How Prenatal Exposures Shape the Infant Brain: insights from infant neuroimaging studies

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Key words: brain development, perinatal, environmental, pregnancy

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Abstract

Brain development during the prenatal period is rapid and unparalleled by any other time during development. Biological systems undergoing rapid development are at higher risk for disorganizing influences. Therefore, certain prenatal exposures impact brain development, increasing risk for negative neurodevelopmental outcome. While prenatal exposures have been associated with cognitive and behavioral outcomes later in life, the underlying macroscopic brain pathways remain unclear. Here, we review studies investigating the association between prenatal exposures and infant brain development focusing on prenatal exposures via maternal physical health factors, maternal mental health factors, and maternal drug and medication use. Further, we discuss the need for studies to consider multiple prenatal exposures in parallel and suggest future directions for this body of research.

Infant neuroimaging for understanding prenatal exposures.

Prenatal exposures (e.g., maternal physical health, maternal mental health, or maternal medication and drug use) pose risk for future neurodevelopmental complications, such as deficits in language and social development, in offspring [1-5]. However, risk alone does not capture individual differences in outcomes—i.e., of those exposed, some never develop deficits. The human brain experiences its most rapid development *in utero* and in the first 20 postnatal weeks [6-8] (see **Box 1**) with an extraordinarily complex array of biological processes, which potentially make the brain highly vulnerable to insults (see **Box 2**). Thus, brain development likely mediates in the associations between prenatal exposures and developmental outcomes. Assessing the impact of prenatal exposures on brain development, and its role in mediating risk, has the potential to elucidate individual differences in developmental outcomes. Accordingly, there is a wealth of studies demonstrating associations between prenatal exposures and brain structure and function in children, adolescents, and adults [9-12].

With its recent increased feasibility [6, 7], infant neuroimaging studies have become the standard for assessing the impact of prenatal exposures on brain development. Acquiring data soon after birth minimizes postnatal influences on individual differences [7], allowing for altered brain development to be attributable largely to prenatal, rather than postnatal, factors. These correlations between prenatal exposures and the infant brain have potential to serve as brain mediators for identifying individual differences in risk of poorer developmental outcomes [13, 14] before behavioral deficits are present [15-18]. Nevertheless, this rapidly growing body of research is nascent.

In this review, we examine the existing studies linking prenatal exposures to variations in brain structure and function using infant neuroimaging (e.g., structural, diffusion weighted,

functional MRI) during the first year of life. We present these studies grouped by exposure type (e.g., maternal physical health, maternal mental health, drug and medication exposures; see **Figure 1** and **Table 1**). Within each exposure type, we present the brain outcomes for a specific exposure (e.g., prenatal, maternal stress), followed by behavioral outcomes for that specific exposure. Then, for exposure type, we present commonalities across each of the specific exposures for that type. Unless otherwise noted, all infants in these studies were scanned around 1 month of postnatal age (**Table 1**). Next, we highlight preliminary findings suggesting that alterations in the infant brain mediate the association between exposures and developmental outcomes. Further, we discuss the need to consider how fetal sex moderates the impact of exposures and to explore unique and shared associations between multiple exposures. Finally, we suggest future directions for this body of research.

Maternal physical health exposures.

Maternal inflammation: Maternal inflammation is a commonly studied exposure in preclinical models that has recently been investigated in humans. Inflammatory cytokines and proteins are activated from a wide range of events (e.g., infection, stress, poor physical health) and can cross the placenta, making them a potential common mechanistic pathway underlying the association between maternal inflammation and infant brain development (see **Multiple exposures**). While many inflammatory cytokines and proteins exist, the impact of only two—interleukin-6 (IL-6) and C-reactive protein (CRP; see **Glossary.**)—have been studied using infant neuroimaging. *IL-6* Higher maternal IL-6 levels during pregnancy related to larger right amygdala volume and stronger bilateral amygdala functional connectivity with sensory processing/integration, salience detection, and memory regions [19]. Using the same sample, maternal IL-6 levels correlated with greater functional connectivity within the salience network,

subcortical-dorsal attention networks, subcortical-cerebellar networks, and visual-dorsal attention networks [20]. Maternal IL-6 level (averaged across pregnancy) also inversely correlated with fractional anisotropy (FA) (see **Glossary**) of the uncinate fasciculus and positively correlated with FA increase in this tract across the first year of life [21]. In an independent study, higher maternal IL-6 levels during the 3rd trimester corresponded to greater connectivity between the left insula (a key node in the salience network) and medial prefrontal cortex and to weaker connectivity between the dorsal anterior cingulate cortex (dACC; another key node in the salience network) and dorsomedial prefrontal cortex [22]. *CRP* Finally, in single study, higher maternal CRP associated with greater connectivity between left insula and right temporoparietal junction and between the right insula and basal ganglia [22].

