INTERPARENTAL CONFLICT AND NEURAL FUNCTIONING IN INFANCY:

AN FMRI STUDY

by

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DISSERTATION ABSTRACT

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Early life stress (ELS) affects the developing brain and impacts capacity for self-regulation and risk for psychopathology. The high spatial resolution of functional magnetic resonance imaging (fMRI) confers an advantage for studying specific neural regions posited to link ELS with subsequent functioning. The first chapter in this dissertation reviews the literature establishing the feasibility and utility of fMRI research with infants and young children. This chapter examines methodological issues and outlines the potential for this technique to make unique contributions to understanding how ELS influences brain development.

The next two chapters present results from a study that employed a functional activation paradigm and resting state functional connectivity MRI (rs-fcMRI) to examine associations between a common source of ELS, non-physical interparental conflict, and neural functioning during infancy. The functional activation paradigm focused on emotional tone of voice as a stimulus relevant to interparental conflict, which is likely salient to infants. Higher levels of interparental conflict (as reported by mothers) were associated with infants (6 to 12 months of age) showing greater reactivity to very angry versus neutral tone of voice in neural regions associated with processing and regulation

of stress and emotion (hypothalamus and rostral anterior cingulate cortex). The rs-fcMRI analysis examined coordinated neural functioning in the absence of stimuli, focusing on the amygdala as a key region for understanding the impact of ELS and the posterior cingulate cortex as part of a group of regions that show higher levels of activity in the absence of stimuli (the default network). The results replicate previous work characterizing the default network in infants and provide novel evidence for the functional connectivity of the amydgala and amygdala subregions during infancy. Interparental conflict was associated with variation in the connectivity of both regions. Thus levels of interparental conflict were associated with neural reactivity to a stressor-relevant stimulus and with patterns of coordinated neural functioning in the absence of such stimuli. These results provide support for the utility of using fMRI with infants to examine early emerging associations between common forms of ELS and brain functioning.

This dissertation includes previously published and co-authored material.

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CHAPTER I

GENERAL INTRODUCTION

Brain development occurs at an incredibly rapid rate over the first several years of life as exemplified by a four-fold increase in brain volume from birth to four years of age (Courchesne et al., 2000) and a 70-80% increase in synaptic density (or connection between neurons) in frontal and primary sensory cortical areas during the first year and half of life (Huttenlocher & Dabholkar, 1997). This development is comprised of processes, such as synapse formation and elimination, that are guided by environmental input (Knudsen, 2004; Majewska & Sur, 2006). Early environmental input thus influences the neurobiological foundations for behavioral functioning across multiple domains (S. E. Fox, Levitt, & Nelson, 2010). These early years of life therefore represent a time of unique opportunity to support healthy development, as well as a time of immense vulnerability.

This vulnerability has been addressed through an extensive literature examining the influences of early life stress (ELS) and the potential for intervention and prevention programs to reduce the likelihood of negative outcomes. Myriad sources of ELS, including low socioeconomic status (SES), parental psychopathology, variation in the quality of caregiving and conflictual family environments, have been shown to be associated with behavioral and biological indices of development (Crockenberg, Leerkes, & Lekka, 2007; Goodman et al., 2011; Hackman & Farah, 2009; Loman, Gunnar, & The Early Experience, Stress, 2010; Pechtel & Pizzagalli, 2011). The National Scientific Counsel on the Developing Child has organized this vast ELS literature into a theoretical

framework that incorporates knowledge about developmental processes and neurobiological systems involved in stress reactivity and regulation. Within this model, experiences of ELS range from positive to tolerable to toxic depending not on the stressor itself, but on an individual's response to the stressor (National Scientific Council on the Developing Child, 2005). In infancy and early childhood, when regulatory capacity is limited, this response is understood to be greatly influenced by contextual factors, and particularly by the presence of supportive caregivers to provide comfort, and facilitate development of adaptive coping strategies (Loman et al., 2010).

The classification of positive stress draws on understanding the stress response as an adaptive means of mobilizing resources to cope with environmental challenges (McEwen, 1998). Positive stress involves moderate arousal of the stress response for a brief period, typically in response to normative experiences, such as going to a new school (National Scientific Council on the Developing Child, 2005). Tolerable stress involves intense arousal of the stress response followed by recovery. Events that are severe, but not chronic, such as witnessing an accident, may elicit tolerable stress. In contrast, toxic stress involves intense arousal of the stress response system with limited opportunity for recovery (National Scientific Council on the Developing Child, 2005). Intense and chronic arousal of the stress response system is understood to have detrimental effects on neural systems that underlie emotional processing and regulatory capacity critical for functioning across multiple domains (Loman et al., 2010). ELS becomes toxic when it influences development of neurobiological systems in a manner that increases risk for physical and mental illness (National Scientific Council on the Developing Child, 2005, 2007).

Neurobiological Framework for the Impact of ELS: Animal Models

The current understanding of how ELS influences neurobiological systems from genes to neural circuitry comes from a confluence of research with animal models and humans. One of the most well studied systems that plays a central role in the potential toxicity of ELS is the hypothalamic-pituitary-adrenal (HPA) axis. The considerable focus on this system is partly attributable to the end product of the HPA-axis, hormones called glucocorticoids (GCs; corticosterone in rodents; cortisol in primates), which in the short term increase access to energy to cope with threat, but also have the capacity to pass through the blood-brain barrier, modulate gene expression, and in chronically high doses, damage neurons (McEwen, 2008; Sapolsky, Romero, & Munck, 2000). Consistently high levels of GCs during specific developmental periods appear to have a profound effect on both the HPA-axis and associated neural circuitry involved in emotional reactivity and regulatory processes (for reviews see Levine, 2005; Sánchez, Ladd, & Plotsky, 2001; Tottenham & Sheridan, 2010; Ulrich-Lai & Herman, 2009).

Activation and regulation of the HPA-axis in response to psychological stressors involves specific cortical and limbic regions. The amygdala is involved in activating the HPA-axis in response to psychological stress, while the hippocampus and parts of the medial prefrontal cortex (MPFC) play important roles in providing negative feedback, which allows for termination of the stress response (Herman et al., 2003; Ulrich-Lai & Herman, 2009). Depending on input from these regions (primarily through indirect connections), the hypothalamus initiates an HPA-axis response by signaling the pituitary with corticotropin releasing hormone (CRH) (Ulrich-Lai & Herman, 2009). Accordingly, there is a high density of GC receptors in the hippocampus, amygdala and MPFC (Reul &

De Kloet, 1985; Sánchez, Young, & Plotsky, 2000), making these regions particularly vulnerable to the effects of chronically high levels of GCs. In turn, changes in the functioning of these regions have implications both for future HPA-axis functioning and for stress reactivity involving the autonomic nervous system (Ulrich-Lai & Herman, 2009).

A large body of animal literature has documented both effects of ELS on the functioning of these regions, and aspects of their developmental trajectories that confer vulnerability during the first years of life. For example, the amygdala contains high levels of CRH receptors (Gray & Bingaman, 1996), which appear to play an important role in amygdala induced activation of the stress response (Adamec & McKay, 1993; Swiergiel, Takahashi, & Kalin, 1993). The immature amygdala is characterized by higher levels of CRH receptors in comparison to the mature amygdala, leading to a 200-fold increase in sensitivity to CRH during early development (Baram & Hatalski, 1998). While this lowered threshold for amygdala activation in response to stress induced CRH release may be adaptive in the context of encoding large amounts of new information about emotionally salient aspects of the environment, it also confers vulnerability for heightened stress reactivity.

The effects of stress on the amygdala can generally be described as increasing excitability, although specific changes are unique to different amygdaloid nuclei. In the central amygdala (CeA), a nucleus with extensive connections with the hypothalamus and brainstem nuclei involved in autonomic reactivity, chronic social stress, acute restraint stress and disruption of caregiving in rodents leads to upregulation of CRH (Albeck et al., 1997; Caldji, Diorio, & Meaney, 2000; Hsu, Chen, Takahashi, & Kalin, 1998).

Upregulation of CRH in the amygdala is in turn associated with the long term behavioral consequences of repeated maternal separations in rodents including anxiety and depressive-like behavioral phenotypes (Sánchez et al., 2001). The basolateral complex of the amygdala (BLA) demonstrates alterations in the balance between excitation and inhibition following aversive stimuli and administration of CRF or GCs (Pelletier, Likhtik, Filali, & Paré, 2005; Rainnie et al., 2004; Roozendaal, McEwen, & Chattarji, 2009). Due to its connectivity with multiple key neural regions, including the hippocampus, MPFC, and striatum, changes in neuronal excitation and synchronization in the BLA have implications for the functioning of neural circuitry central to the stress response system and to the formation of emotional memories (Roozendaal et al., 2009).

Similar to the amygdala, aspects of the early development of the hippocampus may confer specific vulnerability to early environmental stress. For example, research with rodents has demonstrated that the ratio of GC receptor subtypes in the hippocampus changes over the course of development (Vasquez et al., 1996). Tottenham and Sheridan (2010) suggest that the ratio during infancy creates a greater likelihood for consistent occupation of the low affinity receptor, which plays a critical role in the negative feedback of the HPA-axis. Disruption of negative feedback can lead to increased exposure to GCs, which appears to impact the structure and functioning of the hippocampus in addition to other neural regions.

Additionally, the structure and function of neurons in the hippocampus are vulnerable to chronic exposure to GCs even in adult animals (Magarinos & McEwen, 1995), and this vulnerability is likely enhanced during periods of development involving neurogenesis and the growth of axons (Huot, Plotsky, Lenox, & McNamara, 2002). In the

rodent, a stress hyporesponsive (SHRP) period has been documented in which it is difficult to initiate a neuroendocrine stress response. The SHRP coincides with periods of rapid neurogenesis and axonal development in certain regions of the hippocampus (Sapolsky & Meaney, 1986). However, the SHRP can be disrupted by ELS in the form of repeated 3-hour maternal separations which induce HPA-axis reactivity during this period (Huot et al., 2002). Adult rodents exposed to this paradigm during the neonatal period evidence reduction in the density of axons in these hippocampal regions and associated deficits in a hippocampal mediated memory task in adulthood (Huot et al., 2002).

The MPFC is composed of multiple functionally distinct subregions, and regulation of the neuroendocrine stress response differs by subregion. Research with rodents suggests that a region of the dorsal MPFC (DMPFC), the prelimbic cortex, inhibits the HPA-axis specifically with regard to terminating the response to a psychological stressor, while a region of the ventral MPFC (VMPFC), the infralimbic cortex, plays a role in activation of the HPA-axis in response to psychological stress (Radley, Arias, & Sawchenko, 2006; reviewed by Ulrich-Lai & Herman, 2009). While less research has been conducted in non-human primates, for whom the MPFC is structurally and functionally closer to the human MPFC (Öngür & Price, 2000) evidence suggests that, similar to rodents, the VMPFC, and specifically subgenual prefrontal cortex (PFC), is involved in activation of the HPA-axis (Jahn et al., 2010). More generally, the patterns of connectivity between various MPFC subregions and other limbic regions involved in regulation of the neuroendocrine stress response, suggest a central role for the MPFC in coordinating the combined effects of these regions on the stress response (Ulrich-Lai & Herman, 2009; Herman & Mueller, 2006).

Despite the long developmental time course of the MPFC stretching out over several decades (Casey, Giedd, & Thomas, 2000; Fuster, 2002; Mills, Lalonde, Clasen, Giedd, & Blakemore, 2012; Shaw et al., 2008), research also indicates increased vulnerability in the first several years of life. For example, in a rodent model, repeated maternal separations during the postnatal period was found to result in increased levels of a specific transcription factor (affecting expression of a 5-HT receptor subtype, CRH and brain-derived neurotrophic factor) in the MPFC (Uchida et al., 2010). Increased levels of this transcription factor in the MPFC during the postnatal period in turn predicted greater stress reactivity and depression like symptoms in adulthood. However, high levels of this transcription factor in the MPFC in adulthood did not impact subsequent stress reactivity or symptomatology (Uchida et al., 2010).

Converging evidence from research with rodent and non-human primates indicates that ELS is also associated with down regulation of GC receptor expression in the PFC (MPFC in rodents (reviewed by Sánchez et al., 2001) and dorsolateral PFC (DLPFC) and ventrolateral PFC (VLPFC) in non-human primates (Patel, Katz, Karssen, & Lyons, 2008)). Decreased expression of low affinity GC receptors in the PFC appears to be involved in dysregulation of the HPA-axis and specifically with impairments in the negative feedback mechanism (Mizoguchi, Ishige, Aburada, & Tabira, 2003). Downregulation of these low affinity GC receptors in the MPFC in rodents is one of the specific physiological changes associated with long term behavioral outcomes of maternal separation including anxiety and depressive-like behaviors (Caldji et al., 2000). Lower levels of basal neuronal activity have been observed in the MPFC of adult rodents

following maternal separation during the postnatal period (Stevenson, Marsden, & Mason, 2008).

The Influence of ELS on Brain Development in Humans

Research with humans has built on the animal literature and provides converging evidence for the effects of ELS on neural regions involved in regulation of the HPA-axis. This work has employed magnetic resonance imaging (MRI), a technique that provides the spatial resolution necessary to examine the structure (sMRI) and function (fMRI) of specific cortical and subcortical brain regions of interest. Findings with sMRI have included increased amygdala volume in children with histories of early institutional care (characterized by instability and poor quality caregiving; Mehta et al., 2009; Tottenham et al., 2010), and reduced right orbitofrontal cortex volume in 12-year-old children with early experiences of physical abuse (Hanson et al., 2010). Studies employing fMRI have demonstrated increased amygdala reactivity to fearful faces in school-aged children with histories of early institutionalization compared to children raised in their biological families (Tottenham et al., 2011), and enhanced activation in dorsal anterior cingulate (ACC) and several other PFC regions during a task involving cognitive control in adolescents with histories of early maltreatment (Mueller et al., 2010).

These neural differences associated with ELS appear to have implications for socioemotional and regulatory functioning outside of the MRI scanner. Tottenham and colleagues reported that the heightened amygdala reactivity to fearful faces in children with histories of institutionalization mediated the relationship between their early experiences and decreased eye-contact during a dyadic interaction task, indicative of difficulties with social functioning (Tottenham et al., 2011). Smaller orbital frontal cortex

volume in children with histories of physical abuse was associated with difficulties in relationships with family members and with functioning adaptively in school (Hanson et al., 2010). These studies provide important initial empirical evidence for the connections between ELS, brain development and socioemotional and regulatory functioning in children.

There are several important themes to consider as research with humans continues to build on animal models to advance understanding of how ELS effects brain development. First, MRI studies into the effects of ELS have frequently focused on severe stressors, such as maltreatment and institutionalization, with less research examining the effects of more moderator stressors. Notable exceptions include two recent sMRI studies that provide converging evidence for as association between low SES and smaller hippocampal volumes in children (Hanson, Chandra, Wolfe, & Pollak, 2011; Noble, Houston, Kan, & Sowell, 2012). Studies utilizing peripheral measures of neuroendocrine and autonomic nervous system functioning provide additional evidence for the influence of more moderate sources of ELS, such as nonphysical conflict between parents (Davies, Sturge-Apple, Cicchetti, & Cummings, 2007; Moore, 2010) and variation in caregiving that does not fall within the range of maltreatment (Dettling, Parker, Lane, Sebanc, & Gunnar, 2000; Gunnar, Kryzer, Van Ryzin, & Phillips, 2010), on neurobiological development. Animal models of ELS also indicate that variation in the type and duration of a stressor lead to distinct effects on neurobiological development and long term functioning (Levine, 2005; Sánchez, Aguado, Sánchez-Toscano, & Saphier, 1998; Sánchez et al., 2001). Utilizing MRI methods to examine specific neural

correlates of a range of sources of ELS in humans, from more moderate to severe, will be important for understanding differences between toxic, tolerable and positive stress.

Second, as MRI research into effects of ELS in humans remains in the early stages, it will be important to consider the involvement of additional brain regions that have not necessarily been highlighted by the animal literature. In the research to date, multiple brain regions have evidenced differences in structure and functioning associated with ELS depending on the specific measure employed and the stressor of interest. For example, in addition to results involving PFC regions, Mueller and colleagues reported differences in activation patterns in post-central gyrus, striatum and insula for adolescents with histories of early maltreatment (compared to adolescents with no history of maltreatment) performing a cognitive control task (Mueller et al., 2010). In addition to volumetric differences in amygdala and hippocampus, Noble and colleagues demonstrated an association between SES and volumetric differences in brain regions important for language (left superior temporal gyrus (STG) and left inferior frontal gyrus (IFG)) moderated by child age (Noble et al., 2012). Specifically, lower SES predicted smaller volumes in these regions for older children (Noble et al., 2012). Thus while focusing on regions involved in HPA-axis reactivity and regulation provides a useful starting point with a strong theoretical and empirical foundation in the animal literature, it will be very important to conduct whole brain analyses in humans to consider the involvement of different neural regions (Hart & Rubia, 2012). This will be particularly important as researchers begin to examine the neural level of effects of a range of sources of ELS including more moderate stressors.

It has also become increasingly clear that examining coordinated functioning among brain regions, as opposed to any region in isolation, will be critical for understanding the effects of ELS on brain development. Researchers have begun to understand normative brain development in terms of changes in the coordinated functioning, or functional connectivity, of multiple brain regions that form neural networks (Fair et al., 2007, 2009; Gao, Zhu, et al., 2009; Gao et al., 2011). Although not well studied in children, research with adults suggests that stress may disrupt the coordinated functioning of specific neural networks not just in response to a stimulus or task (Admon et al., 2009; Fonzo et al., 2010; van Wingen, Geuze, Vermetten, & Fernández, 2011) but also at rest (Bluhm, Williamson, Osuch, et al., 2009; Rabinak et al., 2011; Sripada et al., 2012; van Marle, Hermans, Qin, & Fernández, 2010). Disrupted patterns of functional connectivity may in turn have important implications for mental health. Mental health disorders, including those closely tied to the stress response system, such as major depression (Anand et al., 2005; Anand, Li, Wang, Lowe, & Dzemidzic, 2009; Bluhm, Williamson, Lanius, et al., 2009; Greicius et al., 2007) and post-traumatic stress disorder (PTSD; (Bluhm, Williamson, Osuch, et al., 2009; Lanius et al., 2010; Rabinak et al., 2011; Sripada et al., 2012), appear to be characterized by patterns of functional connectivity that differ from healthy controls. Such variation in functional connectivity has been shown to predict development of symptoms (Lanius et al., 2010), and with the use of advanced analytic methods, to allow for accurate classification of mental health disorders (Fair et al., 2013; Zeng et al., 2012). Examination of functional connectivity thus has great potential for increasing understanding of how ELS affects risk for subsequent difficulties with mental health.

Finally, in the interest of informing prevention and intervention it will be important to understand not only distal outcomes involving neural structure and functioning, but the potentially unique effects of stress during specific developmental time frames. The animal literature provides examples of how the same stressor applied on different days produces different effects on the stress response system (Van Oers, De Kloet, & Levine, 1998). The levels of stress model emphasizes response to a stressor as determining the toxicity (National Scientific Council on the Developing Child, 2005). This response is influenced both by contextual factors, such as caregiving, and by the neurobiological foundations of the stress response. Normative developmental changes in both of these factors likely create periods in which the potential toxicity of specific forms of ELS varies. Earlier examination of neural development in the context of ELS may shed light on such sensitive periods, gradations between positive, tolerable and toxic stressors, and more generally, on the mechanisms through which the environment influences development.

Overview of Subsequent Chapters

This dissertation addresses the potential for MRI, and specifically blood oxygen level dependent (BOLD) fMRI, during infancy to increase understanding of the effects of ELS. The high spatial resolution of fMRI confers a unique advantage for examining the functioning of neural regions and networks identified in the animal literature, and increasingly in human samples of older children and adults, as important for understanding how ELS increases risk for difficulties across multiple domains. fMRI methods during infancy also have potential for identifying additional neural regions and networks beyond those identified in animal models, which may play a role in the

mechanisms through which ELS impacts development in humans. Despite the advantages, research with fMRI during infancy has remained relatively uncommon due to methodological challenges, including the need for participants to remain still to collect high quality images. While sedation has been used to conduct MRI scans with infants in clinical settings, it is not generally appropriate for research purposes. However, several researchers have pioneered the method of conducting fMRI scans during natural sleep for infants and very young children (Anderson et al., 2001; Dehaene-Lambertz, Dehaene, & Hertz-Pannier, 2002; Redcay, Kennedy, & Courchesne, 2007). An emerging body of literature indicates the potential for collecting high quality fMRI data with infants and young children during natural sleep.

The first chapter (Chapter II) introduces BOLD fMRI during infancy as a promising method for increasing understanding of development in the context of various sources of ELS. Due to the relative novelty of and challenges associated with conducting fMRI with infants during natural sleep, this chapter begins with a review of the literature establishing the feasibility and utility of this method. The review includes studies employing functional activation paradigms to examine neural processing of specific stimuli, and resting state functional connectivity (rs-fcMRI) to characterize the coordinated functioning of neural regions in the absence of specific stimuli. Methodological considerations, including the influence of sleep state on the BOLD signal, effects of motion and the selection of a developmentally appropriate atlas are discussed. Finally, specific ways in which both functional activation paradigms and rs-fcMRI with infants can build on existing literature into the effects of ELS on brain development are explored.

The study presented in Chapter III employed a functional activation paradigm during natural sleep to examine associations between a common source of familial stress, non-physical interparental conflict, and 6-12 month-old infants' neural processing of emotional tone of voice. Emotional tone of voice was conceptualized as a stimulus relevant to interparental conflict that may be salient to infants. The primary question in this study was whether interparental conflict experienced by infants is associated with neural responses to emotional tone of voice, particularly very angry speech. A secondary question was whether, regardless of the level of interparental conflict, infants demonstrate distinct patterns of neural processing for different emotional tones of voice during sleep. These questions have implications both for the sensitivity of infants to emotional tone of voice during sleep, and for the link between a common form of ELS and neural processing of a stressor relevant stimulus, angry tone of voice.

The study presented in Chapter IV employed rs-fcMRI during natural sleep with the same sample of infants to examine associations between nonphysical interparental conflict, and coordinated functioning of neural regions in the absence of a specific stimulus. The rs-fcMRI analyses were conducted on data from a separate fMRI scan during which no stimuli were presented. Analyses focused on the amygdala and amygdala subregions as central to existing models of how ELS impacts development. The posterior cingulate cortex (PCC) was also a focus of analysis as an early emerging component of the default network, a group of brain regions that demonstrate higher levels of activity in the absence of stimulus presentation (Gusnard & Raichle, 2001; Raichle et al., 2001), and which may serve as a neural marker for the effects of ELS (Daniels, Frewen, McKinnon, & Lanius, 2011). This study first sought to replicate previous work

on default network connectivity in infants, and to provide novel evidence for resting state functional connectivity of the amygdala and amygdala subregions in infants. We then examined whether interparental conflict was associated with differences in the resting state functional connectivity of the amygdala and PCC. Further, this study examined whether effects of interparental conflict on amygdala connectivity differed by amygdala subregion due to the animal literature indicating distinct effects of ELS for different amygdala subregions.

It should be noted that discrepancies in the presentation of results for Chapters III and IV are due to the compatibility requirements for the different software programs used for these analyses. To use existing programs created by Washington University for rs-fcMRI analyses it was necessary to transform all images to a different image format and to an adult brain atlas. The details of this process are provided in Chapter IV. Chapter V provides a general discussion of the chapters presented in Chapters II, III and IV.

This dissertation contains previously published and co-authored material. The study described in Chapter III has been published in *Psychological Science* and is co-authored with P. A. Fisher and J. H. Pfeifer (Graham, Fisher, Pfeifer, 2013). The review in Chapter II is co-authored with P. A. Fisher, J. H. Pfeifer and W. Lin, and the study in Chapter IV is co-authored with P. A. Fisher, J. H. Pfeifer and D. A. Fair.

CHAPTER II

UNDERSTANDING HOW EARLY LIFE STRESS SHAPES THE DEVELOPING BRAIN: THE ROLE OF FMRI

P. A. Fisher, J. H. Pfeifer and W. Lin are co-authors on this manuscript. I wrote this manuscript, with my co-authors providing comments and editorial assistance.

Introduction

The consequences of ELS are increasingly understood in terms of their impact on neurobiological systems that modulate the homeostatic stress response, including neural regions and networks central to emotional reactivity and regulation. Functional magnetic resonance imaging (fMRI) represents a powerful tool for examining how key neural regions develop under the influence of psychological stress ranging from more extreme forms, such as maltreatment and institutionalization, to more moderate forms, such as conflict between parents. Although fMRI has not been widely utilized during infancy and toddlerhood due to methodological challenges, existing work provides support for its feasibility and efficacy in characterizing neural functioning during these early developmental periods. This methodology has great potential to build on the framework created by fMRI research with older children and adults for examining the neural underpinnings of adaptive and maladaptive responses to ELS.

The use of fMRI methods with infants and toddlers in research settings is a relatively recent phenomenon, with the early studies in this field conducted just over a

decade ago (Anderson et al., 2001; Dehaene-Lambertz et al., 2002). Collecting high quality MR images requires a participant to remain still throughout one or more scans, lasting 4-8 minutes on average. In childhood and beyond, this is accomplished through providing instructions, practice and incentives. For infants, sedation was originally the method of choice, relegating scanning to clinical settings. However, several researchers have pioneered the technique of conducting fMRI scans with infants during natural sleep in order to obtain high quality images without utilizing sedation (Anderson et al., 2001; Dehaene-Lambertz et al., 2002; Redcay et al., 2007). The success of studies utilizing the natural sleep method has led to increasing utilization of fMRI with infants in research contexts.

The current review focuses specifically on blood oxygen level dependent (BOLD) fMRI. Although structural MRI (sMRI) provides invaluable information with regard to multiple aspects of neural development, functional imaging provides a unique additional source of information not captured through structural imaging. For example, as will be discussed in more detail below, preterm infants without prominent structural neural abnormalities evidence differences in how brain regions are functionally connected (Smyser et al., 2010). In addition, effects of early exposure to stress may manifest first in differences in neural functioning which subsequently lead to the structural differences in brain regions observed in children and adults with histories of early adversity (Tottenham & Sheridan, 2010). It should also be noted that high resolution structural MRI scans are necessary for localizing activity in functional scans, and thus the two measures are well suited to be used in tandem to examine neural development from multiple perspectives. In comparison to other functional neuroimaging modalities used with infants, such as

functional near infrared spectroscopy (fNIRS) and electroencephalography (EEG), fMRI makes a unique contribution due to its higher spatial resolution and capacity for assessment of subcortical regions likely to play a key role in stress reactivity.

The use of fMRI during infancy and toddlerhood has several notable advantages that allow it to build on existing sMRI and fMRI research with older children and adults examining neural level effects of ELS. First, it can provide information about changes in neural functioning specifically attributable to early environmental stress as opposed to processes of recovery, development of compensatory mechanisms and onset of stress-related psychopathology that may occur later in development. Second, through longitudinal designs within a proximal time frame of ELS, this work can lend insight into the mechanisms through which stressors impact neural functioning and subsequent socioemotional development. Finally, this work has the potential to inform prevention and intervention work during early critical developmental periods by providing both i) insight into the specific challenges associated with different types of environmental stress, and ii) a means of examining the neural mechanisms through which interventions affect change.

This review focuses on two fMRI methods widely used with pediatric and adult populations: functional activation paradigms and resting state functional connectivity MRI (rs-fcMRI). Functional activation paradigms are used to understand task or stimulus specific neural functioning, while rs-fcMRI allows for examination of functional connectivity among neural regions in the absence of a specific task. These methods have begun to be explored during infancy and toddlerhood, but have not yet been used to examine consequences of ELS during these developmental periods. First, the feasibility

of using functional activation paradigms with infants and toddlers will be discussed. Studies demonstrating feasibility with regard to adequate sample size and capacity to detect neural processing of sensory stimuli during sleep are reviewed. Next, rs-fcMRI is considered as a potent method for examining the development of functional neural networks beginning in infancy. A discussion of substantive methodological issues pertaining to functional activation paradigms and rs-fcMRI with infants comprises the subsequent section. These issues include effects of sleep state, motion and the choice of an appropriate atlas. The final two sections focus on existing fMRI research as a guide for the potential applications of both functional activation paradigms and rs-fcMRI for understanding early neural development in the context of various sources of environmental stress. Both of these methodologies have potential to make unique contributions to understanding adaptive and maladaptive responses to ELS beginning in infancy.

BOLD fMRI with Infants and Toddlers

Functional Activation Paradigms

Research utilizing functional activation paradigms during natural sleep has involved infants and toddlers ranging from 7 days postnatal (Anderson et al., 2001) to 4 years of age (Redcay et al., 2007). Feasibility has been demonstrated in terms of obtaining adequate sample sizes to address study aims. For example, Dehaene-Lambertz and colleagues (2002) collected functional activation data with 20 infants (2-3 months of age) while Redcay and colleagues (Redcay, Haist, & Courchesne, 2008) reported a sample size of 20 with 10 younger toddlers (mean age 21 months) and 10 older toddlers (mean age 39 months). In the Dehaene-Lambertz and colleagues study (2002) this sample

size was sufficient to identify statistically significant activation in sensory and language processing regions in a random-effects analysis. In the Redcay and colleagues study (2008) the sample size of 10 per group was sufficient to detect statistically significant age group differences in language processing, although statistical thresholds were lowered for certain contrasts. (Issues around statistical thresholds and correction for multiple comparisons are discussed in the context of methodological issues and details for individual studies are provided in Table 2.1).

The merit of functional activation paradigms during natural sleep for infants and toddlers has been demonstrated with regard to observations of neural activity in expected sensory regions indicating basic processing of stimuli. Researchers examining sleeping neonates reported BOLD response to tonal auditory stimuli in expected auditory regions, although the signal was decreased from baseline for 9 of 14 infants (Anderson et al., 2001). However, Dehaene-Lambertz and colleagues observed significant, positive activation and an adult-like hemodynamic response function (HRF) in the auditory cortex of 2-3-month old infants during presentation of speech (Dehaene-Lambertz et al., 2002). Dehaene-Lambertz and colleagues suggest that their use of naturalistic sounds as opposed to a tone may have contributed to their observation of positive BOLD activation in the auditory cortex.

More recently, Blasi and colleagues (2011) reported that the HRF in the auditory cortex of 3-7-month old infants peaks earlier (at approximately 3 seconds post stimulus onset) than a typical adult HRF. To obtain more accurate, but unbiased HRF parameters for analysis at the single subject level, Blasi and colleagues averaged the HRF from the auditory cortex of all subjects excluding the specific subject in the model. Using this

Table 2.1. Review of Functional Activation Studies with Infants and Toddlers During Natural Sleep

Article	Population	N	Scans Lost	Stimuli	Motion	Atlas	Statistical Threshold	Main Findings
Anderson et al., 2001	Healthy term and preterm infants (M=21 days), adult males (M= 34 years)	9 Term; 5 Preterm; 4 Adults	6 infants for motion or not enough images	Tone 60-80 dB (gradually increased and decreased to prevent startle)	Frame removal: images with > 2mm or 3 degrees; Scans excluded: < 50% of images retained or SD > 1 for translation or rotation	NA	% Signal Change	1) BOLD signal decrease to auditory for 9 and increase for 5 infants; 2) Signal change in B superior temporal regions
Blasi et al., 2011	Healthy infants (M=159 days)	21	24 sleep difficulties	Nonvocal (environmental); Nonspeech vocalizations (Neutral, Happy, Sad)	Rigid body transform based on spin-history correction	Infant DL and transformed to Tal	p<0.005 uncorrected, cluster size>=3 voxels	1) Age + associated with L STG activity to Neutral>Nonvoice; 2) L Insula and gyrus rectus activity for Sad>Neutral
Dehaene-Lambertz et al., 2002	Healthy infants (M=79 days)	20 (6 awake, 5 asleep, 9 both)	6 fussiness; 5 artifact or problems with experiment	Forward speech (children's stories); Backward speech (reversed forward)	Frame removal: visual examination	Infant DL and transformed to MNI	voxel p<0.01, cluster p<0.05 corrected for multiple comparisons	1) All sounds > rest: L STG; 2) Forward>Backward: L angular gyrus and mesial parietal lobe; 3) Forward>Backward for Awake>Asleep: R PFC
Dehaene-Lambertz et al., 2010	Healthy infants (M=72 days)	7 (1 awake, 2 asleep, 4 both)	6 fussiness; 11 no activation to sound>rest	Classical music; Mother's speech; Stranger's Speech; For all-Repeated and Varied	Frame removal: visual examination; Adjusted analysis to limit influence of large deviation in signal (>=2.5 SD)	Infant DL	Random-effects: voxel p<0.01, cluster p<0.05 corrected; Fixed-effects: voxel p<0.001, cluster p<0.05 corrected	1) Repetition Suppression Effect: L STG; 2) Laterality effect speech>music in L planum temporale for music>speech in R planum temporale; 3) Mother>stranger in B anterior PFC, L posterior temporal and rest>mother in R amygdala,R insula, R STS, R occipital sulcus
Redcay & Couchesne, 2008	Children with provisional ASD (M=34.9 months), age- (CA; M=35.7 months), and mental age (MA; M=19.6 months) controls	13 ASD; 12 CA; 11 MA	8 sleep difficulties; 1 motion; 2 did not meet criteria for ASD	Simple forward speech; complex forward speech; backward speech	Frame removal: Images with sum of root mean square of parameters > 0.4	Tal	p<.01, corrected at 960 mm^3; Trend level p<.05, corrected at 384 mm^3	1) Forward>rest, both MA>ASD and CA>ASD: frontal, temporal, parietal, occipital regions and cerebellum; 2) Forward>rest for ASD > CA: right hemisphere activation; 3) Receptive language + correlated with R frontal and temporal region activation in ASD group
Redcay et al., 2007	Healthy children (M=45.8 Months)	19 (12 with visual, 13 with auditory)	Auditory: 2 for motion and 6 for waking; Visual: 9 for waking	Vocal (nonspeech); Nonvocal (environmental); Tones; Flashing lights	Frame removal: Images with sum of root mean square of parameters > 0.4; Scans excluded: > 10% of images lost	Tal	p<.005, cluster corrected at 740mm^3	1) Nonvocal>vocal: frontal, temporal (R STG), occipital (B lingual gyrus) and cerebellum 2) Tones>Vocal: frontal, temporal (R STG), and parietal and cerebellum; 3) Rest<visual: B cuneus, B lingual gyrus, L superior occipital gyrus
Redcay et al., 2008	Healthy toddlers (M=21 months) and 3-year-olds (M=39 months)	10 toddlers; 10 3-year-olds	5 sleep difficulties; 1 experimenter error; 2 did not attend	Simple forward speech; complex forward speech; backward speech	Summed distance of translational and rotational parameteres > 0.3	Tal	Voxel p < .01, cluster p< .05, (cluster volume = 960 mm^3); Relaxed for certain contrasts to voxel p<.05.	1) Forward>rest for 3-yo>toddler: B STG, frontal, parietal and occipital regions; 2) Forward>rest for toddler>3-yo: Frontal, parietal, occipital and subcortical regions (no temporal regions)

Note. Studies involving sedation are not included. All experiments conducted during natural sleep with the exception of Dehaene-Lambertz et al., 2002, Dehaene-Lambertz et al., 2010, in which infants were scanned awake and during natural sleep. Atlas abbreviations: Infant DL=Template created by Dehaene-Lambertz et al., 2002; Tal= Talairach & Tournoux. B=Bilateral; L=left; R=right; STG=superior temporal gyrus; ASD=Autism Spectrum Disorder.

adjusted HRF this study reported positive BOLD activation during non-speech vocal stimuli and nonvocal environmental sounds not in primary auditory cortex, but in auditory processing regions of the middle temporal gyri (Blasi et al., 2011). Further support for a positive BOLD response in auditory processing regions during natural sleep comes from a study of 2-to-4 year-olds indicating activation in STG across various types of sounds including tones, nonvocal naturalistic sounds and vocal sounds (Redcay et al., 2007). This study also provided evidence for different patterns of neural reactivity dependent on the type of auditory stimulus presented (Redcay et al., 2007; Table 2.1).

