CHAPTER TWO

Prenatal stress: Effects on fetal and child brain development

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Abstract

The impact of stress on brain health begins in the womb. Both animal and human studies have found that prenatal maternal stress affects the brain and behavior of the offspring. Stressful life events, exposure to a natural disaster, and symptoms of maternal anxiety and depression increase the risk for the child having a range of emotional, behavioral and/or cognitive problems in later life. These include depression, anxiety, Attention Deficit Hyperactivity Disorder (ADHD), and/or conduct disorders. There is an increased risk for other outcomes also, including preterm delivery and reduced telomere length, possibly indicative of an accelerated life history. The causal role of prenatal maternal stress on the etiology of the neurodevelopmental disorders is supported by large population cohorts, which have controlled for a wide range of potential confounders, including postnatal maternal mood. More recently, research has begun to explore the biological correlates and mediators of these findings. These studies suggest that the hypothalamic pituitary adrenal (HPA) axis plays a role in mediating the effects of maternal stress on the fetal brain. Further, in vivo brain imaging research reports that maternal stress is associated with changes in limbic and fronto-temporal networks, and the functional and microstructural connections linking them.

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The structural changes include cortical thinning and an enlarged amygdala. While these studies have been conducted on smaller sample sizes and could not control for many confounders, the observed brain changes do plausibly underlie many of the emotional, behavioral and cognitive changes found to be associated with prenatal stress.

1. Introduction

Research from the last 20 years has reported that maternal stress during pregnancy is associated with an increased risk of emotional, behavioral and cognitive problems in the offspring. These include symptoms of anxiety and depression, ADHD, conduct disorders (O'Connor, Heron, Golding, Beveridge, & Glover, 2002; O'Donnell, Glover, Barker, & O'Connor, 2014), personality disorders (Winsper, Wolke, & Lereya, 2015), cognitive problems (Pearson et al., 2016), and autism spectrum disorders (Kinney, Miller, Crowley, Huang, & Gerber, 2008). Prenatal stress can also cause changes in several other aspects of development. These include an acceleration of life history, with an increased risk of preterm delivery (Wadhwa et al., 2001), earlier menarche in girls (Duchesne, Liu, Jones, Laplante, & King, 2017), and reduced telomere length suggestive of a shortened lifespan (Entringer, de Punder, Buss, & Wadhwa, 2018). Studies also report alterations in immune function (Hahn et al., 2019), increased risk of asthma (Cookson, Granell, Joinson, Ben-Shlomo, & Henderson, 2009), an altered pattern of the microbiome in the child (Hu et al., 2019), and an altered sex ratio at birth with more girls born than boys (Walsh et al., 2019).

These effects may depend on other factors including the type of stress, the time in gestation that the stress is experienced, and the sex of the fetus (Glover & Hill, 2012). For example, the risk of schizophrenia has been found to be especially associated with severe stress in the first trimester (Guo, He, Song, & Zheng, 2019). Interpretation of these findings has been complicated by the potential confounding influence of genetic and perinatal environmental factors, which also can affect child outcome. The latter, for example, includes exposure to prenatal smoking and/or alcohol, maternal socioeconomic status, education, and postnatal maternal and paternal mood. However, large population studies that have controlled for these putative confounding influences still suggest an additional direct effect of prenatal stress on child outcome (Glover, 2019; King & Laplante, 2005; O'Donnell et al., 2014). Not all children are affected by prenatal stress (O'Donnell et al., 2014), and those that are can be affected in different ways.

This is due in part to the specific genetic vulnerabilities of each child, and gene environment interactions. For example, O'Donnell et al. (2017) showed that the child's working memory at 8 years, and a diagnosis of ADHD at 15 years, were only affected by maternal prenatal anxiety if the child had a specific form of COMT, the enzyme which metabolizes catecholamines.

1.1 Fetal programming

The fetal programming theory proposes that the environment in the womb, during different sensitive periods for specific outcomes, can alter the development of the fetus, with a long lasting effect on the child (Barker, 2003). Barker and colleagues developed this concept in relation to their findings that low birthweight, or growing less well in the womb, is associated with vulnerability to cardiovascular disease and the metabolic syndrome later in life. But the concept also applies to the development of the brain. The brain is particularly plastic, or sensitive to environmental influences, in the fetal and early postnatal period. However, changes in the womb do not mean that they cannot be altered again later. For example, some of the neurodevelopmental effects of prenatal life event stress or raised in utero cortisol can be buffered by sensitive attachment between the mother and the child postnatally (Bergman, Sarkar, Glover, & O'Connor, 2010).

