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Examining the Relationship between Perinatal Depression and Neurodevelopment in Infants and Children through Structural and Functional Neuroimaging Research

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Abstract

Depression is the most common perinatal psychiatric disorder but little is known about how it may impact offspring neurodevelopment, as well as the mechanisms by which it may confer transgenerational psychiatric risk. This review presents imaging studies conducted to evaluate the relationship between perinatal depression (PND) and infant and child neurodevelopment. Altered structural and functional connectivity is implicated in children exposed to PND and anxiety. Overall, there are changes in connectivity between amygdala and prefrontal cortex. Studies suggest decreased hippocampal growth in the first six months after birth, decreased cortical thickness in children, and increased amygdala volume that are more pronounced in female offspring. Future research is needed to understand the impact of PND on development so that early interventions which promote mother-infant bonding and cognitive development may improve developmental outcomes in children exposed to PND, reducing later risk of psychopathology.

Keywords

perinatal; postnatal; depression; magnetic resonance imaging; neuroimaging; anxiety; infant; child

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

INFORMED CONSENT

This article does not contain any studies with human or animal subjects performed by any of the authors.

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INTRODUCTION

Depression is the most common perinatal psychiatric disorder, with prevalence rates between 6.5 to 12.9% and higher in lower-income and middle-income countries(Fisher et al., 2012; Gaynes et al., 2005; Howard et al., 2014; Munk-Olsen et al., 2006). The American Psychiatric Association's Diagnostic Statistical Manual of Mental Disorders - Fifth Edition (DSM-5)(APA, 2013) defines perinatal depression (PND) as a major depressive episode (MDE) occurring during pregnancy or within four weeks after delivery. However, the World Health Organization defines the puerperal period as up to one year after delivery(Robertson et al., 2003). There is some evidence to suggest that PND is a distinct entity from nonpuerperal MDE, given its clinical presentation, course, and treatment response (Fox et al., 2018; Hendrick et al., 2000) and the rates of comorbid mental health disorders, particularly anxiety (Dindo et al., 2017; Hendrick et al., 2000; Putnam et al., 2017). Anxiety disorders have a prevalence rate of 21.7% during the third trimester of pregnancy, and 11.1% during the first three postpartum months (Borri et al., 2008; Reck et al., 2008). PND and MDE share a similar symptom profile, and women with PND often present with persistent sadness(APA, 2013; Putnam et al., 2017), anhedonia(APA, 2013; Putnam et al., 2017), guilt(APA, 2013), irritability(APA, 2013; Bernstein et al., 2008), psychomotor agitation(APA, 2013; Bernstein et al., 2008), impaired concentration(APA, 2013; Bernstein et al., 2008), sleep disturbances(APA, 2013), lethargy(APA, 2013), and weight and appetite changes(APA, 2013). Severe PND can include suicidal thoughts (Pope et al., 2013), and a risk for child abuse (Plant et al., 2015), or even infanticide (Spinelli, 2004). Thoughts of self-harm occur in approximately 5–14% of women with PND, and maternal suicide is the leading cause of direct maternal mortality in the first postnatal year, with one in seven deaths due to suicide (Draper et al., 2018; Lindahl et al., 2005).

Heterogeneity is evident in the timing of onset of PND. For some women, this pervasive constellation of symptoms develops in the antenatal period, while others first develop symptoms up to a year postnatally (Goodman, 2004; Robertson et al., 2003). Approximately one in five women with PND continue to experience depression after the first postnatal year, and roughly double that number will experience a relapse in depression in future perinatal periods or other nonpuerperal periods(Robertson et al., 2003). Not all women share equal likelihood of developing PND; the strongest risk factor is a personal history of anxiety or depression before or during pregnancy(Escriba-Aguir et al., 2013; Horowitz et al., 2004; Norhayati et al., 2015; Wisner et al., 2013), and other risk factors include inadequate social support(Escriba-Aguir et al., 2013; Horowitz et al., 2004; Norhayati et al., 2015), high psychosocial stress(Horowitz et al., 2004; Norhayati et al., 2015; Yim et al., 2015), history of abuse or interpersonal violence(Escriba-Aguir et al., 2013), interpersonal difficulties with partners(Norhayati et al., 2015; Yim et al., 2015), poor perceived maternal health(Escriba-Aguir et al., 2013), and low income(Escriba-Aguir et al., 2013; Horowitz et al., 2004; Norhayati et al., 2015; Yim et al., 2015). Biological contributors, the subject of more recent study, may include neurotransmitter, hormonal, and immune deregulation, possibly mediated by genetic or epigenetic susceptibilities (Serati et al., 2016; Yim et al., 2015).