In addition to positive BOLD activation in expected auditory processing regions, patterns of neural activation in sleeping infants indicate registration of speech and vocal properties. Dehaene-Lambertz and colleagues (Dehaene-Lambertz et al., 2002) observed greater activation in the left angular gyrus and precuneus in response to forward versus backward speech in sleeping 2-3 month old infants. In adults these regions have been associated with differentiating between words and non-words (Binder et al., 2000) and with memory retrieval of verbal information (Krause et al., 1999; Nyberg, Forkstam, Petersson, Cabeza, & Ingvar, 2002) respectively. Similar results from a study with sleeping 2-year old children also indicated involvement of the precuneus and angular gyrus in differentiating between forward versus backward speech during natural sleep (Redcay et al., 2008). Interestingly this study also demonstrated developmental changes in language processing from 2-3 years of age, such that for 3 year-olds the brain regions demonstrating greater activation to forward versus backward speech, including STG, were more in line with those observed in adult samples (Redcay et al., 2008). Recent findings also indicate differential neural processing of vocal non-speech based on

emotion category for 3-to-7-month-old infants during natural sleep. Specifically, during sad versus neutral vocalizations, infants demonstrated greater activation in the insula and part of the orbitofrontal cortex (Blasi et al., 2011).

The importance of examining responses to sensory stimuli during natural sleep on an individual subject level was raised in a recent paper by Dehaene-Lambertz and colleagues (Dehaene-Lambertz et al., 2010). The authors reported that less than half of two-month-old infants in their sample demonstrated activation in auditory brain regions when contrasting stimulus presentation to no sound at a statistical threshold of alpha less than .05 uncorrected for multiple comparisons. They suggest that developmental characteristics of the BOLD signal at this early age may account for the lack of observed activation in auditory regions for some infants. There are multiple factors that may influence whether or not a sensory response is evident at a neural level, including sleep state, scanner noise and developmental changes in the BOLD response. In the early stages of this field it therefore seems appropriate to report the presence or absence of activation indicative of basic sensory processing at an individual level prior to proceeding to group analyses.

Resting State Functional Connectivity MRI

While functional activation paradigms during natural sleep can be utilized to characterize neural functioning in the context of specific stimuli, rs-fcMRI provides a means of examining how these regions function in concert with other regions in ways that are not specific to certain stimuli or tasks. This methodology is used to identify correlated neural activity during rest, as indexed through changes in the BOLD signal during an fMRI scan with no stimulus or task (Biswal, Yetkin, Haughton, & Hyde, 1995). Low

frequency changes in the BOLD signal observed in the *absence* of stimuli presentation (task-independent) likely reflect endogenous neural activity (Biswal et al., 1995). Correlations between activation patterns over time are posited to represent connectivity between neural regions. Recent findings provide support for this conceptualization, with patterns of functional connectivity frequently in line with direct or indirect structural connectivity between brain regions (Damoiseaux & Greicius, 2009; Greicius, Supekar, Menon, & Dougherty, 2009; Honey et al., 2009; Shmuel & Leopold, 2008). Importantly, functional neural networks involved during cognitive task performance are also observed during rest through rs-fcMRI methods (Fox & Raichle, 2007). The default network, a group of brain regions that are functionally connected in the adult brain and demonstrate higher levels of activity during rest versus focused tasks (Raichle et al., 2001), has also been a primary focus of rs-fcMRI studies.

For developmental research, rs-fcMRI has the distinct advantage of documenting coordinated neural functioning across the whole brain in the absence of tasks, which are challenging to adjust appropriately for a wide age range (Casey, Galvan, & Hare, 2005; Uddin, Supekar, & Menon, 2010). The absence of stimuli also makes this methodology particularly well suited for infants undergoing fMRI scans during natural sleep. Researchers using rs-fcMRI have indicated the utility of this methodology for studying the functional development of neural networks across a wide age range (Fair et al., 2007, 2008, 2009; Supekar et al., 2010; Supekar, Musen, & Menon, 2009). For example, Fair and colleagues (Fair et al., 2007, 2008, 2009) documented a pattern of developmental changes in the functional connectivity of neural networks from childhood to adulthood

that is characterized by increasing long-range connectivity (between anatomically distant regions) and decreasing short-range (or localized) connectivity.

A relatively similar pattern has been observed across the first 2 years of life with regard to both increasing long-range connectivity (between anatomically distant regions) and decreasing short-range connectivity over time (Gao et al., 2009, 2011; See Table 2.2). Changes across this earlier age range occur at an extremely rapid rate, such that from 2-weeks to 1-year of age the number of regions overlapping with the adult default network that evidence significant functional connectivity during natural sleep increases from 6 to 13 (Gao, Zhu, et al., 2009). Development does not appear to be linear, with many measures, including the number of connections showing statistically significant changes in strength and the efficiency of a large network of 90 regions of interest, indicating less change across the 1 to 2 year age range in comparison to the first year of life (Gao et al., 2011). Both environmental input and normative changes within the developing brain, such as myelination, are posited to account for the observed changes in connectivity during development (Fair et al., 2009) with different processes likely at work depending on the age range of interest (Gao et al., 2011). These results suggest that rapid developmental changes in coordinated neural functioning during the first two years of life and extending through childhood can be captured by rs-fcMRI.

Recent work has drawn attention to the effects of subject motion on developmental rs-fcMRI results (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Van Dijk, Sabuncu, & Buckner, 2012). This issue and the proposed solutions will be discussed in more detail in the next section. However, it should be noted that this work focuses on the biasing effects of motion in research spanning childhood to adulthood,

during which time motion decreases systematically with age. The potential for confounding motion effects and developmental changes in studies of sleeping infants and toddlers will likely be different as movement during scanning is not expected to track with age in the same manner during this time frame. Specifically, while an awake adult is expected to have greater self-control and therefore move less than a child during scanning, there is no reason to expect that a sleeping toddler will move less than a sleeping newborn during scanning.

Methodological Considerations

Successful scan completion. In addition to the promising foundational work using both functional activation paradigms and rs-fcMRI during natural sleep with infants, significant methodological challenges and considerations require attention. First, infants are required to sleep in a novel environment with the loud noises of the MRI machine as well as potential disturbances arising from functional activation paradigm stimuli. Varying success rates have been reported in terms of the number of infants who complete fMRI scanning protocols during sleep. In addition to examining overall success rates, it may be important to consider which aspects of a scanning paradigm cause infants to wake (Tables 2.1 and 2.2). For example, of the infants not completing an auditory experiment in a study of 3-7 month olds with an overall success rate of 47%, 46% did not fall asleep or woke up during preparation for the scan, 29% woke up in the scanner before scanning started and 25% work up during scanning (Blasi et al., 2011). Due to potential differences in success rates for challenging populations, different age groups and specific stimuli presentation, it will also be important to assess whether the capacity to complete scanning protocols during natural sleep is associated with differences in

Table 2.2. Review of Resting State Functional Connectivity Studies with Infants and Toddlers During Natural Sleep

Article	Population	N	Scans Lost	Analysis Type	Motion	Atlas	Statistical Threshold	Findings
Dinstein et al., 2011	Toddlers with autism (M= 29 months), language delay (LD; M=19 months), and typically developing (M=28 months)	29 with autism, 13 with LD, 30 typical	No information provided, data from previous studies	Regressed out stimuli; Anatomically defined ROIs; Whole brain seed-based correlations	Frame removal: criteria not specified	Tal	r>.3 for whole brain seed correlations; Two-tailed t-test p<.05 for group differences.	1) Weaker interhemispheric connectivity for IFG and STG in autism; 2) Autism classification based on connectivity: 21/29 correctly and 7/43 incorrectly identified; 3) IFG connectivity + associated with expressive language and - associated with autism severity
Fransson et al., 2009	Healthy infants delivered by caesarean (M=40 weeks GA)	19	2 for motion	Probabalistic approach to ICA (PICA)	Frame removal: criteria not specified; Scans excluded: criteria not specified	Infant DL	p<.05 (activation versus null across whole brain and time series)	1) 6 networks identified (% variance explained): medial occipital(1.63%), B sensorimotor (3.18%), B temporal (0.70%), parietal (4.78%), anterior PFC (1.60%), B basal ganglia (0.1%); 2) PCC/precuneus to bilateral parietal connectivity observed
Fransson et al., 2011	Healthy infants from Fransson et al., 2009; Healthy adults (M=29 years)	18 Infants; 18 Adults	See Fransson et al., 2009	Voxel-based graph theoretical analysis; Whole brain seed-based correlations of hub regions	For infants see Fransson et al., 2009	Neonatal (Kazemi et al., 2007)	Peak Z-values > 15mm apart for hubs; p<.0005 for seed-based connectivity; Networks at 0.20 < r < 0.40, iteratively	1) Infants: hubs and networks in sensory and motor cortices except for DLPFC, insula and parietal lobule; 2) Adults: hubs and networks in heteromodal cortex espeically in default and frontoparietal attention networks; 3) Small-world network organization in infants
Fransson et al., 2012**	Healthy infants from Fransson et al., 2009; Healthy adults (M=29 years)	18 Infants; 17 adults	See Fransson et al., 2009	Spherical ROIs based on adult and infant atlas coordinates; Power analysis	For infants see Fransson et al., 2009	Neonatal (Kazemi et al., 2007)	NA	1) Infants>adults for average power-law exponent; 2) For adults power-law exponents higher in associative networks and for infants higher in primary sensory networks
Gao 2009	Healthy neonates (M=24 days), 1-yo's (M=13 months,), 2-yo's (M=25 months) and adults (M=30 years)	20 neonates; 24 1-yo's; 27 2-yo's; 15 adults	No information	ICA; graph theory	Frame removal: Criteria not specified, but based on screening unpreprocessed images for abrupt BOLD signal changes	Individual Infant and then MNI	For default network definition: Z>1 to determine voxel-wise connectivity; For correlation matrices p<.05 FDR corrected	1) # default regions identified: Neonates 6; 1-yo 10, 2-yo 13; 2) MPFC and PCC/Rsp identified in all groups with volume of cluster - associated with age; 3) Nonlinear development of default network; 4) PCC/Rsp as default network hub in neonates
Gao 2011	Healthy neonates (M=23 days), 1-yo's (M=13 months), and 2-yo's (M=24 months)	51 neonates; 50 1-yo's; 46 2-yo's	No information	ROIs from adult atlas based on sulcal patterns; graphy theory	Frame removal: Criteria not specified, but based on screening unpreprocessed images for abrupt BOLD signal changes	Individual Infant and then MNI	Whole brain analysis: p<.05 FDR; Regional analysis: p<.05 uncorrected	1) Connection density increases from neonate to 1-yo, but stable from 1-yo to 2-yo; 2) Strength of connectivity for anatomically distant nodes increases with age; 3) Increase in small-worldness with age; 4) B insula consistent hub across age groups
Lin 2008	Healthy neonates (Range=2-4 weeks), 1-yo's, and 2-yo's	16 neonates; 12 1-yo's; 7 2-yo's	18 for motion; 14 premature birth, medical problems, or parent disorder	Manually drawn ROIS; whole brain seed-based correlations	Frame removal: Criteria not specified, but based on screening unpreprocessed images for abrupt BOLD signal changes	Individual Infant	z<1; p<.05 corrected for t-test comparison of the 2 ROIs and for ANOVA of the 3 groups	1) Difference between maximum and minimum signal intensity: 2-yo>neonates; 2) Average strength of connectivity and brain volume evidencing connections to visual and sensorimotor regions increases with age
Liu et al. 2008	Healthy infants (M=12.8 months)	11	From larger structural MRI study with 63% scan success	PICA; Bold time series and power spectra computed for each component	Frame removal: Images with >1 mm or > 1 degree of motion;	Infant DL	NA	1) 16-36 spatially independent components for each subject with 3 in sensorimotor area; 2) More intra- versus interhemispheric connectivity.
Smith et al., 2011	Preterm infants <30 weeks (Range=36-44 weeks PMA for scan); Healthy term infants	Preterm: 10 low and 10 high stress; 10 term	Significant cerebral injury (N not reported)	Whole brain seed-based correlations (ROIs not specified); Group maps compared qualitatively	Frame removal: criteria not specified	Not reported	Qualitative comparisons for rs-fcMRI maps	1) Interhemispheric correlations with R temporal lobe in low stress and term infants, but not high stress infants; 2) Total brain injury + associated with stress; 3) R temporal lobe anistropy - correlated with stress
Smyser et al., 2010	Preterm Infants scanned longitudinally; Term infants (Range=2-3 days)	28 preterm with longitudinal data; 10 term	8 for prominent neuropathology; 10 for motion	Spherical ROIs based on adult atlas coordinates; Whole brain seed-based correlations	Frame removal: Software used to identify frames with motion based on signal change; Scans excluded: < 4 minutes	Individual Infant and then Tal	For t-tests of correlation maps Z>1.65, p<.05; Correlations between connectivity and age p<.05	1) Increasing interhemispheric connectivity with age; 2) Term infants>term age preterm infants: local, long range and interhemispheric connectivity; 3) Connectivity between MPFC and PCC in half of term control infants, but not in preterm infants

Note. Studies involving sedation are not included. All experiments conducted during natural sleep with the exception of Smyser et al., 2010, in which infants were scanned awake and during natural sleep. **Combined EEG and fMRI study. Atlas abbreviations: Infant DL=Template created by Dehaene-Lambertz et al., 2002; Tal= Talairach & Tournoux; Individual Infant=template based on single infant image. ICA=Independent component analysis; PMA=postmenstrual age; GA=gestational age; B=Bilateral; L=left; R=right; MPFC=medial prefrontal cortex; PCC=posterior cingulate cortex; STG=superior temporal gyrus; IFG=inferior frontal gyrus.

infant temperament, symptomatology or other factors that may bias the results of studies. However, the success of auditory functional activation paradigms in samples of toddlers with ASD (reviewed by Pierce, 2011), which is often associated with sensory sensitivity (Lane, Young, Baker, & Angley, 2010), provides support for the potential utility of such paradigms even in high risk infants and toddlers.

Sleep. Another important issue involves understanding the effects of sleep and of variations in sleep stage on results from functional activation paradigms and rs-fcMRI studies. Methodological challenges have thus far prevented the simultaneous use of EEG and fMRI in infants and toddlers to allow for tracking sleep state during scans with this age group. However, pertinent to auditory functional activation paradigms, ERP studies with infants provide support for comparable neural processing of auditory stimuli during sleep and wake (Cheour, Ceponiené, et al., 2002), with preservation of response amplitude and latency across different sleep stages (Martynova, Kirjavainen, & Cheour, 2003). Moreover, it appears that learning involving auditory and basic somatosensory stimuli occurs during sleep for infants (Cheour, Martynova, et al., 2002; Fifer et al., 2010; Reeb-Sutherland et al., 2011), suggesting that these stimuli are processed beyond a basic, sensory level even during sleep.

However, simultaneous EEG and fMRI studies have been conducted with adults, leading to insights regarding the BOLD signal response to auditory stimuli during sleep. This work indicates a potentially reduced area of activation in the auditory cortex during sleep versus wakefulness, but consistent amplitude of activation across sleep stages (Czisch et al., 2002; Portas et al., 2000). The possibility of a reduced area of activation during sleep warrants consideration when determining the sample sizes necessary for

adequate statistical power. Patterns of activation involved in distinguishing between different types of auditory stimuli also demonstrate similarities across sleep and awake states (Portas et al., 2000). For example, a similar pattern of activation to a subject's name versus a tone, involving the middle temporal gyrus (MTG) and orbitofrontal cortex, has been observed across sleep and wakefulness (Portas et al., 2000). These results are in line with findings of sleeping infants and toddlers showing distinct patterns of neural activation in response to different types of auditory stimuli (Redcay et al., 2007) including different emotional tones (Blasi et al., 2011). In contrast, differences in activation patterns between sleep and wake have been reported for regions not involved in auditory processing. Czisch and colleagues reported deactivation in the visual cortex in response to presentation of a story during sleep stages 1 and 2, which they interpreted as a potential sleep protective mechanism (Czisch et al., 2002). Lower levels of activation during sleep compared to wake in higher level processing regions (including the parietal, prefrontal and cingulate cortices) have also been observed in response to auditory stimulation (Portas et al., 2000). These results are consistent with findings of decreased activity in the parietal, prefrontal and cingulate cortices during REM sleep (Maquet et al., 1996). Thus sleep protective mechanisms may result in deactivation in certain sensory processing regions, and lower levels of activation in regions involved in higher levels of processing. This variation depending on sleep state should be contextualized within findings that differences in attentional focus (Sander et al., 2005) or arousal also impact results of fMRI studies with awake subjects (Logothetis, 2008).

Effects of sleep state also represent an important consideration for rs-fcMRI scans. Recent studies have documented preservation of functional connectivity between

default network regions across the transition from an awake state to light sleep (Larson-Prior et al., 2009). However, functional connectivity between cortical regions and between the hippocampus and default network regions has been observed to break down during slow wave sleep (Andrade et al., 2011; Spoormaker et al., 2010). Interestingly, studies to date have consistently demonstrated intact resting state functional connectivity between default network regions in sleeping infants (Gao, Zhu, et al., 2009; Gao et al., 2011; Smyser et al., 2010). This may be due to differences in sleep architecture between infants and adults (Kahn, Dan, Groswasser, Franco, & Sottiaux, 1996; Scher, 2008). In line with this idea, sleeping infants have been shown to demonstrate consistency across sleep stages for ERP components that decrease significantly in amplitude for adults in deeper stages of sleep (Martynova et al., 2003). Moreover, fMRI studies with sleeping adults often utilize some degree of sleep deprivation (to facilitate sleep in the scanner; Andrade et al., 2011; Tanaka et al., 2003), which may impact patterns of resting state functional connectivity as well as neural responses to stimuli presented during sleep. Alternatively, functional connectivity between resting state network regions in infants during awake states may be much more robust, although it has not been possible to assess this with fMRI at present. It should also be noted that aspects of the scanning environment, such as scanner noise, have been associated with decreased magnitude of activation in default network regions for awake adults (Gaab, Gabrieli, & Glover, 2008). The methodological challenges related to sleep stage warrant further investigation with the hope of developing practical solutions for gaining a better understanding of existing and future data.

Motion. As noted previously, subject motion constitutes an extremely important methodological consideration in developmental fMRI studies. Recent work has revealed that even small of amounts of motion (below the accepted standards for high-quality fMRI data) have systematic effects on results of rs-fcMRI analyses (Power et al., 2012; Van Dijk et al., 2012). Motion appears to bias results toward fewer/weaker long range patterns of connectivity and more/greater local patterns of connectivity (Power et al., 2012; Van Dijk et al., 2012). The authors of recent work regarding the effects of motion suggest the need to revisit developmental studies that indicate increasing long range connectivity with age and state that this work is underway with regard to their previously published developmental studies (Power et al., 2012). These findings represent a significant advance in the field of rs-fcMRI as the authors provide a practical solution for examining potential effects of motion and accounting for such effects (Power et al., 2012). However, questions remain about this proposed solution and the field has not yet put forth clear guidelines for handling motion with rs-fcMRI data (Kelly, Biswal, Craddock, Castellanos, & Milham, 2012). Moreover, patterns of motion may be markedly different for sleeping infants and toddlers compared to awake subjects. Sleeping infants have been noted to startle at the beginning of a new scan sequence and settle down as the scan progresses, although efforts have been made to reduce startle by playing consistent background scanner noise (Blasi et al., 2011; Dehaene-Lambertz et al., 2002). A sleeping infant may also have one or two large, circumscribed movements while adjusting sleeping position during a scan, which may require a different approach in comparison to a scan sequence with small amounts of motion throughout. Although averaging across multiple trials may diminish effects of motion to some degree in functional activation

paradigms as compared to rs-fcMRI, it is clear that similar efforts to understand confounds of motion are critical for all types of fMRI research (Power et al., 2012; Van Dijk et al., 2012; Yuan et al., 2009).

Atlas space. Another key methodological consideration of interest for both fMRI and rs-fcMRI research with infants and young children is the choice of an appropriate atlas, which provides a basis for bringing the images of each participant's brain into a common space to allow for group statistical analyses. A predominant way in which atlases are used involves non-linear transformations of individual subjects' MR images to align with the atlas, a process known as normalization. The choice of an atlas is of great importance because the atlas is used to identify the type and anatomical location of the brain tissue that is the source of the signal in BOLD fMRI.

Several approaches have been taken thus far in the infant and toddler fMRI literature with pioneering researchers in this area utilizing creative solutions in the absence of existing atlases for age groups of interest. For research with toddlers focused on ASD, the adult Talaraich atlas has been used for normalization (Dinstein et al., 2011; Eyler, Pierce, & Courchesne, 2012; Redcay & Courchesne, 2008; Redcay et al., 2008). The authors provide evidence that variability of individuals' image alignment with the central sulcus within the toddler age-group is similar to the within group variability seen when normalizing adult images to this atlas (Redcay et al., 2008). However, they note that the coordinates of the Talaraich atlas do not indicate specific neural regions for the toddler group with as much accuracy as in adult samples (Redcay et al., 2008). This technique thus necessitates the use of anatomical landmarks to identify the location of the BOLD signal for the toddler group and therefore does not have the benefit of enabling

easier comparison between adult and infant fMRI results. Additionally, this technique may be problematic because the normalization procedure involves stretching infant brain images to fit an adult brain atlas. As an infant brain image is composed of fewer voxels than an adult brain image, this can lead to less independence among voxels. This is particularly true for studies with younger infants as the neonatal brain is approximately one-half the volume of the adult brain (Knickmeyer et al., 2008).

Other problems with the use of adult templates for infants and young toddlers have come to light and spurred the use of more age-specific atlases. For example, evidence suggests that the use of an adult or even a pediatric atlas with infant MR images (including those of neonates, one and two-year olds) can lead to misclassification of brain tissue due to the significant developmental changes in the brain over the first several years of life (Altaye, Holland, Wilke, & Gaser, 2008; Kazemi, Moghaddam, Grebe, Gondry-Jouet, & Wallois, 2007; Shi et al., 2011), which is improved by using an age-appropriate infant atlas (Altaye et al., 2008; Kazemi et al., 2007; Shi et al., 2011). In light of the problems with the use of an adult or pediatric atlas designed for older children, some researchers have created an atlas based on several subjects acquired in the age range of interest for the particular study (Dehaene-Lambertz et al., 2010, 2002; Gao, Zhu, et al., 2009; Gao et al., 2011). This approach allows for a focus on the developmental age range of interest and does not require stretching images to an adult size brain. However, creating an atlas based on one or two individuals, as opposed to averaging across a larger number of brains, can lead to biases based on the particular morphology of the chosen individual's brain. Moreover, the continued use of different atlases across different

studies will lead to difficulties in drawing comparisons across studies and conducting meta-analyses as the field grows.

More recently, researchers have created high quality, publicly available atlases for infants within various age ranges (Fonov, Evans, Mckinstry, Almli, & Collins, 2009; Sanchez, Richards, & Almli, 2012; Shi et al., 2011). This represents a promising solution that allows for comparison across studies within a specific age range. One of these sets of atlases is particularly noteworthy for providing age-appropriate atlases, including conversion algorithms for coordinates that correspond to frequently used adult atlases, for the neonatal periods up through adulthood (Fonov et al., 2009). Even with these advancements, the best solution for making comparisons across age groups remains unclear. As rapid brain development is evident in MR images across the first two years of life (Knickmeyer et al., 2008) researchers have indicated the importance of using fine grained atlases for each 3 month period or greater during the first year of life (Almli, Rivkin, & McKinstry, 2007; Sanchez et al., 2012). It may therefore be most appropriate to register to a specific atlas for each age group and then transform to a common child or adult atlas if necessary for making comparisons across developmental ages. However, research into the effects of such transformations will be important. Atlases created with longitudinal samples (Shi et al., 2011) may be important for considering developmental changes as opposed to atlases constructed with cross sectional data. With the use of an infant atlas it is important to note that the smaller number of voxels will affect correction for multiple comparisons and lead to statistical thresholds that are noticeably different from those appropriate for adult studies.

fMRI in the Context of Other Developmental Research Methods

The use of fMRI during infancy and toddlerhood will provide an especially potent tool when used in conjunction with the well-refined behavioral research methods and peripheral measures of nervous system functioning frequently used in infant research, including behavioral coding of emotion regulation strategies (Crockenberg & Leerkes, 2004) and measurement of autonomic nervous system activity (preejection period and respiratory sinus arrhythmia; Alkon et al., 2006) in response to a variety of tasks and potential stressors. The specific advantages and disadvantages of fMRI are also complementary to other neuroimaging techniques for infants including EEG and fNIRS. For example, EEG and fNIRS have superior temporal resolution in comparison to fMRI and can also be conducted quietly (in contrast to noisy fMRI sequences). EEG and fNIRS can also be conducted with awake infants engaged in a variety of tasks, which allow for results that may generalize more readily to real world contexts (Lloyd-Fox et al., 2009; Lloyd-Fox, Blasi, & Elwell, 2010). However, fMRI provides the unique advantage of higher spatial resolution throughout the brain, and can better assess responses in subcortical areas thought to play a key role in stress neurobiology. Moreover, fMRI data are acquired in conjunction with high resolution anatomical scans of 1mm resolution and lower, which are then coregistered to the fMRI data (and used for normalization to an atlas) to allow for fairly accurate anatomical localization. The capacity to obtain relatively high resolution images of functional activation throughout the brain may be particularly important for the early stages of this field as *a priori* hypotheses about specific brain regions require a foundation of empirical work. As with these other neuroimaging techniques, the level of complexity involved in fMRI methods is extremely

high allowing for multiple sources of error in measurements. Thus, convergent evidence across modalities (e.g. Fransson et al., 2012) will be crucial for advancing the field.

Examining Effects of ELS with fMRI During Natural Sleep

Functional Activation Paradigms

Lessons from research into developmental disorders. Although functional activation paradigms have not previously been applied with infants in the context of ELS, work with infants at risk for developmental disorders indicates the potential utility for understanding emerging deficits in specific domains. Researchers utilizing functional activation paradigms with toddlers at risk for developing autism spectrum disorders (ASDs) are suggestive of early biological markers of ASD and provide a model for the early neurodevelopmental trajectory of this disorder (Pierce, 2011). This existing body of work has been reviewed in depth by Pierce (2011) and will therefore not be summarized in detail in the present review**.** However, several key points are relevant with regard to the potential advantages of utilizing functional activation paradigms during infancy and toddlerhood. First, this work has allowed for differentiation between neurodevelopmental problems due to residual effects of coping with ASD versus neurodevelopmental markers that emerge prior to the onset of various behavioral symptoms (Pierce, 2011). The effects of early exposure to stress can be considered in an analogous fashion with regard to the initial impact on neural functioning which likely precedes the emergence of behavioral deficits, which may in turn be associated with further changes in neural functioning (or structure) in various domains. A recent review of the neuroimaging literature documenting effects of child maltreatment has highlighted the difficulty of distinguishing sequelae of child maltreatment from neural level effects of psychiatric symptomatology

and use of psychotropic medication, which occur at disproportionately high rates in those who have experienced high levels of early adversity (Hart & Rubia, 2012).

A second relevant point drawn from the ASD literature is that researchers utilizing functional activation paradigms to understand the emergence of ASD have been able to draw conclusions about a specific core domain of interest relevant to the disorder: linguistic processing (Pierce, 2011; Redcay & Courchesne, 2008). Functional activation paradigms focused on domains of interest in terms of the effects of ELS may lead to increasing specificity regarding both the neural regions and domains impacted by stress. For example, researchers have elucidated patterns of neural functioning underlying behavioral differences in cognitive control for children with a history of maltreatment (Mueller et al., 2010) and emotional reactivity and regulation for children with a history of early institutionalization (Tottenham et al., 2011) or a high risk family environment (Taylor, Eisenberger, Saxbe, Lehman, & Lieberman, 2006). However, it remains unclear whether differences in neural functioning and connectivity among the regions highlighted by these studies, including the amygdala, VLPFC and dorsal ACC, represent core features of exposure to ELS during or immediately following the stressor, when prevention and treatment strategies may be most potent.

Examples of prospective longitudinal work from the adult literature. Research with adults provides examples of how prospective longitudinal studies employing functional activation paradigms provide insight into neural functioning within a more proximal time frame of a stressor and indicate potential neural mechanisms underlying adaptive or maladaptive responses to stress. Although these studies have frequently involved military combat, which seems remote from common sources of early

adversity, they nonetheless provide a useful framework to consider. Admon and colleagues (2009) examined neural reactivity to photographs with medical, military or civilian content in a group of men and women during their first week of training (9 months prior to deployment), and again 9 months into their deployment as combat paramedics. They examined whether changes in neural reactivity to stressor-relevant stimuli (medical content) predicted growth in stress related symptoms. They found that greater initial amygdala reactivity (prior to military service), as well as increased hippocampal reactivity and decreased functional coupling of hippocampal and VMPFC activity in response to medical content predicted growth in symptoms of stress related disorders over the 18 month period. Their findings indicate that hyperactivity of the amygdala may be a predisposing factor to stress vulnerability, while the role of the hippocampus in stress related symptomatology can better understood through examining changes in reactivity and functional connectivity over the course of stress exposure. Recent work with a functional activation paradigm targeting risk taking and reward with combat paramedics similarly indicates that heightened amygdala reactivity to risk appears to be a predisposing factor to development of post-traumatic stress disorder (PTSD) symptoms (Admon et al., 2012). Interestingly, the results of this study indicated that decreased nucleus accumbens activity in response to reward over time in combination with pre-existing heightened amygdala reactivity to risk most accurately predicted increases in symptomatology after stress exposure (Admon et al., 2012).

Prospective longitudinal work with functional activation paradigms in adults has also provided insight into longitudinal changes in neural processing of emotional stimuli that may be indicative of an adaptive response to a circumscribed period of severe stress.

Focusing on combat soldiers deployed for 4 months who did not develop PTSD, van Wingen and colleagues documented an increase in amygdala reactivity to angry and fearful faces from pre-deployment to a short term follow-up, with a subsequent return to baseline approximately 22 months after returning from deployment (Van Wingen et al., 2011; van Wingen, Geuze, Vermetten, & Fernández, 2012). The authors suggest that increased amygdala reactivity to potentially threatening stimuli during combat deployment likely represents an adaptive response to a stressful environment, which decreases subsequent to the experience as part of maintaining homeostasis (Van Wingen et al., 2012). Taken together with the research focused on development of stress symptomatology, this work provides insight into neural mechanisms underlying both adaptive and maladaptive changes associated with exposure to severe stress.

These studies provide a basis for thinking about how functional activation paradigms may be used beginning in infancy to understand processes underlying adaptation to environmental stress across early periods of rapid neural development. As functional activation paradigms have been successfully utilized to characterize neural functioning beginning with neonates (Anderson et al., 2001), longitudinal work can now begin at very early stages of development. It is expected that the impact of psychological stress on neural functioning will differ depending on the stage of neural development of specific regions involved in stress reactivity and regulation (Tottenham & Sheridan, 2010), although this has not yet been empirically tested in humans. Work with non-human primates indicates that the amygdala follows a course of rapid development during the early postnatal period (Payne, Machado, Bliwise, & Bachevalier, 2010) during which time psychological stress (maternal separation) appears to have a particularly

negative effect on amygdala gene expression and socioemotional functioning (Sabatini et al., 2007). Animal models indicate that the amygdala is characterized by a high level of sensitivity to excitatory input early in development (Baram & Hatalski, 1998), and heightened amygdala reactivity appears to be an early emerging neural consequence of environmental stress (Sánchez et al., 2001). Thus levels of amygdala reactivity may first be influenced by the early environment (e.g. Tottenham et al., 2010) and then shape subsequent vulnerability (e.g. Admon et al., 2012, 2009). Alternatively, higher levels of amygdala reactivity may be more closely tied to temperamental or genetic factors and simply confer sensitivity to the environment in ways that can be adaptive or maladaptive depending on the context.

The work by van Wingen and colleagues showing a return to baseline levels of amygdala reactivity following a span of time after combat indicates the importance of examining changes in neural functioning for indication of adaptation to differing contexts (Van Wingen et al., 2012). For example, an infant removed from a maltreating home and placed into therapeutic foster care might be expected to show decreased amygdala reactivity to emotional stimuli over time if the therapeutic environment is effective. Even in the absence of such a drastic change in setting, alterations in neural functioning may be observed to correlate with changes in the levels of more common stressors such as interparental aggression or harsh parenting over time. The propensity for neural reactivity to change based on shifts in the environment may be a more important indicator of healthy development than patterns of neural activation in the context of any particular setting.