Fetal programming can be part of a "predictive adaptive response" (Gluckman, Hanson, & Spencer, 2005; Hill, Pickles, Wright, Braithwaite, & Sharp, 2019). These predictive responses may be "plastic decisions made by the embryo/fetus/neonate in response to how it interprets the current environment as a predictor of the future one" (Gluckman, Beedle, Buklijas, Low, & Hanson, 2016). The idea is that the developing fetus adapts for future advantage in a predicted later environment, rather than for immediate survival. Many of the fetal brain changes that are observed in response to prenatal stress, may be adaptive in causing changes in behavior that helped survival for our ancestors in a dangerous environment. For example, an increase in the function of the amygdala, may underlie an increase in anxiety which is associated with an increase in vigilance and a more rapid detection of danger. This could be adaptive and help survival in an environment of real external physical danger, such as in the presence of a predator. The accelerated life history may also be adaptive in conditions of external danger, allowing a greater chance of survival and reproduction.

1.2 The fetal brain

The fetal period is critical for the development of the human brain, and the way it develops can be influenced by the environment. The brain grows most rapidly during the fetal period and during the first year after birth; the newborn brain is about 36% of the volume of the adult brain (Pulli et al., 2019). Fetal brain development is divided into three phases: embryonic period (from conception to the eighth gestational week), early fetal period (up to mid-gestation), and late fetal period (from mid-gestation until birth) (Monk, Lugo-Candelas, & Trumpff, 2019). The developing brain contains billions of neurons, most of which are produced by mid-gestation. Throughout the fetal period, brain development involves neurone production, migration, connection, and differentiation. By 20 weeks, the end of the early fetal period, the brain has the necessary structures for mature functioning, although still with a smooth cortical plate. Neuronal migration peaks between gestational weeks 12 and 20. Myelin is first detected at between 20 and 28 weeks, and enhances the speed and accuracy of neuronal communication. During the later fetal period, the second half of gestation, there is specialization in the different brain regions, and connective pathways and synapses start to form. At week 34, approximately 40,000 new synapses are formed every second, a process that continues into early postnatal life (Pulli et al., 2019). The fetal brain is thus under construction throughout gestation, and its development can be affected by the biological signals it receives. The effects of external chemicals such as tobacco, nicotine, cocaine and certain other drugs are well known. Also important are the endogenous biological signals from the mother, including those caused by maternal obesity (Li et al., 2016; Pulli et al., 2019), immune system function, or alterations caused by her mood or stress. The time in gestation that the stress is experienced, and the stage of fetal brain development, may affect the consequences that it has.

2. Effects of prenatal stress on fetal brain development

2.1 Animal studies

Research with a variety of animals including rats (Maccari et al., 2003; Maccari, Krugers, Morley-Fletcher, Szyf, & Brunton, 2014), guinea pigs (Bennett et al., 2017), and monkeys (Schneider et al., 1998, 2017) has shown that inducing prenatal stress in the laboratory can have enduring effects on the neurodevelopment of the offspring, with alterations in both brain and

behavior. Animal studies can control for postnatal effects by cross-fostering the offspring of prenatally stressed mothers to new mothers who were not prenatally stressed. Increased anxiety and impaired cognition have been frequently observed in the offspring, together with enhanced HPA responsiveness (Emack & Matthews, 2011). Sex differences are often reported too (Glover & Hill, 2012). In general, prenatal stress increases anxiety, depression and stress responses in female offspring rather than in male. Males are more likely to show learning and memory deficits. There is accumulating evidence that a range of epigenetic processes including histone modifications, DNA methylation, and small non-coding RNAs are involved (Hamada & Matthews, 2019).

Weinstock (2017) has reviewed studies of the effects of prenatal stress on neurodevelopment and behavior in rats and mice. Stressing pregnant rodents causes changes in offspring behavior analogous to those observed in humans, including increased anxiety and depression. Deficits in spatial learning and memory have also been shown. Lee, Kim, and Goto (2016) have explored some of the complexities in these effects, showing different outcomes depending both on the nature of the stressor and the nature of the postnatal environment. Pregnant mice were subjected to repeated social defeat stress or restraint stress, and the offspring tested for cognitive and affective functioning. Adult mice exposed to prenatal stress exhibited heightened anxiety, while spatial memory was impaired only by prenatal restraint stress, and not social defeat stress. Some of the neurodevelopmental changes associated with prenatal stress could be counteracted by the postnatal environment (Morley-Fletcher, Rea, Maccari, & Laviola, 2003).

Several of the animal studies of the effects of prenatal stress on the offspring have also studied brain structure (Petit et al., 2015; Stevens, Su, Yanagawa, & Vaccarino, 2013) and connectivity (Goelman, Ilinca, Zohar, & Weinstock, 2014) and found changes similar to those observed in humans. Changes in the developmental trajectory of limbic/paralimbic brain regions central to attention/cognitive processing and emotional/social behavior, including the hippocampus and amygdala have been described (Kraszpulski, Dickerson, & Salm, 2006; Monk et al., 2019). In a rat model, prenatal cold stress both inhibited the growth and development of hippocampal neurons, and induced anxiety-like behavior in the offspring (Lian et al., 2019). Hwang, Ku, and Hashimoto-Torii (2019) have reviewed a range of animal studies discussing how prenatal exposure to various types of stress, including alcohol, drugs, and inflammation, disrupts neuronal migration and causes neuronal migration disorders.