Negative sequelae of PND, in addition to the aforementioned symptoms, present significant risks for both woman and child; in light of these risks, PND has been termed a public health

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problem(Wisner et al., 2006). PND has been associated with pregnancy complications like preeclampsia and operative delivery(Hu et al., 2015), preterm birth, low birth weight, and intrauterine growth restriction(Grote et al., 2010). Stress and anxiety during pregnancy also influence maternal behavior and birth outcomes including maternal substance use, poor nutrition and exercise, preterm labor, preterm birth and low birth weight (Ding et al., 2014; Lobel et al., 2008). PND has also been associated with an impaired maternal-infant relationship (Righetti-Veltema et al., 2002) and an increased risk for behavioral, emotional, and cognitive developmental problems throughout infancy(Murray, 1992), childhood(Hay et al., 2001), and adolescence(Halligan et al., 2007; Hay et al., 2008). For example, PND has been associated with insecure attachment patterns in infants(Murray, 1992), lower intelligence quotient scores in children(Hay et al., 2001) and a risk for the later development of affective disorders in adolescents(Halligan et al., 2007). Antenatal anxiety has additionally been associated with disrupted emotional regulation and later psychopathology in exposed offspring (Beydoun et al., 2008; Glover, 2011; Sandman et al., 2012). Some of the risk factors associated with PND, such as lower socioeconomic status and familial interpersonal stress, could also negatively impact child development (Barker et al., 2012; Murray, 1992). However, current understanding of how maternal PND may impact offspring neurodevelopment, as well as the mechanisms by which PND may confer transgenerational psychiatric risk(Glover, 2011; Janssen et al., 2016; Osborne et al., 2018), remains limited but under active study.

The urgent need for proper diagnosis, effective prevention, and robust treatment for both PND and its transgenerational sequelae warrants investigation into its neural underpinnings not only in perinatal women, but in their offspring. Imaging research into the neurocircuitry of PND will lead to an understanding of the pathophysiology of the disorder, identify clinical subtypes, develop biomarkers of risk and resilience, and lead to novel therapeutics. Imaging research in the infants and children born to women with PND will lead to an understanding of not only what may confer risk in offspring, but also resilience.

Several types of neuroimaging modalities have been utilized in women with PND, such as magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS) and positron emission tomography (PET). However, magnetic resonance (MR) techniques have been favored in studies of women and children due to their availability, versatility, high level of anatomical detail, and relative safety due to a lack of ionizing radiation. MR techniques involve applying a strong external magnetic field to the patient, exciting hydrogen atoms to emit characteristic signals which are then detected by the MRI machine and used to generate images of the patient’s brain. Structural MRI methods are used to examine gray and white matter morphometry. Common methods for examining gray matter volume include manual measurement of a chosen brain region or regions of interest (ROI), voxel-based morphometry (VBM) which is a hypothesis-free approach to examine gray matter differences among groups across the brain (Bandettini, 2009), and surface-based measures which measure the thickness of gray matter as a way of estimating the number of neuronal cell bodies in a given area.

Diffusion tensor imaging (DTI) is an MR method that determines the location, orientation and anisotropy of white matter tracts (Bandettini, 2009). Diffusion in white matter is

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anisotropic, greater in one direction than in others (Beaulieu, 2002). Greater anisotropy and restricted diffusion perpendicular to the principal diffusion direction reflect healthy or mature white matter microstructure(Beaulieu, 2002). Fractional anisotropy is a value between 0 and 1 that describes the degree of anisotropy. A higher value indicates that diffusion occurs along one axis and is anisotropic, while a lower value means that the diffusion unrestricted or isotropic. Reduced fractional anisotropy within white matter tracks is believed to reflect microstructural changes associated with reduced anatomical connectivity, with less diffusion anisotropy when axons are less myelinated (Alexander et al., 2007; Soares et al., 2013). Additional DTI measures, including mean diffusivity, radial diffusivity and axial diffusivity characterize diffusion magnitude. The degree of anisotropic diffusion is affected by tissue barriers such as axonal fibers and the myelin sheath, which are important components to consider when imaging infants and young children when pronounced myelination and axonal fiber development occurs (Dean et al., 2017; Kunz et al., 2014).

Functional MRI (fMRI) measures cerebral blood-oxygenation-level dependent (BOLD) changes in the brain that are tightly correlated to changes in neural activity. Neural co-activation patterns among anatomically separate brain regions is known as functional connectivity (Logothetis et al., 2001; van den Heuvel et al., 2010). fMRI studies may either measure functional connectivity while the subject completes a designated task (task-based fMRI) or while the subject is at rest (resting-state fMRI)(Bandettini, 2009). These fMRI methods enable observation of distinct brain networks, which are groups of brain areas and neural systems that are active together and thus exhibit connectivity(van den Heuvel et al., 2010). It is important to note that while MR is an exciting, non-invasive technique allowing researchers to better understand brain developmental in infants and young children, there are limitations. For example, infant brain MRI white-gray contrast changes over the first 12 months of age and beyond. Many imaging preprocessing steps need to infant-tailored. Further, image analysis tools used for processing and analyzing adult brain MR data can be inadequate for infants, although new computational techniques have been developed and are being refined (Li et al., 2018).

Neuroimaging studies' value in the context of PND is twofold: it lies partly in enhancing understanding of PND's pathophysiology to improve its detection, prevention, and treatment, thus offering relief to the many women suffering from PND and minimizing its negative effects on their offspring's development; it also lies in elucidating how maternal PND impacts offspring normal neurodevelopmental processes so that clinicians may better serve this population. This paper reviews the literature on structural and functional neuroimaging of infants and children of women with PND or perinatal anxiety after a concise review of main imaging findings in maternal PND.

