low number of sadness items in the ECBQ questionnaire at this time point (N = 6).

Table 2: Means, Standard Deviations and Internal Reliabilities for IBQ & ECBQ Dimensions

IBQ-R Dimension	N	M	SD	α
Sadness- 6 months	56	3.59	1.04	0.86
Sadness- 9 months	45	3.73	0.98	0.87
Sadness- 12 months	43	3.82	1.01	0.85
Sadness- 24 months	49	3.05	0.76	0.46
Fear- 6 months	56	2.84	1.06	0.91
Fear- 9 months	44	3.23	1.09	0.91
Fear- 12 months	43	3.40	1.13	0.89
Fear- 24 months	49	2.53	1.04	0.72

Note: Eight out of nine alphas calculated exceeded 0.70, demonstrating adequate internal consistency. Sadness at 24 months was noticeably lower (α = .46).

2.3.1.2 Maternal depressive symptoms

Internal reliability of the CESD measured at each time point was high (α = .83- .91). The distribution of CESD scores was in line with expectations for a non-clinical sample (*mean* ± *SD*, 10.11 ± 7.98) (Radloff, 1977). Correlations between temperament scores and CESD scores at each time point were calculated to examine the need to adjust

for effects of maternal mood on reporting of infant emotionality (Parade & Leerkes, 2008). Results indicated that higher maternal CESD was associated with higher levels of infant sadness at 6-months-of-age (r = .268, p < .01), but not with fear at any time point, or with sadness at other time points. This indicated a need to account for maternal depressive symptoms at the 6-month time point as a covariate in the model examining infant sadness.

2.3.1.3 Maternal Responsivity

A wide range of scores was seen for the HOME responsivity scores ($M \pm SD$, 8.32 ± 1.78, range = 1-11), reflective of wide diversity in the home environments the infants in this study were exposed to.

2.3.2 Primary Analysis

2.3.2.1 Unconditional model for fear growth trajectory

First, we tested a linear growth model in which the intercept factor loading was fixed at 0 (M6) and the linear factor loadings at 0.25, 0.5 and 1.5 (M9, M12 and M24, respectively). However, as indicated from the means at each time point (**Table 2**), the initial increase in expression of fear from M6-M12 was followed by a decrease from M12-M24 (**Figure 2**), and the linear model did not fit the data well (χ^2 (5) = 64.90, p < 0.001, *CFI* = 0.39, *TLI* = 0.27, *RMSEA* = 0.30). To address this nonlinearity, a quadratic growth term was added to the model. This model fit the data (χ^2 (3) = 1.07, p = 0.79, *CFI* = 1.00, *TLI* = 1.10, *RMSEA* < 0.001), and was significantly better than the linear model (chi-square difference test χ^2 (4) = 64.132, p < 0.001).

Thus we used the quadratic model for the remainder of our analyses. In this quadratic model, the non-significant covariance between the intercept and linear slope, as well as the non-significant residual variance in fear at 24-months was restricted to increase reliability of the model results. The model parameters are listed in **Table 3.**

The quadratic model captured an increase (M6-M12) followed by a decrease (M12-M24) in fear (see **Table 2**), reflected in the significant negative mean of the quadratic term (M = -1.34, $p < 0.001$). Additionally, a significant positive linear term (M = 1.8, $p < 0.001$) indicated an overall increase in fear after 6-months-of-age (**Figure 3**).

Table 3. Fear Models

	Unconditional		Amygdala-aI		Amygdala-vMPFC	
Parameter	Estimate	*SE*	Estimate	*SE*	Estimate	*SE*
Intercept Mean	***2.84	0.14	***8.20	3.13	6.97	3.52
Intercept Variance	***0.76	0.18	***0.66	0.16	***0.74	0.18
Linear Growth Term Mean	***1.80	0.38	-12.96	8.67	-10.90	9.22
Linear Growth Term Variance	1.51	2.09	1.82	1.91	1.35	1.95
Intercept & Linear Growth Term Covariance	Restricted		Restricted		Restricted	
Quadratic Growth Term Mean	***-1.34	0.24	8.02	5.83	7.45	5.89
Quadratic Growth Term Variance	0.87	0.89	1.04	0.82	0.76	0.83
Quadratic and Intercept Covariance	-0.13	0.08	-0.09	0.07	†-0.14	0.08
Quadratic & Slope Covariance	-1.02	0.24	-1.27	1.24	-0.88	1.26
Predictors of Intercept						
Amygdala-aI			***3.10	0.72		
amygdala-vMPFC					0.90	0.75
Scan Age			0.00	0.01	0.00	0.01
GA			†-0.15	0.08	-0.11	0.09
Predictors of Linear Growth Term						
Amygdala-aI			**-5.55	2.13		
amygdala-vMPFC					-1.68	1.97
Scan Age			0.05	0.03	†0.05	0.03
GA			†0.37	0.22	0.30	0.15

Predictors of Quadratic Growth				
Term				
Amygdala-aI	2.19	1.44		
amygdala-vMPFC			0.64	1.27
Scan Age	-0.03	0.02	-0.03	0.02
GA	-0.23	0.15	-0.21	0.15

Note: χ^2=chi-square; CFI=Comparative Fit Index; TLI=Tucker and Lewis Index;
† $p < 0.10$. * $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$.

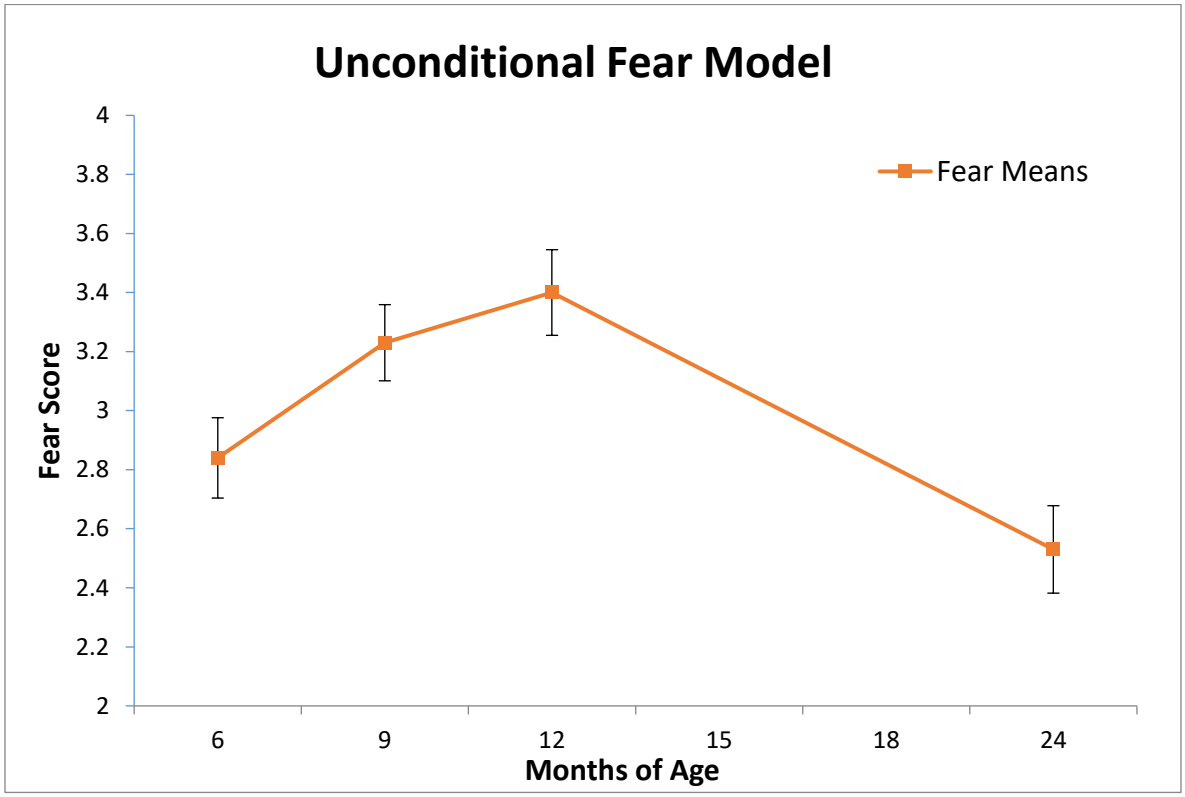

Figure 2. Fear developmental trajectory from 6-24 months of age.

2.3.2.2 Amygdala-aI connectivity predicts growth trajectory of fear

Next, we added amygdala-aI connectivity as a predictor to the unconditional fear model with covariates for GA and age at scan. Amygdala-aI connectivity was significantly, positively associated with the intercept ($b = 0.53$, $p < .001$; **Figure 4A**) and

negatively associated with the linear growth term (b = -0.52, $p < 0.05$). It was not associated with the quadratic growth term (b = 0.31, p = 0.15; **Figure 4B**). Importantly, to ensure results were not driven by the starting point, we included the intercept as a covariate in the pathway from amygdala-aI connectivity to the linear growth term in this model and found that that amygdala-aI connectivity still significantly predicted the linear growth term (b = -4.89, $p < 0.05$). Thus, stronger newborn amygdala-aI connectivity predicted higher levels of fear at 6-months-of-age, consistent with our prior findings (Graham et al., 2016), and less increase in fear expression over the first two years of life independent of the starting point.

2.3.2.3 Maternal responsivity does not alter the association between amygdala-aI connectivity and fear growth

Associations between amygdala-aI connectivity and the fear intercept and linear growth term remained the same after adding maternal responsivity (via HOME responsivity) as a covariate in the model ($p < 0.05$). The association between amygdala-aI connectivity and the quadratic growth term remained non-significant ($p > 0.10$). No significant associations emerged between maternal responsivity and the intercept, linear or quadratic growth terms ($p > 0.05$). To test maternal responsivity as a moderator for the effect of amygdala-aI connectivity on fear growth, we added the interaction between amygdala-aI connectivity and maternal responsivity as a predictor in the model. The interaction between maternal responsivity and amygdala-aI connectivity did not predict the intercept (b = -0.02, SE = 0.13, $p > 0.1$), linear (b = 0.20, SE = 0.40, $p > 0.1$), or quadratic growth terms (b = -0.16, SE = 0.27, $p > 0.1$) of fear when added to the model.

Results suggest newborn amygdala-aI connectivity predicts fear development over the first two years of life independent of maternal responsivity.

2.3.2.4 Amygdala-vMPFC connectivity not significantly associated with fear trajectory

We next tested a separate model, in which we examined the role of amygdala-vMPFC connectivity in fear development over time by adding it as a predictor to the unconditional model of fear growth. No significant main effects of amygdala-vMPFC connectivity were found on the intercept, linear, or quadratic growth terms (see **Table 4**). Thus, unlike newborn amygdala-aI connectivity, amygdala-vMPFC connectivity was not significantly associated with the trajectory of fear growth from 6-24 months-of-age. Results were unchanged after adjusting for maternal responsivity and considering it as a potential moderator.

2.3.3 Unconditional model for sadness growth trajectory

As with fear, to map the trajectory of sadness from 6-24 months-of-age we initially tested the fit of a linear growth model. Intercept factor loadings were fixed at 0 (M6) and linear factor loadings at 0.25, 0.5, and 1.5 (M9, M12, and M24, respectively). However, as indicated from the means at each time point (**Table 2**), the initial increase in expression of sadness from M6-M12 was followed by a decrease from M12-M24 (**Figure 3**), and the linear model did not fit the data well, χ^2 (5) = 12.13, p = 0.03, *CFI* = 0.88, *TLI* = 0.86, *RMSEA* = 0.10. To address this nonlinearity, a quadratic term was added to the model. This model fit the data well (χ^2 (5) = 3.56, p = 0.61, *CFI* = 1.00, *TLI* = 1.04,

RMSEA < 0.001) and was significantly better than the linear model (chi-square difference test [χ^2 (4) = 12.11, $p < 0.025$]). Thus we used the quadratic model for the remainder of our analyses. In this quadratic model, the non-significant residual variance in the linear growth term was restricted to increase reliability of the model results. Specific model parameters are listed in **Table 4.**

Due to the significant association between maternal depressive symptoms and infant sadness at 6-months we initially considered maternal CESD scores as a covariate with sadness at this time point. However, including M6 CESD as a covariate significantly worsened our model fit (χ^2 (4) = 10.18, $p = 0.037$, *CFI* = 0.91, *TLI* = 0.78, *RMSEA* = 0.11; chi-square difference test [χ^2 (1) = 6.62, $p < 0.01$]), and did not alter the significance or direction of the intercept, linear and quadratic growth terms in the unconditional model. Including the covariate also did not alter associations between brain connectivity and these growth terms. Therefore, the final models reported below do not include this covariate.

Table 4. Sadness Models

	Unconditional		Amygdala-aI		Amygdala-vMPFC	
Parameter	Estimate	*SE*	Estimate	*SE*	Estimate	*SE*
Intercept Mean	***3.60	0.13	**8.57	3.34	7.85	3.27
Intercept Variance	***0.66	0.16	***0.66	0.16	***0.66	0.16
Linear Growth Term Mean	*0.87	0.39	-12.21	9.76	-10.25	9.26
Linear Growth Term Variance	Restricted		Restricted		Restricted	
Intercept & Slope Covariance			N/A		N/A	
Quadratic Growth Term Mean	**-0.82	0.25	3.75	6.19	2.94	2.91
Quadratic Growth Term Variance	***0.16	0.04	***0.14	0.04	***0.15	0.04
Quadratic and Intercept Covariance	**-0.22	0.07	**-0.20	0.07	**-0.21	0.07
Quadratic & Linear Growth Term Covariance	N/A		N/A		N/A	

Predictors of Intercept				
Amygdala-aI	1.38†	0.77		
Amygdala-vMPFC			**1.78	0.70
Scan Age	-0.01	0.01	-0.01	0.01
GA	-0.13	0.08	-0.11	0.08
Predictors of Linear Growth Term				
Amygdala-aI	-3.83	2.35		
Amygdala-vMPFC			**-5.73	2.00
Scan Age	0.02	0.03	0.01	0.03
GA	0.34	0.25	0.29	0.23
Predictors of Quadratic Growth Term				
Amygdala-aI	1.72	1.50		
Amygdala-vMPFC			*2.98	1.29
Scan Age	0.00	0.02	0.00	0.02
GA	-0.13	0.16	-0.11	0.15

Note: χ^2=chi-square; CFI=Comparative Fit Index; TLI=Tucker and Lewis Index;
† $p < 0.10$. * $p < .05$. ** $p < 0.01$. *** $p < 0.001$.

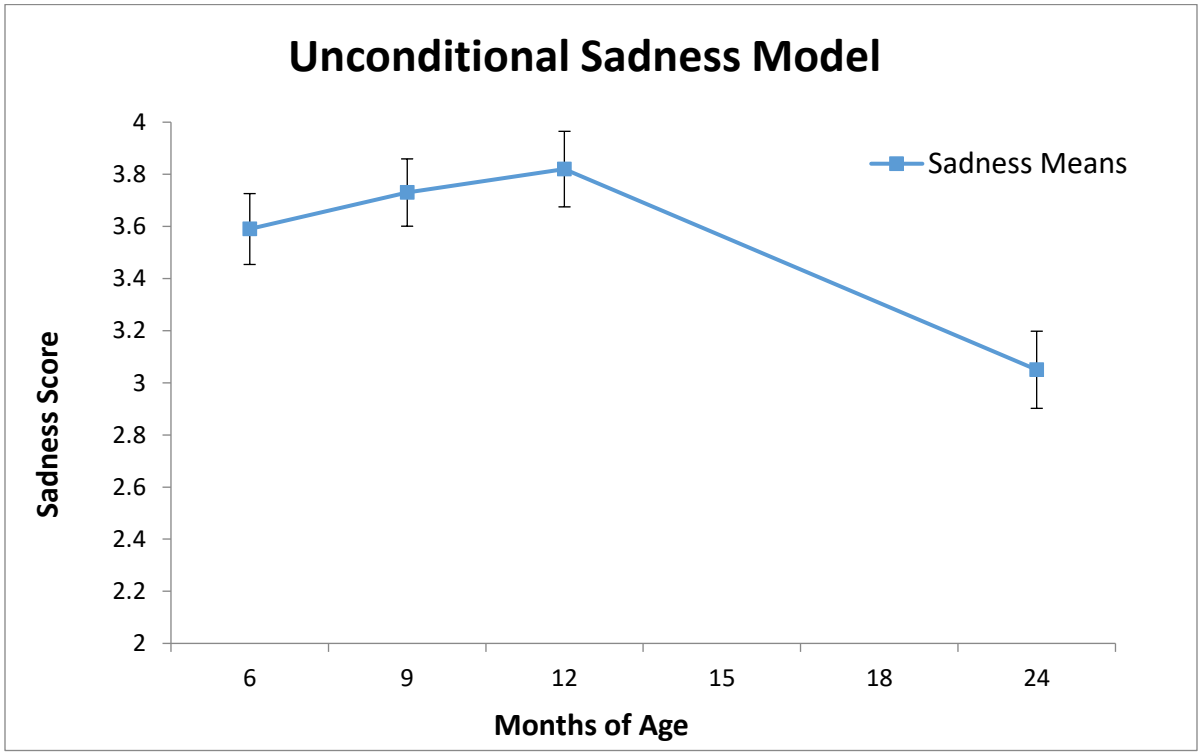

Figure 3. Sadness developmental trajectory from 6-24 months of age.

2.3.3.1 Amygdala-aI connectivity not significantly associated with sadness trajectory

We examined the role of amygdala-aI connectivity in sadness development by adding it as a predictor to the unconditional model of sadness growth. No significant main effects of amygdala-aI connectivity were found on the intercept, linear or quadratic growth terms of sadness (see **Table 4**). Results were unchanged after adjusting for maternal responsivity and considering it as a potential moderator. Thus, newborn amygdala-aI connectivity did not relate to sadness development, and appears to be more specifically related to fear development.

2.3.3.2 Amygdala-vMPFC connectivity predicts sadness trajectory

In a separate model, we examined newborn amygdala-vMPFC connectivity in relation to the sadness growth trajectory. Newborn amygdala-vMPFC connectivity had a significant positive effect on the intercept (b = 1.80, p < .01; **Figure 4C**), indicating that higher amygdala-vMPFC connectivity was associated with greater expression of sadness at 6-months-of-age. This connection also evidenced a significant negative association with the positive linear growth term (b = -5.73, p < 0.01; **Figure 4D**), and significant positive association with the negative quadratic growth term (b = 2.98, p < 0.05; **Figure 4E**). Importantly, inclusion of the intercept as a covariate in the pathway from amygdala-vMPFC connectivity to the linear and quadratic growth terms of this model did not change our results. Amygdala-vMPFC connectivity still significantly predicted both linear (b = -6.43, p < 0.05), and quadratic growth terms (b = 3.98, p < 0.05) after

inclusion of this covariate, indicating that the association between newborn connectivity and change in sadness expression over time was not driven by the initial starting point of sadness expression. Thus higher amygdala-vMPFC connectivity at birth predicted higher sadness at 6 months and less change in sadness over the first two years of life.

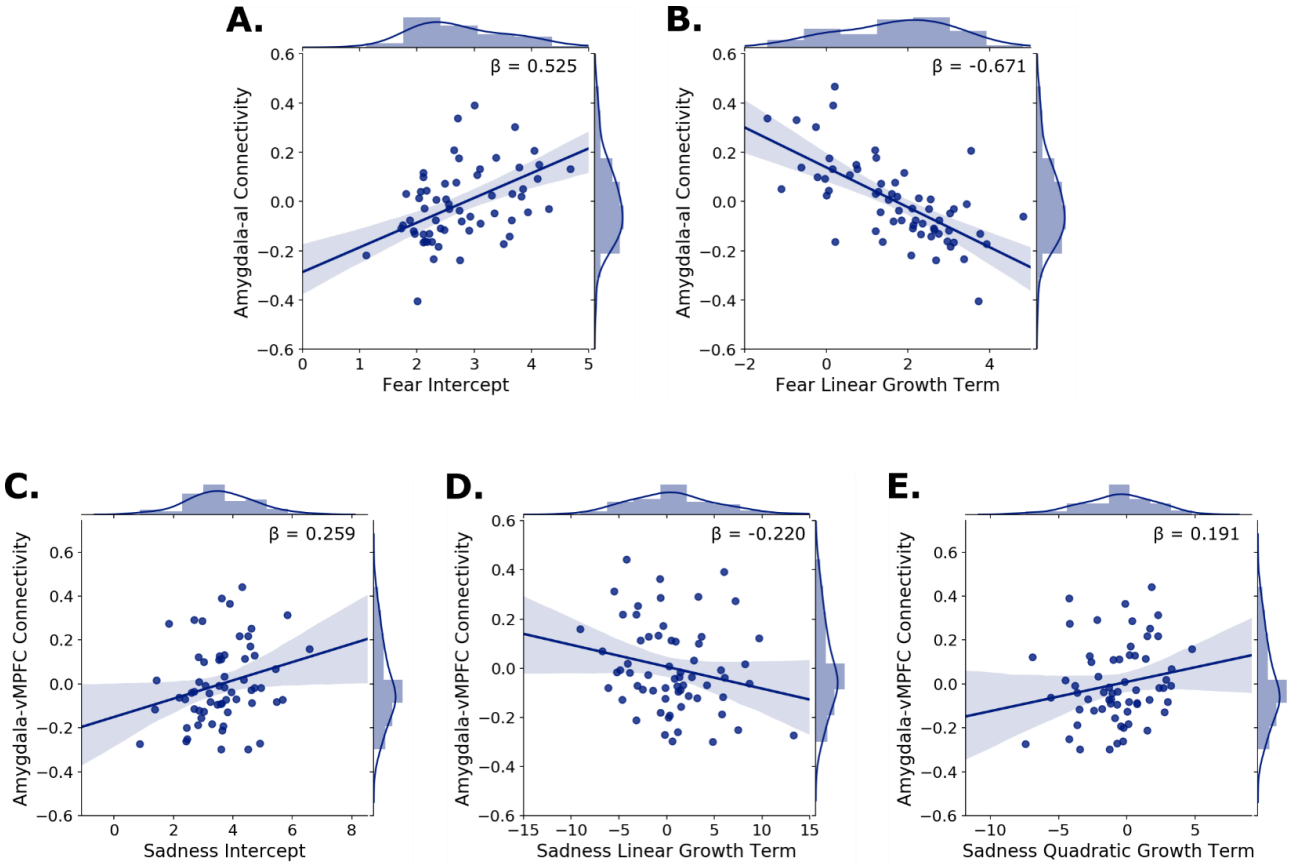

Figure 4. Standardized beta weights showcase significant relationships between sadness and fear growth terms and amygdala-vMPFC and amygdala-aI connectivity. Histograms on x and y axes represent distributions of growth terms and connectivity. Measures have been adjusted to account for variation caused by gestational age at birth and age at scan. **A, B:** Data has been extracted from the conditional fear amygdala-aI connectivity model reported in text. **C, D, E:** Data has been extracted from a conditional sadness amygdala-vMPFC model with variance from the slope unrestricted for data visualization purposes.

2.3.3.3 Maternal responsivity does not alter the association between amygdala-vMPFC connectivity and the sadness trajectory

Associations between amygdala-vMPFC connectivity and sadness intercept, linear and quadratic growth terms remained consistent after adding maternal responsivity as a covariate in the model ($p < .05$). Additionally, no significant relationships between maternal responsivity and the intercept, linear or quadratic growth terms emerged ($p > 0.1$). Maternal responsivity was also tested as a moderator of the effect of amygdala-vMPFC connectivity on sadness growth by evaluating the interaction between responsivity and amygdala-vMPFC connectivity on emerging sadness. The interaction between maternal responsivity and amygdala-vMPFC connectivity was not significantly associated with the intercept (b = -0.18, SE = 0.15, p = 0.23), linear (b = 0.41, SE = 0.42, p = 0.33) or quadratic growth terms (b = -0.30, SE = 0.27, p = 0.27) of the sadness trajectory. These results indicate newborn amygdala-vMPFC connectivity predicts sadness development independent of variation in this measure of maternal responsivity.

2.4. Discussion

2.4.1 Summary of findings

The present study aimed to advance understanding of how newborn limbic-prefrontal brain systems relate to early fear development and the etiology of fear-based psychopathologies. Findings suggest that newborn amygdala functional connectivity is predictive of emerging fear over the first two years of life. Moreover, our current findings indicate some specificity, such that amygdala-aI connectivity is particularly important for fear development and amygdala-vMPFC relates only to sadness development. This suggests potential distinctions in the neural circuitry underlying different components of NE. An overall pattern emerged for both fear and sadness development, in which

stronger newborn amygdala connectivity was associated with greater initial expression of each NE domain at 6-months-of-age, followed by less dynamic change from 6-24 months of age (**Figure 5**). Importantly our findings may not be specifically relevant for fear and sadness, but generally relevant for high versus low arousal states. This may be relevant for amygdala lateralization (Calkins et al., 2002; N. A. Fox, 1991; C. L. Smith et al., 2016).

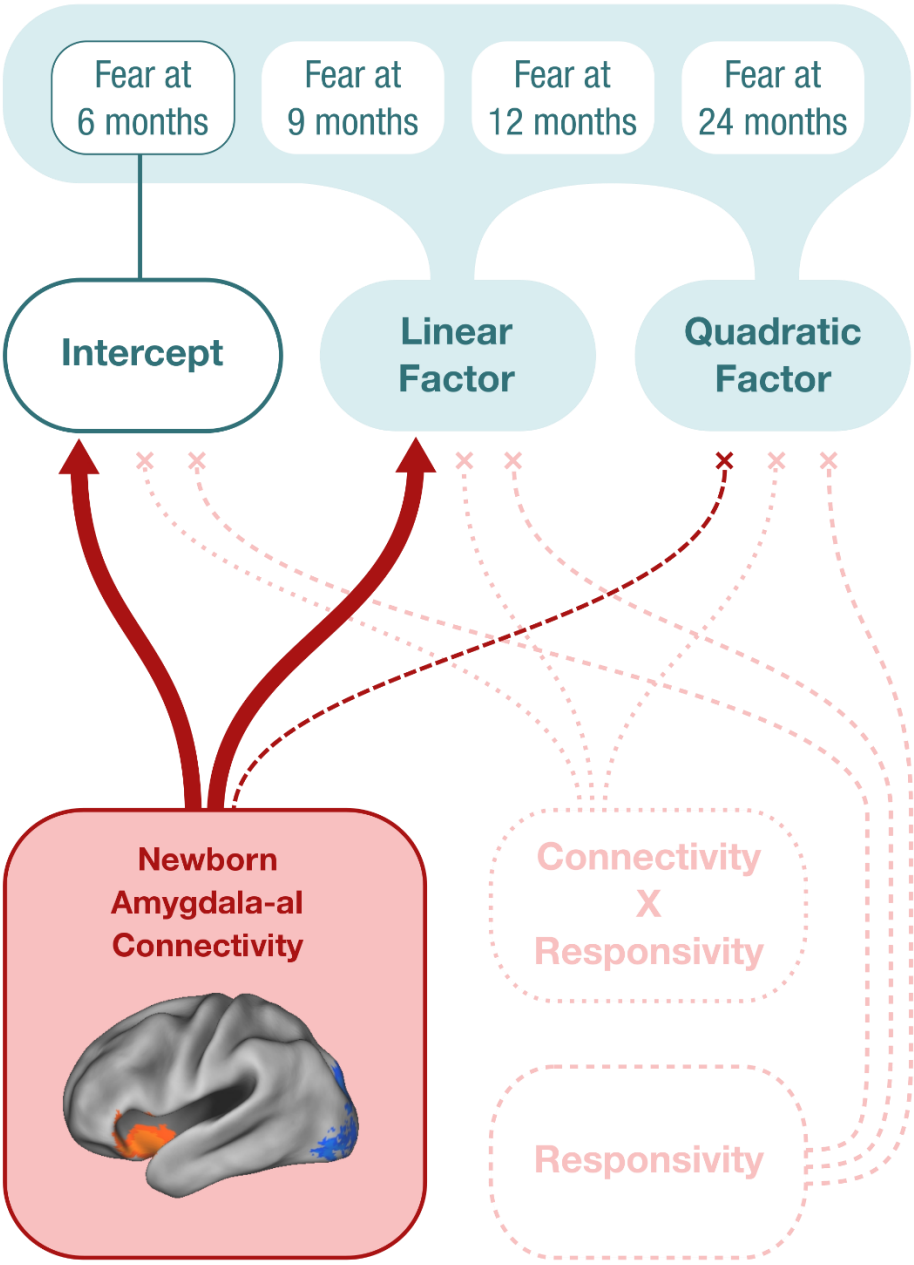

Figure 5. Conceptual model representing the analyses examining newborn amygdala-aI connectivity in relation to fear development. Specifically, amygdala-aI connectivity was considered as a predictor for the intercept, linear, and quadratic factors of the fear trajectory with and without maternal responsivity as a covariate and interaction term. The bolded red line indicates the significant relationship found between amygdala-aI connectivity and the intercept and linear factor of fear. *Note:* Separate models were run to examine each connection in relation to the growth curve for fear and then sadness. All SEM models included gestational age at birth and age at scan as co-variates. 'Connectivity X Responsivity' represents the interaction term used to test the potential

moderating effect of maternal responsivity, and 'Responsivity' represents the main effect of maternal responsivity on fear development. Significant associations ($p < 0.05$) are bolded in red.

2.4.2 Developmental trajectories of fear and sadness are distinct over the first two years of life

Our model captured an increase in fear over the first year of life (M6-M12), followed by a decrease in the second year of life (M12-M24) reflecting the expected trajectory of fear (Partridge et al., 2007). Sadness showed a similar developmental trajectory, increasing from 6-12 months then decreasing from 12-24 months. However, the initial increase and subsequent decline were less pronounced for sadness than for fear (**Figures 1.3 & 1.4**). This suggests that relative to fear, sadness may not involve the same degree of change over the first two years of life. Because the developmental trajectory of sadness has not been examined in prior studies, it is difficult to say what the expected trajectory of this particular aspect of NE looks like. Our findings fit well within the context of what is known about general NE development which increases over the first year then stabilizes (Bridgett et al., 2009; Partridge & Lerner, 2007).

2.4.3 Newborn amygdala-aI connectivity relates to fear development from 6-24 months-of-age

Though models of fear and sadness showed similar developmental trajectories, brain connectivity patterns underlying these trajectories differed. In line with our initial hypothesis, amygdala-aI connectivity was specifically associated with fear development across the first two years of life. Infants with stronger newborn amygdala-aI connectivity

expressed greater fear at 6-months-of-age with less dynamic change over time, including a small increase from 6-9 months and a less pronounced decrease from 9-24 months. These results provide the first evidence that newborn amygdala-aI connectivity is associated with the early developmental trajectory of fear, and that it may be specific to fear as opposed to other aspects of NE. This fits with the conceptualization of fear as representing a distinct component of NE, with distinct neurobiological correlates (Garstein & Rothbart, 2003).

The anterior insula is a key component of the salience network (Seeley et al., 2007), involved in detection of novel salient stimuli through different sensory modalities (Downar et al., 2000, 2002). In line with this role, amygdala-aI connectivity is involved in pathological and subclinical variation in fear (Baur et al., 2013), which involves the detection of potentially threatening stimuli in the environment. Our results fit well within this framework. Specifically, higher newborn amygdala-aI connectivity may increase detection of potentially threatening stimuli earlier in life, resulting in a heighted fear response by 6-months-of-age. The reduced novelty of these stimuli from 9-24 months-of-age, paired with a potential early emergence of emotion regulatory ability, may result in the subsequent decrease in fear expression.

In line with our hypothesis, amygdala-aI connectivity appears to be relevant for the development of fear; however, contrary to our hypothesis, stronger amygdala-aI connectivity was associated with less increase in fear over time. Given the general trajectory of fear development, this finding may suggest stronger newborn amygdala-aI connectivity is associated with more precocious fear development. Alternatively, it is possible higher connectivity may be indicative of a more fixed phenotype involving

decreased plasticity, manifested as less dynamic change in fear expression from 6-24 months.

2.4.4 Amygdala-vMPFC connectivity predicts sadness development

While stronger amygdala-vMPFC connectivity facilitates greater emotional regulatory ability in adults (Silvers et al., 2017), we anticipated the opposite association in infant populations, due to the developmental switch in amygdala-vMPFC functional connectivity (Gee et al., 2013). We hypothesized that stronger, positive amygdala-vMPFC connectivity would be associated with higher levels of NE at 6-months and greater increase in NE over time. Stronger amygdala-vMPFC connectivity was associated with higher levels of sadness at 6-months. However, in contrast to expectations, greater amygdala-vMPFC connectivity was not associated with increasing sadness expression over time. Similar to the association between amygdala-aI connectivity and fear development, stronger amygdala-vMPFC connectivity at birth may indicate a developmental shift in the expected NE trajectory, such that an increase and subsequent decrease in sadness expression occurs earlier in life.

