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Prenatal Maternal Depression and the Neural Development of Social Cognition

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Prenatal Maternal Depression and the Neural Development of Social Cognition

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B.S. William and Mary, 2006

Advisors: W.E. Craighead, Ph.D. and Elaine F. Walker, Ph.D.

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Abstract

Prenatal Maternal Depression and the Neural Development of Social Cognition
By Amy K. Anderson

Depression during pregnancy is prevalent, under-diagnosed, and under-treated. Children of mothers with major depressive disorder (MDD) during pregnancy often exhibit cognitive, social, emotional, and behavioral dysfunction that persists into adolescence and adulthood. Knowledge of how prenatal depression affects children's brain development is necessary to inform practice guidelines for treating depression during pregnancy.

Twenty one mother-child dyads with longitudinally characterized prenatal and postnatal maternal MDD were studied. The children were behaviorally evaluated and scanned (3T fMRI) at 4-6 years of age. During scanning, they completed a social joint attention task that included affective, cognitive conflict, and attentional demands. Independent Component Analysis (ICA) of fMRI data was conducted to assess the impact of prenatal maternal depression (PMD) on both intrinsic and extrinsic connectivity of three select neural processing networks (the left occipital temporal, limbic, and fronto-cingulate networks).

PMD severity was associated with diminished intrinsic activity within the fronto-cingulate and limbic networks during social conflict trials and was not associated with changes intrinsic activity in the left occipital temporal network. Moreover, PMD was related to increased extrinsic connectivity of the left dorsal lateral prefrontal cortex into the limbic network, decreased extrinsic connectivity of the right inferior frontal gyrus into the limbic network, and decreased extrinsic connectivity of the right anterior cingulate into the fronto-cingulate network. PMD was not related to extrinsic connectivity for the left occipital temporal network.

The present study adds to the limited literature in this subject area by characterizing younger children at risk for mood disorders. Results indicate that exposure to PMD leads to disrupted neural development in the intrinsic and extrinsic functional organization of neural networks. The significance of this outcome is relevant to clinical decision-making related to the aggressive management of moderate to severe depression in pregnancy. This study highlights the neurodevelopmental cost to the offspring of unresolved maternal depression and suggests a re-evaluation of the clinical decision to avoid first-line treatment in pregnancy.

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TABLE OF CONTENTS

Tables and Figures

CHAPTER 1:

INTRODUCTION

1.1 Depression during Pregnancy

1.1.1 Prevalence and Conventional Wisdom

As the prevalence of major depressive disorder (MDD) is highest in women during the reproductive years, it is not surprising that MDD is found in approximately 10-18% of pregnancies [1-3].Yet only a minority of these patients receive treatment [3, 4]. The low rates of treatment of prenatal maternal depression (PMD) are attributed to:

1) Under-detection and lack of information: Pregnant women and medical professionals often mistake the symptoms of depression for common side effects of pregnancy itself [3, 5], thus only documenting PMD in less than 25% of PMD cases [4, 6]. Additionally, only 23-57% of medical professionals who commonly deal with pregnant women (midwives, general practitioners) were even aware of the problems associated with PMD [1, 7].

2) Safety concerns: Both patients and doctors shy away from medications as a treatment for PMD due to concerns for the safety and long-term well-being of the fetus and child [3, 4, 8]. Many studies have found various negative side-effects to the fetus and child of long-term SSRI use during pregnancy, including increased rates of miscarriage, preterm birth, heart malformations and pulmonary hypertension in infants, changes in infant Serotonin circuitry [9-11], and neonatal withdrawal[12, 13].

1.1.2 Treatment Options

This has led the FDA and drug manufacturers to issue warnings against the use of SSRIs during pregnancy, especially in the third trimester, leading to extreme

uncertainty on the part of clinicians on how to treat PMD [12]. Fearing possible toxic effects of antidepressants on their unborn children, only 11-13% of depressed women choose to use SSRIs while pregnant, many of whom are taking inadequate doses [3, 6]. Although other forms of treatment are suggested (psychotherapy, homeopathic treatments, electro-convulsive-shock therapy (ECT)), only 18-33% of PMD patients seek any sort of treatment for their depression [3, 6]. In addition, doctors and patients lack adequate information regarding the long term costs and benefits of medication use due to the lack of systematic, longitudinal studies of mother and child outcomes [3, 6, 8]. The under-recognition, under-treatment, and fear of treatment associated with PMD, puts pregnant mothers experiencing PMD and their doctors in a considerable quandary. Thus, more evidence of the long term effects of PMD is needed.

1.1.3 Medications and the Fetus

However, some studies are beginning to contradict the findings of the SSRI exposure studies. A 2012 study reports SSRI use in 1.8-2.8% of all pregnancies. Exposure to SSRIs did not show a correlation with increased risk of heart malformations. Additionally, only about 30% of the exposed newborns, experienced any 'serotonin syndrome' symptoms, and they were mostly mild and fleeting [14]. Often the neonates' exposure to depression itself was not taken into consideration in previous studies. Once maternal depression symptoms were controlled for, the significant effects of SSRI exposure on infant behavior disappeared [11]. For example, Oberlander and colleagues found that the best predictor of externalizing behaviors at age 4 was maternal mood and stress during pregnancy, regardless of SSRI exposure [11]. Recent data suggest that untreated PMD, not prenatal medication exposure, leads to some of the negative perinatal outcomes found [15].

1.1.4 Prenatal Maternal Depression

Unresolved or untreated depression during pregnancy is associated with many health risks and negative behaviors [16], such as poor nutrition, substance abuse, poor prenatal care, obstetric complications, miscarriages, increases in suicidality [12], increased over-the-counter drug use, tobacco use, and minimal use of prenatal vitamins, all of which are known to be harmful for the developing fetus.

Neonatal symptoms of exposure to PMD include abnormal heart rate, preterm birth, low birth weight [17], low APGAR scores, and high neonatal cortisol levels [18]. Prenatal depression may thus represent the first adverse life event for the child related to mental illness and acts as a teratogen on neural development and behavior. This tertagenic effect is often attributed to depression-related increases in maternal stress hormones crossing the placenta, immune system disturbances, or blood flow irregularities [19, 20].

1.1.5 Animal Models of Prenatal Maternal Depression

Animal models also indicate that prenatal exposure to maternal stress negatively impacts the offspring's cognitive, emotional, and behavioral development [12, 21, 22]. In animal models of prenatal stress, a depression-like state is induced in pregnant mothers by stressing them on a daily basis using a variety of methods. The effects on the offspring are subsequently analyzed to model the connection between prenatal stress and negative offspring outcomes. Rats exposed to PMD show decreased numbers of dendrites and smaller dendritic trees in the hippocampus, as well as decreased spatial learning and memory [23]. Prenatal stress also induced abnormal cellular staining patterns in the amygdala and impaired long term potentiation, which negatively affected learning and emotional memory [24]. In a similar experiment, cross-fostering

the neonatal rats to non-stressed mothers did not change the outcome for the offspring, showing that prenatal stress (depression) during the prenatal period can significantly alter brain development independent from post-natal experiences [25].

1.1.6 Long Term Effects of Prenatal Maternal Depression

Prenatally-stressed human infants have impaired habituation and temperament problems [26]. Years later, children exposed to PMD show temperamental styles characterized by negative affective reactivity [27-29] [30] [31], poorer cognitive development [32] [22], and sleep problems [21, 33]. The long term developmental effects of unresolved PMD for the offspring include language deficits, cognitive impairment, impulsivity, Attention Deficit Hyperactivity Disorder (ADHD), behavioral dysregulation, negative affective reactivity, and childhood psychopathology [27, 28] [22, 30-32].These developmental deficits often persist into late adolescence [34] and adulthood. Many observed deficits are independent of postpartum depression and birth complications [21, 31]. Furthermore, prenatal maternal depression and infant cortisol levels, but not postpartum maternal depression, predict infant temperament [35]. These results support the hypothesis that the prenatal period is a particularly vulnerable period for child development [19]. Prenatal depression and its associated stress may thus represent the first adverse life event for a child and have a negative impact on neural development and behavior, beyond the influence of post-partum depression.

1.2 Development of Social Cognition

1.2.1 Joint Attention

Joint attention is the process by which two people share focus on an object. Normally one person directs the other's attention towards the object of interest by

shared eye-gaze, pointing, or using verbal exclamations. Children gain the ability to participate in joint attention as early as 8 months of age but more often around between 11-16 months of age [36]. Both following eye gaze and identifying intention are important skills in joint attention and in helping the child learn to associate objects with their names (language development) and understand the meaning in others' gestures (social communications)[37]. Interactions with adults involving joint attention allow infants to learn about their environment and to develop proper attachment and healthy social and emotional relationships with their caregivers [38].

1.2.2 Joint Attention and Social Cognition

Social cognition is defined as encoding, storing, and processing of information in the brain about members of one's own species[39, 40]. Joint attention is very important for the proper development of social cognition. The ability to engage in social communication and attend to one's environment are fundamental to normal human relationships. Normally, infants are very motivated to engaged in shared attention and will even turn away from other interesting things to do so [38]. Early joint attention skills prepare infants for the more complex social signals involved in everyday conversation and even predict their later social competence at 2.5 years of age [41], as well as social and emotional abilities later in life [42].

The interpretation of social and emotional attention cues allows the child to make inferences about others' emotions, intentions, and desires to develop complex social skills related to reciprocity, inter-subjectivity, and empathy [39, 40, 43]. Around the time of kindergarten, children undergo large, dynamic changes in socialization related to school, non-parent authority figures, and peer groups [44] [45]. Kindergarten and first grade mark a change to a more structured learning environment and the

development of social hierarchies not commonly seen in preschool [46, 47]. During this time period, social cognition begins to become more complex. For this reason, the age group of 4-6 was chosen as a focus of the present study .

The fields of developmental psychology and cognitive psychology have sought to understand both how humans process social information and the neurodevelopment that underlies relevant skills. Social cognition can be disrupted in cases of brain injury [48] , some genetic disorders [49], or in psychological disorders, such as autism, depression, bipolar disorder, and anxiety[50]. It is thought that certain aspects of social cognition, such as facial recognition, are innate, while many others are learned over the course of development and are culturally specific [51].

1.2.3 Social Cognition Neural Circuitry

Research has found that understanding other's states of mind, a skill called Theory of Mind (ToM), is necessary for proper social cognition. The network of brain regions that appear to implement Theory of Mind consists of the superior temporal sulcus (STS), temporal-parietal junction(TPJ), medial prefrontal cortex, temporal poles, and posterior cingulate/precuneus [52]. Implicit social processing (facial recognition, understand body movement) has been linked to activity in the fusiform face area, STS, premotor areas (the mirror neuron system), and the inferior frontal gyrus [53]. Explicit social processing (reasoning about others' mental states) has been linked to activity in the TPJ[54] and medial prefrontal cortex [55].

Another important aspect of social cognition is the development of a sense of self. Similar areas as those described above for ToM are involved in self-development. In addition to those described above, thinking about personal identity from a social perspective also involves the anterior insula, ventral striatum, anterior cingulate cortex,

middle cingulate cortex, and ventrolateral prefrontal cortex [56]. Still other studies have suggested that the amygdala, and orbitofrontal cortex should also be added to the list of brain areas that participate in social cognition [57, 58]. Depending on what aspect of social cognition is being looked at, different brain areas are incorporated into the social cognition neural circuitry. Given the extensive reach of social cognition into most aspects of human life, it is not surprising that there is not a network exclusively used for social cognition, but rather that there is functional overlap with the neural networks involved in emotion, memory, decision making, and reward processing.

Interestingly, the neural circuitry involved in social cognition has been found to function atypically in both autism [52, 59, 60] and depression [61]. Additionally, depression in adults is often associated with behavioral deficits in social functioning and emotional regulation [62-64], most likely a product of this disrupted neural circuitry [61, 65].

1.3 Depression

1.3.1 Neural Circuitry in Adult Major Depression

Many studies have looked at the structural and functional abnormalities associated with depression in adults. These studies show that dysfunction in the prefrontal cortex and striatal regions, which leads to the dysregulation of limbic structures, underlies the emotional behavior seen in depression. For example, in one PET (Positron Emission Topography) study of familial major depression, dysregulation of glucose uptake was seen in the amygdala, the ventral anterior cingulate cortex, the orbito-frontal cortex (OFC), ventrolateral PFC, and dorsomedial PFC, dorsolateral PFC, the anterior insula, the ventral striatum, the posterior cingulate gyrus and the medial

thalamus [66, 67]. Although researchers have proposed many different models of the physiology of depression and they are constantly changing, the following areas have been consistently implicated across models:

1) Hypothalamus and Pituitary: Abnormalities in these areas cause dysregulation in the HPA axis, causing an over-production of stress hormones (such as cortisol), which, in turn, can damage the hippocampus [68, 69] and heighten emotions (especially fear and anxiety).

2) Hippocampus: Volumetric changes in the hippocampus due to cell death have been associated with depression (meta-analysis [70]).

3) Amygdala: Over-activation of the amygdala is associated with negative perception biases in people with depression [71]. Amygdala volume is also found to be abnormal in some studies of depression [72].

4) Prefrontal cortex: Regions of the dorso-lateral and orbitofrontal cortex, which are involved in self-regulation and control of mood via interaction with sub-cortical areas, have been found to be dysregulated in depression [73, 74].

5) Anterior Cingulate: Specifically, the subgenual and rostral anterior cingulate are dysregulated in depression, and the former has been successfully targeted with deep-brain stimulation therapy for extreme cases of depression [75][76].

1.3.2 Symptoms of Pediatric Depression

Depression symptoms can be seen in infancy; these include withdrawal behavior [77], poor regulatory behavior, and negative affective temperament states [78]. In toddlerhood, depression is characterized by decision-making difficulties, self-deprecation, irritability, loneliness, and feeling unloved [79]. In preschoolers,

depression symptoms include frustration, annoyance, anger, indecisiveness, and loneliness. Children with these types of symptoms during the first four years of life, tend to go on to develop diagnosable MDD during middle childhood, adolescence, and adulthood [79].

1.3.3 Neural Circuitry of Pediatric Depression

Given the challenges associated with functionally imaging children (such as movement and attention issues, child and parental anxiety, etc.), especially children with psychological disorders, studies on pediatric depression have been limited. However, those that have succeeded show dysregulation of brains areas similar to those seen in depressed adults. Youths (ages 8-17) with depression (MDD) had less activation in the right dlPFC, inferior PFC and anterior cingulate, parietal lobes, putamen, insula, temporal lobes, and precuneus during various cognitive control tasks [80]. Additionally, depressed children (10-14 years old) show blunted activity in the ACC, caudate, OFC, and the right insula during the reward phase of a reward decision-making task [81]. Another reward study with youths aged 8-17 years found similar results, with blunted striatal response but heightened dorsal lateral and medial PFC during a monetary reward game [82]. Additionally, school-age children with a history of preschool depression showed atypical functional connectivity within the default mode network [83], from the sub-genual cingulate (sgCC) [84] and from the amygdala [85, 86].These studies, among others, signify the functional similarities between pediatric depression patients, high-risk youths, and adults with depression [76]. In light of these similarities, the need to understand the trajectory of the disease state and to identify neural risk markers early in development is clear, with the hope of developing interventions to lessen or halt to progression of depression.

1.4 Network Development

1.4.1 Neural Maturation in Children

As the brain matures, long range connections are strengthened (integration) and local connections are weakened to create more discrete functional brain areas (segregation)[87-89]. Unlike the corresponding functional networks seen in adults, many of these maturing networks appear fragmented and show incomplete patterns of connectivity, due to the functional immaturity of this age group [89]. Research in the field of child brain maturity, has shown that functional networks in children tend to be among areas that are close to one another and that lack integration over multi-modal brain areas [87]. Functional neuroimaging studies in infants, older children (aged 8-12), adolescents, and adults have shown a dramatic re-organization of functional brain networks over the course of development [90]. These functional changes parallel behavioral development in cognitive, attentional, and sensory-motor skills [91, 92]. By the time children are of kindergarten age (4-5 years old), they have typically acquired understanding of primary emotions (happiness, sadness, and anger), rudimentary social skills, gross sensory-motor coordination, attention, memory learning, and the ability to engage in goal-directed behavior [93]. However, on average they still lack many skills which are considered necessary in normative development, namely attention control, understanding of complex social emotions (empathy, guilt), executive functioning, complex decision making, and emotional regulation skills. Many of these capacities do not fully develop until individuals enter their early twenties [90, 92].

1.4.2 Networks in Adults

Using resting state probabilistic independent component analysis (pICA), previous research has identified the following networks in adults: 1) medial visual, 2)

lateral visual, 3) auditory, 4) sensory motor, 5) visual-spatial (involving the posterior parietal and posterior cingulate), 6) executive control, 7) right dorsal visual stream, 8) left dorsal visual stream, 9) language (also called ventral attention system), and 10) default mode network [94-96]. Of these, the networks involving higher order thinking (i.e. the executive control and attention networks) and the default mode network have been found to be immature in children aged 5-8 years [89]. In looking at social cognition, we are interested in the child representation of the adult networks that are involved in executive control and attention, social/emotion processing, and facial processing.

1.4.2.1 Facial Perception

In typically developing adults, the facial processing network includes the fusiform, middle occipital, bilateral STS, anterior cingulate, inferior frontal gyrus, orbital frontal gyrus [97], amygdala, and ventral striatum [98, 99]. Connectivity of these frontal and limbic areas with the temporal lobe creates the Facial Perception Network, allowing for emotional memories and understanding of such complex concepts as empathy [100]. This network is often found to have altered connectivity in patients with psychiatric disorders including bipolar disorder [101] and depression [102].

1.4.2.2 Limbic system

Originally proposed by James Papez in 1937, the limbic system is a group of areas that are involved in emotion-processing, memory, and motivation [103]. Although it is no longer thought of as one system and some even suggest abandoning the term altogether [104] , the term 'limbic system' is still widely used to describe the various systems that participate in emotion and memory. We will refer to this system as the

limbic system or limbic network throughout this paper. Areas commonly included in the limbic system are [105-107]:

1) Hypothalamus - controls many autonomic and endocrine functions. It is involved in emotional and behavioral responses to stimuli.

2) Hippocampus - involved in memory formation.

3) Amygdala - involved in memory as well as reward and fear processing. It is also important for alerting the cortex motivational and salient stimuli.

4) Parts of the cingulate gyrus - involved in autonomic functions, such as heart rate, which are affected by increased emotions. This area is also involved in attention.

5) Orbitofrontal cortex (OFC) - frontal area above the eyes involved in decision making, especially as it relates to reward.

6) Basal ganglia: (in particular the nucleus accumbens) - reward area involved in pleasure seeking and addiction.

7) Septal nuclei, fornix, mammillary bodies, parahippocampus gyrus, parts of the thalmas, entorhinal cortex, and piriform cortex - other areas that are mostly involved in memory formation or emotional regulation.