Developmental timing. Patterns of functioning between regions involved in stress and emotional reactivity networks should also be considered in light of findings that later developing neural circuitry involving more complex processing depends on input from earlier developing circuitry (Le Grand, Mondloch, Maurer, & Brent, 2003). Methods such as psychophysiological interaction analysis (Friston et al., 1997) provide information about functional connectivity in the context of specific tasks or stimuli presented during a functional activation paradigm. The study by Admon and colleagues indicates that higher initial levels of amygdala reactivity (prior to serving as a combat paramedic) to stressor related content predicts weaker functional connectivity between the hippocampus and MPFC after military service, which in turn predicts greater stress symptomatology (Admon et al., 2009). From a developmental perspective the functioning of earlier developing regions involved in stress and emotional reactivity and regulation, such as the amygdala, should be considered as a potential influence on the functioning and connectivity of regions with a more protracted course of development, such as the PFC (Casey et al., 2000; Fuster, 2002; Mills et al., 2012; Shaw et al., 2008).

Types of stimuli. In addition to the importance of considering developmental timing and employing longitudinal methods, it will be important to consider the type of stimuli that may be relevant to a specific stressor or to domains affected by the experience of stress. Auditory paradigms are the most commonly used in fMRI studies with sleeping infants and toddlers, and can target socioemotional domains which appear to be impacted by ELS. Vocal non-speech emotional stimuli (such as crying or laughing) have recently been used to assess early neural processing of emotion (Blasi et al., 2011). Variation in emotional prosody of speech represents another important category of

auditory emotional stimuli that has been commonly used in adult fMRI studies (Wildgruber, Ackermann, Kreifelts, & Ethofer, 2006) and in infant EEG and fNIRs studies (Grossmann, Oberecker, Koch, & Friederici, 2010; Grossmann, Striano, & Friederici, 2005). Personally relevant auditory stimuli, such as parents' voices (Dehaene-Lambertz et al., 2010) or an infants' own cry, represent another important category of socioemotional stimuli that may be particularly relevant to certain familial stressors, such as family conflict. As the field progresses, new and creative functional activation paradigms for infants and toddlers will likely emerge. For example, infant response to somatosensory stimulation, such as hand holding (Coan, Schaefer, & Davidson, 2006), may be relevant to bonding with caregivers. The use of functional activation paradigms with sleeping infants and toddlers represents a largely unexplored and highly promising means of gaining insight into multiple domains of development in the context of a range of environmental stressors.

Resting State Functional Connectivity MRI

Functional activation paradigms and rs-fcMRI as complementary methods for studying ELS. Resting state functional connectivity provides a unique means of examining coordinated neural functioning relevant to the impact of early adversity. While functional activation paradigms shed light on neural processing of stressor relevant stimuli or stimuli within specific domains thought to impacted by ELS, rs-fcMRI allows for assessment of coordinated neural functioning independent of specific tasks or stimuli. As resting state functional connectivity has been posited to reflect a history of repeated coactivation of brain regions (Fair et al., 2008; Kelly et al., 2009), individual differences in infants' neural reactivity to stressor relevant stimuli may precede emerging differences

in functional connectivity in the absence of stimuli. Longitudinal work demonstrating such a pattern would provide important insight into the mechanisms through which specific sources of ELS impact the functional architecture of the brain.

Research with adults has also indicated that while a particular task employed in a functional activation paradigm may only activate a subset of regions involved in a broad domain of functioning, such as memory, rs-fcMRI analysis can yield a more complete understanding of the regions involved (M. D. Fox & Raichle, 2007; Vincent et al., 2006). With sleeping infants, there are more limitations on the types of stimuli and tasks that can be used in the scanner, decreasing the chances of activating the full set of regions involved in a functional domain of interest. The use of rs-fcMRI will therefore be important for gaining a more comprehensive understanding of individual differences in infants' neural functioning associated with ELS.

Default network development and ELS. The potential for applying rs-fcMRI to examine the influence of ELS on brain development in infants and toddlers has only begun to be explored. Several tentative themes have emerged in this small literature including the potential importance of default network development and broad patterns of functional neural network development, such as interhemispheric connectivity. The rapid development of the default network across the first two years of life (Gao, Zhu, et al., 2009; Gao et al., 2011) is likely indicative of plasticity during this time frame. In line with this idea, a comparison of neonates born prematurely versus at full term revealed emerging functional connectivity between two regions of the adult default network, the MPFC and the PCC, in full-term neonates but not in preterm infants at equivalent postmenstrual age (Smyser et al., 2010). These results suggest that the rapid development

of functional connectivity between regions involved in the default network during infancy may be altered by events such as preterm birth. A study focused on adult post-traumatic stress disorder (PTSD) as a consequence of childhood abuse also noted decreased connectivity between a PCC seed region and other default network regions for women with PTSD compared to healthy controls (Bluhm, Williamson, Osuch, et al., 2009). However, the design of the latter study did not allow for differentiation of effects of ELS and current psychopathology.

Although not frequently discussed in the literature regarding ELS (as an exception see Daniels, Frewen, McKinnon, & Lanius, 2011), the default network may represent an important marker of the impact of ELS with implications for future health. Specific differences in connectivity between default network regions have been associated with various mental health disorders in children and adults, including major depression (Greicius et al., 2007), schizophrenia (Mannell et al., 2010) and attention deficit/hyperactivity disorder (Fair et al., 2010; Uddin et al., 2010). Moreover, specific features of depression appear to be associated with distinct patterns of altered connectivity (Zhu et al., 2011). Thus, differences in the coherence of the emerging default network likely have relevance for healthy neurological development and risk for psychopathology.

Broad patterns of resting state functional connectivity relevant to ELS. Another tentatively emerging theme from the small literature focused on rs-fcMRI with infants and toddlers at risk for developmental challenges focuses on interhemispheric connectivity. In a recent review article Uddin and colleagues pointed out a theme within the resting state literature with infants whereby intrahemispheric connectivity appears to

be greater than interhemispheric connectivity within certain functional regions (specifically the sensorimotor area; Liu, Flax, Guise, Sukul, & Benasich, 2008; Uddin et al., 2010). More recent work indicates that the degree of interhemispheric connectivity during infancy may vary based on experiences of ELS. Specifically, the number of stress inducing procedures in a neonatal intensive care unit from birth to term age equivalent predicts decreased interhemispheric connectivity with a right temporal lobe seed region (Smith et al., 2011). Although not focused on ELS, a recent study with sleeping toddlers demonstrated that those with autism evidence less interhemispheric functional connectivity in a region highly involved in language and social cognition (the STG) when compared to those with language delays or assessed as typically developing (Dinstein et al., 2011). Moreover, the authors reported a positive association between interhempispheric connectivity and language development, and a negative association between connectivity and severity of autism (Dinstein et al., 2011). Taken together this work indicates the potential importance of interhemispheric connectivity assessed with rs-fcMRI during natural sleep as an index of neural development that may have implications for behavioral functioning and symptomatology related to ELS.

As a caveat it should be noted that recent findings also provide support for robust interhemispheric functional connectivity in sleeping neonates (Gao et al., 2011). Moreover, other work with rs-fcMRI has emphasized the absence of anterior to posterior functional connectivity in lightly sedated neonates (Fransson et al., 2007), which is in line with research indicating a slower rate of anterior to posterior development of white matter tracts (as opposed to lateral or interhemispheric) as evidenced by diffusion tensor imaging (Dubois et al., 2008; Hermoye et al., 2006). Thus, the possibility of altered long-

range connectivity in the anterior to posterior direction should also be considered as a potential effect of ELS.

Resting state functional connectivity of cortical and limbic regions. Rs-fcMRI also provides a means of examining emerging patterns of functional connectivity among brain regions identified through animal research and work with human adults and children as candidates for linking ELS with subsequent socioemotional functioning. Research with older children and adults has already begun to document developmental changes in the connectivity of regions at the cortical and limbic (cortico-limbic) level of the stress response system using rs-fcMRI. For example, Kelly and colleagues (2009) examined resting state functional connectivity of a subgenual ACC region in children (8-12 years), adolescents (13-17 years) and young adults (19-24 years). The results are in line with other developmental work in indicating increasing long range connectivity over time and suggesting a lack of connectivity along the anterior-posterior axis in children (Kelly et al., 2009). In comparison to parts of the ACC associated with regulation of movement and cognition (motor control, attentional control and conflict monitoring), the connectivity of parts of the ACC associated with emotion regulation (subgenual ACC) and social functioning (perigenual ACC) demonstrated greater developmental changes from childhood to adulthood (Kelly et al., 2009). These results suggest a potentially high level of plasticity for these neural networks supporting socioemotional functioning across this time period.

Using structural imaging methods, specifically diffusion tensor imaging, researchers have demonstrated the early emergence of certain white matter tracts integral to limbic system functioning during prenatal (Huang et al., 2006) and early postnatal

development (Dubois et al., 2008). However, as white matter development is likely not the sole determinant of changes in resting state functional connectivity, which may result from repeated coactivation of certain brain regions (Fair et al., 2008; Kelly et al., 2009), it will be critical to take advantage of rs-fcMRI to examine the early emergence of functional connectivity within cortico-limbic networks thought to link ELS with subsequent socioemotional functioning and risk for psychopathology.

Recent work in adults indicates the potential utility of rs-fcMRI for understanding the impact of proximal stress on neural functioning at the cortico-limbic level of the stress response system. Cortisol, a hormone secreted as an end product of the HPA-axis, increases access to energy to cope with threat and also passes through the blood brain barrier to provide negative feedback to the stress response system and maintain homeostasis (Herman, Ostrander, Mueller, & Figueiredo, 2005; Ulrich-Lai & Herman, 2009). Both administration of a drug that mimics cortisol (Henckens, Van Wingen, Joëls, & Fernández, 2011) and higher levels of baseline endogenous cortisol (Veer et al., 2012) predict variation in resting state functional connectivity of the amygdala, a primary excitatory input to the HPA-axis, and other neural regions that play key roles in regulating HPA-axis functioning including parts of the MPFC (Henckens et al., 2011; Veer et al., 2012), hypothalamus and hippocampus (Henckens et al., 2011). Psychological stress, which increases HPA-axis activity through excitatory input from limbic regions such as the amygdala (Ulrich-Lai & Herman, 2009) also appears to predict variation in resting state functional connectivity of the amygdala. Specifically, a resting state scan conducted after stress induction with emotionally arousing video clips indicated higher levels of functional connectivity between the amygdala, dorsal ACC,

anterior insula and a brainstem region involved in physiological arousal and vigilance, potentially reflecting continued vigilance following the stress induction (Van Marle et al., 2010). This work suggests the possibility of examining concurrent environmental stressors and rs-fcMRI over time to increase understanding of how neural development proceeds in relation to ELS.

Existing research also provides ample support for the capacity of rs-fcMRI focused on cortico-limbic networks to characterize patterns of neural functioning that are relevant to pediatric and adult mental health disorders including depression, bipolar disorder, and anxiety (Dickstein et al., 2010; Fox & Greicius, 2010; Greicius, 2008; Hulvershorn, Cullen, & Anand, 2011; D. Zhang & Raichle, 2010). Moreover, recent findings with depression, a disorder for which the neural substrates are also commonly linked to early adversity (Lupien, McEwen, Gunnar, & Heim, 2009), indicate the utility of rs-fcMRI for investigating how integrated functioning across multiple neural networks, including cortico-limbic networks involved in stress and emotion regulation, is relevant to depressive symptomatology. Sheline and colleagues reported that among depressed adults versus healthy controls an affective network (identified with a subgenual ACC seed), default mode network (identified with a precuneus seed) and cognitive control network (identified with a DLPFC seed) all demonstrated increased resting state functional connectivity with DMPFC (Sheline, Price, Yan, & Mintun, 2010). Greater connectivity of the DMPFC correlated positively with severity of self-reported depression symptoms (Sheline et al., 2010). These findings are interesting in light of the association between sACC and DMPFC functional connectivity and dysregulation in children with preschool onset depression (Gaffrey, Luby, & Belden, 2010). The findings by Sheline

and colleagues also demonstrate the power of rs-fcMRI for examining more complex interactions among multiple neural networks as a means of understanding the impact of early adversity on subsequent socioemotional functioning and risk for psychopathology.

Conclusion

fMRI during natural sleep provides a much needed methodology to investigate changes in neural functioning and connectivity in the context of rapid neural development and environmental stressors during infancy. Combined with behavioral and peripheral indices of nervous system functioning in addition to other complementary functional neuroimaging techniques, sleep fMRI will allow for a more thorough understanding of the impact of ELS in terms of neural level changes that may increase vulnerability or resilience over the course of development. The associated methodological challenges call for increased research into areas such as the effects of sleep state on neural functioning and individual differences that may alter the likelihood of completing scan protocols. We hope that the increasing use of sleep fMRI will allow for insight into these challenges and may shed light on issues not frequently considered. For example, the use of functional activation paradigms during sleep may draw attention to the potential for infants to process stimuli relevant to early environmental stressors even while sleeping. Although the possibility has not yet been investigated, neural processing of stressor relevant stimuli during sleep may represent one mechanism through which early adversity influences brain development.

Building an evidence base documenting associations between ELS and developmental trajectories of neural networks linked to emotional development and risk for psychopathology can provide valuable information for intervention and prevention

efforts. First, such research can demonstrate the need for prevention work around certain high risk environments based on neural level changes that predict subsequent socioemotional functioning. Second, documenting the timing of development across multiple neural networks can contribute to understanding increases or decreases in vulnerability to environmental stress during certain time frames. Third, fMRI with infants and toddlers has great potential to increase understanding of individual differences, such as higher levels of amygdala reactivity, which may contribute to vulnerability or resilience. Finally, this work can be used to gain an increasingly mechanistic understanding of the most effective aspects of intervention strategies.

The next two chapters of this dissertation present findings from an fMRI study with infants focused on a common source of ELS, nonphysical interparental conflict. The first of these chapters focuses on an auditory functional activation paradigm employing emotional tone of voice as a stimulus relevant to interparental conflict. This study highlights the utility of fMRI with infants to increase understanding of a potential mechanism through which a common source of ELS could impact stress and emotion related functioning.

CHAPTER III

WHAT SLEEPING BABIES HEAR: AN FMRI STUDY OF INTERPARENTAL CONFLICT AND INFANTS' EMOTION PROCESSING

This work has been published in *Psychological Science*. I wrote this manuscript, with my co-authors (P. A. Fisher and J. H. Pfeifer) providing comments and editorial assistance. I designed the experiment described in this chapter with input from my co-authors, collected the data with assistance from others, and analyzed the data with input and assistance from my co-authors.

Introduction

Prominent ideas about how the environment shapes development rest on an understanding that brain plasticity during the first years of life confers vulnerability for key neural systems involved in stress and emotion-related functioning. The consequences of ELS have been investigated by examining its impact on these systems (Sánchez et al., 2001). Research with infants and young children has employed peripheral indicators of neuroendocrine functioning (e.g., cortisol; Loman & Gunnar, 2010)and direct measures of brain electroencephalographic activity (Nelson & McCleery, 2008) to increase understanding of how early adversity affects neurobehavioral development.

The high spatial resolution of functional MRI (fMRI), commonly used with older children and adults, has facilitated precise identification of neural networks linking early adversity with subsequent socioemotional functioning. Consistent with animal models examining the consequences of early adversity (Sánchez et al., 2001), this work reveals

the involvement of brain regions tied to initiation and regulation of the HPA-axis stress response, including limbic (Tottenham et al., 2011)and medial prefrontal regions (Treadway et al., 2009). However, the existing knowledge base in this area derives from fMRI research involving older children and adults. This makes it difficult to distinguish effects of *early* stress from subsequent processes of recovery or development of psychopathology. Moreover, a predominant focus on severe stressors, such as institutional rearing or maltreatment (Hart & Rubia, 2012), leaves a gap in the empirical literature regarding effects of more moderate early adversity.

Nonphysical interparental conflict is a more moderate source of early adversity that nevertheless appears to be associated with alterations in stress hormones, behavioral symptoms, and socioemotional problems during childhood (Cummings & Davies, 2010; Davies et al., 2007). Although more sparse than research with older children and adults, research with infants indicates that interparental conflict is associated with differences in physiological and behavioral indices of emotional reactivity and regulation as early as 6 months of age (Crockenberg et al., 2007; Moore, 2010). Interparental conflict may have an impact on early emotional development through decreases in sensitive caregiving (Krishnakumar & Buehler, 2000), as well as direct exposure to aggressive interactions between caregivers (Crockenberg et al., 2007). Basic research suggests that 5-month-old infants discriminate between other people's different emotional states, with expressions of anger eliciting greater attention and arousal than happy or neutral expressions (Balaban, 1995; Grossmann et al., 2010, 2005). Additionally, Moore (2009) showed that infants who witnessed vocal anger toward their mother demonstrated altered parasympathetic nervous system responses to an immediately subsequent stressful

interaction with their mother. Specifically, they showed increased withdrawal of vagal tone and decreased recovery, both of which are indicative of greater physiological reactivity, after this brief exposure to anger (Moore, 2009).

Early exposure to interparental conflict may also increase risk for later emotional and psychological problems. In 6-month-old infants, higher levels of interparental conflict are associated with lower baseline vagal tone (C. Porter, Wouden-Miller, Silva, & Porter, 2003) and greater withdrawal of vagal tone during a stressful interaction-and-recovery period (Moore, 2010), indicative of lower parasympathetic tone and greater stress reactivity respectively. Variation in vagal reactivity acts as a moderator of risk for school-age children exposed to conflict (El-Sheikh & Whitson, 2006; El-Sheikh et al., 2009). Despite the implication that some aspects of nervous-system functioning may be shaped by family conflict during infancy, and subsequently increase risk for school-age children, the ties between early exposure and subsequent vulnerability remain poorly understood. The autonomic and behavioral measures utilized to date represent outputs from multiple neural networks. Candidate neural networks linking early adversity with subsequent risk for psychopathology have not yet been identified.

Recent work demonstrates the feasibility of conducting fMRI research with infants during natural sleep (Redcay et al., 2007), which allows for examination of specific neural regions and networks during the first years of life. This work also draws attention to the sensitivity of infants to environmental stimuli during sleep by documenting distinct patterns of neural activation depending on properties of speech (Dehaene-Lambertz et al., 2002; Redcay et al., 2008) and emotional tone (Blasi et al., 2011). The present study builds on these methodological advances to characterize infants'

neural responses to emotional stimuli in the context of varying levels of interparental conflict.

Method

Participants

Families were recruited through flyers posted at local human-services agencies and advertisements on the local Craigslist.org Web site. Twenty-four infants (8 females, 16 males) aged 6 to 12 months (M = 8.33, SD = 1.90) completed an auditory fMRI paradigm during natural sleep; 20 infants had usable fMRI data. Infants had no known neurological disorders and lived with both biological parents. Exclusion criteria included referrals or investigations by a public child-protective-services agency. To obtain sufficient range in the sample, we assessed interparental conflict during screening using the Problem-Solving Communication subscale from the Marital Satisfaction Inventory, Revised (Snyder, 1997) and selected families based on established norms for distressed versus nondistressed couples (see the Supplemental Material available online for further information about the participants).

Interparental Conflict Measures

Mothers rated nonphysical interparental conflict levels since the birth of the child on the Psychological Aggression subscale of the Revised Conflicts Tactics Scale (Straus, Hamby, Boney-McCoy, & Sugarman, 1996) and the O'Leary-Porter Scale (B. Porter & O'Leary, 1980). The measures were highly reliable (α= .936 and .823, respectively) and correlated, $r(22) = .744$, $p < .001$, which allowed for creation of an average composite score of maternal report of interparental conflict (see the Supplemental Material for more

information about the administration of these measures and the creation of the composite score).

Auditory Stimuli

Auditory stimuli consisted of previously validated nonsense sentences spoken in very angry, mildly angry, happy, and neutral tones of voice by a male adult (Pell, Paulmann, Dara, Alasseri, & Kotz, 2009). Nonsense sentences possessed phonological and grammatical properties of English, but content words were replaced by semantically meaningless sound strings (see the Supplemental Material for more information).

fMRI Data Acquisition

Infants came in for scanning at their regular bedtime. Neuroimaging data were collected on a Siemens Allegra 3.0T scanner with a phased-array coil. Consistent with previous neuroimaging research using auditory stimuli with sleeping toddlers (Redcay et al., 2007), the paradigm consisted of 20-s blocks separated by 15-s rest periods. Blocks for each emotion condition (very angry, mildly angry, happy, and neutral) were presented four times per run in a semicounterbalanced design based on a Williams' Latin square. T2-weighted echo-planar functional scans (9 min, 28 s; 284 whole brain volumes) were acquired during presentation of auditory stimuli. Prospective acquisition correction was applied to adjust slice position and orientation, as well as to regrid residual volume-to-volume motion in real time during data acquisition for the purpose of reducing motion-induced effects (Thesen, Heid, Mueller, & Schad, 2000). See the Supplemental Material for more information on the scanning protocol and data-acquisition process.

fMRI Data Analysis

Neuroimaging data were converted to Neuroimaging Informatics Technology Initiative data format using the MRIConvert program (http://lcni.uoregon.edu/~jolinda/MRIConvert/). Brain images were extracted using the Brain Extraction Tool from the FMRIB Software Library (Beckmann et al., 2006; S. M. Smith, Bannister, Beckmann, & Brady, 2001; S. M. Smith, 2002) and the Brain Surface Extraction tool from BrainSuite09 (Sandor & Leahy, 1997; Shattuck, Sandor-Leahy, Schaper, Rottenberg, & Leahy, 2001). All other preprocessing steps, including realignment, registration, normalization, and smoothing with a 6-mm full-width half-maximum kernel, were accomplished using Statistical Parametric Mapping (SPM) software (SPM8; Wellcome Department of Cognitive Neurology, London, England). Images were normalized to a standard template for the 8- to 11-month age range from the MRI Study of Normal Brain Development (Fonov et al., 2011, 2009). Images with severe motion artifacts (greater than 2 mm of motion or evidencing visual signs of motion artifacts) were removed from runs, which resulted in less than 2 mm of motion per run (maximum = 1.07 mm). At least three (out of four) blocks of each condition were retained from each run.

At the individual-subject level, fixed-effects contrasts were computed to examine neural activation during presentation of each condition (very angry, mildly angry, happy, and neutral) versus rest, as well as the specific contrast of the very angry condition relative to the neutral condition. Motion parameters in six directions were included as regressors of no interest. Functional runs for which the contrast of all auditory conditions to rest did not evidence auditory-cortex activation at a relaxed threshold ($p < .05$,

uncorrected) were excluded from analyses because it was not possible to ascertain whether basic sensory processing of stimuli occurred. Four of the 24 infants did not have at least one functional run for which clear auditory activation was detected and were thus excluded from further analyses. The resulting contrast images were entered into whole-brain random-effects group analyses. We report only results that exceeded a threshold of $p < .05$, family-wise-error (FWE) corrected for multiple comparisons across the whole brain (specifically, $p < .05$ and 75 contiguous voxels, as determined by the NeuroElf AlphaSim toolbox, http://neuroelf.net/). Regions of activation were identified based on anatomical landmarks, although infant template and Montreal Neurological Institute template coordinates are provided in the figure and tables for reference.

Results

Effect of Interparental Conflict on Processing Very Angry Tone of Voice

The primary research question focused on the extent to which the composite interparental conflict score was associated with infants' neural responses to very angry auditory stimuli relative to neutral auditory stimuli. A whole-brain regression with interparental conflict score as the independent variable and neural activity during very angry relative to neutral tone of voice as the dependent variable revealed a significant cluster in rACC as well as a subcortical cluster encompassing parts of the caudate, thalamus, and hypothalamus (Table 3.1). Specifically, higher levels of interparental conflict were associated with greater activation in these regions during presentation of very angry compared with neutral speech (Figs. 3.1a & 3.1b). To depict this association graphically, we extracted mean parameter estimates of activity (averaged across all voxels in each cluster) for each participant from both the rostral ACC and subcortical

cluster during the very angry versus neutral contrast using the MarsBaR region-of-interest toolbox for SPM (Brett, Anton, Valabregue, & Poline, 2002). These mean parameter estimates for each participant in each cluster were then plotted as a function of conflict score. The graphs in Figures 3.1c and 3.1d do not show the results of an additional statistical analysis; rather, they illustrate the positive association between conflict and activation of these regions to very angry relative to neutral speech that was demonstrated statistically with the fMRI analyses. Results remained consistent when we controlled for variation in infant age. These results were specific to the very angry relative to neutral contrast. Exploratory analysis of the association between interparental conflict and neural processing of happy speech are presented in the Supplemental Material.

Table 3.1. Results of the whole brain regression: Positive association between interparental conflict and brain activation in response to very angry relative to neutral tone of voice

		Infant-atlas coordinates			MNI coordinates				
Region	Hemisphere	*x*	*y*	*z*	*x*	*y*	*z*	*k*	*t*
Anterior cingulate	—	3	29	13	4	36	17	88	2.72
Thalamus	Right	3	−1	1	4	−1	1	94	2.80
Thalamus	Left	−6	−4	−2	−7	−5	−3	—	2.29
Caudate	Left	−6	5	7	−7	6	9	—	2.81
Hypothalamus	Left	−6	−1	−5	−7	−1	−6	—	2.08

Note: The table reports only results that exceeded a threshold of $p < .05$, family-wise-error corrected for multiple comparisons across the whole brain (specifically, $p < .05$ and 75 contiguous voxels). The number of voxels within each cluster is indicated by *k*. Coordinates without voxel numbers indicate submaxima within the preceding cluster. MNI = Montreal Neurological Institute.

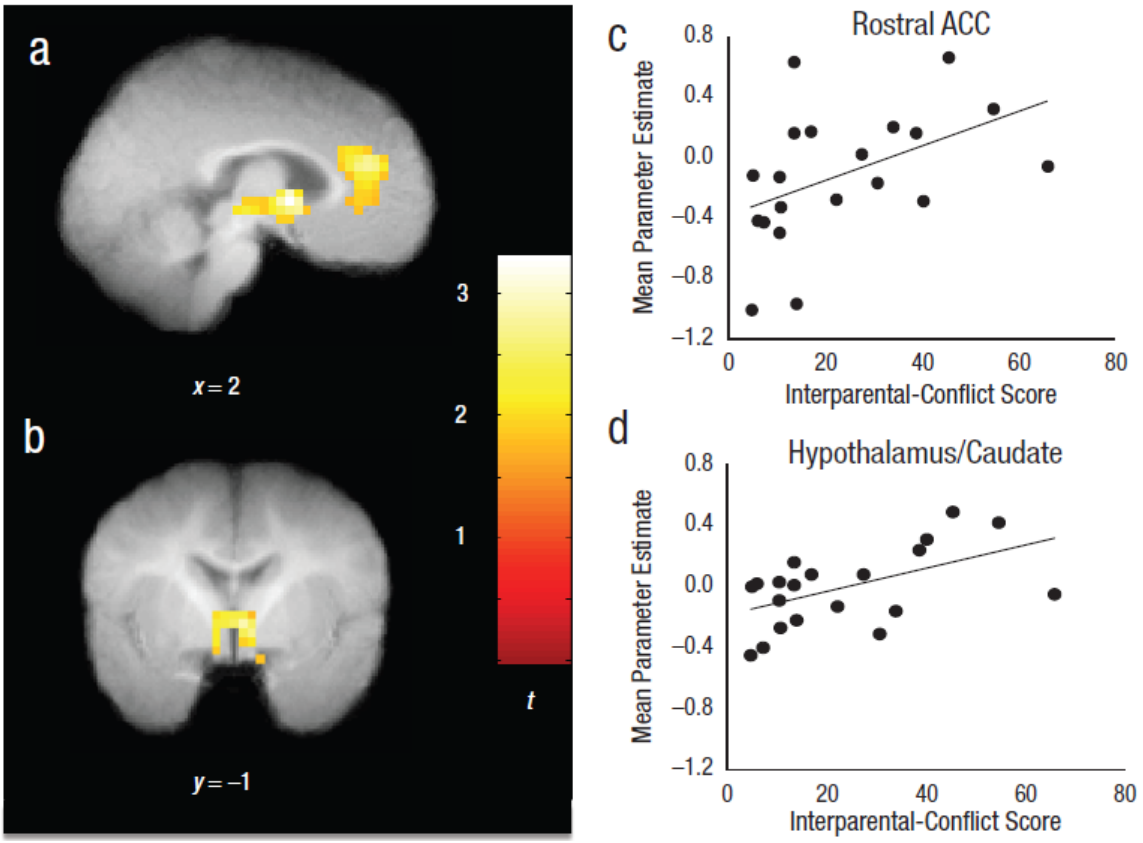


Figure 3.1. Association between interparental conflict scores and neural reactivity to very angry speech relative to neutral speech. Activations that exceeded a threshold of $p < .05$, family-wise-error corrected for multiple comparisons across the whole brain (specifically, $p < .05$ and 75 contiguous voxels), are displayed on the group mean structural image. The brain image in (a) shows activation in the rACC; infant-atlas coordinates: $x = 3$, $y = 29$, $z = 13$; Montreal Neurological Institute coordinates: $x = 4$, $y = 36$, $z = 17$). The images in (a) and (b) show activation in a subcortical cluster including hypothalamus, caudate, and thalamus (infant-atlas coordinates: $x = 3$, $y = –1$, $z = 1$; Montreal Neurological Institute coordinates: $x = 4$, $y = –1$, $z = 1$). The scatter plots (c and d; with best-fitting regression lines) reillustrate the association between conflict score and parameter estimates, separately for these two regions.

Effect of Different Emotional Tones of Voice

Because conflict was associated with neural responses to very angry speech, brain activation during presentation of each emotional tone of voice was examined after regressing out individual differences in conflict (Table 3.2). Direct comparison of activations in response to very angry relative to neutral stimuli did not reveal any clusters surviving FWE correction, although a cluster in the left temporal pole was just below this extent threshold. Comparison of activations in response to happy relative to neutral stimuli revealed significant areas in the left DLPFC, putamen, and medial temporal and occipital cortices.

Table 3.2. Activation to emotion stimuli after regressing out interparental conflict

		Infant-atlas coordinates			MNI coordinates				
Region	Hemisphere	*x*	*y*	*z*	*x*	*y*	*z*	*k*	*t*
Conjunction of all conditions > rest									
Auditory cortex	Right	42	−13	1	51	−16	1	214	4.95
Auditory cortex[a]	Left	−42	−16	7	−51	−20	9	50	3.22
Very angry tone of voice > neutral tone of voice									
Temporal pole[a]	Left	−45	−1	−8	−55	−1	−10	53	2.96
Happy tone of voice > neutral tone of voice									
Lingual gyrus	—	0	−55	5	0	−68	6	473	2.96
Fusiform	Left	−18	−58	−11	−22	−72	−14	—	2.31
Parahippocampal gyrus	Left	−15	−19	−17	−18	−23	−22	—	2.14
Putamen	Left	−21	5	7	−26	6	9	189	2.55
Midcingulate	—	−9	−1	28	−11	−1	36	—	2.00
Supplementary motor area	—	−3	−1	49	−4	−1	63	—	2.00
Superior frontal gyrus	Left	−18	35	22	−22	43	28	107	2.35
Middle frontal gyrus	Left	−33	20	28	−40	25	36	—	1.98

Note: The table reports results that exceeded a threshold of $p < .05$, family-wise-error corrected for multiple comparisons across the whole brain (specifically, $p < .05$ and 75 contiguous voxels), with the exception of one subthreshold cluster for the conjunction analysis and one for very angry tone of voice > neutral tone of voice contrast. The number of voxels within each cluster is indicated by *k*. Coordinates without voxel numbers indicate submaxima within the preceding cluster. No clusters were identified for the mildly angry tone of voice > neutral tone of voice contrast. MNI = Montreal Neurological Institute.
[a]Subthreshold clusters are reported for these activations ($p < .05$, uncorrected; 50 voxels).

Discussion

Although unusually adverse experiences such as institutional rearing or maltreatment are known to affect development of key neural networks, the present study suggests potential effects of a more moderate environmental stressor, nonphysical interparental conflict. By taking advantage of recent methodological advances that allow for investigation of neural functioning during infancy with the high spatial resolution afforded by fMRI (Blasi et al., 2011; Dehaene-Lambertz et al., 2010), this study provides novel evidence of associations between interparental conflict and patterns of infant brain functioning elicited by processing emotional speech during natural sleep.

Higher levels of interparental conflict were associated with greater activation to very angry tone of voice in the rostral ACC and subcortical structures, including the hypothalamus. Although we cannot be certain about the meaning of the activation patterns in these brain regions, many studies indicate their involvement in emotion and stress processing and regulation (Kober et al., 2008). The rostral ACC is implicated in emotion processing and regulation in typical populations (Kober et al., 2008), and its functioning is frequently altered in stress-related disorders (Fonzo et al., 2010; M. J. Kim et al., 2008). Research also demonstrates associations between early adversity and decreased volume of the ACC for adults with (Treadway et al., 2009) and without symptoms of psychopathology (Cohen et al., 2006), although the developmental pathway through which these structural differences emerge remains unknown.

The hypothalamus initiates activity of the HPA-axis. Activity of the HPA-axis in response to psychosocial stress is controlled by limbic brain structures involved in emotion processing and memory, including the amygdala, hippocampus, and ACC

(Pruessner et al., 2010; Ulrich-Lai & Herman, 2009). The hypothalamus is thus viewed as a key link between emotional input, neuroendocrine functioning, and stress reactivity (Kober et al., 2008). Extensive research has focused on alterations in the functioning of the HPA-axis (as indexed by the hormone cortisol) as a result of ELS, including more normative stressors, such as interparental conflict (Davies et al., 2007), and more extreme events, such as neglect and abuse (Bruce, Fisher, Pears, & Levine, 2009). Specific patterns of HPA-axis functioning have also repeatedly been associated with mood disorders in adolescence and adulthood (Lopez-Duran, Kovacs, & George, 2009; Parker, Schatzberg, & Lyons, 2003).