Based on findings suggesting a role for amygdala-vMPFC connectivity in regulation of negative affect and in anxiety and depression (Burghy et al., 2012; Casey & Lee, 2015; Connolly et al., 2017; Kim et al., 2011; Roy et al., 2013b; Wang et al., 2013), we anticipated this connection would be relevant for the early emergence of both fear and sadness. However, our results suggest a specific association only with sadness. While amygdala-vMPFC connectivity has been associated with pathological and subclinical variation in fear (Baur et al., 2013), it has been more consistently associated

with depressive psychopathologies (Almeida et al., 2009; Perlman et al., 2010; Ritchey et al., 2011; Siegle et al., 2007). Our results linking amygdala-vMPFC connectivity to developmental trajectories of sadness expression from 6-24 months of age suggest this connection may already be relevant for variations in mood beginning in infancy.

2.4.5 Variation in maternal responsivity does not affect results

Variation in maternal responsivity did not change or moderate the associations between newborn amygdala connectivity and developmental trajectories of fear or sadness. With 62 subjects the power to detect the interaction was low, so this could potentially be a Type II error. Furthermore, consideration of maternal depressive symptomology at each time point did not impact our results. It should also be noted that while we did see variability in maternal responsivity, more extreme variation may have been required to observe a moderating effect on the newborn amygdala connections. (Burghy et al., 2012; Callaghan et al., 2014; Gee, Gabard-Durnam, et al., 2013; Herringa et al., 2013). In present form, results suggest patterns of coordinated newborn amygdala functioning have implications for the development of fear and sadness through 24-months of age even after adjusting for variation in the postnatal caregiving environment.

2.4.6 Limitations

Several limitations of the present study should be considered. First our small N resulted in reduced power for our interaction analyses, however we still believe these findings are important for their novelty though it remains to be seen what will replicate in larger samples. Next, measures of infant fear and sadness relied on maternal self-report.

Parental report has the advantage of allowing for observation of infant behavior over a long period of time across different contexts (Pelham, 1993; Stifter et al., 2006), and the specific measures used have demonstrated convergent validity with laboratory observation (Braungart-Rieker et al., 2010; Gartstein et al., 2010; Parade and Leerkes, 2008). However, it would be preferable for measurement of these constructs to combine parental report and observational measures. Additionally, while we considered the role of maternal depressive symptoms in potentially biasing report of infant fear and sadness, it is also possible that cultural factors may lead to differences in understanding of and reporting on infant NE (Bosquet et al., 2016; Dragan & Fronczyk, 2011; Gartstein et al., 2016; Montirosso et al., 2011). With regard to the observational measure of maternal responsivity, we note that it was only assessed at the 6-month time point, which limited the capacity to consider how changes in maternal responsivity over the postpartum period may relate to the trajectories of infant fear and sadness.

Another concern relates to our approach of choosing a-priori connections of interest for our analysis at the expense of doing a whole brain exploratory analysis. This decision was based on previous findings implicating these connections in emerging fear at 6-months of age (Graham et al., 2016) and in typical and pathological fear and children and adults (Baur et al., 2013; Casey & Lee, 2015; Etkin & Wager, 2007; Kim et al., 2011; Rabinak et al., 2011; Roy et al., 2013; Sripada et al., 2012). This approach allowed us to conduct a more focused analyses and facilitated the interpretability of our results. However, while these connections represent a natural starting point for examining developing fear, other aspects of amygdala connectivity and large scale brain systems will certainly be relevant for the development of fear in early life.

The BOLD data in this study did not undergo distortion correction. However, multiple steps were taking to ensure the quality of the BOLD data as detailed in the methods section. To confirm results were not driven by a lack of distortion correction, we quantified the average raw BOLD signal across the time series within each ROI and correlated this signal with our outcome measures of interest (fear and sadness growth factors). No significant associations ($p > 0.1$) were found, making it highly unlikely that results were driven by effects of field inhomogeneities on the BOLD signal within the ROIs. Additionally, we would have ideally included more resting state data per subject. However, given the challenges of collecting high quality MRI data with infants, investigators are faced with a decision of correlation values that are increasingly noisy (due to less data inclusion – see Laumann et al., 2015) or fewer subjects that would lead to reduced power (see descriptions in Dosenbach et al., 2017). We excluded infants with less than 4 minutes of high quality data as a natural balance between these two competing issues. Due to limitations in the resolution of MRI and fMRI data, we were also unable to examine amygdala subregions, which are certainly of interest for understanding fear development, and will be an important topic for future investigations when they can be reliability identified using these modalities. Lastly, developmental differences in the underlying physiology of the BOLD signal are not completely understood (Arichi et al., 2012; Hagmann, Grant, & Fair, 2012; Karen et al., 2008; Kozberg et al., 2013; Liao et al., 2010), and further investigation will be needed to consider how they may influence brain-behavior associations at different developmental time points, including in the newborn period.

2.5. Conclusions & Future directions

Overall, the current results provide further evidence that fear is a distinct component of NE with specific neural correlates. Ongoing longitudinal research will be needed to test the idea that these neurobehavioral phenotypes lay the foundation for healthy versus pathological fear development over time, though current research already indicates these newborn connections are relevant for future internalizing symptoms at 2 years of age (Graham et al., 2018; Rogers et al., 2017). Additionally, while the current study evaluates NE expression in relation to amygdala connectivity, it is well known that emotionality is balanced by regulatory capacity (Nigg, 2006). Future work should examine emotion regulatory capacity during this time period to determine how regulatory ability influences associations between newborn amygdala connectivity and emerging NE.

The current study also raises questions about the underlying cause for the pattern of development seen in infants with stronger amygdala-aI connectivity. Specifically, in future work it will be important to consider how maternal emotional state during pregnancy may impact future neonatal amygdala functional connectivity and emerging fear and sadness. Our previous work suggests that elevated concentrations of maternal biological stress mediators (e.g., interleukin 6 and cortisol) during pregnancy are associated with altered newborn amygdala connectivity (Graham et al., 2017, 2018). Further, recent research has identified an association between maternal depressive symptoms during pregnancy and emerging infant sadness via maternal inflammation levels (Gustafsson et al., 2018). Examination of both the antecedents and consequences

of these neural phenotypes and developmental trajectories of negative emotionality will be an important area of ongoing investigation.

Chapter 3: Amygdala connectivity soon after birth supports early emerging emotion regulation

3.1. Introduction

3.1.1. The importance of identifying early neural systems which support emerging emotion regulation

The capacity to modify the duration and intensity of an affective response, known as emotion regulation (ER), allows us to successfully cope with distress (Modecki et al., 2017). Poor emotion regulation contributes to poor mental health outcomes, substance abuse, and internalizing and externalizing behaviors across the lifespan (Aldao et al., 2010, 2016; Keenan, 2000; Phillips et al., 2003b; Taylor & Liberzon, 2007). Already in infancy, poor ER skills are associated with the emergence of internalizing and externalizing behaviors in toddlerhood linked to future risk for mental illness (Dale et al., 2011; Moore et al., 2001). Though ER ability has been identified as a key factor in determining risk for psychopathology, very little is known about how early brain systems support this capacity. Identifying newborn neural phenotypes associated with emerging ER may help elucidate pathways through which early ER skills relate to future socioemotional adjustment and ultimately risk for psychopathology.

Thus, in the current study, we evaluate how neural connectivity at birth supports emerging emotion regulation in early infancy. While emotion regulation is a broad concept which refers to the modification of both positive and negative emotions, the unregulated expression of negative emotion in infancy is of particular concern as it is linked to greater emotional problems later in childhood (Burgess et al., 2003). For this

reason, we have chosen to use a construct of latency to negative affect as our measure of ER, which captures the emotion reactivity component of emotion regulation (Frick et al., 2017, 2019). Next, we examine how neural systems at birth and emotion regulation in infancy contribute to emerging internalizing and externalizing symptomatology in toddlerhood.

3.1.2. Typical development of behavioral and physiological aspects of emotion regulation ability

Emotion regulation is a dynamic process, which changes as a function of development (Aldao et al., 2016). Initially, infants may depend entirely on caregivers to regulate emotions (Spanglar et al., 1994). However, by 6-months-of-age, they begin to rapidly develop their own behavioral strategies to support ER (Cole et al., 2004; Fox & Calkins, 2003; Kopp, 1989; Poehlmann et al., 2011). For example, the ability to consciously, focus and shift attention, advances significantly at this time; allowing infants to avert their gaze when presented with a stressful stimuli (Posner & Petersen, 1990). Gaze aversion, along with hand or foot clasping, attention-seeking, and self-distraction behaviors support early emerging ER in infancy and allow for a change in affect experienced by the infant during stressful situations (Kopp, 1989; Weinberg & Tronick, 1994). However, not all ER behaviors lead to a reduction in distress (Braungart-Rieker & Stifter, 1996; Buss & Goldsmith Hill, 1998). Because regulating negative emotional experiences is a key component of the infant's ability to adaptively cope with the environment (Kopp, 1989), here we employ a measure of latency to distress as our measure of emotion regulation. Through measuring infant latency to distress during a

stress-inducing paradigm, which removes the caregiver's ability to regulate infant emotion, we capture negative emotional reactivity to the paradigm despite infant efforts to independently regulate emotions through various behavioral strategies. Thus we examine ER as the inhibition of negative emotional reactivity (Kopp, 1989).

Physiological systems during infancy also support emotion regulation (Feldman, 2009; Moore et al., 2009; Pratt et al., 2015). In particular, HPA axis activity can also be used as an indicator of infant reactivity and regulation (Ahnert et al., 2004; Khoury et al., 2015). Changes in salivary cortisol in response to a stressor can be used as a measure of cortisol reactivity (Stansbury & Gunnar, 1994). Typically, a greater increase in cortisol release after a stressor occurs in indicates greater HPA reactivity and less regulation of stress (Laurent et al., 2016). Through evaluating both behavioral and physiological supports of emerging emotion regulation, we can elucidate specific mechanisms in infancy which support the development of mental health.

3.1.3. Early brain connectivity as a predictor of emotion regulation

Prior research has consistently found that patterns of frontal EEG asymmetry in infancy are linked to future emotion regulation ability (Fox, 1991; Fox et al., 2001). Specifically, findings suggest right frontal activation is linked to increased negative affect and poor emotion regulation ability, while left frontal activation is linked to greater regulatory ability and decreased negative affect (Smith et al., 2016). More recently, researchers have begun to identify very early neural precursors, already soon after birth, associated with emerging negative emotionality using resting state fMRI to examine coordinated functioning of regions known to be very important for healthy versus

maladaptive emotion regulation later in life. For example, research across two independent datasets identified stronger neonatal amygdala functional connectivity to the anterior insula and medial prefrontal cortex related to heightened emerging negative emotionality (Graham et al., 2016; Rogers et al., 2017; Thomas et al., 2019) indicating the potential relevance of this early neural phenotype for emotion regulation ability. To further our understanding of this work, we now aim to examine an observational measure of emotion regulation. Understanding how neural systems at birth influence a future observational measure of emotion regulation ability will fill a key gap in the literature, linking the rapidly advancing literature on brain development during infancy to emerging emotion regulation skills, and ultimately to mental health outcomes.

3.1.4. Key influences on emerging emotion regulation ability

Early emerging emotion regulatory processes are very susceptible to the contextual influences of the environment, particularly parental behaviors (Hostinar & Gunnar, 2013; Morris et al., 2017). Infants depend on their caregivers to assist in emotion regulation (Braungart-Rieker et al., 1998; Fox & Calkins, 2003). Caregivers must have the ability to respond quickly and accurately to their infant's signals for regulatory help, in order to support regulatory behavior. Thus, maternal responsivity plays a key role in the development of intrinsic emotion regulation ability (Bernier et al., 2016; Thomas et al., 2017). Mothers with elevated depressive symptomatology tend to be less responsive to their infants cues (Feldman, 2003), which may impact infant emerging emotion regulation ability. In addition to maternal behavior, infant cognitive ability also likely plays a key role in emerging regulation capacity, as cognitive skills likely contribute to

emotion regulation tactics to reduce distress (Wolfe & Bell, 2007). While emotion regulation and cognitive ability are related, they represent distinct constructs that should be evaluated separately (Bell & Wolfe, 2004).

3.1.5. Present Study

In this longitudinal study, we examine amygdala resting state functional connectivity in the neonatal period in relation to emerging emotion regulation at 6-months-of-age. Next, we test whether emotion regulation in infancy relates to future externalizing and internalizing symptomatology in toddlerhood. Lastly, we consider emotion regulation at 6-months-of-age as a potential mediator between newborn amygdala connectivity and problem behaviors in toddlerhood. In contrast to our prior work, methodological advances in infant neuroimaging data processing have allowed us to conduct our functional connectivity analyses in surface-space, rather than volume-space. This has greatly improved the signal to noise ratio of our functional brain data, allowing for the improved spatial accuracy of our results. The current study also offers a nuanced view of emerging emotion regulation in infancy through the use of an observational indicator of emotion regulation.

3.2. Methods and materials

3.2.1. Participants

Infants and mothers included in this study (N = 59 with neonatal rs-fcMRI data, N= 37 with behavioral data at 6-months-of-age, N = 29 with behavioral data at 24-months-of-age) were part of an ongoing longitudinal study of mother-infant dyads

conducted at the University of California Irvine. Recruitment occurred during mother's first trimester of pregnancy. Criteria for exclusion were: maternal use of psychotropic medications or systemic corticosteroids during pregnancy, infant birth before 34 weeks' gestation, and infant genetic, congenital, or neurological disorder. Infant gestational age at birth (M = 39 weeks, SD = 1.5) fit well within our criteria for inclusion. Functional and structural MRI scans were conducted when infants were approximately 4-weeks-of-age (M = 27 days SD = 11.2*).* Behavioral and physiological follow-up data were collected when infants were 6-months-of-age (M = 5.5 months SD = 0.56) and 24-months-of-age (M = 23.5 months SD = 0.75*).* Demographic information is provided in **Table 2.1**. The Institutional Review Board at the University of California, Irvine approved all procedures.

Table 2.1. Demographics	
Variable	**Percentage**
Infant Sex	
Male	55.9
Female	44.1
Highest level of maternal formal education	
High School or GED	15.3
Technical or Vocational School	13.6
Some College, but no degree	30.5
Associates Degree	5.1
Bachelors Degree	18.6
Graduate Degree	11.9
Certificate	5.1
Maternal race/ethnicity combined	
White non-Hispanic	44.1
Black non-Hispanic	3.4
Asian non-Hispanic	6.8
Mult races non-Hispanic	8.5
White Hispanic	28.8
Asian Hispanic	1.7
Mult races Hispanic	6.8

3.2.2. MRI and fMRI data acquisition and surface-based processing

3.2.2.1. Data acquisition

Infants were scanned during natural sleep at UC-Irvine's Neuroscience Imaging Center using a TIM Trio, Siemens Medical System 3.0 T scanner and a 32-channel head coil. A structural T2-weighted image (TR = 3200 ms, echo time = 255 ms, resolution = 1 x 1 x 1 mm, 4.18 min) and a structural T1-weighted image (MP-RAGE TR = 2400 ms, inversion time = 1200 ms, echo time = 3.16 ms, flip angle = 8°, resolution = 1 × 1 x 1 mm, 6.18 min) were acquired for each subject. An echoplanar imaging (EPI) sequence sensitive to the blood oxygen level-dependent (BOLD) contrast (TR = 2000 ms; TE = 30

ms; FOV = 220 x 220 x 160 mm; flip angle = 77°) was used to obtain fMRI data. Full brain coverage was obtained using 32 ascending-interleaved 4 mm axial slices with a 1 mm slip and steady-state magnetization was assumed after 4 frames (8 ~ s). Functional data was obtained in a single scan consisting of 150 volumes for early participants (N = 8), and increased to 195 volumes for the remaining participants (N = 54) in later stages of the study to increase the likelihood of acquiring a sufficient number of volumes for analysis. Only functional scans with at least 4 min of data (after volume removal for motion) were included in the present study.

3.2.2.2. fMRI data processing

All fMRI data was processed using a custom modification of the existing Human Connectome Project (HCP) imaging processing pipeline (Glasser et al., 2013) optimized for neonate functional data. This pipeline consists of five stages: 1) PreFreeSurfer: denoises and corrects for bias field distortions, extracts brain from structural T1 and T2-weighted images, aligns structural images to atlas (NIH Pediatric Template; Sanchez 2012), and delineates grey matter from white matter based on tissue classes in the T2w image, 2)FreeSurfer: refines grey and white matter delineation based on 10 manually delineated brain atlases, 3)PostFreeSurfer: generates individualized grey, white matter, subcortical segmentations for each subject, 4)DCANBOLDProc: denoises fMRI data and filters out frames with high motion (FD > 0.3 mm), aligns fMRI data to structural images, constructs parcellated timeseries based on HCP's 360 ROI atlas template (Glasser et al., 2016), 5)Executive Summary: used for quality assessment for each subject, generates

images of: delineated surfaces, atlas-structural registration, structural-fMRI registration, and a greyplot representing the fMRI signal across all greyordinates after processing.

3.2.3. Amygdalae regions of interest

3.2.3.1. Segmentation of Amygdalae

Individual right and left amygdalae were segmented using a multi-modality, multi-template based automatic method combining T1 and T2 weighted high-resolution images (Wang et al., 2014), followed by manual correction in ITK-Snap (Yushkevich et al., 2006). For details on this procedure see our prior work (Graham et al., 2016; Thomas et al., 2019). These individualized amygdalae ROIs were used as seed regions for rs-fcMRI analyses. Specifically, the time course of the BOLD signal was averaged across the voxels within each amygdala ROI, and then correlated with the time course for all other surface greyordinates throughout the cortex. This resulted right and left cortical greyordinate connectivity maps for both the left and right amygdala, which were used as predictors of emotion regulation in regression models employing cluster-based detection to account for multiple comparisons (Eklund et al., 2016).

3.2.3.2. A-priori amygdalae connections to anterior insula, vMPFC and MPFC

Given the modest sample size for the present study, we chose to first analyze prior amygdala connections relevant for emerging infant negative emotionality and cognitive ability (Am-aI, Am-vMPFC, Am-MPFC; Graham et al., 2016). Because these a-priori ROIs were originally extracted from a volume-based processing pipeline, the 4dfp to Nifti tool was used to move the volumetric ROIs to surface space (Snyder et al., 2019).

Follow up analyses examined the right and left cortical greyordinate maps described above.

3.2.4. Measurement of infant behaviors

3.2.4.1. Still Face Paradigm

The still-face episode of the still-face paradigm (Tronick et. al, 1978) offers a unique opportunity to examine infant emotion regulation in the absence of parental aide in regulation of emotions. Infants are strapped into a car seat while their mothers stare at them with a blank expression on their face. This still-face reliably increases infant distress, likely due to the infants' violations of expectations about their mothers' responsiveness (Braungart-Rieker et al., 1998; Mesman et al., 2009; Toda & Fogel, 1993; Weinberg & Tronick, 1994). In this scenario, infants have been found to perform variety of behaviors to regulate their negative emotions (Braungart-Rieker et al., 1998; Rothbart et al., 1992). The still-face paradigm was conducted when infants were approximately 6-months-of-age. The paradigm included 5 2-minute episodes in the following order: play episode, still-face episode, play episode, still-face episode, and play episode. Though mothers were asked to maintain a neutral face and not touch their infant throughout the entire still-face episode, mothers often broke still-face for brief periods of time (N = 28, <5 second intervals) throughout the 2 minute episode. To examine the impact of mother's breaking still-face on latency to distress, we conducted independent sample T-tests to examine mean differences in latency to distress between mothers' who did and did not break still face. No significant differences between latency to distress were found between infant's whose mothers did versus did not break still face. However, because

breaking still face is a violation of the still-face episode and may have impacted our measure of emotion regulation behavior in ways we failed to capture here, we chose to keep this as a covariate for our analyses.

Behavioral coding of latency to distress, was coded as latency to the first expression of negative affect. Negative affect included anger, sadness, and frustration. Brows may have been sharply furrowed and eyes may have been tightly closed or the corners of the mouth were turned downward. This also included mixed negative/positive facial expressions includes elements of both negative and positive. For example, the infant may have had brows drawn together and corners of the mouth raised (Sullivan et al., 2015). Infant negative affect during the first still-face episode was coded by two independent coders (percent agreement > 85%, Kappa= 0.80) in 5-second intervals using a previously established coding scheme (Sullivan et al., 2015). Latency to distress, the number of seconds before the infant expressed negative affect (*M* = 42.2 seconds, days *SD* = 42.1*)*, was calculated as an indicator of infant negative emotional reactivity, here we conceptualize this as emotion regulation. Greater latency to distress has previously been associated with greater occurrence of regulatory behaviors (Frick et al., 2017; Mayes & Carter, 1990). Importantly, not all regulatory behaviors are associated with decreases in negative affect (Braungart-Rieker & Stifter, 1996; Buss & Goldsmith, 1998) which is why we chose to use the construct of latency to distress as our indicator of emotion regulation.

3.2.4.2. Infant cognitive development

Infant cognitive development was assessed at 6-months-of-age using the Cognitive composite score from the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III; Bayley, 2006). This, commonly used, standardized measure of infant development includes an assessment of emerging attention, memory, and sensory motor skills. Bayley's cognitive composite score was used as an indicator of how cognitively developed each infant was at the 6-month time point (*M* = 103.6 *SD* = 9.1). Examining overall infant cognitive development was important in order to distinguish emotion regulation from general cognitive development.

3.2.4.3. Infant salivary cortisol as physiological indicator of emotion regulation

Infant salivary cortisol was measured at 4 time points during the still-face paradigm to characterize changes in cortisol which occurred in response to the first still-face episode. Infant saliva samples were taken immediately upon arrival to the lab (T0; *M* = 0.26 ug/dL *SD* = 0.3), prior to the start of the still-face paradigm (T1; *M* = 0.25 ug/dL SD = 0.29) and 10 minutes (T2; *M* = 0.22 ug/dL *SD* = 0.14) and 30 minutes (T3; *M* = 0.25 ug/dL *SD* = 0.26) after the still-face episode. Outliers in each sample > 3 SD above the mean were windsorized

3.2.4.4. Early childhood clinical symptomatology

Early childhood internalizing and externalizing symptomatology were assessed at 2-years-of-age using a maternal self-report measure known as the Child Behavior Check List (CBCL) (Achenbach & Ruffle, 2000). From the CBCL, internalizing (*M* = 5.1 *SD* = 6.1*)* and externalizing (*M* = 7.2 SD = 7.2) symptomatology raw scores were used as

measures of early childhood symptomatology. Analyses employing this measure adjusted for caregiver mood at the time of reporting to account for this potential source of bias.

3.2.4.5. Postnatal caregiving environment

3.2.4.5.1. Observational measure of maternal responsivity

The quality of the postnatal caregiving environment was assessed using the Home Observation for Measurement of the Environment (HOME) Inventory (Bradley et al., 2003) when infants were 6-months-of-age. Assessments were completed by observers who achieved reliability with a certified administrator of the inventory (95% agreement on two consecutive videos) prior to the home visit. During the home visit, the infant's activities and interactions in their caregiving environment were observed and a semi-formal interview with the mother was conducted. The subscale HOME Responsivity scale (*M* = 8.6 *SD* = 1.5*)* was used in our analyses as a measure of maternal responsiveness to the infant.

3.2.4.5.2. Maternal self-report measure of depressive symptomatology

The 20-item Center for Epidemiological Studies of Depression Scale (CESD; (Radloff, 1977)) was used to assess maternal depression. Mothers reported on symptoms of depression over the past week on a 4-point scale, ranging from 0 (rarely or none of the time) to 3 (most or all of the time). The mean score was used in analyses. Maternal depressive symptomatology was assessed when infants were 3 mo (N = 53, M = 0.57, SD = 0.52), 6mo (N = 51, *M* = 0.55, *SD* = 0.51*)*, 9mo (N = 41, *M* = 0.43, *SD* = 0.37*)*, 12mo (N = 37, *M* = 0.55, *SD* = 0.47*)* and 24-months-of-age (N = 38, *M* = 0.50, *SD* = 0.44*)*. To

examine the impact of maternal depressive symptoms on infant outcomes at 2-years-of-age, we created two averages to account for maternal depressive symptomatology from 1-6 months of age (N = 55, M = 0.60, SD = 0.51), and 6-24 months of age (N= 51, M= 0.54, SD= 0.44) for each mother with at least 2 time points of data.

3.3. Preliminary Analyses

3.3.1. Examining trajectories of infant salivary cortisol release

Infant saliva samples were taken immediately upon arrival to the lab (T0; *M* = 0.26 ug/dL *SD* = 0.3), prior to the start of the still-face paradigm (T1; *M* = 0.25 ug/dL SD = 0.29) and 10 minutes (T2; *M* = 0.22 ug/dL *SD* = 0.14) and 30 minutes (T3; *M* = 0.25 ug/dL *SD* = 0.26) later. The central tendency and variability of cortisol at each time point indicated highly variable data across time, as seen in other studies evaluating infant cortisol change over time (O'Connor et al., 2017; Ursache et al., 2014). Due to this variability, we chose to employ a unique machine learning algorithm created in our laboratory to examine trajectories of cortisol release across infants.

Specifically, we used a functional random forest algorithm to classify 3 distinct trajectories of infant salivary cortisol release over time during the still-face-paradigm (N= 53). Changing in cortisol between T0 and T1 likely characterized the infant's response to the novel environment. Cortisol levels typically peak in infants 20-25 minutes after the initiation of a stressor (Ramsay & Lewis, 2003), so we anticipated seeing an increase in cortisol 20-25 minutes after our still-face episode, between the T2 and T3 time point for each subgroup. Interestingly, this was not the case for all of our subgroups. In the diagram below (**Figure 1**), the still-face stressor, which occurred between T0 and T1, is

indicated by a yellow highlighted line, time values presented on the x-axis indicate minutes after the still face episode. Infants in subgroup 1 had a sharp increase in cortisol between T0 and T1, presumably caused by the novel environment, this increase in cortisol continued between T1 and T2, in response to the still face stressor, this was followed by a decrease in between T2 and T3, an expected response for infants who are able to successfully regulate in the face of a stressor. Infants in subgroup 2, showed a similar increase in cortisol between T0 and T1, potentially due to the novel environment, followed by a decrease in cortisol release in response to the still-face stressor. The negative quadratic slope between T2 and T3 suggests underdeveloped HPA functioning in subgroup 2, which we would expect to be associated with poor regulatory ability. Lastly, subgroup 3 was characterized by a sharp decrease in cortisol between T0 and T1 in response to the novel environment, followed by an increase in cortisol, between T1 and T2 in response to the still-face stressor, and a slight decrease prior to T3. Subgroup 3 showed an unanticipated decrease in response to the novel environment and the anticipated decrease in cortisol activity after the still face episode, which we would expect to be associated with greater regulatory ability.

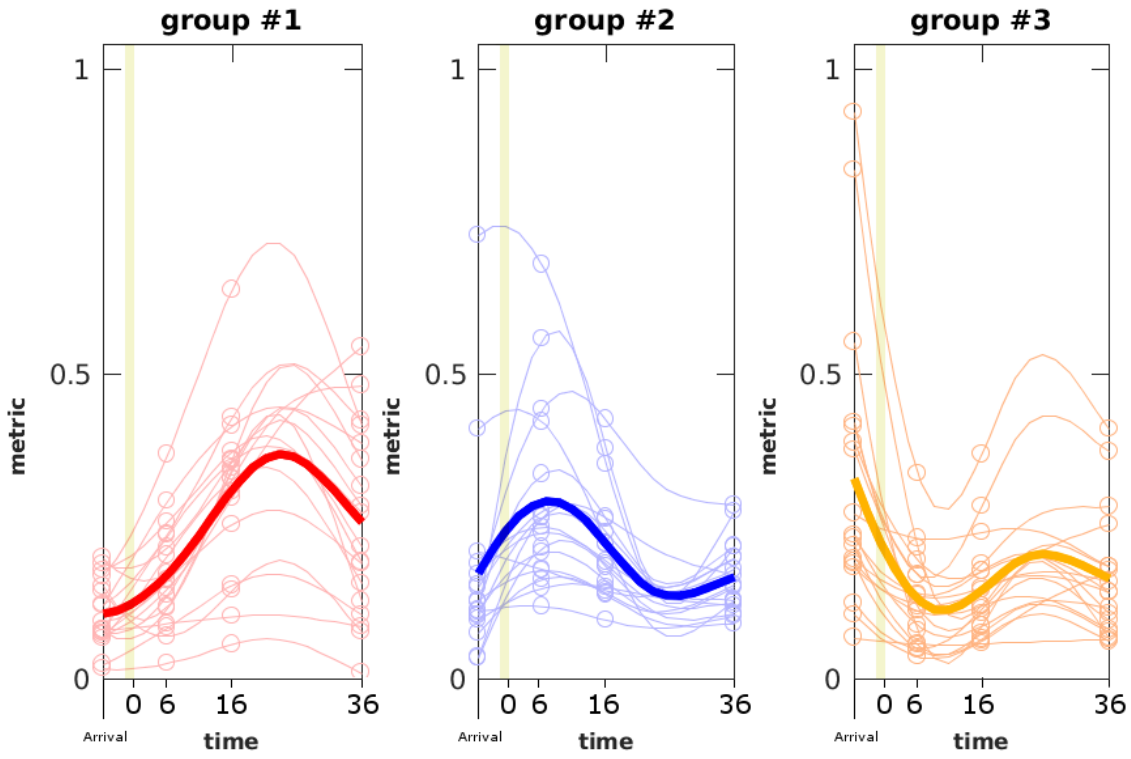

Figure 1 Graph represents change in cortisol over time. Y axis indicates magnitude of salivary cortisol. X axis indicates time. Groups 1, 2 and 3 represent subgroups 1 (N=18), 2 (N=17) and 3 (N=18) respectively.

3.3.2. Analytic approach

We first examine associations between a-priori neonatal amygdala functional connections (Am-aI, Am-vMPFC and Am-MPFC) and a behavioral indicator of emotion regulation at 6-months-of-age. We decided on this focused approach supported by previous studies given the modest sample size for this study. We follow up with whole brain analyses to identify additional potential connections relevant for emerging emotion regulation that may serve as a basis for future studies in this area. Next, we examine how our behavioral indicator of emotion regulation in infancy relates to subsequent internalizing and externalizing symptomatology in toddlerhood. Lastly, we consider

emotion regulation in infancy as a potential mediator for associations between newborn amygdala connectivity and internalizing and externalizing behaviors in toddlerhood. All analyses examining associations between the neonatal brain and emotion regulation included covariates for infant gestational age at birth, postnatal age at scan, sex, and mom breaking still-face during the still-face episode. Because literature has suggested differences in right and left amygdala connectivity- we chose to look at right and left a-priori amygdala connections separately in relation to emerging emotion regulatory ability (Jung et al., 2018).

3.4. Results

3.4.1. Right amygdala a priori connections to vMPFC and MPFC at birth linked to behavioral indicator of emotion regulation in infancy

We conducted multiple regression analyses to examine the a priori neonatal right amygdala connections (Am-MPFC and right- Am-vMPFC connectivity) as the independent variables, covariates for gestational age at birth, infant sex, and breaking still-face, and latency to distress as the dependent variable. Results indicated stronger right amygdala-MPFC connectivity (Ram-MPFC; $\beta = 0.29$, $p < 0.05$) and weaker right amygdala-vMPFC connectivity (Ram-vMPFC; $\beta = -0.27$, $p < 0.05$) at birth were associated with greater emotion regulation at 6-months of age (See **Fig. 2a** and **2b** below). Interestingly, greater amygdala connectivity to our more dorsal MPFC region predicted more emotion regulation, while greater amygdala connectivity to our ventral MPFC region predicted less. Results remained the same after adjusting for infant

cognitive ability, maternal responsivity, and average maternal depressive symptomatology from 1-6 months.