Importantly, these associations between maternal inflammation during pregnancy and infant brain structure and function are correlated with developmental outcomes in infancy. The larger right amygdala volume and stronger left amygdala functional connectivity further correlated with poorer impulse control in infants measured at 24 months of age [19]. The greater change in FA in the uncinate fasciculus correlated with lower cognitive scores on the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) at 12 months of age [21]. Lastly, the greater connectivity between the dorsal anterior cingulate and medial prefrontal cortex corresponded to lower cognitive scores on the BSID at 14 months of age [22]. Additionally, strong negative relationship between IL-6 and both cognitive scores at 12 months and working memory at age 2 were observed [19, 21]. In contrast, higher maternal IL-6 and CRP during the 3rd trimester related to higher cognitive scores (BSID-III) in toddlers at 14 months of age [22].

Maternal Adiposity and Nutrition: There is growing evidence of maternal adiposity (body fat) and nutrition during pregnancy being linked to variations in infant brain development. Infants born to overweight or obese mothers exhibited altered functional connections located in sensory, reward, cognitive, and motor regions [23] and weaker connectivity between the dACC and prefrontal cortex (PFC) [24]. Infants from obese mothers also had lower FA values in multiple white matter regions [25]. In addition, higher pre-pregnancy body-mass index (BMI) associated with higher local thalamic connectivity and lower fronto-thalamic connectivity in neonates [26]. Related to maternal adiposity, variations in maternal nutrition, such as micronutrient iron, have been linked to infant brain development. Self-reported prenatal iron intake and cord blood ferritin levels had an inverse correlation with FA values in cortical gray matter [27]. To date, studies linking maternal adiposity and nutrition during pregnancy, infant brain development, and developmental outcomes are lacking.

Commonalities: Across the studies of maternal physical health factors, several commonalities emerge. Across studies, maternal inflammatory proteins during pregnancy were related regions of the salience network and the amygdala [19, 20, 22]. For studies of prenatal maternal obesity, associations were consistently found between maternal BMI and regions involved in reward processing and evaluation [23, 26].

Maternal mental health exposures.

Maternal stress: The experiencing stress is universal and ranges from normal and elevated levels for an individual [28]. Prenatal maternal stress has been linked to infant brain development using numerous measures, (e.g., self-report, biological, and social support). *Self-report measures* Using self-report measures, increased maternal perceived and pregnancy-specific stress in the 3rd trimester was associated with weaker hippocampal–cingulate cortex and

stronger hippocampal–temporal lobe functional connectivity in offspring [29]. Exposure to prenatal, maternal stress also corresponded to weaker connectivity between the left amygdala and thalamus, hypothalamus, and peristriate cortex in infants born preterm, than in infants born extremely preterm that did not have prenatal maternal stress exposure [30]. Additionally, preterm infants exposed to prenatal, maternal stress exhibited weaker connectivity between the left amygdala and thalamus, hypothalamus, and peristriate cortex compared to preterm infants unexposed to prenatal maternal stress [30]. Finally, self-reported prenatal stress was associated with weaker functional connectivity, but greater structural connectivity between the amygdala and medial prefrontal cortex in infants [31]. *Cortisol* Cortisol is an important stress hormone in the body, can cross the placenta, and is a well-studied biological marker of psychological stress [18]. Higher prenatal maternal cortisol levels in the 2nd trimester has been associated with weaker hippocampal–cingulate cortex and stronger hippocampal–temporal lobe functional connectivity [29]. For female infants, higher prenatal maternal cortisol levels were related to stronger bilateral amygdala functional connectivity with cortical regions; whereas, for male infants, high prenatal maternal cortisol levels were related to weaker bilateral amygdala functional connectivity with the same regions [18]. Similarly, sex differences in the association between prenatal maternal cortisol and infant amygdala microstructure and structural connectivity have been observed [32]. *Social Support* Socioeconomic disadvantage can also contribute to higher levels of maternal psychosocial stress. Infants born to mothers experiencing lower socioeconomic status had greater volumes in the right occipital lobe, left temporal pole, left inferior frontal lobe, and ACC [33] and altered striatal and ventrolateral PFC connectivity [34].

As with maternal inflammation, *in utero* stress exposure and corresponding neuroimaging findings have been associated with later developmental outcomes. Higher prenatal maternal

cortisol and stronger right amygdala–supramarginal gyrus functional connectivity was related to higher internalizing symptoms at 24 months using the Child Behavior Checklist [18]. Additionally, lower maternal perceived stress and higher infant functional connectivity between the right hippocampus and dACC was associated with higher infant memory score at 4 months [29]. Regions associated with prenatal maternal socioeconomic status further correlated with externalizing symptom and behavioral inhibition at 2 years, measured by the Infant-Toddler Social Emotional Assessment [34] and poorer language scores [33].