METHODS

Papers were searched on MEDLINE, PsychINFO, Web of Science, Scopus, Embase, PubMed, and Cochrane with the following key words: ("diffusion imaging" or "brain mapping" or "brain morphology" or "connectome" or "neural systems" or "connectivity" or "dti" or "fmri" or "functional mri" or "functional neuroimaging" or "diffusion imaging" or

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"diffusion tensor imaging" or "functional neuroimaging" or "magnetic resonance imaging (MRI)" or "magnetic resonance spectroscopy (MRS)" or "mri" or "neuroimaging" or "positron emission tomography (PET)" or "structural mri" or "tomography" or "volumetric based morphometry" or "volume positron emission" or "volume based morphometry" or "resting state") AND ("pregnancy" or "antepartum" or "perinatal" or "motherhood" or "postpartum" or "maternal" or "antenatal" or "postnatal" or "prepartum" or "peripartum" or "mother" or "fetus" or "fetal" or "infant" or "child" or "adolescent") AND ("depression" or "depressive"). This review is limited to papers published in English on mothers evaluated prior to six months postnatal and their children up to age ten, with a focus on papers published in the last five years. Additional articles were identified by reviewing bibliographies of review articles identified within the literature search. Fourteen papers were reviewed in total.

REVIEW OF NEUROIMAGING FINDINGS IN MATERNAL PERINATAL DEPRESSION

As recently reviewed, (Duan C et al., 2017) the main functional MRI imaging studies in women with PND show differences in activity and connectivity between different brain regions compared to those in healthy postnatal women. Task-based, or BOLD activation, fMRI studies show differences between healthy postnatal and postnatal depressed women in the activity of the right(Moses-Kolko et al., 2010; Silverman et al., 2011; Silverman et al., 2007; Wonch et al., 2016) and left(Moses-Kolko et al., 2010) amygdala(Barrett et al., 2012), posterior orbitofrontal cortex(Silverman et al., 2007), insula(Silverman et al., 2007), striatum(Moses-Kolko et al., 2011; Silverman et al., 2007), left dorsomedial prefrontal cortex(Moses-Kolko et al., 2010), thalamus(Barrett et al., 2012), and temporal cortex(Barrett et al., 2012). Task-based fMRI studies also show differences in functional connectivity between the left dorsomedial prefrontal cortex and the left amygdala (Moses-Kolko et al., 2010), as well as between the amygdala and the right insular cortex (Wonch et al., 2016), for postnatal depressed women. Resting-state fMRI neuroimaging studies, though fewer in number than task-based fMRI, report differences in activity between healthy and depressed postnatal women. Postnatal depressed women differed from their non-depressed counterparts in connectivity between the right hippocampus and right dorsolateral prefrontal cortex, the right amygdala and left dorsolateral prefrontal cortex, and among the anterior cingulate cortex, left dorsolateral prefrontal cortex, and bilateral amygdala(Deligiannidis et al., 2013). A recent study additionally reported functional connectivity differences in the dorsomedial prefrontal cortex in women with PND vs. healthy postnatal women(Deligiannidis et al., 2018). Postnatal depressed and non-depressed women may additionally differ in connectivity between the posterior cingulate cortex and right amygdala (Chase et al., 2014).

In addition to fMRI methods, structural DTI imaging methods as well as molecular studies using PET and MRS techniques have been used to investigate potential differences in neurobiology between postnatal depressed and non-depressed women(Duan C et al., 2017). DTI studies of fractional anisotropy show differences in the left anterior limb of the internal capsule, the right retrolenticular internal capsule, and in two clusters within the body of the

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corpus callosum, suggesting alterations in structural connectivity both within circuits and between hemispheres (Silver et al., 2018). Molecular studies using PET show differences between women with PND and healthy postnatal women in monoamine oxidase-A density in the prefrontal cortex and anterior cingulate cortex(Sacher et al., 2015) and in serotonin receptor binding in several brain areas(Moses-Kolko et al., 2008). MRS-based molecular studies investigating gamma-aminobutyric acid A (GABA) concentrations in the occipital cortex(Deligiannidis et al., 2018; Epperson et al., 2006) and the anterior cingulate cortex(Deligiannidis et al., 2018) reported no difference in GABA concentrations between depressed and non-depressed postnatal women which is in contrast to that reported in nonpuerperal major depressive disorder (MDD) (Sanacora et al., 1999). Only three studies examined glutamate MRS in PND: one reported increased dorsolateral prefrontal cortex glutamate MRS concentrations in PND(Rosa et al., 2017), one reported increased medial prefrontal cortex glutamate MRS concentrations in PND(McEwen et al., 2012) and one reported no difference in anterior cingulate gyrus glutamate(de Rezende et al., 2018). Research has recently begun to utilize these techniques in women with perinatal depression vs. healthy postnatal women and as of yet, there is no research that has examined potential differences in either functional or structural connectivity between PND and MDD.

REVIEW OF STRUCTURAL MRI FINDINGS IN INFANTS

Depression

A 2013 study examined 157 mother-infant dyads to determine if antenatal maternal depression is associated with neonatal amygdala structure (Rifkin-Graboi et al., 2013). Investigators measured depression using the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1996) at 26 weeks gestation. Neonates underwent DTI within two weeks of birth. In mothers with “high” antenatal depression, there was significantly lower fractional anisotropy and axial diffusivity in the right amygdala of neonates. However, there was no significant difference in amygdala volume. Table 1 summarizes neuroimaging findings in offspring of mothers with PND.