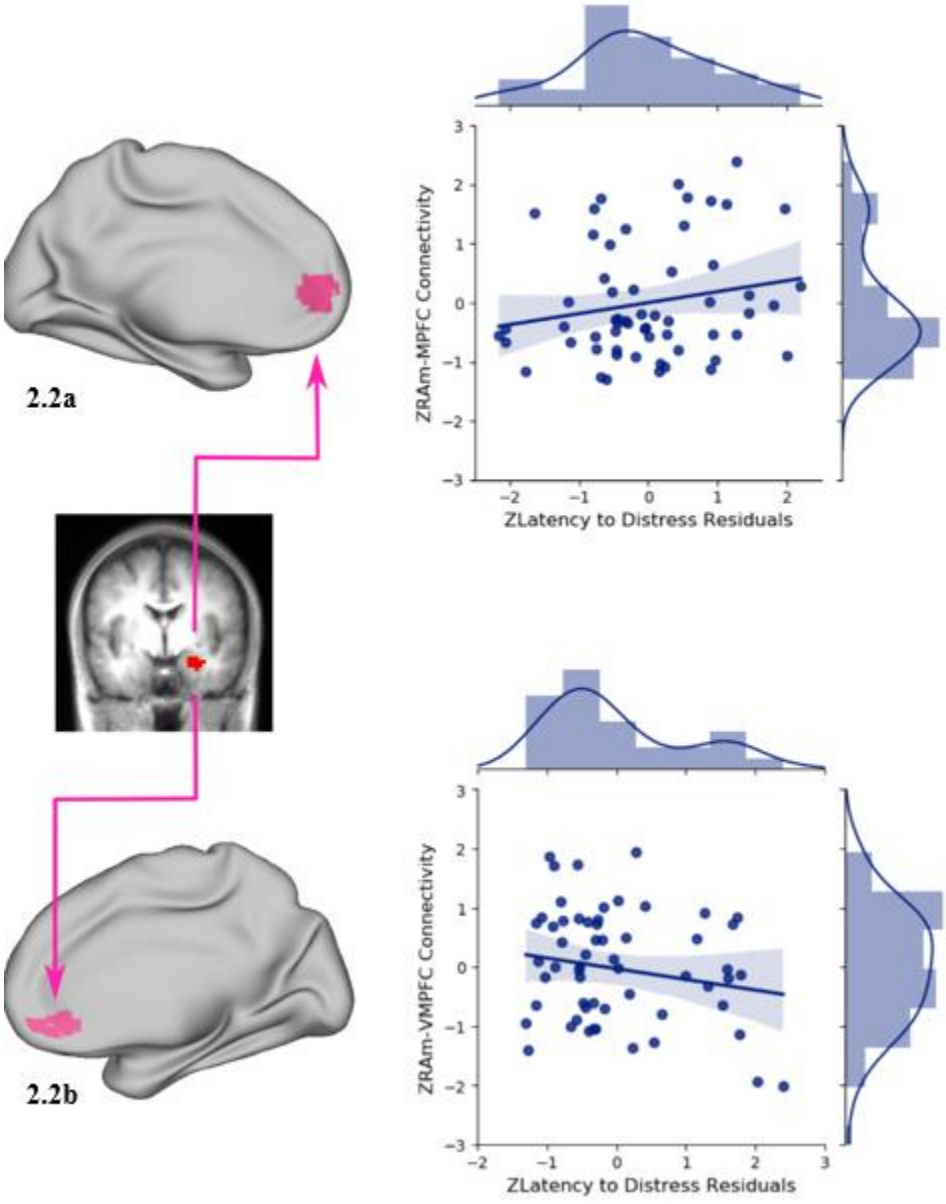

Figure 2a Amygdala- medial prefrontal cortex (Am-MPFC) region of interest indicated on left, Am-MPFC connectivity indicated on y axis, latency to distress residuals (after controlling for age at scan, gestational age at birth, infant sex and maternal breaking still face) on x axis. **Figure 2b** Amygdala-ventromedial prefrontal cortex (Am-vMPFC) region of interest indicated on left, Am-vMPFC connectivity indicated on y axis, latency to distress residuals (after controlling for age at scan, gestational age at birth, infant sex and maternal breaking still face) on x axis.

3.4.2. Left Amygdala a-priori connections previously associated with cognitive ability and emerging negative emotionality are unassociated with behavioral indicator of emotion regulation

We next conducted multiple regression analyses to examine the a priori neonatal left amygdala connections (left Am-MPFC, left Am-vMPFC, left Am- left insula, left Am-right insula) as the independent variables, with covariates for gestational age at birth, infant sex, and breaking still-face, and latency to distress as the dependent variable. Results indicated left amygdala connectivity to a-priori ROIs at birth was not associated with future emotion regulation. Results remained unchanged after adjusting for infant cognitive ability, maternal depressive symptomatology and average maternal depressive symptomatology from 1-6 months.

3.4.3. Identifying additional amygdala connections at birth which support emerging emotion regulation

Next, we employed multiple regression analyses using an in-house modified version of Mplus to examine whole brain neonatal amygdala connectivity in relation to latency to distress. We included gestational age at birth, postnatal age at scan, and breaking still face as covariates and examined right and left amygdala separately. Estimates of right and left amygdala connectivity were standardized and run through a cluster-detection algorithm, based on previously defined guidelines (Eklund et al., 2016). To correct for multiple comparisons, clusters were ordered by size, permutated, and clusters above/below a z-score of 3.1, p of 0.001, and with a cluster size great than 50

were retained (see **Table 2**). Results remained the same after adjusting for infant sex, cognitive ability, maternal responsivity, and average maternal depressive symptomatology from 1-6 months.

Results for the right amygdala indicated stronger connectivity to the fusiform gyrus, middle temporal gyrus, posterior cingulate cortex and anterior orbital frontal cortex was associated with increased emotion regulation. Additionally, weaker right amygdala connectivity to the primary visual cortex (V1), mid-insular region, and posterior insular region was associated with increased emotion regulation. The association between weaker amygdala to visual cortex connectivity and emotion regulation was the strongest finding (cluster size = 623, z-value < -3.1), indicating a potentially important role for amygdala integration into the visual system for emerging emotion regulation. See **Figure 3a.**

We next examined left amygdala connections relevant for emerging emotion regulation. For the left amygdala, stronger connectivity to the extrastriate visual cortex and weaker connectivity to primary motor cortex was associated with greater emotion regulation at 6-months-of-age. See **Figure 3b**.

Table 2.2

Right Amygdala	**Hem**	**x**	**y**	**z**	**Z**	**Cluster size**
Mid-insular region	R	38	12	-2	-	50
Posterior Insula	L	-39	-23	2	-	64
Posterior Cingulate Cortex	R	8	-60	16	+	100
Orbital frontal cortex	L	-28	60	-6	+	102

Middle temporal Gyrus	R	55	-38	-23	+	131
Fusiform gyrus	L	-65	-42	0	+	146
Primary Visual Cortex (V1)	R	11	-77	10	-	623
Left Amygdala	**Hem**	**x**	**y**	**z**	**Z**	**Cluster size**
Primary Motor Cortex (PMC)	L	-10	-4	44	-	76
Extrastriatal Visual Cortex (EVC)	R	17	-79	-10	+	88

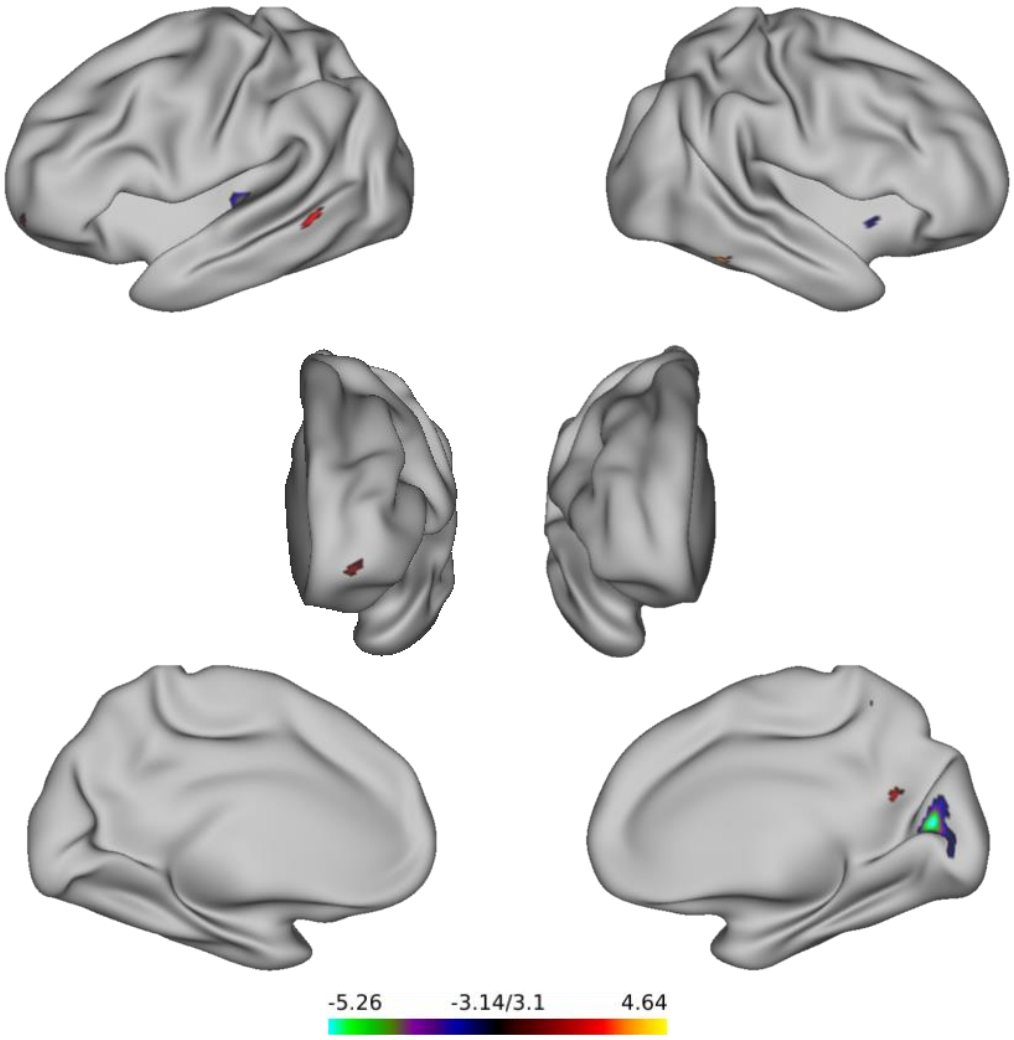

Figure 3a Right amygdala connections soon after birth associated with emotion regulation at 6-months-of-age.

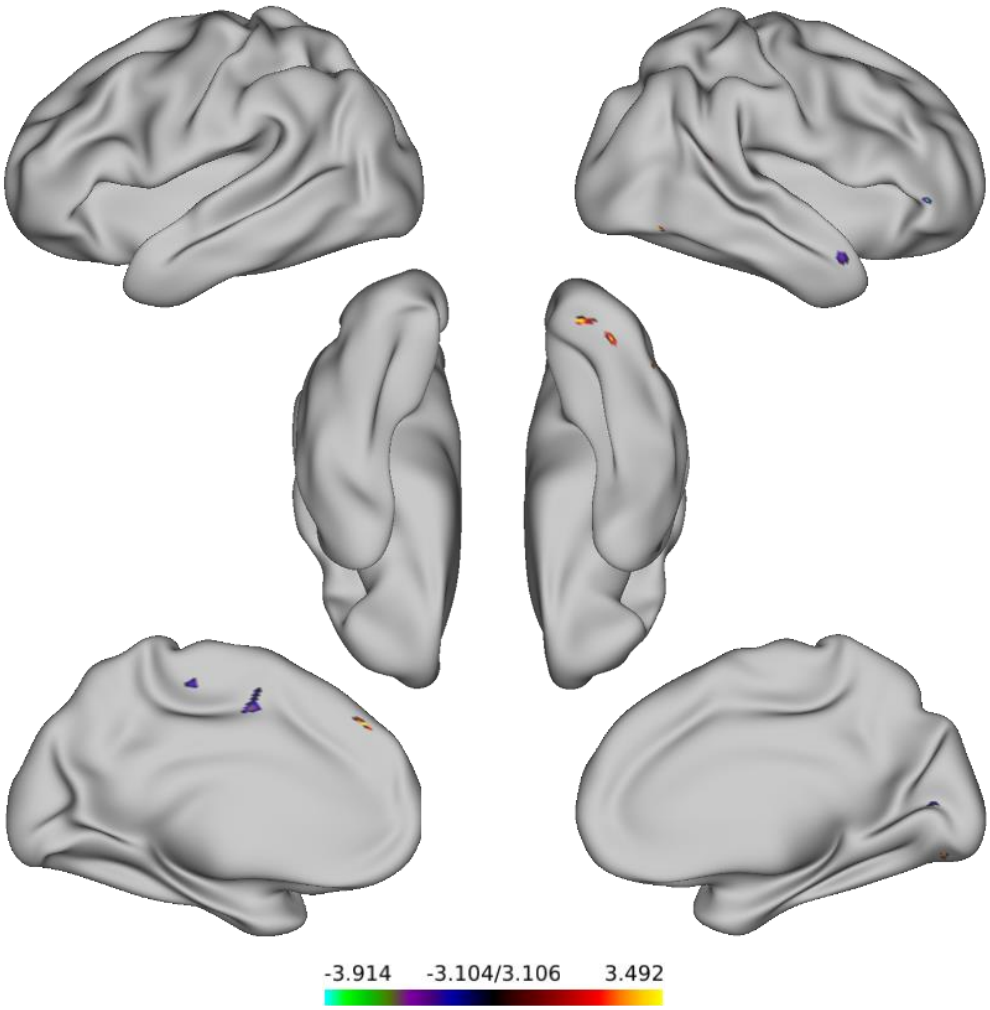

Figure 3b Left amygdala connections soon after birth associated with emotion regulation at 6-months-of-age.

3.4.4. Emotion regulation in infancy associated with future internalizing symptomatology

To examine future implications of poor emotion regulation at 6-months of age we next examined the relationship between emotion regulatory ability at 6-months of age and

internalizing and externalizing symptomatology at 2 years of age. We adjusted both models for maternal breaking still-face, and average maternal depressive symptomatology from 6-24 months-of-age. Results indicated greater emotion regulation at 6-months of age was associated with less internalizing symptomatology at 2-years of age ($\beta = -0.29$, $p < 0.05$). No association was found between our measure of emotion regulation and future externalizing symptomatology ($\beta = -0.22$, $p = 0.15$). Given the relationship between emotion regulation and future internalizing symptomatology, we next sought to examine if emotion regulation mediated a relationship between amygdala connectivity at birth and future internalizing symptoms.

3.4.5. Emotion regulation as a mediator for the association between amygdala connectivity at birth and future internalizing symptomatology

To evaluate emotion regulatory ability as a potential mediator for the association between newborn amygdala phenotypes and future internalizing symptomatology, we decided to focus on our a-priori results and most robust exploratory result. Specifically, we examined if emotion regulatory ability at 6-months-of-age mediated a relationship between right amygdala- vMPFC, MPFC or V1 connectivity at birth and internalizing symptomatology at 2-years-of-age.

3.4.6. Previously identified right amygdala connections mediate association between emotion regulation and future internalizing symptomatology

We first examined the indirect effect of RAm- vMPFC, and RAm-MPFC connectivity at birth on future internalizing symptomatology. Specifically, we regressed

gestational age at birth, infant age at scan, infant sex, maternal breaking still face and Ram-vMPFC and Ram-MPFC connectivity on our behavioral indicator of emotion regulation, latency to distress. In the same model, we also regressed latency to distress, Ram-MPFC, Ram-vMPFC, and average maternal depressive symptomatology from 6-24 months on to internalizing symptomatology at 24-months-of-age. Results indicated emotion regulation mediated the association between stronger RAm- vMPFC connectivity at birth and increased internalizing symptomatology (indirect effect = 0.08; 95% CI: 0.00, 0.24; based on 5,000 bootstrap samples.) Additionally, emotion regulation mediated the association between stronger RAm-MPFC connectivity at birth and decreased internalizing symptomatology at 24-months-of-age (indirect effect = -0.09; 95% CI: -0.26, -0.01; based on 5,000 bootstrap samples.)

Next we examined the indirect effect of right amygdala-V1 (RAm-V1) connectivity at birth on internalizing symptomatology in a separate model. Specifically we regressed RAm-V1 connectivity on to latency to distress, and latency to distress, Ram-V1 connectivity and average maternal depressive symptomatology on to internalizing symptomatology. The extracted RAm-V1 connection from our whole brain-analysis had already been adjusted for infant gestational age at birth, age at scan and maternal breaking still face, thus we did not adjust for these factors again in this model. Emotion regulation at 6-months-of-age mediated an association between stronger Ram-V1 connectivity at birth and increased internalizing symptomatology in toddlerhood (indirect effect = -0.17; 95% CI: -0.41, -0.04; based on 5,000 bootstrap samples.)

3.4.7. Neonatal amygdala connections supporting emotion regulation unrelated to physiological measure of emotion regulation in infancy

We next evaluated if amygdala connections at birth which supported our behavioral indicator of emotion regulation, latency to distress, also related to our physiological indicator of emotion regulation, cortisol release over time. Specifically, we ran an ANCOVA for each a priori amygdala connection linked to latency to distress to see if amygdala connections which supported emotion regulation varied significantly in mean strength across our identified cortisol groupings. Each analysis was adjusted for infant gestational age at birth, age at scan, and breaking still face. Due to a lack of infants with both cortisol trajectory measures and brain data at birth, the number of subjects in each subgroup decreased for the following analyses (N=29).

We first examined the effect of RAm-vMPFC and RAm-MPFC connectivity on cortisol grouping. Right amygdala- vMPFC and MPFC connectivity at birth had no impact on cortisol grouping. Next, we examined the effect of our most robust whole brain analysis result, RAm-V1 connectivity on cortisol trajectory subgrouping. Because this connection was already adjusted for gestational age at birth, age at scan and breaking still face in our whole brain analysis- we did not make any additional adjustments to our model, thus we ran an ANOVA to examine this effect. Results showed no significant effect of RAm-V1 connectivity on cortisol trajectory grouping.

3.4.8. Cortisol trajectory subgrouping relates to future internalizing symptomatology

We next examined if internalizing symptomatology or externalizing symptomatology at 2-years-of-age, related to our physiological indicator of emotion regulation, cortisol release over time. Specifically, we ran an ANCOVA for internalizing and externalizing symptomatology to see if mean differences existed between cortisol subgroups. A trend level effect of cortisol trajectory subgrouping on internalizing symptomatology at 2-years of age was found after adjusting for breaking still face ($F(2, 25) = 3.0$, $p < 0.1$). Post-hoc testing showed a trend level difference in internalizing symptomatology between subgroups 2 and 3 ($p < 0.1$). Overall conceptual model of results depicted below (**Figure 4**).

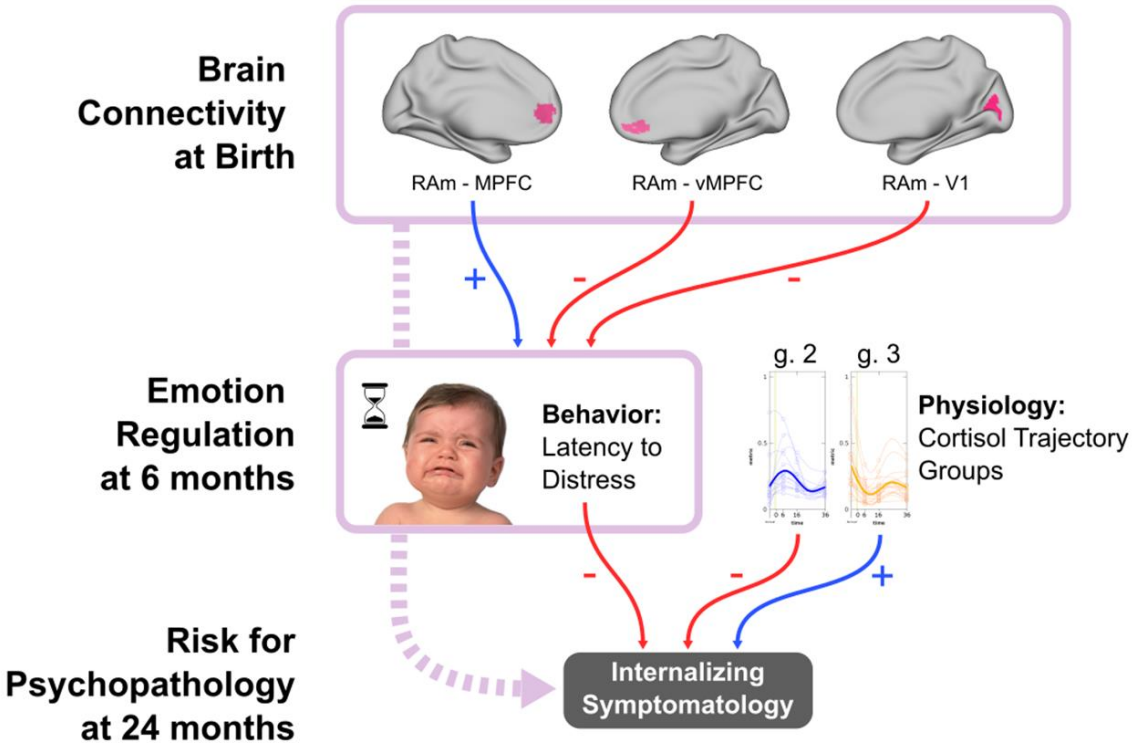

Figure 4. Increased connectivity between right amygdala and medial prefrontal cortex (RAm-vMPFC) and decreased connectivity between right amygdala and ventral medial prefrontal cortex (RAm-vMPFC) and right amygdala and visual cortex (RAm-V1)

associated with greater emotion regulation at 6-months-of-age, as indicated by increased latency to distress. Greater emotion regulation at 6-months-of-age associated with decreased risk for psychopathology, as indicated by internalizing symptomatology at 24-months-of-age. Physiology at 6-months-of-age, as indicated by cortisol trajectory subgroups, associated with internalizing symptomatology at 24-months-of-age. Specifically, cortisol trajectory subgroup 2 associated with decreased future internalizing symptomatology and cortisol subgroup 3 associated with increased future internalizing symptomatology.

3.5 Discussion

3.5.1. Amygdala connectivity at birth is associated with emerging emotion regulation

Though critical for every day coping with distress, the neural correlates of emotion regulation in infancy have yet to be thoroughly investigated. To this end, this study adds several key findings to the literature. Our results indicate that distinct right and left amygdala connections at birth support our measure of emerging emotion regulation at 6-months-of-age. Interestingly, the results mimic findings in the literature with adults in terms of implicating distinct roles for more dorsal versus ventral regions of the MPFC in emotion regulation. The results also provide some indication for an early role of what has been termed “top down” versus “bottom up” processing, such that stronger amygdala connectivity to primary sensory and motor regions demonstrate associations with poorer emotion regulation, whereas stronger amygdala connectivity to higher order processing regions are associated with greater emotion regulation. We also discovered a relationship between emotion regulation and future internalizing symptomatology, such that, greater emotion regulation in infancy was associated with decreased internalizing symptomatology in toddlerhood. Lastly, we found that emotion regulation mediates a relationship between specific amygdala connections soon after birth

and future internalizing symptomatology at 2-years-of-age. Overall, our findings indicate that already soon after birth, amygdala connectivity supports emerging emotion regulation in infancy, which appears to be a pathway for the emergence of internalizing symptoms in toddlerhood.

3.5.1.1 A priori- results indicate distinct roles for dorsal versus ventral regions of the MPFC in emotion regulation

Interestingly, the distinction between ventral versus more dorsal MPFC connectivity emerges earlier than previously understood. Our a-priori analyses indicate stronger RAm-MPFC connectivity and weaker RAm-vMPFC connectivity at birth are associated with greater emotion regulation. The findings for the RAm-vMPFC connection are in line with findings in adults implicating a role for this connection in the production of negative affect (Barrash et al., 2000; Hiser & Koenigs, 2018). Moreover, prior findings from Chapter 1 indicate stronger amygdala-vMPFC connectivity soon after birth predicts greater negative emotionality; it is likely that our current findings fit into this framework, such that stronger amygdala-vMPFC connectivity soon after birth is associated with greater unregulated negative affect. Alternatively, stronger connectivity between the amygdala and more dorsal MPFC has been associated with greater emotion regulation in adult populations (Banks et al., 2007; Ochsner et al., 2002). Already soon after birth, this connection appears to be associated with a high fear, high cognition phenotype (Graham et al., 2016), therefore it is likely this region is more involved with emotion regulation soon after birth. Overall, stronger amygdala-vMPFC coupling seems to be associated with increased generation of negative emotion (Hiser & Koenigs, 2018),

while amygdala-MPFC coupling shows the opposite pattern, with increased coupling associated with increased emotion regulation (Banks et al., 2007). Thus a dichotomy between dorsal and ventral MPFC connectivity to the amygdala exists already soon after birth.

Interestingly, neonatal amygdala- anterior insula connectivity was unrelated to emerging emotion regulation in infancy. It is possible that given this connection's previous association with fear in infancy (Graham et al., 2016, Thomas et al., 2019) this connection is more involved in the production rather than regulation of negative affect. It is also worth noting that only right amygdala a-priori connections appeared to be relevant for emerging emotion regulation. While this may have been a result of differential connectivity between amygdalae (Jung et al., 2018) it is likely due to the nature of the a-priori ROIs that were tested themselves. I.e. there were more right amygdala than left amygdala connections.

3.5.1.2 Whole brain, exploratory analyses suggest an early pattern of top down versus bottom up processing contributing to emerging infant emotion regulation

Our exploratory, whole brain analyses shows that the integration of additional regions into the amygdala at birth supports early emerging emotion regulation. Distinct results were found for the right versus left amygdala. However, an overall pattern emerged indicating that stronger amygdala connectivity to regions involved in sensory integration, emotion regulation, and large scale brain systems supporting cognitive functioning, are associated with better emotion regulation. In contrast, greater neonatal amygdala connectivity to primary sensory and motor regions, are associated with weaker

emotion regulation in infancy. These results suggest an early pattern of top down versus bottom up processing soon after birth contributing to emerging emotion regulation in infancy.

Interestingly, there are similarities in the specific functional connections observed to predict emotion regulation at 6-months-of-age, and those associated with emotion regulation in adults. Firstly, stronger amygdala integration into default mode network regions, posterior cingulate and middle temporal gyrus soon after birth emerged as a significant predictor of emotion regulation at 6-months-of-age. Research with adults documents stronger amygdala integration into default mode network regions, posterior cingulate and middle temporal gyrus to be linked to the increased negative emotional valence of stimuli (Dutta et al., 2019). It is not known whether this connection serves a similar purpose during infancy, but perception of the negatively valenced still-face stressor is a logical precursor to emotion regulation. Increased neonatal coordinated functioning of the amygdala and orbital frontal cortex also predicted higher levels of emotion regulation at 6 months-of-age. This finding was in line with research in adults indicating a role for amygdala-orbital frontal connectivity in emotion regulation (Ochsner et al., 2004). It appears that already soon after birth this functional connection is relevant for emotion regulation.

Additional neonatal amygdala connections relevant for emotion regulation in infancy may have impacted the infants' ability to engage in regulatory behaviors. In particular, less visual sensory integration into the right amygdala soon after birth was associated with greater emotion regulation 6-months-of-age. Stronger integration into the visual cortex may be associated with weaker emotion regulation partially due to the

biased competition model of attention. This model suggests that there is competition for processing resources in the visual cortex. Salient stimuli have an advantage in terms of competition for neural representation (Desimone & Duncan, 1995). Amygdala projections to the visual cortex influence visual processing according to the valence of the stimulus. Negatively valenced stimuli, in particular, evoke stronger responses in the visual cortex and use more processing resources (Pessoa & Ungerleider, 2004). Given the negative valence of the paradigm employed in our study, the still-face paradigm,(J. Braungart-Rieker et al., 1998; Mesman et al., 2009; Toda & Fogel, 1993) it is possible that increased Am-V1 connectivity consumes more processing resources, making it difficult for the infant to utilize the regulatory strategy of attention shifting, thus resulting in decreased emotion regulatory behavior. Similarly, stronger amygdala integration into the motor cortex soon after birth was associated with decreased emotion regulation in infancy. Increased amygdala integration into the motor cortex has previously been shown to result in freezing behavior or "braking" in the face of a negative emotional stimuli (Sagaspe et al., 2011; Xu et al., 2019). It is possible that increased amygdala coordinated functioning with primary motor cortex in the neonatal period confers a greater tendency for such freezing behavior, versus beginning to engage in and develop more effective strategies for regulating emotions.

3.5.2. Emotion regulation in infancy appears to be a pathway through which early patterns of amygdala connectivity may influence subsequent internalizing behavior

In addition to elucidating neonatal amygdala connections which support emotion regulation behavior in infancy, our results also indicate that already in infancy emotion

regulation is associated with future internalizing symptomatology, such that, greater emotion regulation in infancy predicts less internalizing symptomatology in toddlerhood. This result fit well with previous literature indicating greater emotion regulation at 6-months-of-age predicts less future internalizing symptomatology at 18-months-of-age (Moore et al., 2001) and literature in children (Kim-Spoon et al., 2013; Raver et al., 2017) and adolescents (Hatzenbuehler et al., 2008) linking poor emotion regulation to increased internalizing symptomatology.

Our findings also indicate that already in the newborn period amygdala connectivity relates to internalizing symptomatology in toddlerhood via emotion regulation. Specifically, stronger RAm-MPFC and weaker RAm-vMPFC connectivity moderated an association between greater emotion regulatory ability and lower internalizing symptomatology at 2 years of age. Interestingly, these connections appear to support the same constructs in children and adults based on prior studies (Kim et al., 2011b; Qin et al., 2014; Wang et al., 2013). In children, Am-MPFC and Am-vMPFC connectivity have been associated with anxiety (Kim et al., 2011b; Qin et al., 2014), while in adulthood, increased perfusion of the amygdala and reduced perfusion of the vMPFC has been linked to risk for future depression (L. Wang et al., 2013).

In the current study, emotion regulation behavior also mediated an association between weaker right amygdala- V1 connectivity and lower internalizing symptomatology. Overall, our findings suggest that specific connections and overall patterns of connectivity, in line with findings in children, adolescents and adults, are already apparent in the neonatal period and relate to an early time point in infancy at which we can begin to see evidence of emotion regulation. These analyses suggest that

our measure of emotion regulation is relevant for subsequent internalizing behaviors, which supports the importance of early emerging emotion regulation. Further, the mediation models, while underpowered, provide preliminary evidence to indicate that early emerging emotion regulation may serve as pathways through which patterns of brain connectivity evident soon after birth, influence later behavior problems and symptoms. This highlights the potential importance of providing support for very early development of emotion regulation skills.

3.5.3. Physiological response to stress may represent another pathway for the development of internalizing behaviors.

Interestingly, our physiological measure of emotion regulation was unrelated to our behavioral indicator of emotion regulation. Moreover, amygdala connections at birth which support emerging emotion regulation, were unrelated to the physiological changes that occurred. This is surprising given that the amygdala and mPFC strongly innervate the lateral hypothalamus (Reppucci & Petrovich, 2016). However, infant's physiological response to stress still significantly related to future internalizing symptomatology. Specifically, subgroup 2, characterized by an increase in cortisol after arrival to the lab and a decrease in cortisol 20 minutes after the still-face episode, had significantly lower internalizing symptomatology than subgroup 3, characterized by a decrease in cortisol after arriving in lab and an increase in cortisol 20 minutes after the still-face episode. This result was unexpected and does not fit into the literature. Over the first year of life, infants typically show increases in cortisol in response to stressors (Gunnar & Quevedo, 2007), including the still-face (Provenzi et al., 2016). These increases can typically be

buffered or reduced by the input of a responsive caregiver (Stansbury & Gunnar, 1994; Wu & Feng, 2020). Given the nature of the still face paradigm, buffering of the stress-response by the caregiver is not possible, potentially suggesting decreases in cortisol may be associated with intrinsic emotion regulation. However, given the lack of association between subgroup 2 and our measure of the emotional reactivity component of emotion regulation, the decrease in cortisol seen in subgroup 2 in response to the still-face episode may be associated with a regulatory aspect of emotion regulation captured by the presence of specific regulatory behaviors.

While infant's physiological response to the stressor was unrelated to our behavioral indicator of emotion regulation, it did relate to future internalizing, indicating that the physiological response may represent another pathway for the development of internalizing behaviors. This idea is further supported by our result indicating that the neural connections which support emotion regulation are unrelated to the physiological response, which again suggests a distinct pathway.