These finding also converge with extensive research using animal models, which points to the ACC and hypothalamus as part of neural networks that link early psychosocial adversity to subsequent difficulties with regulation of emotions and stress (Loman et al., 2010). However, this study is the first to document an association between an environmental stressor and the functioning of these specific brain regions during infancy. These regions were identified based on a whole-brain regression as opposed to a priori specification as regions of interest. This allowed for a more independent test of whether the findings in this study converge with existing knowledge about the role of these brain regions based on animal models and research with older children and adults (Hart & Rubia, 2012).

This study also provides novel evidence regarding infants' neural processing of happy and angry emotional speech during sleep, regardless of the level of interparental conflict. The findings are broadly in line with those of a recent fMRI study indicating differentiation of sad relative to neutral vocalizations in sleeping 3- to 7-month-olds

(Blasi et al., 2011), although this study did not find differentiation between happy and neutral stimuli. We may have been better able to observe the latter pattern because of differences in the age ranges sampled and the stimuli (nonsense speech vs. emotional vocalizations).

Limitations of the present study include the lack of observational assessment of interparental conflict and of a high-intensity positive-affect condition (e.g., very happy) to test whether the effects are specific to anger rather than high-intensity emotion more generally. Additionally, recruitment through Craigslist and human-services agencies may have skewed the sample toward individuals of lower socioeconomic status. We also were unable to monitor and control for sleep state, which is an important issue to be addressed in future work (see the Supplemental Material). Future research will also benefit from longitudinal investigations and inclusion of behavioral measures to assess whether changes in neural functioning mediate between exposure to environmental stress and socioemotional development.

Despite these limitations, the present findings indicate that during a period when infants are particularly vulnerable because of their complete dependence on caregivers and high levels of neural plasticity, moderate sources of environmental stress may be related to neural functioning in areas central to emotion and stress-related processes. Moreover, far from being oblivious to parents' conflict, infants' processing of stressor-relevant stimuli, such as angry tone of voice, may occur even during sleep.

The results of this study provide evidence for the utility of a functional activation paradigm to increase understanding of the effects of a common source of ELS on brain functioning during infancy. These results specifically address the association between

level of interparental conflict and infants' neural processing of a stressor relevant stimulus, very angry tone of voice. The next chapter extends this work by using rs-fcMRI to characterize coordinated neural functioning at rest, in the absence of a stressor specific stimulus.

CHAPTER IV

INTERPARENTAL CONFLICT AND RESTING STATE FUNCTIONAL CONNECTIVITY OF THE AMYGDALA AND DEFAULT NETWORK DURING INFANCY

P. A. Fisher, J. H. Pfeifer and D. A. Fair. are co-authors on this manuscript. I wrote this manuscript, with my co-authors providing comments and editorial assistance. I designed the experiment described in this chapter with input from my co-authors, collected the data with assistance from others, and analyzed the data with input and assistance from my co-authors.

Introduction

Infancy is a time of rapid neural development associated with high levels of neural plasticity (S. E. Fox et al., 2010; Knudsen, 2004). Research with animals has repeatedly demonstrated the unique impact of psychosocial stress on the brain during early periods of development (Levine, 2005; Sánchez, Ladd, & Plotsky, 2001; Tottenham & Sheridan, 2010; Ulrich-Lai & Herman, 2009). Research with humans provides support for the impact of ELS on the brain with associated consequences for behavioral functioning across multiple domains (Burghy et al., 2012; Tomoda et al., 2009; Tottenham et al., 2011; Treadway et al., 2009). However, this research has typically occurred years after stress exposure. An accumulating body of work demonstrates the feasibility of using fMRI with infants in a research context (Anderson et al., 2001; Dehaene-Lambertz et al., 2002; Redcay et al., 2007), a methodology that provides the spatial resolution necessary to study brain regions thought to play important roles in the

impact of ELS. By conducting fMRI scans with infants during natural sleep researchers have been able to delineate the coordinated functioning of cortical and subcortical brain regions beginning in the first several weeks of life (Fransson et al., 2007, 2009; Gao, Zhu, et al., 2009; Gao et al., 2011; Smyser et al., 2010). This foundational work provides a basis for examining the effects of ELS on brain functioning within a more proximal time frame, before the onset of subsequent neurobiological processes associated with resiliency or development of stress related psychopathology.

Nonphysical interparental conflict represents a common form of ELS. A large body of literature has focused on nonphysical interparental conflict, documenting associations with behavioral and physiological indices of emotion regulatory difficulties in children (Cummings & Davies, 2002, 2010; Davies & Cicchetti, 2004). A smaller body of work extends these findings down to infancy, demonstrating that higher levels of interparental psychological aggression predict differences in emotion regulatory capacity as assessed by behavioral response to a novel toy in 6-month-olds (Crockenberg et al., 2007). Nonphysical interparental conflict has also been associated with infants' vagal tone, an index of parasympathetic nervous system functioning closely associated with emotion regulatory capacity (Beauchaine, Gatzke-Kopp, & Mead, 2007; Beauchaine, 2001; Calkins & Dedmon, 2000; Degangi, Dipietro, Greenspan, & Porges, 1991). Higher levels of interparental conflict predict lower baseline parasympathetic tone (C. Porter et al., 2003), and greater withdrawal of parasympathetic tone in response to a stressful mother-infant dyadic interaction (Moore, 2010). These results indicate that the impact of nonphysical interparental conflict may begin well before childhood, during the first year of life.

Building on the research focused on infant behavior and peripheral nervous system functioning, we recently used fMRI during natural sleep to examine associations between nonphysical interparental conflict and 6-12-month-old infants' brain functioning (Graham, Fisher, & Pfeifer, 2013). Higher levels of conflict were found to be associated with increased reactivity to very angry versus neutral tone of voice in a region of the MPFC (specifically the rACC) and subcortical regions including parts of the thalamus, caudate and hypothalamus (Graham et al., 2013). These brain regions are consistent with those implicated by animal models (Sánchez et al., 2001; Tottenham & Sheridan, 2010) and neuroimaging work with older children and adults (Loman et al., 2010) as likely candidates for linking ELS with subsequent difficulties with emotion and stress related functioning. This study indicates that the functioning of these regions may be associated with a common and relatively moderate source of ELS during the first year of life. However, it remains unclear whether a moderate stressor such as interparental conflict is associated with neural functioning in the absence of a stressor relevant stimulus, such as emotional tone of voice. Moreover, the previous study did not examine the extent to which interparental conflict is associated with the coordinated functioning, or functional connectivity, of neural regions likely vulnerable to the effects of ELS.

Rs-fcMRI represents a powerful method for examining the coordinated functioning of neural regions in the absence of a specific stimulus or task. This methodology identifies spontaneous, low frequency changes in the BOLD signal at rest (without a stimulus or task), which are thought to reflect endogenous neural activity (Biswal et al., 1995). Correlated patterns of activity between regions are known as functional connections (Biswal et al., 1995). This methodology has frequently been used

to study functional connectivity among a group of brain regions that demonstrate higher levels of activity in the absence of externally oriented tasks, known as the default network (Gusnard & Raichle, 2001; Raichle et al., 2001). Groups of brain regions typically activated together for task demands also demonstrate functional connections during rest (M. D. Fox & Raichle, 2007; Seeley et al., 2007). The absence of stimuli makes this methodology particularly well suited for infants undergoing MRI scans during natural sleep to prevent movement detrimental to image acquisition.

Rs-fcMRI studies have frequently focused on the default network, which includes (among other regions) the PCC, precuneus, regions of the MPFC, lateral parietal lobes and medial temporal lobes (Greicius, Krasnow, Reiss, & Menon, 2003; Gusnard & Raichle, 2001; Raichle et al., 2001). Although the significance of the default network for behavioral functioning remains under investigation (Andrews-Hanna, 2012), it has been relatively well characterized with regard to its developmental trajectory (Fair et al., 2008, 2009; Gao, Zhu, et al., 2009; Gao et al., 2011; Supekar et al., 2010), and associations with mental health outcomes (M. D. Fox & Greicius, 2010; Uddin et al., 2010; Whitfield-Gabrieli & Ford, 2012). Most pertinent to the present study is evidence for rapid development of the default network during the first year of life. The number of default network regions exhibiting significant functional connectivity more than doubles (from 6 to 13) over the period spanning 2-weeks to 1-year of age (Gao, Zhu, et al., 2009). Development does not appear to be linear, as less change is evident in the following year (Gao et al., 2011). The rapid development of the default network during the first year of life may indicate increased plasticity and sensitivity to environmental input during this time.

Associations between ELS and default network functioning have been reported both in infants and in adults. Preterm birth has been associated with delayed emergence of functional connectivity between the PCC and MPFC. Specifically, functional connectivity between the MPFC and the PCC was noted in full-term neonates, but not preterm infants at equivalent postmenstrual age (Smyser et al., 2010). Research with adults also provides evidence for an association between ELS and diminished connectivity of the PCC with default network regions, although ELS is confounded with stress related psychopathology in some of this work. Compared to healthy controls, women with PTSD associated with childhood abuse demonstrate decreased connectivity of the PCC with default network regions including MPFC, bilateral parietal cortex and bilateral MTG (Bluhm, Williamson, Osuch, et al., 2009). The PTSD group also evidenced lower connectivity of the PCC to the insula, and regions more typically associated with the effects of ELS, including the amygdala and hippocampus (Bluhm, Williamson, Osuch, et al., 2009). Recent work indicates that adults with a history of childhood abuse but no psychiatric diagnosis also show decreased connectivity between the PCC and MPFC, compared to healthy adults without ELS (Philip et al., 2013). Although not focused on ELS, a small study (with 8 subjects) of individuals involved in car and workplace accidents found that greater PCC to amygdala resting state functional connectivity 6 weeks post accident predicted greater PTSD symptoms at 12 weeks post accident (Lanius et al., 2010). Taken together, these studies indicate that default network functioning may be disrupted by stressful life events with particular emphasis on connectivity between PCC and MPFC for ELS. Moreover, altered PCC connectivity to

regions more typically associated with ELS, such as the amygdala, appears to be associated with PTSD in adults.

More recently, researchers have also demonstrated the utility of rs-fcMRI for understanding the coordinated functioning of subcortical regions with strong empirical and theoretical ties to the impact of ELS. The amygdala is a key region of interest due to a large body of animal literature demonstrating the impact of ELS on the amygdala with consequences for subsequent behavioral functioning (for reviews see Sánchez, Ladd, & Plotsky, 2001; Tottenham & Sheridan, 2010). Neuroimaging work in humans with older children and adults also provides evidence for the impact of ELS on amygdala structure (Driessen et al., 2000; Mehta et al., 2009; Schmahl, Vermetten, Elzinga, & Bremner, 2003; Tottenham et al., 2010) and function (Dannlowski et al., 2012; Taylor et al., 2006; Tottenham et al., 2011). The human neuroimaging literature has also repeatedly indicated a role for the amygdala in stress related psychopathology, such as PTSD (Hayes, Hayes, & Mikedis, 2012; Shin, Rauch, & Pitman, 2006).

Rs-fcMRI studies of the amygdala have increased understanding of the coordinated functioning of both the whole amygdala and amygdala subregions in humans. In adults, the whole amygdala demonstrates significant resting state functional connectivity with regions identified in animal models of amygdala connectivity (Amaral & Price, 1984; Barbas & De Olmos, 1990; Ghashghaei & Barbas, 2002; Price, 2003), and models of amygdala functional connectivity derived from human task based fMRI involving emotional content (Stein et al., 2007), including the ACC, PCC, mid-cingulate, parahippocampal gyrus, insula and areas in the PFC (Bickart, Hollenbeck, Barrett, & Dickerson, 2012; Etkin, Prater, Schatzberg, Menon, & Greicius, 2009; Roy et al., 2009).

In line with the idea that rs-fcMRI captures correlated activity due to both direct and indirect anatomical connections (Damoiseaux & Greicius, 2009; Greicius et al., 2009; Honey et al., 2009; Shmuel & Leopold, 2008), resting state functional connectivity of the amygdala also involves regions with which it does not have known direct anatomical connections (Roy et al., 2009).

The examination of amygdala subregions with rs-fcMRI represents an important step as the amygdala is known to be composed of multiple subnuclei with distinct cytoarchitecture and functional roles (Davis, 2006; Heimer et al., 1999; Jolkkonen & Pitkanen, 1998; Russchen, Bakst, Amaral, & Price, 1985). Moreover, animal research demonstrates unique roles for different amygdala subdivisions in mediating the effects of stress (Albeck et al., 1997; Caldji et al., 2000; Hsu et al., 1998; Pelletier et al., 2005; Rainnie et al., 2004). For example, the basolateral amygdala plays a unique role in the effects of stress on learning and memory through its connections with the hippocampus among other regions (Roozendaal et al., 2009).

Rs-fcMRI has been used to examine the functional connectivity of amygdala subregions derived from mapping cytoarchitecture in postmortem brain tissue. The most commonly used probabilistic maps based on cytoarchitecture include nuclei grouped into laterobasal (LB), centromedial (CM) and superficial (SF) subregions (Amunts et al., 2005). Rs-fcMRI studies of these subregions demonstrate good consistency with known pathways for sensory input and other connections of these subregions from the animal literature (Etkin et al., 2009; Roy et al., 2009). For example, consistent with its role in learning and memory, the LB subregion demonstrates stronger positive connectivity with the STG and hippocampus compared to the other subregions (Roy et al., 2009). A study

focused on the LB and CM amygdala subregions demonstrated a high level of consistency in the unique patterns of connectivity for these regions across two independent samples, and when compared with the findings of Roy and colleagues (Etkin et al., 2009). Additional support for utility of rs-fcMRI for examining the connectivity of amygdala subregions defined by cytoarchitecture comes from a study which derived amygdala subregions from examining the relative strength of resting state functional connectivity of all voxels within the amygdala to specific prefrontal regions (Bickart et al., 2012). The subregions defined by this procedure converge to a large degree with the probabilistic maps based on cytoarchitecture (Bickart et al., 2012). Taken together these findings provide support for the use of probabilistic maps of amygdala subregions based on cytoachitecture in rs-fcMRI studies.

Recent work has indicated the potential for rs-fcMRI to characterize the connectivity of the amygdala and its subregions in children. Qin and colleagues characterized the resting state functional connectivity of the CM and LB amygdala in 7-to-9-year-old children as compared to 19-to-22-year old adults (Qin, Young, Supekar, Uddin, & Menon, 2012). For the combined CM and LB amygdala subregions children demonstrated weaker connectivity compared with adults in multiple regions including cingulate gyrus, insula, sensorimotor cortex, premotor cortex, superior parietal lobe, DLPFC, VMPFC and subcortical regions including caudate, putamen, cerebellum and brainstem (Qin et al., 2012). Children also displayed little differentiation in patterns of connectivity for each subregion, with significant differences only for greater CM compared to LB connectivity with temporal pole and perirhinal cortex (Qin et al., 2012). In contrast adults demonstrated stronger CM versus LB connectivity to dorsal ACC and

multiple subcortical regions, including thalamus, putamen, and caudate, and stronger LB versus CM connectivity to perirhinal cortex and multiple cortical regions including STG, MTG, motor cortex and inferior parietal cortex (Qin et al., 2012). These findings were replicated in a second independent sample of children and adults, indicating these amygdala subregions can be reliably used for rs-fcMRI analyses in children (Qin et al., 2012).

Rs-fcMRI studies of the amygdala have also provided insight into potential effects of ELS on the coordinated functioning of the amygdala with other neural regions important for emotion processing and regulation. Healthy adults with a history of childhood abuse show increased resting state connectivity between the whole amygdala and VMPFC compared to those with no experience of ELS (at the trend level; Philip et al., 2013). It should be noted that this study only examined resting state connectivity between the amygdala and the VMPFC as opposed to conducting a whole brain analysis. Rs-fcMRI studies focused on combat related PTSD have used a whole brain analysis approach and reported greater connectivity between the amygdala and right posterior insula for the PTSD group versus healthy participants with combat exposure (Rabinak et al., 2011; Sripada et al., 2012). This work also indicates that PTSD is associated with lower positive connectivity between amygdala and hippocampus and lower negative connectivity between amygdala and rACC (a region within the MPFC; Sripada et al., 2012). These studies indicate that stress is associated with altered resting state functional connectivity of the amygdala to brain regions frequently associated with the impact of ELS, the MPFC and hippocampus, in addition to a region less frequently studied in the ELS literature, the insula.

Functional connectivity of amygdala subregions in relation to ELS has not yet been examined. However, resting state functional connectivity of amygdala subregions does seem to be altered in anxiety disorders (Etkin et al., 2009; Hahn et al., 2011; Roy et al., 2013), which share some of the neurobiological markers of ELS (Dannlowski et al., 2012). Adults with Generalized Anxiety Disorder (GAD) were found to show less distinct connectivity patterns for the CM and LB amygdala compared to healthy adults (Etkin et al., 2009). In addition, both subregions demonstrated greater positive functional connectivity to the right DLPFC in the GAD group. Within the GAD group, greater positive functional connectivity between the amygdala subregions and the DLPFC was in turn associated with lower anxiety. Etkin and colleagues therefore interpret increased amygdala to DLPFC connectivity as potentially underlying cognitive strategies employed by GAD patients to cope with anxiety (Etkin et al., 2009). A study of adolescents with GAD found some support for increased overlap in functional connectivity patterns between CM and LB amygdala as evidenced by increased left CM connectivity to regions also functionally connected to the LB amygdala (Roy et al., 2013). In contrast to the work with adults, this study reported unique connectivity patterns associated with GAD for each amygdala subregion (LB, CM and SF). Among other findings, the GAD group demonstrated greater connectivity between CM amygdala and posterior insula, which was associated with greater anxiety (Roy et al., 2013). This work provides support for the idea that examining resting state functional connectivity of amygdala subregions provides unique insight into the neural basis of anxiety disorders.

Rs-fcMRI studies have captured developmental changes in connectivity patterns of the default network and amygdala, and indicated the sensitivity of these patterns to

ELS, and their relevance for stress related psychopathology. The present study therefore has two interrelated aims: 1) to characterize the functional connectivity of the amygdala and the PCC (part of the default network) during the first year of life, a time of vulnerability in terms of neural plasticity and dependence on caregivers; and 2) to examine associations between a common source of ELS, nonphysical interparental conflict, and the functional connectivity of these regions. Based on previous literature examining the default network during infancy, we hypothesized that we would see evidence for resting state functional connectivity among multiple default network regions (Gao, Zhu, et al., 2009). Due to the lack of previous studies examining amygdala or amygdala subregion functional connectivity during infancy, we did not put forth specific hypotheses regarding functional connectivity of these regions.

We hypothesized that higher levels of interparental conflict would predict decreased connectivity between the PCC and the MPFC based on the research with preterm infants (Smyser et al., 2010) and the adult literature regarding ELS and the default network (Philip et al., 2013). We hypothesized that higher levels of interparental conflict would predict altered connectivity between the whole amygdala and the rACC and hypothalamus regions identified as more reactive to angry tone of voice in our previous study (Graham et al., 2013). We did not put forth specific hypotheses regarding associations between interparental conflict and the amygdala subregions due to limited prior work in humans examining effects of ELS on these subregions. However, based on the animal literature we hypothesized that interparental conflict would demonstrate distinct patterns of associations with each subregion. Due to the early stages of this literature we took a whole brain analysis approach in addition to testing associations

between interparental conflict and connectivity of specific, *a priori* regions of interest (ROIs), namely the MPFC, rACC and hypothalamus.

Method

Participants

Families were recruited through advertisements on Craigslist and flyers posted in the community and at local human services agencies. The Problem Solving Communication subscale from the Marital Satisfaction Inventory-Revised (Snyder, 1997) was used during the screening process to assess level of interparental conflict. Families were selected based on established norms for distressed versus non-distressed couples in order to obtain a range of conflict in the sample. Inclusionary criteria included infants having no known neurological disorders, and living with both biological parents. Exclusionary criteria included referrals or investigations involving any member of the family by a public child protective services agency. Scans were attempted for 39 infants as part of a study protocol including one anatomical scan, two functional scans during an auditory paradigm and one resting state functional scan during which no stimuli were presented.

Twenty-three infants 6-12-months-of-age (M=8.35, SD=1.94; 8 Female) completed the two scans necessary for the current analysis (the anatomical and resting state functional scans). Scanning for each infant was attempted on up to two visits to the scan center. Sixteen infants did not complete both the anatomical and resting state scans due to difficulty falling asleep at the scan center or waking up prior to or during a scan sequence. For the 23 infants included in analysis, race and ethnicity were representative of the community in which recruitment occurred (82.6% Caucasian and 17.4% other or

more than one race; 21.7% Hispanic). Educational attainment for mothers was as follows: 8.7% did not complete high-school or a test equivalent, 21.7 % completed high-school or a test equivalent, 34.8% completed some community college, and 34.6% completed at least one year or more of a standard 4-year college. The median category for gross annual household income was $30,000–$39,999, based on a 12-point scale: 1 (*less than $4,999 per year*) to 12 (*$100,000 or more per year*). Infants included in analysis did not differ significantly from the rest of the sample with regard to any of the demographic variables.

Interparental Conflict Measures

Mothers reported levels of non-physical interparental conflict on the Psychological Aggression scale of the Revised Conflicts Tactics Scale (CTS2; Straus, Hamby, Boney-McCoy, & Sugarman, 1996) and the O'Leary-Porter Scale (OPS;Porter & O'Leary, 1980). The CTS2 was adapted to ask about interparental aggression since childbirth (as opposed to the previous year). The CTS2 response categories indicate the frequency of aggressive behaviors: 0 (*this has never happened*), 1 (once), 2 (twice), 3 (*3–5 times*), 4 (*6–10 times*), 5 (*11–20 times*), or 6 (*more than 20 times*). Consistent with the scoring instructions, responses with a range were recoded to a single number (i.e., 4 [*3–5 times*], 8 [*6–10 times*], and so on; Straus et al., 1996). Maternal report of psychological aggression toward and received from her partner were highly correlated (r = .941, p < .001). The mean was therefore used as a composite score of psychological aggression in the infant's home (α=.937).

The OPS was adapted for infants to ask about the frequency of arguments in front of the 'infant' (instead of the 'child'). One item regarding physical hostility was also removed from the scale due to the focus of the study on non-physical conflict. The total

sum score from the OPS was used to represent the frequency of verbal hostility in the presence of the infant (α=.834). Maternal report on the OPS and the Psychological Aggression scale of the CTS2 were highly correlated (r (22) = .698, p < .001) and were therefore averaged to create a composite of the overall level of non-physical conflict in the home.

Scanning Protocol

For the first study session families came to the neuroimaging center and learned about MRI safety and scan procedures with a mock scanner. Parents completed an MRI screening form for their infant (Lewis Center for NeuroImaging MRI Screening Questionnaire) and signed a release for their infant's physician to fill out the screening form. Parents also completed questionnaires regarding family conflict and demographic information. Families were given a CD of scan noises to take home and play for three nights prior to the scan session to allow infants to become accustomed to the noises.

Scan sessions were scheduled for infants' regular bedtimes. Infants were placed on the scanner bed and fitted with Bilsom pneumatic headphones after they fell asleep. Soft padding was placed between the earphones and the inside wall of the head coil for further sound protection and to stabilize head movements. Throughout the scan session two researchers remained in close proximity to the infant to watch for indications of wakefulness or distress.

fMRI Data Acquisition

Neuroimaging data were collected during natural sleep on a Siemens Allegra 3.0T scanner with a phased array coil. First, an 8 minute high-resolution T1-weighted MP-RAGE scan was obtained (TR=2500ms, TE=4.38 ms, TI=1100ms, flip angle=8°, matrix

size 256x192, FOV=256mm, 160 slices, 1mm in-plane resolution, 1mm thick) followed by two T2 weighted functional scans during presentation of auditory stimuli (consisting of different emotional tones of voice). An additional T2-weighted echo-planar functional scan with no stimuli was then collected to obtain resting state data (TR=2000ms, TE=30ms, flip angle=80°, matrix size 64x64, FOV=200mm, 32 slices, 3.125mm in-plane resolution, 4mm thick, 180 whole brain volumes). For all functional scans prospective acquisition correction (PACE) was applied to adjust slice position and orientation, as well as to re-grid residual volume-to-volume motion in real-time during data acquisition for the purpose of reducing motion-induced effects (Thesen et al., 2000).

fMRI Analysis

Data preprocessing. The MRIConvert program (http://lcni.uoregon.edu/~jolinda/MRIConvert/) was used to convert neuroimaging data to Neuroimaging Informatics Technology Initiative data format. Brain images were separated from the rest of the head tissue with the Brain Extraction Tool from the FMRIB Software Library (Beckmann et al., 2006; S. M. Smith et al., 2001; S. M. Smith, 2002) and the Brain Surface Extraction tool from BrainSuite09 (Sandor & Leahy, 1997; Shattuck et al., 2001). Statistical Parametric Mapping (SPM) software (SPM8; Wellcome Department of Cognitive Neurology, London, England) was used for realignment of functional images, registration to the anatomical scan, and normalization to a standard infant template (8- to 11-month age range) from the MRI Study of Normal Brain Development (Fonov et al., 2011, 2009). For compatibility with software for rs-fcMRI analysis maintained by Neuro-Imaging Laboratory (Washington University), the normalized time series images were then converted to the Talairach and Tournoux atlas

(Talairach & Tournoux, 1988) and into 4-dimensional floating point format using Caret Software (Van Essen et al., 2001).

rs-fcMRI preprocessing. Preprocessing steps specifically designed for resting state functional connectivity data were conducted to account for signal stemming from non-neuronal processes (M. D. Fox & Raichle, 2007). These steps followed established procedures described in previous work including, temporal band-pass filtering (0.009 Hz $< f <$ 0.08 Hz), regression of rigid body head motion parameters in 6 directions, regression of the whole brain signal, regression of ventricular signal averaged from a ventricular region mask, regression of white matter signal averaged from a white matter mask and regression of first order derivative terms for the whole brain,ventricular,and white matter signals (Fair et al., 2007, 2009). In addition to the regression of head motion parameters relative to the reference frame during connectivity preprocessing, additional steps were taken to examine movement of a given frame relative to the previous frame, known as framewise displacement (FD; Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). This method yields a 6 dimensional time series representing frame-to-frame motion of the 6 rigid body parameters, as described by $FD_i = |\Delta d_{ix}| + |\Delta d_{iy}| + |\Delta d_{iz}| + |\Delta \alpha_i| + |\Delta \beta_i| + |\Delta \gamma_i|$, where $\Delta d_{ix} = d_{(i-1)x} - d_{ix}$, and so on. This formula sums the absolute values of volume-by-volume changes in the six rigid body parameters. We used a volume censoring approach in which we removed volumes associated with greater than .3 mm FD. One volume preceding and two volumes following were also removed to account for temporal blurring (Power et al., 2012). The maximum percentage of volumes removed from a scan was 22.5% (M=7.10, range=1.70-22.5).

Brain regions of interest.

Default network ROIs. The PCC has been identified as an early emerging hub of the default network during infancy (Gao, Lin, et al., 2009) and was therefore chosen as an appropriate ROI for examining default network activity in 6-to-12-month-olds. A VMPFC ROI was used to test the specific hypothesis that higher interparental conflict would predict lower PCC to VMPFC connectivity. The PCC and VMPFC ROIs were 12mm spheres identified in previous research focused on the default network (M. D. Fox et al., 2005), and used in research documenting the developmental trajectory of the default network from childhood to adulthood (Fair et al., 2008, 2009).

Amygdala and amygdala subregions. Amygdala ROIs were obtained from FSL's Juelich histological atlas. These ROIs are based on stereotaxic, probabalistic maps (created with cytoarchitectonic mapping and 3-D reconstruction) of the whole amygdala and three subregions: superficial (SF) laterobasal (LB) and centromedial (CM; Amunts et al., 2005). The SF subregion includes the anterior amygdaloid area, amygdalopyriform transition area, the amygdaloid-hippocampal area and the ventral and posterior cortical nuclei. The LB subregion includes the lateral, basolateral, basomedial, and paralaminar nuclei. The CM subregion includes the central nucleus and the medial nucleus. The accuracy of these maps for children was examined in postmortem brain tissue from a 10-year-old child (J. E. Kim et al., 2010). The position and relative size of all subregions were found to be similar for the child amygdala with the exception of a smaller size of the SF amygdala proportional to the CM and LB in the child amygdala (J. E. Kim et al., 2010). Figure 4.1, Panel A (in the Results section) shows the amygdala subregion ROIs displayed on a representative infant structural brain image that has been normalized to the

infant template, and transformed to Talairach and Tournoux atlas space. ROIs for the left and right side were combined creating bilateral ROIs for the whole amygdala and each subregion.

Infant fMRI ROIs. The rACC and hypothalamus ROIs were derived from clusters identified by the analysis of the auditory functional activation paradigm also utilized with this sample of infants (Graham et al., 2013). Specifically, the ROIs resulted from a whole brain regression of maternal report of interparental conflict on the contrast of very angry versus neutral speech. Higher conflict was associated with greater activation in these regions during presentation of very angry versus neutral speech.

Analysis Plan

For the whole amygdala, amygdala subregions and PCC ROIs, voxelwise functional connectivity maps were created by correlating the time course of the voxels within each ROI with the time course of every other voxel in the brain during the resting state scan. This produced a whole group functional connectivity map for each ROI. For the amygdala subregions paired two-tailed t-tests were also used to directly compare whole brain connectivity between the subregions (LB versus CM, LB versus SF, and CM versus SF). These t-tests produced maps illustrating differences in patterns of connectivity between the subregions.

Whole brain voxelwise regressions were used to examine associations between interparental conflict and connectivity while controlling for infant age. Separate regression analyses were conducted for the amygdala, amygdala subregions and PCC ROIs with interparental conflict as the independent variable, infant age as a covariate and whole brain voxelwise connectivity as the dependent variable. For all of the whole brain

analyses, thresholding based on Monte Carlo simulation was implemented to account for multiple comparisons (Forman et al., 1995). Correction for $p<0.05$ voxel clusters required a threshold of 53 contiguous voxels with a Z-value> 2.25.

To examine the hypothesized associations of interparental conflict with connectivity between specific ROIs (amygdala ROIs to the fMRI ROIs and PCC to VMPFC), we extracted the time courses for these regions over the course of the resting state scan for each infant. We then created a correlation matrix to determine the strength of the correlation (*r* value) between relevant pairs of ROIs. We ran separate regressions with interparental conflict as the independent variable, infant age as a covariate and the *r* values representing the connectivity between relevant pairs of ROIs as the dependent variable. The results of these regressions indicate whether interparental conflict significantly predicted resting state connectivity between ROIs. All analyses were conducted with software maintained by Neuro-Imaging Laboratory (Washington University).

Results

Whole Group Connectivity Maps

PCC ROI. Activity in the PCC was positively correlated with activity in a number of regions typically identified as part of the default network in adults (M. D. Fox et al., 2005; Greicius et al., 2003) including VMPFC, bilateral lateral parietal cortex, parahippocampal gyrus, inferior temporal cortex and left (DLPFC; superior frontal gyrus, BA 6). The whole group connectivity map for the PCC ROI is shown in Figure 4.2, Panel A.

The PCC evidenced negative correlations with spontaneous activity in regions identified in the adult literature as frequently activated during task based imaging studies and negatively correlated with default network activity in resting state studies (Damoiseaux et al., 2006; De Luca, Beckmann, De Stefano, Matthews, & Smith, 2006; M. D. Fox et al., 2005; Fransson, 2005) including bilateral insula extending into IFG, right supplementary motor area (SMA), bilateral middle temporal (MT) area and right DLPFC. Additionally, negative correlations were identified between the PCC and bilateral thalamus and parts of brainstem and cerebellum.

Amygdala and amygdala subregion ROIs. The whole group functional connectivity map for the amygdala revealed positive correlations between spontaneous activity in the amygdala and dorsal, subgenual and rostral ACC, encompassing the rACC ROI derived from the fMRI study. Amygdala activity was also positively correlated with the caudate, thalamus, hypothalamus, encompassing the subcortical ROI from the fMRI study. Additional regions demonstrating positive connectivity with the amygdala included the hippocampus and hippocampal gyrus, bilateral STG, MTG and insula. Negative connectivity to the amygdala was observed bilaterally in middle frontal gyrus (DLPFC), PCC, precuneus, fusiform gyrus, parietal lobe (extending into inferior parietal lobule, and somatosensory cortex), brainstem and cerebellum, and left cuneus (Figure 4.1, Panel B).

The connectivity maps for each subregion demonstrated overlap in multiple regions including positive connectivity with bilateral thalamus and rACC and negative connectivity with PCC. However, the patterns of connectivity were also distinct in multiple regions.

CM versus SF amygdala. In comparison to the SF amygdala, the CM amygdala demonstrated greater positive connectivity with regions including bilateral STG (BA 22, 41), lateral premotor and motor cortex, right posterior middle frontal gyrus (BA 6), lateral somatosensory cortex, insula, thalamus, caudate, putamen, left IFG, left lingual gyrus, and brainstem regions. Regions demonstrating greater negative connectivity with the CM relative to SF amygdala included bilateral rostral middle frontal gyrus (BA 10)**,** precuneus**,** somatosensory cortex association cortex (BA 3 and 5), and mid-cingulate (BA 24).

Relative to the CM amygdala, activity in the SF amygdala was more positively associated with activity in bilateral medial frontal gyrus (BA25) extending into subgenual ACC (BA 32) on the right, bilateral temporal pole (BA 38), bilateral IFG, and parahippocampal gyrus. Relative to the CM amygdala, activity in the SF amygdala was more negatively associated with activity in bilateral inferior parietal lobule and bilateral cerebellum.

CM versus LB amygdala. In comparison to the LB amygdala, the CM amygdala demonstrated greater positive connectivity with multiple cortical regions bilaterally including sensorimotor cortex (BA 43), lateral motor and premotor cortex, STG (BA 22), IFG, and insula. The CM amygdala also evidenced greater positive connectivity with subcortical regions bilaterally including thalamus and caudate, putamen, and globus pallidus. Regions demonstrating greater negative connectivity with the CM relative to LB amygdala included right middle frontal gyrus (BA 10), bilateral somatosensory association cortex (BA 5) and superior parietal cortex (BA 7), and left PCC.