Anxiety

The first study to analyze the relationship between maternal anxiety and infant neurodevelopment in the first six months of life included 175 mother-infant dyads (Qiu et al., 2013). The State-Trait Anxiety Inventory(Spielberger et al., 1970) was used to assess anxiety in women at 26 weeks gestation and at three months following delivery. 175 neonates underwent structural MRI near birth, aged five to 17 days, and 35 infants aged six months underwent follow-up structural MRI. They found that the left hippocampus grew more slowly in the first six months with higher antenatal maternal anxiety and was smaller in volume at six months with higher postnatal maternal anxiety. The right hippocampus also grew slower in the first six months with higher antenatal maternal anxiety, but grew larger in the first six months with higher postnatal maternal anxiety.

Elaborating on this work, a whole brain structural approach studied the relationship between antenatal anxiety and the corticolimbic system in 54 mother-infant dyads (Rifkin-Graboi et al., 2015). There were no effects of antenatal maternal anxiety on infant amygdala

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microstructure. However, in infants of mothers with high antenatal anxiety, there was lower fractional anisotropy in five areas: right cerebellum; right insular cortex; perception areas (right middle occipital, inferior temporal, bilateral superior temporal, left postcentral); personal, social, emotional processing areas (right angular region, right uncinate fasciculus, posterior cingulate, parahippocampus); cognitive and emotional regulation areas (right dorsolateral prefrontal, inferior frontal, inferior fronto-occipital fasciculus). Mothers with high antenatal anxiety also had infants with lower axial diffusivity in the left lateral orbitofrontal region and left inferior cerebellar peduncle, but higher axial diffusivity in the genu of the corpus callosum.

REVIEW OF FUNCTIONAL MRI FINDINGS IN INFANTS

Depression

Expanding upon their previous work using structural MRI (Qiu et al., 2013) to include functional MRI techniques in a study of 24 mother-infant dyads, maternal depression was assessed using the EPDS at 26 weeks gestation and three months after delivery (Qiu et al., 2015). Infants underwent resting state fMRI at six months. In infants exposed to higher antenatal maternal depressive symptoms, there was increased connectivity between the amygdala and areas in three brain networks. In the emotional regulation network, there was increased connectivity to the left insula and bilateral medial prefrontal cortex (anterior cingulate, medial orbitofrontal, ventromedial prefrontal cortices). In the sensory and perceptual network, there was increased connectivity to the left superior, middle, and temporal cortices. Finally, in the emotional memory network, there was increased connectivity to the left entorhinal cortex.

Alterations in both functional and structural amygdala-prefrontal connectivity in younger infants, 4.1–7.5 weeks old, who were exposed to antenatal maternal depression has additionally been reported (Posner et al., 2016). Previous studies focused on infants at six months old. In studying younger infants, Posner et al. hoped to separate the effect of antenatal maternal depression from postnatal maternal depression. 64 mother-infant dyads were included, of which 20 infants had in utero exposure to antenatal maternal depression. Mothers were assessed between 34 and 37 weeks gestation using the Center for Epidemiological Studies Depression scale (CES-D)(Radloff, 1977). Infants with *in utero* exposure to antenatal maternal depression had less functional connectivity between the amygdala and bilateral dorsal prefrontal cortex, as well as less structural connectivity between the right amygdala and right ventral prefrontal cortex.

REVIEW OF STRUCTURAL MRI FINDINGS IN CHILDREN

Depression

The relationship between self-reported maternal depressive symptoms and brain structure in preschool-aged children has recently been examined (Lebel et al., 2016). The EPDS was used to assess maternal depression and was completed once during each trimester and once two to three months postnatal. In this study, 52 children were scanned between the ages of 2.6 and 5.1 years old, measuring cortical thickness and white matter structure. Furthermore,

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since antenatal and postnatal maternal depressive symptoms can have different clinical presentations and occur at different stages of fetal/neonatal/infant neurodevelopment, antenatal vs. postnatal depression may differentially impact the offspring's neurodevelopment. To better understand the potential differential impact on offspring, antenatal and postnatal maternal depressive symptoms were examined separately.

EPDS scores from the second trimester were associated with cortical thinning in right inferior frontal and middle temporal region, as well as with white matter tracts emanating from the inferior frontal area. Only the correlation with cortical thickness survived correction for postnatal EPDS. EPDS scores during the first and third trimesters were not significantly related to cortical thickness. When examining sex differences, there was a significant sex-by-EPDS interaction for cortical thickness in the right middle temporal region. Although both boys and girls had significant relationships, girls showed a stronger, more negative association between EPDS scores and cortical thickness.

In the postnatal period, self-reported depressive symptoms were negatively correlated with children's right superior frontal cortical thickness and with white matter measures of fibers originating from that region; these results remained significant after correction for antenatal depression. There was also a significant sex-by-postnatal EPDS interaction for axial, radial, and mean diffusivity values in white matter tracts emanating from the superior frontal region, with only boys showing significance. These results suggest divergent influences of perinatal maternal depressive symptoms on cortical morphology and white matter microstructure in preschool-aged children.