3.6. Conclusions, Limitations and Future Directions

Several limitations of the present study should be considered. First and foremost, our sample size was small so power was low and in particular, moderator effects may have been missed (Type II error) due to low power. Thus, replication in larger samples is needed to confirm the findings. However, findings are novel and should stimulate more work to evaluate the early development model.

In regards to our measure of emotion regulation, additional variables not recorded in the current study are surely important. For example, infant mobility may impact on

interactions between caregiver and infant (Franchak et al., 2018), which could have potentially impacted our measure of infant emotion regulation. Additionally, while laboratory assessments offer a unique opportunity to examine infant behavior in a controlled setting, the setting itself can often impact behavior. It is possible that our measure of emotion regulation was impacted by the laboratory setting. While it was beyond the scope of this study to examine other measures, it will be interesting to see whether they converge in future studies. In regards to our amygdala connectivity, it is likely that subregions of the amygdala have distinct functional connectivity patterns (Jiang et al., 2019). The present studies did not offer the spatial resolution to evaluate differences in functional connectivity between these subregions. Future work should be done to elucidate how distinct amygdala subregions support emerging emotion regulation. Moreover, while it has been shown that caregivers may play a protective role in dampening HPA activity from infancy through early childhood (Gunnar & Quevedo, 2007; Gunnar et al., 2009) in the current study we did not have the power to evaluate the impact of the caregiving environment on cortisol reactivity during the still-face paradigm. Future work should consider this important covariate. Furthermore, while our study examined the emotional reactivity component of emotion regulation, future work should consider how the newborn brain relates to the regulatory aspect of emotion regulation.

Overall, these studies provides evidence that emerging emotion regulation in infancy ties together an association between the brain at birth and future internalizing symptomatology, highlighting the importance of providing support for the development of emotion regulation skills in infancy.

Chapter 4: Emotion regulation and reactivity support emerging executive functions.

4.1. Introduction

4.1.1. The importance of executive function

Executive function (EF) is defined as a set of cognitive abilities involved in flexible, purposeful, goal-directed behavior (Miyake et al., 2000). One dominant model of EF is composed of three distinct, but also closely related factors: inhibitory control (the ability to refrain from preponent responses), working memory (the capacity to retain and manipulate information relevant to the task at hand), and shifting (the ability to disengage from an irrelevant task set, and reengage with a relevant task set) (Diamond, 2013; Miyake et al., 2000). These frequently measured factors appear to be related, but show sufficient distinction to warrant examining them separately (Miyake et al., 2000). Early emerging EF skills are associated with school readiness (Fitzpatrick & Pagani, 2012), academic performance (Mischel et al., 1988; Prager et al., 2016) and are strongly linked to mental health outcomes throughout the lifespan (Bettis et al., 2017; Pennington & Ozonoff, 1996; Zelazo, 2020). The developmental course of early EF also relates to subsequent development across domains. Early EF skills are associated with EF in late adolescence (Eigsti et al., 2006) and future internalizing and externalizing symptomatology in childhood (Murray & Kochanska, 2002). EF skills in early life also provide a foundation for healthy development, with implications for academic (Blair & Razza, 2007; Mulder et al., 2017) and social functioning (Carlson et al., 2004; Hughes & Ensor, 2005).

4.1.2. Development of executive function

EF is generally assumed to develop in early life in a hierarchical manner; complex forms of EF stem from the integration and development of related, but more basic cognitive skills (Garon et al., 2008). For example, strategies to redirect attentional focus in toddlerhood have been shown to predict EF performance in childhood (Eigsti et al., 2006). Specifically, early skills like redirecting attention and effortful control in toddlerhood are the precursors of emerging EF (Diamond, 2013). Moreover, more general cognitive ability in toddlerhood, supports greater EF abilities in childhood (Wu et al., 2017). Additionally, the developing ability to control and plan motor actions has been correlated with simple inhibition and working memory at 18-months-of-age (Gottwald et al., 2016). In addition to attentional orienting, more general cognitive abilities, and sensorimotor skills (Gottwald et al., 2016; Wu et al., 2017), specific neurobiological supports for early EF development have been hypothesized. The prefrontal cortex, which develops rapidly over the first two years of life (Hodel, 2018), is hypothesized to be foundational for subsequent emerging EF (Diamond, 2002; Garon et al., 2008), in particular the dorsolateral and ventrolateral prefrontal cortex (Diamond, 2013).

4.1.3. Aspects of the postnatal environment that contribute to the development of executive function

In terms of the broader environment, socioeconomic status (SES) has been shown to influence the development of EF abilities, although mechanisms are not well understood. Living in poverty, relative to not living in poverty is related to lower EFs in

children (Lipina & Evers, 2017). Specifically, 6-14 month-old infants from lower SES environments (as defined by parents' educational background, parents' occupational background, dwelling, and overcrowding conditions) have been found to perform fewer consecutive correct responses, and make more perseverative and non-perseverative errors, on the A-not-B task, a task assessing rudimentary skills relevant for subsequent EF (Lipina et al., 2005). Moreover, higher income-to-needs ratios have been associated with better performance on working memory tasks in 54-month-old toddlers (Hackman et al., 2015). SES may influence development of EF through availability of learning resources, opportunities in the home environment, as well as the time and guidance provided by caregivers (Hackman et al., 2015). For example, variation in access to computers and home literacy activities has been shown to mediate a relationship between low SES and EF (Lipina et al., 2013). Moreover, SES likely influences development through the quality, sensitivity, and responsivity of caregiving (Hackman et al., 2015). The caregiving environment, particularly maternal responsivity, may exert a strong impact on emerging EF (Fay-Stammbach et al., 2014). Specifically, sensitive caregiving can promote the infants internalization of regulatory strategies (Bernier et al., 2012). As such, sensitive, engaging interactions with caregivers may be associated with increased EF competence (Rhoades et al., 2011).

4.1.4. How negative emotionality and emotion regulation relate to executive function

Emotion regulation (ER) occurs through the use of attention and other regulatory strategies employed to modify emotional reactivity. ER thus stems from an interaction between emotional reactivity, and a control aspect that regulates reactivity. This is

particularly important in the regulation of negative emotionality, as dysregulation of negative emotionality leads to increased distress (Riediger et al., 2011) and subsequent poor mental health outcomes (Buehler et al., 2007; Kring & Caponigro, 2010; Svaldi et al., 2012; Weiss et al., 2015). As a result, ER can be conceptualized and measured both as regulatory behaviors and as latency to negative emotional output in the context of situation which commonly elicits distress (Frick et al., 2017).

ER and EF represent distinct, but related constructs. Both ER and EF involve cognitive control. However, EF represents a broader measure of cognitive control, while ER is focused on the cognitive control involved in modulating affect (Galvagno et al., 2019). The construct of ER describes behaviors specifically used to regulate emotions to handle internal or external stressors and emotional input; whereas the construct of EF is focused on the maintenance of goal-directed cognitive processes beyond the regulation of emotion. The distinction between ER and EF becomes slightly more complex when considering "hot" EF, which is defined as emotionally-motivated goal directed behavior as opposed to "cold" EF, defined as motivationally-neutral goal directed behavior (Zelazo et al., 2007; Rueda et al., 2013). Hot EF is EF that operates in emotionally and motivationally significant contexts,(Zelazo & Carlson, 2012) and involves some of the same brain regions as ER. Specifically, research implicates the orbital frontal cortex in both hot EF and ER in the form of emotion suppression (Garon et al., 2008; Ohira et al., 2006) Like, hot EF, ER often occurs in emotion laden contexts, however, ER specifically focuses on the regulation of emotion versus achieving another goal in this context (Zelazo et al., 2007).

Developmental associations between EF and ER are bidirectional, which implies that breakdowns or perturbations in one area may lead to disruption in the consolidation of the other (Sudikoff et al., 2015). For example, poorly regulated emotions interfere with performance on tasks with high EF demands (Zelazo & Cunningham, 2007). Moreover, poorly regulated negative emotionality has been associated with worse EF in preschoolers (Ferrier et al., 2014).

4.1.5. Early negative emotionality and emotion regulation may lay the foundation for subsequent emerging executive function skills

Negative emotionality emerges rapidly over the first year of life. Increasing negative emotionality during this period has been reliably documented and is considered to be part of a normative developmental trajectory (Gartstein et al., 2010; Partridge et al., 2007). Not surprisingly it is also possible to observe emerging ER skills during this early developmental period (Garstein & Rothbart, 2003; Esther M. Leerkes & Wong, 2012). These include visual attentional orienting, an early form of top down ER and also part of the precursive abilities that become EF, which allows infants to consciously disengage from stressful stimuli and reorient to more neutral or positive stimuli, (Crockenberg & Leerkes, 2004; Reynolds & Romano, 2016), and self-soothing behaviors such as hand and foot clasping, self-manipulation and non-nutritive-sucking (Derryberry & Rothbart, 1981; Thomas et al., 2017). The early development of negative emotionality and ER, and the known relevance of negative emotionality and ER to EF, has led to interest in how early negative emotionality and ER may relate to subsequently emerging EF skills. One specific component of early emerging ER that may subsequently serve as a critical

component of EF is the modulation of attention (Conway & Stifter, 2012; Eigsti et al., 2006; Stifter & Braungart, 1995). For example, strategies to redirect attentional focus in toddlerhood have been shown to predict EF performance in childhood (Eigsti et al., 2006).

Prior research provides support for the conceptualization of early ER as providing a foundation for subsequently emerging EF (Blankson et al., 2013; Feldman, 2009; Ursache et al., 2012). Greater ER in the neonatal period has been associated with greater EF at 5-years-of-age (Feldman, 2009). Moreover, ER at age 3 predicts growth in working memory and impulse control skills from age 3 to 4 (Blankson et al., 2013). However, work also indicates that a specific match between levels of negative emotionality and ER may be particularly relevant for EF. Specifically, the interaction between ER and negative emotional reactivity at 15 months-of-age has been shown to predict EF at 48 months-of-age (Feldman, 2009; Ursache et al., 2012). These findings indicate that high negative emotional reactivity paired with high regulation is associated with greater EF, while high reactivity paired with low regulation predicts worse EF. This indicates that the relationship between negative emotional reactivity and future outcomes is moderated by the regulation of this reactivity. Thus it appears important to assess both levels of ER and negative emotionality in relation to EF. While this interaction has already been examined in relation to a general composite of EF in early life, how ER and emotional reactivity, before the age of one, relate to specific EFs, such as working memory, shifting ability and impulse control, in toddlerhood remains unknown.

4.1.6. Present Study

In the present study we examine how infant negative emotional reactivity interacts with early regulatory behaviors to lay a foundation for subsequent emerging EF skills in toddlerhood. We utilize the construct of latency to distress as the negative emotional reactivity component of ER, and focus on regulatory behaviors including control of visual attention as our primary measures of the regulatory aspect of early ER. We further examine the potential for infant negative emotional reactivity to interact with environmental factors known to influence early EF skills with a focus on the caregiving environment and SES. This work aims to advance understanding of how early negative emotional reactivity relates to subsequent emerging EF skills and the role of internal factors, specifically early ER skills, and external factors, caregiving behaviors and SES, in determining these associations.

4.2 Methods

4.2.1. Participants

Infants included in this study are subsamples from a larger longitudinal study in which mothers were recruited during the first trimester of pregnancy. Mothers were excluded if they used psychotropic medication, corticosteroids, alcohol, or drugs during the pregnancy. Additionally they were excluded if there was a known congenital, genetic or neurologic disorder of the fetus (e.g. fragile X, Down syndrome). Demographic variables are provided in Supplementary Material Table 1. Assessment of emotionality and ER was completed (N=106) when infants were 6-months-of-age (months M= 5.86, SD= 0.49; days M= 11.79, SD= 8.97), and an assessment of EF abilities were completed at 24-months-of-age (M= 23.88, SD= 0.82; days M= 12.89, SD= 9.91) with three tasks.

Infants who completed both the 6-month and 24-month assessments were included in analyses, resulting in slightly different sample sizes due to variation in the total number completing each EF task (shifting ability, N= 62; impulse control, N= 71; working memory, N = 69) at 24-months-of-age). To examine potential differences between our subsamples and the larger sample we conducted independent sample T-tests to examine mean differences in key constructs relevant to EF between the subsamples and larger sample of all infants with data at 6 months. No significant differences were found for average maternal depressive symptomatology, regulatory behavior, emotional reactivity, attentional orienting, our SES measure, or maternal responsivity between infants in our subsamples versus the larger sample.

4.2.2. Infant emotionality and ER

4.2.2.1. Still Face

Protocol

The still-face episode of the still-face paradigm (Tronick et al., 1978) allows for the unique opportunity to assess infant ER and emotionality in the absence of parental aide in regulation of emotions. Mothers stare at their infants with a blank expression on their face as infants are strapped into a car seat. This, known as the still-face, has been shown to reliably increase infant distress, likely due to the violation of the infant's expectation of their mother's responsiveness (J. Braungart-Rieker et al., 1998; Mesman et al., 2009; Toda & Fogel, 1993; Weinberg & Tronick, 1994). During the still-face episode, infants perform a variety of behaviors in an attempt to regulate their negative emotional response (J. Braungart-Rieker et al., 1998; Rothbart, M.K., Ziaie, H., O'Boyle, 1992).

When infants were approximately 6-months-of-age the still face paradigm was conducted. It included 5 2-minute episodes in the following order: play episode, still-face episode, play episode, still-face episode, and play episode.

Behavioral coding

Two observers coded infant behaviors during the still-face paradigm using a modified version of a published coding scheme (original: (Moore et al., 2009); modified: (Sullivan et al., 2015)). Infant behavior was coded in increments of 5 seconds for three mutually exclusive behavioral categories: (a) affect, (b) gaze, (c) regulatory behavior. Infant behaviors were coded through three separate viewings of the video, one for each behavioral category. Reliability on the specific coding scheme was established by analyzing percentage agreement and Cohen's kappa. First reliability was established between coders and the creators of the original coding scheme on 20 videos (>80% reliability for all behaviors). Next, observers achieved reliability with the creators of the modified version of the coding scheme, used in the present study on 5 videos (88% agreement, Kappa= 0.87). Lastly, reliability was established between coders on 20 videos for all behaviors coded.

Coding of deviation from Still Face Protocol

Though mothers were asked to maintain a neutral face and not touch their infant throughout the entire still-face episode, mothers often broke still face for brief periods of time (N=39) throughout the 2 minute episode. Because breaking still face may have impacted our measure of negative emotionality here and because it is a violation of the still-face episode, it was included as a covariate in analyses.

Negative emotional reactivity

Latency to distress, the number of seconds before the infant expressed negative affect (*M* = 42.2 seconds, days *SD* = 42.1*),* was calculated as an indicator of infant emotional reactivity. Longer latency to distress was characterized as lower negative emotional reactivity. Our coding of negative affect included sadness, frustration and anger. Eyes may have been tightly closed, the corners of the mouth turned downward or brows sharply furrowed. This also included elements of both negative and positive facial expressions. For example, the infant may have had the corners of its mouth raised with its brows drawn together. Reliability was high for coding of affect (88.8%, Kappa= 0.80): Gaze (90%, Kappa= 0.80), Affect (88.8%, Kappa= 0.80), and Regulatory behavior (84.1%, Kappa= 0.65). Because of the slightly lower kappa for regulatory behavior, all reliability for regulatory behavior was assessed every 20 videos. If percentage agreement for regulatory behaviors was <80% for any given video, coders would conference regarding the behavior until a consensus was reached.

Attentional orienting

Attentional orienting, the percentage of time the infant spent gazing away from its mother, was calculated as an indicator of infant attentional orienting. Infant attentional orienting was coded as present or absent by two independent coders in 5-second intervals. Our coding of attentional orienting included Gaze Away and Gaze Toward. Gaze Away included intervals in which the infant was facing the parent with eyes closed, and intervals in which the infant was looking at the parent's hands or clothing. Gaze Toward was the default code, so if the direction of gaze was ambiguous this was coded, additionally this included looking in the direction of the parent's hair or chin, not simply the eyes.

Other regulatory behaviors

The percentage of time the infant spent engaged in other regulatory behaviors was calculated during the first still-face episode. Our coding of other regulatory behaviors included Escape, Attention Seeking, Exploratory and Regulatory behaviors. Regulatory behaviors included deliberate behavior by the infant such as sucking on a body part or object, auto-manipulation (e.g. lip smacking), manual manipulation (e.g. hand clasping, playing with foot), rhythmic rocking or kicking or movement of head, stroking of self, limbic motion (with gaze directed towards limbic motion), and pulling clothes. Exploratory behaviors included intervals in which the infant was touching an object while the gaze was directed towards the object. Escape behaviors included intervals in which the infant was attempting to get out of the chair. Attention-seeking behaviors included intervals in which the infant was trying to get the parent's attention.

4.2.3. Early environment

4.2.3.1. Maternal Caregiving: Maternal Responsivity

Quality of the postnatal caregiving environment was assessed when infants were 6-months-of-age using the Home Observation for Measurement of the Environment (HOME) Inventory (Bradley et al., 2003). Trained observers made assessments after achieving reliability with a certified administrator of the inventory (95% agreement on two consecutive videos.) Visits to the home were done to observe the infant's activity and interactions in their caregiving environment. We used the subscale HOME Responsivity to assess the extent of maternal responsiveness to the infant for our analyses (M= 8.32, SD= 1.68).

4.2.3.2. Maternal Depressive Symptomatology

The 20-item Center for Epidemiological Studies of Depression Scale (CESD; (Radloff, 1977)) was used to assess maternal depression. Mothers reported on symptoms of depression over the past week on a 4-point scale, ranging from 0 (rarely or none of the time) to 3 (most or all of the time) when infants were 6, 9, 12, and 24-months-of-age. The mean score was used in analyses. To account for the postnatal caregiving environment across a larger span of time, an average of maternal depressive symptomatology (M= 0.51,SD= 0.41) was created from scores when infants were 6 (M= 0.53 , SD= 0.51), 9 (M= 0.42 , SD= 0.35), 12 (M= 0.52 , SD= 0.46), and 24-months-of-age (M= 0.46, SD= 0.40). Internal reliability across time points was high ($\alpha = 0.87$).

4.2.3.2. Socioeconomic status

Income-to-needs (ITN) was measured as the ratio between annual family income and the federal poverty threshold, accounting for the size of the household. Specifically, the annual family income was divided by the Federal Poverty Threshold for a family of that size, in the year the data were collected, 2011. This resulted in classifications of living within or near the poverty line (ITN<2) and living above the poverty line (ITN>2). Specifically 42.5% of the sample fell within the range designated as living with or near the poverty line and 57.5% were designated as living above the poverty line. This measure was used as an indicator of the broader environment.

4.2.4 EF at 24-months-of-age

4.2.4.1. Working Memory Ability (WM)

Working memory was assessed using the Spin the pots task (Hughes & Ensor, 2005) at 24 months. The spin-the-pots task is a widely used search task designed to probe working memory in toddlers and young children. A spinning tray containing 8 opaque pots with distinct visual appearances has stickers placed inside 6 of the 8 pots. On each trial, the experimenter places a cloth over the tray and spins it. Participants must then try to remember which pots have stickers in them. The score is calculated by taking the total number of possible trials (16) minus the number of errors (number of turns taken to recover the stickers unsuccessfully) (M= 8.01, SD= 4.07, range= 3-16).

4.2.4.2. Shifting Ability

Shifting ability was assessed using the Minnesota Executive Function Scale for early childhood (Carlson & Shaefer 2012) at 24 months. In this task children sort cards by placing them in one of two plastic boxes. Cards are sorted based on the pictures on the boxes, and the picture on the card according to a rule supplied by the experimenter. Each level is comprised of 5 trials, after which children must sort according to a new rule. Children advance to the next level only if they correctly sort 4 of 5 cards (M= 10.00, SD= 4.55, range= 0-19).

4.2.4.3. Impulse control

Impulse control was assessed using the Snack delay task (Kochanska et al., 1996, 2000) at 24 months. Children were instructed to wait with a desired snack placed on the table in front of them until an experimenter rang a bell before eating the desired snack.

The task was composed of four trials, with each trial involving a longer wait time (10, 15, 20 and 30 seconds). Scoring was consistent with the procedure established by Kochanska and colleagues (Kochanska et al., 1996, 2000), specifically the total score across all trials was calculated. Higher scores were indicative of waiting longer to reach for or eat the snack (M= 5.44, SD= 2.37, range= 1-9).

4.2.5. Covariates

4.2.5.1. General infant cognitive capacity

At 6-months infant cognitive development at was assessed with the Cognitive Scale composite score from Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III; Bayley, 2006). This is a standardized, widely used, measure of infant development. The Cognitive Scale includes developmentally appropriate assessment of emerging interest in and understanding of the environment, as well as emerging sensorimotor, memory and attention skills (M= 104.43, SD= 10.70).

4.3. Analyses

4.3.1. Preliminary analyses

We first examined associations between shifting ability, impulse control and working memory. Correlations between EF measures were strong enough to be related, but not strong enough to be the same (r = .54-.08) therefore we chose to examine these constructs separately. We also evaluated intercorrelations between all study variables, reported in Supplementary Materials Table 2.

4.3.2. Set-up for analyses

Hierarchical linear regression models (one for each EF at 24-months-of-age) were then used to examine: (1) whether negative emotionality at 6-months-of-age interacted with attentional orienting at 6-months-of-age to predict EF, (2) whether negative emotionality interacted with regulatory ability to predict EF, (3) whether negative emotionality interacted with income-to-needs to predict EF. All analyses were re-done with covariates for mother's violation of still-face and infant cognitive ability to ensure results stayed the same. Three stage hierarchical multiple regressions were conducted with each measure of EF as the dependent variable. To evaluate the impact of attentional orienting and regulatory ability on emerging EF, we controlled for the potential impact of the external environment (maternal responsivity and SES Status). Therefore, maternal responsivity and SES status were entered at stage one of the regression. Negative emotional reactivity and attentional orienting were entered at stage two, and the interaction between negative emotional reactivity or attentional orienting and regulatory ability entered at stage three. When evaluating the impact of the external environment, we controlled for regulatory ability (attentional orienting and regulatory ability). Therefore, attentional orienting and negative emotional reactivity were entered at stage one of the regression. Maternal responsivity and SES status were entered at stage two, and the interaction between maternal responsivity/SES status and negative emotional reactivity were entered at stage three. Significant interactions were probed by conducting a set of simple slope analyses controlling for the same covariates as in the main models.

4.4. Results

4.4.1. Primary Analyses

4.4.1.1. The association between negative emotional reactivity and shifting ability was moderated by attentional orienting

We examined attentional orienting as a potential moderator of an association between negative emotional reactivity and shifting ability. The interaction between latency to distress and gaze away was associated future shifting ability ($\beta = -0.48$, $p < 0.01$). Additionally, there was a significant main effect of SES status on shifting ability, such infants not living in poverty had greater shifting ability than infants living in poverty ($\beta = 0.41$, $p<0.01$). See Table 1 below. This association persisted after adjusting for mom's violation of still face and infant cognitive ability. Thus it appears the association between negative emotional reactivity and shifting ability is moderated by attentional orienting. To probe the interaction further we conducted a simple slopes analysis, controlling for the same covariates as in the main model.

4.4.1.1.2. Probing the interaction between negative emotional reactivity and shifting ability suggested distinct effects for high and low attentional orienting

Associations between negative emotional reactivity and shifting ability were examined at high versus low attentional orienting, specifically at ± 1 SD from the mean employing a simple slopes analysis. Results indicated negative emotional reactivity was positively associated with shifting ability at a trend level when attentional orienting was high ($\beta = -0.26$, $p< 0.1$), and negatively associated with shifting ability when attentional orienting was low ($\beta = 0.90$, $p<0.01$). Thus negative emotional reactivity was associated with shifting ability, such that for infants with higher attentional orienting greater

negative emotional reactivity was associated with greater shifting ability, and for infants with lower attentional orienting greater negative emotional reactivity was associated with less shifting ability.

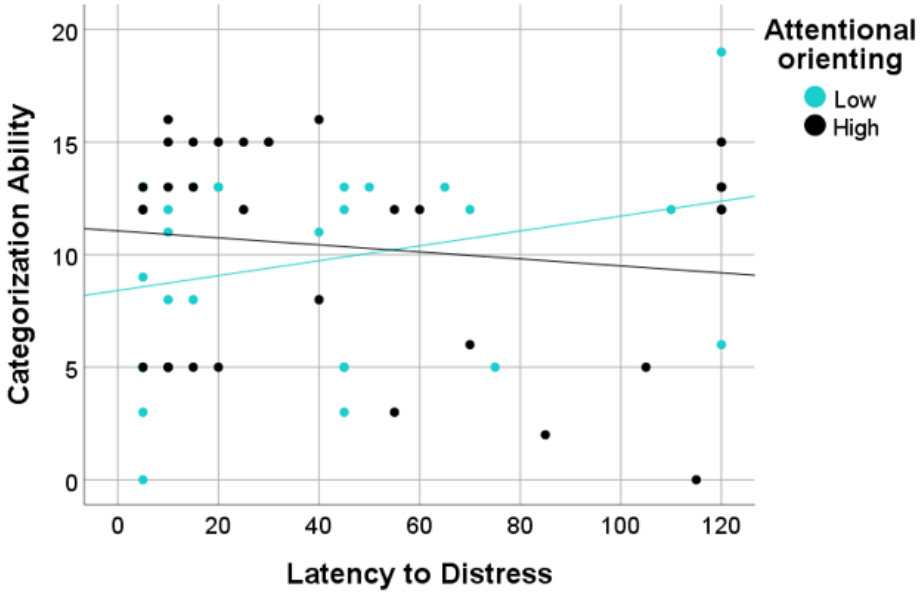

Figure 1: Shifting ability and negative emotional reactivity by high attentional orienting and low attentional orienting. (Based on a median split)

4.4.1.2. The association between negative emotional reactivity and working memory was moderated by attentional orienting

In a separate model, we examined attentional orienting as a potential moderator of an association between negative emotional reactivity and working memory. The interaction between latency to distress and gaze away was associated with future working memory at a trend level (β= -0.26, $p< 0.1$). Additionally, a trend level main effect of SES status on working memory was found (β= 0.21, $p< 0.1$) indicating infants not living in poverty had greater working memory than infants living in poverty. See Table 2 below.

These associations persisted after adjusting for mom's violation of still face and infant cognitive ability. Although the interaction between negative emotional reactivity and attentional orienting was not significantly associated with working memory, we probed the interaction as a post-hoc analyses to explore whether a similar patterns of results would emerge as for shifting.

4.4.1.2.1. Probing the interaction between negative emotional reactivity and working memory suggested distinct effects for high and low attentional orienting

Although the interaction was not significant, we probed the interaction to examine whether the overall pattern would be consistent with the finding for shifting. We examined simple slopes to indicate associations between negative emotional reactivity and working memory at high versus low levels of attentional orienting (± 1 SD from the mean). Results indicated latency to distress was not significantly associated with working memory when attentional orienting was high or low, but the direction of effects was opposite such that the slope was negative for latency to distress and working memory when attentional orienting was high (β= -0.17, p= 0.29), but positive when attentional orienting was low (β= 0.40, p= 0.17). Thus the overall pattern was consistent with the finding for shifting although care should be taken in interpreting these results due to the small effect sizes and lack of statistical significance.

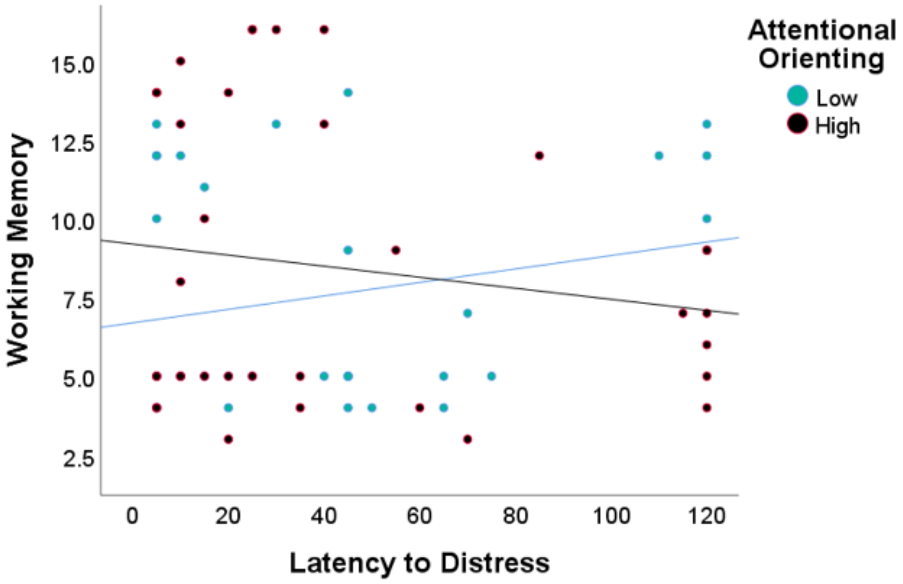

Figure 2: Working memory and negative emotional reactivity by high attentional orienting and low attentional orienting. (Based on a median split.)

4.4.1.3. Moderation by attentional orienting of the association between negative emotional reactivity and future impulse control did not reach significance threshold

In another model, we examined attentional orienting as a potential moderator of an association between negative emotional reactivity and impulse control. The interaction between latency to distress and gaze away at 6-months-of-age was not significantly unassociated with impulse control at 24-months-of-age. See Table 3 below. Results remained consistent after adjusting for mom's violation of still face and infant cognitive ability. Thus attentional orienting did not reach our threshold for moderating an

association between negative emotional reactivity and future impulse control.

Table 1. Hierarchical Regression Analysis of Predictors of Categorization Ability						
Predictor Variables	*Regression 1*		*Regression 2*		*Regression 3*	
	β	*S.E.*	β	*S.E.*	β	*S.E.*
SES Status	0.39**	1.08	0.39**	1.09	0.41**	1
Maternal Responsivity	-0.14	0.36	-0.15	0.36	-0.18	0.33
Latency to Distress			0.09	0.01	0.34*	0.02
Percentage Gaze Away			0.14	2.59	-0.09	2.74
Latency to Distress X Gaze Away					-0.48**	0.76
R^2	0.17		0.21		0.35	
ΔR^2	0.17		0.03		0.14	
†p<0.1,*p<0.05 , **p<0.01, ***p<0.001						

Table 2. Hierarchical Regression Analysis of Predictors of Working Memory						
Predictor Variables	*Regression 1*		*Regression 2*		*Regression 3*	
	β	*S.E.*	β	*S.E.*	β	*S.E.*
SES Status	0.21†	0.98	0.19	1	0.21†	0.99
Maternal Responsivity	-0.15	0.33	-0.14	0.33	-0.16	0.33
Latency to Distress			0	0.01	0.13	0.01
Percentage Gaze Away			0.15	2.38	0.03	2.74
Latency to Distress X Gaze Away					-0.26†	0.76
R^2	0.06		0.09		0.13	
ΔR^2	0.06		0.02		0.04	
†p<0.1,*p<0.05 , **p<0.01, ***p<0.001						

Table 3. Hierarchical Regression Analysis of Predictors of Impulse Control						
Predictor Variables	*Regression 1*		*Regression 2*		*Regression 3*	
	β	*S.E.*	β	*S.E.*	β	*S.E.*
SES Status	-0.12	0.57	-0.12	0.58	-0.12	0.58
Maternal Responsivity	-0.11	0.18	-0.1	0.19	-0.1	0.19
Latency to Distress			-0.02	0.01	0.03	0.01
Percentage Gaze Away			0.12	1.41	0.07	1.63
Latency to Distress X Gaze Away					-0.1	0.45
R^2	0.03		0.04		0.04	
ΔR^2	0.03		0.01		0.01	
†p<0.1,*p<0.05 , **p<0.01, ***p<0.001						

4.4.2. Secondary Analyses

4.4.2.1. Other moderating effects of regulatory behaviors on an association between negative emotional reactivity and future EFs also did not reach our significance threshold

In 3 additional separate models, we examined regulatory behavior and a potential moderator of an association between negative emotionality and future EFs. The interaction between latency to distress and other regulatory behaviors at 6-months-of-age was not significantly unassociated with future task switching, impulse control or working memory at 24-months-of-age. However, there was a significant main effect of SES status on shifting ability, such infants not living in poverty had greater shifting ability than infants living in poverty ($\beta = 0.40$, $p<0.01$). Additionally, a trend level main effect of SES status on working memory was found ($\beta = 0.24$, $p< 0.1$) indicating infants not living in poverty had greater working memory than infants living in poverty. See Tables 4-6. Results remained consistent after adjusting for mom's violation of still face and infant cognitive ability. Thus it appears other regulatory behaviors did not moderate an association between negative emotional reactivity and future executive functions.