Relative to the CM amygdala, activity in the LB amygdala was more positively associated with activity in bilateral hippocampus and hippocampal gyrus, STG (BA38), MTG (BA 21) and insula, and right supramarginal gyrus (BA 40). Relative to the CM amygdala, activity in the LB amygdala was more negatively associated with activity in the bilateral cerebellum.

LB versus SF amygdala. In comparison to the SF amygdala, the LB amygdala demonstrated greater positive connectivity with multiple regions bilaterally including MTG (BA 21), inferior temporal gyrus (BA 20), STG (BA 13 and 22), parahippocampal gyrus, DMPFC (BA 8), left premotor cortex (BA 6), hippocampus and right caudate head. Regions demonstrating greater negative connectivity with the LB relative to SF amygdala included right lateral motor and premotor cortex, bilateral lingual gyrus (BA 18), and left cerbellum.

Relative to the LB amygdala, activity in the SF amygdala was more positively associated with activity bilaterally in putamen, globus pallidus, caudate body, parahippocampal gyrus, and inferior frontal gryus. Relative to the LB amygdala, activity in the SF amygdala was more negatively associated with activity bilaterally in the precuneus, caudate tail and SMA (BA 6) extending into medial portions of the motor cortex. Figure 4.2, Panel B shows the direct comparison between each subregion.

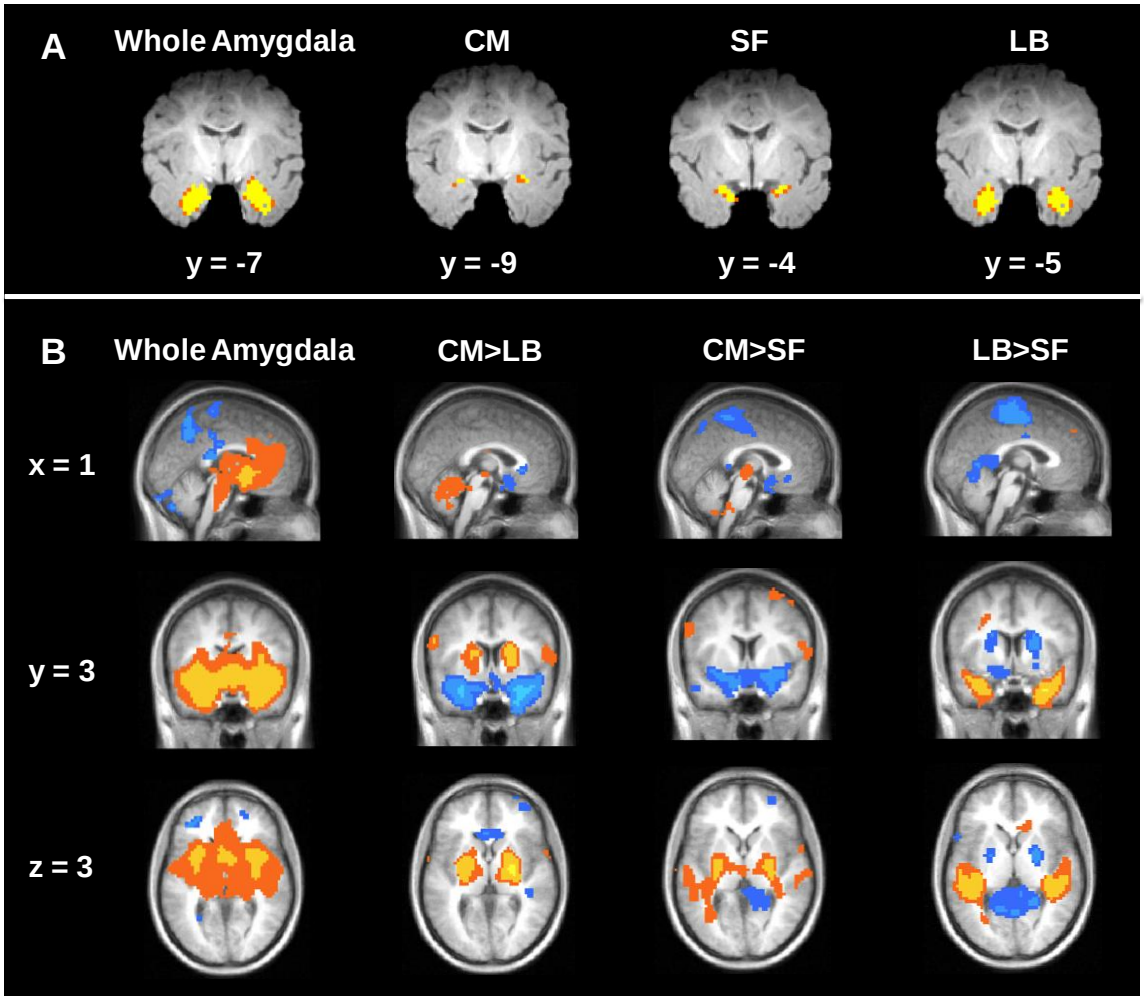


Figure 4.1. Amygdala ROIs and whole group rs-fcMRI maps. Panel A shows the whole amygdala and amygdala subregion ROIs displayed on a representative structural image from one infant. The structural image was normalized to the infant template and then transformed to adult space based on the Talairach and Tournoux atlas. The first column of Panel B shows the whole group voxelwise functional connectivity map for the whole amygdala ROI. Subsequent columns in Panel B show direct comparisons between the voxelwise functional connectivity maps for the subregion ROIs. Images in Panel B are displayed on an adult template in Talairach and Tournoux space. Displayed at coordinates corresponding to Figure 1 in the article by Roy and colleagues to facilitate comparison (Roy et al., 2009). $p < .05$, corrected for multiple comparisons based on a Monte Carlo simulation ($Z>2.25$ and 53 contiguous voxels).

Interparental Conflict Regressions

For the analyses examining associations between interparental conflict and functional connectivity, results are reported with regard to the whole group connectivity

map for the relevant ROI. For example, if the whole group evidenced negative connectivity between an ROI and a brain region, and conflict was associated with greater positive connectivity to the same region, we would infer that conflict predicted less negative coupling between the two regions.

PCC ROI. The whole brain regression of interparental conflict on connectivity of the PCC indicated that higher conflict was associated with less positive connectivity of the PCC to bilateral precuneus and paracentral lobule and less negative connectivity to left mid-posterior insula and claustrum. Higher conflict was also associated with greater negative connectivity of the PCC to right cerebellum extending into fusiform and left SMA. Results are presented in Table 4.1 and displayed in Figure 4.2, Panel B.

We extracted the resting state time courses for the PCC and MPFC ROIs to examine potential effects of conflict on connectivity between these two regions in a more focused analysis. Consistent with the whole brain analysis, interparental conflict was not significantly associated with the correlation between the PCC and MPFC.

Table 4.1. Results of Whole Brain Regression of Interparental Conflict on rs-fcMRI Map of Posterior Cingulate Cortex ROI

			Talairach			
Region	BA	Hemisphere	x	y	z	Z-value
Claustrum		Left	-34	5	4	2.85
Insula	13	Left	-45	-2	4	2.82
Paracentral Lobule and Precuneus	5/7	Left	-10	-39	52	-3.54
Cerebellum extending and Fusiform		Right	30	-39	-21	-3.16
Precentral Gyrus/SMA	6	Left	-10	-19	72	-2.83
Precuneus	7	Right	18	-65	38	-2.61
Paracentral Lobule	5	Right	11	-35	53	-2.55

Note. Infant age was included as a covariate. The table reports only results that exceeded a threshold of $p < .05$, corrected for multiple comparisons across the whole brain based on Monte Carlo simulation (specifically, $Z>2.25$ and 53 contiguous voxels). Subpeaks within the same regions are included only if they are > 10mm apart. BA=Brodmann Area; SMA=Supplementary motor area.

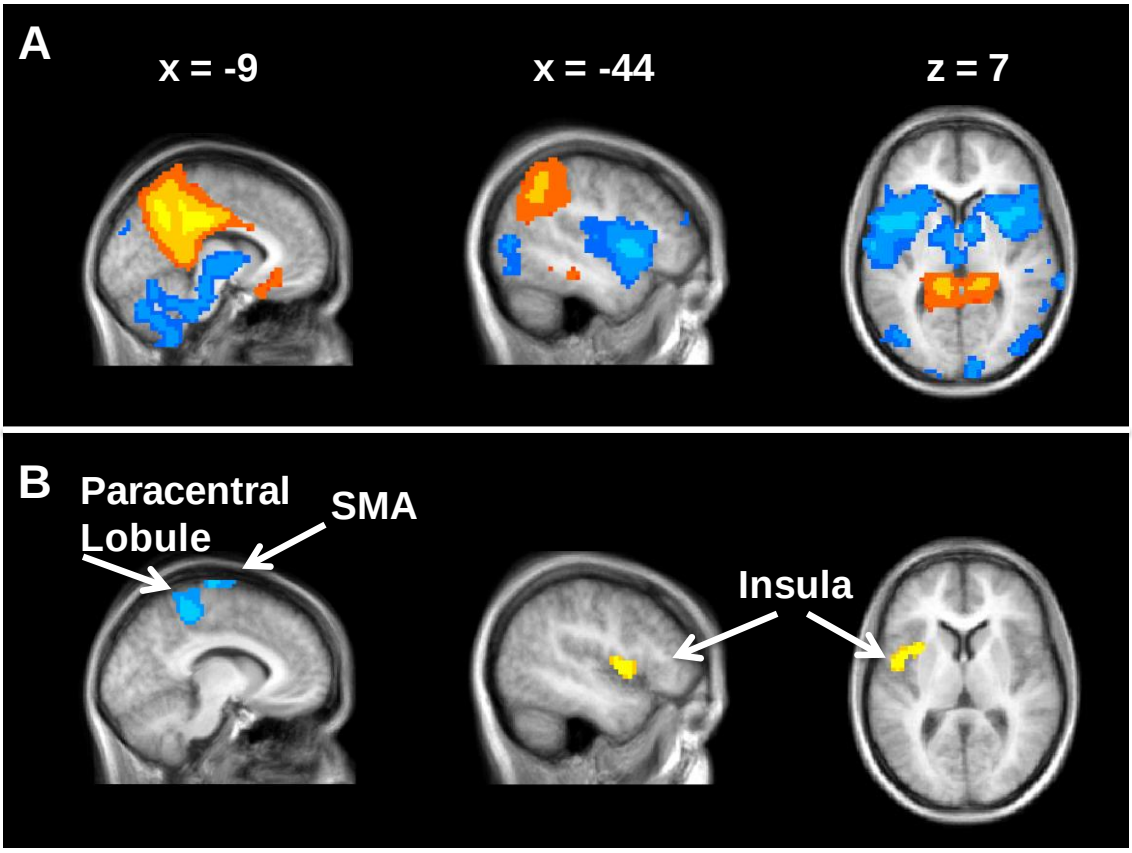


Figure 4.2. Whole group rs-fcMRI map and interparental conflict regression for PCC ROI. Panel A shows the whole group voxelwise functional connectivity map for the PCC at coordinates corresponding to the regression results displayed in Panel B. Panel B shows less positive connectivity between the PCC and left paracentral lobule/precuneus, and greater negative connectivity between the PCC and left SMA associated with higher interparental conflict. Panel B also shows less negative connectivity between the PCC and right insula/claustrum associated with higher interparental conflict. Displayed on an adult template in Talairach and Tournoux space. $p < .05$, corrected for multiple comparisons based on a Monte Carlo simulation ($Z>2.25$ and 53 contiguous voxels).

Amygdala and amygdala subregion ROIs. The whole brain regression of interparental conflict on connectivity of the whole amygdala indicated that higher conflict was associated with less positive connectivity of the amygdala to the right posterior insula extending into the claustrum and the right hippocampus. Higher conflict was also

associated with less negative connectivity of the amygdala to a region in the left somatosensory cortex extending into paracentral lobule and precuneus.

CM amygdala. For the CM amygdala, higher conflict was associated with less positive connectivity to the right insula and less negative connectivity to the left somatosensory cortex and left DLPFC. Higher conflict was also associated with greater negative connectivity between the CM amygdala and bilateral PCC. In comparison to the conflict regression for the whole amygdala, the strength of the association between conflict and less negative connectivity with the left somatosensory cortex was stronger for the CM amygdala. The insula region identified in the CM amygdala conflict regression was larger in size and located posteriorly and dorsally compared to the insula region identified in the whole amygdala regression.

SF amygdala. For the SF amygdala, higher conflict was associated with less negative connectivity with the left precuneus and right cerebellum. Higher conflict was also associated with greater positive connectivity between the SF amygdala and left somatosensory cortex, and greater negative connectivity with the right lateral somatosensory cortex.

LB amygdala. For the LB amygdala, higher conflict was associated with less positive connectivity to the right parahippocampal gyrus. Results of the regression analyses for all of the amygdala ROIs are reported in Table 4.2. As the results differed by subregion, Figure 4.3 displays the results of the regressions for the CM, SF and LB amygdala, but not for the whole amygdala.

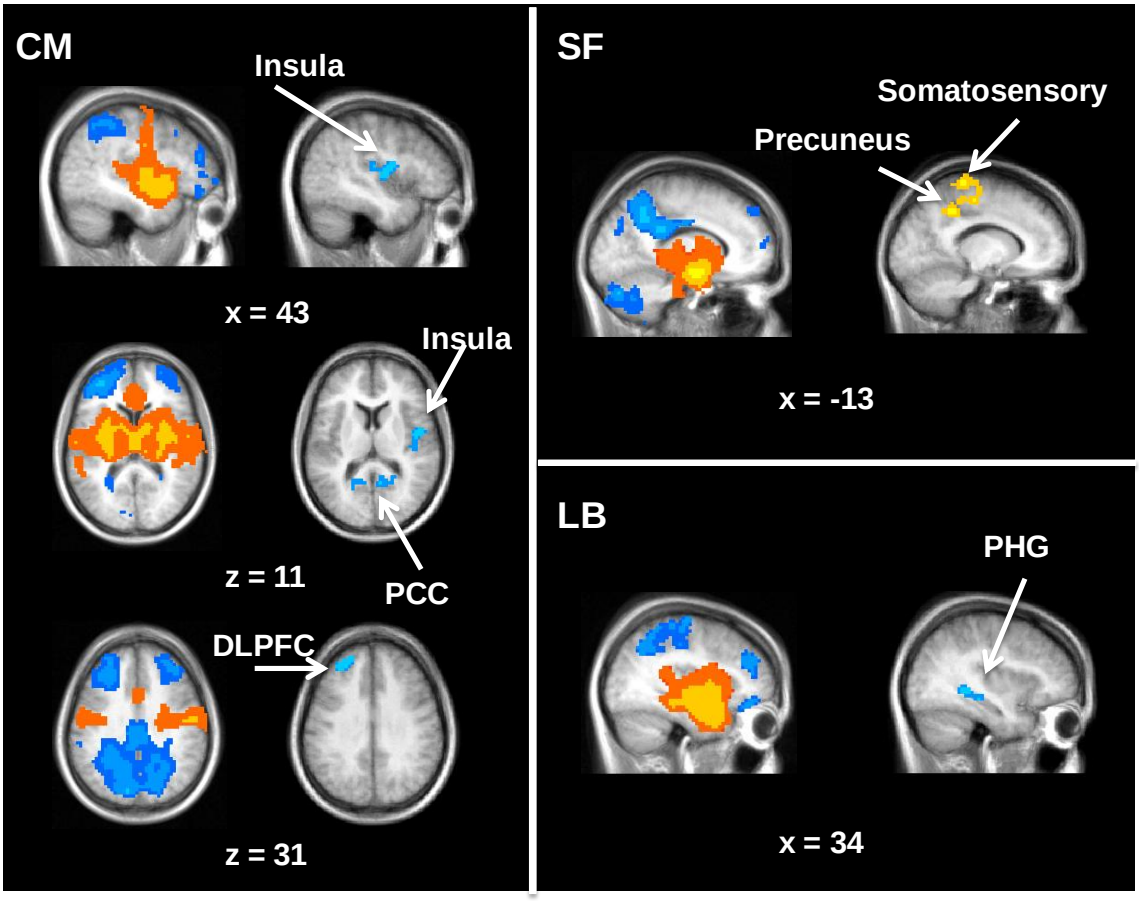


Figure 4.3. Interparental conflict regressions on rs-fcMRI maps of amygdala subregion ROIs. In each panel the images on the left show the whole group voxelwise functional connectivity map for the amygdala subregion at coordinates corresponding to the regression results on the right. For the CM amygdala, the column on the right shows less positive connectivity to the right insula, greater negative connectivity to bilateral PCC and less negative connectivity to left DLPFC associated with higher interparental conflict. For the SF amygdala, the image on the right shows less negative connectivity to the left precuneus and greater positive connectivity to left somatosensory cortex associated with higher interparental conflict. For the LB amygdala, the image on the right shows less positive connectivity to the right parahippocampal gyrus. Displayed on an adult template in Talairach and Tournoux space. $p < .05$, corrected for multiple comparisons based on a Monte Carlo simulation ($Z>2.25$ and 53 contiguous voxels). PHG=parahippocampal gyrus.

Table 4.2. Results of Whole Brain Regression of Interparental Conflict on rs-fcMRI Maps of Amygdala ROIs

			Talairach			
Region	BA	Hemisphere	x	y	z	Z-value
Whole Amygdala						
Postcentral gyrus/somatosensory	3	Left	-20	-35	65	2.64
Precuneus	7	Left	-17	-46	42	2.54
Insula	13	Right	39	-3	-10	-3.31
Hippocampus		Right	31	-46	3	-2.77
Claustrum		Right	35	-13	-7	-2.37
Centromedial Amygdala						
Postcentral gyrus/somatosensory	3	Left	-30	-34	47	3.18
Postcentral gyrus/somatosensory	2	Left	-45	-26	46	2.44
Posterior Cingulate	30	Left	-22	-55	6	-2.93
Insula	13	Right	46	-6	14	-2.90
			40	-14	6	-2.64
Superior Frontal Gyrus/DLPFC	9	Left	-25	42	30	-2.83
Medial Frontal Gyrus/DLPFC	9	Left	-17	37	24	-2.27
Posterior Cingulate	30	Right	15	-54	11	-2.43
Laterobasal Amygdala						
Parahippocampal Gyrus	19	Right	34	-42	-1	-3.11
Superficial Amygdala						
Precuneus	7	Left	-17	-46	42	3.12
Cerebellum		Right	3	-73	-40	3.01
Postcentral gyrus/somatosensory	3	Left	-16	-35	66	2.94
Medial Frontal Gyrus/SMA	6	Left	-14	-24	52	2.67
Postcentral gyrus/somatosensory	3	Right	47	-15	55	-2.49

Note. Infant age was included as a covariate. The table reports only results that exceeded a threshold of $p < .05$, corrected for multiple comparisons across the whole brain based on Monte Carlo simulation (specifically, $Z>2.25$ and 53 contiguous voxels). Subpeaks within the same regions are included only if they are > 10mm apart. BA=Brodmann Area; SMA=Supplementary motor area; DLPFC=Dorsolateral prefrontal cortex.

Amygdala ROI connectivity to fMRI ROIs. We extracted the resting state time courses for the amygdala ROIs and the two fMRI ROIs to specifically examine potential effects of conflict between these regions. This more focused set of regressions was in line

with the results of the whole brain regressions indicating that interparental conflict was not significantly associated with the correlation between any of the amygdala ROIs and either of the fMRI ROIs.

Discussion

The present study examined resting state functional connectivity of the amygdala and default network in infancy, and potential associations with a common source of ELS, nonphysical interparental conflict. The observed patterns of connectivity for the default network ROI converge with findings in adults and one study of a similar age group, indicating reliable identification of this network in infants. As a whole group, infants demonstrated connectivity between the PCC region and multiple regions considered to be part of the adult default network (M. D. Fox et al., 2005; Greicius et al., 2003) including the VMPFC, bilateral lateral parietal cortex, parahippocampal gyrus, inferior temporal cortex and left superior frontal cortex. Our findings are in line with previous work demonstrating that by 1 year of age infants evidence resting state functional connectivity among multiple default network regions (Gao, Zhu, et al., 2009). Our results differ from previous work with 1-year-old infants (Gao, Zhu, et al., 2009) only with regard to the inclusion of the left superior frontal cortex, although this finding is in line with adult work on resting state connectivity of the PCC (M. D. Fox et al., 2005; Greicius et al., 2003). Overall there is a striking similarity between the findings in the present study and that of Gao and colleagues (Gao, Zhu, et al., 2009), especially considering their use of a different analytic method (a data driven approach versus our use of an a priori PCC ROI), and the wider age range in our sample.

It is also interesting to note the overlap with adult default network studies using a PCC seed region approach (M. D. Fox et al., 2005; Greicius et al., 2003), with the only difference being the lack of an additional more dorsal and rostral MPFC region for the infants. As noted by Gao and colleagues, the adult default network appears to be more intact in infants than in children (Gao et al., 2011; Gao, Zhu, et al., 2009) indicating a potentially nonlinear pattern of development. However, changes in default network connectivity from infancy through childhood have not yet been directly examined.

Although care should be take in interpreting negative correlations in rs-fcMRI due to the potential influence of global signal regression during data processing (Chai, Castañón, Ongür, & Whitfield-Gabrieli, 2012; Murphy, Birn, Handwerker, Jones, & Bandettini, 2009; Weissenbacher et al., 2009), it is interesting to note that the observed pattern of negative correlations with the PCC seed region is generally consistent with research in adults. Research with adults demonstrates patterns of negative connectivity between the default network and regions typically activated by tasks requiring attention (Damoiseaux et al., 2006; De Luca et al., 2006; M. D. Fox et al., 2005; Fransson, 2005). The negative correlations evident in the present study between PCC and SMA, MT, right DLPFC and bilateral insula line up particularly well with the original studies in adults utilizing a PCC seed based approach (as in the present study) to examine negative connectivity with the default network (M. D. Fox et al., 2005; Fransson, 2005). To our knowledge this is the first study in infants to report this pattern of results. The meaning of these results will require further investigating as infants do not demonstrate the behavioral capacity to engage in tasks that typically elicit the activation of these regions in adults.

Interparental conflict demonstrated associations both with connectivity among default network regions and with the patterns of negative correlations among the PCC and regions associated with task engagement in adults. Contrary to our hypothesis, higher conflict was not associated with less connectivity between the PCC and MPFC either in the whole brain analysis or in a more direct examination of the connectivity between these two regions. Higher conflict was associated with decreased positive connectivity between the PCC and nearby medial parietal default network regions including parts of the precuneus and paracentral lobule bilaterally. Decreased connectivity of more proximal default network regions has not previously been associated with ELS. However, the only previous study with infants focused on preterm birth (Smyser et al., 2010), which likely represents a form of stress quite distinct from a familial stressor, such as interparental conflict. This finding could be interpreted with regard to the observed developmental pattern of decreasing local connectivity and increasing connectivity among anatomically distant regions with age (Fair et al., 2007, 2008, 2009; Gao et al., 2011). The association between interparental conflict and decreased local connectivity would then be indicative of a more mature system.

Examining the developmental trajectory of medial parietal involvement in the default network across the first several years of life provides a different context for interpretation. This trajectory is characterized by a non-linear trend in which an increasingly large area of medial parietal cortex is included in the default network from 1 to 2 years of age with a subsequent decrease in the area of medial parietal involvement from 2 years of age to adulthood (Gao, Zhu, et al., 2009). In our sample, interparental conflict is associated with decreased connectivity to parts of the precuneus and

paracentral lobule that fall at the edge of a large medial parietal cluster in the whole group map of PCC connectivity. Thus, interparental conflict may be associated with a less mature pattern of default network connectivity with regard to the non-linear developmental trajectory across the first two years of life. Longitudinal studies and analytic methods involving graph theory will likely be helpful in gaining a better understanding of this association between interparental conflict and default network connectivity.

Interparental conflict also evidenced associations with PCC connectivity to regions typically negatively correlated with the default network in adults, including the insula and SMA. Negative correlations between the default network and regions frequently activated for tasks appears to be an important component of neural organization with implications for task performance (Hampson, Driesen, Roth, Gore, & Constable, 2010; Kelly, Uddin, Biswal, Castellanos, & Milham, 2008) and mental health (Chai et al., 2011; H. Liu et al., 2012). Anxiety disorders have been associated with decreased strength of negative correlation between default network and task positive regions (Stern, Fitzgerald, Welsh, Abelson, & Taylor, 2012) and difficulty disengaging the default network during task performance (Daniels et al., 2010).

In addition to inclusion in a general task positive set of regions that demonstrate negative correlations with the default network (Damoiseaux et al., 2006; De Luca et al., 2006; M. D. Fox et al., 2005; Fransson, 2005), both the insula and SMA have been associated with salience detection and related motor output (Downar, Crawley, Mikulis, & Davis, 2002; Menon & Uddin, 2010; Seeley et al., 2007). The insula in particular appears to be play a central role in detecting the personal relevance of both environmental

stimuli and aspects of internal state (Craig, 2009; Menon & Uddin, 2010). In line with this role of salience detection and response to personally relevant stimuli, both regions have also been implicated in the underlying neurobiology of stress related psychopathology. Activity in the SMA has been found to be associated with PTSD across fMRI studies involving both cognitive-emotional stimuli unrelated to trauma and trauma specific stimuli (Hayes et al., 2012). Decreased grey matter volume in the SMA has also been found in adults with complex PTSD related to childhood trauma, with greater severity of abuse and current symptomatology negatively correlated with SMA volume (Thomaes et al., 2010). Decreased grey matter volume in the insula has also been associated with PTSD (Chen et al., 2006) and with child maltreatment in healthy adults (Dannlowski et al., 2012). Resting state fMRI studies have indicated decreased spontaneous activity of insula (Yin et al., 2011) and decreased connectivity between the PCC and insula (Bluhm, Williamson, Osuch, et al., 2009) associated with PTSD. The literature thus provides support for the relevance of connectivity between default network regions and the insula and SMA for task engagement and mental health, and for the potential for stress and associated psychopathology to alter this connectivity. These regions have not previously been a focus of research into the effects of ELS, but continued use of rs-fcMRI to examine functional neural networks beginning in infancy may shed light on their relevance.

The present study provides novel evidence for resting state functional connectivity of the whole amygdala and amygdala subregions during the first year of life. Interestingly, the patterns of connectivity for the whole amygdala were similar to those observed in resting state connectivity studies of the amydgala in adults (Bickart et al.,

2012; Etkin et al., 2009; Roy et al., 2009). Regions displaying positive connectivity with the amygdala included ACC, insula, STG, caudate, thalamus, hypothalamus and hippocampus. Some of these functional connections, such as those between amygdala and regions of the MPFC, appear to underlie regulatory functions in adults (Banks, Eddy, Angstadt, Nathan, & Phan, 2007; Goldin, McRae, Ramel, & Gross, 2008; Lieberman et al., 2007) that are clearly beyond the behavioral capacity of 6-12-month old infants. Thus the significance of these patterns of connectivity at a behavioral level remain unclear. A recent study directly comparing amygdala resting state functional connectivity in children and adults reported that although amygdala connectivity to a widely distributed network of cortical and subcortical regions was evident in 7-9-year-old children, many of these connections were significantly weaker when compared to adult connectivity (Qin et al., 2012). Although the present study cannot speak to the relative strength of these connections in infants versus children and adults, based on the work of Qin and colleagues and the maturation of behaviors relying on amygdala connectivity, it is likely that the strength of these connections will change over the course of development.

Despite the similarity of the overall pattern of findings with research in adults, there were also notable differences including a lack of negative connectivity between the amygdala and DMPFC regions evident in the work of Roy and colleagues with adults (Roy et al., 2009). In addition, our results indicate negative connectivity between the amygdala and fusiform gyrus in contrast to the positive connectivity evident in adult samples (Bickart et al., 2012; Etkin et al., 2009; Roy et al., 2009). A shift in the valence of amygdala functional connectivity with cortical regions over the course of development is in line with a recent functional activation MRI study documenting a change in valence

of amygdala to MPFC connectivity across the transition from childhood to adolescence (Gee et al., 2013). Other patterns of negative connectivity for the amygdala in the present study were consistent with those observed in adults (Roy et al., 2009), and included negative correlations with bilateral DLPFC, PCC, precuneus, and cerebellum.

The patterns of connectivity for the amygdala subregions were also surprisingly in line with research in adults (Bickart et al., 2012; Etkin et al., 2009; Roy et al., 2009) and adolescents (Roy et al., 2013) indicating different distinct patterns of connectivity for each subregion. For example, similar to adult studies (Etkin et al., 2009; Roy et al., 2009), we observed greater connectivity of the LB amygdala to STG, hippocampus and parahippocampal gyrus in comparison to the CM and SF amygdala. The findings of greater CM amygdala connectivity to subcortical regions including thalamus and caudate relative to the other subregions is also in line with the adult literature (Etkin et al., 2009; Roy et al., 2009). These results are surprising given recent work indicating a lack of differentiation in resting state functional connectivity of these subregions for children. Qin and colleagues reported that only connectivity to temporal pole and perirhinal cortex differentiated between the patterns for the LB and CM amygdala in 7-9 year old children. In light of the present study, these findings indicate that development of amygdala subregion connectivity may follow a non-linear developmental trajectory similar to the default network (Fair et al., 2008; Gao et al., 2011; Gao, Zhu, et al., 2009). However, it will be necessary to assess whether factors unique to fMRI work with infants, such as scanning during natural sleep, play a role in the more adult-like patterns of resting state networks observed during infancy versus childhood.

The rACC and hypothalamus ROIs identified in the fMRI study as showing greater reactivity to very angry tone of voice for infants in higher conflict homes (Graham et al., 2013), demonstrated positive resting state connectivity to the amygdala in the present study. This finding provides support for the connectivity of these regions to limbic circuitry posited to play an important role in the impact of ELS on development. However, contrary to our hypotheses, interparental conflict was not associated with differences in resting state connectivity between the amygdala (or any amygdala subregion) and these two regions. It is possible that over time, repeated activation of these regions in response to very angry tone of voice would lead to altered functional connectivity with the amygdala in the absence of a stressor relevant stimulus. Longitudinal work examining associations between reactivity to stressor relevant stimuli and development of resting state functional connectivity networks will be necessary to address this possibility.

Although interparental conflict was not associated with resting state connectivity between the amygdala and the fMRI ROIs, it was associated with amygdala connectivity to other regions potentially relevant for understanding the effects of ELS. In line with the animal literature regarding effects of ELS on the amygdala, the results were distinct for the different amygdala subregions. For the the LB amygdala conflict was associated with decreased positive connectivity between the amygdala and the parahippocampal gyrus. This result is in line with the extensive animal literature and neuroimaging work in older children and adults indicating a central role for the amygdala and hippocampus in the impact of ELS on development (Dannlowski et al., 2012; Tottenham & Sheridan, 2010). A recent rs-fcMRI study also indicated decreased positive resting state functional

connectivity between the whole amygdala and hippocampus for adults with combat related PTSD compared to soldiers without PTSD (Sripada et al., 2012). This result is also in line with animal studies indicating extensive connectivity between the LB amygdala and hippocampus, which plays an important role in mediating the effects of stress on learning and memory (Roozendaal et al., 2009).

For the CM amygdala, interparental conflict was associated with connectivity to regions implicated in sensory processing, emotion regulation and the default network. The finding of an association between interparental conflict and connectivity of the CM amygdala to both the insula and somatosensory cortex is interesting in light of animal research identifying pathways between the insula and the CM amygdala (Reynolds & Zahm, 2005), and from sensory processing regions through the CM amygdala to hypothalamic nuclei controlling peripheral nervous system functioning (Amaral, Price, Pitkänen, & Carmichael, 1992; Barbas, Saha, Rempel-Clower, & Ghashghaei, 2003). The insula plays an important role in integrating information about internal physiological state and salient sensory cues in the environment (Nieuwenhuys, 2012). The association between conflict and connectivity of the CM amygdala to both a sensory region and the insula may indicate modulation of pathways involved in processing both interoceptive and external sensory cues with implications for autonomic nervous system functioning. Previous work has demonstrated an association between interparental conflict and autonomic nervous system functioning in infancy (Moore, 2010; C. Porter et al., 2003). Future research could provide a bridge between these findings by examining whether variation in CM amygdala functional connectivity to insula and sensory regions predicts autonomic nervous system functioning during infancy.

Altered amygdala to insula connectivity has previously been implicated in stress related psychopathology, although these studies have examined the amygdala as a whole. The two extant studies utilizing whole brain analyses to examine amygdala resting state functional connectivity in PTSD have both indicated increased connectivity between the whole amygdala and right posterior insula for soldiers with combat related PTSD versus soldiers without PTSD (Rabinak et al., 2011; Sripada et al., 2012). Researchers using fMRI to examine reactivity to emotion stimuli have provided evidence for increased functional connectivity between the amygdala and insula after exposure to severe combat stress (Van Wingen et al., 2011) and decreased connectivity between amygdala and insula for women with domestic violence related PTSD compared to healthy controls (Fonzo et al., 2010). However, the present findings are the first to demonstrate an association between ELS and functional connectivity between the amygdala and insula during infancy. Amygdala to insula connectivity may be relevant both for exposure to ELS during early developmental periods and for stress related psychopathology in adulthood.

Interparental conflict was also associated with lower negative connectivity between the CM amygdala and the left DLPFC, a region frequently implicated in emotion regulation (Peña-Gómez, Vidal-Piñeiro, Clemente, Pascual-Leone, & Bartrés-Faz, 2011). This result is interesting in light of evidence that increased CM and LB amygdala resting state connectivity to DLPFC in adults with generalized anxiety disorder (GAD) may serve as a compensatory strategy (Etkin et al., 2009). In individuals with GAD, greater connectivity of the CM and LB amygdala to the DLPFC was associated with lower anxiety symptoms (Etkin et al., 2009). Future studies could explore the association

between ELS and the connectivity of these regions with regard to infants displays of fear and emerging regulatory capacity.