2.2 Human studies

Most of the human studies have used magnetic resonance imaging (MRI) to study the effects of prenatal stress on the brain of the child. However, a few have used electroencephalography (EEG) (Adamson, Letourneau, & Lebel, 2018). Maternal depression during pregnancy has been related to right frontal EEG asymmetry in neonates (Diego et al., 2004), which has been suggested to be an indicator of risk for developing negative affectivity and behavioral inhibition. Changes in right frontal EEG activation have also been reported in relation to anxiety symptoms (Field et al., 2003); these types of changes have been associated with withdrawal behavior.

Several types of MRI have been used to examine the effects of prenatal stress on human brain development, including structural, diffusion, and functional MRI. These study the basic structure, white matter connectivity and microstructure, and neuronal activity, respectively (Jenkinson & Chappell, 2018). Neuronal activity can be studied both at rest (resting state fMRI) and during a task (task fMRI). The age of the offspring in the MRI scans has varied considerably, including adolescents or adults (Favaro, Tenconi, Degortes, Manara, & Santonastaso, 2015; Marečková et al., 2018), young children (Buss, Davis, Muftuler, Head, & Sandman, 2010; Wen et al., 2017) and infants or newborn (Lautarescu et al., 2019; Rifkin-Graboi et al., 2013).

Pulli et al. (2019) have reviewed some of these MRI studies and comment that many possible confounders including infant sex, birthweight, and age, and maternal prenatal alcohol, smoking, medication, SES, ethnicity, age and BMI can all affect outcomes and are often not all controlled for. Most of the studies are quite small with well under 100 subjects, and so it was not possible to control for multiple confounders, as the large populations studies, with several thousand subjects, looking at psychometric outcomes (e.g., O'Donnell et al., 2014) have done.

However, these MRI studies do give interesting insights into the structural and functional brain changes associated with prenatal stress, and how these may underlie many of the emotional, behavioral and cognitive changes observed. The findings are generally consistent with the larger population behavioral studies. Increased volume of the amygdala could underlie increases in anxiety or vigilance, and reduced cortical gray matter is consistent with depression and with cognitive problems. With the studies on newborns, any differences were not due to the nature of the postnatal care. Several studies have observed differences between males and females, as in the animals studies.

2.2.1 Structural MRI studies

Structural MRI provides information on the gross anatomy of the brain and investigates how prenatal stress may affect characteristics including local gray matter density, cortical thickness, and the shape and size of anatomical structures. Table 1 summarizes these studies.

The most consistently replicated findings are those of changes in the frontal and temporal lobes, including cortical thinning (Davis et al., 2019; El Marroun et al., 2016; Lebel et al., 2016; Sandman, Buss, Head, & Davis, 2015) and reductions in gray matter volume (Buss et al., 2010; Favaro et al., 2015; Marečková et al., 2018). One study has reported increased gray matter volume (i.e., in the left caudal middle frontal area, El Marroun et al., 2016). Decreased volume of the cerebellum has also been reported (Buss et al., 2010). Findings in the parietal lobe are inconsistent, with two studies reporting decreased volumes (Buss et al., 2010; Marečková et al., 2018) in children and adults, while one study reported increased volume in several areas of the parietal lobe in adolescents (McQuaid, Darcey, Avalos, Fishbein, & VanMeter, 2019). However, the latter findings were part of a study which used a retrospective measure of PTSD which was administered over 10 years after birth, without controlling for postnatal mood.

Changes have also been observed in the limbic system, with increases in amygdala volume reported in both children (Acosta et al., 2019; Wen et al., 2017) and adults (Jones et al., 2019). However no differences were found in neonates exposed to maternal stress (Lugo-Candelas et al., 2018; Rifkin-Graboi et al., 2013). Decreased volume of the hippocampus has been reported in children exposed to maternal anxiety (Qiu et al., 2013); and decreased volume of the anterior cingulate cortex in adults whose mothers experienced stressful life events during pregnancy (Marečková et al., 2018).

Some of these studies also highlight the possible importance of timing in regards to exposure to stress, and the age at which the child is assessed. Buss et al. (2010) reported changes in gray matter volume when children were exposed to maternal stress at 19 weeks gestational age but not at 25 and 31 weeks, while Sandman et al. (2015) reported associations with cortical thinning which were strongest for exposure at 25 weeks. One longitudinal study reported no differences in hippocampal volume at the neonatal time point, but found that the prenatally stressed group showed reduced hippocampal volume at 6 months, suggesting slower growth in the postnatal period (Qiu et al., 2013).