To further examine if antenatal and postnatal maternal depressive symptoms collectively or independently contribute to brain development in children, 235 children aged 4.5 years old underwent structural MRI, with a focus on the amygdala(Wen et al., 2017). Only children with normal birth weight, gestational age, and APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) scores greater than eight were included to avoid potential confounding effects on brain development. Women's depressive symptoms were assessed using the EPDS at 26 weeks of pregnancy and three months postnatally. Women were again assessed at one, two, three, and four and one-half years postnatally using the Beck's Depression Inventory-II (BDI-II)(Beck et al., 1996). EPDS and BDI-II scores were standardized. The researchers found no evidence of interaction or independent effects of antenatal and postnatal maternal depressive symptoms on amygdala volume. However, there was a non-statistically significant trend for a relationship between antenatal maternal depressive symptoms and left amygdala volume. When examining gender effects, greater antenatal maternal depressive symptoms predicted larger right amygdala volumes in girls, while controlling for postnatal maternal depressive symptoms.

While there were also no interaction effects of postnatal maternal depressive symptoms on amygdala microstructure, greater postnatal maternal depressive symptoms significantly predicted greater right amygdala fractional anisotropy in the overall sample. When examining gender differences in amygdala microstructure, greater postnatal maternal depressive symptoms predicted higher right amygdala fractional anisotropy values in girls, while adjusting for antenatal maternal depressive symptoms. Boys did not show any

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significant effects of antenatal and postnatal maternal depressive symptoms on the amygdala microstructure (Wen et al., 2017).

These findings also mirror findings by Buss et al., that higher maternal cortisol during pregnancy was associated with larger amygdala volumes in seven-year-old girls but not in boys(Buss et al., 2012). Taken together, these results demonstrate that some effects of maternal depression may be gender-specific and underscore the importance of taking gender into account when examining the neurodevelopmental pathways that may later contribute risk for depression or other psychiatric illnesses.

To assess whether antenatal maternal depressive symptoms are associated with long-term changes in child brain development, 81 children, aged six to nine years old, underwent structural MRI (Sandman et al., 2015). Mothers were assessed for symptoms of maternal depression at 19, 25, and 31 weeks gestation using the CES-D. Sandman et al. found that antenatal maternal depression was associated with cortical thinning in children. In utero exposure to maternal depression at 19, 25, and 31 weeks gestation was associated with 8%, 19%, and 7% overall cortical thinning in children aged six to nine years old, respectively. Furthermore, children exposed to in utero maternal depression at 25 weeks gestation had a 24% thinning of the frontal lobes that was most prominent in the right superior, medial orbital, and frontal pole.

In a large study, 654 children aged six to ten years old underwent structural MRI (El Marroun et al., 2016). Maternal and paternal depressive symptoms were assessed using the Brief Symptom Inventory (BSI)(Derogatis et al., 1983) at 20.6 weeks of gestation, and only maternal depressive symptoms were again assessed at postnatal year three. Antenatal and postnatal maternal depressive symptoms were not associated with total brain volume, the hippocampus, or the amygdala. However, children exposed to maternal depressive symptoms *in utero* showed a thinner superior frontal cortex in the left hemisphere, which remained significant when covariates (e.g., paternal depressive symptoms, ethnicity) were added to the model. Additionally, antenatal maternal depressive symptoms were significantly associated with larger cortical surface area in the caudal middle frontal region. These results allude to potential effects of antenatal maternal depressive symptoms affecting cortical thickness and surface area in children six to nine years later.

The same research group additionally examined the same children's white matter microstructure using DTI (El Marroun et al., 2018). Identical to the above study, maternal and paternal depressive symptoms were assessed with the BSI at 20.6 weeks of gestation, while only maternal depressive symptoms were again assessed at the child's age of three. Exposure to maternal depressive symptoms during pregnancy was significantly associated with higher mean diffusivity in the left uncinate fasciculus and cingulum bundle, while significantly negatively associated with lower fractional anisotropy in the right cingulum bundle. While no significant associations of maternal depressive symptoms at the child's age of three years with white matter characteristics were observed, there was a trend toward significance for a lower fractional anisotropy in the cingulum bundle.

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To examine structural differences in slightly older children exposed to maternal depressive symptoms, researchers compared 17 children exposed to maternal depressive symptoms since birth and 21 children not exposed (Lupien et al., 2011). Women were administered the CES-D at five, 17, 30, 42, 60, 84, and 156 months to assess whether their children were continually or never exposed to maternal depressive symptoms since birth. All children were medication-free and scanned using structural MRI at age ten, with a specific focus on hippocampal and amygdala volumes. Children who were exposed to maternal depressive symptoms since birth revealed larger left and right amygdala volumes compared with children not exposed. The researchers found no group difference in hippocampal volumes. Further, no sex differences, main effect, or interaction were significant (Lupien et al., 2011).

These combined findings of increased amygdala volume echo results of studies conducted in children previously reared in orphanages(Mehta et al., 2009; Tottenham et al., 2010), suggesting that children exposed to maternal depression show similar brain abnormalities as those with other forms of early adversity. Overall, the results emphasize the importance of preventing, identifying, and treating perinatal depression.