Finally, interparental conflict was associated with CM amygdala functional connectivity to bilateral PCC, posterior and ventral to the PCC default network ROI used in the present study. Recent work indicates that PTSD related to child abuse (Bluhm, Williamson, Osuch, et al., 2009) and traumatic accidents (Lanius et al., 2010) is associated with alterations in default network connectivity to limbic regions, and specifically PCC to amygdala connectivity. Weaker resting state functional connectivity between the amygdala and the PCC has also been observed in adults with social anxiety disorder compared with healthy controls (Hahn et al., 2011). Moreover, Hahn and colleagues reported a negative correlation between PCC to amygdala connectivity and anxiety scores across socially anxious individuals and controls (Hahn et al., 2011). These findings are in line with evidence that the PCC plays an important role in modulating amygdala activity (Stein et al., 2007). The present study indicates that ELS may be associated with altered connectivity between amygdala and PCC during early stages of development prior to the emergences of anxiety disorders. In line with this possibility, a recent study reported that higher cortisol levels during early childhood predicted increased negative resting state connectivity between the amygdala and PCC in adolescence (Burghy et al., 2012).

Interparental conflict was also associated with SF amygdala connectivity to another default network region, the precuneus. However, while higher interparental conflict predicted increased negative connectivity between the CM amygdala and bilateral PCC, it was associated with decreased negative coupling between the SF

amygdala and precuneus. These results suggest potentially distinct effects of ELS on amygdala connectivity to default network regions depending on amygdala subregion.

The associations between interparental conflict and connectivity of the SF amygdala also overlapped with the CM amygdala with regard to connectivity with somatosensory cortex. Higher interparental conflict predicted greater positive connectivity of the SF amygdala to the left somatosensory cortex and greater negative connectivity of the SF amygdala to the right somatosensory cortex. The associations between interparental conflict and amygdala connectivity to the somatosensory cortex are intriguing with regard to the extensive animal literature documenting the effects of maternal licking and grooming on amygdala development in rats (Caldji et al., 1998, 2000). Affectionate physical contact with caregivers also predicts healthy development across multiple domains in human infants (Feldman, Eidelman, & Rotenberg, 2004; Feldman & Eidelman, 2003; Hertenstein, 2002), although the neural mechanisms remain unexplored. As interparental conflict has previously been associated with less sensitive caregiving practices (Frosch, Mangelsdorf, & McHale, 2000; Kanoy, Ulku-Steiner, Cox, & Burchinal, 2003), it is possible that infants in high conflict homes receive less affectionate physical contact, or more aversive physical contact, leading to altered connectivity between the amygdala and somatosensory cortex. However, future research will be needed to examine whether the amount and nature of physical contact between caregivers mediates this association between interparental conflict and amygdala to somatosensory cortex connectivity.

The present study provides novel evidence for the functional connectivity of the amygdala in human infants and confirms previous findings of connectivity among

multiple default network regions by 1 year of age. Later in life the connectivity of these regions is associated with mental health outcomes, making it particularly important to understand early patterns of connectivity and the potential influence of ELS. Nonphysical interparental conflict, a common form of ELS previously associated with behavioral and physiological indices of emotion regulation in infants (Crockenberg et al., 2007; Moore, 2010; C. Porter et al., 2003), was associated with differences in the connectivity of the default network and the amygdala. The results did not support our hypotheses regarding associations between conflict and specific pairs of regions, including amygdala connectivity to seed regions from an fMRI study with this sample. However, at this early stage of examining associations between ELS and functional neural networks in infancy it will likely be informative to conduct exploratory whole brain analyses.

Several themes emerged from these whole brain analyses in the present study that might serve as a basis for future research. First, interparental conflict was associated with altered connectivity among default network regions (although not specifically between the PCC and MPFC). Thus, in addition to events such as preterm birth, more common, moderate sources of ELS may be associated with default network connectivity during infancy. Second, interparental conflict was associated with altered connectivity of both the PCC and amygdala to the insula. Previous work has indicated that the insula is a hub, or highly interconnected region, across the first several years of life (Fransson, Aden, Blennow, & Lagercrantz, 2011; Gao et al., 2011), and plays an important role in salience detection of visceral and environmental stimuli in adulthood (Craig, 2009; Menon & Uddin, 2010). Taken together with the present findings, this work suggests that examining effects of ELS on the development of insula connectivity may help provide a

more integrated understanding of the widespread effects of ELS across multiple domains of functioning.

Third, the amygdala subregions evidenced different patterns of connectivity, and distinct associations with interparental conflict. These results converge with the animal literature and indicate a potentially non-linear trajectory for the development of amygdala subregions in humans. Finally, interparental conflict was associated with amygdala connectivity to regions implicated in sensory processing, emotion regulation and the default network. Thus, rs-fcMRI analyses may be informative in terms of understanding the effects of ELS not only on limbic regions typically associated with stress and emotion regulation, but on distributed networks involved in processing, integrating and reacting to environmental stimuli.

Challenges associated with the present study include the use of amygdala subregion probability maps based on research with adults. Although the utility of these maps for children has previously been demonstrated (J. E. Kim et al., 2010), cyotarchitectural mapping of the infant amygdala will be necessary to confirm their accuracy for infant studies. However, the results of the present study, indicating the potential importance of amygdala subregion connectivity for understanding effects of ELS in infancy, provide support for the need for such maps. It should also be noted that the resting state scan in the present study occurred after a functional activation scan involving auditory stimuli. Future work will benefit from counterbalancing scan order to check for potential effects of preceding scans. Finally, we were not able to monitor sleep state in the present study. Several studies have indicated altered default network connectivity across different sleep stages (Andrade et al., 2011; Spoormaker et al., 2010).

Similar to previous rs-fcMRI studies with sleeping infants (Gao et al., 2011; Gao, Zhu, et al., 2009), the patterns of functional connectivity observed in the present study are in line with patterns observed in older awake subjects and expected patterns based on the animal literature. Nonetheless, methodological advances allowing for monitoring of sleep state in infants during fMRI will provide important information about variability in connectivity due to differences in sleep stage.

Despite these challenges, the findings of the present study provide support for the utility of rs-fcMRI with infants to characterize the coordinated functioning of neural regions thought to be important for understanding the impact of ELS. This work highlights that brain regions frequently examined in the context of ELS, such as the amygdala, function in coordination with multiple other regions throughout the brain. This work also provides support for associations between a common, moderate source of ELS and neural functioning in the absence of a stressor relevant stimulus. Examining how various sources of ELS affect development of coordinated brain functioning will likely lend insight into the challenges frequently faced by individuals with experiences of early adversity.

CHAPTER V

CONCLUSION

Summary of Findings

This dissertation uses fMRI during natural sleep to examine associations between a common source of ELS, nonphysical interparental conflict, and infants' neural functioning. This work builds on studies demonstrating the possibility of using fMRI during natural sleep with infants and toddlers (Dehaene-Lambertz et al., 2002; Redcay et al., 2007). The use of fMRI confers the unique advantage of providing high enough spatial resolution to examine specific cortical and subcortical neural regions. However, this technique has not previously been used during infancy to examine associations between a familial source of ELS and neural functioning.

Chapter II reviews the research establishing a foundation for the use of fMRI during natural sleep with infants and toddlers. Evidence is provided for the utility of functional activation paradigms, in which stimuli are presented during sleep, and for rs-fcMRI, in which coordinated neural functioning is assessed at rest, in the absence of stimuli presentation. Research with functional activation paradigms has predominantly made use of auditory stimuli. These studies have led to increased understanding of normative developmental changes in neural processing of language (Redcay et al., 2008), and patterns or neural processing associated with later diagnosis of developmental disorders (Pierce, 2011). Research with rs-fcMRI has provided evidence for rapid development of functional neural networks across the first several years of life (Gao et al., 2011; Gao, Zhu, et al., 2009) and for the potential for rs-fcMRI to capture altered

developmental patterns associated with developmental disorders (Dinstein et al., 2011) and preterm birth (Smyser et al., 2010). This chapter also presents important methodological issues that require attention with the use of functional activation paradigms and rs-fcMRI with infants during natural sleep. Finally, this chapter argues for the utility of fMRI during natural sleep for understanding effects of ELS on the brain within a more proximal time frame, prior to processes of recovery or development of mental health problems frequently associated with ELS.

The first empirical chapter (Chapter III) presents the results of an experiment using a functional activation paradigm to examine the association between nonphysical interparental conflict and infants neural processing of a stressor relevant stimulus, very angry tone of voice. This study employed stimuli comprised of nonsense speech in different emotional tones of voice (very angry, angry, happy and neutral) designed by Pell and colleagues (Pell et al., 2009). This allowed for a focus on emotional tone of voice versus semantic content of sentences. Higher interparental conflict was associated with increased reactivity to very angry tone of voice in the rACC and a subcortical cluster encompassing hypothalamus and parts of the thalamus and caudate. Regardless of the level of interparental conflict, infants demonstrated distinct patterns of processing for different emotional tones of voice. This study provides novel evidence for an association between nonphysical interparental conflict and infants neural processing of very angry tone of voice. The results also indicate that neural regions frequently implicated in the animal literature as central for understanding the impact of ELS, including the MPFC and hypothalamus, may also play a role in the effects of ELS on human infants. Finally, these results build on existing work indicating the utility of auditory functional activation

paradigms with infants during natural sleep, and provide the first evidence from an fMRI study for infants neural processing of emotional speech during sleep.

The second empirical chapter (Chapter IV) presents the results of a study using rs-fcMRI to examine functional neural networks in infancy and associations with nonphysical interparental conflict. This study focused on a separate resting state scan, in which no stimuli were presented, conducted with the same sample of infants described in Chapter III. Seed based whole brain analyses were used to examine resting state functional connectivity of a default network region, the PCC, and a region central to the literature examining effects of ELS on development, the amygdala. We also examined patterns of connectivity for three amygdala subregions. The results provide a replication of previous work demonstrating functional connectivity of multiple default network regions in infancy, and novel evidence for resting state functional connectivity of the amygdala and amygdala subregions during infancy. Distinct patterns of connectivity were observed for the different amygdala subregions, indicating that even during the first year of life, the unique development of amygdala subregions should be considered.

Interparental conflict was associated with differences in the patterns of resting state functional connectivity for the PCC and for the amygdala. The results did not support hypotheses regarding associations between interparental conflict and connectivity between specific pairs of regions including the PCC and an MPFC default network region, and the amygdala and the rACC and hypothalamus regions from the functional activation study. However, conflict was associated with PCC connectivity to another default network region, the precuneus, and with amygdala connectivity to regions implicated in emotion regulation, the DLPFC, and typically associated with the effects of

ELS, the parahippocampal gyrus. Moreover, several interesting themes emerged, including the potential importance of considering insula connectivity, basic sensory processing regions and distinct contributions of different amygdala subregions for understanding the effects of ELS in human infants.

Implications of Findings and Future Directions

Taken together these chapters provide support for the utility of fMRI during natural sleep to examine associations between ELS and the functioning of specific neural regions and networks during infancy. As described in Chapter I, the levels of stress model characterizes ELS as positive, tolerable or toxic based on an individual's response to stress, and whether this pattern of responding over time leads to neurobiological changes that increase risk for mental or physical illness (National Scientific Council on the Developing Child, 2005). Toxic stressors tend to be chronic in nature, with repeated activation of the stress response system leading to neurobiological changes associated with poor developmental outcomes (Loman et al., 2010). The levels of stress model builds on animal literature demonstrating the vulnerability of the developing brain to stress, and the associated consequences for regulatory functioning and other aspects of development (Sánchez et al., 2001). Although research with humans has provided additional support for this model, the use of fMRI to examine the functioning of cortical and subcortical brain regions has been restricted to older children and adults. Moreover, previous work with humans examining effects of ELS on the brain has focused predominantly on extreme stressors, such as a maltreatment or institutionalization.

Nonphysical interparental conflict represents a moderate and common form of ELS likely to be chronic in nature while both parents reside in the same house. The

findings presented in Chapter III indicate that infants in homes with higher levels of interparental conflict show greater reactivity to very angry tone of voice in brain regions thought to play an important role in linking ELS with subsequent risk for psychopathology. These findings provide support for conceptualizing interparental conflict as a toxic stressor. For infants in higher conflict homes the response to a stressor relevant stimulus is characterized by greater involvement of brain regions tightly linked to stress related psychopathology. However, longitudinal work will be necessary to examine whether interparental conflict continues to be associated with this response to angry tone of voice, and whether this response predicts developmental outcomes.

The findings presented in Chapter IV indicate the utility of rs-fcMRI for examining the coordinated functioning of neural regions in the absence of a stressor relevant stimulus. Even for chronic sources of ELS, it is expected that there will be periods of time in which infants are not exposed to stimuli relevant to the stressor. The results demonstrate that functional connectivity among regions likely vulnerable to the effects of ELS and associated with psychopathology in adults, can be characterized by this methodology in infants. The amygdala demonstrated positive connectivity with both of the brain regions identified in the functional activation study, the rACC and the hypothalamus. This provides evidence for the hypothesized connectivity of these regions to other regions involved in reactivity and regulation of the HPA-axis and frequently associated with the impact of ELS. However, interparental conflict was not associated with differences in the connectivity of these regions to the amygdala. Eventually, interparental conflict might be associated with altered resting state functional connectivity of these regions at rest due to repeated exposure to angry tone of voice. This

would be in line with the hypothesis that resting state connectivity emerges due to repeated, frequent coactivation of regions over time (Fair et al., 2007; Kelly et al., 2009; Power, Fair, Schlaggar, & Petersen, 2010).

The associations between interparental conflict and resting state functional connectivity among brain regions typically associated with the effects of ELS as well as regions implicated in the default network, sensory processing and emotion regulation, indicates the potential utility of statistical techniques better suited for characterizing organization of neural networks. Graph theoretical approaches have been successfully utilized to capture development of neural networks from infancy (Fransson et al., 2011; Gao et al., 2011) through childhood and adulthood (Fair et al., 2007, 2008, 2009). Such an approach simultaneously takes into account resting state connectivity among multiple brain regions and characterizes their organization into functional neural networks (Power et al., 2010). A graph theoretical approach would likely allow for a more succinct characterization of the associations between conflict and the connectivity of the amygdala and PCC found in the present study.

There are multiple potential avenues for building on the research presented in this dissertation. First, assessment of family functioning is best achieved with a multi-method approach involving behavioral observation in addition to questionnaire measures. Future work utilizing more in depth assessment and examining multiple aspects of family functioning, including the interparental relationship and the parent-infant relationship, will be critical for understanding how the family environment influences brain development. Second, it will be critical to examine associations between fMRI measures, infant behavior and autonomic nervous system and neuroendocrine functioning. This will

facilitate placing the fMRI research in the context of existing studies documenting associations between family functioning and infant behavior and peripheral measures of the autonomic nervous system and neuroendocrine functioning. Moreover, longitudinal work employing multiple measures will allow for examination of changes in brain functioning as mediators of the impact of family functioning on behavioral and physiological regulation. Such work has the potential to increase understanding of toxic stress as fMRI research into the development of PTSD in adults has demonstrated (Admon et al., 2009; van Wingen et al., 2012)

There is also a need for future research to examine the methodological issues presented in Chapter II. As discussed in detail in Chapter II, the effects of sleep state on functional activation and rs-fcMRI studies remain under investigation. At present, simultaneously collection of fMRI and EEG data necessary for ascertaining sleep state has not been accomplished with infants. However, the feasibility of such work in adults indicates a high likelihood that it will become possible to safely conduct this research with infants in the future. It is currently possible to obtain measures of peripheral nervous system functioning during a scan and measures of neuroendrocrine functioning before and after scanning. Researchers interested in ELS, could utilize such measurement to ascertain whether infants with high levels of ELS show different reactivity to the scanning environment that may have implications for their observed brain activity.

The studies presented in this dissertation draw attention to the potential for both functional activation and rs-fcMRI studies with infants to increase understanding of how ELS influences development. This work has potential to bridge gaps between the human literature and animal literature. Future fMRI work beginning in infancy and employing

longitudinal methods may also provide a more nuanced understanding of how individuals exposed to ELS develop psychopathology or adaptive coping strategies that confer resilience.

APPENDIX

SUPPLEMENTARY INFORMATION FOR CHAPTER III

Method

Participants

Scans were attempted for 39 infants with 24 completing the scanning protocol. For each infant, up to two visits to the Lewis Center were made to attempt scanning. Fifteen infants did not complete the scanning protocol due to difficulty falling asleep at the scan center or waking during the protocol. For the 24 infants scanned successfully, race and ethnicity were representative of the community in which recruitment occurred (83.3% Caucasian and 16.67% other or more than one race; 20.8% Hispanic). The median category for gross annual household income was $25,000–$29,999, based on a 12-point scale: 1 (*less than $4,999 per year*) to 12 (*$100,000 or more per year*). With regard to educational attainment for mothers, 8.3% did not complete high-school or a test equivalent, 20.9 % completed high-school or a test equivalent, 37.5% completed some community college, and 33.4% completed at least one year or more of a standard 4-year college. Recruitment through Craigslist and local public sector human services agencies may have skewed the sample towards being of lower socioeconomic-status. Infants scanned successfully did not differ significantly from the rest of the sample with regard to age, gender, race, ethnicity or family income.

Interparental Conflict Measures

Both measures of interparental conflict, the Psychological Aggression scale of the Conflicts Tactics Scale-Revised (CTS2; Straus, Hamby, Boney-McCoy, & Sugarman, 1996) and the O'Leary-Porter Scale (OPS; B. Porter & O'Leary, 1980), were adapted in

minor ways to focus on infancy and were scored as suggested by the creators of the measures and in a manner consistent with the research literature.

The CTS2 was adapted to ask about partner aggression since childbirth (as opposed to the previous year). Maternal report of aggression toward and received from her partner on the psychological aggression subscale was included in the present study. The response categories on the CTS2 include ranges denoting the frequency with which a behavior occurred**.** The response categories are as follows: 0 (*this has never happened*), 1 (once), 2 (twice), 3 (*3–5 times*), 4 (*6–10 times*), 5 (*11–20 times*), or 6 (*more than 20 times*). Responses indicating a range were recoded to a single number in the middle of the range (i.e., 4 [*3–5 times*], 8 [*6–10 times*], and so on) to represent frequency of aggression as suggested by the author of the measure (Straus et al., 1996). Maternal psychological aggression toward and received from her partner were highly correlated (r = .867 $p <$ .001) and were therefore averaged to create a composite score of psychological aggression in the home (α=.936).

The OPS was adapted for infants to ask about the frequency of arguments in front of the 'infant' (instead of the 'child'). This adaptation simply involved changing the word 'child' to 'infant.' In addition, one item about physical expressions of hostility was removed from the scale in order to focus on the level of non-physical conflict in the home. The total sum score represents frequency of verbal hostility in the presence of the infant (α=.823).

Maternal report on the CTS2 (Psychological Aggression scale) and the OPS were combined by taking the average of the two in order to capture the overall level of non-physical conflict in the home. Combining the measures was warranted from a

theoretical perspective, as both measures focus on non-physical conflict in the home, and from an empirical perspective due to the high correlation between them (r (22) = .744, p < .001).

Auditory Stimuli

The emotion category for each sentence was identified by 24 native English speaking adults based on a forced choice of 7 possible emotions including neutral (Pell et al., 2009). The mean percentage of correct category identification for the sentences in each emotion condition in the present study are as follows: very angry (*M*=100%), mildly angry (*M*=97%), happy (*M*=75%) and neutral (*M*=97%). Emotional intensity for each sentence in an emotion category other than neutral was rated on a 5 point scale (with 5 indicating the highest level of emotional intensity; Pell et al., 2009). Mean emotional intensity for the sentences included in each emotion condition in the present study was as follows: very angry (*M*=4.35, *SD*=.13), mildly angry (*M*=3.30, *SD*=.09) and happy (*M*=3.39, *SD*=.12). Mean and maximum amplitude for the sentences included in each emotion condition are presented below (Supplementary Table 3.1).

Scanning Protocol

Prior to scanning families came in to the neuroimaging center to fill out questionnaires, as well as learn about MRI safety and scanning procedures with infants. During this session parents completed a screening form regarding potential MRI contraindications for their infant (Lewis Center for NeuroImaging MRI Screening Questionnaire) and signed a release for their infant's physician to fill out the screening form. Parents were given a CD of scan noises to play for three nights prior to the scan session in order to allow infants to become accustomed to the noises. Families came in

for scanning at their infants' regular bedtime. Once asleep the infant was placed on the scanner bed. Bilsom pneumatic headphones were then placed on the infant to attenuate noise from the MRI scanner and to present auditory stimuli. Additional soft padding was used between the earphones and the inside wall of the head coil for further sound protection and to stabilize head movements. Two researchers remained in the room throughout scanning to ensure infants' safety and monitor for any signs of wakefulness or distress.

fMRI Data Acquisition

Scan parameters for the T2 weighted functional scans were as follows: TR=2000ms, TE=30ms, flip angle=80°, matrix size 64x64, FOV=200mm, 32 slices, 3.125mm in-plane resolution, 4mm thick. A high-resolution T1-weighted MP-RAGE scan lasting 8min was also obtained (TR=2500ms, TE=4.38 ms, TI=1100ms, flip angle=8°, matrix size 256x192, FOV=256mm, 160 slices, 1mm in-plane resolution, 1mm thick).

Results

Effects of Interparental Conflict on Processing Happy Tone of Voice

To examine whether the association between interparental conflict and neural activity during very angry greater than neutral tone of voice is specific to very angry tone of voice we conducted a whole brain regression of interparental conflict on the happy greater than neutral contrast. We found no overlap between the brain areas identified in this analysis and those identified in the regression of interparental conflict on very angry compared to neutral. This suggests that the association between interparental conflict and neural activity in the rostral ACC and subcortical cluster including caudate, thalamus and

hypothalamus, is specific to very angry as opposed to happy tone of voice. Although there was no overlap among the regions, interparental conflict was associated with neural activity during happy versus neutral tone of voice in two clusters centered in the right posterior insula extending into the somatosensory cortex and auditory cortex, and in the left posterior insula extending into the somatosensory cortex (see Supplementary Table 3.2 and Supplementary Figure 3.1). When we covaried for the unique effect of age the cluster on the left extended down to include activation in the left amygdala, extending anterior, superior and lateral to the following peak: Infant xyz= -12, -7 ,-17; MNI xyz= -15, -9, -22; *t*=4.45 (see Supplementary Table 3.2 and Supplementary Figure 3.1).

Most importantly, we conducted an additional analysis to directly test whether the association between conflict and response to very angry speech relative to neutral was statistically greater than the association between conflict and response to happy relative to neutral speech. The results indicate that interparental conflict demonstrates a greater positive association with neural activity in the rostral ACC (above statistical threshold for multiple comparisons, Infant xyz= 6, 29, 4; MNI xyz= 7, 36, 5; *t*=2.61, k=100) and in the subcortical regions encompassing parts of the hypothalamus (with a cluster size below the statistical threshold for multiple comparisons, Infant xyz= 3, 2, 4; MNI xyz= 4, 2, 5; *t*=2.34, k=17) during presentation of very angry relative to neutral tone of voice than during presentation of happy relative to neutral tone of voice. These results remained consistent when including the age covariate. Taken together these additional analyses indicate that the association between interparental conflict and neural activity during very angry tone of voice relative to neutral is specific to very angry as opposed to happy tone of voice.

Methodological Issues Relevant to Results

In the present study we did not monitor sleep state during fMRI data collection, which places limitations on our understanding of how variation in sleep state may have affected the results. Research employing simultaneous EEG and fMRI data collection in infants and toddlers to allow for tracking sleep state during functional activation paradigms has not yet been published due to methodological challenges. However, ERP studies with infants provide support for comparable neural processing of auditory stimuli during sleep and wake (Cheour, Ceponiené, et al., 2002), with preservation of response amplitude and latency across different sleep stages (Martynova et al., 2003). Moreover, it appears that learning involving auditory and basic somatosensory stimuli occurs during sleep for infants (Cheour, Martynova, et al., 2002; Fifer et al., 2010; Reeb-Sutherland et al., 2011). With regard to BOLD signal changes during sleep versus wake, research with infants (Dehaene-Lambertz et al., 2002) and adults (Czisch et al., 2002; Portas et al., 2000) indicates similar patterns of auditory and linguistic processing in sleep and wake states, with potential dampening of responses during sleep. Thus it seems more likely that the findings would be stronger rather than weaker in an awake state, although future research in this area employing simultaneous EEG and fMRI will be necessary.

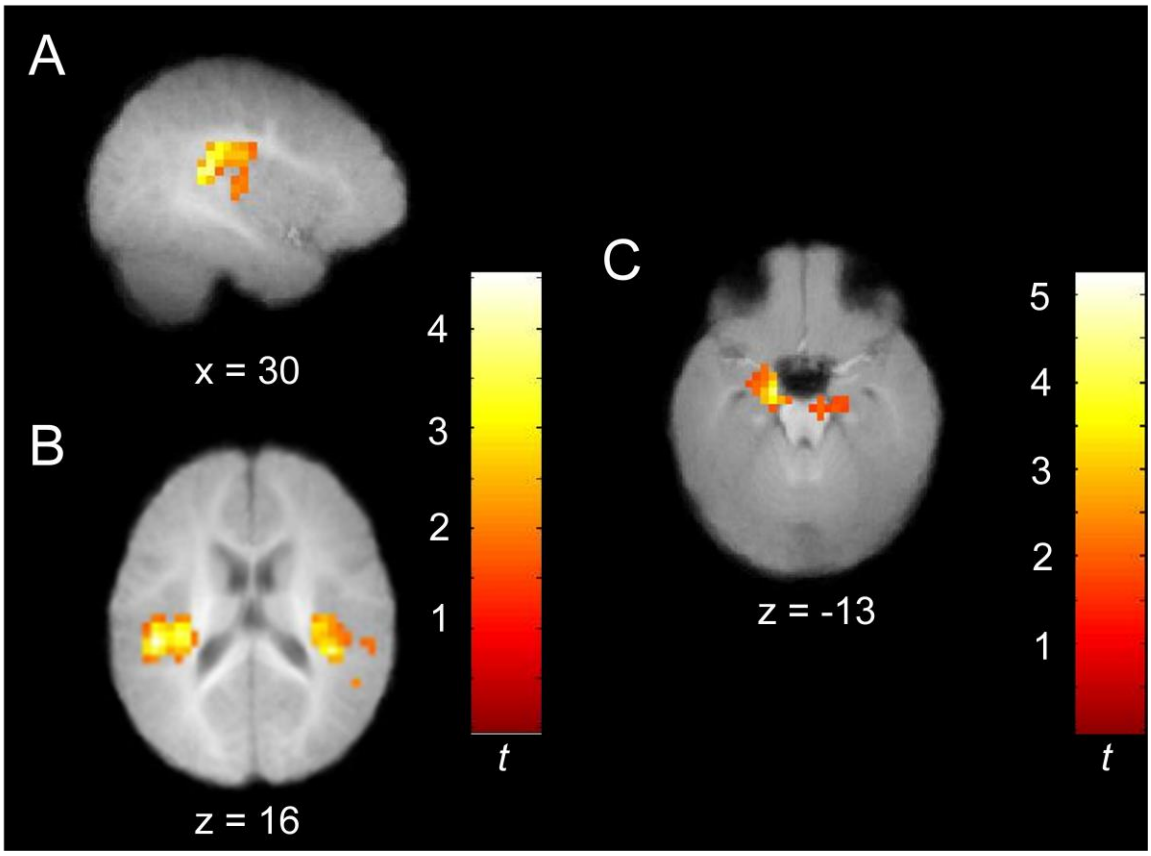
Supplementary Table 3.1. Amplitude for Each Emotion Condition

Emotion	Very Angry		Mildly Angry		Happy		Neutral	
	Mean Amp	Max Amp	Mean Amp	Max Amp	Mean Amp	Max Amp	Mean Amp	Max Amp
Mean	69.21	84.73	69.61	85.92	70.43	83.66	70.17	83.82
SD	1.28		1.36		1.49		0.93	

Supplementary Table 3.2. Increased activation associated with higher interparental conflict for happy > neutral

			Infant Atlas			MNI Atlas				
Regression	Region		x	y	z	x	y	z	*k*	*t*
Positive correlation between conflict and happy > neutral	Posterior Insula	L	-36	-22	16	-44	-27	21	401	4.54
	Somatosensory	L	-36	-16	37	-44	-20	48		4.49
	Posterior Insula	R	36	-34	10	44	-42	13	194	4.41
	Somatosensory	R	30	-25	22	37	-31	28		3.82
	Auditory Cortex	R	42	-22	10	51	-27	13		2.63

Note. Activations FWE corrected ($p < .05$, 75 voxels). Coordinates without voxel numbers indicate submaxima within preceding cluster. *k* refers to the number of voxels within each cluster. *t* refers to the *t* statistic of the corresponding coordinates (local maxima or submaxima). An additional activation area encompasing part of the left amygdala was evident after adding the age covariate to the regression of conflict on happy>neutral (Infant xyz= -12,-7 ,-17; MNI xyz= -15, -9, -22; *t*=4.45).



Supplementary Figure 3.1. Results are p<.05 FWE corrected. Displayed on group mean structural image. Panels A and B show greater activity in the right somatosensory cortex (panel A) and bilateral posterior insula (Panel B) associated with higher conflict score for the happy > neutral nonsense speech contrast. Panel C shows greater activity in the left amygdala associated with higher conflict score for the happy > neutral nonsense speech contrast when age is included as a covariate.

REFERENCES CITED

Adamec, R. E., & McKay, D. (1993). Amygdala kindling, anxiety, and corticotrophin releasing factor (CRF). *Physiology & Behavior*, *54*(3), 423–431. doi:10.1016/0031-9384(93)90230-D

Admon, R., Lubin, G., Rosenblatt, J. D., Stern, O., Kahn, I., Assaf, M., & Hendler, T. (2012). Imbalanced Neural Responsivity to Risk and Reward Indicates Stress Vulnerability in Humans. *Cerebral Cortex*. doi:10.1093/cercor/bhr369

Admon, R., Lubin, G., Stern, O., Rosenberg, K., Sela, L., Ben-Ami, H., & Hendler, T. (2009). Human vulnerability to stress depends on amygdala's predisposition and hippocampal plasticity. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(33), 14120–5. doi:10.1073/pnas.0903183106

Albeck, D. S., McKittrick, C. R., Blanchard, D. C., Blanchard, R. J., Nikulina, J., McEwen, B. S., & Sakai, R. R. (1997). Chronic social stress alters levels of corticotropin-releasing factor and arginine vasopressin mRNA in rat brain. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *17*(12), 4895–903. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9169547

Alkon, A., Lippert, S., Vujan, N., Rodriguez, M. E., Boyce, W. T., & Eskenazi, B. (2006). The ontogeny of autonomic measures in 6- and 12-month-old infants. *Developmental Psychobiology*, *48*(3), 197–208. doi:10.1002/dev.20129

Almli, C. R., Rivkin, M. J., & McKinstry, R. C. (2007). The NIH MRI study of normal brain development (Objective-2): newborns, infants, toddlers, and preschoolers. *NeuroImage*, *35*(1), 308–25. doi:10.1016/j.neuroimage.2006.08.058

Altaye, M., Holland, S., Wilke, M., & Gaser, C. (2008). Infant brain probability templates for MRI segmentation and normalization. *Neuroimage*, *43*(4), 721–730. doi:10.1016/j.neuroimage.2008.07.060.Infant

Amaral, D. G., & Price, J. L. (1984). Amygdalo-cortical projections in the monkey (Macaca fascicularis). *The Journal of Comparative Neurology*, *230*(4), 465–96. doi:10.1002/cne.902300402

Amaral, D. G., Price, J., Pitkänen, A., & Carmichael, S. (1992). Anatomical organization of the primate amygdaloid complex. In J. Aggleton (Ed.), *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction* (pp. 1–66). New York: Wiley-Liss, Inc.

Amunts, K., Kedo, O., Kindler, M., Pieperhoff, P., Mohlberg, H., Shah, N. J., Habel, U., et al. (2005). Cytoarchitectonic mapping of the human amygdala, hippocampal region and entorhinal cortex: intersubject variability and probability maps. *Anatomy and Embryology*, *210*(5-6), 343–52. doi:10.1007/s00429-005-0025-5

Anand, A., Li, Y., Wang, Y., Lowe, M. J., & Dzemidzic, M. (2009). Resting state corticolimbic connectivity abnormalities in unmedicated bipolar disorder and unipolar depression. *Psychiatry Research: Neuroimaging*, *171*(3), 189–98. doi:10.1016/j.pscychresns.2008.03.012

Anand, A., Li, Y., Wang, Y., Wu, J., Gao, S., Bukhari, L., Mathews, V. P., et al. (2005). Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. *Biological Psychiatry*, *57*(10), 1079–88. doi:10.1016/j.biopsych.2005.02.021

Anderson, A. W., D, P., Marois, R., Colson, E. R., D, M., Peterson, B. S., Duncan, C. C., et al. (2001). Neonatal auditory activation detected by functional magnetic resonance imaging. *Magnetic Resonance Imaging*, *19*, 1–5.

Andrade, K. C., Spoormaker, V. I., Dresler, M., Wehrle, R., Holsboer, F., Sämann, P. G., & Czisch, M. (2011). Sleep Spindles and Hippocampal Functional Connectivity in Human NREM Sleep. *The Journal of Neuroscience*, *31*(28), 10331–9. doi:10.1523/JNEUROSCI.5660-10.2011

Andrews-Hanna, J. R. (2012). The brain's default network and its adaptive role in internal mentation. *The Neuroscientist*, *18*(3), 251–70. doi:10.1177/1073858411403316

Balaban, M. T. (1995). Affective Influences on Startle in Five-Month-Old Infants: Reactions to Facial Expressions of Emotion. *Child Development*, *66*(1), 28. doi:10.2307/1131188

Banks, S. J., Eddy, K. T., Angstadt, M., Nathan, P. J., & Phan, K. L. (2007). Amygdala-frontal connectivity during emotion regulation. *Social Cognitive and Affective Neuroscience*, *2*(4), 303–12. doi:10.1093/scan/nsm029

Baram, T. Z., & Hatalski, C. G. (1998). Neuropeptide-mediated excitability: a key triggering mechanism for seizure generation in the developing brain. *Trends in Neurosciences*, *21*(11), 471–6. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9829688

Barbas, H., & De Olmos, J. (1990). Projections from the amygdala to basoventral and mediodorsal prefrontal regions in the rhesus monkey. *The Journal of Comparative Neurology*, *300*(4), 549–71. doi:10.1002/cne.903000409

Barbas, H., Saha, S., Rempel-Clower, N., & Ghashghaei, T. (2003). Serial pathways from primate prefrontal cortex to autonomic areas may influence emotional expression. *BMC Neuroscience*, *4*, 25. doi:10.1186/1471-2202-4-25

Beauchaine, T. P. (2001). Vagal tone, development, and Gray's motivational theory: Toward an integrated model of autonomic nervous system functioning in psychopathology. *Development and Psychopathology*, *13*, 183–214.