Table 4. Hierarchical Regression Analysis of Predictors of Impulse Control						
Predictor Variables	*Regression 1*		*Regression 2*		*Regression 3*	
	β	*S.E.*	β	*S.E.*	β	*S.E.*
SES Status	-0.12	0.57	-0.13	0.59	-0.12	0.59
Maternal Responsivity	-0.11	0.18	-0.1	0.19	-0.1	0.19
Latency to Distress			-0.01	0.01	-0.03	0.01
Regulatory Behavior			0.07	1.54	0.1	1.75
Latency to Distress X Regulatory Behavior					0.08	0.41
R^2	0.03		0.03		0.03	
ΔR^2	0.03		0		0	
†p<0.1,*p<0.05 , **p<0.01, ***p<0.001						

Table 5. Hierarchical Regression Analysis of Predictors of Working Memory						
Predictor Variables	*Regression 1*		*Regression 2*		*Regression 3*	
	β	*S.E.*	β	*S.E.*	β	*S.E.*
SES Status	0.21†	0.98	0.24†	1.01	0.24†	1.02
Maternal Responsivity	-0.15	0.33	-0.17	0.33	-0.17	0.33
Latency to Distress			0.08	0.01	0.08	0.01
Regulatory Behavior			-0.17	2.5	-0.18	2.9
Latency to Distress X Regulatory Behavior					-0.02	0.69
R^2	0.06		0.09		0.09	
ΔR^2	0.06		0.02		0	
†p<0.1,*p<0.05 , **p<0.01, ***p<0.001						

Table 6. Hierarchical Regression Analysis of Predictors of Categorization Ability						
Predictor Variables	*Regression 1*		*Regression 2*		*Regression 3*	
	β	*S.E.*	β	*S.E.*	β	*S.E.*
SES Status	.39**	1.08	.40**	1.12	0.40**	1.13
Maternal Responsivity	-0.14	0.36	-0.15	0.37	-0.15	0.37
Latency to Distress			0.13	0.01	0.13	0.02
Regulatory Behavior			0.03	3	0.01	3.35
Latency to Distress X Regulatory Behavior					-0.04	0.75
R^2	0.17		0.19		0.19	
ΔR^2	0.17		0.02		0	
†p<0.1,*p<0.05 , **p<0.01, ***p<0.001						

4.4.2.2. Moderating effects of the caregiving environment on the association between negative emotional reactivity and future EFs did not reach our significance threshold

In 3 additional separate models, we examined the caregiving environment as a potential moderator of an association between negative emotional reactivity and future EFs. The interaction between maternal responsivity and negative emotional reactivity was not significantly associated with future task switching, impulse control and working memory at 24-months-of-age. See Tables 7-9. Results remained consistent after adjusting for mom's violation of still face and infant cognitive ability. As a follow-up analysis, we additionally examined the potential for maternal depressive symptomatology, known to impact maternal responsivity, as a moderating factor. The interaction between average maternal depressive symptomatology from 3-24 months and negative emotional reactivity at 6-months remained unassociated with future task switching, impulse control, and working memory at 24-months. See Tables 10-12.

Table 7. Hierarchical Regression Analysis of Predictors of Impulse Control						
Predictor Variables	*Regression 1*		*Regression 2*		*Regression 3*	
	β	*S.E.*	β	*S.E.*	β	*S.E.*
Percentage Gaze Away	0.12	1.36	0.11	1.42	0.12	1.44
Regulatory Behavior	0.05	1.47	0.06	1.53	0.06	1.54
Latency to Distress			-0.02	0.01	-0.02	0.01
Maternal Responsivity			-0.1	0.19	-0.1	0.19
Latency to Distress X Maternal Responsivity					-0.02	0.38
R^2	0.02		0.03		0.03	
ΔR^2	0.02		0.01		0	
†p<0.1,*p<0.05 , **p<0.01, ***p<0.001						

Table 8. Hierarchical Regression Analysis of Predictors of Working Memory						
Predictor Variables	*Regression 1*		*Regression 2*		*Regression 3*	
	β	*S.E.*	β	*S.E.*	β	*S.E.*
Percentage Gaze Away	0.18	2.33	0.16	2.42	0.16	2.44
Regulatory Behavior	-0.09	2.41	-0.1	2.54	-0.1	2.56
Latency to Distress			0	0.01	0	0.01
Maternal Responsivity			-0.13	0.34	-0.13	0.34
Latency to Distress X Maternal Responsivity					-0.04	0.67
R^2	0.04		0.06		0.06	
ΔR^2	0.04		0.02		0	
†p<0.1,*p<0.05 , **p<0.01, ***p<0.001						

Table 9. Hierarchical Regression Analysis of Predictors of Categorization Ability						
Predictor Variables	*Regression 1*		*Regression 2*		*Regression 3*	
	β	*S.E.*	β	*S.E.*	β	*S.E.*
Percentage Gaze Away	0.18	2.67	0.18	2.8	0.18	2.81
Regulatory Behavior	0.12	3.03	0.12	3.14	0.1	3.16
Latency to Distress			0	0.02	-0.02	0.02
Maternal Responsivity			-0.13	0.39	-0.13	0.4
Latency to Distress X Maternal Responsivity					0.09	0.78
R^2	0.05		0.07		0.07	
ΔR^2	0.05		0.02		0.01	
†p<0.1,*p<0.05 , **p<0.01, ***p<0.001						

Table 10. Hierarchical Regression Analysis of Predictors of Impulse Control						
Predictor Variables	*Regression 1*		*Regression 2*		*Regression 3*	
	β	*S.E.*	β	*S.E.*	β	*S.E.*
Percentage Gaze Away	0.12	1.36	0.12	1.42	0.12	1.43
Regulatory Behavior	0.06	1.47	0.07	1.54	0.05	1.59
Latency to Distress			-0.04	0.01	-0.05	0.01
Maternal Depression			0.05	0.73	0.03	0.75
Latency to Distress X Maternal Depression					0.08	0.27
R^2	0.02		0.02		0.03	
ΔR^2	0.02		0		0.01	
†p<0.1,*p<0.05 , **p<0.01, ***p<0.001						

Table 11. Hierarchical Regression Analysis of Predictors of Working Memory						
Predictor Variables	*Regression 1*		*Regression 2*		*Regression 3*	
	β	*S.E.*	β	*S.E.*	β	*S.E.*
Percentage Gaze Away	0.18	2.33	0.18	2.44	0.18	2.46
Regulatory Behavior	-0.09	2.41	-0.09	2.56	-0.1	2.64
Latency to Distress			-0.01	0.01	-0.02	0.01
Maternal Depression			-0.03	1.26	-0.04	1.3
Latency to Distress X Maternal Depression					0.05	0.47
R^2	0.04		0.04		0.05	
ΔR^2	0.04		0		0	
†p<0.1,*p<0.05 , **p<0.01, ***p<0.001						

Table 12. Hierarchical Regression Analysis of Predictors of Categorization Ability						
Predictor Variables	*Regression 1*		*Regression 2*		*Regression 3*	
	β	*S.E.*	β	*S.E.*	β	*S.E.*
Percentage Gaze Away	0.18	2.67	0.18	2.81	0.17	2.84
Regulatory Behavior	0.12	3.03	0.13	3.11	0.12	3.18
Latency to Distress			-0.05	0.02	-0.05	0.02
Maternal Depression			0.11	1.53	0.09	1.59
Latency to Distress X Maternal Depression					0.07	0.56
R^2	0.05		0.06		0.06	
ΔR^2	0.05		0.01		0	
†p<0.1,*p<0.05 , **p<0.01, ***p<0.001						

4.4.2.3. The moderating influence of SES status on the association between negative emotionality and future EFs did not reach our significance threshold

In a separate model, we examined SES status as a potential moderator of an association between negative emotionality and future EFs. The interaction between income-to-needs and negative emotional reactivity was unassociated with future

measures of task switching, impulse control, or working memory at 24-months-of-age. See Tables 13-15. However, there was a significant main effect of SES status on shifting ability, such infants not living in poverty had greater shifting ability than infants living in poverty ($\beta = 0.39$, $p < 0.01$). Additionally, a trend level main effect of SES status on working memory was found ($\beta = 0.23$, $p < 0.1$) indicating infants not living in poverty had greater working memory than infants living in poverty. Thus it appears that SES did not moderate an association between negative emotional reactivity and future EFs in this sample.

Table 13. Hierarchical Regression Analysis of Predictors of Impulse Control						
Predictor Variables	*Regression 1*		*Regression 2*		*Regression 3*	
	β	*S.E.*	β	*S.E.*	β	*S.E.*
Percentage Gaze Away	0.12	1.36	0.14	1.41	0.14	1.39
Regulatory Behavior	0.06	1.47	0.09	1.54	0.12	1.54
Latency to Distress			-0.06	0.01	-0.07	0.01
SES Status			-0.14	0.59	-0.17	0.58
Latency to Distress X SES					0.2	0.29
R^2	0.02		0.04		0.08	
ΔR^2	0.02		0.02		0.04	
†p<0.1,*p<0.05 , **p<0.01, ***p<0.001						

Table 14. Hierarchical Regression Analysis of Predictors of Categorization Ability						
Predictor Variables	*Regression 1*		*Regression 2*		*Regression 3*	
	β	*S.E.*	β	*S.E.*	β	*S.E.*
Percentage Gaze Away	0.18	2.67	0.14	2.63	0.14	2.66
Regulatory Behavior	0.12	3.03	0.05	3	0.05	3.02
Latency to Distress			0.06	0.02	0.07	0.02
SES Status			.38**	1.13	.39**	1.14
Latency to Distress X SES					-0.02	0.57
R^2	0.05		0.19		0.19	
ΔR^2	0.05		0.14		0	
†p<0.1,*p<0.05 , **p<0.01, ***p<0.001						

Table 15. Hierarchical Regression Analysis of Predictors of Working Memory						
Predictor Variables	*Regression 1*		*Regression 2*		*Regression 3*	
	β	*S.E.*	β	*S.E.*	β	*S.E.*
Percentage Gaze Away	0.18	2.32	0.15	2.41	0.14	2.4
Regulatory Behavior	-0.09	2.41	-0.12	2.54	-0.16	2.57
Latency to Distress			0.02	0.01	0.04	0.01
SES Status			0.21	1.02	0.23†	1.02
Latency to Distress X SES					-0.16	0.51
R^2	0.04		0.08		0.12	
ΔR^2	0.04		0.04		0.02	
†p<0.1,*p<0.05 , **p<0.01, ***p<0.001						

4.5. Discussion

4.5.1. Summary of Results

The current study evaluates associations between early regulatory strategies, emotional reactivity in infancy and subsequently emerging EF during toddlerhood. Visual attentional orienting, an early emerging regulatory strategy, moderated associations

between emotional reactivity during infancy and emerging EF skills in toddlerhood. In particular, two potential phenotypes in infancy emerged as associated with greater EF skills in toddlerhood, a high regulatory ability- high emotional reactivity phenotype, and a low regulatory ability- low emotional reactivity phenotype.

4.5.2. Attentional orienting moderates a relationship between negative emotional reactivity and future EF

Researchers have proposed several models in which attentional control is considered to be a core component of working memory (Baddeley, 1996; Cowan & Morey, 2006; Kane & Engle, 2002; Klingberg et al., 2002). Moreover, both attentional control and working memory have been shown to have some of the same neural supports, including the superior frontal and intraparietal cortex (Klingberg et al., 2002; Reynolds & Romano, 2016). In adulthood, greater attentional control has been associated with greater working memory (Conway et al., 2001). Specifically, adults who are able to retain longer digit spans are able to maintain attention in the face of distracting stimuli. In infancy, the development of attentional orienting systems have been hypothesized to support early emerging working memory (Reynolds & Romano, 2016). Moreover, greater attentional orienting in infants has been associated with greater EF in toddlerhood (Kraybill et al., 2019). Interestingly, we did not find main effects for attentional orienting or negative emotional reactivity on future EF, though our results fit well into this framework, and add a regulatory component, as attentional orienting is often a regulatory strategy employed by infants to reduce negative affect (Stifter & Braungart, 1995). Additional work in adults suggests improvements in working memory result in subsequent improvements in

attentional orienting and reductions in trait anxiety (Sari et al., 2016). Our work suggests associations between attentional orienting, working memory and negative emotionality may exist already in early life. Given the relationship between attentional orienting, working memory, and negative emotionality, it is unsurprising that attentional orienting and negative emotional reactivity in infancy interact to predict future working memory in toddlerhood.

4.5.3. Emerging emotion regulatory skills in infancy appear to be relevant for emerging EF skills in toddlerhood

While prior work has considered the caregiving environment as a key factor interacting with negative emotionality to influence subsequent outcomes (Belsky et al., 1998; Poehlmann et al., 2011), this current study considers the infants own emerging ER skills as a key factor as well. Specifically, prior results indicate children with higher negative emotionality are more vulnerable to negative parenting, but also benefit more from positive parenting supporting the differential susceptibility model (Slagt et al., 2016). In line with this model, it appears that infants with greater negative emotional reactivity require more regulatory ability and infants with lower negative emotional reactivity require less regulatory ability to develop EF skills over time.

4.5.4. The moderating influence of SES, maternal responsivity and maternal depressive symptomatology on the association between negative emotionality and future EF did not reach our significance threshold

The present study did not find a reliable moderating effect of SES or the caregiving measures on the association between negative emotionality and future EF. While this hypothesis was not supported, power for moderating effects was limited.

However main effects were found between working memory and SES, and shifting and SES, such that infants from environments above the poverty line had greater EF than infants from environments below the poverty line. Our results are surprising in light of previous work which showed infants high in negative emotionality were more susceptible to the effects of both positive and negative parenting, which subsequently lead to positive and negative child adjustment respectively (Slagt et al., 2016).

These findings do not indicate a moderating effect of caregiving on the association between infant negative emotionality and subsequent EF. There are several possible reasons for this. First, our low sample size resulted in low power which likely impacted our results. Next, prior studies have frequently not accounted for variability in the infants' own regulatory capacity. Additionally, in this relatively high functioning sample, limited occurrence of high levels of maternal depressive symptomatology or severely compromised caregiving, i.e., limited range on these measures, may have further compromised power contributing to the lack of observed moderation. Furthermore, we may need to consider the full interaction between negative emotionality, infant regulatory ability and the maternal caregiving environment, which we were underpowered to do in the current study. Overall, findings suggest the match between an infant's own ER skills and their level of emotionality was more important than the match between their emotionality and SES.

4.6. Limitations and Future Directions

While this study adds a significant contribution to the existing literature, a variety of limitations exist. Firstly, there was likely an impact of the laboratory environment on our measures of negative emotional reactivity and regulation. While being able to control for random factors may allow for greater accuracy, it also likely misses key aspects of the home environment which influence these measures in typical day to day life. Future work should include parental self-report measures to allow for observation of infant behavior over a longer period of time across different contexts (Pelham, 1993; Stifter et al., 2006). Measures in the home environment likely provide a more holistic view on EF ability, attentional orienting and regulatory behaviors. Secondly, the lack of quantifying specific regulatory behaviors, due to inability to achieve reliability, may have prevented us from seeing a relationship between more general regulatory behaviors and future EF. Specific regulatory behaviors may moderate an association between negative emotionality and EF. For example, given that greater sensorimotor ability is associated with greater EF (Gottwald et al., 2016), it is possible that motor ER behaviors may moderate an association between negative emotionality and future EF. Thirdly, because our measure of maternal responsivity was only assessed when infants were 6-months-of-age, and due to our reduced power, we have a limited capacity to consider how changes in maternal responsivity over this postpartum period may relate to EFs in toddlerhood. Lastly, all of our EF tasks required a degree of social engagement, thus infants with more social affiliative behaviors may perform better on these tasks outside of their EF abilities.

4.7. Conclusion

Overall our findings indicate that regulatory ability in the form of attentional orienting moderates an association between negative emotionality and future EF. It appears that a match between levels of negative emotional reactivity and regulation skills during infancy helps lay a foundation for improved EF skills in toddlerhood. When considering the different pathways to better EF skills in toddlerhood, certain factors may increase risk for specific psychopathologies in adulthood. While greater negative emotional reactivity paired with greater regulation may be associated with better EF in toddlerhood, there could be a cost for this in adulthood, depending on the emotion regulatory strategy employed. For example, individuals with anxiety disorders experience increased negative emotional reactivity (Tan et al., 2012), actively engage in a harmful ER strategy known as suppression (Amstadter, 2008) and tend to have greater EF abilities (White et al., 2017). Thus it is possible that while these phenotypes lead to better EF in toddlerhood, they may be associated with future psychopathology or future positive development.

Supplementary Material

Table 1. Demographics	
Variable	Percentag
Infant Sex	
Male	53.8
Female	46.2
Highest level of maternal formal education	
Primary, Elementary, or Middle School	2.8
High School or GED	13.2
Technical or Vocational School	9.4
Some College, but no degree	31.1
Associates Degree	6.6
Bachelors Degree	22.6
Graduate Degree	11.3
Certificate	2.8
Mom's race/ethnicity	
White non-Hisp	42.5
Black non-Hisp	1.9
Asian non-Hisp	6.6
Other non-Hisp	0.9
Mult races non-Hisp	7.5
White Hisp	34
Asian Hisp	1.9
Other Hisp	1.9
Mult races Hisp	2.8
Total Income	
Below $15,000	10.4
$15,000 - $29,999	17.9
$30,000 - $49,999	22.6
$50,000 - $100,000	36.8
Over $100,000	12.3

Table 2. Intercorrelations										
Variables	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
(1)Maternal Responsivity	1.00									
(2)Cognitive Ability	.201*	1.00								
(3)Regulatory Behavior Present	0.01	0.06	1.00							
(4)Away	-0.09	-0.15	-0.02	1.00						
(5)Working Memory	-0.14	-0.01	-0.11	0.19	1.00					
(6)Impulse Control	-0.11	-0.06	0.06	0.12	0.08	1.00				
(7)Income-to-needs ratio	0.17	0.12	0.15	0.11	0.20	-0.12	1.00			
(8)Average Maternal Depressive Symptomatology	-.207*	-0.04	-0.08	0.06	0.00	0.05	-0.18	1.00		
(9)Negative emotionality	0.01	-0.18	0.17	0.08	0.00	0.01	-0.09	0.08	1.00	
(10)Categorization ability	-0.15	0.08	0.14	0.20	0.24	0.25	.390**	0.12	0.05	1.00
(11)Mom's violation of still-face	-0.01	0.13	.321**	-.287**	-0.06	0.12	-0.06	-0.17	-0.08	0.02
†p<0.1,*p<0.05 , **p<0.01, ***p<0.001										

Chapter 5: Discussion

5.1. Overview of findings from Study 1 and 2

This dissertation presents work from three research studies which investigate the extent to which infants early brain functioning and emerging emotion regulation relate to subsequent behavior problems and executive functioning in toddlerhood. Results from the first study revealed that already by the time of birth, individual differences in amygdala connectivity are relevant for the expression of fear and sadness over the first two-years-of-life. On average, developmental patterns of change in fear and sadness involved an increase over the first year of life followed by a decline through the second year of life. This indicated, as prior work has (Bridgett et al., 2009; Partridge, 2007) that changes in negative affect in early life, including an increase during the first 12-months, are a normative part of development. Interestingly, examination of the rs-fcMRI of the neonatal amygdala revealed that components of negative emotionality had distinct neural supports evident already soon after birth. Specifically, coordinated functioning between the amygdala and anterior insula supported fear development, while coordinated function between the amygdala and ventromedial prefrontal cortex supported sadness development. These connections appear to be associated with individual variability in the early developmental trajectory of negative emotionality.

While our first study discovered that the early development of distinct aspects of negative emotionality had distinct neural supports, to further this work, our second study examined associations between the brain at birth, emotion regulation in infancy, and risk for internalizing symptomatology in toddlerhood. Importantly, emotion regulation was characterized through behavioral observation of negative emotional reactivity, as opposed

to parent report, in this study. Overall results revealed that distinct amygdala connections soon after birth supported emerging emotion regulation and future internalizing symptomatology. Specifically, neonatal Am-MPFC connectivity was associated with emotion regulation, while Am-aI connectivity was not. This suggests coordinated functioning between the amygdala and the insula relates more closely to the developmental trajectory of negative emotionality. Moreover, regional specificity was observed for the MPFC, such that stronger right amygdala-MPFC and weaker right amygdala-vMPFC connectivity at birth were associated with greater emotion regulation behavior at 6-months-of-age. Already very early in life a distinction appears to exist between more dorsal versus ventral MPFC in enhancing versus regulating or dampening the expression of negative emotionality.

After evaluating a-priori connections, we broadened our analysis to examine how amygdala connections across the neonatal brain supported emerging emotion regulation. Follow-up whole brain analyses demonstrated a pattern of weaker neonatal amygdala integration into primary sensory and motor regions and stronger amygdala integration into higher order processing regions associated with greater emotion regulation in infancy. Next, we examined future implications of emotion regulation in infancy and discovered greater emotion regulation in infancy was associated with less internalizing symptomatology in toddlerhood. Furthermore, we discovered emotion regulation mediated a relationship between amygdala connectivity at birth and future internalizing symptomatology. Specifically, emotion regulation mediated relationships between: stronger amygdala-vMPFC connectivity and increased internalizing symptomatology, stronger amygdala-MPFC connectivity and decreased internalizing symptomatology, and

stronger amygdala-V1 connectivity and increased internalizing symptomatology. This provides evidence that emerging emotion regulation represents a path through which patterns of amygdala coordinated functioning at birth relate to subsequent internalizing symptomatology.

Together results from the first two studies indicate that already soon after birth, brain connectivity is associated with behavioral outcomes from 6-24 months of age, including negative emotionality and emotion regulation. Study 1 utilizes parental self-report measures to evaluate how a-priori amygdala connections support emerging negative emotionality. Study 2 considers the negative response to a specific stressor as an indicator of emotion regulation by adding a behavioral observation. Furthermore, in addition to evaluating a-priori connections, study 2 examines whole-brain greyordinate-wise connectivity of the amygdala, which reveals the potential importance of amygdala connections to primary and secondary sensory-motor regions for early emerging emotion regulation in infancy. Both studies indicate that the relevance of Am-vMPFC and Am-aI for both healthy and maladaptive expressions of negative emotionality, observed across the lifespan in prior studies, emerges very early in development. Moreover, both studies indicate early specificity in terms of connections related to different aspects of negative emotionality (Am-vMPFC versus Am-aI) and connections related to higher or lower emotional reactivity (amygdala connectivity to more dorsal versus ventral MPFC).

5.1.1. Conclusions from Study 1 and 2

5.1.1.1. Neural circuitry from infancy to adulthood relevant for negative emotionality and emotion regulation appears to be preserved.

Interestingly, amygdala connections supporting emerging negative emotionality and emotion regulation in infancy, appear to support the same constructs in older children and adults based on prior studies. In adults, coordinated functioning between the amygdala and aI may be associated with variability in state anxiety, such that stronger Am-aI connectivity is associated with greater state anxiety (Baur et al., 2013). Moreover, coordinated functioning between the amygdala and vMPFC appears to be associated with negative emotionality as indicated by normative and pathological variation in internalizing symptomatology in adolescents, and depression, anxiety, (Burghy et al., 2012; Connolly et al., 2017; Kim, Gee, et al., 2011b; Roy et al., 2013a; L. Wang et al., 2013) and emotion regulation (Casey & Lee, 2015; Silvers et al., 2017) in adults. Furthermore, amygdala integration into the more dorsal medial prefrontal cortex may be associated with emotion regulation in adults, such that stronger Am-MPFC connectivity is linked to effective negative affect reduction during reappraisal (Banks et al., 2007; Ochsner et al., 2002). Importantly these results suggest that already in early infancy a distinction exists between dorsal and ventral MPFC in terms of how the connectivity of these regions to the amygdala relates to emotion regulation. Such a distinction has also frequently been identified in studies with adults (Etkin et al., 2011; Gee, et al., 2011a) and in animal models (Caballero et al., 2019; Peters et al., 2009). Thus amygdala connections relevant for negative emotionality and emotion regulation in infancy appear to be preserved throughout the lifespan based on comparison of our results with prior studies. Longitudinal studies will be needed in the future for direct comparisons to be made. Our results have implications for how we understand the development of

normative and pathological negative emotionality across the lifespan, and implications for interventions aimed at the first year of life.

Differences in how dorsal and ventral MPFC connections to the amygdala impact NE and ER in infants versus older populations may be partially due to age-related changes in coupling between these regions. Prior research suggests how activity in the amygdala and MPFC is correlated changes from childhood to adulthood. Specifically, activity in the MPFC and amygdala may be positively correlated in early in life, which is associated with increased emotional reactivity, while activity in the MPFC and amygdala may be negatively correlated later in adolescence, which is associated with decreased emotional reactivity (Gee et al., 2013). Our results suggest regional differences between ventral and dorsal regions exist within the MPFC already soon after birth. Moreover, activity in the vMPFC and activity in the amygdala may be positively correlated, such that stronger connectivity between these regions results in increased negative emotionality and decreased regulatory ability, while activity in the more dorsal MPFC and amygdala activity may be negatively correlated, such that stronger connectivity results in increased emotion regulation behavior. This raises questions about how regional connectivity within the MPFC to the amygdala changes across the lifespan.

Overall, our findings provide support for potential consistency in terms of patterns of amygdala functional connectivity relevant for negative emotionality and emotion regulation during infancy and adulthood. Moreover, this indicates some potential consistency in the neural mechanisms underlying rudimentary and more developed aspects of negative emotionality and emotion regulation.

5.1.1.2. Sensory processing and integration regions play a key role in emotion regulation in infancy

Despite the consistency with research in adults, the findings presented in this dissertation also indicate a potentially important role for primary sensory and motor systems, in emotion regulation in infancy. Specifically, our findings indicate that increased amygdala integration into the motor cortex soon after birth may be associated with less effective emotion regulation in infancy. Moreover, stronger amygdala integration into the visual cortex may be associated with poorer emotion regulation and less control of visual attention.

Why stronger integration into the visual cortex may be associated with weaker emotion regulation may be partially explained by the biased competition model of attention. This model suggests that there is competition for processing resources in the visual cortex. Salient stimuli have an advantage in terms of competition for neural representation (Desimone & Duncan, 1995). Amygdala projections to the visual cortex influence visual processing according to the valence of the stimulus. Negatively valenced stimuli, in particular, evoke stronger responses in the visual cortex and use more processing resources (Pessoa & Ungerleider, 2004). Given the negative valence of the paradigm employed in our study, the still-face paradigm,(Braungart-Rieker et al., 1998; Mesman et al., 2009; Toda & Fogel, 1993) it is possible that increased amygdala integration into the visual cortex consumes more processing resources, making it difficult for the infant to utilize the regulatory strategy of attention shifting, thus resulting in decreased emotion regulation.

Increased amygdala integration into the motor cortex soon after birth, is also associated with weaker emotion regulation in infancy. Infants engage in a variety of emotion regulatory strategies which require motor activity to reduce their negative affect (Stifter & Braungart, 1995). In particular self-soothing behaviors such as hand and foot clasping, self-manipulation and non-nutritive-sucking are commonly used regulatory behaviors (Derryberry & Rothbart, 1981; Thomas et al., 2017). Increased coordinated functioning between the amygdala and motor cortex may confer a greater tendency for freezing behavior in the face of a negative emotional stimuli (Sagaspe et al., 2011; Xu et al., 2019), which potentially impacts the infants ability to engage in these more effective strategies for regulating emotions, thus reducing their capacity for emotion regulation.

Given the association between amygdala integration into motor and visual cortices and emotion regulation, and given that emotion regulatory behavior in infancy involves rudimentary processes like shifting visual attention and thumb sucking (Braungart-Rieker & Stifter, 1996), it is appears that sensory processing and integration play a key role in emotion regulation in infancy. Overall, it appears that visual attention in infancy is foundational for emerging emotion regulation and therefore our strong finding implicating associations between amygdala-visual cortex connectivity and emotion regulation is not surprising.

5.2. Overview of findings from Study 3

The third study showed how the emotional reactivity component of emotion regulation, is balanced by a regulatory component to predict subsequent executive functioning in toddlerhood. Specifically results indicated attentional orienting ability

moderated a relationship between negative emotionality and future shifting and working memory ability. Furthermore, results showed that a high emotional reactivity paired with high-regulation and low-reactivity paired with low-regulation phenotype at 6-months-of-age predicted greater executive function skills at 24-months-of-age. This suggests infants with lower emotional reactivity may require less regulatory behavior to develop EF skills, while infants with greater emotional reactivity may require greater levels of emotion regulation to perform better on executive function tasks. Importantly, these results point to the potential impact of negative emotionality on executive function, in that greater negative emotionality may be associated with reduced executive function if unregulated (Feldman, 2009; Ferrier et al., 2014; Sudikoff et al., 2015; Ursache et al., 2012). Interestingly, no potential influences in the external environment, previously found to be important for supporting development of EF, moderated the association between infant emotional reactivity and subsequent EF skills. Intrinsic emotion regulation skills already in the first 6-months thus appear to be particularly important for future executive functioning.

5.2.1. Study 3 Conclusions

5.2.1.1. Attentional orienting ability plays a key role in associations between negative emotional reactivity in infancy and executive function in toddlerhood

This study represents an important step in linking attentional orienting ability, negative emotionality and executive function. Results indicate attentional orienting ability moderates associations between negative emotional reactivity infancy and future executive function. This is unsurprising given the role of attentional orienting in

emerging emotion regulation and executive function. Specifically, greater attentional orienting has been associated with greater executive function in toddlerhood and adulthood (Conway et al., 2001; Kraybill et al., 2019). In terms of emotion regulation, attentional orienting is commonly employed by infants to reduce negative emotional reactivity (Stifter & Braungart, 1995). Thus it is possible that attentional orienting is used to decrease negative emotional reactivity in infancy and toddlerhood allowing for improved executive functioning. Overall, emotion regulation in infancy already appears to be relevant for variability in executive function in toddlerhood. Together our three studies improve understanding of how the brain at birth contributes to emerging emotion regulation, and how emotion regulation in infancy is associated with future outcomes in toddlerhood.

5.3.0. General conclusions across studies

5.3.1. Already soon after birth the newborn brain confers susceptibility to risk for future psychopathology

Already soon after birth amygdala connectivity relates to emerging risk for future psychopathology through its associations with the reactivity and regulation of negative affect. The regulation of negative affect is particularly important because it is tied to the ability to cope with everyday distress (Riediger et al., 2011). Moreover, difficulties regulating negative emotionality comprise a central feature across many mental health disorders (Berking & Wupperman, 2012; Buehler et al., 2007; Cisler et al., 2010; Kring & Caponigro, 2010; Svaldi et al., 2012; Weiss et al., 2015). Furthermore, our results indicate emotion regulation mediates an association between the brain at birth and

internalizing symptomatology in toddlerhood. Given associations between amygdala connectivity soon after birth and emotion regulation and negative emotionality in infancy, it appears that the newborn brain reflects susceptibility to risk for future psychopathology.

5.3.2. Attentional orienting in infancy moderates associations between negative emotional reactivity in infancy and emerging executive function

Already in infancy attentional orienting ability moderates associations between negative emotional reactivity in infancy and future executive function. This finding, though underpowered due to our low sample size, was in line with prior findings which link greater attentional orienting in infants to greater EF in toddlerhood (Kraybill et al., 2019). Interestingly, we did not find main effects for attentional orienting or negative emotional reactivity on future EF, though our results fit well into this framework, and add a regulatory component, as attentional orienting is often a regulatory strategy employed by infants to reduce negative affect (Stifter & Braungart, 1995). Our results are also in line with prior findings linking improvements in executive function to subsequent improvements in attentional orienting and reductions in trait anxiety (Sari et al., 2016). Our work suggests associations between attentional orienting, executive function and negative emotionality may exist already very early in life.