The limbic network has been identified in various independent component analysis studies. In the following figure modified from Yeo et al, 2011, the limbic network is shown in cream. This network appears both in the 7-network parcellation (shown in the figure) and the 17-network parcellation (not shown)[108]. Interestingly, dysfunction of the limbic system has been found to be associated with negative affect,

impaired social functioning, and genetic risk for depression [109] and childhood depression [110], and is known to be affected during the prenatal period [111].

1.4.2.3 Cognitive Control Networks

Peterson, Schlagger, and colleagues have extensively researched networks involved in top-down control of cognition, using connectivity analysis. They propose a dual-network theory of cognitive control, which includes two frontal networks [112, 113]: 1) the fronto-parietal, which initiates attention, monitors feedback, and adjusts cognitive control accordingly and 2) the cingulo-opercular, which maintains attention and cognitive control.

The adult frontal-parietal network incorporates frontal areas, namely the dorsal lateral prefrontal cortex (dlPFC), the dorsal frontal cortex (dFC) (incorporating premotor/preSMA, frontal eye fields) and middle cingulate (mCC), and posterior areas, including the interior parietal lobule (IPL), intraparietal sulcus (IPS), and precuneus. Wang et al also include the right temporal-parietal junction in this network[114], although Dosenbach et al and Fair et al do not [88, 112, 113]. The compilation of these areas enables this network's involvement in conflict processing, anticipation, and attention regulation [114]. The adult cingulo-opercular network involves the dorsal anterior cingulate cortex/medial superior frontal cortex (dACC/msFC), the anterior frontal cortex (aFC), the anterior insula/inferior frontal gyrus (also called the frontal opercular) (aI/fO), and the anterior thalamus [115]. These two networks may be linked via an error-processing part of the cerebellum [113][88].

CHAPTER 2:

METHODS

2. 1 Subjects

2. 1. 1 Subject Identification

Potential child-mother dyads were identified from a longitudinal study of the effects of perinatal depression and antidepressant medication use during pregnancy conducted by the Emory Women's Mental Health Program (WMHP). The WMHP established a large database of mother-child pairs who have been clinically followed through pregnancy to the present day. In the WMHP, each pregnant woman received an initial evaluation including demographic, socioeconomic, social support, diagnostic, psychiatric history, life events, and childhood trauma information and follow-up evaluations during pregnancy and through the postpartum period.

2. 1. 2 Subject Inclusion/Exclusion

To be included in this child imaging study, mothers must have had a primary DSM-IV diagnosis of MDD from the SCID (Structure Clinical Interview for DSM Disorders), at least 5 visits with Beck Depression Inventory (BDI) assessments[116] during pregnancy, and at least 2 visits with BDI assessments during the first 25 weeks of the postpartum period. In addition, the child must have been born full term and of normative birth weight (2.5kg+) and be 54-78 months (4.5-6.5 years) of age at the time of study enrollment. Mothers were excluded if they had: 1) a positive test for drugs of abuse during pregnancy, 2) abnormal thyroid test during pregnancy 3) pregnancy complications (e.g. gestational diabetes, preeclampsia), 4) labor complications 5) postpartum child complications, 6) genetic defects, or 7) admission to the NICU (neonatal intensive care unit). In addition, children were excluded if they had major

traumas, serious physical injuries, neurological illnesses, physical/sexual abuse or neglect, or were taking any medications at the time of enrollment.

After consideration of all inclusion and exclusion factors, 183 mother-child dyads were identified as appropriate for recruitment (approximately 15% of the original database). Many of these no longer lived in the area or did not have current contact information. Some did not want to participate because they did not feel comfortable having their child scanned. In the end, 21 mother-child pairs (11.5%) agreed to participate (11 males, average child age = 5.52 years).

2.1.3 Calculating Prenatal Depression Burden

The severity of PMD was determined using the multiple (5 to 8) BDI scores [117] collected by the WMHP during pregnancy. BDIs were administered across pregnancy (range = 1-38 weeks), with scores spanning all trimesters of gestation (average first BDI = 8.8 +/- 3.8 weeks; average last BDI = 36.3 +/- 2.0 weeks).The burden of PMD was estimated by calculating the area under the curve (AUC) of the multiple BDI scores across pregnancy (across at least two trimesters) and then standardizing the AUC to 40 weeks. Postpartum measures were collected in a similar manner, by calculating the AUC of BDI scores across the first 25 weeks after the child's birth. BDI scores have been identified as a valid method of measuring depression during pregnancy and the postpartum period [118].

2.1.4 Medications

All mothers had a history of moderate to severe depression and most subjects were on antidepressants (either SSRIs or Buproprion) at some point during pregnancy. Following the methods used by the WMHP, medication exposure is reported in terms of weeks exposed during pregnancy (standardized to a 40-week pregnancy), regardless

of dose. This is because dose exposures cannot be compared across different types of medications (even within the SSRI class)[119, 120]. Furthermore, even when all subjects are taking the same medication, bio-availability levels, placental passage rates, and placental binding proteins vary greatly from person to person [121], making it difficult to assess how much medication the neonate received.

2.2 Behavioral Methods

Behavioral assessments administered included:

1) The Preschool Age Psychiatric Assessment (PAPA) [122-124] combined with the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL) [125], which both screen for childhood psychiatric disorders.
2) The child behavioral checklist (CBCL), which assesses externalizing and internalizing behaviors [9].
3) The Social Responsiveness Screen (SRS), which assesses social behavioral deficits [126].
4) The Autism Diagnostic Observation Schedule Module III (A-DOS) [127], which screens for autistic-like behavior.
5) Three sub-sections (Block Design, Receptive Vocabulary, and Picture Concepts) of the Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III) [128] (following the guidelines specified in the Treatment of Adolescents with Depression Study - TADS [129]), which provides a developmental measure of IQ.

2.2.1 Purpose of Behavioral Assessments

The assessment team (Amy Anderson, Dr. Opal Ousley, and Anjana Muralidharan) used the child interview (IQ, ADOS), the parent interview (K-SADS/PAPA), and the written parental assessments (SRS, CBQ, and CBCL) to create a consensus opinion focused on elements of child development and behavior. The parent interview (K-SADS/PAPA) and child play assessment (ADOS) provided a qualitative and diagnostic measure of child development, while the parent written assessments provided a quantitative estimate of child behavior, temperament, and social development. A summary of these information was conveyed to the parents via a written report. However, this was not a diagnostic report.

Additionally, the quantitative data were subsequently used in multivariate linear regression analyses to evaluate the neurocognitive correlates of the burden of PMD on social cognition. The relevant test scores from the aforementioned assessment scales (including CBCL T-scores, SRS T-scores) were regressed against the AUC of PMD (modeled parametrically), as well as modeled in AFNI with the ICA results. Other variables such as age, sex, postpartum depression burden, and mothers' current BDI scores were also modeled in these regression analyses (in AFNI and SAS) to control for confounds and to look at the interactions among variables. The following participant variables were collected but not used in analyses: CBQ scores, ADOS scores, K-SADS/PAPA interview reports, and IQ scores. This was due to incomplete data (CBQ), unreliable data (IQ scores), and non-quantifiable data (ADOS and K-SADS/PAPA).

2.2.2 Parent Interview (K-SADS/PAPA)

To define the behavioral and diagnostic status of the study subjects, a parent interview, referred to as the K-SADS/PAPA, that merged sections of two instruments

used to assess psychopathological behavior in preschoolers and older children. The K-SADS/PAPA, was created by Anjana Muralidharan, with supervision by Drs Craighead, Tone, and Ousley, by carefully merging sections of the Preschool Age Psychiatric Assessment (PAPA) [122] and the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL) [125]. It was necessary to combine these two assessments due to the age of the children being assessed. At the time of child assessment (2007-2010), the PAPA did not yield DSM diagnoses and the K-SADS was not validated for children as young as 5 years of age. Additionally, time constraints and measure overlap prevented the administration of both the complete PAPA and the complete K-SADS. By integrating a detailed preschool-age assessment with a standard children's diagnostic assessment, and taking into account the most recent literature on preschool diagnosis, the clinical interview used in the present study provided a thorough assessment of a population for which no gold standard clinical interview exists.

First, sections of particular interest to the study goals from the PAPA were selected to obtain detailed, age-appropriate behavioral information about the children. These included Play and Peer Relationships, Depression, Hypomania and Mania, Anxious Affect, Separation Anxiety, and Attention Deficit Hyperactivity Disorder. Second, several sections were chosen from the K-SADS including Depression, Bipolar Disorder, Social Phobia, Agoraphobia, Generalized Anxiety Disorder, Separation Anxiety Disorder, and Attention Deficit Hyperactivity Disorder. Thirdly, within each section, the items from the PAPA were matched to the corresponding items from the K-SADS. The rating scale for the K-SADS items were placed next to the matching PAPA items to allow simultaneous rating of the symptoms on the two different measures,

using the more age-appropriate PAPA language when possible. If extra probing questions were necessary to rate a particular K-SADS item, these questions were also inserted and asked at the same time. K-SADS items not queried in the section of the PAPA were added to the end of the section. In this way, the detailed age-appropriate information gathered from the PAPA could be used to make DSM-IV diagnoses via simultaneous rating on supplemental items from the K-SADS. Lastly, disorders not queried in the selected sections of the PAPA were added at the end of the assessment by inserting the K-SADS screening and supplemental sections for the following disorders: Post-Traumatic Stress Disorder, Obsessive-Compulsive Disorder, Conduct Disorder, Oppositional Defiant Disorder, and Psychotic Symptoms.

At the end of each section, a diagnostic data page was generated to synthesize the information gathered and make a diagnostic decision. To maintain age-appropriate diagnostic criteria, the current literature on preschool diagnosis was consulted for a number of disorders. As a result, while all the diagnostic pages of the K-SADS/PAPA allow the clinician to make a diagnosis based on traditional DSM-IV criteria, for certain disorders the clinician can also use modified criteria obtained from relevant empirical papers. Modified criteria are provided for the following diagnoses: depression [130], social phobia and separation anxiety disorder [131], and bipolar disorder [132]. Each section of the K-SADS/PAPA contributes information to a possible diagnosis. A report was then generated by Anjana Muralidharan, which was sent to the other assessors for the purpose of discussing all information gathered about the subject, coming up with a consensus diagnosis, and writing the report sent to the parents as part of the agreement related to study participation.

2.2.3 Child Assessments

2.2.3.1 Play Assessment (ADOS)

The Autism Diagnostic Observation Schedule (ADOS), an instrument designed for use in assessing individual who may have Autism Spectrum Disorders [127], consists of several structured and semi-structured interactive tasks. The examiner guides the child through a number of activities (such as making a puzzle, storytelling, drawing, and playing make-believe) that involve social behavior. During these tasks, the examiner observes and documents the child's speech patterns, non-verbal gestures, body language, speech/play reciprocity, emotional expressions, and empathy and rates the child using research-driven scales.

The section of the ADOS used in this study (Part III) was chosen as it is designed for young children who are verbal. Since our subjects are not Autistic, the ADOS scores could not be used for quantitative analysis. However, the ADOS did serve an important two-fold purpose: 1) to allow the examiner to evaluate the child's social and cognitive skills, information was used in conjunction with the parental report assessments and the K-SADS/PAPA to form a consensus description of any social or psychology abnormalities, and 2) to allow the examiner to develop positive rapport with the child, which enhanced the child's comfort and level of cooperation during scanning.

2.2.3.2 Intelligence Assessment (WPPSI-III)

All participating children were administered three subtest of the 3rd Edition of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) is an intelligence test for children ages 2.5 - 7.25 years of age [128]. The WPPSI-III has 14 subtests and yields subtest scores, as well as composite and total scores. Due to time

constraints, administration of the complete test was not feasible. Therefore, the following subtests were chosen: Block Design (child views the model of the blocks and then tries to recreate it with 2-4 colored blocks), Receptive Vocabulary (child must point to the picture of the word spoken by the examiner), and Picture Concepts (child must choose how pictures of items go together based on common characteristics). The combination of these subtests generates a total score reflective of the score that would be achieved if the whole test was taken. Overall or full scores estimates are based on normative data, with average total scores ranging from 90-109. Scores below 70 (which approximately 2% of children earn) represent an extremely low IQ and scores above 130 an extremely high IQ. Subtest scores are generated using a normative table (supplied with test), which takes into account the sex and age (in months) of the child. Scores are reported in terms of raw scores, t-scores, and percentages.

There has been some disagreement in the field as to the reliability of the WPPSI-III and its ability to accurately rate a child's intelligence. It is widely recognized that familiarity with the test can greatly increase the child's scores by increasing his/her comfort level. Additionally, we noted in our participates that attention level and mood, which can both rapidly fluctuate in young children, can dramatically change the child's score. Therefore, we decided not to include these IQ scores in the final analysis as they were deemed to be unreliable estimates.

2.2.4 Written Assessments - Parental Report

2.2.4.1 Child Behavioral Checklist (CBCL)

The Child Behavior Checklist (CBCL) is a paper-and-pencil parent-report measure used to identify problem behavior in children. It was developed by Thomas Achenbach [9].There are currently two versions of the CBCL, the preschool checklist

(CBCL/1½-5), which we used for assessment at the first study time point and the school-age version (CBCL/6-18), which we used at the second study time point. The CBCL/1½-5 [9] consists of 99 statements about the child in which the parent responds with the following: not true, somewhat/sometimes, or very true/very often.

Scores can be generated that describe levels of internalizing (such as anxious or depressed), externalizing (such as aggressive and oppositional) and total behavioral problems. Various subscales, including DSM-oriented scales (affective problems, anxiety problems, pervasive development problems, attention deficit/hyperactivity problems, oppositional defiant problem) and syndrome scales (emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems, and aggressive behavior) also yield scores. Of these we used only the internalizing, externalizing, and total sub-scales for analysis. Scoring of the CBCL is based on normative sample data, adjusted for gender and age (in three month increments).

In a Dutch general population sample (n=1600), predictive correlations of the initial CBCL scores and ratings taken 14 years later were significant [133]. In this study, internalizing problems, in particular Withdrawn Syndrome and Social Problems were the most salient predictors of psychological issues later in life. Similar results were found in an American sample [134, 135]. More recently, parents' and teacher' ratings of childhood anxiety and depression using the CBCL at age 5 predicted the children's self-reported depression symptoms at age later in life [136]. These results, among others, provide evidence that parents' CBCL ratings of their children behavior at age 5 have adequate validity [137].

Previous studies have found maternal depression and gender were to correlate with mothers' ratings of their children on the CBCL [138, 139]. However, mothers'

ratings were still reliable after removing the variance from these confounding variables [140]. This finding highlights the importance of acquiring the mother's current psychological state at the time of the child's behavioral evaluation. We did this by collecting a Beck Depression Inventory (BDI) assessment from the mother at the time she filled out the CBCL.

2.2.4.2 Social Responsiveness Scale (SRS)

The SRS measures the severity of social impairments that are related to autism spectrum disorder (ASD) in children aged 4-18 [126]. The SRS is a series of 65 questions, which a parent or teacher responds to using a Likert scale (range 0-3). It comprises 5 subscales: social awareness, social cognition, social communications, social motivation, and Autistic mannerisms, and yields a total impairment score.

Interpretation of the SRS is based on the total score, for which a T-score of 76 or higher is considered severely impaired. A score of 60-75 indicates mild/moderate ASD deficits. T-scores are based on standardization with a normative population of 1600+ children [126]. The SRS shows strong reliability and adequate internal consistency. It is highly correlated with results for the Autism Diagnostic Interview-Revised (ADI-R), a much more time-intensive behavioral assessment [126, 141].

2.3 Imaging Methods

2.3.1 fMRI

Functional Magnetic Resonance Imaging (fMRI) is a non-invasive technique to observe brain activity by using a strong magnetic field and electro-magnetic currents to measure the hemodynamic correlates of neural activity via the Blood Oxygen Level Dependent (BOLD) contrast [142]. As such, fMRI requires no radiation or contrast

agents and is relatively risk-free, making it a very useful tool for research. However, few fMRI studies have been conducted on small children, mostly due to the necessity for stillness when being imaged, the lack of child-appropriate fMRI-compatible tasks, the inability of children to maintain attention and comprehend task instructions in the MRI environment, and parents' fears about the safety of their children is such research studies [143].

2.3.2 Imaging Children

Our procedure for conducting successful functional and structural imaging of young children consisted of two phases, a familiarization phase and the scanning phase. The familiarization phase involved explaining and experiencing the scanning procedures through the use of a social story, a mock scanner, and various props. The child also interacted with the real scanner by assisting and watching a stuffed animal and/or parent being inserted into the scanner. During this phase, the child also learned how to complete the computer task to be used during the functional imaging scan. When necessary, the child was inserted into the scanner without the functional and structural scans being completed for purposes of acclimation. This familiarization phase is typically completed across one session, although more sessions were allowed when needed. The purpose of the familiarization phase was to optimize the child's engagement and interest, provide positive feedback for task completion, and to redirect attention away from anxiety-provoking stimuli and towards a non-threatening stimulus (see details below).

2.3.2.1 Familiarization Phase

During the familiarization phase of this project, the following procedures were followed:

1) The examiner reviewed the consent form with the mother. During this time, the child played with age-appropriate games on the floor nearby.
2) The examiner read a "social story" to the child. The story described the upcoming events using both words and pictures. The character in the social story was "Mr. Monk," a stuffed monkey that was given to the child to hold during the story and throughout the day. Other physical props used during the storytelling included real headphones and a catcher's mask (representing the head-coil). The story described the activities to come: playing a computer game, lying down in a 'funny looking bed', putting on headphones, putting on a mask, and playing a computer game while lying down. During the story, the examiner asked the child to put on the headphones and catcher's mask.
3) The examiner showed the child pictures of what the image of his/her brain would look like. The child was encouraged to ask questions about the day's events to come. The examiner asked for assent from the child.
4) Behavioral assessments were performed. Doing the behavioral testing before the scan was crucial as it allowed the examiner to develop rapport with the child (and parent) and to address any concerns the child had about the scan.
5) The child went to the mock scanner (located in the Emory Autism Resource Center) and lay down on the scanner bed. The examiner and the child made loud noises with various toys to stimulate the loud noises that the MRI scanner makes. The child was encouraged to stay still for as long as possible. He or she held a timer during this process. Positive reinforcement was given for still behavior. In some cases, the child chose to skip going to the mock scanner and went directly to the MRI scanning phase after the behavioral assessments.

2.3.2.2 Scanning Phase

The following procedures were followed on the day of the fMRI scan:

1) Before going to the scanner, the examiner instructed the child on how to play the computer game, by using a 5 minute training task on a laptop computer. The child was instructed to “Look for the whole picture, and push the button on the same side as the picture." Verbal praise was given. The child continued to perform the training task until it was clear that the child understood how to play the game.

2) The child, parent, and examiner went to the hospital MRI scanner room. The child was given the opportunity to push the elevator buttons and then asked to follow the diamonds on the floor, and ring the doorbell at the scanner control room. This was deemed important because it distracted the child from worrying about the impending scan. Children also tended to find the Emory Hospital's basement location of the BITC scanner somewhat foreboding and scary. Therefore, keeping them distracted lessened their fears.