Table 1 Structural MRI studies.

Outcome in offspring	Prenatal stress assessment	Sample	References
No difference in right *amygdala* volume	EPDS (26 weeks)	n = 157 (neonates)	Rifkin-Graboi et al. (2013)
Slower growth in *hippocampal* volume (no difference at birth but smaller volumes at 6 months)	STAI (26 weeks, 3 months)	n = 175 (neonates) n = 35 (6 months)	Qiu et al. (2013)
No difference between untreated depression and controls. SSRI exposed: Increased gray matter volume in right amygdala and right insula.	CESDS, SADS (19/39 weeks)	n = 98 (infants)	Lugo-Candelas et al. (2018)
Cortical thinning (primarily in right *frontal* lobes). Association at 25 weeks	CESDS (19/25/31 weeks)	n = 81 (age 7 years)	Sandman et al. (2015)
No difference for history of depression but no SSRI. SSRI exposed -more likely to have Chiari I malformations	Diagnosis of depression/SSRI	n = 33 SSRI (66 controls), n = 30 history (60 controls), (age 1–2 years)	Knickmeyer et al. (2014)
Cortical thinning in right inferior *frontal* and middle *temporal* regions	EPDS (2^{nd} trimester)	n = 52 (age 2.6–5.1 years)	Lebel et al. (2016)
Greater left relative amygdala volume in girls compared to boys. Association in second trimester	PRAQ-2	n = 27 (age 4 years)	Acosta et al. (2019)
Increased volume in right *amygdala* in girls but not boys	EPDS (26 weeks)	n = 235 (age 4.5 years)	Wen et al. (2017)

Decreased GM in prefrontal cortex, premotor cortex, medial temporal lobe, lateral temporal cortex, postcentral gyrus, cerebellum. Association at 19 weeks	PAS (19,25,31 weeks)	n = 35 (age 6–9 years)	Buss et al. (2010)
Cortical thinning in superior *frontal* cortex in left hemisphere. Larger caudal middle frontal area in left hemisphere	BSI (20 weeks)	n = 654 (age 6–10 years)	El Marroun et al. (2016)
Cortical thinning in *frontal* and *temporal* regions	PSS (average)	n = 74 (age 7 years)	Davis et al. (2019)
Increased volume in *amygdala* in girls	Impact of event scale (quebec ice storm)	n = 68 (age 11 years)	Jones et al. (2019)
Increased GM in posterior *parietal* cortex**,** bilateral intraparietal sulcus, left superior parietal lobule, inferior parietal lobule	PTSD (retrospective)	n = 83 (age 11–14 years)	McQuaid et al. (2019)
Lower overall GM volume in mid-dorsolateral frontal cortex, anterior cingulate cortex and precuneus. *Hippocampal volume* no association with prenatal stress, but with postnatal anxiety	Stressful life events, (20 weeks)	n = 93 (age 23–24 years)	Marečková et al. (2018)
Decreased GM in left medial *temporal* lobe and *amygdala*	Interview	n = 35 (age 25 years), females	Favaro et al. (2015)

BSI, brief symptom inventory; CESDS, centre for epidemiological studies depression scale; EPDS, edinburgh postnatal depression scale; PAS, pregnancy anxiety scale; PRAQ, pregnancy related anxiety; SADS, schedule for affective disorders and schizophrenia; STAI, state trait anxiety inventory; GM, gray matter.

Adapted from Scheinost, D., Sinha, R., Cross, S. N., Kwon, S. H., Sze, G., Constable, R. T., et al. (2017). Does prenatal stress alter the developing connectome? *Pediatric Research, 81*(1–2), 214–226.

Most of this research did not account for relevant potential confounders such as postnatal maternal depression. However, some report that the associations were independent of postnatal stress (Buss et al., 2010; Favaro et al., 2015). Some also found different effects of prenatal stress depending on the sex of the child. Wen et al. (2017) and Acosta et al. (2019) reported larger amygdala volume in girls, but not boys, and Jones et al. (2019) found that when controlling for postnatal factors prenatal stress was associated with a larger amygdala volumes in girls, but not in boys. One study only examined females (Favaro et al., 2015)

Some studies have examined the effects of SSRIs. Babies exposed to SSRIs in utero showed increase gray matter volume in the limbic system (Lugo-Candelas et al., 2018), increased rates of Chiari I malformations (Knickmeyer et al., 2014), and changes in white matter microstructure (Jha et al., 2016) and connectivity (Lugo-Candelas et al., 2018). This highlights the importance of controlling for psychotropic medication in studies of maternal prenatal stress.