5.3.3. Moderating influence of caregiving environment on associations between the newborn brain, emerging emotion regulation and executive function did not reach our threshold for significance

The moderating influence of the caregiving environment on associations between the newborn brain, emerging emotion regulation and executive function did not reach our threshold for non-zero effect. Prior studies confirm the importance of the caregiving environment for development in these areas (Crockenberg & Leerkes, 2004; Fay-Stammbach et al., 2014; Esther M. Leerkes & Crockenberg, 2003; Morris et al., 2017). Most pertinent to the moderating role of the caregiving environment tested in these studies, there is evidence to suggest that implications of neurobiological phenotypes during infancy and early emerging ER skills for subsequent development of EF may differ depending on the caregiving environment (Frick et al., 2017; Haley & Stansbury, 2003; Esther M. Leerkes & Crockenberg, 2003; Rhoades et al., 2012). However, studying these associations likely requires larger sample sizes and greater power than was available here (Marek et al., 2020). It is likely that power here was simply insufficient to detect the effect reliably. Moreover, some prior findings have relied upon distressed samples to detect moderating effects of the caregiving environment (Grant et al., 2010; Miller et al., 2019) whereas this was a normative sample. Inadequate representation of low end variation in caregiving may have reduced capacity to detect effects in the present studies.

5.4.0. Limitations and Future Directions

While these studies add a significant contribution to the existing literature, a variety of limitations exist. First, we must consider the impact of the laboratory environment on our measure of regulatory behavior. While the laboratory environment allows for greater control over potential additional causes of variance over a short period

of time, it also likely misses key influences, such as context over time, on this measure outside of the lab which may be captured through parental self-report measures. Alternatively, we must consider the impact of self-report on maternal depressive symptomatology. While parental self-report allows for the observation of behavior over a longer period of time across different contexts (Pelham 1993, Stifter et al., 2006), there are many potential confounding factors that may impact the parental perception. Multi-method assessment of these constructs including both self-report and observational measures will be important for future research. Furthermore, additional factors not captured in the current studies may have impacted our measures of both the emotional reactivity and the regulatory component of emotion regulation. For example, infant mobility has been shown to have an impact on interactions between caregiver and infant (Franchak et al., 2018), which may have impacted infant emotion regulation. Future work should measure and covary for infant mobility.

Next, our measure of maternal responsivity was only assessed when infants were 6-months-of-age, thus we have a limited capacity to consider how changes in maternal responsivity over the postpartum period relate to negative emotionality, emotion regulation and executive function. The examination of maternal responsivity across multiple time points would offer a greater window into how the caregiving environment over the first two years of life supports these constructs. Similarly, our measure of emotion regulation was only assessed at the 6-month time point, also allowing for a limited capacity to consider how changes in emotion regulation in infancy relate to the brain soon after birth and executive function. The quantification of emotion regulation across multiple time points over the first two years of life could allow for a better picture

of how the newborn brain relates to emotion regulation development, which could be much more informative.

Additionally, our sample size was not very large for any of our analyses. Future work should attempt to duplicate our findings in a larger cohort, as brain behavioral phenotype associations become more reproducible with sample sizes ≥ 2,000 (Marek et al., 2020). Moreover, a greater sample size would allow for additional analyses, such as the examination of a three-way interaction between components in the external environment, such as maternal responsivity, infant negative emotional reactivity and infant regulatory behavior in relation to future executive function skills.

Furthermore, future work should consider how amygdala connectivity at birth relates to future attentional control and other regulatory behaviors, to elucidate how the brain at birth supports the regulatory component of emotion regulation. Moreover, the quantification of specific regulatory behaviors will be needed, to examine how the brain soon after birth supports distinct aspects of regulatory behavior.

In regards to amygdala connectivity, it is likely that subregions of the amygdala have distinct connectivity patterns. While our study did not have the resolution to evaluate differences in functional connectivity among these subregions, future research will be need to test appropriate methods for identifying and segmenting these subregions to understand their potentially distinct roles in supporting emerging emotion regulation. Furthermore, building on the results of these studies will necessitate taking a systems level approach to characterizing brain functional organization. Here we use a-priori and seed-based analyses with individualized amygdala regions of interest as a first step in understanding the neural foundations of emotion regulation in infancy. However,

research in adult populations (Dutta et al., 2019; van der Horn et al., 2016) demonstrates that examining brain network organization allows for a more thorough characterization of functional brain organization relevant for emotion regulation.

Lastly, these studies were conducted in a healthy normative population, limiting our ability to make conclusions about the impact of psychopathologies on emerging emotion regulation. A greater range of maternal responsivity and depressive symptomatology may impact associations between the brain at birth, emotion regulation in infancy, and emerging behaviors in toddlerhood. For example, for infants high in negative emotionality, low maternal responsivity has been associated with less attentional orienting-based emotion regulation strategies (Thomas et al., 2017). Our results suggest this may have implications for future executive function in toddlerhood. Moreover, greater prenatal maternal depressive symptomatology has been associated with increased amygdala-insula and amygdala-vMPFC functional connectivity at 6-months-of-age (Qiu et al., 2015). Thus it is possible that greater maternal depressive symptomatology may be associated with increased infant fear and decreased emotion regulation skills.

5.5. Summary and Conclusions

The findings presented in this dissertation help characterize associations between the newborn brain, emotion regulation in infancy and executive function in toddlerhood. Specifically, they highlight how distinct amygdala connections support emerging emotion regulation with consideration of the caregiving environment. Moreover they examine how the regulatory component of emotion regulation moderates associations between emotional reactivity and executive function at 2-years-of-age. Furthermore, they

showcase the importance of investigating brain-behavior relationships on a longitudinal scale, as complex developmental trajectories can significantly alter the interpretation of findings, depending on the time point. From this work, it can be hypothesized that specific amygdala functional connectivity patterns may confer risk for future psychopathology already soon after birth. Together our three studies showcase the extent to which infants brain functioning soon after birth and early emerging emotion regulation interact with hypothesized environmental influences in predicting subsequent behavior and executive functioning.

References

Achenbach, T. M., & Ruffle, T. M. (2000). The child behavior checklist and related forms for assessing behavioral/emotional problems and competencies. *Pediatrics in Review*, *21*(8), 265–271. https://doi.org/10.1542/pir.21-8-265

Adamson, L. B., & Frick, J. E. (2003). The still face: A history of a shared experimental paradigm. *Infancy*, *4*(4), 451–473. https://doi.org/10.1207/S15327078IN0404_01

Ahnert, L., Gunnar, M. R., Lamb, M. E., & Barthel, M. (2004). Transition to child care: Associations with infant-mother attachment, infant negative emotion, and cortisol elevations. *Child Development*, *75*(3), 639–650. https://doi.org/10.1111/j.1467-8624.2004.00698.x

Aldao, A., Gee, D. G., De Los Reyes, A., & Seager, I. (2016). Emotion regulation as a transdiagnostic factor in the development of internalizing and externalizing psychopathology: Current and future directions. *Development and Psychopathology*, *28*(4pt1), 927–946. https://doi.org/10.1017/S0954579416000638

Aldao, A., Nolen-hoeksema, S., & Schweizer, S. (2010). Clinical Psychology Review Emotion-regulation strategies across psychopathology : A meta-analytic review. *Clinical Psychology Review*, *30*(2), 217–237. https://doi.org/10.1016/j.cpr.2009.11.004

Almeida, J. R. C. de, Versace, A., Mechelli, A., Hassel, S., Quevedo, K., Kupfer, D. J., & Phillips, M. L. (2009). Abnormal Amygdala-Prefrontal Effective Connectivity to Happy Faces Differentiates Bipolar from Major Depression. *Biological Psychiatry*, *66*(5), 451–459. https://doi.org/10.1016/j.biopsych.2009.03.024

Amstadter, A. (2008). Emotion regulation and anxiety disorders. *Journal of Anxiety*

Disorders, *22*(2), 211–221. https://doi.org/10.1016/j.janxdis.2007.02.004

Arichi, T., Fagiolo, G., Varela, M., Melendez-calderon, A., Allievi, A., Merchant, N., Tusor, N., Counsell, S. J., Burdet, E., Beckmann, C. F., & Edwards, A. D. (2012). NeuroImage Development of BOLD signal hemodynamic responses in the human brain. *NeuroImage*, *63*(2), 663–673. https://doi.org/10.1016/j.neuroimage.2012.06.054

Baddeley, A. (1996). The fractionation of working memory. *Proceedings of the National Academy of Sciences of the United States of America*, *93*(24), 13468–13472. https://doi.org/10.1073/pnas.93.24.13468

Banihashemi, L., Bertocci, M. A., Alkhars, H. M., Versace, A., Northrup, J. B., Lee, V. K., Schmithorst, V. J., Samolyk, A., Taylor, M., English, G. E., Stiffler, R. S., Aslam, H. A., Bonar, L., Panigrahy, A., Hipwell, A. E., & Phillips, M. L. (2020). Limbic white matter structural integrity at 3 months prospectively predicts negative emotionality in 9-month-old infants: a preliminary study. *Journal of Affective Disorders*, *273*, 538–541. https://doi.org/10.1016/j.jad.2020.04.029

Banks, S. J., Eddy, K. T., Angstadt, M., Nathan, P. J., & Luan Phan, K. (2007). Amygdala-frontal connectivity during emotion regulation. *Social Cognitive and Affective Neuroscience*, *2*(4), 303–312. https://doi.org/10.1093/scan/nsm029

Barrash, J., Tranel, D., & Anderson, S. W. (2000). Acquired personality disturbances associated with bilateral damage to the ventromedial prefrontal region. *Developmental Neuropsychology*, *18*(3), 355–381. https://doi.org/10.1207/S1532694205Barrash

Baur, V., Hänggi, J., Langer, N., & Jäncke, L. (2013). Resting-state functional and

structural connectivity within an insula-amygdala route specifically index state and trait anxiety. *Biological Psychiatry*, *73*(1), 85–92. https://doi.org/10.1016/j.biopsych.2012.06.003

Bebko, G., Bertocci, M., Chase, H., Dwojak, A., Bonar, L., Almeida, J., Perlman, S. B., Versace, A., Schirda, C., Travis, M., Gill, M. K., Demeter, C., Diwadkar, V., Sunshine, J., Holland, S., Kowatch, R., Birmaher, B., Axelson, D., Horwitz, S., … Phillips, M. L. (2015). Decreased amygdala-insula resting state connectivity in behaviorally and emotionally dysregulated youth. *Psychiatry Research - Neuroimaging*, *231*(1), 77–86. https://doi.org/10.1016/j.pscychresns.2014.10.015

Beckmann, C. F., Jenkinson, M., Woolrich, M. W., Behrens, T. E. J., Flitney, D. E., Devlin, J. T., & Smith, S. M. (2006). Applying FSL to the FIAC data: Model-based and model-free analysis of voice and sentence repetition priming. *Human Brain Mapping*, *27*(5), 380–391. https://doi.org/10.1002/hbm.20246

Bell, M. A., & Wolfe, C. D. (2004). Emotion and cognition: An intricately bound developmental process. *Child Development*, *75*(2), 366–370. https://doi.org/10.1111/j.1467-8624.2004.00679.x

Belsky, J., Hsieh, K. H., & Crnic, K. (1998). Mothering, fathering, and infant negativity as antecedents of boys' externalizing problems and inhibition at age 3 years: Differential susceptibility to rearing experience? *Development and Psychopathology*, *10*(2), 301–319. https://doi.org/10.1017/S095457949800162X

Berking, M., & Wupperman, P. (2012). Emotion regulation and mental health: Recent findings, current challenges, and future directions. In *Current Opinion in Psychiatry* (Vol. 25, Issue 2, pp. 128–134). https://doi.org/10.1097/YCO.0b013e3283503669

Bernier, A., Carlson, S. M., & Whipple, N. (2016). From External Regulation to Self-Regulation: Early Parenting Precursors of Young Children's Executive Functioning. *Child Development*, *81*(1), 326–339. https://doi.org/10.1111/j.1467-8624.2009.01397.x

Bettis, A. H., Coiro, M. J., England, J., Murphy, L. K., Zelkowitz, R. L., Dejardins, L., Eskridge, R., Adery, L. H., Yarboi, J., Pardo, D., & Compas, B. E. (2017). Comparison of two approaches to prevention of mental health problems in college students: Enhancing coping and executive function skills. *Journal of American College Health*, *65*(5), 313–322. https://doi.org/10.1080/07448481.2017.1312411

Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (n.d.). *Functional connectivity in the motor cortex of resting human brain using echo-planar MRI*. *9*, 537–541.

Blair, C., & Razza, R. P. (2007). Relating effortful control, executive function, and false belief understanding to emerging math and literacy ability in kindergarten. *Child Development*, *78*(2), 647–663. https://doi.org/10.1111/j.1467-8624.2007.01019.x

Blankson, A. N., O'Brien, M., Leerkes, E. M., Marcovitch, S., Calkins, S. D., & Weaver, J. M. (2013). Developmental Dynamics of Emotion and Cognition Processes in Preschoolers. *Child Development*, *84*(1), 346–360. https://doi.org/10.1111/j.1467-8624.2012.01841.x

Bosquet, M., White, M. T., Hails, K., Cabrera, I., & Wright, R. J. (2016). Infant Behavior and Development Full length article The Infant Behavior Questionnaire-Revised : Factor structure in a culturally and sociodemographically diverse sample in the United States. *Infant Behavior and Development*, *43*, 24–35. https://doi.org/10.1016/j.infbeh.2016.04.001

Bradley, R. H., Caldwell, B. M., & Corwyn, R. F. (2003). *The Child Care HOME Inventories : assessing the quality of family child care homes*. *18*, 294–309. https://doi.org/10.1016/S0885-2006(03)00041-3

Braungart-Rieker, J., Garwood, M. M., Powers, B. P., & Notaro, P. C. (1998). Infant Affect and Affect Regulation During the Still-Face Paradigm With Mothers and Fathers: The Role of Infant Characteristics and Parental Sensitivity. *Developmental Psychology*, *34*(6), 1428–1437. https://doi.org/10.1037/0012-1649.34.6.1428

Braungart-Rieker, J. M., & Stifter, C. A. (1996). Infants' Responses to Frustrating Situations: Continuity and Change in Reactivity and Regulation. *Child Development*, *67*(4), 1767–1779. https://doi.org/10.1111/j.1467-8624.1996.tb01826.x

Bridgett, D. J., Gartstein, M. A., Putnam, S. P., McKay, T., Iddins, E., Robertson, C., Ramsay, K., & Rittmueller, A. (2009). Maternal and contextual influences and the effect of temperament development during infancy on parenting in toddlerhood. *Infant Behavior and Development*, *32*(1), 103–116. https://doi.org/10.1016/j.infbeh.2008.10.007

Buehler, C., Lange, G., & Franck, K. L. (2007). Adolescents' cognitive and emotional responses to marital hostility. *Child Development*, *78*(3), 775–789. https://doi.org/10.1111/j.1467-8624.2007.01032.x

Burgess, K. B., Marshall, P. J., Rubin, K. H., & Fox, N. A. (2003). Infant attachment and temperament as predictors of subsequent externalizing problems and cardiac physiology. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *44*(6), 819–831. https://doi.org/10.1111/1469-7610.00167

Burghy, C. a, Stodola, D. E., Ruttle, P. L., Molloy, E. K., Armstrong, J. M., Oler, J. a, Fox, M. E., Hayes, A. S., Kalin, N. H., Essex, M. J., Davidson, R. J., & Birn, R. M. (2012). Developmental pathways to amygdala-prefrontal function and internalizing symptoms in adolescence. *Nature Neuroscience*, *15*(12), 1736–1741. https://doi.org/10.1038/nn.3257

Buss A., K., & Goldsmith Hill, H. (1998). Fear and Anger Regulation in Infancy: effects on the temporal dynamics of affective expression. *Child Development*, *69*(2), 359–374. https://doi.org/0009-3920/98/6902-0018$01.00

Caballero, J. P., Scarpa, G. B., Remage-Healey, L., & Moorman, D. E. (2019). Differential effects of dorsal and ventral medial prefrontal cortex inactivation during natural reward seeking, extinction, and cue-induced reinstatement. *ENeuro*, *6*(5). https://doi.org/10.1523/ENEURO.0296-19.2019

Calkins, S. D., Dedmon, S. E., Gill, K. L., Lomax, L. E., & Johnson, L. M. (2002). *Frustration in Infancv : Imdications for Emotion Regulation , Physiological Processes , and Temperament*. *3*(2), 175–197.

Callaghan, B. L., Sullivan, R. M., Howell, B., & Tottenham, N. (2014). The international society for developmental psychobiology Sackler symposium: Early adversity and the maturation of emotion circuits-A cross-species analysis. *Developmental Psychobiology*, *56*(8), 1635–1650. https://doi.org/10.1002/dev.21260

Cameron, L. D., Carroll, P., & Hamilton, W. K. (2018). Child Abuse & Neglect Evaluation of an intervention promoting emotion regulation skills for adults with persisting distress due to adverse childhood experiences. *Child Abuse & Neglect*, *79*(March), 423–433. https://doi.org/10.1016/j.chiabu.2018.03.002

Carlson, S. M., Mandell, D. J., & Williams, L. (2004). Executive function and theory of mind: Stability and prediction from ages 2 to 3. *Developmental Psychology*, *40*(6), 1105–1122. https://doi.org/10.1037/0012-1649.40.6.1105

Casey, B. J., & Lee, F. S. (2015). Optimizing treatments for anxiety by age and genetics. *Annals of the New York Academy of Sciences*, *1345*(1), 16–24. https://doi.org/10.1111/nyas.12746

Chrousos, G. P., & Gold, P. W. (1992). The Concepts of Stress and Stress System Disorders: Overview of Physical and Behavioral Homeostasis. *JAMA: The Journal of the American Medical Association*, *267*(9), 1244–1252. https://doi.org/10.1001/jama.1992.03480090092034

Chrousos, G. P., & Kino, T. (2009). Glucocorticoid Signaling in the Cell. *Annals of the New York Academy of Sciences*, *1179*(1), 153–166. https://doi.org/10.1111/j.1749-6632.2009.04988.x

Cisler, J. M., Olatunji, B. O., Feldner, M. T., & Forsyth, J. P. (2010). Emotion regulation and the anxiety disorders. *Journal of Psychopathology and Behavioral Assessment*, *32*(1), 68–82. https://doi.org/10.1007/s10862-009-9161-1.Emotion

Cole, P. M., Martin, S. E., Dennis, T. A., Marin, S. E., & Dennis, T. A. (2004). Emotion regulation as a scientific construct: methodological challenges for child development research. *Child Development*, *75*(2), 317–333. https://doi.org/10.1111/j.1467-8624.2004.00673.x

Connolly, C. G., Ho, T. C., Blom, E. H., LeWinn, K. Z., Sacchet, M. D., Tymofiyeva, O., Simmons, A. N., & Yang, T. T. (2017). Resting-state functional connectivity of the amygdala and longitudinal changes in depression severity in adolescent depression.

Journal of Affective Disorders, *207*(June 2016), 86–94. https://doi.org/10.1016/j.jad.2016.09.026

Conway, A. R. A., Cowan, N., & Bunting, M. F. (2001). The cocktail party phenomenon revisited: The importance of working memory capacity. *Psychonomic Bulletin and Review*, *8*(2), 331–335. https://doi.org/10.3758/BF03196169

Conway, A., & Stifter, C. A. (2012). Longitudinal Antecedents of Executive Function in Preschoolers. *Child Development*, *83*(3), 1022–1036. https://doi.org/10.1111/j.1467-8624.2012.01756.x

Cowan, N., & Morey, C. C. (2006). Visual working memory depends on attentional filtering. *Trends in Cognitive Sciences*, *10*(4), 139–141. https://doi.org/10.1016/j.tics.2006.02.001

Crockenberg, S. C., & Leerkes, E. M. (2004). Infant and maternal behaviors regulate infant reactivity to novelty at 6 months. *Developmental Psychology*, *40*(6), 1123–1132. https://doi.org/10.1037/0012-1649.40.6.1123

Crockett, E. E., Holmes, B. M., Granger, D. A., & Lyons-Ruth, K. (2013). Maternal disrupted communication during face-to-face interaction at 4 months: Relation to maternal and infant cortisol among at-risk families. *Infancy*, *18*(6), 1111–1134. https://doi.org/10.1111/infa.12015

Dale, L. P., O'Hara, E. A., Schein, R., Inserra, L., Keen, J., Flores, M., & Porges, S. W. (2011). Measures of infant behavioral and physiological state regulation predict 54-month behavior problems. *Infant Mental Health Journal*, *32*(4), 473–486. https://doi.org/10.1002/imhj.20306

Dawson, G., Frey, K., Panagiotides, H., Osterling, J., & Hessl, D. (1997). Infants of

depressed mothers exhibit atypical frontal brain activity: A replication and extension of previous findings. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *38*(2), 179–186. https://doi.org/10.1111/j.1469-7610.1997.tb01852.x

Degnan, K. A., & Fox, N. a. (2007). Behavioral inhibition and anxiety disorders: multiple levels of a resilience process. *Development and Psychopathology*, *19*(3), 729–746. https://doi.org/10.1017/S0954579407000363

Denny, B. T., Inhoff, M. C., Zerubavel, N., Davachi, L., & Ochsner, K. N. (2015). Getting Over It. *Psychological Science*, *26*(9), 1377–1388. https://doi.org/10.1177/0956797615578863

Derryberry, D., & Rothbart, M. K. (1981). Development of Individual Differences in Temperament. *Advances in Developmental Psychology*, *1*(January), 37–86.

Desimone, R., & Duncan, J. (1995). Neural Mechanisms of Selective Visual Attention. *Annual Review of Neuroscience*, *18*, 193–222. https://doi.org/10.1146/annurev-psych-122414-033400

Diamond, A. (2002). Normal development of prefrontal cortex from birth to young adulthood: cognitive functions, anatomy, and biochemistry. In D. Stuss & R. Knight (Eds.), *Principles of frontal lobe function*. Oxford University Press. https://doi.org/10.1093/acprof

Diamond, A. (2013). Executive functions. *Annual Review of Psychology*, *64*, 135–168. https://doi.org/10.1146/annurev-psych-113011-143750

Dosenbach, N. U. F., Fair, D. A., Miezin, F. M., Cohen, A. L., Wenger, K. K., Dosenbach, R. A. T., Fox, M. D., Snyder, A. Z., Vincent, J. L., Raichle, M. E., Schlaggar, B. L., & Petersen, S. E. (2007). Distinct brain networks for adaptive and

stable task control in humans. *Proceedings of the National Academy of Sciences*, *104*(26), 11073–11078. https://doi.org/10.1073/pnas.0704320104

Dosenbach, Nico U.F., Koller, J. M., Earl, E. A., Miranda-Dominguez, O., Klein, R. L., Van, A. N., Snyder, A. Z., Nagel, B. J., Nigg, J. T., Nguyen, A. L., Wesevich, V., Greene, D. J., & Fair, D. A. (2017). Real-time motion analytics during brain MRI improve data quality and reduce costs. *NeuroImage*, *161*(August), 80–93. https://doi.org/10.1016/j.neuroimage.2017.08.025

Downar, J., Crawley, A. P., Mikulis, D. J., & Davis, K. D. (2000). A multimodal cortical network for the detection of changes in the sensory environment. *Nature Neuroscience*, *3*(3), 277–283. https://doi.org/10.1038/72991

Downar, J., Crawley, A. P., Mikulis, D. J., & Davis, K. D. (2002). A Cortical Network Sensitive to Stimulus Salience in a Neutral Behavioral Context Across Multiple Sensory Modalities. *Journal of Neurophysiology*, *87*(1), 615–620. https://doi.org/10.1152/jn.00636.2001

Dragan, W. Ł., & Fronczyk, K. (2011). *Psychometric properties of the Polish adaptation of the Infant Behavior Questionnaire — Revised (IBQ-R)*. *35*(6), 542–549. https://doi.org/10.1177/0165025411422181

Dutta, A., McKie, S., Downey, D., Thomas, E., Juhasz, G., Arnone, D., Elliott, R., Williams, S., Deakin, J. F. W., & Anderson, I. M. (2019). Regional default mode network connectivity in major depressive disorder: modulation by acute intravenous citalopram. *Translational Psychiatry*, *9*(1). https://doi.org/10.1038/s41398-019-0447-0

Eigsti, I. M., Zayas, V., Mischel, W., Shoda, Y., Ayduk, O., Dadlani, M. B., Davidson,

M. C., Aber, J. L., & Casey, B. J. (2006). Predicting cognitive control from preschool to lateadolescence and young adulthood. *Psychological Science*, *17*(6), 478–484. https://doi.org/10.1111/j.1467-9280.2006.01732.x

Eklund, A., Nichols, T. E., & Knutsson, H. (2016). Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates. *Proceedings of the National Academy of Sciences of the United States of America*, *113*(28), 7900–7905. https://doi.org/10.1073/pnas.1602413113

Ellis, B. J., Boyce, W. T., Belsky, J., Bakermans-Kranenburg, M. J., & van Ijzendoorn, M. H. (2011). Differential susceptibility to the environment: an evolutionary--neurodevelopmental theory. *Development and Psychopathology*, *23*(2011), 7–28. https://doi.org/10.1017/S0954579410000611

Engle, J. M., & Mcelwain, N. L. (2011). Parental Reactions to Toddlers' Negative Emotions and Child Negative Emotionality as Correlates of Problem Behavior at the Age of Three. *Social Development*, *20*(2), 251–271. https://doi.org/10.1111/j.1467-9507.2010.00583.x

Erk, S., Mikschl, A., Stier, S., Ciaramidaro, A., Gapp, V., Weber, B., & Walter, H. (2010). *Acute and Sustained Effects of Cognitive Emotion Regulation in Major Depression*. *30*(47), 15726–15734. https://doi.org/10.1523/JNEUROSCI.1856-10.2010

Espy, K. A., Kaufmann, P. M., McDiarmid, M. D., & Glisky, M. L. (1999). Executive functioning in preschool children: Performance on A-not-B and other delayed response format tasks. *Brain and Cognition*, *41*(2), 178–199. https://doi.org/10.1006/brcg.1999.1117

Etkin, A, Egner, T., & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal. *Trends in Cognitive Sciences*, *15*(2), 85–93. https://doi.org/10.1016/j.tics.2010.11.004.Emotional

Etkin, Amit, Egner, T., & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. In *Trends in Cognitive Sciences* (Vol. 15, Issue 2, pp. 85–93). https://doi.org/10.1016/j.tics.2010.11.004

Etkin, Amit, & Wager, T. D. (2007). Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *The American Journal of Psychiatry*, *164*(10), 1476–1488. https://doi.org/10.1176/appi.ajp.2007.07030504

Fair. (2010). Maturing thalamocortical functional connectivity across development. *Frontiers in Systems Neuroscience*, *4*(May), 1–10. https://doi.org/10.3389/fnsys.2010.00010

Fair, D. A., Schlaggar, B., Cohen, A. L., & Miezin, F. (2007). A method for using blocked and event-related fMRI data to study "resting state" functional connectivity. *Neuroimage*, *35*(1), 396–405. https://doi.org/10.1016/j.neuroimage.2006.11.051.A

Fair, D., Nigg, J. T., Iyer, S., Bathula, D., Mills, K. L., Dosenbach, N. U. F., Schlaggar, B. L., Mennes, M., Gutman, D., Bangaru, S., Buitelaar, J. K., Dickstein, D. P., Di Martino, A., Kennedy, D. N., Kelly, C., Luna, B., Schweitzer, J. B., Velanova, K., Wang, Y.-F., … Milham, M. P. (2012). Distinct neural signatures detected for ADHD subtypes after controlling for micro-movements in resting state functional connectivity MRI data. *Frontiers in Systems Neuroscience*, *6*(February), 80. https://doi.org/10.3389/fnsys.2012.00080

Fay-Stammbach, T., Hawes, D. J., & Meredith, P. (2014). Parenting Influences on Executive Function in Early Childhood: A Review. *Child Development Perspectives*, *8*(4), 258–264. https://doi.org/10.1111/cdep.12095

Feldman, R. (2003). Infant-mother and infant-father synchrony: The coregulation of positive arousal. *Infant Mental Health Journal*, *24*(1), 1–23. https://doi.org/10.1002/imhj.10041

Feldman, R. (2009). The development of regulatory functions from birth to 5 Years: Insights from premature infants. *Child Development*, *80*(2), 544–561. https://doi.org/10.1111/j.1467-8624.2009.01278.x

Feldman, R., Granat, A., Pariente, C., Kanety, H., Kuint, J., & Gilboa-Schechtman, E. (2009). Maternal Depression and Anxiety Across the Postpartum Year and Infant Social Engagement, Fear Regulation, and Stress Reactivity. *Journal of the American Academy of Child and Adolescent Psychiatry*, *48*(9), 919–927. https://doi.org/10.1097/CHI.0b013e3181b21651

Fenoglio, K. A., Chen, Y., & Baram, T. Z. (2006). Neuroplasticity of the hypothalamic-pituitary-adrenal axis early in life requires recurrent recruitment of stress-regulating brain regions. *Journal of Neuroscience*, *26*(9), 2434–2442. https://doi.org/10.1523/JNEUROSCI.4080-05.2006

Ferrier, D. E., Bassett, H. H., & Denham, S. A. (2014). Relations between executive function and emotionality in preschoolers: Exploring a transitive cognition-emotion linkage. *Frontiers in Psychology*, *5*(MAY). https://doi.org/10.3389/fpsyg.2014.00487

Feştilă, D., Ghergie, M., Muntean, A., Matiz, D., & Şerbănescu, A. (2014). Suckling and

non-nutritive sucking habit: What should we know? *Clujul Medical*, *87*(1), 11–14. https://doi.org/10.15386/cjm.2014.8872.871.df1mg2

Field, T., & Goldson, E. (1984). Pacifying effects of nonnutritive sucking on term and preterm neonates during heelstick procedures. *Pediatrics*, *74*(6), 1012–1015.

Field, T. M. (1981). Infant gaze aversion and heart rate during face-to-face interactions. *Infant Behavior and Development*, *4*(1), 307–315. https://doi.org/10.1016/S0163-6383(81)80032-X

Fitzpatrick, C., & Pagani, L. S. (2012). Toddler working memory skills predict kindergarten school readiness. *Intelligence*, *40*(2), 205–212. https://doi.org/10.1016/j.intell.2011.11.007

Fonov, V., Evans, A. C., Botteron, K., Almli, C. R., McKinstry, R. C., & Collins, D. L. (2011). Unbiased average age-appropriate atlases for pediatric studies. *NeuroImage*, *54*(1), 313–327. https://doi.org/10.1016/j.neuroimage.2010.07.033

Forbes, E. E., Ph, D., Hariri, A. R., Martin, S. L., Silk, J. S., Moyles, D. L., Fisher, P. M., Brown, S. M., Ryan, N. D., Birmaher, B., Axelson, D. A., Dahl, R. E., & Al, E. T. (2009). Altered Striatal Activation Predicting Real-World Positive Affect in Adolescent Major Depressive Disorder. *American Journal of Psychiatry*, *166*(1), 64–73. https://doi.org/10.1176/appi.ajp.2008.07081336.Altered

Forbes, E. E., Ryan, N. D., Phillips, M. L., Manuck, S. B., Worthman, C. M., Moyles, D. L., Tarr, J. A., Sciarrillo, S. R., & Dahl, R. E. (2010). Healthy Adolescents' Neural Response to Reward: Associations With Puberty, Positive Affect, and Depressive Symptoms. *Journal of the American Academy of Child and Adolescent Psychiatry*, *49*(2), 162–172. https://doi.org/10.1097/00004583-201002000-00010

Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci*, *8*(9), 700–711. https://doi.org/10.1038/nrn2201

Fox, N. A. (1991). If It's Not Left, It's Right: Electroencephalograph Asymmetry and the Development of Emotion. *American Psychologist*, *46*(8), 863–872. https://doi.org/10.1037/0003-066X.46.8.863

Fox, N. A., & Calkins, S. D. (2003). The development of self-control of emotion: Intrinsic and extrinsic influences. *Motivation and Emotion*, *27*(1), 7–26. https://doi.org/10.1023/A:1023622324898

Fox, N. A., Henderson, H. A., H., R. K., Calkins, S. D., & Schmidt, L. A. (2001). Continuity and discontinuity of behavioral inhibition and exuberance: psychophysiological and behavioral influences across the first four years. *Child Development*, *72*(1), 1–21. papers2://publication/uuid/6E6FE0B5-EA0C-409E-9835-19F059479AD4

Franchak, J. M., Kretch, K. S., & Adolph, K. E. (2018). See and be seen: Infant–caregiver social looking during locomotor free play. *Developmental Science*, *21*(4), 1–13. https://doi.org/10.1111/desc.12626

Frank, D. W., Dewitt, M., Hudgens-Haney, M., Schaeffer, D. J., Ball, B. H., Schwarz, N. F., Hussein, A. A., Smart, L. M., & Sabatinelli, D. (2014). Emotion regulation: Quantitative meta-analysis of functional activation and deactivation. *Neuroscience and Biobehavioral Reviews*, *45*, 202–211. https://doi.org/10.1016/j.neubiorev.2014.06.010

Frick, M. A., Brocki, K. C., Wåhlstedt, C., Sonuga-Barke, E. J. S., & Uppsala universitet

Humanistisk-samhällsvetenskapliga vetenskapsområdet. (2019). *Self-Regulation in Childhood Developmental Mechanisms and Relations to ADHD Symptoms.*

Frick, M. A., Forslund, T., Fransson, M., Johansson, M., Bohlin, G., & Brocki, K. C. (2017). The role of sustained attention, maternal sensitivity, and infant temperament in the development of early self-regulation. *British Journal of Psychology*, *109*(2), 277–298. https://doi.org/10.1111/bjop.12266

G Weaver, I. C., Meaney, M. J., & Szyf, M. (2006). *Maternal care effects on the hippocampal transcriptome and anxiety-mediated behaviors in the offspring that are reversible in adulthood*. www.pnas.orgcgidoi10.1073pnas.0507526103

Gago Galvagno, L. G., De Grandis, M. C., Clerici, G. D., Mustaca, A. E., Miller, S. E., & Elgier, A. M. (2019). Regulation during the second year: Executive function and emotion regulation links to joint attention, temperament, and social vulnerability in a Latin American sample. *Frontiers in Psychology*, *10*(JULY). https://doi.org/10.3389/fpsyg.2019.01473

Gao, W., Alcauter, S., Elton, A., Hernandez-Castillo, C. R., Smith, J. K., Ramirez, J., & Lin, W. (2015). Functional network development during the first year: Relative sequence and socioeconomic correlations. *Cerebral Cortex*, *25*(9), 2919–2928. https://doi.org/10.1093/cercor/bhu088

Gao, W., Alcauter, S., Smith, J. K., Gilmore, J., & Lin, W. (2015). Development of human brain cortical network architecture during infancy. *Brain Structural Function*, *220*(2), 1173–1186. https://doi.org/10.1002/aur.1474.Replication

Gao, W., Lin, W., Grewen, K., & Gilmore, J. H. (2017). Functional Connectivity of the Infant Human Brain. *The Neuroscientist*, *23*(2), 169–184.

https://doi.org/10.1177/1073858416635986

Garon, N., Bryson, S. E., & Smith, I. M. (2008). Executive Function in Preschoolers: A Review Using an Integrative Framework. *Psychological Bulletin*, *134*(1), 31–60. https://doi.org/10.1037/0033-2909.134.1.31

Garstein, M., & Rothbart, M. K. (2003). Studying infant temperament via a revision of the Infant Behavior Questionnaire. *Infant Behavior & Development*, *26*, 64–86.