3) Upon entering the MRI control room, the examiner went in first and turned on the lights. Scanner control rooms are often kept dark so that the technician can look at the brain images with more clarity. However, the darkness tends to scare small children.

4) Once in the scanner control room, the child was asked to show the scanner technician Mr. Monk and was introduced to the technician, "Mr. Robert." The child observed the scanner from the control room window. The child and parent were then asked to remove any metal from their bodies and pockets.

5) The examiner put a PowerPoint slide show of interesting pictures that were displayed inside the scanner. The child chose from the available slide shows: baby animals, action figures/superheroes, dolls/fairies/princesses, cars/trucks/planes/trains, or children's toys.

6) Once inside the scanner room and next to the scanner bed, the child was given the option of putting the monkey in the scanner first. The child assisted in placing Mr. Monk in the scanner bed and putting the headphones and mask (head coil) on him. The child was then allowed to operate the buttons that make the bed move into the scanner. If the child was still scared, s/he followed the same procedures to put his/her mother into the scanner. After this, if the child was scared, she/he was encouraged to crawl on top of his/her mother and enter the scanner together. This procedure was effective in helping the child recognize the safety of being inserted into the MRI and typically reduced visible signs of anxiety. If the child was not anxious she/he was placed directly into the scanner without putting Mr. Monk or a parent in first.

7) The child was then positioned in the scanner with the parent standing beside him or her, holding onto the child's leg. The child wore earplugs (if they desired) and child-sized headphones (all) to reduce noise. The technician then placed foam wedges around the child's head to minimize movement, positioned the child in the scanner bore, and adjusted the mirror attached to the head coil so that the child could see the computer screen (on which the PowerPoint show was ongoing). We found that it was important that the technician spoke in a child-friendly manner during this time and explained the various steps to the child so that she/he did not become anxious. If the technician was not able to do this

effectively, the examiner assisted by narrating the process to the child. We also found that is crucial that the technician perform these tasks quickly, as the children tended to have a limited time period in which they were willing to be cooperative, especially when anxious.

8) The technician and study investigator returned to the MRI control room. The examiner talked to the child through the headphones, providing praise, reminders, warnings, and instructions. The approximately 10 minute fMRI run was completed first. Reminders about how to perform the task were given as necessary. During this run, the study investigator watched the button press box to make sure the child was responding in a timely manner. If he or she stopped responding, it typically signaled that the child was in distress and wanted to get out. During these cases, the study investigator sought to reassure the child by speaking through the headset. In addition, as talking causes motion corruption, the study investigator sometimes needed to remind the child not to talk to the parent or to himself/herself during the scan. If talking or motion was excessive, the functional scan needed to be restarted.

9) The four-minute structural MRI run was completed next. During this scan, the PowerPoint slide show was again projected into the scanner. However, some children did not complete this step, as they felt tired or did not want to be in the scanner anymore.

10) After the child was taken out of the scanner, the study investigator showed the child his/her brain image on the computer screen. The examiner pointed out the nose, ears, neck, and eyes to orient the child. The examiner also asked the child about his or her experience.

11) After exiting the scanner, the child was re-presented the figures for the Joint Attention Task and asked to describe the emotion on the men's faces as 'happy' or 'not happy.' This was done to ascertain whether the child accurately perceived the emotional expressions of the computer figures.
12) Outside of the scanner control room, the child received a toy and a t-shirt with a brain and study logo on it for his/her participation.

2.3.3 fMRI Methods for this Study

Child participants underwent an MRI session of approximately 15 minutes. During this time, the children performed a multi-condition Joint Attention Task (JAT) (10.5 minutes) and rested while a 4-minute high resolution anatomical scan (T1) was acquired.

2.3.3.1 fMRI Parameters

MR images were acquired using a Siemens MAGNETOM TIM Trio 3T whole-body scanner (Siemens, Erlangen, Germany) and Siemens transmit-receive head coil located in the Biomedical Imaging Technology Center (BITC) in Emory Hospital. Scout structural brain images for head alignment were acquired using a spin echo, T1-weighted pulse sequence (TR = 500 msec, TE = 20 msec, flip angle = 90°). A magnetization-prepared rapid gradient echo (MPRAGE) sequence [144] was also acquired to generate 3D anatomic data at an isotropic resolution of 1 x 1 x 1 mm for 3D analysis and visualization of task-related activations. Functional T2-weighted echoplanar images (EPIs) [slice thickness = 3 mm, slices = 33, flip angle = 90°, matrix = 64 x 64 x 64; TR =2000 msec, TE = 30 msec, voxel size = 3 x 3 x 3mm] were acquired during task performance. A resting state fMRI scan was not acquired.

2.3.3.2 fMRI Tasks for Children

At the time of this study's design, very few fMRI studies had been conducted in young children, especially at ages as young as four years of age. The few studies that did exist used sleeping or sedated children or resting state fMRI [145-148]. Therefore, we designed a custom task that was age-appropriate, did not require reading ability, and was short enough to hold the attention of 4-6 year-olds.

2.3.3.3 Joint Attention Task

We designed a non-verbal joint attention task (JAT) for this study that was intended to fulfill two study goals including: 1) engaging developing neural networks related to social, cognitive, and affective behaviors in an age appropriate manner, and 2) minimizing the fMRI task duration (10.5 minutes) so that 4-6 years olds could feasibly complete it. The joint attention task explicitly tapped coordinated attention, in which the participating child alternates looks between objects and an adult computer-animated figure. The task comprised six trial types that varied in emotional salience (happy vs. neutral), in the congruence of attentional cues with the location of the target stimulus (incongruent vs. congruent), and in their social content (human figures vs. arrows), also called social vs. non-social attentional cues.

During the four social trial types, one of five different computer-animated, human adult male upper body images made in POSER4 by Meta Creations (Figure 2-1) was center-presented, with target stimuli appearing to his left and his right. These target stimuli consisted of interesting, but emotionally neutral, age-appropriate, non-human, images, such as cars, toys, animals, and foods. A non-target distracter stimulus (scrambled version of the target image) appeared on the opposite side. During the two non-social trials, a centrally-presented box appeared instead of the POSER figure.

The joint attention stimuli were quasi-dynamic, such that the POSER figure appeared to turn his head toward the left or the right during the trial so that his gaze was directed toward one side of the screen or the other. Additionally, during two of the four social trials, his facial expression changed, from neutral to smiling. Motion was simulated by presenting a forward-facing figure for 0.9 sec followed by the same figure facing to the left or right for a duration mean of 1.16 sec (range of 0.13 to 2 sec). The head-turn angle ranged from 13 to 18 degrees. The non-social stimuli were also dynamic, with the centrally-presented box turning into an arrow that pointed toward one side or the other of the screen.

Directionality of both gaze or arrow cues and location of target stimuli was randomized with a 50:50 distribution between left and right. Participants were instructed to attend and respond to the position of the target stimulus (left or right side of screen), as quickly as possible using a left or right button--press response on an MRI-compatible button box. A fixation cross was presented after each stimulus response for 5 seconds. This task did not require reading ability or knowledge of left and right.

After the scanning session was completed, the children reviewed the POSER figures outside the scanner. For each figure, the child participant was asked to label the face as 'happy' or 'not happy'. This provided behavioral evidence that the participating children perceived the posed emotions accurately. As a group, the children correctly labeled the happy and neutral emotional expressions with high accuracy (average 94 ± 8% correct, range = 80-100%)(Table 3-1). These results suggest that the POSER images validly depict both happy and neutral facial emotions.

2.3.3.4 Task Contrasts

The seven following planned contrasts isolated the neural correlates of processing emotion perception, social signaling, and cognitive conflict:

1) CH>CN (congruent happy vs. congruent neutral)

2) IH>IN (incongruent happy vs. incongruent neutral)

3) CS>CNS (congruent social (happy and neutral) vs. congruent non-social

4) IS>INS (incongruent social (happy and neutral) vs. incongruent non-social

5) I>C (all incongruent vs. all congruent)

6) IS>CS (incongruent social (IH+IN) vs. congruent social (CH+CN))

7) INS>CNS (incongruent non-social vs. congruent non-social)

2.3.3.4.1 Emotion perception

In order to examine the impact of study variables on the neural representation of the implicit processing of facial expressions of emotion (happiness) and the interaction between emotional and attentional cognitive processing, the following contrasts were planned:

1) CH>CN - Congruent happy versus congruent neutral

   -This contrast examines the effect of positive emotional cues (a smiling face) over and above no emotional cues (a neutral face) (see Figure 2-1).

2) IH>IN - Incongruent happy versus incongruent neutral

   - This contrast examines the same effect but in the context of cognitive conflict (in which the social cues are pointing the subjects towards the non-target stimulus).

2.3.3.4.2 Social signaling

In order to look at the effect of study variables on social cues as compared to non-social cues, the following contrasts were planned:

3) CS>CNS - All congruent social cues (including happy (CH) and neutral (CN) POSER figures attending to the target stimuli) versus congruent non-social signals (arrows pointing towards the target).

-This contrast was designed to isolate the effect of triadic social attentional signals independent of cognitive conflict.

4) IS>INS - All incongruent social cues (POSER figures (IH+IN) turning towards the non-target) versus non-social signals (arrows pointing to the non-target)

-The contrast was designed to isolate the effect of social signals within the context of cognitive conflict.

2.3.3.4.3 Cognitive conflict

The following contrasts were planned to look at cognitive conflict as it is modified by emotion and social cues:

5) I>C - All incongruent trials (where cues direct attention to the non-target image) versus all congruent trials (in which cues point towards the target image).

- This contrast was designed to examine the neural response to cognitive conflict across all stimulus conditions.

6) IS>CS - All incongruent social POSER stimuli (IH+IN) versus all congruent social POSER stimuli (CH+CN).

- This contrast was designed to examine the neural response to social cognitive conflict.

7) INS>CNS - Non-social incongruent arrow versus congruent arrow trials.

-This contrast was designed to tap non-social cognitive conflict.

2.4 Data Analysis

2.4.1 Preprocessing

Raw MR images were preprocessed using Analysis of Functional NeuroImages (AFNI) software [149]. The following specific image processing steps were conducted: (1) despiking using 3dDespike, (2) slice time-correction using 3dTshift, (3) de-obliquing using 3dWarp, (4) motion correction using 3dvolreg, (5) normalization of the functional images into anatomical space using auto tlrc and 3dresample, (6) removal of motion residuals using 3dDeconvolve, (7) Gaussian spatial smoothing with a 5 mm kernel using 3dmerge, (8) de-trending to remove linear trends and non-linear drift, and (9) scaling to percent signal change.

The child subject images were normalized to an adult EPI template. In previous research by Burgund et al, it was found that the small systematic errors in registration between the child brains and adult templates did not result in spurious differences in fMRI activation between groups [150].

2.4.2 Independent Component Analysis

Independent component analysis (ICA) is a computational method for taking a complex multivariate signal and separating it into its components by grouping together data points with similar time-series (blind source separation). ICA assumes mutual statistical independence of non-Gaussian signals [151]. Observed fMRI data is assumed to be a linear combination of a number of independent components, in which each component is attributed to one original source or to noise. Therefore, ICA serves to

separate out these signals into their original sources and to eliminate the sources that are noise (such as physiological signals - heartbeat, breathing, motion-related signals, and MRI scanner-related signals) [151]. ICA has been found to reliably identify consistent networks in individuals by comparing repeated scans across time [152]. It has also be found to reliably reduce artifacts and to reduce dimensionality (number of voxels), creating a robust and informative dataset [153]. The program Icasso was used to increase the reliability of the networks found. Icasso was conducted using 20 resampling cycles, each of which started with a different initial condition for FastICA in order to generate the desired number of components. Components generated using Icasso are based on a centroid estimate from all resampling cycles and are more reliable because they have been estimated multiple times. Reliability measures are reported using the quality (stability) index, Iq, which should be very close to 1 if the network is reliable [154].

2.4.2.1 Motion Reduction using ICA at the Individual Level

As anticipated for MRI studies of awake, behaving children, motion artifacts persisted after image preprocessing, despite our efforts to reduce motion using the methods described above (See Sections 2.3.2.1 and 2.3.3.2). Due to excessive stripping and motion, an artifact pre-screening using ICA was conducted on each individual subject using the fMRI toolbox GIFT in MATLAB [155]. In solving for 20 components at the individual level, artifacts such as scanner artifacts, subject movement, and physiological noise were grouped into unique components based on their time series data. For each subject, components displaying signs of confounding artifacts were removed from the subject's dataset, consistent with prior research [156, 157].

2.4.3 Group Independent Component Analysis

2.4.3.1 Network Identification using ICA

fMRI data analysis at the group level consisted of a step-wise data dimensionality reduction approach [89, 158, 159], in which independent component analysis (ICA) was also implemented using the MATLAB GIFT toolbox [155], solving for 20 components[160] . In following with many resting state studies, 20 components was found to be the ideal number of components with which to insure homogeneity in networks while not splitting networks into sub-network components [160].

FMRI time series for all subjects were first compressed though principle component analysis (PCA). This was followed by group spatial ICA, preformed on the subjects' aggregate data, creating the 20 group components. Icasso (20 iterations using random initial starting points) was used in this process to ensure the creation of reproducible and stable components. Using the group spatial components, individual subject spatial maps and their corresponding time courses were back-reconstructed for each component using GICA3 [155, 161].

From the group spatially independent and temporally coherent networks, components of brain activation, candidate neural processing networks consistent with the attention, conflict, emotional, and social processing aspects of the JAT were identified, consistent with Calhoun et al, 2004 [161]. These canonical components of activation were used for further investigation of the impact of PMD on social, emotional and cognitive neurodevelopment by conducting both intrinsic and extrinsic network analysis.

2.4.3.3 Intrinsic Network Analysis

In addition to resting state data analysis for which it is best known, ICA can also be used in task-driven datasets (sometimes called task-specific ICA parcellation) in an effort to examine the effects of task on network organization [157, 158].

To investigate the effects of PMD on the activation of the networks of interest, beta values were extracted for the ICA-derived components for selected task condition contrasts, following Zhang, 2012 [153, 155, 157, 161, 162]. This was done by regressing the subjects' time courses for each component with the modeled hemodynamic response for the six trial types (CH, CN, CNS, IH, IN, INS), giving a beta value (beta weight) for each of the trial types (1-6) for each subject (1-15) for each component (1-20). This value represents degree of synchrony between the individual subject's time course for the component of interest and the predicted hemodynamic response for the trial type or in other words how engaged the network of interest was for a particular subject during a particular trial type. To obtain beta weights for task contrast, beta weights were subtracted from each other (example IH>IN => IH beta- IN beta). The resulting beta values were then linearly regressed with behavioral measures [155, 156] using SAS Enterprise software, Version 4.3. Other study variables of interest, including age, mom's current level of depression, and postpartum depression burden, were also added as variables of interest in the SAS regression analysis. Sex was not included in this analysis.

2.4.3.3 Extrinsic Network Analysis

As mentioned above, single subject component spatial maps were back-reconstructed from the group spatial components [155, 161]. This allowed us to make inferences concerning differences in the spatial organization of the chosen components

as modulated by subject variables (in this case PMD). Using a multivariate linear regression analysis in AFNI, the effect of the burden of PMD on the whole-brain functional connectivity of components of interest was tested. The covariates of age and sex were added in this regression analysis. Results produced brain areas that were differentially integrated into the network based on the level of PMD. Since the chosen networks were made up of mostly positive loading areas, brain areas positively correlated with PMD were interpreted as being more integrated into the network when PMD was high, while areas negatively correlated with PMD were considered to be less integrated into the network when PMD was high.

2.4.3.4 Statistical Corrections

When analyzing fMRI datasets, which typically comprise of 10^5 voxels, the problem of multiple comparisons is always an issue, leading to the possibility of false positives. One approach used to correct for this is the permutation-based Monte Carlo simulation using alphasim in AFNI. Monte Carlo simulations provide a cluster size (k value) or number of contiguous voxels in which each voxel is significant at an uncorrected threshold, by using simulated null datasets [163, 164]. For this study, all extrinsic network effects are described at a cluster-level correction for multiple comparisons ($p=0.005$ corrected to $p=0.05$, $k=18$) based on 10,000 Monte Carlo simulations.

For the intrinsic network results, beta values were extracted from the components, which mitigated the multiple comparison problem. However, we still used a corrected threshold determined with the Bonferroni Method. All intrinsic network effects were thresholded using a Bonferonni Correction [165] in which the alpha level of $p=0.05$ was divided by the number of contrasts examined (7) for a corrected p-value

of 0.007. This approach to protecting Type I error is both simple and conservative, limiting the chances of false positives in our intrinsic network results.

2.5 Expected Outcomes - Intrinsic Connectivity

For the three domains of the joint attention task (JAT) (emotion perception, social signaling, and cognitive conflict), the contrasts (see Section 2.3.3.4) relating to each domain were expected to activate known networks related to the functioning of the respective network. Based on the literature on adult functional networks, the expected outcomes of the intrinsic connectivity analysis were as follows for three domains:

2.5.1 Emotion perception

It was hypothesized that the contrasts related to emotional perception (CH>CN and IH>IN) would activate the limbic system, as this system is involved in the processing of the salience and content of expressed emotion [105]. Additionally, these contrasts were hypothesized to activate a facial perception network [100, 166], as this network is involved in the processing of facial expressions.

2.5.2 Social signaling

The contrasts related to social cues (CS>CNS and IS>INS) were hypothesized to activate a face processing network, as it is necessary to process faces and facial expressions in order to comprehend social signals [100, 166]. Additionally, these contrasts (especially the incongruent version) were hypothesized to activate a prefrontal network, as complex social signals are known to be associated with prefrontal brain areas [98, 110].

2.5.3 Cognitive conflict

The contrasts related to cognitive conflict (I>C, IS>CS, and INS>CNS) were hypothesized to activate prefrontal networks [167, 168], known to be necessary for the processing of cognitive conflict. Additionally, the social conflict contrast (IS>CS) was hypothesized to activate the face processing network [100], due to the presence of social cues and facial expressions.