A few of these studies have associated the observed brain changes with the behavior of the offspring. Cortical thinning in prefrontal areas of the right hemisphere was associated with externalizing behavior at 7 years (Sandman et al., 2015) and cortical thinning, primarily in frontal and temporal regions, was associated with elevated depressive symptoms in adolescence (Davis et al., 2019). Cortical thinning has been found in major depressive disorder independently of prenatal stress (Suh et al., 2019). The amygdala is a brain structure involved in emotional regulation, and larger amygdala volumes are associated with behavioral disorders. Jones et al. (2019) reported that the subjective stress of being exposed to a Canadian Ice storm in late pregnancy was associated with a larger amygdala volume and this explained higher levels of externalizing behavior at 11 years. When adjusting for postnatal factors, the effect was only significant in girls. There were no associations with internalizing behavior. Acosta et al. (2019) reported that pregnancy-specific anxiety was associated with larger left amygdala volumes, which was linked to more emotional symptoms and overall difficulties.

2.2.2 Diffusion MRI studies

One of the mechanisms by which prenatal maternal stress may affect fetal brain development is by disruption of the white matter circuitry (Sarkar et al., 2014), and this can be shown by diffusion MRI. Diffusion MRI characterizes water molecular motion and is sensitive to the microstructural

properties of tissue, such as axon size, density and myelination, as well as being able to provide information on anatomical connectivity, the wiring of the brain (Jenkinson & Chappell, 2018) White matter has a prolonged maturation which continues from the prenatal period until well after birth and into later life (Dubois et al., 2014). The biological significance of diffusion MRI findings is often unclear, but low anisotropy and high diffusivity are typically believed to reflect lower microstructural organization, reductions in myelination, and axonal damage. Table 2 summarizes the studies which have examined the relationship between maternal prenatal stress and diffusion metrics.

Despite some inconsistencies, the overall results suggest that prenatal stress is associated with white matter changes in limbic and frontal areas

Table 2 Diffusion MRI studies.

Outcome in offspring	Stress assessment	Sample	References
Increased MD, AD, RD in left *uncinate fasciculus* and increased AD in right uncinate fasciculus	STAI, stressful life events (prenatal)	n = 251 (premature neonates)	Lautarescu et al. (2019)
Decreased FA in *right amygdala*	EPDS (26 weeks)	n = 157 (neonates)	Rifkin-Graboi et al. (2013)
Decreased FA in a range of areas (insula, DLPFC, right middle occipital cortex, angular gyrus, uncinate, posterior cingulate, etc.)	STAI (26 weeks)	n = (54 neonates)	Rifkin-Graboi et al. (2015)
Decreased structural connectivity between right *amygdala* and right ventral *PFC*	CESDS (32 weeks)	n = 64 (neonates)	Posner et al. (2016)
No difference for untreated depression. For SSRI exposed: Lower FA, increased MD and RD for multiple fiber bundles	Diagnosis of depression/ SSRI use	n = 54 history, n = 27 SSRI, + matched controls (neonates)	Jha et al. 2016
Decreased neurite density, increased MD, RD, AD in *right frontal* white matter microstructure	EPDS, STAI (28 & 35 weeks)	n = 101 infants	Dean et al. (2018)

Continued

Table 2 Diffusion MRI studies.—cont'd

Outcome in offspring	Stress assessment	Sample	References
No difference between untreated depression and controls. For SSRI exposed: Increased connectivity between right amygdala and right insula	CESDS, SADS (19–39 weeks)	n = 98 infants	Lugo-Candelas et al. (2018)
Decreased RD and MD in white matter emanating from inferior *frontal* area. Did not survive correction for postpartum EPDS	EPDS (11,17,32 weeks)	n = 52 (age 2.6–5.1 years)	Lebel et al. (2016)
Decreased FA, Increased MD in *amygdala-frontal* tract and *cingulum*. Associations for thirrd trimester	EPDS (11,16,31 weeks)	n = 54 (age 4 years)	Hay et al. (2019)
Higher right amygdala FA in overall sample and in girls but not boys	EPDS (26 weeks)	n = 235 (age 4.5 years)	Wen et al. (2017)
Increased FA and *decreased RD* in right *uncinate fasciculus*	Life events (prenatal)	n = 22 (age 7 years)	Sarkar et al. (2014)
Decreased FA in left *cingulum*	Stressful life events (20 weeks)	n = 93 (age 22–23 years)	Marečková et al. (2018)

CESDS, centre for epidemiological studies depression scale; EPDS, edinburgh postatal depression scale; STAI, state trait anxiety inventory; SLE, stressful life events; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity; FA, fractional anisotropy; SSRI, selective serotonin reuptake inhibitors; PFC, prefrontal cortex; DLPFC, dorsolateral prefrontal cortex.
Adapted from Scheinost, D., Sinha, R., Cross, S. N., Kwon, S. H., Sze, G., Constable, R. T., et al. (2017). Does prenatal stress alter the developing connectome? *Pediatric Research, 81*(1–2), 214–226.