Anxiety

As perinatal anxiety disorders are common and can have significant negative effects on the mother and child(Nicol-Harper et al., 2007; Stein et al., 2012), it is important to understand if there is an association between perinatal anxiety and child neurodevelopment. To examine antenatal anxiety and possible changes in child gray matter volume, antenatal anxiety was assessed at nineteen, twenty-five, and thirty-one weeks gestation using a ten-item self-report scale on pregnancy anxiety (Buss et al., 2010). Thirty-five children between the ages of six and nine were assessed for psychiatric and medical conditions, then scanned using structural MRI. Anxiety at 19 weeks gestation was associated with gray matter volume reductions in the prefrontal cortex, premotor cortex, medial temporal lobe, lateral temporal cortex, postcentral gyrus, and the cerebellum extending to the middle occipital gyrus and the fusiform gyrus. Self-reported pregnancy anxiety at 25 and 31 weeks gestation were not significantly associated with gray matter volume (Buss et al., 2010). While this study is the first to indicate that self-reported anxiety in pregnancy is related to distinctive patterns of structural brain development in healthy children, future research is needed to further understand how antenatal and postnatal anxiety affects brain development across the lifespan.

REVIEW OF FUNCTIONAL MRI FINDINGS IN CHILDREN

Depression

To further examine gender-dependent amygdala functional connectivity in children with maternal depressive symptoms in early life, resting-state fMRI was utilized in children aged four and one-half years (Soe et al., 2018). 128 mother-child dyads (57 boys and 71 girls) were included. Depressive symptoms were assessed using the EPDS at 26 weeks gestation and three postnatal months, in addition to the BDI-II at 12, 24, 36, and 54 postnatal months. EPDS and BDI-II scores were standardized. Antenatal maternal depressive symptoms were quantified as a standardized score at 26 weeks gestation, whereas postnatal maternal

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depressive symptoms were quantified as the average of postnatal standardized scores. Maternal depressive symptoms had no association with cortico-striato-amygdala network in boys. However, when comparing antenatal to postnatal maternal depressive symptoms, girls had lower functional connectivity between the left amygdala, right insula, putamen, bilateral subgenual anterior cingulate cortex, and left caudate. They also had lower functional connectivity between the right amygdala, left orbitofrontal cortex, insula, and temporal pole.

Task-based functional MRI was used to study amygdala functioning in six to nine year-old children performing emotional face matching tasks (van der Knaap et al., 2018). Mothers were assessed using the BSI during the antenatal period, between 20 and 25 weeks, and postnatally, when the child was three years old. Nineteen children of mothers with antenatal depression were compared to 20 children of mothers without antenatal depression and found to have significantly increased amygdala responses to negative emotional faces. There were no significant findings when comparing children of mothers with postnatal depressive symptoms three years following birth.

DISCUSSION

There is growing evidence of an association between maternal perinatal depression and anxiety and infant and child neurodevelopmental and psychological outcomes (Bergman et al., 2007; Davis et al., 2007; Hay et al., 2008; O'Connor et al., 2003). This literature builds upon an abundant preclinical literature demonstrating antenatal stress impacts early postnatal behavioral and cognitive development, a process referred to as 'early-life programming' (Frasch et al., 2018). Human studies have begun to examine if associations between perinatal depression/anxiety are causal rather than due to other unmeasured variables/ confounders or genetic continuity(Glover, 2011). Studies using structural and functional MRI to examine infant and child neurodevelopment are currently limited but recently growing in number. Current studies in infants and children suggest that PND is associated with both functional and structural connectivity changes. The most often studied region is the amygdala, which is a key structure of the salience network. The salience network (SN) is a paralimbic-limbic network active both at rest and during task-related activity which integrates sensory, emotional and cognitive information to contribute to social behavior and self-awareness. The SN often includes the dorsal anterior cingulate cortex, anterior insula, amygdala, ventral striatum, dorsomedial thalamus, hypothalamus and the substantia nigra/ ventral tegmental area (Seeley et al., 2007). In addition to neurodevelopmental changes in the salience network brain regions, areas of the default mode network also appear involved. The default mode network is a diffuse, discrete network of connected brain regions most active at rest and involved in monitoring of the external environment and internal mentation. Although studies differ, this network often includes the medial prefrontal cortex, posterior cingulate cortex, precuneus and inferior parietal lobule(Buckner et al., 2008).

The mechanisms underlying these changes are unknown, but may involve endocrine (Nugent et al., 2015), inflammation (Plant et al., 2016), epigenetic (Lester et al., 2018), genetic or gene-environment (Abbott et al., 2018) pathways. Maternal prenatal depression and anxiety may have differential effects on fetal neurodevelopment and infant/child outcomes even though they are highly associated (Ibanez et al., 2015; O'Connor et al., 2002). Additionally,

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antenatal vs. postnatal effects may work through different mechanisms and have differential effects. For example, postnatal maternal mental health and parental stimulation partially account for effects of antenatal anxiety on offspring cognitive function (Ibanez et al., 2015). Effects may also differ by sex (Gifford et al., 2017), so sex differences in the effects of perinatal depression/anxiety must be examined given sex differences in the prevalence of many psychiatric illnesses. The current literature suggests that expression of placental genes regulating fetal glucocorticoid exposure is associated with maternal anxiety and depression(O'Donnell et al., 2012) and that sex differences in placental response could lead to greater fetal glucocorticoid exposure in female but not male offspring(Mina et al., 2015). Other studies indicate that prenatal maternal stress induces changes in the placenta and fetal brain serotonin systems which could be moderated by fetal sex (St-Pierre et al., 2016). These placental alterations could lead to adverse neurodevelopment or a risk for the later development of psychiatric illness.