CHAPTER 2: FIGURES AND TABLES

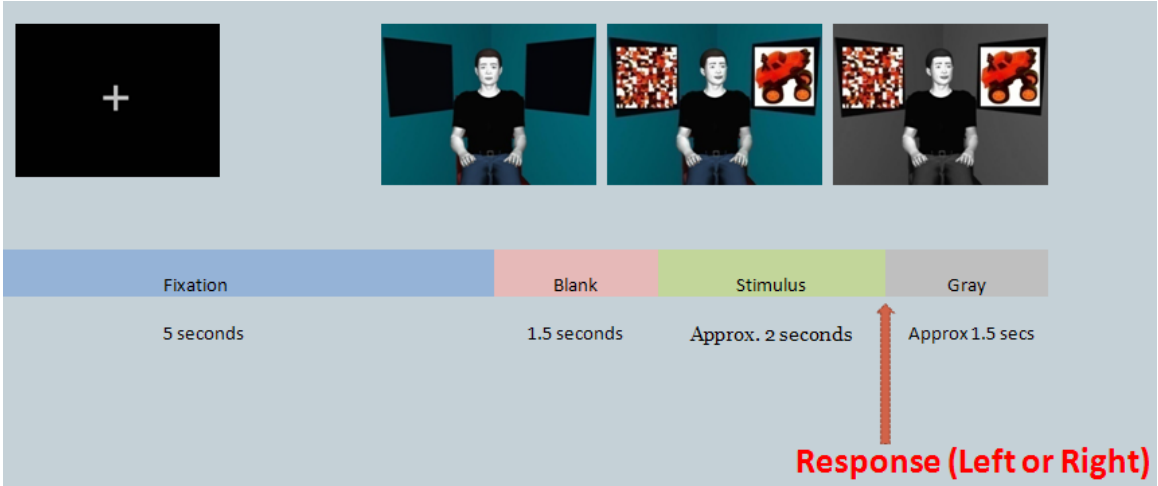

Figure 2-1: Joint Attention Task (JAT): Example of one of 60 trials. Each trial is 10 seconds long, starting with 5 seconds of fixation (first picture). This is an example of a congruent neutral (CN) trial. The second picture shows a neutral figure staring straight ahead. In the third picture, the figure turns his head towards the target object (the truck on the right). This is a congruent movement because the figure is looking at the target object (the truck). A quick switch between the two images creates a sense of biological movement. In the last figure, the background turns grey, after the child's response. This let the child know that he or she responded but did not indicate whether the answer was correct or not.

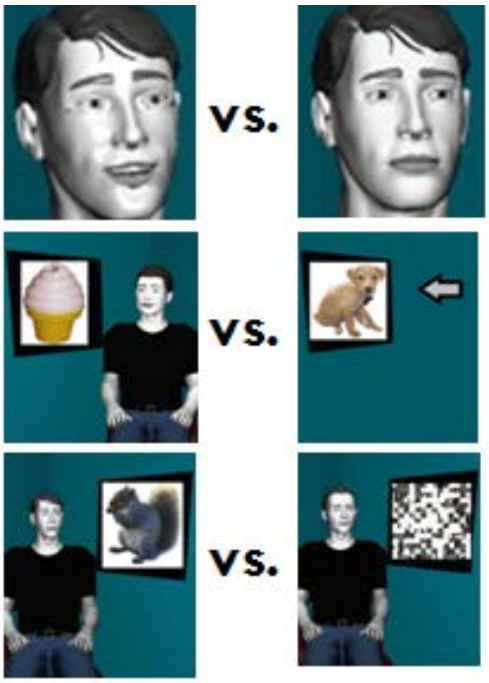

Figure 2-2: Joint Attention Contrasts: This figure shows the three types of contrasts designed for the joint attention task. The top two pictures show a close-up of the contrast of happy versus neutral faces, which allows for the examination of emotional processing. The second set of pictures shows an example of the social processing contrast in which the POSER figures (social cues) were compared to an arrow (non-social). The last set of pictures shows an example of a cognitive conflict contrast. In this case, trials in which the cues were orientated towards the target image (the squirrel in this case) were compared to trials in which the cues were orientated towards the non-target image (the scrambled picture).

CHAPTER 3:

RESULTS

3.1 Subjects

Twenty-one children were scanned and behaviorally evaluated. Six children were excluded from data analysis for the following reasons: one child was receiving growth hormone supplementation, two children did not complete their scans, and the fMRI data for three children was corrupted by excessive head motion. Fifteen children (6 males, average age 5.6 +/- 0.7 years) had integral imaging and behavioral datasets and were therefore included in the fMRI data analyses. All subjects included were Caucasian and non-Hispanic. Fourteen out of 15 mothers were married at the time of the child's birth. Level of maternal education ranged from 13-18 years (average 15.5 ± 1.5 years). The average pregnancy length was 38.5 ± 1.4 weeks. The average baby weight was 3.22 ± 0.37 kg, range = 2.5-3.64 kg (7.10 ± 0.82 lbs, range = 5.51-8.03 lbs) Demographic and behavioral variables are reported in Table 3-1.

3.1.1 Maternal Depression Variables

All mothers had a history of moderate to severe depression, with a primary diagnosis of MDD from the SCID. An average of 6.3 ± 1.1 (range = 5-8) BDI assessments were collected across pregnancy (range = 1-38 weeks of pregnancy). Scores were collected in at least 2 trimesters across the sample (average first BDI = 8.8 ± 3.8 weeks; average last BDI = 36.3 ± 2.0 weeks). The BDI AUC data reflecting PMD burden in our sample ranged from 28 to 738 (Figure 3-1) with a mean of 335 ± 224 (standardized to 40 weeks of pregnancy).

The burden of postpartum depression was calculated over the six months (25 weeks) after the child's birth, using at least 3 BDI scores (average postpartum BDI

scores = 4.6 ± 0.99, range = 3-6 BDI scores). The average BDI AUC burden of postpartum depression (PPMD) was calculated to be 212.0 ± 171.4 (range = 33.9-553.1) over the 25 week period. This is equivalent to an average individual BDI score of 8.5, which is very similar to the average BDI score during pregnancy (8.4 pts). Consistent with previous findings [117], postpartum and prenatal maternal depression severity were highly correlated (p=0.001) in our study sample (Figure S-1).

Maternal BDI measured at the time of the child's scan averaged 6.0 ± 5.2 points (range = 0-15). As expected, this measure of BDI was correlated with both PMD burden of depression (p=0.007) and PPMD burden of depression (p=0.02).

3.1.2 Medication Exposure

Fourteen out of 15 mothers were taking antidepressant medications during pregnancy. Medications taken by these subjects included selective serotonin reuptake inhibitors (SSRIs) [escitalopram (n=1), fluoxetine (n=2), paroxetine (n=1), sertraline (n=6), and a combination of sertraline and fluoxetine (n=1)], a serotonin-noreprinephrine reuptake inhibitor (SNRI) [venlafaxine (n=2)], and an atypical antidepressant [buproprion (n=1)] (Figure 3-2). The average number of weeks exposed to antidepressants for the 14 subjects taking them was 35.9 ± 7.6 weeks (range = 16.4-40 weeks).

3.2 Behavioral Results

3.2.1 Joint Attention Task Results

The analysis of task reaction time data (Table 3-2) demonstrated that response times for the congruent non-social trials (CNS, mean = 1430 ± 520 ms) were significantly faster than for the incongruent non-social trials (INS, mean = 1600 ± 520

ms) (CNS>INS, p=0.004). In contrast, reaction times for the congruent social trials (CS) were not significantly faster than those for the incongruent social trials (IS) (p=0.22). No other task condition comparisons yielded evidence of significant differences.

3.2.2 Behavioral Assessments

Results of the behavioral assessments are reported in Table 3-1.

3.2.2.1 CBCL Results

Average total CBCL t-scores were 42.2 ± 7.7 (range = 28-52). Average internalizing CBCL t-scores were slightly higher at 45.1 ± 8.7 (range = 22-62), while externalizing CBCL t-scores were on par with the total scores, averaging 42.3 ± 8.3 (range = 28-57). Notably no children had t-scores that exceeded 65, which is used as the clinical cut-off point.

CBCL t-scores were normally distributed and were not transformed for statistical analysis. T-scores for total CBCL symptoms were not significantly correlated with PMD severity (p=0.14). However, there was a non-significant positive trend toward a correlation between externalizing CBCL symptoms and PMD severity (p=0.08); internalizing CBCL symptoms and PMD severity were not significantly correlated (p= 0.34) (Figure S-2).

3.2.2.2 SRS Results

Average SRS t-scores were 44.6 ± 5.6 (range = 36-56). No child met the criteria (a t-score above 60) for autism spectrum disorder (ASD) symptoms. However, two children did have elevated scores (above 60) for one of the five sub-scores (see Section 2.2.4.2 for SRS sub-score description). SRS t-scores were normally distributed and were not transformed when used in various statistical analyses. SRS t-scores were not

significantly correlated with PMD severity (p=0.18). However, SRS t-scores were positively correlated with internalizing CBCL (p=0.01).

3.2.2.3 Other Measures

Various other behavioral measures (not included in the statistical analyses) include: IQ percentile (average = 77.2% ± 17.3%, range = 46-95%) and ADOS raw scores (13.2 ± 3.73 pts, range = 9-23 pts). The PAPA/kSADs interview did not result in a quantifiable outcome and is therefore not reported. Although some children showed elevated symptom levels for certain disorders (mostly anxiety and ADHD), no child met diagnostic threshold for any disorder.

3.3 Group ICA Results

3.3.1 Networks Identified

Of the twenty spatially discrete components derived from group ICA, four components were identified as motion/noise artifacts, as done previously [157]. Components that are artifacts can be clearly recognized, for example a ring around the skull, or activation in the eyeballs or ventricles. All networks had an Iq value very close to one (average = 0.978 +/- 0.005, range = 0.970-0.988). Values close to one indicate reliable networks.

The remaining 16 components representing plausible neural networks were identified as follows: occipital-cerebellar, ventral medial prefrontal cortex, motor network, occipital cortex, incomplete default-mode network with noise, orbito-frontal cortex, parietal cortex, **limbic/paralimbic cortex**, right temporal cortex, occipital cortex and posterior cingulate, dorsal prefrontal cortex, **left occipital temporal cortex**, sensory-motor cortex, bilateral insula with noise, right temporal cortex, and **fronto-**

cingulate network. It is noteworthy that, unlike the corresponding functional networks seen in adults, many of these networks appear fragmented and show incomplete patterns of connectivity, perhaps due to the functional immaturity of this age group [89].

From these 16 networks, three theoretically-motivated functional units or networks of activated brain areas were identified (in bold text). Three brain networks were chosen for further investigation, as they incorporated brain areas consistent with involvement in one or more of the three domains of the JAT-based task (emotional regulation, social cue processing, and cognitive control). They suggested the functional integration (increased long-range connections) of spatially distributed brain areas to create networks similar to those seen in adults performing similar tasks [88]. Based on their peak voxel locations (in MNI space), these components were referred to as the limbic network, left occipital-temporal network, and the fronto-cingulate network, respectively (Table 3-3, Figure 3-3). The remaining thirteen networks are described in the supplementary figures (Figure S-6).

3.3.2 Intrinsic Network Connectivity

The effects of PMD and other study variables on the intrinsic functional connectivity of the networks of interest are for specific task contrasts, rather than task-wide data. A Bonferroni-corrected p-value was calculated ($p = 0.05$ divided by 7, the number of contrasts) to be $p = 0.007$ [165]. However, due to the exploratory nature of this study, both corrected and uncorrected outcomes are reported. A summary of all intrinsic connectivity results can be found in Table 3-4.

3.3.2.1 Occipital-Temporal Network

This component represents the ventral visual processing stream engaged in processing face information related to social signaling [169, 170]. As such, the network analysis focused on social cognition both at the level of implicit processing of facial emotional expression and social stimulus conflict processing. Network responses related to emotional face perception were isolated by the contrast between trials that presented happy versus neutral faces, controlling for the incongruent condition (i.e., incongruent happy > incongruent neutral (IH>IN)), as this contrast was more attentionally salient than stimulus-congruent stimuli (CH>CN). Neither the burden of PMD nor postpartum depression was significantly correlated with activity within this network for this contrast (IH>IN). Age was also not correlated with network connectivity. However, both SRS and internalizing CBCL scores were independently negatively correlated with the IH>IN contrast beta values (both p=0.02) (Figure 3-3D). Additionally, SRS and internalizing CBCL were correlated with each other (p=0.01) and neither term was significant when modeled together (p = 0.225 and p = 0.227, respectively). These variables (SRS and internalizing symptoms) did not interact with mothers' BDI, PMD, or postpartum depression to influence network activity.

The contrast of CH>CN did not show any significant relationships between PMD or any other study variables with the intrinsic connectivity of the left occipital-temporal network.

3.3.2.2 Limbic Network

In adults, this organization of co-activated limbic and paralimbic brain areas subserves functions related to emotion perception, salience processing, and sensory representation [105, 106]. Based on the limbic network's inferred functional attributes,

contrasts isolating the processing of emotional versus non-emotional stimuli were selected [(CH>CN) and (IH>IN)]. However, these contrasts were not associated with significant effects of PMD or other study variables on limbic network connectivity. However, the contrast of incongruent happy and neutral men minus incongruent arrows (i.e., IS>INS) identified significant effects of study variables on network organization. In this model (F=8.60, p=0.002), postpartum depression (p=0.009), age (p=0.01), externalizing CBCL symptoms (p=0.01) and PMD (p=0.01) were found to be significantly related to limbic network activity. Thus, as the externalizing CBCL scores, age, or PMD burden increased, intrinsic activity within the network increased. As postpartum depression burden increased, network connectivity decreased.

3.3.2.3 Fronto-Cingulate Network

This component represents a possible combination of two cognitive control networks (the fronto-parietal and the cingulo-opercular networks) seen in adults during cognitive control, planning, and decision making activities [114] [115]. Since this network is putatively involved in cognitive control, the cognitive conflict contrasts (I>C, INS>CNS, and IS>CS) were explored to examine the influence of PMD on the network's organization. The comparisons of stimulus incongruent and congruent conditions for the contrasts I>C and INS>CNS were not associated with significant relationships between network activity and any of the study variables. However, for the incongruent social versus congruent social contrast (i.e., IS>CS), the ANOVA (F=5.84, P = 0.01) indicated a significant effect of study variables on network connectivity. This model indicated that internalizing symptoms (P = 0.018) and PMD burden (P = 0.016) were associated, positively and negatively respectively, with intrinsic connectivity of the Fronto-Cingulate network, when controlling for mothers' current BDI scores. There

was no significant interaction between internalizing symptoms and PMD (P = 0.75) or between internalizing symptoms and mother's current BDI score (P = 0.25).

However, the contrast of incongruent social versus incongruent non-social stimulus trials (i.e., IS>INS) was found to be the most significant in relation to study variables. In an ANOVA model (F=13.82, P=0.0008), the interaction between age and internalizing CBCL contributed significantly in a positive fashion (p = 0.0009), while PMD (p = 0.002) contributed negatively. Thus as PMD increases, intrinsic connectivity within this network decreases. In an opposite fashion, as age and internalizing CBCL symptoms increase, intrinsic connectivity within the network increases.

3.3.3 Extrinsic Network Connectivity

All study variable effects on network extrinsic connectivity reflect a task-wide analysis (specific contrasts of trial types were not examined) and a permutation-based cluster-level correction (p=0.005, k=18 voxels; corrected p <0.05) based on 10,000 Monte Carlo simulations [163].

3.3.3.1 Occipital-Temporal Network

As PMD burden increased, two extrinsic brain areas were negatively correlated with network activity: the right pre-supplementary motor area (pre-SMA), (9 0 54 mm) (Figure 3-4A) and the left inferior frontal gyrus (IFG)/pars triangularis (-54 18 18 mm) (Figure 3-4B). Thus, at higher levels of PMD exposure, these two areas appeared to be less functionally integrated into the occipital-temporal network. No areas were significantly positively correlated with this network as a function of PMD burden.

When controlling for age and sex, no areas were integrated into this network in relation to increases in PMD. This may be because this was the only network that was significantly related to gender (Figure 3-7). It appears to have large functional sex

differences in this age group. Females differentially integrate areas of the left superior frontal gyrus, left fusiform, and left cerebellum into the network. Males, on the other hand, differentially integrate multiple areas of the right temporal cortex. It is interesting to note the distinct lateralization (males = right; females = left) of these results.

3.3.3.2 Limbic Network

Limbic network activity was positively correlated with PMD for the left ventral anterior temporal cortex (-42 12-15 mm, BA 38) (Figure 3-4C). This area represents the most rostral part of the temporal lobe and superior temporal gyrus and corresponds to the anterior STS. Thus, at higher levels of PMD exposure, this area appeared more functionally integrated into the child's limbic network. No brain areas were significantly negatively correlated with activity for this network as a function of PMD burden.

When controlling for age and sex, PMD was positively correlated with the integration of the left dlPFC (which is part of the medial frontal gyrus) and also known as BA46 (Figure 3-6A). The area is made up of 39 voxels located at -45 36 24 mm and is known to be involved in executive functioning, planning, working memory, and affect regulation. As PMD increases, this area is more integrated into the limbic network. Additionally, PMD was also negatively correlated with the integration of the right inferior frontal gyrus (IFG), a 25 voxel area located at 42 24 12 mm (Figure 3-6B). This area is a motor, cognitive, and emotional regulatory hub and is often integrated into the limbic system. As PMD increases, this area is less integrated into the limbic network.

3.3.3.3 Fronto-Cingulate Network

Fronto-cingulate network activity was negatively correlated with PMD burden for three right posterior brain areas; the middle occipital gyrus (36 -72 15 mm) (Figure 3-5A), the precuneus/BA31 (18 -66 21 mm) (Figure 3-5B), and the superior parietal lobule (24 -48 66 mm) (Figure 3-5C). Thus, as PMD increased, connectivity of the fronto-cingulate network to these areas decreased. No areas were significantly positively correlated with this network as a function of PMD burden.

When controlling for age and sex, PMD was negatively correlated with a 52 voxel C-shaped area of the right anterior cingulate (including both the ventral (BA24) and dorsal anterior cingulate (BA32)) at 15 0 33 mm and 15 14 43 mm, respectively (Figure 3-6C). These areas are known to be involved in emotional conflict processing and emotional regulation and are strongly affected by stroop tasks. As PMD increases, the integration of this area into the fronto-cingulate network decreases.

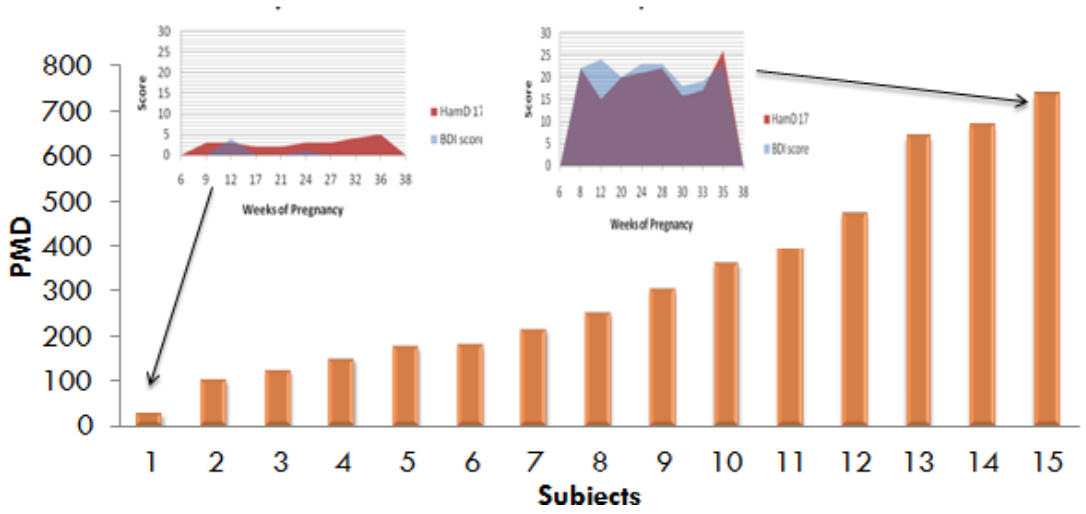

Figure 3-1: Range of Beck Depression Inventory (BDI) scores over the course of pregnancy, based on area under the curve (AUC) calculations for 5+ prenatal visits and standardized to 40 weeks of pregnancy.