in the child's brain. The studies have examined different forms of prenatal stress, and different tracts, and at different ages of the child. Increases in diffusivity (mean diffusivity, radial diffusivity, or axial diffusivity) have been reported in the amygdala (Wen et al., 2017), frontal white matter (Dean et al., 2018; Lebel et al., 2016), amygdala-frontal tracts (Hay et al., 2019) and the uncinate fasciculus (Lautarescu et al., 2019; Sarkar et al., 2014) as well as the cingulum (Hay et al., 2019, Marečková et al., 2018). Reductions in fractional anisotropy (FA) have been reported in a range of limbic and frontal areas (Hay et al., 2019; Rifkin-Graboi et al., 2015).

The finding of changes in the FA of the amygdala have differed depending on the age of the child. Prenatal stress exposure was associated with a decrease in FA in a sample of neonates (Rifkin-Graboi et al., 2013), but an increase in FA in a sample of children (Wen et al., 2017).

The uncinate fasciculus connects the amygdala with the frontal cortex and abnormalities in this tract in children and adults have been associated with antisocial behavior and mood disorders. It is thus of interest that this tract has been shown to be abnormal following prenatal stress in different studies, one in preterm neonates (Lautarescu et al., 2019) and one in 7-year-old children (Sarkar et al., 2014). The effects in this tract were compared in both of these studies with those in another tract, the inferior longitudinal fasciculus, which has not been consistently reported to be involved in social and emotional behavior, and which as predicted, showed no changes in diffusion MRI. Other studies have also reported prenatal stress-related changes in areas including the uncinate fasciculus, with reductions in FA (Rifkin-Graboi et al., 2013, 2015) and higher diffusivity (Dean et al., 2018).

A decrease in neurite density has been observed in the right frontal white matter of infants exposed to prenatal stress (Dean et al., 2018). Posner et al. (2016) found a decrease in structural connectivity between right amygdala and right ventral prefrontal cortex. Lebel et al. (2016) reported an inverse correlation between maternal prenatal EPDS scores and radial diffusivity and mean diffusivity in the white matter of inferior frontal areas in children, but these results lost significance when controlling for postnatal symptoms of depression.

As with the findings reported for structural MRI, sex appears to be an important factor, with maternal stress affecting the brain development of male and female offspring in different ways (Dean et al., 2018). Some studies have reported results observed only in females (Wen et al., 2017), or only in males (Hay et al., 2019).

Hay et al. (2019) have recently shown that white matter microstructure changes in the right amygdala pathway were associated with externalizing behavioral symptoms, and in males these changes in white matter development mediated the relationship between third trimester depressive symptoms and this externalizing behavior.

2.2.3 Functional MRI studies

Changes in the neurodevelopment of offspring exposed to prenatal stress can also be studied by using resting state fMRI (rs-fMRI) or task fMRI. fMRI infers dynamic changes in brain activity by measuring hemodynamic changes

(i.e., BOLD, blood oxygenation level dependent effect) (Jenkinson & Chappell, 2018). Rs-fMRI provides information about spontaneous brain activity and the functional connectivity of brain regions, even if they are not directly linked structurally (Scheinost et al., 2017). Task-related fMRI analyses allow researchers to locate and analyse brain activity in response to a task. Studies of prenatal stress and functional brain connectivity have, as with diffusion MRI, primarily found changes in the associations between the amygdala and other regions (Table 3).

Qiu et al. (2015) have found increased connectivity between the amygdala and several areas including the left temporal cortex, insula, and medial orbitofrontal and ventromedial prefrontal cortices in 6 month old babies exposed to prenatal symptoms of depression. Scheinost et al. (2016) have

Table 3 Resting state functional MRI studies.

Outcome in offspring	Stress assessment	Sample	References
Reduced connectivity between left amygdala and subcortical regions (thalamus, hypothalamus and peristriate cortex)	Retrospective review of chart	n = 26 (preterm neonates)	Scheinost et al. (2016)
Increased negative connectivity between amygdala (right and left) and dorsal prefrontal cortex.	CESDS (32 weeks)	n = 64 (neonates)	Posner et al. (2016)
Increased connectivity between amygdala and several areas (left temporal cortex, insula, bilateral ACC, medial orbitofrontal ventromedial prefrontal cortex)	EPDS (26 weeks)	n = 24 (age 6 months)	Qiu et al. (2015)
Reduced connectivity between left amygdala and bilateral subgenual ACC and left caudate, and between right amygdala and left OFC, insula and temporal pole. In girls but not in boys	EPDS (26 weeks)	n = 128 (age 4.5 years)	Soe et al. (2018)
Increased connectivity between left medial temporal lobe and pregenual cortex	Interview	n = 35 (age 25 years), females	Favaro et al. (2015)

CESDS, center for epidemiological studies depression scale; EPDS, edinburgh postnatal depression scale; OFC, orbitofrontal cortex; ACC, anterior cingulate cortex.