Beauchaine, T. P., Gatzke-Kopp, L., & Mead, H. K. (2007). Polyvagal Theory and developmental psychopathology: Emotion dysregulation and conduct problems from preschool to adolescence. *Biological Psychology*, *74*, 174–184. doi:10.1016/j.biopsycho.2005.08.008

Beckmann, C. F., Jenkinson, M., Woolrich, M. W., Behrens, T. E. J., David, 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. doi:10.1002/hbm.20246.Applying

Bickart, K. C., Hollenbeck, M. C., Barrett, L. F., & Dickerson, B. C. (2012). Intrinsic amygdala-cortical functional connectivity predicts social network size in humans. *The Journal of Neuroscience*, *32*(42), 14729–41. doi:10.1523/JNEUROSCI.1599-12.2012

Binder, J. R., Frost, J. A., Hammeke, T. A., Bellgowan, P. S. F., Springer, J. A., Kaufman, J. N., & Possing, E. T. (2000). Human Temporal Lobe Activation by Speech and Nonspeech Sounds. *Cerebral Cortex*, *10*, 512–528.

Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine*, *34*(4), 537–41. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8524021

Blasi, A., Mercure, E., Lloyd-Fox, S., Thomson, A., Brammer, M., Sauter, D., Deeley, Q., et al. (2011). Early Specialization for Voice and Emotion Processing in the Infant Brain. *Current Biology*, *21*(14), 1–5. doi:10.1016/j.cub.2011.06.009

Bluhm, R. L., Williamson, P. C., Osuch, E. a, Frewen, P. a, Stevens, T. K., Boksman, K., Neufeld, R. W. J., et al. (2009). Alterations in default network connectivity in posttraumatic stress disorder related to early-life trauma. *Journal of Psychiatry & Neuroscience*, *34*(3), 187–94. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2674971&tool=pmcentrez&rendertype=abstract

Bluhm, R. L., Williamson, P., Lanius, R., Théberge, J., Densmore, M., Bartha, R., Neufeld, R., et al. (2009). Resting state default-mode network connectivity in early depression using a seed region-of-interest analysis: decreased connectivity with caudate nucleus. *Psychiatry and Clinical Neurosciences*, *63*(6), 754–61. doi:10.1111/j.1440-1819.2009.02030.x

Bruce, J., Fisher, P. a, Pears, K. C., & Levine, S. (2009). Morning cortisol Levels in preschool-aged foster children: differential effects of maltreatment type. *Developmental Psychobiology*, *51*(1), 14–23. doi:10.1002/dev.20333

Burghy, C. A., Stodola, D. E., Ruttle, P. L., Molloy, E. K., Armstrong, J. M., Oler, J. a, Fox, M. E., et al. (2012). Developmental pathways to amygdala-prefrontal function and internalizing symptoms in adolescence. *Nature Neuroscience*, (November), 1–8. doi:10.1038/nn.3257

Caldji, C., Diorio, J., & Meaney, M. J. (2000). Variations in maternal care in infancy regulate the development of stress reactivity. *Biological Psychiatry*, *48*(12), 1164–74. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11137058

Caldji, C., Tannenbaum, B., Shakti, S., Francis, D., Plotsky, P. M., & Meaney, M. J. (1998). Maternal care during infancy regulates the development of neural systems mediating the expression of fearfulness in the rat. *Proceedings of the National Academy of Sciences*, *95*(April), 5335–5340. Retrieved from http://www.pnas.org/content/95/9/5335.short

Calkins, S. D., & Dedmon, S. E. (2000). Physiological and behavioral regulation in two-year-old children with aggressive/destructive behavior problems. *Journal of Abnormal Child Psychology*, *28*, 103–118.

Casey, B. J., Galvan, A., & Hare, T. A. (2005). Changes in cerebral functional organization during cognitive development. *Current Opinion in Neurobiology*, *15*(2), 239–44. doi:10.1016/j.conb.2005.03.012

Casey, B. J., Giedd, J. N., & Thomas, K. M. (2000). Structural and functional brain development and its relation to cognitive development. *Biological Psychology*, *54*(1-3), 241–57. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11035225

Chai, X. J., Castañón, A. N., Ongür, D., & Whitfield-Gabrieli, S. (2012). Anticorrelations in resting state networks without global signal regression. *NeuroImage*, *59*(2), 1420–8. doi:10.1016/j.neuroimage.2011.08.048

Chai, X. J., Whitfield-Gabrieli, S., Shinn, A. K., Gabrieli, J. D. E., Nieto Castañón, A., McCarthy, J. M., Cohen, B. M., et al. (2011). Abnormal medial prefrontal cortex resting-state connectivity in bipolar disorder and schizophrenia. *Neuropsychopharmacology*, *36*(10), 2009–17. doi:10.1038/npp.2011.88

Chen, S., Xia, W., Li, L., Liu, J., He, Z., Zhang, Z., Yan, L., et al. (2006). Gray matter density reduction in the insula in fire survivors with posttraumatic stress disorder: a voxel-based morphometric study. *Psychiatry Research*, *146*(1), 65–72. doi:10.1016/j.pscychresns.2005.09.006

Cheour, M., Ceponiené, R., Leppänen, P., Alho, K., Kujala, T., Renlund, M., Fellman, V., et al. (2002). The auditory sensory memory trace decays rapidlyin newborns. *Scandinavian Journal of Psychology*, *43*, 33–39. Retrieved from http://onlinelibrary.wiley.com/doi/10.1111/1467-9450.00266/abstract

Cheour, M., Martynova, O., Näätänen, R., Erkkolall, R., Sillanpää, M., Kero, P., Raz, A., et al. (2002). Speech sounds learned by sleeping newborns. *Nature*, *415*(6872), 599–600. doi:10.1038/415599a

Coan, J. A., Schaefer, H. S., & Davidson, R. J. (2006). Lending a hand: social regulation of the neural response to threat. *Psychological Science*, *17*(12), 1032–9. doi:10.1111/j.1467-9280.2006.01832.x

Cohen, R. a, Grieve, S., Hoth, K. F., Paul, R. H., Sweet, L., Tate, D., Gunstad, J., et al. (2006). Early life stress and morphometry of the adult anterior cingulate cortex and caudate nuclei. *Biological Psychiatry*, *59*(10), 975–82. doi:10.1016/j.biopsych.2005.12.016

Courchesne, E., Chisum, H. J., Townsend, J., Cowles, A., Covington, J., Egaas, B., Harwood, M., et al. (2000). Normal Brain Development and Aging : Quantitative Analysis at in Vivo MR. *Neuroradiology*, *216*, 672–682.

Craig, A. D. (2009). How do you feel--now? The anterior insula and human awareness. *Nature Reviews Neuroscience*, *10*, 59–70. Retrieved from http://europepmc.org/abstract/MED/19096369

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. doi:10.1037/0012-1649.40.6.1123

Crockenberg, S. C., Leerkes, E. M., & Lekka, S. K. (2007). Pathways from marital aggression to infant emotion regulation : The development of withdrawal in infancy. *Infant Behavior & Development*, *30*, 97–113. doi:10.1016/j.infbeh.2006.11.009

Cummings, E. M., & Davies, P. T. (2002). Effects of marital conflict on children: recent advances and emerging themes in process-oriented research. *Journal Of Child Psychology And Psychiatry*, *43*(1), 31–63.

Cummings, E. M., & Davies, P. T. (2010). *Marital Conflict and Children: An Emotional Security Perspective* (p. 320). New York: The Guilford Press.

Czisch, M., Wetter, T. C., Kaufmann, C., Pollmächer, T., Holsboer, F., & Auer, D. P. (2002). Altered processing of acoustic stimuli during sleep: reduced auditory activation and visual deactivation detected by a combined fMRI/EEG study. *NeuroImage*, *16*(1), 251–8. doi:10.1006/nimg.2002.1071

Damoiseaux, J. S., & Greicius, M. D. (2009). Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity. *Brain Structure & Function*, *213*(6), 525–33. doi:10.1007/s00429-009-0208-6

Damoiseaux, J. S., Rombouts, S. A. R. B., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., & Beckmann, C. F. (2006). Consistent resting-state networks across healthy subjects. *Proceedings of the National Academy of Sciences*, *103*(37), 13848–13853.

Daniels, J. K., Frewen, P., McKinnon, M. C., & Lanius, R. a. (2011). Default mode alterations in posttraumatic stress disorder related to early-life trauma: a developmental perspective. *Journal of Psychiatry & Neuroscience*, *36*(1), 56–9. doi:10.1503/jpn.100050

Daniels, J. K., Mcfarlane, A. C., Bluhm, R. L., Moores, K. A., Clark, C. R., Shaw, M. E., Williamson, P. C., et al. (2010). Switching between executive and default mode networks in posttraumatic stress disorder: alterations in functional connectivity. *Journal of Psychiatry & Neuroscience*, *35*(4), 258–266. doi:10.1503/jpn.090175

Dannlowski, U., Stuhrmann, A., Beutelmann, V., Zwanzger, P., Lenzen, T., Grotegerd, D., Domschke, K., et al. (2012). Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. *Biological Psychiatry*, *71*(4), 286–93. doi:10.1016/j.biopsych.2011.10.021

Davies, P. T., & Cicchetti, D. (2004). Toward an integration of family systems and developmental psychopathology approaches. *Development and Psychopathology*, 477–481.

Davies, P. T., Sturge-Apple, M. L., Cicchetti, D., & Cummings, E. M. (2007). The Role of Child Adrenocortical Functioning in Pathways Between Interparental Conflict and Child Maladjustment. *Developmental Psychology*, *43*(4), 918 –930. doi:10.1037/0012-1649.43.4.918

Davis, M. (2006). Neural systems involved in fear and anxiety measured with fear-potentiated startle. *The American Psychologist*, *61*(8), 741–56. doi:10.1037/0003-066X.61.8.741

De Kloet, E. R., Vreugdenhil, E., Oitzl, M. S., & Joels, M. (1998). Brain Corticosteroid Receptor Balance in Health and Disease. *Endocrine Reviews*, *19*(3), 269 –301.

De Luca, M., Beckmann, C. F., De Stefano, N., Matthews, P. M., & Smith, S. M. (2006). fMRI resting state networks define distinct modes of long-distance interactions in the human brain. *NeuroImage*, *29*(4), 1359–67. doi:10.1016/j.neuroimage.2005.08.035

Degangi, G. A., Dipietro, J. A., Greenspan, S. I., & Porges, S. W. (1991). Psychophysiological characteristics of the regulatory disordered infant. *Infant Behavior and Development*, *14*(1), 37–50. doi:10.1016/0163-6383(91)90053-U

Dehaene-Lambertz, G., Dehaene, S., & Hertz-Pannier, L. (2002). Functional Neuroimaging of Speech Perception in Infants. *Science*, *298*, 2013–2015. doi:10.1126/science.1077066

Dehaene-Lambertz, G., Montavont, A., Jobert, A., Allirol, L., Dubois, J., Hertz-Pannier, L., & Dehaene, S. (2010). Language or music, mother or Mozart? Structural and environmental influences on infants' language networks. *Brain & Language*, *114*(2), 53–65. doi:10.1016/j.bandl.2009.09.003

Dettling, A. C., Parker, S. W., Lane, S., Sebanc, A., & Gunnar, M. R. (2000). Quality of care and temperament determine changes in cortisol concentrations over the day for young children in childcare. *Psychoneuroendocrinology*, *25*(8), 819–36. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10996476

Dickstein, D. P., Gorrostieta, C., Ombao, H., Goldberg, L. D., Brazel, A. C., Gable, C. J., Kelly, A. M. C., et al. (2010). Fronto-temporal spontaneous resting state functional connectivity in pediatric bipolar disorder. *Biological Psychiatry*, *68*(9), 839–46. doi:10.1016/j.biopsych.2010.06.029

Dinstein, I., Pierce, K., Eyler, L. T., Solso, S., Malach, R., Behrmann, M., & Courchesne, E. (2011). Disrupted neural synchronization in toddlers with autism. *Neuron*, *70*(6), 1218–25. doi:10.1016/j.neuron.2011.04.018

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*, 615–620.

Driessen, M., Herrmann, J., Stahl, K., Zwaan, M., Meier, S., Hill, A., Osterheider, M., et al. (2000). Magnetic resonance imaging volumes of the hippocampus and the amygdala in women with borderline personality disorder and early traumatization. *Archives of General Psychiatry*, *57*(12), 1115–22. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11115325

Dubois, J., Dehaene-Lambertz, G., Perrin, M., Mangin, J.-F., Cointepas, Y., Duchesnay, E., Le Bihan, D., et al. (2008). Asynchrony of the early maturation of white matter bundles in healthy infants: quantitative landmarks revealed noninvasively by diffusion tensor imaging. *Human Brain Mapping*, *29*(1), 14–27. doi:10.1002/hbm.20363

El-Sheikh, M., Kouros, C. D., Erath, S., Cummings, E. M., Keller, P., & Staton, L. (2009). Marital conflict and children's externalizing behavior: interactions between parasympathetic and sympathetic nervous system activity. *Monographs of the Society for Research in Child Development*, *74*(1), vii, 1–79. doi:10.1111/j.1540-5834.2009.00501.x

El-Sheikh, M., & Whitson, S. (2006). Longitudinal relations between marital conflict and child adjustment: Vagal regulation as a protective factor. *Journal of Family Psychology*, *20*(1), 101037/0893–320020130. Retrieved from http://psycnet.apa.org/journals/fam/20/1/30/

Etkin, A., Prater, K. E., Schatzberg, A. F., Menon, V., & Greicius, M. D. (2009). Disrupted amygdalar subregion functional connectivity and evidence of a compensatory network in generalized anxiety disorder. *Archives of General Psychiatry*, *66*(12), 1361–72. doi:10.1001/archgenpsychiatry.2009.104

Eyler, L. T., Pierce, K., & Courchesne, E. (2012). A failure of left temporal cortex to specialize for language is an early emerging and fundamental property of autism. *Brain*, *135*, 949–60. doi:10.1093/brain/awr364

Fair, D. A., Cohen, A., Dosenbach, N. U. F., Church, J. A., Miezin, F. M., Barch, D. M., Raichle, M. E., et al. (2008). The maturing architecture of the brain's default network. *Proceedings of the National Academy of Sciences*, *105*(10), 4028–32. Retrieved from http://www.pnas.org/content/105/10/4028.short

Fair, D. A., Cohen, A. L., Power, J. D., Dosenbach, N. U. F., Church, J. A., Miezin, F. M., Schlaggar, B. L., et al. (2009). Functional brain networks develop from a "local to distributed" organization. *PLoS Computational Biology*, *5*(5), e1000381. doi:10.1371/journal.pcbi.1000381

Fair, D. A., Dosenbach, N. U. F., Church, J. A., Cohen, A. L., Brahmbhatt, S., Miezin, F. M., Barch, D. M., et al. (2007). Development of distinct control networks through segregation and integration. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(33), 13507–12. doi:10.1073/pnas.0705843104

Fair, D. A., Nigg, J. T., Iyer, S., Bathula, D., Mills, K. L., Dosenbach, N. U. F., Schlaggar, B. L., et al. (2013). Distinct neural signatures detected for ADHD subtypes after controlling for micro-movements in resting state functional connectivity MRI data. *Frontiers in Systems Neuroscience*, *6*. doi:10.3389/fnsys.2012.00080

Fair, D. A., Posner, J., Nagel, B. J., Bathula, D., Dias, T. G. C., Mills, K. L., Blythe, M. S., et al. (2010). Atypical default network connectivity in youth with attention-deficit/hyperactivity disorder. *Biological Psychiatry*, *68*(12), 1084–91. doi:10.1016/j.biopsych.2010.07.003

Feldman, R., & Eidelman, A. I. (2003). Direct and indirect effects of breast milk on the neurobehavioral and cognitive development of premature infants. *Developmental Psychobiology*, *43*(2), 109–19. doi:10.1002/dev.10126

Feldman, R., Eidelman, A. I., & Rotenberg, N. (2004). Parenting stress, infant emotion regulation, maternal sensitivity, and the cognitive development of triplets: a model for parent and child influences in a unique ecology. *Child Development*, *75*(6), 1774–91. doi:10.1111/j.1467-8624.2004.00816.x

Fifer, W. P., Byrd, D. L., Kaku, M., Eigsti, I.-M., Isler, J. R., Grose-Fifer, J., Tarullo, A. R., et al. (2010). Newborn infants learn during sleep. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(22), 10320–3. doi:10.1073/pnas.1005061107

Fonov, V. S., 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), 313–27. doi:10.1016/j.neuroimage.2010.07.033

Fonov, V. S., Evans, A. C., Mckinstry, R. C., Almli, C. R., & Collins, D. L. (2009). Unbiased nonlinear average age-appropriate brain templates from birth to adulthood. *NeuroImage*, *47*(Supplement 1), S102. doi:10.1016/S1053-8119(09)70884-5

Fonzo, G. a, Simmons, A. N., Thorp, S. R., Norman, S. B., Paulus, M. P., & Stein, M. B. (2010). Exaggerated and disconnected insular-amygdalar blood oxygenation level-dependent response to threat-related emotional faces in women with intimate-partner violence posttraumatic stress disorder. *Biological Psychiatry*, *68*(5), 433–41. doi:10.1016/j.biopsych.2010.04.028

Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A., & Noll, D. C. (1995). Improved Assessment of Significant Activation in Functional Magnetic Resonance Imaging (fMRI): Use of a Cluster-Size Threshold. *Magnetic Resonance in Medicine*, *33*(5), 636–647. doi:10.1002/mrm.1910330508

Fox, M. D., & Greicius, M. D. (2010). Clinical applications of resting state functional connectivity. *Frontiers in Systems Neuroscience*, *4*, 1–13. doi:10.3389/fnsys.2010.00019

Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience*, *8*(9), 700–11. doi:10.1038/nrn2201

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(27), 9673–8. doi:10.1073/pnas.0504136102

Fox, S. E., Levitt, P., & Nelson, C. a. (2010). How the timing and quality of early experiences influence the development of brain architecture. *Child Development*, *81*(1), 28–40. doi:10.1111/j.1467-8624.2009.01380.x

Fransson, P. (2005). Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis. *Human Brain Mapping*, *26*(1), 15–29. doi:10.1002/hbm.20113

Fransson, P., Aden, U., Blennow, M., & Lagercrantz, H. (2011). The Functional Architecture of the Infant Brain as Revealed by Resting-State fMRI. *Cerebral Cortex*, *21*, 145–154. doi:10.1093/cercor/bhq071

Fransson, P., Metsäranta, M., Blennow, M., Aden, U., Lagercrantz, H., & Vanhatalo, S. (2012). Early Development of Spatial Patterns of Power-Law Frequency Scaling in fMRI Resting-State and EEG Data in the Newborn Brain. *Cerebral Cortex*. doi:10.1093/cercor/bhs047

Fransson, P., Skiöld, B., Engström, M., Hallberg, B., Mosskin, M., Aden, U., Lagercrantz, H., et al. (2009). Spontaneous brain activity in the newborn brain during natural sleep--an fMRI study in infants born at full term. *Pediatric Research*, *66*(3), 301–5. doi:10.1203/PDR.0b013e3181b1bd84

Fransson, P., Skiöld, B., Horsch, S., Nordell, A., Blennow, M., Lagercrantz, H., & Aden, U. (2007). Resting-state networks in the infant brain. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(39), 15531–6. doi:10.1073/pnas.0704380104

Friston, K. J., Buechel, C., Fink, G. R., Morris, J., Rolls, E., & Dolan, R. J. (1997). Psychophysiological and modulatory interactions in neuroimaging. *NeuroImage*, *6*(3), 218–29. doi:10.1006/nimg.1997.0291

Frosch, C. A., Mangelsdorf, S. C., & McHale, J. L. (2000). Marital behavior and the security of preschooler-parent attachment relationships. *Journal of Family Psychology*, *14*, 144–161.

Fuster, J. M. (2002). Frontal lobe and cognitive development. *Journal of Neurocytology*, *31*, 373–85. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12815254

Gaab, N., Gabrieli, J. D. E., & Glover, G. H. (2008). Resting in peace or noise: scanner background noise suppresses default-mode network. *Human Brain Mapping*, *29*(7), 858–67. doi:10.1002/hbm.20578

Gaffrey, M., Luby, J., & Belden, A. (2010). Subgenual cingulate connectivity in children with a history of preschool-depression. *Neuroreport*, *21*(18), 1182–8. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3008372/

Gao, W., Gilmore, J. H., Giovanello, K. S., Smith, J. K., Shen, D., Zhu, H., & Lin, W. (2011). Temporal and spatial evolution of brain network topology during the first two years of life. *PloS one*, *6*(9), e25278. doi:10.1371/journal.pone.0025278

Gao, W., Lin, W., Chen, Y., Gerig, G., Smith, J. K., Jewells, V., & Gilmore, J. H. (2009). Temporal and spatial development of axonal maturation and myelination of white matter in the developing brain. *American Journal Of Neuroradiology*, *30*(2), 290–6. doi:10.3174/ajnr.A1363

Gao, W., Zhu, H., Giovanello, K. S., Smith, J. K., Shen, D., Gilmore, J. H., & Lin, W. (2009). Evidence on the emergence of the brain's default network from 2-week-old to 2-year-old healthy pediatric subjects. *Proceedings of the National Academy of Sciences*, *106*(16), 6790–6795. Retrieved from http://www.pnas.org/content/106/16/6790.short

Gee, D. G., Humphreys, K. L., Flannery, J., Goff, B., Telzer, E. H., Shapiro, M., Hare, T., et al. (2013). A Developmental Shift from Positive to Negative Connectivity in Human Amygdala-Prefrontal Circuitry. *Journal of Neuroscience*, *33*(10), 4584–4593. doi:10.1523/JNEUROSCI.3446-12.2013

Ghashghaei, H. T., & Barbas, H. (2002). Pathways for emotion: interactions of prefrontal and anterior temporal pathways in the amygdala of the rhesus monkey. *Neuroscience*, *115*(4), 1261–79. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12453496

Goldin, P., McRae, K., Ramel, W., & Gross, J. (2008). The neural bases of emotion regulation: reappraisal and suppression of negative emotion. *Biological Psychiatry*, *63*, 577–586. doi:10.1016/j.biopsych.2007.05.031

Goodman, S. H., Rouse, M. H., Connell, A. M., Broth, M. R., Hall, C. M., & Heyward, D. (2011). Maternal depression and child psychopathology: a meta-analytic review. *Clinical Child and Family Psychology Review*, *14*(1), 1–27. doi:10.1007/s10567-010-0080-1

Graham, A. M., Fisher, P. A., & Pfeifer, J. H. (2013). What Sleeping Babies Hear: A Functional MRI Study of Interparental Conflict and Infants' Emotion Processing. *Psychological Science*. doi:10.1177/0956797612458803

Gray, T. S., & Bingaman, E. W. (1996). The amygdala: corticotropin-releasing factor, steroids, and stress. *Critical Reviews in Neurobiology*, *10*(2), 155–68. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8971127

Greicius, M. D. (2008). Resting-state functional connectivity in neuropsychiatric disorders. *Current Opinion in Neurology*, *21*(4), 424–30. doi:10.1097/WCO.0b013e328306f2c5

Greicius, M. D., Flores, B. H., Menon, V., Glover, G. H., Solvason, H. B., Kenna, H., Reiss, A. L., et al. (2007). Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. *Biological Psychiatry*, *62*(5), 429–37. doi:10.1016/j.biopsych.2006.09.020

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(1), 253–8. doi:10.1073/pnas.0135058100

Greicius, M. D., Supekar, K., Menon, V., & Dougherty, R. F. (2009). Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cerebral Cortex*, *19*(1), 72–8. doi:10.1093/cercor/bhn059

Grossmann, T., Oberecker, R., Koch, S. P., & Friederici, A. D. (2010). The developmental origins of voice processing in the human brain. *Neuron*, *65*(6), 852–8. doi:10.1016/j.neuron.2010.03.001

Grossmann, T., Striano, T., & Friederici, A. D. (2005). Infants' electric brain responses to emotional prosody. *Neuroreport*, *16*(16), 1825–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16237335

Gunnar, M. R., Kryzer, E., Van Ryzin, M. J., & Phillips, D. a. (2010). The rise in cortisol in family day care: associations with aspects of care quality, child behavior, and child sex. *Child Development*, *81*(3), 851–69. doi:10.1111/j.1467-8624.2010.01438.x

Gusnard, D., & Raichle, M. (2001). Searching for a baseline: functional imaging and the resting human brain. *Nature Reviews Neuroscience*, *2*, 685–694. Retrieved from http://199.231.18.229/cores/mialab/fijc/Files/2002/121802_Gusnard_Nature_Rev_Neurosci_2001.pdf

Hackman, D. a, & Farah, M. J. (2009). Socioeconomic status and the developing brain. *Trends in Cognitive Sciences*, *13*(2), 65–73. doi:10.1016/j.tics.2008.11.003

Hahn, A., Stein, P., Windischberger, C., Weissenbacher, A., Spindelegger, C., Moser, E., Kasper, S., et al. (2011). Reduced resting-state functional connectivity between amygdala and orbitofrontal cortex in social anxiety disorder. *NeuroImage*, *56*(3), 881–9. doi:10.1016/j.neuroimage.2011.02.064

Hampson, M., Driesen, N., Roth, J. K., Gore, J. C., & Constable, R. T. (2010). Functional connectivity between task-positive and task-negative brain areas and its relation to working memory performance. *Magnetic Resonance Imaging*, *28*(8), 1051–7. doi:10.1016/j.mri.2010.03.021

Hanson, J. L., Chandra, A., Wolfe, B. L., & Pollak, S. D. (2011). Association between income and the hippocampus. *PloS One*, *6*(5), e18712. doi:10.1371/journal.pone.0018712

Hanson, J. L., Chung, M. K., Avants, B. B., Shirtcliff, E. a, Gee, J. C., Davidson, R. J., & Pollak, S. D. (2010). Early stress is associated with alterations in the orbitofrontal cortex: a tensor-based morphometry investigation of brain structure and behavioral risk. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *30*(22), 7466–72. doi:10.1523/JNEUROSCI.0859-10.2010

Hart, H., & Rubia, K. (2012). Neuroimaging of child abuse: a critical review. *Frontiers in Human Neuroscience*, *6*, 1–24. doi:10.3389/fnhum.2012.00052

Hayes, J. P., Hayes, S. M., & Mikedis, A. M. (2012). Quantitative meta-analysis of neural activity in posttraumatic stress disorder. *Biology of Mood & Anxiety Disorders*, *2*(1), 9. doi:10.1186/2045-5380-2-9

Heimer, L., De Olmos, J., Alheid, G., J, P., Sakamoto, N., Shinoda, K., Marksteiner, J., et al. (1999). The human basal forebrain Part II. In F. E. Bloom, A. Bjorklund, & T. Hokfelt (Eds.), *The Primate Nervous System, Part 3* (pp. 57–226). Amsterdam: Elsevier Science.

Henckens, M. J. A. G., Van Wingen, G. A., Joëls, M., & Fernández, G. (2011). Corticosteroid Induced Decoupling of the Amygdala in Men. *Cerebral Cortex*, 1–10. doi:10.1093/cercor/bhr313

Herman, J. P., Figueiredo, H., Mueller, N. K., Ulrich-Lai, Y., Ostrander, M. M., Choi, D. C., & Cullinan, W. E. (2003). Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamo–pituitary–adrenocortical responsiveness. *Frontiers in Neuroendocrinology*, *24*(3), 151–180. doi:10.1016/j.yfrne.2003.07.001

Herman, J. P., & Mueller, N. K. (2006). Role of the ventral subiculum in stress integration. *Behavioural Brain Research*, *174*(2), 215–24. doi:10.1016/j.bbr.2006.05.035

Herman, J. P., Ostrander, M. M., Mueller, N. K., & Figueiredo, H. (2005). Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *29*(8), 1201–13. doi:10.1016/j.pnpbp.2005.08.006

Hermoye, L., Saint-Martin, C., Cosnard, G., Lee, S.-K., Kim, J., Nassogne, M.-C., Menten, R., et al. (2006). Pediatric diffusion tensor imaging: normal database and observation of the white matter maturation in early childhood. *NeuroImage*, *29*(2), 493–504. doi:10.1016/j.neuroimage.2005.08.017

Hertenstein, M. J. (2002). Touch: Its Communicative Functions in Infancy. *Human Development*, *45*, 70–94.

Honey, C., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J. P., Meuli, R., & Hagmann, P. (2009). Predicting human resting-state functional connectivity from structural connectivity. *Proceedings of the National Academy of Sciences*, *106*(6), 2035. Retrieved from http://www.pnas.org/content/106/6/2035.short

Hsu, D. T., Chen, F. L., Takahashi, L. K., & Kalin, N. H. (1998). Rapid stress-induced elevations in corticotropin-releasing hormone mRNA in rat central amygdala nucleus and hypothalamic paraventricular nucleus: an in situ hybridization analysis. *Brain Research*, *788*(1-2), 305–10. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9555067

Huang, H., Zhang, J., Wakana, S., Zhang, W., Ren, T., Richards, L. J., Yarowsky, P., et al. (2006). White and gray matter development in human fetal, newborn and pediatric brains. *NeuroImage*, *33*(1), 27–38. doi:10.1016/j.neuroimage.2006.06.009

Hulvershorn, L. a, Cullen, K., & Anand, A. (2011). Toward dysfunctional connectivity: a review of neuroimaging findings in pediatric major depressive disorder. *Brain Imaging and Behavior*, *5*(4), 307–28. doi:10.1007/s11682-011-9134-3

Huot, R. L., Plotsky, P. M., Lenox, R. H., & McNamara, R. K. (2002). Neonatal maternal separation reduces hippocampal mossy fiber density in adult Long Evans rats. *Brain Research*, *950*, 52–63.

Huttenlocher, P. R., & Dabholkar, a S. (1997). Regional differences in synaptogenesis in human cerebral cortex. *The Journal of Comparative Neurology*, *387*(2), 167–78. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9336221

Jahn, A. L., Fox, A. S., Abercrombie, H. C., Shelton, S. E., Oakes, T. R., Davidson, R. J., & Kalin, N. H. (2010). Subgenual prefrontal cortex activity predicts individual differences in hypothalamic-pituitary-adrenal activity across different contexts. *Biological Psychiatry*, *67*(2), 175–81. doi:10.1016/j.biopsych.2009.07.039

Jolkkonen, E., & Pitkanen, A. (1998). Intrinsic Connections of the Rat Amygdaloid Complex: Projections Originating in the Central Nucleus. *The Journal of Comparative Neurology*, *72*, 53–72.

Kahn, A., Dan, B., Groswasser, J., Franco, P., & Sottiaux, M. (1996). Normal sleep architecture in infants and children. *Journal of Clinical Neurophysiology*, *13*(3), 184. Retrieved from http://journals.lww.com/clinicalneurophys/Abstract/1996/05000/Normal_Sleep_Architecture_in_Infants_and_Children.2.aspx

Kanoy, K., Ulku-Steiner, B., Cox, M., & Burchinal, M. (2003). Marital Relationship and Individual Psychological Characteristics That Predict Physical Punishment of Children. *Journal of Family Psychology*, *17*(1), 20 –28. doi:10.1037/0893-3200.17.1.20

Kazemi, K., Moghaddam, H. A., Grebe, R., Gondry-Jouet, C., & Wallois, F. (2007). A neonatal atlas template for spatial normalization of whole-brain magnetic resonance images of newborns: preliminary results. *NeuroImage*, *37*(2), 463–73. doi:10.1016/j.neuroimage.2007.05.004

Kelly, A. M. C., Biswal, B. B., Craddock, R. C., Castellanos, F. X., & Milham, M. P. (2012). Characterizing variation in the functional connectome: promise and pitfalls. *Trends in Cognitive Sciences*, *16*(3), 181–188. doi:10.1016/j.tics.2012.02.001

Kelly, A. M. C., Di Martino, A., Uddin, L. Q., Shehzad, Z., Gee, D. G., Reiss, P. T., Margulies, D. S., et al. (2009). Development of anterior cingulate functional connectivity from late childhood to early adulthood. *Cerebral Cortex*, *19*(3), 640–57. doi:10.1093/cercor/bhn117

Kelly, A. M. C., Uddin, L. Q., Biswal, B. B., Castellanos, F. X., & Milham, M. P. (2008). Competition between functional brain networks mediates behavioral variability. *NeuroImage*, *39*(1), 527–37. doi:10.1016/j.neuroimage.2007.08.008

Kim, J. E., Lyoo, I. K., Estes, A. M., Renshaw, P. F., Shaw, D. W., Friedman, S. D., Kim, D. J., et al. (2010). Laterobasal Amygdalar Enlargement in 6- to 7-Year-Old Children With Autism Spectrum Disorder. *Archives of General Psychiatry*, *67*(11), 1187–1197.

Kim, M. J., Chey, J., Chung, A., Bae, S., Khang, H., Ham, B., Yoon, S. J., et al. (2008). Diminished rostral anterior cingulate activity in response to threat-related events in posttraumatic stress disorder. *Journal of Psychiatric Research*, *42*(4), 268–77. doi:10.1016/j.jpsychires.2007.02.003

Knickmeyer, R. C., Gouttard, S., Kang, C., Evans, D., Wilber, K., Smith, J. K., Hamer, R. M., et al. (2008). A structural MRI study of human brain development from birth to 2 years. *Journal of Neuroscience*, *28*(47), 12176–12182.

Knudsen, E. I. (2004). Sensitive periods in the development of the brain and behavior. *Journal of Cognitive Neuroscience*, *16*(8), 1412–25. doi:10.1162/0898929042304796

Kober, H., Barrett, L. F., Joseph, J., Bliss-Moreau, E., Lindquist, K., & Wager, T. D. (2008). Functional grouping and cortical-subcortical interactions in emotion: a meta-analysis of neuroimaging studies. *NeuroImage*, *42*(2), 998–1031. doi:10.1016/j.neuroimage.2008.03.059

Krause, B. J., Schmidt, D., Mottaghy, F. M., Taylor, J., Halsband, U., Herzog, H., Tellmann, L., et al. (1999). Episodic retrieval activates the precuneus irrespective of the imagery content of word pair associates. A PET study. *Brain*, *122*, 255–63. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10071054

Krishnakumar, A., & Buehler, C. (2000). Interparental Conflict and Parenting Behaviors: A Meta-Analytic Review. *Family Relations*, *49*(1), 25–44.