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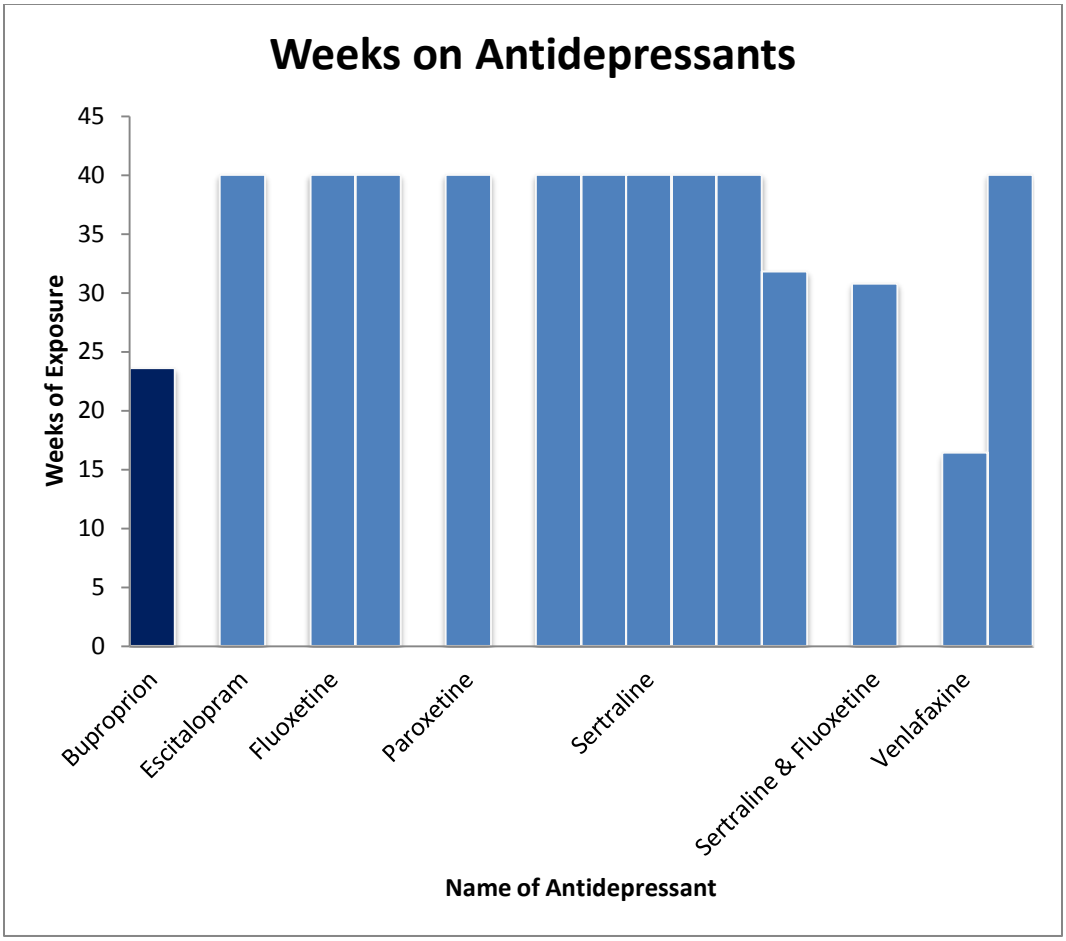


Figure 3-2: Antidepressant medications by subject. Of the 15 subjects, 14 were on antidepressant medication during pregnancy. Medications taken by these subjects include serotonin reuptake inhibitors [escitalopram (n=1), fluoxetine (n=2), paroxetine (n=1), sertraline (n=6), a combination of sertraline and fluoxetine (n=1), venlafaxine (n=2)] and an atypical antidepressant [buproprion (n=1)]. The above bar graph shows the number of subjects on each medication and the weeks the neonate was exposed to the given medication (standardized to a 40 week pregnancy).

Subjects (n=15)	Average	Standard Dev.	Range
Age of Child at Scan	5.61 years	0.68 years	4.58 - 6.50 years
BDIs during Pregnancy	6.3 visits	1.05 visits	5 - 8 visits
BDIs during Postpartum	4.6 visits	0.99 visits	3 - 6 visits
PMD Burden over 40 weeks	335.2 BDI pts	223.8 BDI pts	28.1-738.34 BDI pts
PMD Burden avg/week	8.4 BDI points	5.4 BDI points	0.7 - 18.5 BDI pts
Postpartum MD (25 wks)	212.0 BDI pts	171.4 BDI pts	33.9 -553.1 BDI pts
PMD Burden avg/week	8.5 BDI points	6.9 BDI points	1.4 - 22.12 BDI pts
Behavioral Assessments at 5 years of age:			
BDI of mother	6.0 BDI points	5.2 BDI points	0 - 15 BDI points
CBCL total t-scores	42.2	7.7	28 - 52
Internalizing t-scores	45.1	8.7	33 - 62
Externalizing t-scores	42.3	8.3	28 - 57
SRS total t-scores	44.6	5.6	36 - 56
Joint Attention Task	94% accuracy	8% accuracy	80 - 100 % accuracy
IQ percentile	77.2 %	17.3 %	46 - 95 %

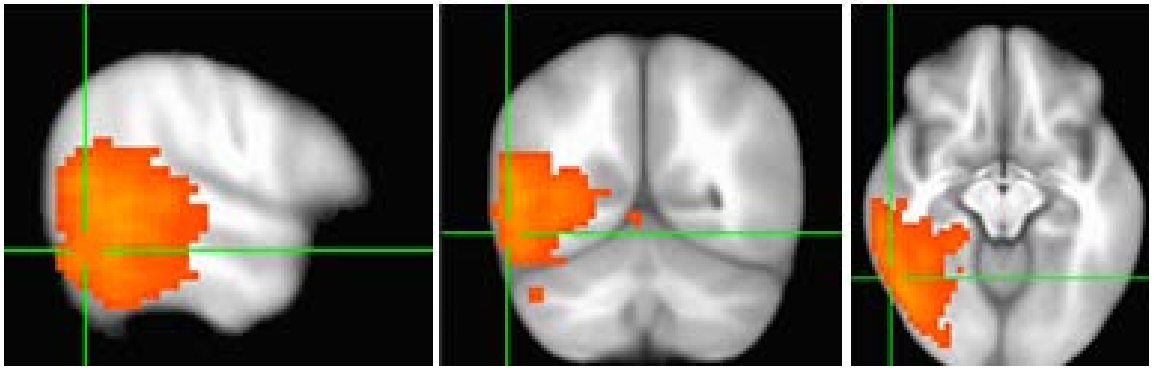
Table 3-1: Demographic and behavioral variables for subjects included in analysis.

Trial Type	Average Time(ms)	Standard Deviation (ms)
Congruent Neutral (CN)	1437	535
Congruent Happy (CH)	1401	460
Congruent Non-Social (CNS)	1428	524
Incongruent Neutral (IN)	1443	451
Incongruent Happy (IH)	1427	496
Incongruent Non-Social (INS)	**1586**	510

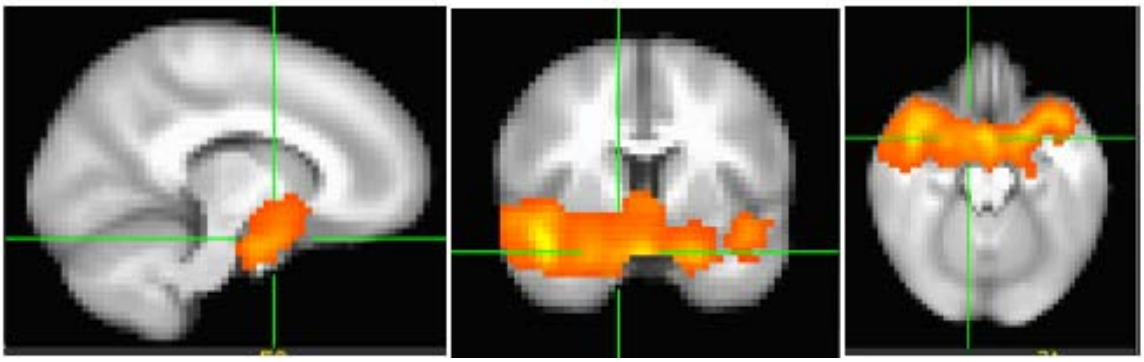
Table 3-2: Reaction time data for six trial types. Significantly longer trial types are indicated in bold.

Network Name (# of Voxels)	Side	Brain Area (abbreviation/Brodmann area)	MNI coordinates (x y z mm)		
Occipital Temporal (2834)	Left	Superior Temporal Gyrus (STS/BA22)	-41	-27	3
	Left	Middle Temporal Gyrus (BA22)	-58	-32	3
	Left	Lingual Gyrus (BA18)	-22	-74	-3
	Left	Fusiform Gyrus (FG/BA37)	-50	-55	-15
	Left	Middle Occipital Gyrus (BA19)	-38	-80	3
	Left	Parahippocampal Gyrus (BA36)	-25	-36	-9
Limbic (3120)	Left	Posterior insula (BA13)	-40	-17	-3
	Left	Superior Temporal Gyrus (STS/BA38)	-39	6	-15
	Right	Superior Temporal Gyrus (STS/BA38)	43	7	-13
	Left	Inferior Frontal Gyrus (IFG/BA47)	-43	13	-4
	Right	Inferior Frontal Gyrus (IFG/BA47)	40	18	-15
	Medial	Ventral Anterior Cingulate cortex (ACC/BA24)	0	33	-4
	Left	Nucleus Accumbens	-5	2	-10
	Right	Caudate Nucleus	9	9	-3
	Left	Amygdala	-17	-1	-11
	Right	Amygdala	22	-7	-11
	Left	Hippocampus (BA28)	-16	-16	-15
	Medial	Brainstem	-1	-10	-11
Fronto-Cingulate (6000)	Left	Dorsolateral Prefrontal Cortex (dlPFC/BA9)	-39	18	39
	Right	Dorsolateral Prefrontal Cortex (dlPFC/BA9)	43	37	27
	Right	Medial Prefrontal Cortex (mPFC/BA9)	24	37	29
	Left	Superior Prefrontal Cortex (BA10)	-9	63	18
	Left	Dorsal Anterior Cingulate Cortex (ACC/BA24)	-10	9	29
	Right	Middle Cingulate Cortex (MCC/BA24)	4	-9	37
	Right	Inferior Frontal Gyrus (IFG/BA47)	54	18	-3
	Right	Anterior Insula (BA13)	43	13	-5
	Right	Precuneus (BA7)	3	-57	51
	Left	Superior Temporal Gyrus (aSTS/BA21,22)	-57	12	-3
	Right	Superior Temporal Gyrus (aSTS/BA21,22)	39	13	-10

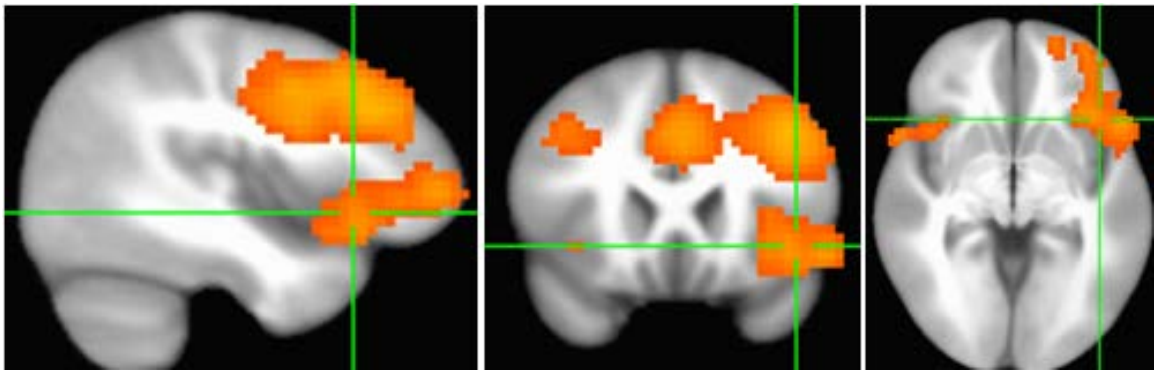
Table 3-3: Coordinates in MNI space for three networks chosen from group level independent component analysis.



A. Left Occipital-Temporal Network (-55 -55 -10 mm)



B. Limbic Network (-39 6 -15 mm)



C. Fronto-Cingulate network (3 9 36 mm)

Figure 3-3 ABC: The three chosen networks related to the JAT task conditions. Peak voxel activations in MNI space. Left=left.

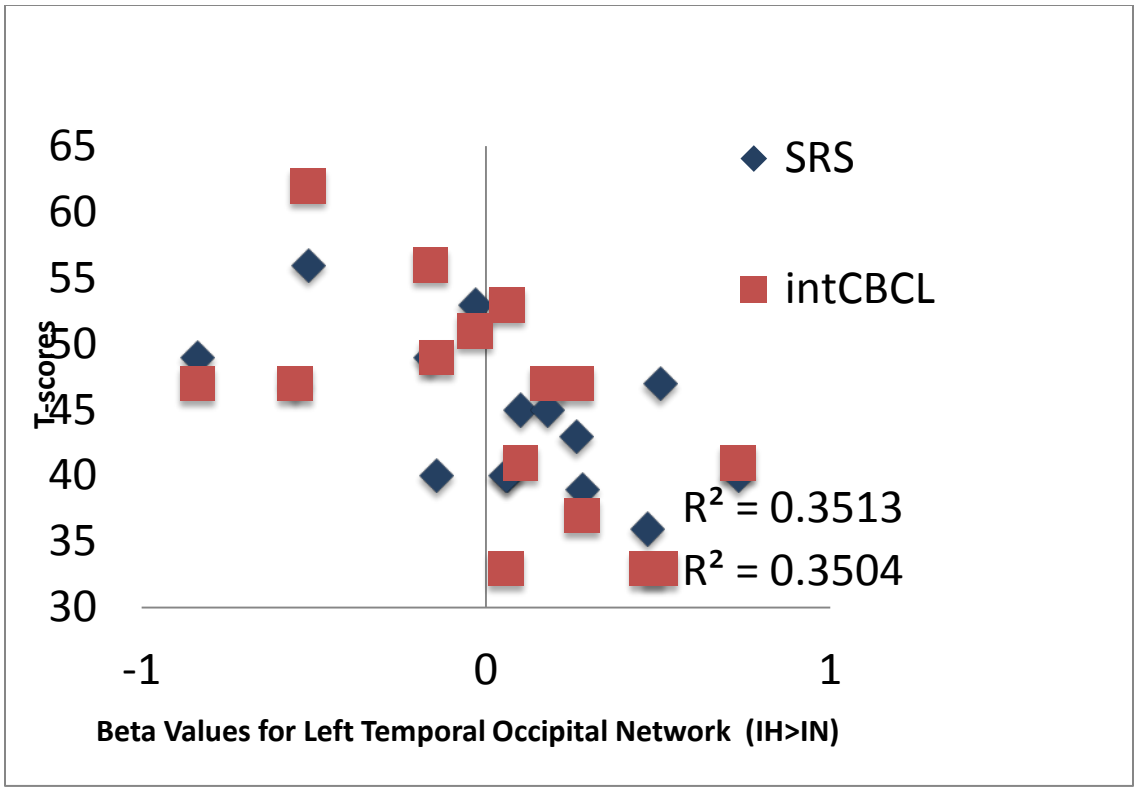
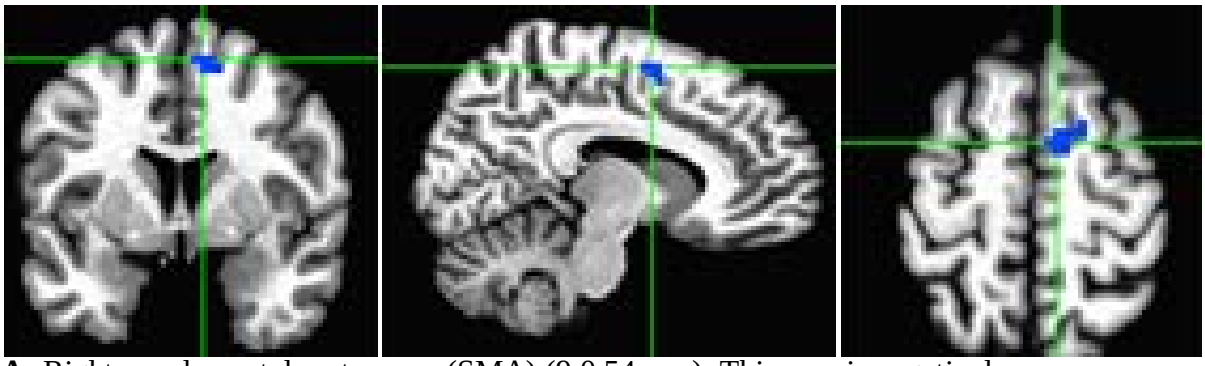


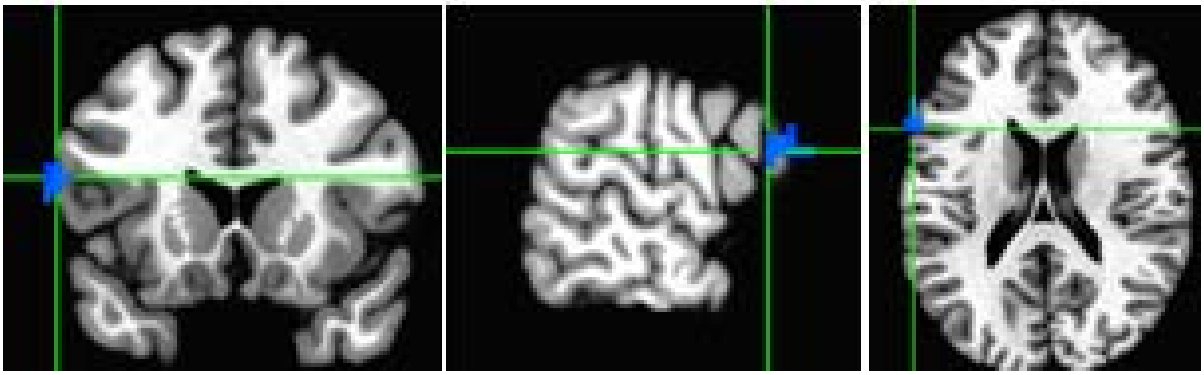
Figure 3-3D: Graph of the t-scores of correlations of both the social responsiveness scale (SRS) and the sub-scale for internalizing behaviors from the child behavioral checklist (CBCL) with the beta values for the left temporal occipital network for the contrast IH>IN.