Adapted from Scheinost, D., Sinha, R., Cross, S. N., Kwon, S. H., Sze, G., Constable, R. T., et al. (2017). Does prenatal stress alter the developing connectome? *Pediatric Research, 81*(1–2), 214–226.

reported reduced connectivity between the amygdala and subcortical areas including the thalamus in a sample of preterm neonates and Posner et al. (2016) reported reduced connectivity between the amygdala and the dorsal prefrontal cortex in neonates exposed to prenatal depression. In a study of adults exposed to prenatal stress in utero (Favaro et al., 2015) increased connectivity was observed between the left medial temporal lobe and the pregenual cortex. Soe et al. (2018) found altered functional connectivity between the amygdala and cortico-striatal circuitry in young children after exposure to prenatal depression in girls but not in boys, again emphasizing potential sex differences in the effects of prenatal stress. This pathway is essential for emotional perception and regulation.

There have been fewer task functional MRI studies. Children born to mothers with prenatal depression exhibited increased amygdala responses when presented with pictures of negative emotional faces compared with controls (van der Knaap et al., 2018). Sarkar and colleagues (submitted for publication) have investigated brain networks in 7-year-old children exposed to varying degrees of prenatal life event stress, using a rewarded Continuous Performance Task. They found associations between prenatal stress with later aberrations in brain function in a network of regions crucial for sustained attention and reward. Mennes, Stiers, Lagae, and Van den Bergh (2019) used fMRI to examine activity in response to a task indicative of cognitive control in 20-year-old men. They found an association between prenatal maternal anxiety and brain activity in a number of prefrontal cortical areas, in particular a number of right lateralized clusters. They describe endogenous cognitive control as the ability to generate control over decisions, strategies, conflicting information and so on, from within oneself, without external signals, and suggest that the differences in brain activity that they observed may underlie problems with such cognitive control.

2.3 Different types of stress

Tables 1–3 show that many different types of prenatal stress have been found to be associated with alterations in the brain development of the child. These range from symptoms of anxiety (Mennes et al., 2019; Qiu et al., 2013)' pregnancy-specific anxiety (Acosta et al., 2019; Buss et al., 2010), symptoms of depression (Ong et al., 2019), life events (Sarkar et al., 2014), or the natural disaster of a Canadian ice storm (Jones et al., 2019).

This is similar to the findings with prenatal stress on the offspring's psychopathology, which also have been shown to be altered by many types of stress. An increased risk of schizophrenia is unusual as it is only associated with very severe stress. It has been associated with exposure to an earthquake in China (Guo et al., 2019), the death of a close relative (Khashan et al., 2008), or the Dutch Hunger Winter (Susser et al., 1996), but only with exposure in the first trimester. In schizophrenia there is an altered migration pattern of the neurons, and this migration largely takes place in early to mid-gestation (Monk et al., 2019).

The rest of the brain continues to develop connections all through pregnancy and beyond. Many types of stress can occur together, such as symptoms of anxiety and depression. In some behavioral or cognitive studies where both have been measured together, symptoms of anxiety were associated with more adverse outcomes than those of depression (e.g., O'Donnell et al., 2017). There is some evidence that pregnancy-specific anxiety (worry about the outcome of the pregnancy for the mother or the child) is a distinct syndrome (Huizink, Mulder, Robles de Medina, Visser, & Buitelaar, 2004), and has some effects independently of other forms of anxiety or stress. These include altered methylation pattern of the glucocorticoid receptor in the newborn cord blood (Hompes et al., 2013), and the pattern of the microbiome in the newborn meconium (Hu et al., 2019). It has also been found to be associated with temperamental variation in young infants (Huizink, de Medina, Mulder, Visser, & Buitelaar, 2002) and their cognitive development (Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2003). Buss et al. (2010) have shown that high levels of maternal pregnancy-specific anxiety were associated with lower inhibitory control in girls and lower visuospatial working memory performance in both boys and girls. They found that neither state anxiety nor depression explained any additional variance after accounting for pregnancy-specific anxiety (Buss, Davis, Hobel, & Sandman, 2011). No studies have so far determined the cause of this specific effect of pregnancy-specific anxiety, independently of other symptoms of anxiety. It would be interesting to investigate whether it was associated with previous experiences of the mother, including early trauma or abuse.