Gartstein, M. A., Bogale, W., & Meehan, C. L. (2016). Adaptation of the Infant Behavior Questionnaire-Revised for use in Ethiopia: Expanding cross-cultural investigation of temperament development. *Infant Behavior and Development*, *45*, 51–63. https://doi.org/10.1016/j.infbeh.2016.09.004

Gartstein, M. A., & Marmion, J. (2008). Fear and positive affectivity in infancy: Convergence/discrepancy between parent-report and laboratory-based indicators. *Infant Behavior and Development*, *31*(2), 227–238. https://doi.org/10.1016/j.infbeh.2007.10.012

Gartstein, M. A., Putnam, S. P., & Rothbart, M. K. (2012). ETIOLOGY OF PRESCHOOL BEHAVIOR PROBLEMS: CONTRIBUTIONS OF TEMPERAMENT ATTRIBUTES IN EARLY CHILDHOOD. *Infant Mental Health Journal*, *33*(2), 197–211. http://onlinelibrary.wiley.com/doi/10.1002/imhj.21312/epdf

Gartstein, M. a, Bridgett, D. J., Rothbart, M. K., Robertson, C., Iddins, E., Ramsay, K., & Schlect, S. (2010). A latent growth examination of fear development in infancy: Contributions of maternal depression and the risk for toddler anxiety. *Developmental Psychology*, *46*(3), 651–668. https://doi.org/10.1037/a0018898

Gee, D. G., Gabard-Durnam, L. J., Flannery, J., Goff, B., Humphreys, K. L., & Telzer, E. H. (2013). Early developmental emergence of human amygdala – prefrontal connectivity after maternal deprivation. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(39), 15638–15643. https://doi.org/10.1073/pnas.1307893110/-/DCSupplemental.www.pnas.org/cgi/doi/10.1073/pnas.1307893110

Gee, D. G., Humphreys, K. L., Flannery, J., Goff, B., Telzer, E. H., Shapiro, M., Hare, T. A., Bookheimer, S. Y., & Tottenham, N. (2013). A developmental shift from positive to negative connectivity in human amygdala-prefrontal circuitry. *Journal of Neuroscience*, *33*(10), 4584–4593. https://doi.org/10.1523/JNEUROSCI.3446-12.2013

Gjone, H., & D, J. I. M. S. P. H. (1997). A Longitudinal Twin Study of Temperament and Behavior Problems : Common Genetic or Environmental Influences ? *Journal of the American Academy of Child & Adolescent Psychiatry*, *36*(10), 1448–1456. https://doi.org/10.1097/00004583-199710000-00028

Glasser, M. F., Coalson, T. S., Robinson, E. C., Hacker, C. D., Harwell, J., Yacoub, E., Ugurbil, K., Andersson, J., Beckmann, C. F., Jenkinson, M., Smith, S. M., & Van Essen, D. C. (2016). A multi-modal parcellation of human cerebral cortex. *Nature*, *536*(7615), 171–178. https://doi.org/10.1038/nature18933

Glasser, M. F., Sotiropoulos, S. N., Wilson, J. A., Coalson, T. S., Fischl, B., Andersson, J. L., Xu, J., Jbabdi, S., Webster, M., Polimeni, J. R., Essen, D. C. Van, Jenkinson, M., & Hcp, W. (2013). NeuroImage The minimal preprocessing pipelines for the Human Connectome Project. *NeuroImage*, *80*, 105–124.

https://doi.org/10.1016/j.neuroimage.2013.04.127

Gore, W. L., & Widiger, T. A. (2018). Negative emotionality across diagnostic models: RDoC, DSM-5 section III, and FFM. *Personality Disorders: Theory, Research, and Treatment*, *9*(2), 155–164. https://doi.org/10.1037/per0000273

Gottwald, J. M., Achermann, S., Marciszko, C., Lindskog, M., & Gredebäck, G. (2016). An Embodied Account of Early Executive-Function Development: Prospective Motor Control in Infancy Is Related to Inhibition and Working Memory. *Psychological Science*, *27*(12), 1600–1610. https://doi.org/10.1177/0956797616667447

Graham, A. M., Buss, C., Rasmussen, J. M., Rudolph, M. D., Demeter, D. V., Gilmore, J. H., Styner, M., Entringer, S., Wadhwa, P. D., & Fair, D. A. (2016). Implications of newborn amygdala connectivity for fear and cognitive development at 6-months-of-age. *Developmental Cognitive Neuroscience*, *18*, 12–25. https://doi.org/10.1016/j.dcn.2015.09.006

Graham, A. M., Pfeifer, J. H., Fisher, P. A., Carpenter, S., & Fair, D. A. (2015). Early life stress is associated with default system integrity and emotionality during infancy. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *56*(11), 1212–1222. https://doi.org/10.1111/jcpp.12409

Graham, A. M., Pfeifer, J. H., Fisher, P. A., Lin, W., Gao, W., & Fair, D. A. (2015). Developmental Cognitive Neuroscience The potential of infant fMRI research and the study of early life stress as a promising exemplar. *Accident Analysis and Prevention*, *12*, 12–39. https://doi.org/10.1016/j.dcn.2014.09.005

Graham, A. M., Rasmussen, J. M., Entringer, S., Ward, E. Ben, Rudolph, D., Gilmore, J.

H., Styner, M., Wadhwa, P. D., Fair, D. A., & Buss, C. (2018). Maternal Cortisol Concentrations During Pregnancy and Sex Specific Associations with Neonatal Amygdala Connectivity and Emerging Internalizing Behaviors. *Biological Psychiatry*. https://doi.org/10.1016/j.biopsych.2018.06.023

Graham, A. M., Rasmussen, J. M., Rudolph, M. D., Heim, C. M., Gilmore, H., Styner, M., Potkin, S. G., Entringer, S., Wadhwa, P. D., Fair, D. A., & Buss, C. (2017). Maternal Systemic Interleukin-6 During Pregnancy is Associated with Newborn Amygdala Phenotypes and Subsequent Behavior at 2-years-of-age. *Biological Psychiatry*. https://doi.org/10.1016/j.biopsych.2017.05.027

Grant, K. A., McMahon, C., Reilly, N., & Austin, M. P. (2010). Maternal sensitivity moderates the impact of prenatal anxiety disorder on infant responses to the still-face procedure. *Infant Behavior and Development*, *33*(4), 453–462. https://doi.org/10.1016/j.infbeh.2010.05.001

Gunnar, M. (1992). Reactivity of the hypothalamic-pituitary-adrenocortical system to stressors in normal infants and children. *Pediatrics*, *90*(3), 491–497.

Gunnar, M., & Quevedo, K. (2007). The neurobiology of stress and development. *Annual Review of Psychology*, *58*, 145–173. https://doi.org/10.1146/annurev.psych.58.110405.085605

Gunnar, M. R., Brodersen, L., Nachmias, M., Buss, K., & Rigatuso, J. (1996). Stress reactivity and attachment security. *Developmental Psychobiology*, *29*(3), 191–204. https://doi.org/10.1002/(SICI)1098-2302(199604)29:3<191::AID-DEV1>3.0.CO;2-M

Gunnar, M. R., Talge, N. M., & Herrera, A. (2009). Stressor paradigms in developmental

studies: What does and does not work to produce mean increases in salivary cortisol. *Psychoneuroendocrinology*, *34*(7), 953–967. https://doi.org/10.1016/j.psyneuen.2009.02.010

Gustafsson, H. C., Grieve, P. G., Werner, E. A., Desai, P., & Monk, C. (2018). Newborn electroencephalographic correlates of maternal prenatal depressive symptoms. *Journal of Developmental Origins of Health and Disease*, *9*(4), 381–385. https://doi.org/10.1017/S2040174418000089

Gustafsson, Hanna C., Sullivan, E. L., Battison, E. A. J., Holton, K. F., Graham, A. M., Karalunas, S. L., Fair, D. A., Loftis, J. M., & Nigg, J. T. (2020). Evaluation of maternal inflammation as a marker of future offspring ADHD symptoms: A prospective investigation. *Brain, Behavior, and Immunity*, *89*(April), 350–356. https://doi.org/10.1016/j.bbi.2020.07.019

Gustafsson, Hanna C, Sullivan, E. L., Nousen, E. K., Sullivan, C. A., Huang, E., Rincon, M., Nigg, J. T., & Loftis, J. M. (2018). Maternal Prenatal Depression Predicts Infant Negative Affect via Maternal Inflammatory Cytokine Levels. *Brain Behavior and Immunity*. https://doi.org/10.1016/j.bbi.2018.06.011

Gyurak, A., Gross, J. J., & Etkin, A. (2011). Explicit and implicit emotion regulation: a dual-process framework. *Cognition & Emotion*, *25*(3), 400–412. https://doi.org/10.1080/02699931.2010.544160

Hackman, D. A., Gallop, R., Evans, G. W., & Farah, M. J. (2015). Socioeconomic status and executive function: Developmental trajectories and mediation. *Developmental Science*, *18*(5), 686–702. https://doi.org/10.1111/desc.12246

Hagmann, P., Grant, P. E., & Fair, D. A. (2012). MR connectomics: a conceptual

framework for studying the developing brain. *Frontiers in Systems Neuroscience*, *6*, 43. https://doi.org/10.3389/fnsys.2012.00043

Haley, D. W., & Stansbury, K. (2003). Infant Stress and Parent Responsiveness: Regulation of Physiology and Behavior during Still-Face and Reunion. *Child Development*, *74*(5), 1534–1546. https://doi.org/10.1111/1467-8624.00621

Hanford, L. C., Schmithorst, V. J., Panigrahy, A., Lee, V., Ridley, J., Bonar, L., Versace, A., Hipwell, A. E., & Phillips, M. L. (2018). The impact of caregiving on the association between infant emotional behavior and resting state neural network functional topology. *Frontiers in Psychology*, *9*(OCT). https://doi.org/10.3389/fpsyg.2018.01968

Harman, C., Rothbart, M. K., & Posner, M. I. (1997). Distress and attention interactions in early infancy. *Motivation and Emotion*, *21*(1), 27–43.

Hatzenbuehler, M. L., McLaughlin, K. A., & Nolen-Hoeksema, S. (2008). Emotion regulation and internalizing symptoms in a longitudinal study of sexual minority and heterosexual adolescents. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *49*(12), 1270–1278. https://doi.org/10.1111/j.1469-7610.2008.01924.x

Herringa, R. J., Birn, R. M., Ruttle, P. L., Burghy, C. A., Stodola, D. E., Davidson, R. J., & Essex, M. J. (2013). Childhood maltreatment is associated with altered fear circuitry and increased internalizing symptoms by late adolescence. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(47), 19119–19124. https://doi.org/10.1073/pnas.1310766110

Hiser, J., & Koenigs, M. (2018). The Multifaceted Role of the Ventromedial Prefrontal Cortex in Emotion, Decision Making, Social Cognition, and Psychopathology.

Biological Psychiatry, *83*(8), 638–647. https://doi.org/10.1016/j.biopsych.2017.10.030

Hodel, A. S. (2018). Rapid infant prefrontal cortex development and sensitivity to early environmental experience. *Developmental Review*, *48*(10), 113–144. https://doi.org/10.1016/j.dr.2018.02.003

Hostinar, C. E., & Gunnar, M. R. (2013). The Developmental Psychobiology of Stress and Emotion in Childhood. *Handbook of Psychology, Second Edition*, 121–141. https://doi.org/10.1002/9781118133880.hop206005

Hostinar, C. E., Stellern, S. A., Schaefer, C., Carlson, S. M., & Gunnar, M. R. (2012). Associations between early life adversity and executive function in children adopted internationally from orphanages. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(SUPPL.2), 17208–17212. https://doi.org/10.1073/pnas.1121246109

Houck, C. D., Hadley, W., Barker, D., Brown, L. K., Hancock, E., & Almy, B. (2016). *An Emotion Regulation Intervention to Reduce Risk Behaviors Among at-Risk Early Adolescents*. 71–82. https://doi.org/10.1007/s11121-015-0597-0

Hughes, C., & Ensor, R. (2005). *Executive function and theory of mind in 2 year olds: a family affair? 28*(2), 645–668.

Jamnik, M. R., & DiLalla, L. F. (2019). Health outcomes associated with internalizing problems in early childhood and adolescence. *Frontiers in Psychology*, *10*(JAN), 1–11. https://doi.org/10.3389/fpsyg.2019.00060

Jansen, J., Beijers, R., Riksen-Walraven, M., & de Weerth, C. (2010). Cortisol reactivity in young infants. *Psychoneuroendocrinology*, *35*(3), 329–338.

https://doi.org/10.1016/j.psyneuen.2009.07.008

Jiang, Y., Tian, Y., & Wang, Z. (2019). Causal Interactions in Human Amygdala Cortical Networks across the Lifespan. *Scientific Reports*, *9*(1). https://doi.org/10.1038/s41598-019-42361-0

Jung, Y. H., Shin, J. E., Lee, Y. I., Jang, J. H., Jo, H. J., & Choi, S. H. (2018). Altered amygdala resting-state functional connectivity and hemispheric asymmetry in patients with social anxiety disorder. *Frontiers in Psychiatry*, *9*(APR), 1–9. https://doi.org/10.3389/fpsyt.2018.00164

Kane, M. J., & Engle, R. W. (2002). The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: An individual-differences perspective. *Psychonomic Bulletin and Review*, *9*(4), 637–671. https://doi.org/10.3758/BF03196323

Karen, T., Morren, G., Haensse, D., Bauschatz, A. S., Bucher, H. U., & Wolf, M. (2008). *Hemodynamic Response to Visual Stimulation in Newborn Infants Using Functional Near-Infrared Spectroscopy*. *460*, 453–460. https://doi.org/10.1002/hbm.20411

Kassing, F., Godwin, J., Lochman, J. E., Coie, J. D., Bierman, K. L., Dodge, K. A., Greenberg, M. T., McMahon, R. J., & Pinderhughes, E. E. (2019). Using Early Childhood Behavior Problems to Predict Adult Convictions. *Journal of Abnormal Child Psychology*, *47*(5), 765–778. https://doi.org/10.1007/s10802-018-0478-7

Keenan, K. (2000). Emotion dysregulation as a risk factor for child psychopathology. *Clinical Psychology: Science and Practice*, *7*(4), 418–434. https://doi.org/10.1093/clipsy.7.4.418

Kelsey, C., Farris, K., & Grossmann, T. (2020). *Variability in functional brain network*

connectivity is associated with differences in newborn infants' affect and behavior. https://doi.org/10.1101/2020.07.15.204271

Khoury, J. E., Gonzalez, A., Levitan, R., Masellis, M., Basile, V., & Atkinson, L. (2015). Infant Emotion Regulation Strategy Moderates Relations between Self-Reported Maternal Depressive Symptoms and Infant HPA Activity. *Infant and Child Development*, *18*(6), n/a-n/a. https://doi.org/10.1002/icd.1916

Kim-Spoon, J., Cicchetti, D., & Rogosch, F. A. (2013). A Longitudinal Study of Emotion Regulation, Emotion Lability-Negativity, and Internalizing Symptomatology in Maltreated and Nonmaltreated Children. *Child Development*, *84*(2), 512–527. https://doi.org/10.1111/j.1467-8624.2012.01857.x

Kim, M. J., Gee, D. G., Loucks, R. A., Davis, F. C., & Whalen, P. J. (2011a). Anxiety Dissociates dorsal and ventral medial prefrontal cortex functional connectivity with the amygdala at rest. *Cerebral Cortex*, *21*(7), 1667–1673. https://doi.org/10.1093/cercor/bhq237

Kim, M. J., Gee, D. G., Loucks, R. A., Davis, F. C., & Whalen, P. J. (2011b). Anxiety Dissociates dorsal and ventral medial prefrontal cortex functional connectivity with the amygdala at rest. *Cerebral Cortex*, *21*(7), 1667–1673. https://doi.org/10.1093/cercor/bhq237

Kim, M. J., Loucks, R. A., Palmer, A. L., Brown, A. C., Solomon, K. M., Marchante, A. N., & Whalen, P. J. (2011). The structural and functional connectivity of the amygdala: From normal emotion to pathological anxiety. *Behavioural Brain Research*, *223*(2), 403–410. https://doi.org/10.1016/j.bbr.2011.04.025

Klingberg, T., Forssberg, H., & Westerberg, H. (2002). Increased brain activity in frontal

and parietal cortex underlies the development of visuospatial working memory capacity during childhood. *Journal of Cognitive Neuroscience*, *14*(1), 1–10. https://doi.org/10.1162/089892902317205276

Kochanska, G., Murray, K., Jacques, T. Y., Koenig, A. L., & Vandegeest, K. A. (1996). Inhibitory Control in Young Children and Its Role in Emerging Internalization. *Child Development*, *67*(2), 490–507. https://doi.org/10.2307/1131828

Kochanska, G., Murray, K. T., & Harlan, E. T. (2000). Effortful Control in Early Childhood: Continuity and Change, Antecedents, and Implications for Social Development. In *Developmental Psychology* (Vol. 36, Issue 2).

Kohlboeck, G., Romanos, M., Teuner, C. M., Holle, R., Tiesler, C. M. T., Hoffmann, B., Schaaf, B., Lehmann, I., Herbarth, O., Koletzko, S., Bauer, C. P., Von Berg, A., Berdel, D., & Heinrich, J. (2014). Healthcare use and costs associated with children's behavior problems. *European Child and Adolescent Psychiatry*, *23*(8), 701–714. https://doi.org/10.1007/s00787-013-0504-9

Kopp, C. B. (1989). Regulation of distress and negative emotions: A developmental view. *Developmental Psychology*, *25*(3), 343–354. https://doi.org/10.1037/0012-1649.25.3.343

Kostyrka-Allchorne, K., Wass, S. V., & Sonuga-Barke, E. J. S. (2020). Research Review: Do parent ratings of infant negative emotionality and self-regulation predict psychopathology in childhood and adolescence? A systematic review and meta-analysis of prospective longitudinal studies. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *61*(4), 401–416. https://doi.org/10.1111/jcpp.13144

Kozberg, M. G., Chen, B. R., Deleo, S. E., Bouchard, M. B., & Hillman, E. M. C. (2013). *Resolving the transition from negative to positive blood oxygen level-dependent responses in the developing brain*. https://doi.org/10.1073/pnas.1212785110/-/DCSupplemental.www.pnas.org/cgi/doi/10.1073/pnas.1212785110

Kraybill, J. H., Kim-Spoon, J., & Bell, M. A. (2019). Infant attention and age 3 executive function. *Yale Journal of Biology and Medicine*, *92*(1), 3–11.

Kring, A. M., & Caponigro, J. M. (2010). Emotion in Schizophrenia. *Current Directions in Psychological Science*, *19*(4), 255–259. https://doi.org/10.1177/0963721410377599

Laumann, T. O., Gordon, E. M., Adeyemo, B., Snyder, A. Z., Joo, S. J., Chen, M. Y., Gilmore, A. W., McDermott, K. B., Nelson, S. M., Dosenbach, N. U. F., Schlaggar, B. L., Mumford, J. A., Poldrack, R. A., & Petersen, S. E. (2015). Functional System and Areal Organization of a Highly Sampled Individual Human Brain. *Neuron*, *87*(3), 658–671. https://doi.org/10.1016/j.neuron.2015.06.037

Laurent, H. K., Harold, G. T., Leve, L., Shelton, K. H., & Van Goozen, S. H. M. (2016). Understanding the unfolding of stress regulation in infants. *Development and Psychopathology*, *28*(4), 1431–1440. https://doi.org/10.1017/S0954579416000171

Leerkes, Ester M, Blankson, N. A., & O'Brien, M. (2009). Differential Effects Of Maternal Sensitivity To Infant Distress And Non-Distress On Social-Emotional Functioning. *Child Development*, *80*(3), 762–775. https://doi.org/doi:10.1111/j.1467-8624.2009.01296.x.

Leerkes, Esther M., & Crockenberg, S. C. (2003). The Impact of Maternal Characteristics and Sensitivity on the Concordance Between Maternal Reports and Laboratory

Observations of Infant Negative Emotionality. *Infancy*, *4*(4), 517–539. https://doi.org/10.1207/S15327078IN0404_07

Leerkes, Esther M., & Wong, M. S. (2012). Infant Distress and Regulatory Behaviors Vary as a Function of Attachment Security Regardless of Emotion Context and Maternal Involvement. *Infancy*, *17*(5), 455–478. https://doi.org/10.1111/j.1532-7078.2011.00099.x

Legerstee, M., Corter, C., & Kienapple, K. (1990). Hand, Arm, and Facial Actions of Young Infants to a Social and Nonsocial Stimulus. *Child Development*, *61*(3), 774–784. https://doi.org/10.1111/j.1467-8624.1990.tb02820.x

Lemery, K. S., Goldsmith, H. H., Klinnert, M. D., & Mrazek, D. a. (1999). Developmental models of infant and childhood temperament. *Developmental Psychology*, *35*(1), 189–204. https://doi.org/10.1037/0012-1649.35.1.189

Lévesque, J., Joanette, Y., Mensour, B., Beaudoin, G., Leroux, J. M., Bourgouin, P., & Beauregard, M. (2004). Neural basis of emotional self-regulation in childhood. *Neuroscience*, *129*(2), 361–369. https://doi.org/10.1016/j.neuroscience.2004.07.032

Liao, S. M., Gregg, N. M., White, B. R., Zeff, B. W., Bjerkaas, K. A., Inder, T. E., & Culver, J. P. (2010). Neonatal hemodynamic response to visual cortex activity : high-density near-infrared spectroscopy study. *Journal of Biomedical Optics*, *15*(2), 1–9. https://doi.org/10.1117/1.3369809

Lipina, S. J., & Evers, K. (2017). Neuroscience of childhood poverty: Evidence of impacts and mechanisms as vehicles of dialog with ethics. *Frontiers in Psychology*, *8*(JAN), 1–13. https://doi.org/10.3389/fpsyg.2017.00061

Lipina, S., Segretin, S., Hermida, J., Prats, L., Fracchia, C., Camelo, J. L., & Colombo, J.

(2013). Linking childhood poverty and cognition: Environmental mediators of non-verbal executive control in an Argentine sample. *Developmental Science*, *16*(5), 697–707. https://doi.org/10.1111/desc.12080

Lipscomb, S. T. (Oregon S. U., Leve, L. D., Shaw, D. S., Neiderhiser, J. M., Scaramella, L. V., Ge, X., Conger, R. D., Reid, J. B., & Ress, D. (2012). Trajectories of parenting and child negative emotionality during infancy and toddlerhood: A longitudinal analysis. *Development and Psychopathology*, *24*(1), 167–179. https://doi.org/10.1111/j.1467-8624.2011.01639.x

Marek, S., Tervo-Clemmens, B., Calabro, F. J., Montez, D. F., Kay, B. P., Hatoum, A. S., Rose Donohue, M., Foran, W., Miller, R. L., Feczko, E., Miranda-Dominguez, O., Graham, A. M., Chen, J., Newbold, D. J., Zheng, A., Seider, N. A., Van, A. N., Laumann, T. O., Thompson, W. K., … Dosenbach, N. (2020). Towards Reproducible Brain-Wide Association Studies. *BioRxiv*, *11*, 15–18. https://doi.org/10.1101/2020.08.21.257758

Mayes, L. C., & Carter, A. S. (1990). Emerging Social Regulatory Capacities as Seen in the Still-Face Situation. In *Source: Child Development* (Vol. 61, Issue 3).

McGrath, J. M., Records, K., & Rice, M. (2008). Maternal depression and infant temperament characteristics. *Infant Behavior and Development*, *31*(1), 71–80. https://doi.org/10.1016/j.infbeh.2007.07.001

McLaughlin, K. A., Peverill, M., Gold, A. L., Alves, S., & Sheridan, M. A. (2015). Child Maltreatment and Neural Systems Underlying Emotion Regulation. *Journal of the American Academy of Child and Adolescent Psychiatry*, *54*(9), 753–762. https://doi.org/10.1016/j.jaac.2015.06.010

McRae, K., Misra, S., Prasad, A. K., Pereira, S. C., & Gross, J. J. (2012). Bottom-up and top-down emotion generation: Implications for emotion regulation. *Social Cognitive and Affective Neuroscience*, *7*(3), 253–262. https://doi.org/10.1093/scan/nsq103

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure and Function*, 1–13. https://doi.org/10.1007/s00429-010-0262-0

Mesman, J., van IJzendoorn, M. H., & Bakermans-Kranenburg, M. J. (2009). The many faces of the Still-Face Paradigm: A review and meta-analysis. *Developmental Review*, *29*(2), 120–162. https://doi.org/10.1016/j.dr.2009.02.001

Miezin, F. M., Maccotta, L., Ollinger, J. M., Petersen, S. E., & Buckner, R. L. (2000). Characterizing the hemodynamic response: effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing. *NeuroImage*, *11*, 735–759. https://doi.org/10.1006/nimg.2000.0568

Milad, M. R., & Quirk, G. J. (2012). Fear Extinction as a Model for Translational Neuroscience: Ten Years of Progress. *Annual Review of Psychology*, *63*(1), 129–151. https://doi.org/10.1146/annurev.psych.121208.131631

Milad, M. R., Wright, C. I., Orr, S. P., Pitman, R. K., Quirk, G. J., & Rauch, S. L. (2007). Recall of Fear Extinction in Humans Activates the Ventromedial Prefrontal Cortex and Hippocampus in Concert. *Biological Psychiatry*, *62*(5), 446–454. https://doi.org/10.1016/j.biopsych.2006.10.011

Miller, N. V, Hane, A. A., Degnan, K. A., Fox, N. A., & Chronis-Tuscano, A. (2019). Investigation of a developmental pathway from infant anger reactivity to childhood inhibitory control and ADHD symptoms: interactive effects of early maternal

caregiving. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *60*(7), 762–772. https://doi.org/10.1111/jcpp.13047

Mills, K. L., Bathula, D., Dias, T. G. C., Iyer, S. P., Fenesy, M. C., Musser, E. D., Stevens, C. A., Thurlow, B. L., Carpenter, S. D., Nagel, B. J., Nigg, J. T., & Fair, D. A. (2012). Altered cortico-striatal-thalamic connectivity in relation to spatial working memory capacity in children with ADHD. *Frontiers in Psychiatry*, *3*(January), 2. https://doi.org/10.3389/fpsyt.2012.00002

Mischel, W., Shoda, Y., & Peake, P. K. (1988). The nature of adolescent competencies predicted by preschool delay of gratification. In *Journal of Personality and Social Psychology* (Vol. 54, Issue 4). Toner & Smith.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The Unity and Diversity of Executive Functions and Their Contributions to Complex "Frontal Lobe" Tasks: A Latent Variable Analysis. *Cognitive Psychology*, *41*(1), 49–100. https://doi.org/10.1006/cogp.1999.0734

Modecki, K. L., Zimmer-gembeck, M. J., & Guerra, N. (2017). *Emotion Regulation , Coping , and Decision Making : Three Linked Skills for Preventing Externalizing Problems in Adolescence*. *00*(0), 1–10. https://doi.org/10.1111/cdev.12734

Montirosso, R., Cozzi, P., Putnam, S. P., Gartstein, M. A., & Borgatti, R. (2011). Studying cross-cultural differences in temperament in the first year of life: United States and Italy. *International Journal of Behavioral Development*, *35*(1), 27–37. https://doi.org/10.1177/0165025410368944

Moog, N. K., Entringer, S., Rasmussen, J. M., Styner, M., Gilmore, J. H., Kathmann, N., Heim, C. M., Wadhwa, P. D., & Buss, C. (2017). Intergenerational Effect of

Maternal Exposure to Childhood Maltreatment on Newborn Brain Anatomy. *Biological Psychiatry*, *83*(2), 120–127. https://doi.org/10.1016/j.biopsych.2017.07.009

Moore, G. A., Cohn, J. F., & Campbell, S. B. (2001). Infant affective responses to mother's still face at 6 months differentially predict externalizing and internalizing behaviors at 18 months. *Developmental Psychology*, *37*(5), 706–714. https://doi.org/10.1037//0012-1649.37.5.706

Moore, G. A., Hill-soderlund, A. L., Propper, C. B., Calkins, S. D., Mills-koonce, W. R., & Cox, M. J. (2009). *Mother – Infant Vagal Regulation in the Face-To-Face Still-Face Paradigm Is Moderated by Maternal Sensitivity*. *80*(1), 209–223.

Morris, A. S., Criss, M. M., Silk, J. S., & Houltberg, B. J. (2017). The Impact of Parenting on Emotion Regulation During Childhood and Adolescence. *Child Development Perspectives*, *11*(4), 233–238. https://doi.org/10.1111/cdep.12238

Mulder, H., Verhagen, J., Van der Ven, S. H. G., Slot, P. L., & Leseman, P. P. M. (2017). Early executive function at age two predicts emergent mathematics and literacy at age five. *Frontiers in Psychology*, *8*(OCT), 1–14. https://doi.org/10.3389/fpsyg.2017.01706

Mulej Bratec, S., Xie, X., Schmid, G., Doll, A., Schilbach, L., Zimmer, C., Wohlschläger, A., Riedl, V., & Sorg, C. (2015). Cognitive emotion regulation enhances aversive prediction error activity while reducing emotional responses. *NeuroImage*, *123*, 138–148. https://doi.org/10.1016/j.neuroimage.2015.08.038

Murayama, Y., Bießmann, F., Meinecke, F. C., Müller, K. R., Augath, M., Oeltermann, A., & Logothetis, N. K. (2010). Relationship between neural and hemodynamic

signals during spontaneous activity studied with temporal kernel CCA. *Magnetic Resonance Imaging*, *28*(8), 1095–1103. https://doi.org/10.1016/j.mri.2009.12.016

Murray, K. T., & Kochanska, G. (2002). Effortful control: factor structure and relation to externalizing and internalizing behaviors. *Journal of Abnormal Child Psychology*, *30*(5), 503–514.