Network	Contrast	Intrinsic Connectivity Results	Interpretation
Occipital Temporal	IH>IN	• SRS (p=0.02) • Int. CBCL (p=0.02)	SRS ↑ = Network Connectivity ↓ iCBCL ↑ = Network Connectivity ↓
Limbic	IS>INS	• F=8.60, p=0.002 o postpartum MDD (p=0.009) o age (p=0.01) o ext. CBCL (0.01) o PMD (p=0.01)	PPMD ↑ = Network Connectivity ↓ age↑ = Network Connectivity ↑ eCBCL ↑ = Network Connectivity ↑ PMD↑ = Network Connectivity ↑
Fronto-Cingulate	IS>CS	• F =5.84, p=0.01 o int. CBCL (0.02) o PMD (0.02)	iCBCL ↑ = Network Connectivity ↑ PMD ↑ = Network Connectivity ↓
	IS>INS	• F=13.82, p=0.0008 o age x int. CBCL (p=0.009) o PMD (p=0.002)	iCBCL and age ↑ = Network Connectivity ↑ PMD ↑ = Network Connectivity ↓

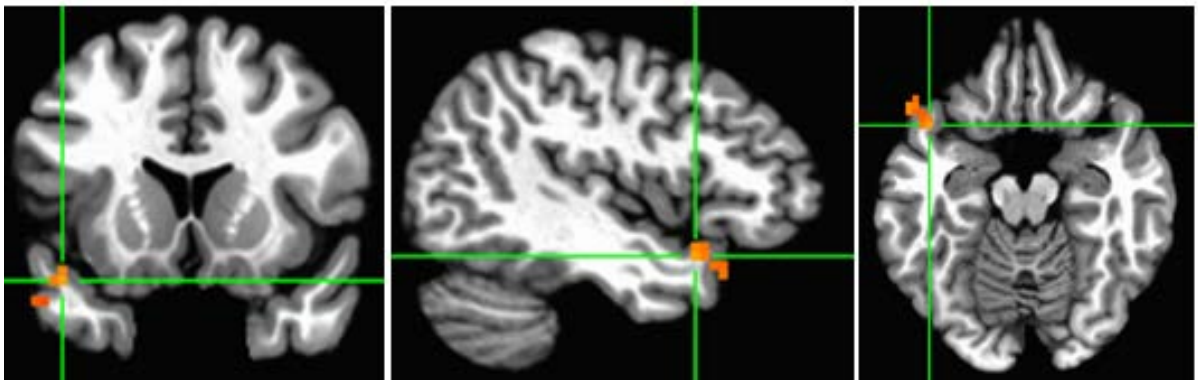
Table 3-4: Summary of intrinsic connectivity results for all three networks. Positive relationships are shown in red, while negative relationships are shown in blue.



A: Right supplemental motor area (SMA) (9 0 54 mm). This area is negatively correlated with PMD in the occipital-temporal network

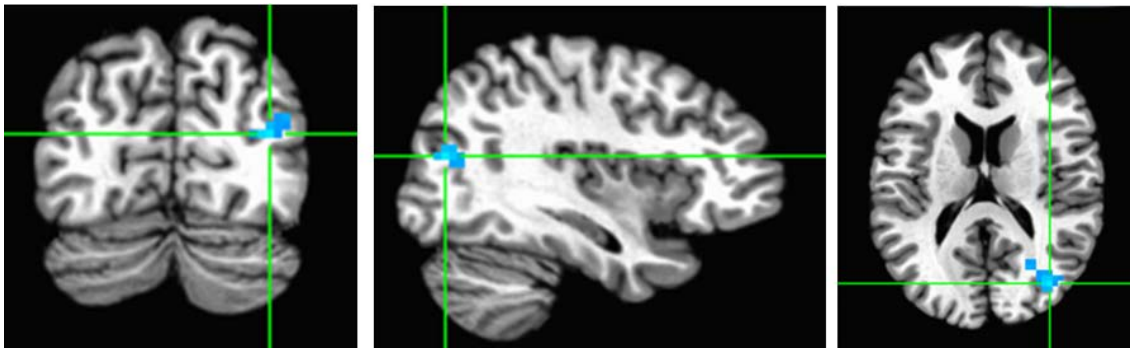


B: Left inferior frontal gyrus (IFG) (-54 18 18 mm). This area is negatively correlated with PMD in the occipital-temporal network

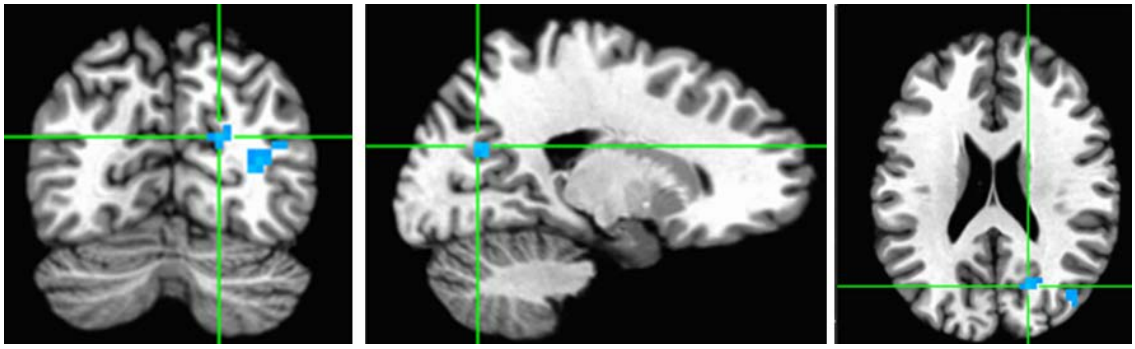


C: Left ventral anterior temporal cortex/BA38 (-42, 12, -15 mm). This area is positively correlated with PMD in the limbic network.

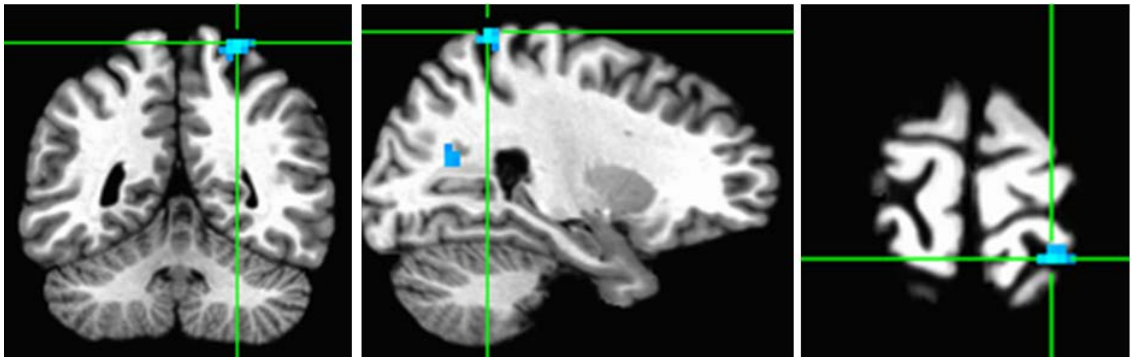
Figure 3-4 ABC: Areas of extrinsic connectivity between prenatal maternal depression (PMD) for the occipital-temporal (A and B) and limbic networks (C). All results are pictured at p=0.005, k=18 voxels. Left=left.



A. Middle occipital gyrus (36 -72 15 mm). This area is negatively correlated with PMD burden for the fronto-cingulate network.

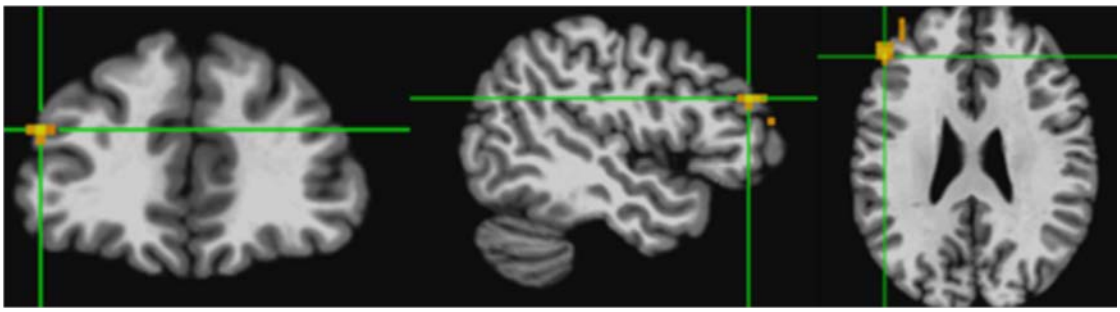


B. Right Precuneus/BA31 (18, -66, 21 mm). This areas is negatively correlated with PMD burden for the fronto-cingulate network.

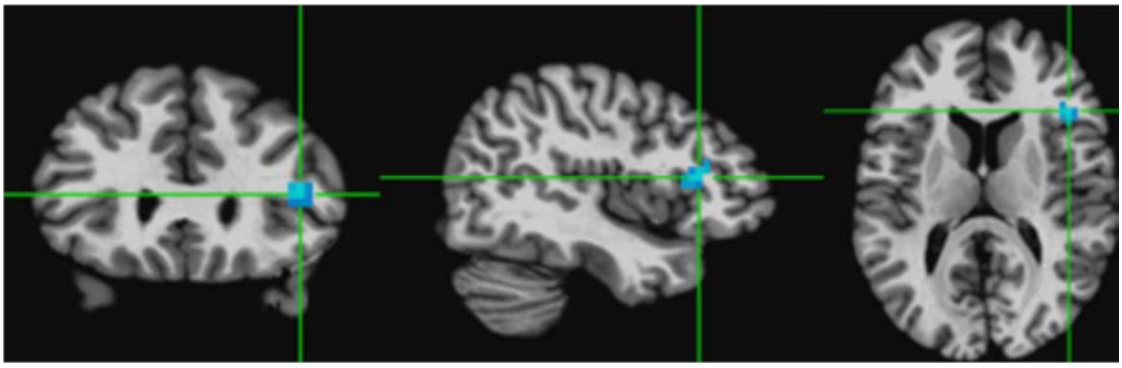


C. Superior parietal lobule (24 -48 66 mm). This area is negatively correlated with PMD burden for the fronto-cingulate network.

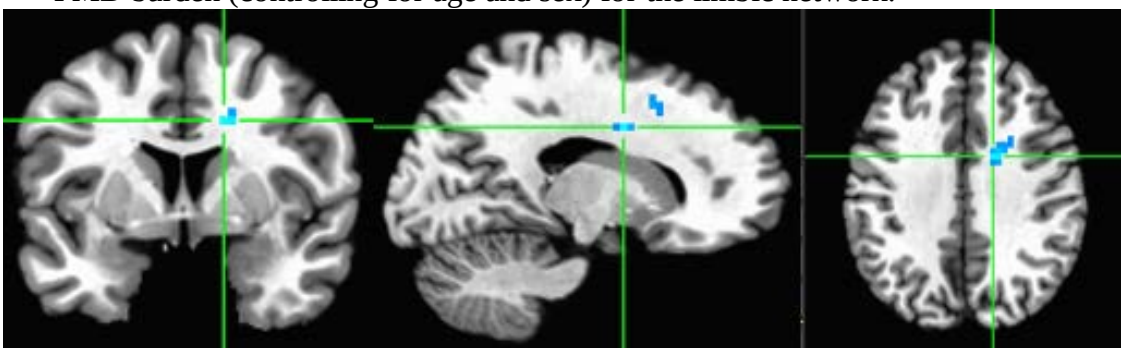
Figure 3-5 ABC: Areas of extrinsic connectivity for the fronto-cingulate network. All results are pictured at p=0.005, k=18 voxels. Left=left.



A. Left dorsal lateral prefrontal cortex (-45 36 24 mm). This area is positively correlated with PMD burden (controlling for age and sex) for the limbic network.



B. Right inferior frontal gyrus (42 24 12 mm). This area is negatively correlated with PMD burden (controlling for age and sex) for the limbic network.



C. Right anterior cingulate (15 0 33 mm). This area is negatively correlated with PMD burden (controlling for age and sex) for the fronto-cingulate network.

Figure 3-6: Areas of extrinsic connectivity between prenatal maternal depression (PMD), controlling for age and sex. All results are pictured at p=0.005, k=18 voxels. Left=left.

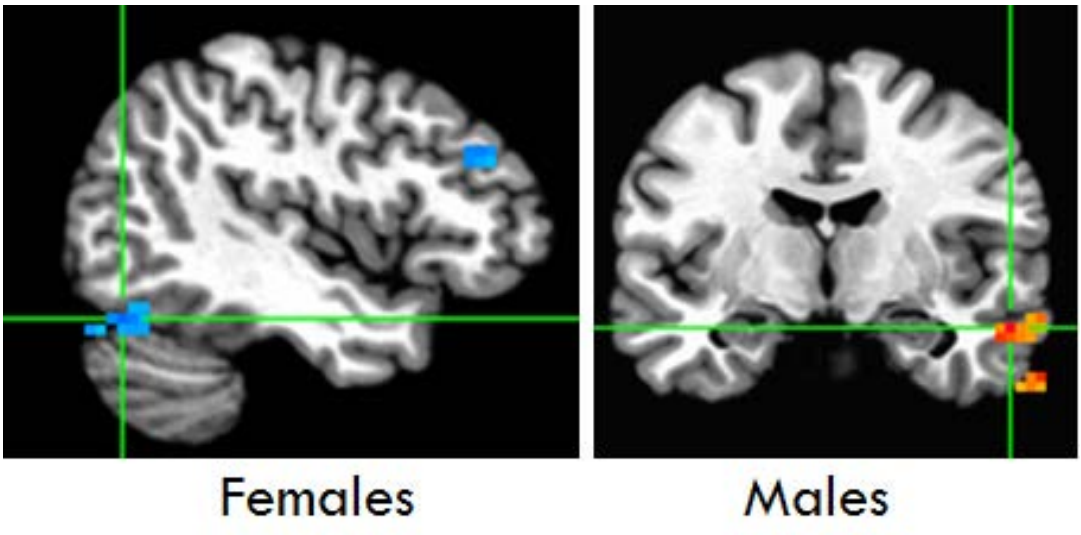


Figure 3-7: Gender differences seen in the occipital-temporal network. Females differentially integrate areas of the left superior frontal gyrus, left fusiform, and left cerebellum into the network. Males, on the other hand, differentially integrate multiple areas of the right temporal cortex.

CHAPTER 4:

DISCUSSION

Overview

Study outcomes indicate that PMD is associated with neurodevelopmental alterations in offspring as they transition from early to middle childhood. Three specific groups of contrasts between task conditions probed emotion perception, social signaling, and stimulus conflict processes for three theoretically motivated networks related to these processes. The effects of PMD on both intrinsic functional connectivity within the networks and network functional connectivity with brain areas outside the network were determined.

4.1 Occipital-Temporal network

4.1.1 Maturity

In typically developing adults, the face processing network includes the fusiform gyrus, middle occipital gyrus, bilateral STS, anterior cingulate cortex, inferior frontal gyrus, orbital frontal gyrus [97, 100], and amygdala and ventral striatum [98, 99]. The child version of this network, seen in this study, includes the left STS (BA22), left middle temporal gyrus, left fusiform (BA37), lingual gyrus (BA18), middle occipital gyrus(BA19), and parahippocampal gyrus (BA36). It appears to not be fully mature as it lacks connections to frontal cortical areas including the anterior cingulate cortex, the orbital frontal gyrus, and the inferior frontal gyrus, normally seen in the adult version of this network [97, 100]. However, we are uncertain of whether this is normal for children of this age-group.

4.1.2 Intrinsic Connectivity

The intrinsic functional organization of this sensory processing pathway was not significantly affected by PMD, or its interaction with other study variables. The most significant association of study variables with occipital-temporal network activity involved the contrast of stimulus-incongruent happy trials with incongruent neutral trials (IH > IN). For this contrast, activity for this network representation of the left ventral visual processing pathway was negatively related to child social behavioral ability (SRS) and internalizing behaviors (internalizing CBCL). If greater network connectivity is related to more effective or efficient face information processing ability, then the observed negative associations are consistent with diminished social abilities and anxiety or mood symptoms.

4.1.3 Extrinsic Connectivity

The engagement of two brain areas involved in behavioral regulation and deliberation with the occipital-temporal network was negatively affected by increasing PMD burden. The left IFC is central to behavioral, emotional, and cognitive regulation [58, 171]. The pre-SMA is involved in controlled action selection, inhibiting automated response in favor or more deliberative choices, and transitioning between responses [172-174]. An inference of these changes in extrinsic connectivity for the occipital-temporal network is that PMD exposure dose-dependently uncouples action planning and response regulatory mechanisms from the neural processing of social cues. Resulting dysregulated social perception would perhaps contribute to risk for later life mood, anxiety, or drug use disorders.

It is interesting that when age and sex were controlled for in the extrinsic connectivity model, PMD no longer has a significant effect. It appears that sex

differences, namely the strong laterality differences (Figure 3-7) between males and females may be masking any PMD effects. A larger sample size would be necessary to see any effects of PMD beyond these sex differences. It is also noteworthy that the lack of PMD finding extrinsically is consistent with the lack of PMD finding in the intrinsic domain. Given the relationship with SRS and internalizing CBCL scores in the intrinsic results, it would be interesting to look at the relationship between these measures extrinsically.

4.2 Limbic network

4.2.1 Maturity

The limbic network identified in the present child sample is very similar in its organization to the adult limbic system, which is known to include the hypothalamus, hippocampus, amygdala, anterior thalamus, parahippocampal gyrus, ventral anterior cingulate cortex, ventral striatum, and orbitofrontal cortex and is critical to emotional behavior and motivation [105, 106]. The adult limbic system is also known to have connections to the STS and IFG via the insula [175]. Therefore, the observed child limbic paralimbic network [which includes the hipppocampus, amygdala, brainstem, ventral striatum (caudate nucleus and nucleus accumbens), ventral anterior cingulate, superior temporal sulcus, and inferior frontal gyrus, and insula] (Table 3-3, Figure 3-3) appears to be of a mature functional organization in this group of children.

4.2.2 Intrinsic Connectivity

The most salient contrast for this network related to its sensitivity to study variables was IS>INS (incongruent social vs. incongruent non-social attentional cues). The IS>INS contrast was also found to be behaviorally salient. In post-scan interviews, many children commented on the incongruent happy trials. One child even stated “that

little man was trying to trick me!" For this contrast, the functional influence of PMD on the organization of this network was positive, such that as PMD increased, the intrinsic connectivity of the network increased. Externalizing CBCL symptoms were also positively related to network activity. These relationships suggest that exposure to PMD may predispose affected children towards externalizing disorders such as drug use and disruptive disorders by heightening the reactivity of limbic processing of socio-emotional stimuli.