In general, it is not known whether different types of stress have any different effects on early brain development. It is possible that this may underlie some of the inconsistencies in the effects of prenatal stress in the literature, but this is still unknown.

3. Underlying mechanisms

Some of the biological mechanisms for the effects of prenatal stress on the later behavior and cognition of the offspring are starting to be understood (Monk et al., 2019). Based on work on animal models, many of the studies of underlying mechanisms in humans have focused on the HPA axis and the role of cortisol. In rodent models, removing the adrenal gland or injecting corticosteroids in the pregnant dam can block or replicate some of the effects of prenatal stress on the offspring (Zagron & Weinstock, 2006). This is the most studied system in humans also, although many other pathways are likely to be involved.

Maternal exposure to synthetic glucocorticoids during pregnancy is associated with poorer mental health in childhood and adolescence (Khalife et al., 2013). Bergman et al. (2010) showed that altered cognitive function in infants was associated with higher levels of cortisol in the amniotic fluid. The children of mothers who had consumed high levels of liquorice during pregnancy (which contains a natural inhibitor of 11-β-hydroxysteroid dehydrogenase type II (11β-HSD2), the enzyme which converts cortisol to its inactive form cortisone in the placenta), and were thus exposed to higher levels of cortisol in utero, were over three times more likely to show ADHD symptoms, as well as lower IQ scores and earlier puberty (Raikkonen et al., 2017).

The function of the HPA axis can be changed by many different types of stress, and this may explain why such varied stressors can be involved in the fetal programming of the brain. However, it is not known which stress-induced biological changes in the mother are involved. Maternal cortisol responses may be part of the mechanism, but not the major part. Unlike in most species, in humans, the placenta releases large amounts of CRH into the maternal circulation in all mothers as pregnancy advances, and this in turn releases cortisol. This makes the mother's HPA axis less sensitive to external stress as gestation increases (Bleker, Roseboom, Vrijkotte, Reynolds, & de Rooij, 2017). Her immune system and proinflammatory cytokines may well be involved but more evidence is needed for this. A history of early maternal trauma has been associated with elevated levels (Blackmore et al., 2011).

However, the fetus may be exposed to raised levels of cortisol independently of changes in maternal levels, when the mother is feeling stressed, because of increased passage of cortisol through the placenta.

Glover, Bergman, Sarkar, and O'Connor (2009) have found a greater correlation between maternal and amniotic fluid levels of cortisol when the mother had higher levels of anxiety. The fetal levels will thus also be higher if the maternal levels are. Several research groups have found that prenatal stress or anxiety is associated with an altered expression of several enzymes in the placenta, including a down regulation of 11 b-HSD2, the enzyme which metabolizes cortisol (e.g., O'Donnell et al., 2012).

Only a few studies have associated maternal or amniotic fluid cortisol levels with the brain structure of the child. Buss et al. (2012) have looked at associations with maternal prenatal cortisol levels. After accounting for the effects of some potential confounding pre- and postnatal factors, higher maternal blood cortisol levels in earlier but not later gestation were found to be associated with a larger right amygdala volume in 7-year-old girls but not in boys. Also, higher maternal cortisol levels in early gestation were associated with more affective problems in the girls, and this was mediated, in part, by the amygdala volume. Graham et al., 2019 have found that higher maternal cortisol levels were associated with stronger amygdala connectivity to brain regions involved in sensory processing and integration, as well as the default mode network in girls, and with weaker connectivity to these brain regions in boys. Sandman et al. (2018) examined the association between maternal blood CRH levels during pregnancy and the brain structure of the child at 7 years. They found an association between CRH levels throughout pregnancy and cortical thinning, primarily in the temporal and frontal regions. These associations were also stronger in girls. The authors were not able to show a causal link between the CRH levels and the cortical thinning, but propose it as a possibility. Sarkar and colleagues (submitted for publication) probed brain networks in 7-year-old children exposed to varying degrees of prenatal life event stress, using a rewarded Continuous Performance Task. They also had measures of amniotic fluid cortisol. The associations observed with the cortisol were overlapping but different from those with the life event stress, suggesting that exposure to higher levels of cortisol in utero may explain some, but not all, of the brain changes.

Even though most of the research on the underlying biological mechanisms for the effects of prenatal stress on fetal brain development has been on the HPA axis, the immune system is very likely to be involved also. Rasmussen et al. (2019) have shown that maternal interleukin-6 concentration during pregnancy was associated with variations in the frontolimbic circuitry in the newborn, and this in turn correlated with the infant's cognition at 12 months.

4. Conclusions

There is considerable evidence that prenatal stress plays a causal role in a range of neurodevelopmental disorders. The brain changes underlying this are starting to be uncovered although many questions remain. Do different types of stress have different effects? To what extent are boys and girls affected differently? And how can prenatal effects on the brain be altered postnatally?

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