Narusyte, J., Ropponen, A., Alexanderson, K., & Svedberg, P. (2017). Internalizing and externalizing problems in childhood and adolescence as predictors of work incapacity in young adulthood. *Social Psychiatry and Psychiatric Epidemiology*, *52*(9), 1159–1168. https://doi.org/10.1007/s00127-017-1409-6

Nelson, B. D., Fitzgerald, D. A., Klumpp, H., Shankman, S. A., & Phan, K. L. (2015). Prefrontal engagement by cognitive reappraisal of negative faces. *Behavioural Brain Research*, *279*, 218–225. https://doi.org/10.1016/j.bbr.2014.11.034

Nigg, J. T. (2006). Temperament and developmental psychopathology. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *47*(3–4), 395–422. https://doi.org/10.1111/j.1469-7610.2006.01612.x

Nigg, J. T. (2017). Annual Research Review: On the relations among self-regulation, self-control, executive functioning, effortful control, cognitive control, impulsivity, risk-taking, and inhibition for developmental psychopathology. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *58*(4), 361–383. https://doi.org/10.1111/jcpp.12675

Nigg, J. T., Karalunas, S. L., Gustafsson, H. C., Bhatt, P., Ryabinin, P., Mooney, M. A., Faraone, S. V, Fair, D. A., & Wilmot, B. (2020). Evaluating chronic emotional dysregulation and irritability in relation to ADHD and depression genetic risk in

children with ADHD. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *61*(2), 205–214. https://doi.org/10.1111/jcpp.13132

Nozaki, Y., & Mikolajczak, M. (2020). Extrinsic emotion regulation. *Emotion (Washington, D.C.)*, *20*(1), 10–15. https://doi.org/10.1037/emo0000636

O'Connor, T. G., Scheible, K., Sefair, A. V., Gilchrist, M., Blackmore, E. R., Winter, M. A., Gunnar, M. R., Wyman, C., Carnahan, J., Moynihan, J. A., & Caserta, M. T. (2017). Immune and neuroendocrine correlates of temperament in infancy. *Development and Psychopathology*, *29*(5), 1589–1600. https://doi.org/10.1017/S0954579417001250

Ochsner, K. N., Bunge, S. A., Gross, J. J., & Gabrieli, J. D. E. (2002). Rethinking feelings: an FMRI study of the cognitive regulation of emotion. *Journal of Cognitive Neuroscience*, *14*(8), 1215–1229. https://doi.org/10.1162/089892902760807212

Ochsner, K. N., Ray, R. D., Cooper, J. C., Robertson, E. R., Chopra, S., Gabrieli, J. D. E., & Gross, J. J. (2004). For better or for worse: Neural systems supporting the cognitive down- and up-regulation of negative emotion. *NeuroImage*, *23*(2), 483–499. https://doi.org/10.1016/j.neuroimage.2004.06.030

Ogawa, S., Lee, A. R. K., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Biophysics*, *87*, 9868–9872. https://doi.org/10.1016/0005-2736(76)90348-5

Ohira, H., Nomura, M., Ichikawa, N., Isowa, T., Iidaka, T., Sato, A., Fukuyama, S., Nakajima, T., & Yamada, J. (2006). Association of neural and physiological responses during voluntary emotion suppression. *NeuroImage*, *29*(3), 721–733. https://doi.org/10.1016/j.neuroimage.2005.08.047

Pan, J., Zhan, L., Hu, C. L., Yang, J., Wang, C., Gu, L., Zhong, S., Huang, Y., Wu, Q., Xie, X., Chen, Q., Zhou, H., Huang, M., & Wu, X. (2018). Emotion regulation and complex brain networks: Association between expressive suppression and efficiency in the fronto-parietal network and default-mode network. *Frontiers in Human Neuroscience*, *12*. https://doi.org/10.3389/fnhum.2018.00070

Parade, S. H., & Leerkes, E. M. (2008). The Reliability and Validity of the Infant Behavior Questionnaire Revised. *Infant Behavioral Development*, *31*(4), 637–646. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2655727/

Partridge, Ty (Department of Psychology, Wayne State University, D. U., & Lerner, Jacqueline (Lynch School of Education, Boston College, Chesnut Hill, MA, U. (2007). A Latent Growth-Curve Approach to Difficult Temperament. *Infant and Child Development*, *16*(1), 255–265. https://doi.org/10.1002/icd.465

Patrick, C. (1994). Emotion and Psychopathy: Startling new insights. *Psychophysiology*, *31*, 319–330.

Pe, M. L., Raes, F., & Kuppens, P. (2013). The Cognitive Building Blocks of Emotion Regulation: Ability to Update Working Memory Moderates the Efficacy of Rumination and Reappraisal on Emotion. *PLoS ONE*, *8*(7). https://doi.org/10.1371/journal.pone.0069071

Pelham, B. (1993). The Idiographic Nature of Human Personality: Examples of the Idographic Self-Concept. *Journal of Personality and Social Psychology*, *64*(4), 665–677.

Pennington, B. F., & Ozonoff, S. (1996). Executive functions and developmental psychopathology. *Journal of Child Psychology and Psychiatry and Allied*

Disciplines, *37*(1), 51–87. https://doi.org/10.1111/j.1469-7610.1996.tb01380.x

Perlman, S. B., Ph, D., Wisner, K. L., James, J., Saul, a T., & Phillips, M. L. (2010). and Effective Connectivity With Amygdala in Response to Negative Emotional Faces in Postpartum Depression. *Depression*, *November*, 1373–1380. https://doi.org/10.1176/appi.ajp.2010.09081235

Pessoa, L., & Ungerleider, L. G. (2004). Neuroimaging studies of attention and the processing of emotion-laden stimuli. *Progress in Brain Research*, *144*(1995), 171–182. https://doi.org/10.1016/S0079-6123(03)14412-3

Peters, J., Kalivas, P. W., & Quirk, G. J. (2009). *Extinction circuits for fear and addiction overlap*. *787*, 279–288. https://doi.org/10.1101/lm.1041309.16

Phelps, E. A., & LeDoux, J. E. (2005). Contributions of the amygdala to emotion processing: From animal models to human behavior. *Neuron*, *48*(2), 175–187. https://doi.org/10.1016/j.neuron.2005.09.025

Phillips, M. L., Drevets, W. C., Rauch, S. L., & Lane, R. (2003a). Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biological Psychiatry*, *54*(5), 504–514. https://doi.org/10.1016/S0006-3223(03)00168-9

Phillips, M. L., Drevets, W. C., Rauch, S. L., & Lane, R. (2003b). *Neurobiology of Emotion Perception II : Implications for Major Psychiatric Disorders*. https://doi.org/10.1016/S0006-3223(03)00171-9

Pitskel, N. B., Bolling, D. Z., Kaiser, M. D., Crowley, M. J., & Pelphrey, K. A. (2011). How grossed out are you? The neural bases of emotion regulation from childhood to adolescence. *Developmental Cognitive Neuroscience*, *1*(3), 324–337. https://doi.org/10.1016/j.dcn.2011.03.004

Poehlmann, J., Schwichtenberg, A. J. M., Shlafer, R. J., Hahn, E., Bianchi, J.-P., & Warner, R. (2011). Emerging self-regulation in toddlers born preterm or low birth weight: differential susceptibility to parenting? *Development and Psychopathology*, *23*(1), 177–193. https://doi.org/10.1017/S0954579410000726

Posner, M. I., & Petersen, S. E. (1990). The attention system of the human brain. *Annual Review of Neuroscience*, *13*, 25–42. https://doi.org/10.1146/annurev.ne.13.030190.000325

Posner, Michael I., Rothbart, M. K., Sheese, B. E., & Voelker, P. (2012). Control networks and neuromodulators of early development. *Developmental Psychology*, *48*(3), 827–835. https://doi.org/10.1037/a0025530

Posner, Michael I, & Rothbart, M. K. (1998). *Attention , self-regulation and consciousness*. *353*(1377), 1915–1927. https://doi.org/10.1098/rstb.1998.0344

Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage*, *59*(3), 2142–2154. https://doi.org/10.1016/j.neuroimage.2011.10.018

Power, J. D., Schlaggar, B. L., & Petersen, S. E. (2015). Recent progress and outstanding issues in motion correction in resting state fMRI. *NeuroImage*, *105*, 536–551. https://doi.org/10.1016/j.neuroimage.2014.10.044

Prager, E. O., Sera, M. D., & Carlson, S. M. (2016). Executive function and magnitude skills in preschool children. *Journal of Experimental Child Psychology*, *147*(3), 126–139. https://doi.org/10.1016/j.jecp.2016.01.002

Pratt, M., Singer, M., Kanat-Maymon, Y., & Feldman, R. (2015). Infant negative

reactivity defines the effects of parent-child synchrony on physiological and behavioral regulation of social stress. *Development and Psychopathology*, *27*(4), 1191–1204. https://doi.org/10.1017/S0954579415000760

Provenzi, L., Giusti, L., & Montirosso, R. (2016). Do infants exhibit significant cortisol reactivity to the Face-to-Face Still-Face paradigm? A narrative review and meta-analysis. *Developmental Review*, *42*, 34–55. https://doi.org/10.1016/j.dr.2016.07.001

Putnam, S. P., Gartstein, M. A., & Rothbart, M. K. (2006). *Measurement of fine-grained aspects of toddler temperament : The Early Childhood Behavior Questionnaire*. *29*, 386–401. https://doi.org/10.1016/j.infbeh.2006.01.004

Putnam, S. P., Rothbart, M. K., & Gartstein, M. A. (2008). Homotypic and Heterotypic Continuity of Fine-grained Temperament during Infancy, Toddlerhood, and Early Childhood. *Infant and Child Development*, *17*, 387–405. https://doi.org/10.1002/ICD.582

Qin, S., Young, C. B., Duan, X., Chen, T., Supekar, K., & Menon, V. (2014). Amygdala subregional structure and intrinsic functional connectivity predicts individual differences in anxiety during early childhood. *Biological Psychiatry*, *75*(11), 892–900. https://doi.org/10.1016/j.biopsych.2013.10.006

Qiu, A., Anh, T. T., Li, Y., Chen, H., Rifkin-Graboi, A., Broekman, B. F. P., Kwek, K., Saw, S.-M., Chong, Y.-S., Gluckman, P. D., Fortier, M. V, & Meaney, M. J. (2015). Prenatal maternal depression alters amygdala functional connectivity in 6-month-old infants. *Translational Psychiatry*, *5*(2), e508. https://doi.org/10.1038/tp.2015.3

Rabinak, C. A., Angstadt, M., Welsh, R. C., Kenndy, A. E., Lyubkin, M., Martis, B., & Luan Phan, K. (2011). Altered amygdala resting-state functional connectivity in

post-traumatic stress disorder. *Frontiers in Psychiatry*, *2*(NOV), 1–8. https://doi.org/10.3389/fpsyt.2011.00062

Radloff, L. S. (Center for E. S. N. I. of M. H. (1977). Radloff 1977 CES-D.pdf. *Applied Psychological Measurement*, *1*(3), 385–401.

Ramsay, D., & Lewis, M. (2003). Reactivity and Regulation in Cortisol and Behavioral Responses to Stress. *Child Development*, *74*(2), 456–464. https://doi.org/10.1111/1467-8624.7402009

Rauss, K., & Pourtois, G. (2013). What is bottom-up and what is top-down in predictive coding. *Frontiers in Psychology*, *4*(MAY). https://doi.org/10.3389/fpsyg.2013.00276

Raver, C. C., Roy, A. L., Pressler, E., Ursache, A. M., & McCoy, D. C. (2017). Poverty-related adversity and emotion regulation predict internalizing behavior problems among low-income children ages 8-11. *Behavioral Sciences*, *7*(1). https://doi.org/10.3390/bs7010002

Reppucci, C. J., & Petrovich, G. D. (2016). Organization of connections between the amygdala, medial prefrontal cortex, and lateral hypothalamus: a single and double retrograde tracing study in rats. *Brain Structure and Function*, *221*(6), 2937–2962. https://doi.org/10.1007/s00429-015-1081-0

Rey, G., Piguet, C., Benders, A., Favre, S., Eickhoff, S. B., Aubry, J. M., & Vuilleumier, P. (2016). Resting-state functional connectivity of emotion regulation networks in euthymic and non-euthymic bipolar disorder patients. *European Psychiatry*, *34*, 56–63. https://doi.org/10.1016/j.eurpsy.2015.12.005

Reynolds, G. D., & Romano, A. C. (2016). The Development of Attention Systems and

Working Memory in Infancy. *Frontiers in Systems Neuroscience*, *10*(March), Article 15. https://doi.org/10.3389/fnsys.2016.00015

Rhoades, B. L., Greenberg, M. T., & Blair, C. (2012). Demographic and Familial Predictors of Early Executive Function Development. *Journal of Experimental Child Psychology*, *108*(3), 638–662. https://doi.org/10.1016/j.jecp.2010.08.004.Demographic

Riediger, M., Wrzus, C., Schmiedek, F., Wagner, G. G., & Lindenberger, U. (2011). Is Seeking Bad Mood Cognitively Demanding? Contra-Hedonic Orientation and Working-Memory Capacity in Everyday Life. *Emotion*, *11*(3), 656–665. https://doi.org/10.1037/a0022756

Ritchey, M., Dolcos, F., Eddington, K. M., Strauman, T. J., & Cabeza, R. (2011). Neural correlates of emotional processing in depression: Changes with cognitive behavioral therapy and predictors of treatment response. *Journal of Psychiatric Research*, *45*(5), 577–587. https://doi.org/10.1016/j.jpsychires.2010.09.007

Rogers, C. E., Sylvester, C. M., Mintz, C., Kenley, J. K., Shimony, J. S., Barch, D. M., & Smyser, C. D. (2017). Neonatal Amygdala Functional Connectivity at Rest in Healthy and Preterm Infants and Early Internalizing Symptoms. *Journal of the American Academy of Child & Adolescent Psychiatry*, *56*(2), 157–166. https://doi.org/10.1016/j.jaac.2016.11.005

Rothbart, M.K., Ziaie, H., O'Boyle, C. (1992). Self-regulation and emotion in infancy. In N. Eisenberg & R.A. Fabes (Eds.). In *Emotion and its regulation in early development: New directions for child development, No. 55: The Jossey-Bass education series* (Issue 55, pp. 7–23).

Roy, A. K., Fudge, J. L., Kelly, C., Perry, J. S. A., Daniele, T., Carlisi, C., Benson, B., Xavier Castellanos, F., Milham, M. P., Pine, D. S., & Ernst, M. (2013a). Intrinsic functional connectivity of amygdala-based networks in adolescent generalized anxiety disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *52*(3), 290-299.e2. https://doi.org/10.1016/j.jaac.2012.12.010

Roy, A. K., Fudge, J. L., Kelly, C., Perry, J. S. A., Daniele, T., Carlisi, C., Benson, B., Xavier Castellanos, F., Milham, M. P., Pine, D. S., & Ernst, M. (2013b). Intrinsic functional connectivity of amygdala-based networks in adolescent generalized anxiety disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. https://doi.org/10.1016/j.jaac.2012.12.010

Rudolph, M. D., Graham, A., Feczko, E., Miranda-Dominguez, O., Rasmussen, J., Nardos, R., Entringer, S., Wadhwa, P. D., Buss, C., & Fair, D. A. (2018). Maternal IL-6 during pregnancy can be estimated from the newborn brain connectome and predicts future working memory performance in offspring. *Nat Neurosci*, 1–36.

Ruocco, A. C., Amirthavasagam, S., Choi-Kain, L. W., & McMain, S. F. (2013). Neural correlates of negative emotionality in borderline personality disorder: An activation-likelihood-estimation meta-Analysis. *Biological Psychiatry*, *73*(2), 153–160. https://doi.org/10.1016/j.biopsych.2012.07.014

Sagaspe, P., Schwartz, S., & Vuilleumier, P. (2011). Fear and stop: A role for the amygdala in motor inhibition by emotional signals. *NeuroImage*, *55*(4), 1825–1835. https://doi.org/10.1016/j.neuroimage.2011.01.027

Sari, B. A., Koster, E. H. W., Pourtois, G., & Derakshan, N. (2016). Training working memory to improve attentional control in anxiety: A proof-of-principle study using

behavioral and electrophysiological measures. *Biological Psychology*, *121*, 203–212. https://doi.org/10.1016/j.biopsycho.2015.09.008

Schiller, D., & Delgado, M. R. (2010). Overlapping neural systems mediating extinction, reversal and regulation of fear. *Trends in Cognitive Sciences*, *14*(6), 268–276. https://doi.org/10.1016/j.tics.2010.04.002

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., Reiss, A. L., & Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci*, *27*(9), 2349–2356. https://doi.org/10.1523/JNEUROSCI.5587-06.2007

Shaw, D. S., Bell, R. Q., & Gilliom, M. (2000). A truly early starter model of antisocial behavior revisited. *Clinical Child and Family Psychology Review*, *3*(3), 155–172. https://doi.org/10.1023/A:1009599208790

Siegle, G. J., Thompson, W., Carter, C. S., Steinhauer, S. R., & Thase, M. E. (2007). Increased Amygdala and Decreased Dorsolateral Prefrontal BOLD Responses in Unipolar Depression: Related and Independent Features. *Biological Psychiatry*, *61*(2), 198–209. https://doi.org/10.1016/j.biopsych.2006.05.048

Silvers, J. A., Insel, C., Powers, A., Franz, P., Helion, C., Martin, R. E., Weber, J., Mischel, W., Casey, B. J., & Ochsner, K. N. (2017). VlPFC-vmPFC-Amygdala Interactions Underlie Age-Related Differences in Cognitive Regulation of Emotion. *Cerebral Cortex*, *27*(7), 3502–3514. https://doi.org/10.1093/cercor/bhw073

Slagt, M., Dubas, J. S., Deković, M., & van Aken, M. A. G. (2016). Differences in sensitivity to parenting depending on child temperament: A meta-analysis. *Psychological Bulletin*, *142*(10), 1068–1110. https://doi.org/10.1037/bul0000061

Smith, C. L., Diaz, A., Day, K. L., & Bell, M. A. (2016). Infant frontal electroencephalogram asymmetry and negative emotional reactivity as predictors of toddlerhood effortful control. *Journal of Experimental Child Psychology*, *142*, 262–273. https://doi.org/10.1016/j.jecp.2015.09.031

Smith, S., Bannister, P. R., Beckmann, C., Brady, M., Clare, S., Flitney, D., Hansen, P., Jenkinson, M., Leibovici, D., Ripley, B., Woolrich, M., & Zhang, Y. (2001). FSL: New tools for functional and structural brain image analysis. *NeuroImage*, *13*(6), 249. https://doi.org/10.1016/S1053-8119(01)91592-7

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, *17*(3), 143–155. https://doi.org/10.1002/hbm.10062

Spanglar, G., Schieche, M., Ilg, U., Maier, U., & Ackermann, C. (1994). Maternal sensitivity as an external organizer for biobehavioral regulation in infancy. *Developmental Psychobiology*, *27*(7), 425–437. https://doi.org/10.1002/dev.420270702

Sripada, R. K., King, A. P., Garfinkel, S. N., Wang, X., Sripada, C. S., Welsh, R. C., & Liberzon, I. (2012). Altered resting-state amygdala functional connectivity in men with posttraumatic stress disorder. *Journal of Psychiatry and Neuroscience*, *37*(4), 241–249. https://doi.org/10.1503/jpn.110069

Stansbury, K., & Gunnar, M. R. (1994). ADRENOCORTICAL ACTIVITY AND EMOTION REGULATION. *Monographs of the Society for Research in Child Development*, *59*(2–3), 108–134. https://doi.org/10.1111/j.1540-5834.1994.tb01280.x

Stein, M. B., Simmons, A. N., Feinstein, J. S., & Paulus, M. P. (2007). Increased

amygdala and insula activation during emotion processing in anxiety-prone subjects. *American Journal of Psychiatry*, *164*(2), 318–327. https://doi.org/10.1176/appi.ajp.164.2.318

Stifter, Cynthia (The Pennsylvania State University, University Park, PA, U., Willoughby, Michael (The University of North Carolina, Chapel Hill, NC, U., & Towe-Goodman, Nissa (The Pennsylvania State Univresity, University Park, PA, U. (2006). Agree or Agree to Disagree? Assessing the Convergence between Parents and Observers on Infant Temperament. *Infant and Child Development*, *17*(2008), 407–426. https://doi.org/10.1002/icd

Stifter, C. A., & Braungart, J. M. (1995). The Regulation of Negative Reactivity in Infancy: Function and Development. *Developmental Psychology*, *31*(3), 448–455. https://doi.org/10.1037/0012-1649.31.3.448

Sudikoff, E., Bertolin, M., Danielle, L., & Kaufman, D. (2015). Relationships between Executive Function and Emotional Regulation in Healthy Children. *Journal of Neurology and Psychology*, *S*(2), 8.

Sullivan, E. L., Holton, K. F., Nousen, E. K., Barling, A. N., Sullivan, C. A., Propper, C. B., & Nigg, J. T. (2015). Early identification of ADHD risk via infant temperament and emotion regulation: A pilot study. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *56*(9), 949–957. https://doi.org/10.1111/jcpp.12426

Svaldi, J., Griepenstroh, J., Tuschen-Caffier, B., & Ehring, T. (2012). Emotion regulation deficits in eating disorders: A marker of eating pathology or general psychopathology? *Psychiatry Research*, *197*(1–2), 103–111. https://doi.org/10.1016/j.psychres.2011.11.009

Tan, P. Z., Forbes, E. E., Dahl, R. E., Ryan, N. D., Siegle, G. J., Ladouceur, C. D., & Silk, J. S. (2012). Emotional Reactivity and Regulation in Anxious and Non-anxious Youth. *Journal of Child Psychology and Psychiatry*, *53*(2), 197–206. https://doi.org/10.1111/j.1469-7610.2011.02469.x.Emotional

Taylor, S. E., Eisenberger, N. I., Saxbe, D., Lehman, B. J., & Lieberman, M. D. (2006). Neural Responses to Emotional Stimuli Are Associated with Childhood Family Stress. *Biological Psychiatry*, *60*(3), 296–301. https://doi.org/10.1016/j.biopsych.2005.09.027

Taylor, S. F., & Liberzon, I. (2007). *Neural correlates of emotion regulation in psychopathology*. *11*(10). https://doi.org/10.1016/j.tics.2007.08.006

Thomas C., J., Campbell S., T., Tomfohr-Madsen, L., & Giesbrecht F., G. (2017). Developmental Origins of Infant Emotion Regulation: Mediation by Temperamental Negativity and Moderation by Maternal Sensitivity. *Developmental Psychology*, *53*(4), 611–628. https://doi.org/10.1037/dev0000279.supp

Thomas, E., Buss, C., Rasmussen, J. M., Entringer, S., Ramirez, J. S. B., Marr, M., Rudolph, M. D., Gilmore, J. H., Styner, M., Wadhwa, P. D., Fair, D. A., & Graham, A. M. (2019). Newborn amygdala connectivity and early emerging fear. *Developmental Cognitive Neuroscience*, *37*(December 2018), 100604. https://doi.org/10.1016/j.dcn.2018.12.002

Thomas, J. C., Letourneau, N., Campbell, T. S., Tomfohr-Madsen, L., & Giesbrecht, G. F. (2017). Developmental origins of infant emotion regulation: Mediation by temperamental negativity and moderation by maternal sensitivity. *Developmental Psychology*, *53*(4), 611–628. https://doi.org/10.1037/dev0000279

Thomson, K., Burnham, P., & Jonathan, R. (2015). Brief Report of Preliminary Outcomes of an Emotion Regulation Intervention for Children with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, 3487–3495. https://doi.org/10.1007/s10803-015-2446-1

Toda, S., & Fogel, A. (1993). Infant response to the still-face situation at 3 and 6 months. *Developmental Psychology*, *29*(3), 532–538. https://doi.org/10.1037//0012-1649.29.3.532

Townsend, J. D., Torrisi, S. J., Lieberman, M. D., Sugar, C. A., Bookheimer, S. Y., & Altshuler, L. L. (2013). Frontal-Amygdala connectivity alterations during emotion downregulation in bipolar i disorder. *Biological Psychiatry*, *73*(2), 127–135. https://doi.org/10.1016/j.biopsych.2012.06.030

Tozzi, L., Doolin, K., Farrel, C., Joseph, S., Keane, V. O., & Frodl, T. (2017). Journal of A ff ective Disorders Functional magnetic resonance imaging correlates of emotion recognition and voluntary attentional regulation in depression : A generalized psycho- physiological interaction study. *Journal of Affective Disorders*, *208*(October), 535–544. https://doi.org/10.1016/j.jad.2016.10.029

Tronick, E., Als, H., Adamson, L., Wise, S., & Brazelton, T. B. (1978). The Infant's Response to Entrapment between Contradictory Messages in Face-to-Face Interaction. *Journal of the American Academy of Child Psychiatry*, *17*(1), 1–13. https://doi.org/10.1016/S0002-7138(09)62273-1

Ursache, A., Blair, C., Granger, D. A., Stifter, C., & Voegtline, K. (2014). Behavioral reactivity to emotion challenge is associated with cortisol reactivity and regulation at 7, 15, and 24 months of age. *Developmental Psychobiology*, *56*(3), 474–488.

https://doi.org/10.1002/dev.21113

Ursache, A., Blair, C., Stifter, C., Voegtline, K., & Family Life Project Investigators. (2012). Emotional reactivity and regulation in infancy interact to predict executive functioning in early childhood. *Developmental Psychology*, *49*(1), 127–137. https://doi.org/10.1037/a0027728

van der Horn, H. J., Liemburg, E. J., Aleman, A., Spikman, J. M., & van der Naalt, J. (2016). Brain Networks Subserving Emotion Regulation and Adaptation after Mild Traumatic Brain Injury. *Journal of Neurotrauma*, *33*(1), 1–9. https://doi.org/10.1089/neu.2015.3905

Viviani, R. (2013). Emotion regulation, attention to emotion, and the ventral attentional network. *Frontiers in Human Neuroscience*, *7*(November), 1–24. https://doi.org/10.3389/fnhum.2013.00746

Wakschlag, L. S., Briggs-Gowan, M. J., Carter, A. S., Hill, C., Danis, B., Keenan, K., McCarthy, K. J., & Leventhal, B. L. (2007). A developmental framework for distinguishing disruptive behavior from normative misbehavior in preschool children. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *48*(10), 976–987. https://doi.org/10.1111/j.1469-7610.2007.01786.x

Wang, J., Vachet, C., Rumple, A., Gouttard, S., Ouziel, C., Perrot, E., Du, G., Huang, X., Gerig, G., & Styner, M. (2014). Multi-atlas segmentation of subcortical brain structures via the AutoSeg software pipeline. *Frontiers in Neuroinformatics*, *8*(February), 7. https://doi.org/10.3389/fninf.2014.00007

Wang, L., Paul, N., Stanton, S. J., Greeson, J. M., & Smoski, M. J. (2013). Loss of sustained activity in the ventromedial prefrontal cortex in response to repeated stress

in individuals with early-life emotional abuse: Implications for depression vulnerability. *Frontiers in Psychology*, *4*(JUN), 1–9. https://doi.org/10.3389/fpsyg.2013.00320

Weinberg, M. K., & Tronick, E. Z. (1994). Weinberg, M. K., & Tronick, E. Z. (1994). Beyond the face: An empirical study of infant affective configurations of facial, vocal, gestural, and regulatory behaviors. Child development, 65(5), 1503-1515.. *Child Development*, *65*(5), 1503–1515.

Weinberg, M. K., & Tronick, E. Z. (1998). The impact of maternal psychiatric illness on infant development. *Journal of Clinical Psychiatry*, *59*(SUPPL. 2), 53–61.

Weiss, N. H., Tull, M. T., Davis, L. T., Searcy, J., Williams, I., & Gratz, K. L. (2015). A Preliminary Experimental Investigation of Emotion Dysregulation and Impulsivity in Risky Behaviours. *Behaviour Change*, *32*(02), 127–142. https://doi.org/10.1017/bec.2015.5

White, L. K., Moore, T. M., Calkins, M. E., Wolf, D. H., Satterthwaite, T. D., Leibenluft, E., Pine, D. S., Gur, R. C., & Gur, R. E. (2017). An Evaluation of the Specificity of Executive Function Impairment in Developmental Psychopathology. *Journal of the American Academy of Child and Adolescent Psychiatry*, *56*(11), 975-982.e3. https://doi.org/10.1016/j.jaac.2017.08.016

Wilcox, C. E., Pommy, J. M., & Adinoff, B. (2016). Neural circuitry of impaired emotion regulation in substance use disorders. *American Journal of Psychiatry*, *173*(4), 344–361. https://doi.org/10.1176/appi.ajp.2015.15060710

Willcutt, E. G., Doyle, A. E., Nigg, J. T., Faraone, S. V., & Pennington, B. F. (2005). Validity of the executive function theory of attention-deficit/ hyperactivity disorder:

A meta-analytic review. *Biological Psychiatry*, *57*(11), 1336–1346. https://doi.org/10.1016/j.biopsych.2005.02.006

Wolfe, C. D., & Bell, M. A. (2007). The integration of cognition and emotion during infancy and early childhood: Regulatory processes associated with the development of working memory. *Brain and Cognition*, *65*(1), 3–13. https://doi.org/10.1016/j.bandc.2006.01.009

Wu, M., Liang, X., Lu, S., & Wang, Z. (2017). Infant motor and cognitive abilities and subsequent executive function. *Infant Behavior and Development*, *49*(March), 204–213. https://doi.org/10.1016/j.infbeh.2017.09.005

Wu, Q., & Feng, X. (2020). Infant emotion regulation and cortisol response during the first 2 years of life: Association with maternal parenting profiles. *Developmental Psychobiology*. https://doi.org/10.1002/dev.21965

Wu, X., Lin, P., Yang, J., Song, H., Yang, R., & Yang, J. (2016). Dysfunction of the cingulo-opercular network in first-episode medication-naive patients with major depressive disorder. *Journal of Affective Disorders*, *200*, 275–283. https://doi.org/10.1016/j.jad.2016.04.046

Xie, X., Mulej, S., Schmid, G., Meng, C., Doll, A., Wohlschläger, A., Finke, K., Förstl, H., Zimmer, C., Pekrun, R., Schilbach, L., Riedl, V., & Sorg, C. (2016). NeuroImage How do you make me feel better ? Social cognitive emotion regulation and the default mode network. *NeuroImage*, *134*, 270–280. https://doi.org/10.1016/j.neuroimage.2016.04.015

Xu, Z., Adler, A., Li, H., Pérez-Cuesta, L. M., Lai, B., Li, W., & Gan, W. B. (2019). Fear conditioning and extinction induce opposing changes in dendritic spine remodeling

and somatic activity of layer 5 pyramidal neurons in the mouse motor cortex. *Scientific Reports*, *9*(1). https://doi.org/10.1038/s41598-019-40549-y

Yamamoto, T., Toki, S., Siegle, G. J., Takamura, M., Takaishi, Y., Yoshimura, S., Okada, G., Matsumoto, T., Nakao, T., Muranaka, H., Kaseda, Y., Murakami, T., Okamoto, Y., & Yamawaki, S. (2017). Increased amygdala reactivity following early life stress: A potential resilience enhancer role. *BMC Psychiatry*, *17*(1), 1–11. https://doi.org/10.1186/s12888-017-1201-x

Yushkevich, P. A., Piven, J., Hazlett, H. C., Smith, R. G., Ho, S., Gee, J. C., & Gerig, G. (2006). User-guided 3D active contour segmentation of anatomical structures: Significantly improved efficiency and reliability. *NeuroImage*, *31*(3), 1116–1128. https://doi.org/10.1016/j.neuroimage.2006.01.015

Zelazo & Cunningham, W., P. D. (2007). Executive function: Mechanisms underlying emotion regulation. *Handbook of Emotion Regulation*, *12*(11), 135–158. https://doi.org/10.1177/1545968309354536

Zelazo, P. D. (2020). Executive Function and Psychopathology: A Neurodevelopmental Perspective. *Annual Review of Clinical Psychology*, *16*, 431–454. https://doi.org/10.1146/annurev-clinpsy-072319-024242

Zelazo, P. D., & Carlson, S. M. (2012). Hot and Cool Executive Function in Childhood and Adolescence: Development and Plasticity. *Child Development Perspectives*, *6*(4), 354–360. https://doi.org/10.1111/j.1750-8606.2012.00246.x