Of the neural processing networks examined, the functional connectivity of only the limbic network was significantly correlated with the burden of postpartum depression over the 6 month postnatal period. This negative association suggests that the functional organization of this network is sensitive to dose-dependent disruption by maternal depression in the postpartum period. It would be of interest as to whether the driving factor for this effect is related to a neurodevelopmental outcome of the association of maternal depression with relatively poor postnatal maternal care for the infant and/or attachment issues. The fact that prenatal and postpartum depression have opposite effects on this network may be because of the differential experience of affective vs. vegetative symptoms in prenatal and postpartum depression, respectively. However, sub-scores for these domains or answers to individual questions on the BDI would be necessary to address this theory.

Child age was also significantly, positively associated with network activity suggesting that some level of neurodevelopment of limbic connectivity occurs over the age group observed (4-6 years), despite the fact that the network appears to be mature overall.

4.2.3 Extrinsic Connectivity

PMD severity also correlated positively with the functional integration of the ventral anterior superior temporal cortex (ventral bank of the anterior STS) into the network. This region is central to the fine grained coding of gaze direction [176]. This result suggests that exposure to PMD engages high-level gaze perception with limbic network information processing. This may be a compensatory or adaptive response of brain functional connectivity, which enable the development or maintenance of social cognition for this at-risk sample. Alternatively, this may be a mechanism by which extra attention is given to other's emotions, thus creating a heightened response to social cues, which may in turn lead to increased emotional reactivity.

After controlling for age and sex, two different regulatory areas show significant relationships with PMD for the limbic network. The left dorsal-lateral prefrontal cortex (dlPFC) is positively related to PMD and thus it is recruited into the limbic network as PMD increases. This area is involved in working memory, cognitive conflict, and emotional regulation. Given these functional attributes and the fact that the dlPFC is not normally part of the limbic system, the integration of this area may serve as a compensatory mechanism by which children exposed to large amounts of PMD who have an overactive limbic network (as seen in the intrinsic results) need additional cognitive regulation from the dlPFC. Interestingly, PMD has a negative relationship with another regulatory area, the right inferior frontal gyrus, such that as PMD increases, the integration of this area into the limbic system decreases. This area is normally integrated into the limbic network and is in charge of action, cognitive, and emotional regulation. The decreases in functional integration of this area may lead to the limbic network being hyper-sensitive (as seen in the intrinsic results) and thus make

it necessary for the dlPFC to take over some of its regulatory role. This change in functional connectivity is unusual and thus possibly quite inefficient. Inefficient functional connectivity throughout childhood has been shown to lead to permanent inefficiencies in functional networks over time, and increase the risk for the development of psychopathology [76].

4.3 Fronto-Cingulate network

4.3.1 Maturity

The organization of the data-derived child fronto-cingulate network is consistent with a combined version of the two adult executive function networks, the fronto-parietal and cingulo-opercular networks. The adult frontal-parietal network incorporates the dlPFC, intraparietal sulcus, medial cingulate cortex, premotor/preSMA, frontal eye fields, and the right tempo-parietal junction, enabling its involvement in task initiation and conflict monitoring[114]. The adult cingulo-opercular network involves the dorsal anterior cingulate cortex, bilateral anterior prefrontal areas (including inferior frontal gyrus), inferior parietal cortex, anterior insula, and thalamus, and is implicated in sustained attention and cognitive control [115]. Given the areas involved in the child fronto-cingulate network, namely the dlPFC(BA9), medial prefrontal cortex, superior prefrontal cortex (BA10), middle cingulate cortex (BA24), inferior frontal gyrus (BA47), anterior insula (BA13), precuneus (BA7), and STS(BA21/22), this network seems to represent a combination of these two known adult networks. However, a major difference in organization between these two networks and the observed child fronto-cingulate network is that the child version lacks connectivity to parietal cortex, namely the inter-parietal sulcus (IPS), the right temporal parietal junction (rTPJ), the

inferior parietal lobule (IPL), and to the thalamus. The IPS is involved in visual spatial attention and understanding the intent of others [177, 178]), while the rTPJ is involved in the distinction between self and others [179],enhanced social ability [180], value-based decision making [181]. The IPL is involved in understanding emotions in facial stimuli and other sensory information [182]). Interestingly, the fronto-cingulate network observed in our population is very similar to that seen by Fair et al in normally-developing children[88]. This is not surprising, however, as immature child frontal-parietal connectivity is supported by structural and functional connectivity studies [183] in this age group.

4.3.2 Intrinsic Connectivity

Most notably, the intrinsic connectivity of this network was sensitive to PMD severity for activation related to social signaling when the human and arrow attentional cues were presented in the task-incongruent configuration (IS>INS). Less network functional connectivity was associated with increasing PMD severity for this contrast. This robust relationship may represent the greatest neurodevelopmental cost of PMD exposure, a dose-dependent disruption in social cognitive ability. The further observation that fronto-cingulate network activity was related to increased internalizing symptoms, suggests that this neurodevelopmental disruption may underlie the increased risk for mood and anxiety disorders associated with prenatal stress. Consistent with a developmentally emerging risk for mood and anxiety disorders, increasing internalizing symptoms (as they interact with age) were associated with increased intrinsic activity of the fronto-cingulate network. This increased activity within the fronto-cingulate network may be a compensatory mechanism, by which increasing behavioral issues

require greater activity within the fronto-cingulate network in order to control emotional labiality.

4.3.3 Extrinsic Connectivity

Interestingly, PMD severity was associated with decreased fronto-cingulate connectivity with distributed sites in the right posterior brain, including precuneus and inter-parietal sulcus (IPS), which are normally part of a mature cognitive control network. Given that the association with the parietal regions was no longer seen when the covariates of age and sex were added into the analysis, they were probably a function of age differences within the sample. However, when age and sex were controlled for, the ventral/dorsal anterior cingulate (BA24/32) was negatively correlated with exposure to PMD. Therefore, this early life adversity may represent the source of diminished regulatory ability due to the lack of integration of this crucial regulatory area into the fronto-cingulate network. The observed "dose-dependent" effect of PMD on the functional organization of the fronto-cingulate network suggests that diminished functional engagement of the neural representation of conflict processing and attentional and behavioral regulation to social and conflict stimuli represents a neurodevelopmental cost of this and perhaps other forms of prenatal adversity.

4.4 Overview of Results

The severity of PMD burden was associated with diminished intrinsic activity within the fronto-cingulate network and increased intrinsic activity within the limbic network. The severity of PMD exposure was not associated with intrinsic connectivity for the left occipital-temporal network. In addition to PMD, the functional organization

of selective neural processing networks was also found to be sensitive to child age, behavioral development, social development, and postpartum depression.

For the extrinsic connectivity results, the severity of PMD exposure was negatively associated with the integration of brain areas (the right inferior frontal gyrus and the anterior cingulate) that are crucial to proper function for both the limbic and fronto-cingulate networks, respectively. The lack of integration of these necessary areas may indicate a sub-optimal due to PMD exposure. In addition, the child limbic network shows increased connectivity to the left dlPFC with exposure to PMD. This may be a compensatory measure, as this area is not normally integrated into the limbic system.

It was noteworthy that the effect of PMD and other study variables on network connectivity was either dependent on or exaggerated by the processing of incongruent attentional stimuli. This may reflect a possible greater attentional command for incongruent stimuli. It is also interesting that, in general, the task processes that best matched the presumed functional attributes of each network did not reveal the impact of PMD or other study variables. This observation may reflect immature functional differentiation (lack of specialization) in the networks in 4-6 year olds, and thus an overlap of network functioning domains.

4.4.1 Limitations

The present study is the first of its kind and is therefore exploratory in nature, with an emphasis on hypothesis generation. Due to its small sample size, results should be interpreted with caution pending a replication study. Although this population is well-controlled and well-characterized, there are some explanatory variables, such a paternal psychological states, parenting style, attachment type, and stressful events occurring during early childhood that we were unable to measure. Further studies on

this population with larger sample sizes are necessary to draw more meaningful conclusions.

Another limitation of this study is the lack of normative brain data for children, leading to the lack of a gold standard being available for the preprocessing and standardization of child brain images into anatomical space. As brain imaging studies in children increase, presumably a standard brain atlas for children will be developed and made accessible to researchers, solving this problem.

Lastly, due to the neurodevelopmental motivation to characterize the effect of PMD on neural processing networks and take advantage of the effect of data dimensionality reduction on defining brain-behavior relationships, more conventional mass univariate brain-wide analysis was not reported. Although we believe the network-level analysis provides us more relevant information in regards to brain maturation and dysregulation, this approach limits the comparison of study findings with the limited other fMRI studies done for this age group.

Despite these limitations, this study is timely and informative as a motivation and guide for similar studies of the risks of prenatal depression and other earliest life adversities and provides a first approximation of the possible teratogenic effects of PMD on social cognitive development and the maturation of neural networks.

4.5 Concluding Remarks

The results of the present study provide support for the hypothesis that PMD leads to the disrupted neural development of exposed offspring in the intrinsic and extrinsic functional organization of neural networks related to affective, social, and cognitive functioning in a dose-dependent fashion. Altered network connectivity can be

seen in the following ways: 1) decreased integration of regulatory areas, 2) possible adaptive or compensatory mechanisms, and 3) altered intrinsic connectivity in the fronto-cingulate and limbic networks.

The correlation between PMD and altered network connectivity is clearly evident in the fronto-cingulate and limbic networks, as exposure to PMD leads to important regulatory areas of these networks being minimally integrated. This creates sub-optimal networks and results in the dysregulation of socio-emotional processing (as reflected by the correlation of these networks with internalizing and externalizing behaviors, respectively). While the altered network connectivity of regulatory areas is punitive in general, it is especially concerning in networks relating to social emotion processing (such as those described here – the limbic and fronto-cingulate networks) and in children of such a young age, as this may cause disruption in social learning and dysregulation of emotional systems, thus laying the foundation for the development of psychopathology.

Altered functional connectivity can also be seen explicitly with the addition of compensatory mechanisms, such as the integration of the left dlPFC into the limbic system as a result of exposure to PMD. This additional connectivity to the left dlPFC may indicate a mechanism by which these children attempt to maintain emotional balance, especially in regard to social cue processing, in an already hyper-emotional state (as indicated by increases in limbic network activity seen in the intrinsic results). As this area is not normally associated with the limbic system, it may be replacing the regulatory role that the right inferior frontal gyrus (which is less integrated into the limbic network) would normally be playing, albeit in a much less efficient fashion.

Lastly, altered connectivity can also be seen in the increase in network activity in the limbic network and the decrease in network activity in the fronto-cingulate network for the processing of social cognitive conflict cues (IS>INS) with exposure to PMD. Additionally, these changes are related to increases in extrinsic and intrinsic behavioral symptomology for the limbic and fronto-cingulate network, respectively. Thus, the dose-dependent changes in intrinsic network activity with exposure to PMD may provide a mechanism by which children exposed to PMD become overly emotional and have difficulty regulating their behavior using their frontal cortexes. The combination of these two changes is likely to produce mood and anxiety symptoms as well as atypical social behaviors. Interestingly, this type of inefficient emotional regulation due to the uncoupling of the prefrontal cortex and limbic system is often seen in adults with depression [76].

The presence of altered functional connectivity in children provides support for the self-organizing principle of depressive disorder, a theory in which interactions between brain areas that occur frequently throughout development will become more stable over time, cementing any dysfunctional connectivity seen in childhood by the time the child is an adult [184].

4.5.1 Implications

Thus, PMD negatively effects both network activity and functional connectivity and thus may represent the earliest life adversity. The significance of this outcome is relevant to clinical decision-making related to the aggressive management of moderate to severe depression in pregnancy. This decision is dominated by the concern for the safety of the unborn offspring due to possible adverse effects related to the use of SSRIs and other first line medications of proven efficacy in the treatment of depression.

This decision often results in an untreated or under-treated illness. However, recently more medical professionals are taking the risks of untreated depression into consideration and are acknowledging the value to pharmacological treatment during pregnancy [14]. The results of this dissertation work add to the growing literature on the negative consequences of prenatal maternal depression, highlighting the neurodevelopmental cost to the offspring, and further suggesting the need for caution in decisions concerning the avoidance of first-line treatment during pregnancy. Additionally, these findings will serve as inspiration for similar lines of research in the future, in an effort to further elucidate the neural underpinnings, trans-generational transmission, and development of psychopathology.

Network	Adult Network	Maturity	Intrinsic Results	Extrinsic Results with PMD
Occipital-Temporal Network	Facial Perception Network	**Not fully mature** ⇨ lacks connections to frontal areas (such as ACC, OFC, and IFG)	PMD was not related to this network. The network was negatively related to **SRS and int. CBCL scores** ⇨ decreased facial processing ⇨ diminished social abilities and/or anxiety/mood symptoms	PMD was not related to this network. Significant sex differences. ⇨ Sex differences may be masking PMD effects
Limbic Network	Limbic System	**Mature** - includes most of the known brain areas	Connectivity was positively related to **PMD and ext. CBCL** ⇨ increased emotional processing ⇨ increased emotional volatility ⇨ externalizing behaviors	PMD was positively correlated with **Left dlPFC** ⇨ Compensation for an overactive limbic system PMD was negatively correlated with **Right IFG** ⇨ Lack of regulatory ability ⇨ Overactive limbic network
Fronto-cingulate Network	1) Fronto-parietal network 2) Cingulo-opercular Network	**Not mature** -lacks connections to the posterior brain (parietal cortex) and sub-cortical areas	Connectivity was negatively related to **PMD** ⇨ disruption of social cognitive ability and decreased regulatory mechanisms and positively related to **int. CBCL scores x age** ⇨ extra regulation of emotions needed due to rumination or emotional labiality especially in the older age group (6-6.5 years)	PMD was negatively correlated with **Right Anterior Cingulate** ⇨ Lack of social emotional regulation ⇨ Increased internalizing symptoms

Table 4-1: Summary of the most important findings and their interpretations.

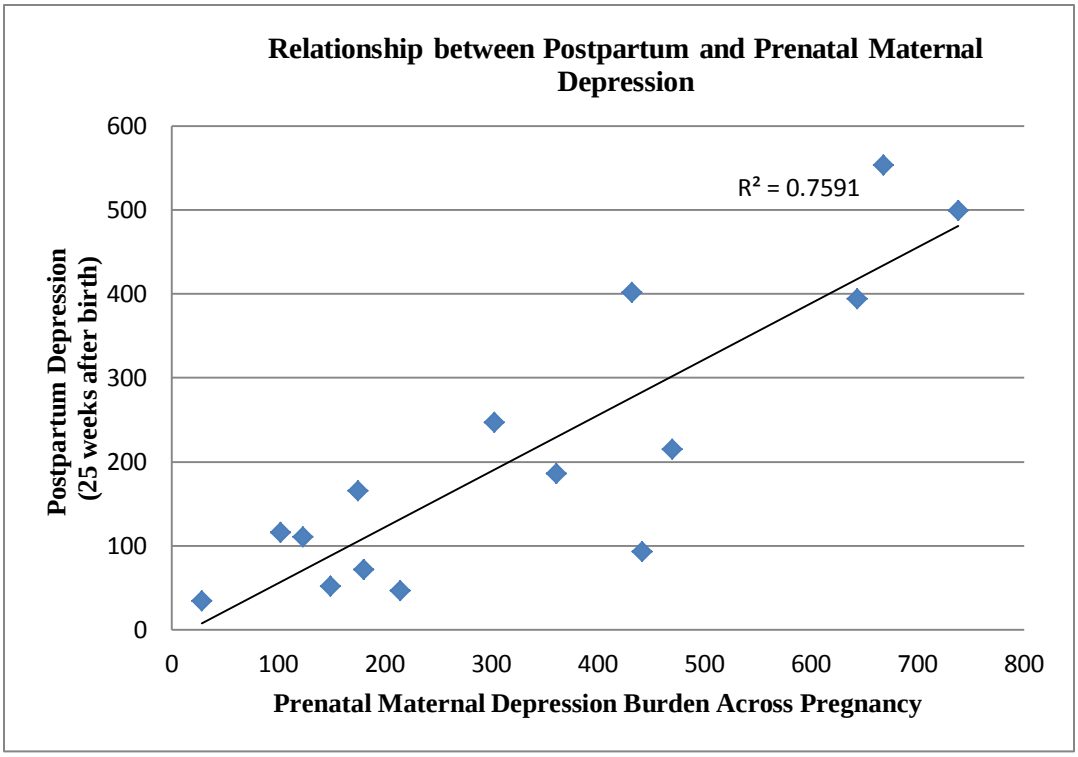


Figure S-1: Correlation between prenatal maternal depression and postpartum depression across subjects (p=0.001).

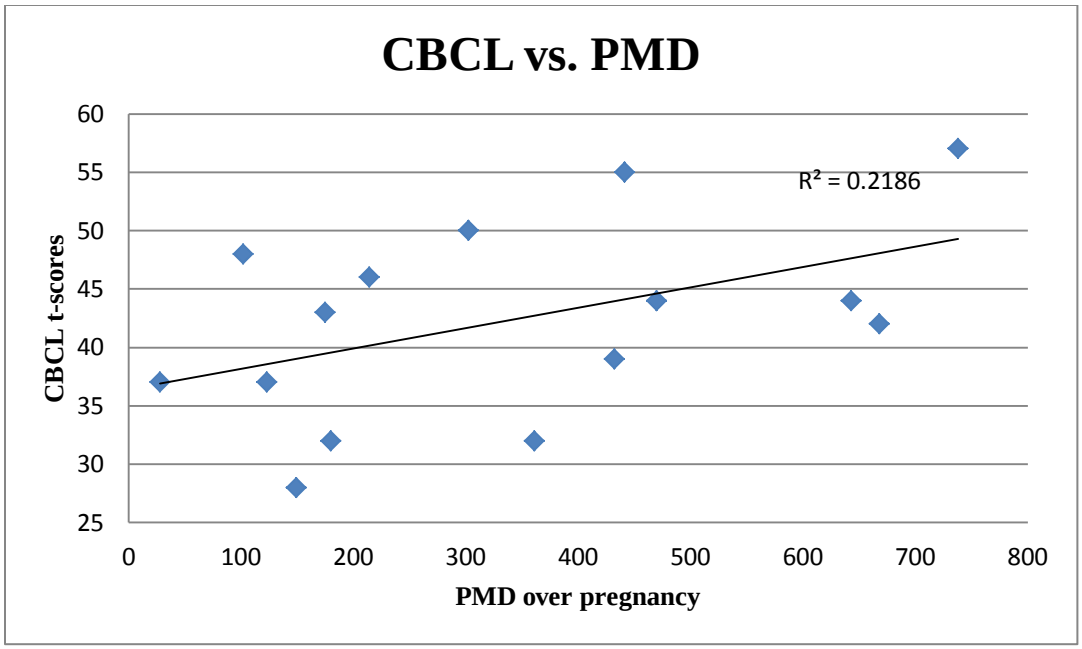


Figure S-2: Correlation between CBCL and PMD (p=0.14).