Lane, A. E., Young, R. L., Baker, A. E. Z., & Angley, M. T. (2010). Sensory processing subtypes in autism: association with adaptive behavior. *Journal of Autism and Developmental Disorders*, *40*(1), 112–22. doi:10.1007/s10803-009-0840-2

Lanius, R. a, Bluhm, R. L., Coupland, N. J., Hegadoren, K. M., Rowe, B., Théberge, J., Neufeld, R. W. J., et al. (2010). Default mode network connectivity as a predictor of post-traumatic stress disorder symptom severity in acutely traumatized subjects. *Acta Psychiatrica Scandinavica*, *121*, 33–40. doi:10.1111/j.1600-0447.2009.01391.x

Larson-Prior, L. J., Zempel, J. M., Nolan, T. S., Prior, F. W., Snyder, A. Z., & Raichle, M. E. (2009). Cortical network functional connectivity in the descent to sleep. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(11), 4489–94. doi:10.1073/pnas.0900924106

Le Grand, R., Mondloch, C. J., Maurer, D., & Brent, H. P. (2003). Expert face processing requires visual input to the right hemisphere during infancy. *Nature Neuroscience*, *6*(10), 1108–12. doi:10.1038/nn1121

Levine, S. (2005). Developmental determinants of sensitivity and resistance to stress. *Psychoneuroendocrinology*, *30*(10), 939–46. doi:10.1016/j.psyneuen.2005.03.013

Lieberman, M. D., Eisenberger, N. I., Crockett, M. J., Tom, S. M., Pfeifer, J. H., & Way, B. M. (2007). Putting feelings into words: affect labeling disrupts amygdala activity in response to affective stimuli. *Psychological Science*, *18*(5), 421–8. doi:10.1111/j.1467-9280.2007.01916.x

Liu, H., Kaneko, Y., Ouyang, X., Li, L., Hao, Y., Chen, E. Y. H., Jiang, T., et al. (2012). Schizophrenic patients and their unaffected siblings share increased resting-state connectivity in the task-negative network but not its anticorrelated task-positive network. *Schizophrenia Bulletin*, *38*(2), 285–94. doi:10.1093/schbul/sbq074

Liu, W.-C., Flax, J. F., Guise, K. G., Sukul, V., & Benasich, A. a. (2008). Functional connectivity of the sensorimotor area in naturally sleeping infants. *Brain Research, 1223*, 42–9. doi:10.1016/j.brainres.2008.05.054

Lloyd-Fox, S., Blasi, A., & Elwell, C. E. (2010). Illuminating the developing brain: the past, present and future of functional near infrared spectroscopy. *Neuroscience and Biobehavioral Reviews*, *34*(3), 269–84. doi:10.1016/j.neubiorev.2009.07.008

Lloyd-Fox, S., Blasi, A., Volein, A., Everdell, N., Elwell, C. E., & Johnson, M. H. (2009). Social perception in infancy: a near infrared spectroscopy study. *Child Development*, *80*(4), 986–99. doi:10.1111/j.1467-8624.2009.01312.x

Logothetis, N. K. (2008). What we can do and what we cannot do with fMRI. *Nature*, *453*(7197), 869–878. doi:10.1038/nature06976

Loman, M. M., Gunnar, M. R., & The Early Experience, Stress, and N. D. C. (2010). Early experience and the development of stress reactivity and regulation in children. *Neuroscience and Biobehavioral Reviews*, *34*(6), 867–76. doi:10.1016/j.neubiorev.2009.05.007

Lopez-Duran, N. L., Kovacs, M., & George, C. J. (2009). Hypothalamic-pituitary-adrenal axis dysregulation in depressed children and adolescents: a meta-analysis. *Psychoneuroendocrinology*, *34*(9), 1272–83. doi:10.1016/j.psyneuen.2009.03.016

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience*, *10*(6), 434–45. doi:10.1038/nrn2639

Magarinos, A. M., & McEwen, B. S. (1995). Stress-induced atrophy of apical dendrites of hippocampal CA3c neurons: involvement of glucocorticoid secretion and excitatory amino acid receptors. *Neuroscience*, *69*(1), 89–98.

Majewska, A. K., & Sur, M. (2006). Plasticity and specificity of cortical processing networks. *Trends in Neurosciences*, *29*(6), 323–9. doi:10.1016/j.tins.2006.04.002

Mannell, M. V, Franco, A. R., Calhoun, V. D., Cañive, J. M., Thoma, R. J., & Mayer, A. R. (2010). Resting state and task-induced deactivation: A methodological comparison in patients with schizophrenia and healthy controls. *Human Brain Mapping*, *31*(3), 424–37. doi:10.1002/hbm.20876

Maquet, P., Péters, J. M., Aerts, J., Delfiore, G., Degueldre, C., Luxen, A., & Franck, G. (1996). Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. *Nature*, *383*(6596), 163–166. Retrieved from http://www-psych.stanford.edu/~knutson/ans/maquet96.pdf

Martynova, O., Kirjavainen, J., & Cheour, M. (2003). Mismatch negativity and late discriminative negativity in sleeping human newborns. *Neuroscience Letters*, *340*(2), 75–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12668240

McEwen, B. S. (1998). Protective and Damaging Effects of Stress Mediators. *The New England Journal of Medicine*, *338*(3), 171–179. Retrieved from http://www.nejm.org/doi/full/10.1056/NEJM199801153380307

McEwen, B. S. (2008). Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. *European Journal of Pharmacology*, *583*(2-3), 174–85. doi:10.1016/j.ejphar.2007.11.071

Mehta, M. A., Golembo, N. I., Nosarti, C., Colvert, E., Mota, A., Williams, S. C. R., Rutter, M., et al. (2009). Amygdala, hippocampal and corpus callosum size following severe early institutional deprivation: the English and Romanian Adoptees study pilot. *Journal of Child Psychology and Psychiatry*, *50*(8), 943–51. doi:10.1111/j.1469-7610.2009.02084.x

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure & Function*, *214*(5-6), 655–67. doi:10.1007/s00429-010-0262-0

Mills, K. L., Lalonde, F., Clasen, L. S., Giedd, J. N., & Blakemore, S.-J. (2012). Developmental changes in the structure of the social brain in late childhood and adolescence. *Social Cognitive and Affective Neuroscience*, 1–9. doi:10.1093/scan/nss113

Mizoguchi, K., Ishige, A., Aburada, M., & Tabira, T. (2003). Chronic stress attenuates glucocorticoid negative feedback: involvement of the prefrontal cortex and hippocampus. *Neuroscience*, *119*(3), 887–897. doi:10.1016/S0306-4522(03)00105-2

Moore, G. A. (2009). Infants' and mothers' vagal reactivity in response to anger. *Journal of Child Psychology and Psychiatry*, *50*(11), 1392–1400. doi:10.1111/j.1469-7610.2009.02171.x

Moore, G. A. (2010). Parent conflict predicts infants' vagal regulation in social interaction. *Development and Psychopathology*, *22*(1), 23–33. doi:10.1017/S095457940999023X

Mueller, S. C., Maheu, F. S., Dozier, M., Peloso, E., Mandell, D., Leibenluft, E., Pine, D. S., et al. (2010). Early-life stress is associated with impairment in cognitive control in adolescence: an fMRI study. *Neuropsychologia*, *48*(10), 3037–44. doi:10.1016/j.neuropsychologia.2010.06.013

Murphy, K., Birn, R. M., Handwerker, D. a, Jones, T. B., & Bandettini, P. a. (2009). The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? *NeuroImage*, *44*(3), 893–905. doi:10.1016/j.neuroimage.2008.09.036

National Scientific Council on the Developing Child. (2005). Excessive Stress Disrupts the Architecture of the Developing Brain: Working Paper No. 3. Retrieved from www.developingchild.harvard.edu

National Scientific Council on the Developing Child. (2007). The Timing and Quality of Early Experiences Combine to Shape Brain Architecture: Working Paper No. 5. Retrieved from www.developingchild.harvard.edu

Nelson, C. a, & McCleery, J. P. (2008). Use of event-related potentials in the study of typical and atypical development. *Journal of the American Academy of Child and Adolescent Psychiatry*, *47*(11), 1252–61. doi:10.1097/CHI.0b013e318185a6d8

Nieuwenhuys, R. (2012). The insular cortex: a review. *Progress in Brain Research*, *195*, 123–63. doi:10.1016/B978-0-444-53860-4.00007-6

Noble, K., Houston, S., Kan, E., & Sowell, E. R. (2012). Neural correlates of socioeconomic status in the developing human brain. *Developmental Science*, *15*(4), 516–527. doi:10.1111/j.1467-7687.2012.01147.x

Nyberg, L., Forkstam, C., Petersson, K. M., Cabeza, R., & Ingvar, M. (2002). Brain imaging of human memory systems: between-systems similarities and within-system differences. *Cognitive Brain Research*, *13*(2), 281–92. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11958972

Öngür, D., & Price, J. L. (2000). The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cerebral Cortex*, *10*(3), 206–19. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10731217

Parker, K. J., Schatzberg, A. F., & Lyons, D. M. (2003). Neuroendocrine aspects of hypercortisolism in major depression. *Hormones and Behavior*, *43*(1), 60–66. doi:10.1016/S0018-506X(02)00016-8

Patel, P. D., Katz, M., Karssen, A. M., & Lyons, D. M. (2008). Stress-induced changes in corticosteroid receptor expression in primate hippocampus and prefrontal cortex. *Psychoneuroendocrinology*, *33*(3), 360–7. doi:10.1016/j.psyneuen.2007.12.003

Payne, C., Machado, C. J., Bliwise, N. G., & Bachevalier, J. (2010). Maturation of the hippocampal formation and amygdala in Macaca mulatta: a volumetric magnetic resonance imaging study. *Hippocampus*, *20*(8), 922–35. doi:10.1002/hipo.20688

Pechtel, P., & Pizzagalli, D. a. (2011). Effects of early life stress on cognitive and affective function: an integrated review of human literature. *Psychopharmacology*, *214*(1), 55–70. doi:10.1007/s00213-010-2009-2

Pell, M. D., Paulmann, S., Dara, C., Alasseri, A., & Kotz, S. a. (2009). Factors in the recognition of vocally expressed emotions: A comparison of four languages. *Journal of Phonetics*, *37*(4), 417–435. doi:10.1016/j.wocn.2009.07.005

Pelletier, J. G., Likhtik, E., Filali, M., & Paré, D. (2005). Lasting increases in basolateral amygdala activity after emotional arousal: implications for facilitated consolidation of emotional memories. *Learning & Memory*, *12*(2), 96–102. doi:10.1101/lm.88605

Peña-Gómez, C., Vidal-Piñeiro, D., Clemente, I. C., Pascual-Leone, Á., & Bartrés-Faz, D. (2011). Down-regulation of negative emotional processing by transcranial direct current stimulation: effects of personality characteristics. *PloS One*, *6*(7), e22812. doi:10.1371/journal.pone.0022812

Philip, N. S., Sweet, L. H., Tyrka, A. R., Price, L. H., Bloom, R. F., & Carpenter, L. L. (2013). Decreased default network connectivity is associated with early life stress in medication-free healthy adults. *European Neuropsychopharmacology*, *23*(1), 24–32. doi:10.1016/j.euroneuro.2012.10.008

Pierce, K. (2011). Early functional brain development in autism and the promise of sleep fMRI. *Brain Research*, *1380*, 162–74. doi:10.1016/j.brainres.2010.09.028

Portas, C. M., Krakow, K., Allen, P., Josephs, O., Armony, J. L., & Frith, C. D. (2000). Auditory processing across the sleep-wake cycle: simultaneous EEG and fMRI monitoring in humans. *Neuron*, *28*(3), 991–9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11163282

Porter, B., & O'Leary, K. D. (1980). Marital discord and childhood behavior problems. *Journal of Abnormal Child Psychology*, *8*(3), 287–95. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7410730

Porter, C., Wouden-Miller, M., Silva, S., & Porter, A. (2003). Marital harmony and conflict: Links to infants' emotional regulation and cardiac vagal tone. *Infancy*, *4*(2), 297–307. Retrieved from http://www.tandfonline.com/doi/abs/10.1207/S15327078IN0402_09

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. doi:10.1016/j.neuroimage.2011.10.018

Power, J. D., Fair, D. A., Schlaggar, B. L., & Petersen, S. E. (2010). The development of human functional brain networks. *Neuron*, *67*(5), 735–48. doi:10.1016/j.neuron.2010.08.017

Price, J. L. (2003). Comparative aspects of amygdala connectivity. *Annals of the New York Academy of Sciences*, *985*, 50–58. Retrieved from http://onlinelibrary.wiley.com/doi/10.1111/j.1749-6632.2003.tb07070.x/full

Pruessner, J. C., Dedovic, K., Pruessner, M., Lord, C., Buss, C., Collins, L., Dagher, A., et al. (2010). Stress regulation in the central nervous system: evidence from structural and functional neuroimaging studies in human populations. *Psychoneuroendocrinology*, *35*(1), 179–91. doi:10.1016/j.psyneuen.2009.02.016

Qin, S., Young, C. B., Supekar, K., Uddin, L. Q., & Menon, V. (2012). Immature integration and segregation of emotion-related brain circuitry in young children. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(20), 7941–6. doi:10.1073/pnas.1120408109

Rabinak, C. A., Angstadt, M., Welsh, R. C., Kenndy, A. E., Lyubkin, M., Martis, B., & Phan, K. L. (2011). Altered amygdala resting-state functional connectivity in post-traumatic stress disorder. *Frontiers in Psychiatry*, *2*(November), 62. doi:10.3389/fpsyt.2011.00062

Radley, J. J., Arias, C. M., & Sawchenko, P. E. (2006). Regional differentiation of the medial prefrontal cortex in regulating adaptive responses to acute emotional stress. *The Journal of Neuroscience*, *26*(50), 12967–76. doi:10.1523/JNEUROSCI.4297-06.2006

Raichle, M. E., Macleod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences*, *98*, 676–682.

Rainnie, D. G., Bergeron, R., Sajdyk, T. J., Patil, M., Gehlert, D. R., & Shekhar, A. (2004). Corticotrophin releasing factor-induced synaptic plasticity in the amygdala translates stress into emotional disorders. *The Journal of Neuroscience*, *24*(14), 3471–9. doi:10.1523/JNEUROSCI.5740-03.2004

Redcay, E., & Courchesne, E. (2008). Deviant Functional Magnetic Resonance Imaging Patterns of Brain Activity to Speech in 2 – 3-Year-Old Children with Autism Spectrum Disorder. *Biological Psychiatry*, *64*, 589–598. doi:10.1016/j.biopsych.2008.05.020

Redcay, E., Haist, F., & Courchesne, E. (2008). Functional neuroimaging of speech perception during a pivotal period in language acquisition. *Developmental Science*, *11*(2), 237– 252. doi:10.1111/j.1467-7687.2008.00674.x

Redcay, E., Kennedy, D. P., & Courchesne, E. (2007). fMRI during natural sleep as a method to study brain function during early childhood. *NeuroImage*, *38*, 696 – 707. doi:10.1016/j.neuroimage.2007.08.005

Reeb-Sutherland, B. C., Fifer, W. P., Byrd, D. L., Hammock, E. A. D., Levitt, P., & Fox, N. A. (2011). One-month-old human infants learn about the social world while they sleep. *Developmental Science*, *14*(5), 1134–41. doi:10.1111/j.1467-7687.2011.01062.x

Reul, J. M. H. M., & De Kloet, E. R. (1985). Two Receptor Systems for Corticosterone in Rat Brain: Microdistribution and Differential Occupation. *Endocrinology*, *117*(6), 2505–2511. doi:10.1210/endo-117-6-2505

Reynolds, S. M., & Zahm, D. S. (2005). Specificity in the projections of prefrontal and insular cortex to ventral striatopallidum and the extended amygdala. *The Journal of Neuroscience*, *25*(50), 11757–67. doi:10.1523/JNEUROSCI.3432-05.2005

Roozendaal, B., McEwen, B. S., & Chattarji, S. (2009). Stress, memory and the amygdala. *Nature Reviews Neuroscience*, *10*, 423–433. doi:10.1038/nrn2651

Roy, A. K., Fudge, J. L., Kelly, A. M. C., Perry, J. S. a, Daniele, T., Carlisi, C., Benson, B., et al. (2013). 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. doi:10.1016/j.jaac.2012.12.010

Roy, A. K., Shehzad, Z., Margulies, D. S., Kelly, A. M. C., Uddin, L. Q., Gotimer, K., Biswal, B. B., et al. (2009). Functional connectivity of the human amygdala using resting state fMRI. *NeuroImage*, *45*(2), 614–26. doi:10.1016/j.neuroimage.2008.11.030

Russchen, F. T., Bakst, I., Amaral, D. G., & Price, J. L. (1985). The amygdalostriatal projections in the monkey. An anterograde tracing study. *Brain Research*, *329*(1-2), 241–57. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3978445

Sabatini, M. J., Ebert, P., Lewis, D. a, Levitt, P., Cameron, J. L., & Mirnics, K. (2007). Amygdala gene expression correlates of social behavior in monkeys experiencing maternal separation. *The Journal of Neuroscience*, *27*(12), 3295–304. doi:10.1523/JNEUROSCI.4765-06.2007

Sanchez, C. E., Richards, J. E., & Almli, C. R. (2012). Neurodevelopmental MRI brain templates for children from 2 weeks to 4 years of age. *Developmental Psychobiology*, *54*(1), 77–91. doi:10.1002/dev.20579

Sánchez, M. M., Aguado, F., Sánchez-Toscano, F., & Saphier, D. (1998). Neuroendocrine and immunocytochemical demonstrations of decreased hypothalamo-pituitary-adrenal axis responsiveness to restraint stress after long-term social isolation. *Endocrinology*, *139*(2), 579. Retrieved from http://endo.endojournals.org/content/139/2/579.short

Sánchez, M. M., Ladd, C. O. C. O., & Plotsky, P. M. P. M. (2001). Early adverse experience as a developmental risk factor for later psychopathology: evidence from rodent and primate models. *Development and Psychopathology*, *13*, 419–449. Retrieved from http://journals.cambridge.org.libproxy.uoregon.edu/action/displayFulltext?type=1&fid=82067&jid=DPP&volumeId=13&issueId=03&aid=82066&bodyId=&membershipNumber=&societyETOCSession=

Sánchez, M. M., Young, L. J., & Plotsky, P. M. (2000). Distribution of corticosteroid receptors in the rhesus brain: relative absence of glucocorticoid receptors in the hippocampal formation. *The Journal of Neuroscience*, *20*(12), 4657–4668. Retrieved from http://neuro.cjb.net/content/20/12/4657.short

Sander, D., Grandjean, D., Pourtois, G., Schwartz, S., Seghier, M. L., Scherer, K. R., & Vuilleumier, P. (2005). Emotion and attention interactions in social cognition: brain regions involved in processing anger prosody. *NeuroImage*, *28*(4), 848–58. doi:10.1016/j.neuroimage.2005.06.023

Sandor, S., & Leahy, R. (1997). Surface-based labeling of cortical anatomy using a deformable atlas. *IEEE Transactions on Medical Imaging*, *16*(1), 41–54. doi:10.1109/42.552054

Sapolsky, R. M., & Meaney, M. J. (1986). Maturation of the adrenocortical stress response: Neuroendocrine control mechanisms and the stress hyporesponsive period. *Brain Research Reviews*, *11*(1), 65–76. doi:10.1016/0165-0173(86)90010-X

Sapolsky, R. M., Romero, L., & Munck, A. U. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocrine Reviews*, *21*(1), 55– 89. Retrieved from http://edrv.endojournals.org/content/21/1/55.short

Scher, M. S. (2008). Ontogeny of EEG-sleep from neonatal through infancy periods. *Sleep Medicine*, *9*(6), 615–36. doi:10.1016/j.sleep.2007.08.014

Schmahl, C., Vermetten, E., Elzinga, B. M., & Bremner, J. D. (2003). Magnetic resonance imaging of hippocampal and amygdala volume in women with childhood abuse and borderline personality disorder. *Psychiatry Research: Neuroimaging*, *122*(3), 193–198. doi:10.1016/S0925-4927(03)00023-4

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., Reiss, A. L., et al. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *The Journal of Neuroscience, 27*(9), 2349–56. doi:10.1523/JNEUROSCI.5587-06.2007

Shattuck, D. W., Sandor-Leahy, S. R., Schaper, K. A., Rottenberg, D. A., & Leahy, R. M. (2001). Magnetic resonance image tissue classification using a partial volume model. *NeuroImage*, *13*(5), 856–76. doi:10.1006/nimg.2000.0730

Shaw, P., Kabani, N. J., Lerch, J. P., Eckstrand, K., Lenroot, R., Gogtay, N., Greenstein, D., et al. (2008). Neurodevelopmental trajectories of the human cerebral cortex. *The Journal of Neuroscience*, *28*(14), 3586–94. doi:10.1523/JNEUROSCI.5309-07.2008

Sheline, Y. I., Price, J. L., Yan, Z., & Mintun, M. a. (2010). Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(24), 11020–5. doi:10.1073/pnas.1000446107

Shi, F., Yap, P.-T., Wu, G., Jia, H., Gilmore, J. H., Lin, W., & Shen, D. (2011). Infant brain atlases from neonates to 1- and 2-year-olds. *PloS One*, *6*(4), e18746. doi:10.1371/journal.pone.0018746

Shin, L. M., Rauch, S. L., & Pitman, R. K. (2006). Amygdala, Medial Prefrontal Cortex, and Hippocampal Function in PTSD. *Annals of the New York Academy of Sciences*, *1071*, 67–79. doi:10.1196/annals.1364.007

Shmuel, A., & Leopold, D. a. (2008). Neuronal correlates of spontaneous fluctuations in fMRI signals in monkey visual cortex: Implications for functional connectivity at rest. *Human Brain Mapping*, *29*(7), 751–61. doi:10.1002/hbm.20580

Smith, G. C., Gutovich, J., Smyser, C. D., Pineda, R., Newnham, C., Tjoeng, T. H., Vavasseur, C., et al. (2011). Neonatal intensive care unit stress is associated with brain development in preterm infants. *Annals of Neurology*, *70*(4), 541–9. doi:10.1002/ana.22545

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, *17*(3), 143–55. doi:10.1002/hbm.10062

Smith, S. M., Bannister, P., Beckmann, C., & Brady, M. (2001). FSL: New tools for functional and structural brain image analysis. *NeuroImage*, (13), 2001. Retrieved from http://c3s2i.free.fr/cv/fsl.pdf

Smyser, C. D., Inder, T. E., Shimony, J. S., Hill, J. E., Degnan, A. J., Snyder, A. Z., & Neil, J. J. (2010). Longitudinal Analysis of Neural Network Development in Preterm Infants. *Cerebral Cortex*, *20*(12), 2852–2862. doi:10.1093/cercor/bhq035

Snyder, D. K. (1997). *Marital Satisfaction Inventory—Revised*. CA: Western Psychological Services.

Spoormaker, V. I., Schröter, M. S., Gleiser, P. M., Andrade, K. C., Dresler, M., Wehrle, R., Sämann, P. G., et al. (2010). Development of a large-scale functional brain network during human non-rapid eye movement sleep. *The Journal of Neuroscience*, *30*(34), 11379–87. doi:10.1523/JNEUROSCI.2015-10.2010

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 & Neuroscience*, *37*(4), 241–9. doi:10.1503/jpn.110069

Stein, J. L., Wiedholz, L. M., Bassett, D. S., Weinberger, D. R., Zink, C. F., Mattay, V. S., & Meyer-Lindenberg, A. (2007). A validated network of effective amygdala connectivity. *NeuroImage*, *36*(3), 736–45. doi:10.1016/j.neuroimage.2007.03.022

Stern, E. R., Fitzgerald, K. D., Welsh, R. C., Abelson, J. L., & Taylor, S. F. (2012). Resting-state functional connectivity between fronto-parietal and default mode networks in obsessive-compulsive disorder. *PloS One*, *7*(5), e36356. doi:10.1371/journal.pone.0036356

Stevenson, C. W., Marsden, C. a, & Mason, R. (2008). Early life stress causes FG-7142-induced corticolimbic dysfunction in adulthood. *Brain Research*, *1193*, 43–50. doi:10.1016/j.brainres.2007.11.062

Straus, M. A., Hamby, S. L., Boney-McCoy, S., & Sugarman, D. B. (1996). The Revised Conflict Tactics Scales (CTS2). *Journal of Family Issues*, *17*(3), 283–316.

Supekar, K., Musen, M., & Menon, V. (2009). Development of large-scale functional brain networks in children. *PLoS Biology*, *7*(7), e1000157. doi:10.1371/journal.pbio.1000157

Supekar, K., Uddin, L. Q., Prater, K., Amin, H., Greicius, M. D., & Menon, V. (2010). Development of functional and structural connectivity within the default mode network in young children. *NeuroImage*, *52*(1), 290–301. doi:10.1016/j.neuroimage.2010.04.009.Development

Swiergiel, A. H., Takahashi, L. K., & Kalin, N. H. (1993). Attenuation of stress-induced behavior by antagonism of corticotropin-releasing factor receptors in the central amygdala in the rat. *Brain Research*, *623*(2), 229–34. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8221104

Talairach, P., & Tournoux, J. (1988). *Co-planar Stereotaxic Altas of the Human Brain*. Stuttgart, Germany: Georg Thieme Verlag.

Tanaka, H., Fujita, N., Takanashi, M., Hirabuki, N., Yoshimura, H., Abe, K., & Nakamura, H. (2003). Effect of stage 1 sleep on auditory cortex during pure tone stimulation: evaluation by functional magnetic resonance imaging with simultaneous EEG monitoring. *American Journal of Neuroradiology*, *24*(10), 1982–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/14625220

Taylor, S. E., Eisenberger, N. I., Saxbe, D. E., Lehman, B. J., & Lieberman, M. D. (2006). Neural responses to emotional stimuli are associated with childhood family stress. *Biological Psychiatry*, *60*(3), 296–301. doi:10.1016/j.biopsych.2005.09.027

Thesen, S., Heid, O., Mueller, E., & Schad, L. R. (2000). Prospective acquisition correction for head motion with image-based tracking for real-time fMRI. *Magnetic Resonance in Medicine*, *44*(3), 457–65. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10975899

Thomaes, K., Dorrepaal, E., Draijer, N., De Ruiter, M. B., Van Balkom, A. J., Smit, J. H., & Veltman, D. J. (2010). Reduced anterior cingulate and orbitofrontal volumes in child abuse-related complex PTSD. *The Journal of Clinical Psychiatry*, *71*(12), 1636–44. doi:10.4088/JCP.08m04754blu

Todd, R. M., Evans, J. W., Morris, D., Lewis, M. D., & Taylor, M. J. (2011). The changing face of emotion: age-related patterns of amygdala activation to salient faces. *Social Cognitive and Affective Neuroscience*, *6*(1), 12–23. doi:10.1093/scan/nsq007

Tomoda, A., Suzuki, H., Rabi, K., Sheu, Y.-S., Polcari, A., & Teicher, M. H. (2009). Reduced prefrontal cortical gray matter volume in young adults exposed to harsh corporal punishment. *NeuroImage*, *47 Suppl 2*, T66–71. doi:10.1016/j.neuroimage.2009.03.005

Tottenham, N., Hare, T. A., Millner, A., Gilhooly, T., Zevin, J. D., & Casey, B. J. (2011). Elevated amygdala response to faces following early deprivation. *Developmental Science*, *14*(2), 190–204. doi:10.1111/j.1467-7687.2010.00971.x

Tottenham, N., Hare, T. A., Quinn, B. T., McCarry, T. W., Nurse, M., Gilhooly, T., Millner, A., et al. (2010). Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. *Developmental Science*, *13*(1), 46–61. doi:10.1111/j.1467-7687.2009.00852.x

Tottenham, N., & Sheridan, M. A. (2010). A review of adversity, the amygdala and the hippocampus: a consideration of developmental timing. *Frontiers in Human Neuroscience*, *3*(68), 1–18. doi:10.3389/neuro.09.068.2009

Treadway, M. T., Grant, M. M., Ding, Z., Hollon, S. D., Gore, J. C., & Shelton, R. C. (2009). Early adverse events, HPA activity and rostral anterior cingulate volume in MDD. *PloS One*, *4*(3), e4887. doi:10.1371/journal.pone.0004887

Uchida, S., Hara, K., Kobayashi, A., Funato, H., Hobara, T., Otsuki, K., Yamagata, H., et al. (2010). Early life stress enhances behavioral vulnerability to stress through the activation of REST4-mediated gene transcription in the medial prefrontal cortex of rodents. *The Journal of Neuroscience*, *30*(45), 15007–18. doi:10.1523/JNEUROSCI.1436-10.2010

Uddin, L. Q., Supekar, K., & Menon, V. (2010). Typical and atypical development of functional human brain networks: insights from resting-state fMRI. *Frontiers in Systems Neuroscience*, *4*, 1–12. doi:10.3389/fnsys.2010.00021

Ulrich-Lai, Y., & Herman, J. P. (2009). Neural regulation of endocrine and autonomic stress responses. *Nature Reviews Neuroscience*, *10*, 397–409. doi:10.1038/nrn2647

Van Dijk, K. R. a., Sabuncu, M. R., & Buckner, R. L. (2012). The Influence of Head Motion on Intrinsic Functional Connectivity MRI. *NeuroImage*, *59*(1), 431–438. doi:10.1016/j.neuroimage.2011.07.044

Van Essen, D. C., Drury, H. a, Dickson, J., Harwell, J., Hanlon, D., & Anderson, C. H. (2001). An integrated software suite for surface-based analyses of cerebral cortex. *Journal of the American Medical Informatics Association*, *8*(5), 443–59. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=131042&tool=pmcentrez&rendertype=abstract

Van Marle, H. J. F., Hermans, E. J., Qin, S., & Fernández, G. (2010). Enhanced resting-state connectivity of amygdala in the immediate aftermath of acute psychological stress. *NeuroImage*, *53*(1), 348–54. doi:10.1016/j.neuroimage.2010.05.070

Van Oers, H. J., De Kloet, E. R., & Levine, S. (1998). Early vs. late maternal deprivation differentially alters the endocrine and hypothalamic responses to stress. *Developmental Brain Research*, *111*(2), 245–52. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9838147

Van Wingen, G. A., Geuze, E., Vermetten, E., & Fernández, G. (2011). Perceived threat predicts the neural sequelae of combat stress. *Molecular Psychiatry*, *16*(6), 664–71. doi:10.1038/mp.2010.132

Van Wingen, G. A., Geuze, E., Vermetten, E., & Fernández, G. (2012). The neural consequences of combat stress: long-term follow-up. *Molecular Psychiatry*, *17*(2), 116–118. Retrieved from http://www.nature.com/mp/journal/vaop/ncurrent/full/mp2011110a.html

Veer, I. M., Oei, N. Y. L., Spinhoven, P., Van Buchem, M. a, Elzinga, B. M., & Rombouts, S. a R. B. (2012). Endogenous cortisol is associated with functional connectivity between the amygdala and medial prefrontal cortex. *Psychoneuroendocrinology*, *37*(7), 1039–1047. doi:10.1016/j.psyneuen.2011.12.001

Vincent, J. L., Snyder, A. Z., Fox, M. D., Shannon, B. J., Andrews, J. R., Raichle, M. E., & Buckner, R. L. (2006). Coherent spontaneous activity identifies a hippocampal-parietal memory network. *Journal of Neurophysiology*, *96*(6), 3517–31. doi:10.1152/jn.00048.2006

Weissenbacher, A., Kasess, C., Gerstl, F., Lanzenberger, R., Moser, E., & Windischberger, C. (2009). Correlations and anticorrelations in resting-state functional connectivity MRI: a quantitative comparison of preprocessing strategies. *NeuroImage*, *47*(4), 1408–16. doi:10.1016/j.neuroimage.2009.05.005

Whitfield-Gabrieli, S., & Ford, J. M. (2012). Default mode network activity and connectivity in psychopathology. *Annual Review of Clinical Psychology*, *8*, 49–76. doi:10.1146/annurev-clinpsy-032511-143049

Wildgruber, D., Ackermann, H., Kreifelts, B., & Ethofer, T. (2006). Cerebral processing of linguistic and emotional prosody: fMRI studies. *Progress in Brain Research*, *156*, 249–68. doi:10.1016/S0079-6123(06)56013-3

Yin, Y., Li, L., Jin, C., Hu, X., Duan, L., Eyler, L. T., Gong, Q., et al. (2011). Abnormal baseline brain activity in posttraumatic stress disorder: a resting-state functional magnetic resonance imaging study. *Neuroscience Letters*, *498*(3), 185–9. doi:10.1016/j.neulet.2011.02.069

Yuan, W., Altaye, M., Ret, J., Schmithorst, V., Byars, A. W., Plante, E., & Holland, S. K. (2009). Quantification of head motion in children during various fMRI language tasks. *Human Brain Mapping*, *30*(5), 1481–9. doi:10.1002/hbm.20616

Zeng, L.-L., Shen, H., Liu, L., Wang, L., Li, B., Fang, P., Zhou, Z., et al. (2012). Identifying major depression using whole-brain functional connectivity: a multivariate pattern analysis. *Brain*, *135*(Pt 5), 1498–507. doi:10.1093/brain/aws059

Zhang, D., & Raichle, M. E. (2010). Disease and the brain's dark energy. *Nature Reviews Neurology*, *6*, 15–28. Retrieved from http://www.nature.com/nrneurol/journal/v6/n1/abs/nrneurol.2009.198.html

Zhu, X., Wang, X., Xiao, J., Liao, J., Zhong, M., Wang, W., & Yao, S. (2011). Evidence of a Dissociation Pattern in Resting-State Default Mode Network Connectivity in First-Episode, Treatment-Naive Major Depression Patients. *Biological Psychiatry*. doi:10.1016/j.biopsych.2011.10.035