Additionally, there is an emerging literature focusing on maternal antenatal use of serotonin reuptake inhibitors (SRI) and their effects on fetal brain development (Gingrich et al., 2017; Hanley et al., 2012; Lugo-Candelas et al., 2018). As Table 1 shows, the majority of studies did not measure maternal antenatal psychotropic use: only two studies excluded mothers who used antidepressant medication before or during pregnancy(El Marroun et al., 2016), one study did not exclude mothers on medication, but ran analyses removing any woman who took antidepressants (Lebel et al., 2016), and one study did exclude women on antidepressants, but ended up having no women on antidepressants (Buss et al., 2010). This leaves ten of the fourteen studies reviewed not measuring and/or reporting maternal psychotropic use. This is a critical piece and future studies need to tease out effects due to antenatal medication use versus maternal psychopathology on fetal brain development. Future studies should further examine other variables, e.g. presence of domestic violence, food insecurity or nutrition, smoking/alcohol/substance use, and chronic medical conditions that could confound results.

With improved clinical understanding of both normal neurodevelopment and how PND may shape offspring neurodevelopment, effective prevention and treatment of problems specific to this population will move closer within reach. A better understanding of the pathophysiology of PND will lead to novel treatments which could reduce the impact of maternal PND on offspring development. In addition, early interventions which promote mother-infant bonding and cognitive development may improve developmental outcomes in children exposed to PND, reducing later risk of psychopathology (Fontein-Kuipers et al., 2014). Early treatment of PND, especially in the antenatal period, in concert with meeting the psychosocial needs of pregnant and postpartum women, will ensure that their health, and the health of their offspring, is secure.

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Table 1.

Findings of reviewed structural and functional imaging studies in infants and children of mothers with perinatal depression and anxiety

Structural MRI in Infants				
Depression				
Author (year)	**Method**	**Sample**	**Symptom Rating**	**Findings**
(Rifkin-Graboi et al., 2013)	Structural MRI, DTI	n = 157 (157 neonates near birth, aged 14 days or younger)	Edinburgh Postnatal Depression Scale Antenatal: 26 weeks gestation	High prenatal maternal depression: ↓ FA and ↓ AD in the right amygdala of neonates No difference in amygdala volume Did not report measurement of antenatal psychotropic use
Anxiety				
Author (year)	**Method**	**Sample**	**Symptom Rating**	**Findings**
(Qiu et al., 2013)	Structural MRI	n = 175 (175 neonates near birth, aged 5–17 days 35 infants aged 6 months at follow up)	State-Trait Anxiety Inventory Antenatal: 26 weeks gestation Postnatal: 3 months after delivery	Left hippocampus: - ↓ growth in first 6 months with higher prenatal maternal anxiety - ↓ volume at 6 months with higher postnatal maternal anxiety Right hippocampus: - ↓ growth in first 6 months with higher prenatal maternal anxiety - ↑ growth in first 6 months with higher postnatal maternal anxiety Did not report measurement of antenatal psychotropic use
(Rifkin-Graboi et al., 2015)	Structural MRI, DTI	n = 54 (54 neonates near birth, aged 5–17 days)	State-Trait Anxiety Inventory Antenatal: 26–28 weeks gestation Postnatal: 3 months after delivery Infant Toddler Socio-Emotional Assessment questionnaire	High prenatal maternal anxiety: - No effect on amygdala microstructure - ↓ FA: * right cerebellum * right insular cortex * perception areas (right middle occipital, inferior temporal, bilateral superior temporal, left postcentral) * personal, social, emotional processing areas (right angular region, right uncinate fasciculus, posterior cingulate, parahippocampus) * cognitive and emotional regulation areas (right dorsolateral prefrontal, inferior frontal, inferior fronto-occipital fasciculus) - ↓ AD: Left lateral orbitofrontal region, left inferior cerebellar peduncle - ↑ AD: Genu of the corpus callosum Did not report measurement of antenatal psychotropic use
Functional MRI in Infants				
Depression				
Author (year)	**Method**	**Sample**	**Symptom Rating**	**Findings**
(Qiu et al., 2015)	fMRI, resting-state	n = 24 (24 infants aged 6 months)	Edinburgh Postnatal Depression Scale Antenatal: 26 weeks gestation Postnatal: 3 months after delivery	Higher prenatal maternal depression: ↑ Functional connectivity between the amygdala and areas of the • Emotional regulation network – left insula and bilateral medial prefrontal cortex (anterior cingulate, medial orbitofrontal, ventromedial prefrontal cortices) • Sensory and perceptual network – left superior, middle, temporal cortices • Emotional memory network – left entorhinal cortex