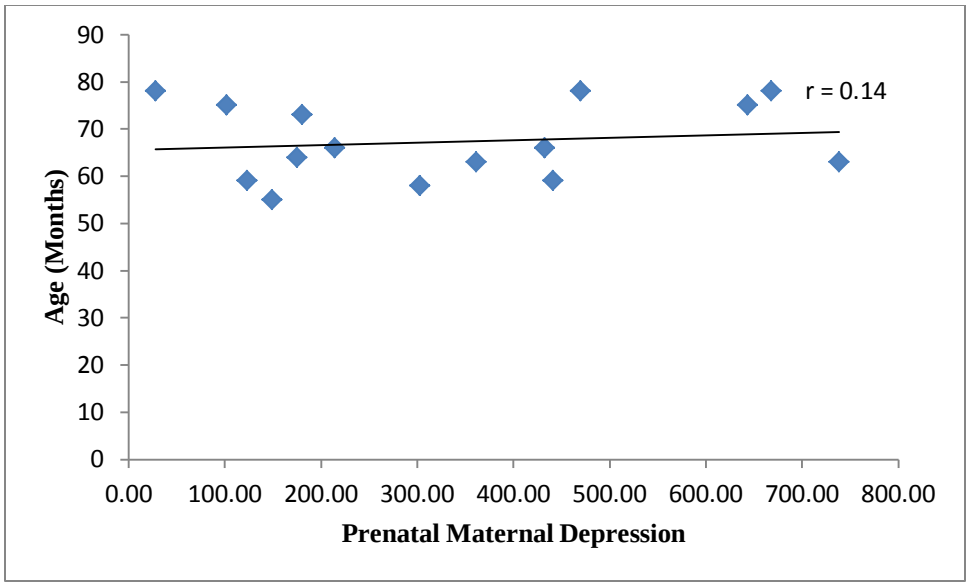


Figure S-3: There is no correlation between PMD and age.

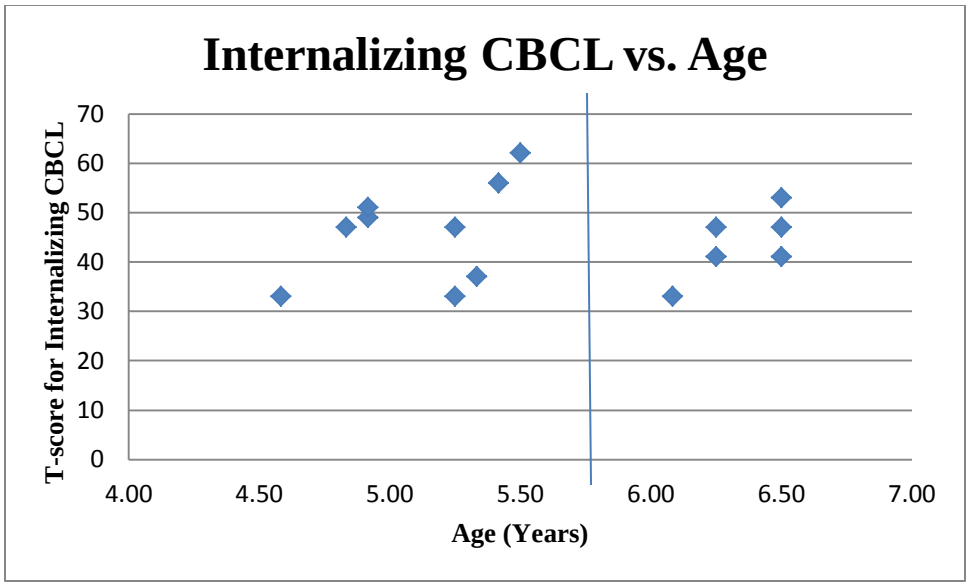


Figure S-4: Modeling Internalizing CBCL vs. Age

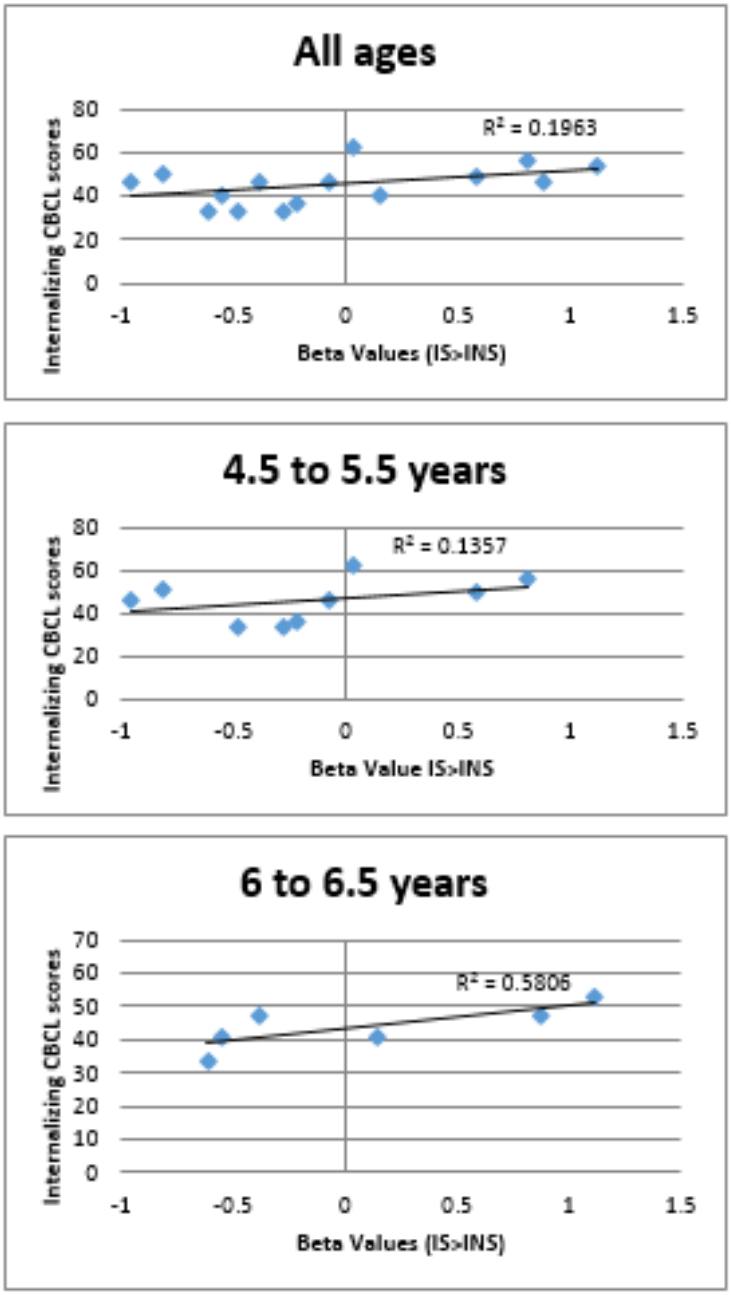
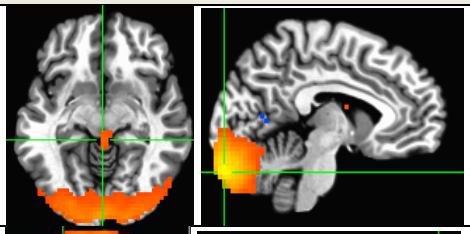
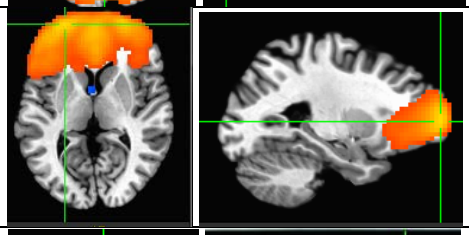
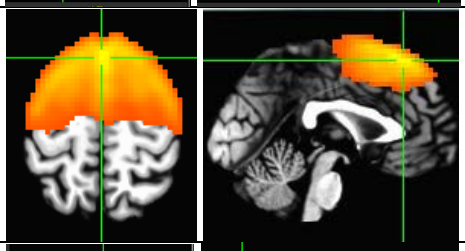
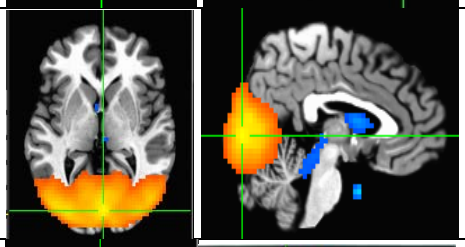
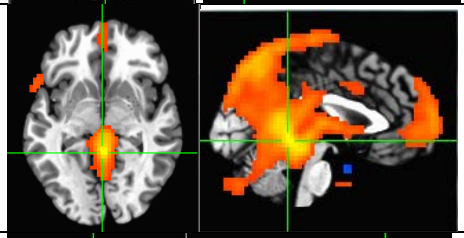
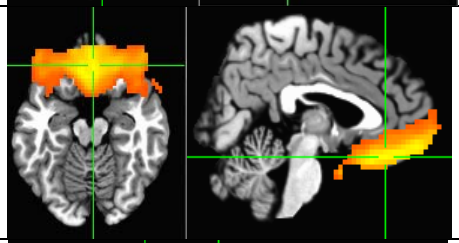
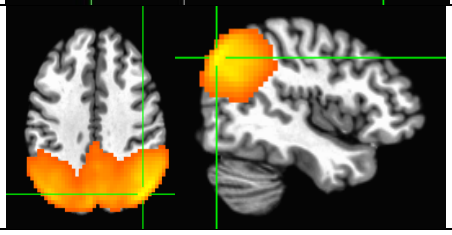


Figure S-5: Intrinsic Connectivity for fronto-cingulate network during IS>INS contrast correlations with internalizing CBCL by individual age group (as determined from the age distribution in Figure S-4).

Name of Network	Visuals	# of Voxels # of Cluster Noise Level	Peak Activation of main cluster (x y x mm)
Occipital-cerebellar		3585 voxels 4 clusters	-6 -90 -27 mm
Ventral prefrontal cortex		4562 voxels 4 clusters	-24 57 6 mm
Motor cortex		4162 2 clusters	0 30 54 mm
Occipital cortex		5337 voxels 5 clusters **Some noise**	3 -81 3 mm
Default-mode network (incomplete)		3412 voxels 12 clusters **Very noisy**	0 -42 -3 mm
Orbitofrontal cortex		2891 voxels 4 clusters	3 33 -15 mm
Parietal cortex		5489 voxels 5 clusters	42 -72 36 mm

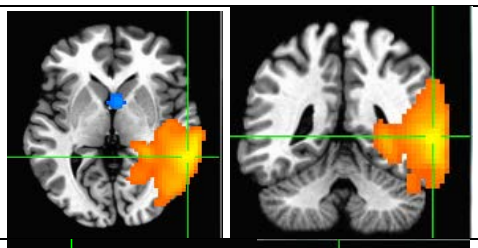
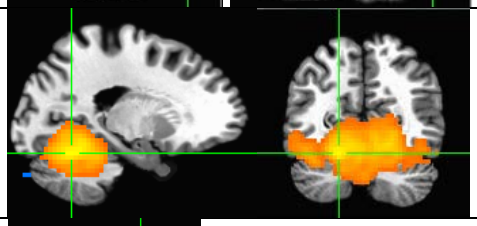
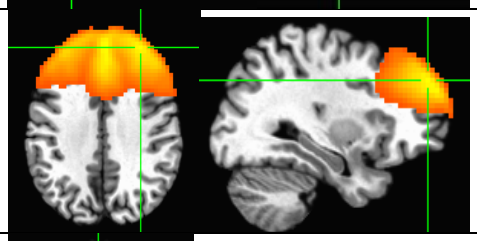
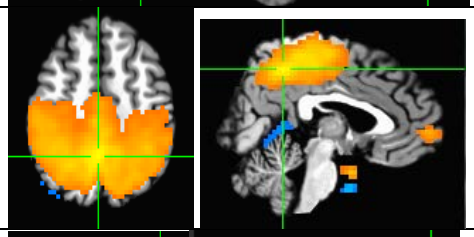
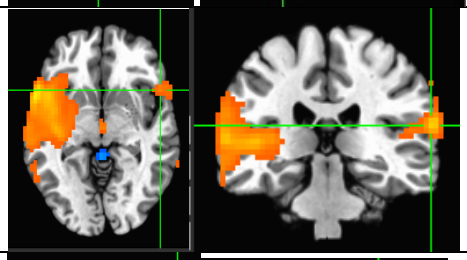
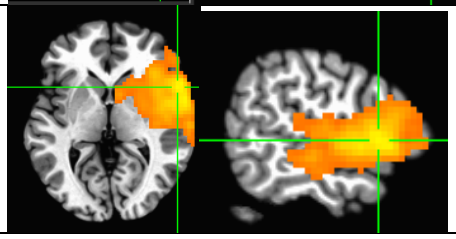
Right temporal cortex		3893 voxels 3 clusters	57 -42 3 mm
Occipital cortex and posterior cingulate		4149 voxels 4 clusters	-18 -57 -18 mm
Dorsal prefrontal cortex		4749 voxels 3 clusters	30 48 33 mm
Sensory-motor cortex		5824 voxels 8 clusters **Some noise**	3-48 45 mm
Bilateral insula		3077 voxels 8 clusters **Very noisy**	-57 9 0 mm
Right temporal		4382 6 clusters	54 12 3mm

Figure S-6: Other networks not chosen for further analysis. Images are displayed at p=0.005. Left=left.

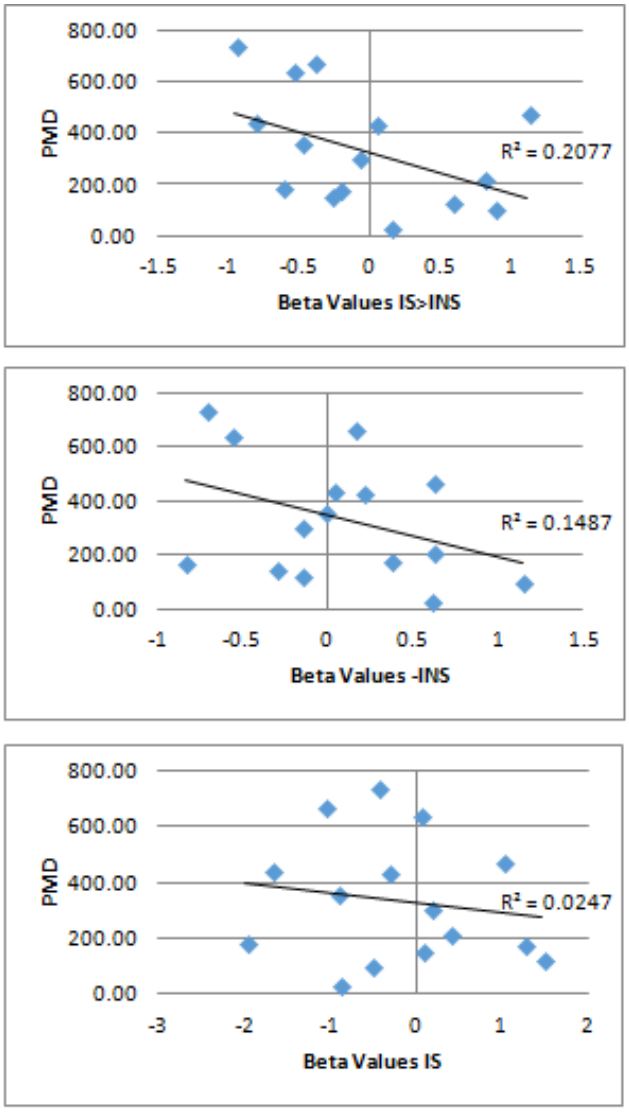


Figure S-7: Intrinsic connectivity correlation between beta values and prenatal maternal depression (PMD) for the contrast IS>INS (incongruent social vs. incongruent non-social) for the fronto-cingulate network. The correlation between IS>INS and PMD has a p-value of 0.09 and a R^2 value of 0.2077. This seems to mostly be driven by the non-social condition (second graph).

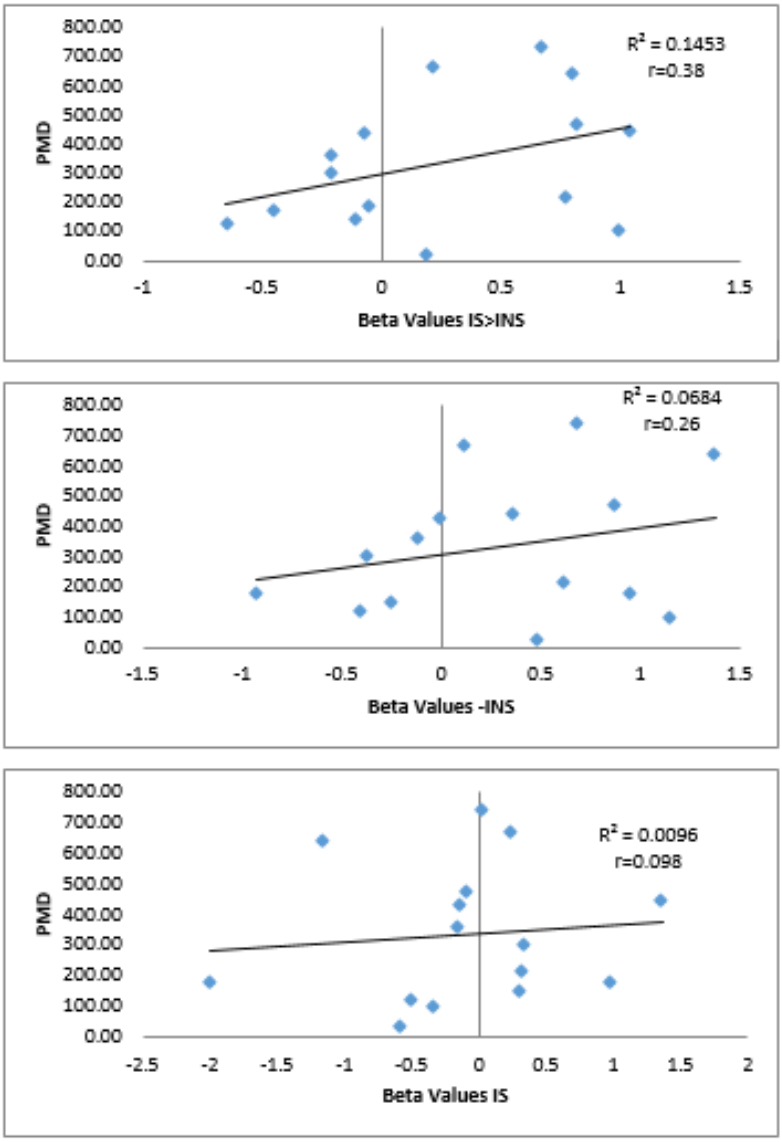


Figure S-8: Intrinsic connectivity correlation between beta values and prenatal maternal depression (PMD) for the contrast IS>INS (incongruent social vs. incongruent non-social) for the limbic network. The correlation between IS>INS and PMD has a R^2 value of 0.15. This correlation is not driven by the INS condition or the IS condition. It seems to be a product of the comparison between them.

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