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Structural MRI in Infants				
				Did not report measurement of antenatal psychotropic use
(Posner et al., 2016)	fMRI, resting-state and diffusion MRI, tractography	n = 64 (20 infants with and 44 infants without in utero exposure to prenatal maternal depression, aged 4.1 to 7.5 weeks)	Center for Epidemiological Studies Depression scale Antenatal: 34 and 37 weeks gestation	Resting-state fMRI: ↓ Functional connectivity between amygdala and bilateral dorsal prefrontal cortex Tractography: ↓ Structural connectivity between right amygdala and right ventral prefrontal cortex Did not report measurement of antenatal psychotropic use
Structural MRI in Children				
Depression				
Author (year)	**Method**	**Sample**	**Symptom Rating**	**Findings**
(Lebel et al., 2016)	Structural MRI, cortical thickness, tractography and DTI	n = 52 20 female; 32 male, aged 2.6-5.1	Edinburgh Postnatal Depression Scale was completed once during each trimester and once 2–3 months postnatal.	Higher antenatal maternal depression: ↓ cortical thickness in right inferior frontal and middle temporal region and with white matter tracts emanating from the inferior frontal area Higher postnatal maternal depression: ↓ cortical thickness in superior frontal and with white matter measures of fibers originating from that region Antenatal psychotropic use was controlled for in statistical analyses
(Wen et al., 2017)	Structural MRI and DTI	n = 342 4.5 years of age. 203 (95 boys and 108 girls) had good T1 data 188 (88 boys and 100 girls) had good DTI data.	Edinburgh Postnatal Depression Scale Antenatal: 26 weeks' gestation Postnatal: 3 months The Beck's Depression Inventory-II Postnatal: 1, 2, 3 and 4.5 years postpartum.	MRI Results Higher antenatal maternal depression: ↑ left amygdala volume in girls DTI Results Higher antenatal maternal depression: ↑ right amygdala FA Did not report measurement of antenatal psychotropic use
(Sandman et al., 2015)	Structural MRI	n = 81 (81 children aged 6–9 years old)	Centers for Epidemiologic Studies Depression scale (CES-D) Prenatal: 19, 25, and 31 weeks gestation	Exposure to prenatal maternal depression in utero at • 19 weeks gestation: 8% overall cortical thinning in children aged 6–9 years old • 25 weeks gestation: 19% overall cortical thinning (24% thinning of frontal lobes, most prominent in the right superior, medial orbital, frontal pole) in children aged 6–9 years old • 31 weeks gestation: 7% overall cortical thinning in children aged 6–9 years old Did not report measurement of antenatal psychotropic use
(El Marroun et al., 2016)	Structural MRI	n = 654 327 male, 327 female, mean age of 7.9 years at the MRI assessment, children aged 6–9	Brief Symptom Inventory Parental: 20.6 weeks of gestation Postnatal: 3 years	Higher prenatal maternal depression: ↓ cortical thickness in superior frontal cortex in the left hemisphere ↑ cortical surface area in the caudal middle frontal region. Women with antenatal psychotropic use were excluded from study
(El Marroun et al., 2018)	DTI	n = 636 (322 male, 314 female) children aged 6–9	Brief Symptom Inventory Parental: 20.6 weeks of gestation Postnatal: 3 years	Higher prenatal maternal depression: ↑ mean diffusivity in the left uncinate fasciculus and cingulum bundle ↓ FA in the right cingulum bundle. Women with antenatal psychotropic use were excluded from study
(Lupien et al., 2011)	Structural MRI	n = 38 17 maternal depressive exposure group (7 boys and 10 girls) and 21 were no maternal	Center for Epidemiologic Studies Depression Scale Postnatal: 5, 17, 30, 42, 60, 84, and 156 months	Children exposed to maternal depressive symptoms ↑ left and right amygdala volumes Did not report measurement of antenatal psychotropic use

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Structural MRI in Infants				
		depressive exposure group (10 boys and 11 girls). children aged 10		
Anxiety				
Author (year)	**Method**	**Sample**	**Symptom Rating**	**Findings**
(Buss et al., 2010)	Structural MRI	n = 35 (18 male, 17 female) aged 6–9	10-item pregnancy anxiety scale Prenatal: 19, 25, and 31 weeks' gestation	Maternal anxiety at 19 weeks' gestation: ↓ gray matter volume in the prefrontal cortex, premotor cortex, medial temporal lobe, lateral temporal cortex, postcentral gyrus, and the cerebellum extending to the middle occipital gyrus and the fusiform gyrus. While women with antenatal psychotropic use were not excluded from the study, the final sample included no women with antenatal psychotropic use
Functional MRI in Children				
Depression				
Author (year)	**Method**	**Sample**	**Symptom Rating**	**Findings**
(Soe et al., 2018)	BOLD resting state	n = 128 (57 male and 71 female children aged 4.5 years old)	Standardized Edinburgh Postnatal Depression Scale and Beck's Depression Inventory-II scores Antenatal: 26 weeks gestation Postnatal: average score at 3, 12, 24, 36, 54 months after delivery	In female children exposed to antenatal v. postnatal depression: ↓ Functional connectivity between left amygdala, right insula, putamen, bilateral subgenual anterior cingulate cortex, left caudate ↓ Functional connectivity between right amygdala, left orbitofrontal cortex, insula, temporal pole Did not report measurement of antenatal psychotropic use
(van der Knaap et al., 2018)	BOLD activation, emotional face matching task	n = 31 (15 children aged 6–9 years old exposed to antenatal maternal depressive symptoms 16 children aged 6–9 years old not exposed to antenatal maternal depressive symptoms)	Brief Symptoms Inventory score Antenatal: 20–25 weeks gestation Postnatal: 3 years after delivery	In children exposed to antenatal depression: ↑ amygdala responses to negative emotional faces Did not report measurement of antenatal psychotropic use

Key: MRI: magnetic resonance imaging; DTI: diffusion tensor imaging; FA: fractional anisotropy; AD: axial diffusivity; BOLD: blood oxygen level dependent