Maternal depression: Maternal depression during pregnancy represents another common maternal, mental health exposure studied with infant neuroimaging. Several studies have been interested in potential intergenerational transmission of maternal depression and therefore focused on the amygdala for its role in socioemotional processes [35]. Maternal depressive symptoms during pregnancy have been associated with the microstructure of the right amygdala in neonates, such that greater symptoms correspond to lower fractional anisotropy and axial diffusivity [36]. In addition, prenatal maternal depressive symptoms were associated with greater functional connectivity between the amygdala to left temporal cortex, insula and bilateral ACC, medial orbitofrontal cortex and ventromedial PFC [37] and greater negative connectivity between the amygdala and dorsal PFC [38] in offspring. Finally, correlations between depressive symptoms during pregnancy and bilateral amygdala volume were only found in male infants [39] (see **Sex differences.** for further discussion).

In addition to the amygdala, the hippocampus is a region of interest for neuroimaging studies of prenatal exposure to maternal depression due to its putative role in depression [40]. Prenatal, maternal depressive symptoms have been associated with lower hippocampal volumes in infants [41]. Neonatal *FKBP5*, a gene involved in stress response, moderated this association

[41]. Higher prenatal maternal depressive symptoms were also correlated with weaker hippocampal–cingulate cortex and stronger hippocampal–temporal lobe functional connectivity [29]. Additionally, infant genotype served as moderator of the relationship between prenatal, maternal depression and infant amygdala and hippocampus morphometry [42].

While several studies have found associations between prenatal maternal depression and infant brain structure and function, there are a dearth of studies further linking maternal depression and infant brain development to developmental outcomes.

Maternal anxiety: Commonly co-occurring with stress and depression [43, 44], infant neuroimaging studies have also assessed the impact of maternal anxiety. Greater maternal anxiety during pregnancy was correlated with lower FA and axial diffusivity but not gray matter volume in the right amygdala in neonates [45]. Prenatal, maternal distress (measures as a composite of depression and anxiety symptoms) was associated with greater brain diffusivity and lower infant neurite density [46]. While no relationship between prenatal, maternal anxiety and hippocampal volume were observed at birth, higher prenatal, maternal anxiety was related with slower bilateral hippocampal volume growth from birth to 6 months of age [47]. Finally, a gene by environment interaction has been reported for prenatal maternal anxiety symptoms and amygdala and hippocampal volumes in neonates. Variants in the brain-derived neurotropic factors gene Val66Met moderated the impact of anxiety during pregnancy on amygdala and hippocampal volumes in infants [48], suggesting epigenetic modifications. Like maternal depression, there are a lack of studies examining how prenatal maternal anxiety and infant brain development are further associated with developmental outcomes.

Commonalities: In sum, studies of *in utero* exposure to maternal mental health factors and infant brain development have focused on prenatal maternal distress (see **Glossary**). Given

the overlap of stress, anxiety, and depression, common affected circuits (e.g., the amygdala [30, 36-38] and hippocampus [29, 41, 49] have been observed (see **Multiple exposures** for more on this). Outside of maternal distress, a lack of investigations of other mental health disorders—for example, prepartum psychosis—exist. Common among several of the studies was the evidence of the variations in infant brain development being further associated with developmental outcomes, such as impulse control or internalizing symptoms [18, 21].

Maternal drug use and medication exposures.

Drug exposures: Common forms of prenatal drug exposure include nicotine (primarily cigarette smoking), alcohol, cannabis, cocaine, and opioid use [50]. While legal, use of alcohol and smoking during pregnancy is controversial and, generally, not recommended due to detrimental effects on offspring [51]. *Smoking* Frontal lobe and cerebellar volumes were smaller in very low birth weight and gestational age infants exposed to smoking *in utero* [52]. In contrast, larger temporal and occipital lobes were also observed for prenatal smoking exposure [53]. Similarly, in infants with poly-drug exposure, functional connectivity in the lateral and medial frontal lobes associated with prenatal nicotine exposure [54]. *Alcohol* Infants with prenatal alcohol exposure had lower total gray matter volume and wide-spread lower regional gray matter volume [53, 55]. Prenatal alcohol exposure also corresponded to altered connectivity with the motor cortex [54].

In addition to legal drugs, the long-term developmental consequents of prenatal exposures to illicit drugs (cannabis, cocaine, heroin) is well-characterized [51]. *Cannabis* Lower gray matter volume in the frontal and occipital lobes, higher FA in several tracts, and higher N-acetylaspartate (NAA; a marker of neuronal injury) concentrations in the white matter was associated with prenatal cannabis exposure [53]. In infants with poly-drug exposure, reduced

connectivity in caudate and cerebellum were specific to prenatal cannabis exposure [56]. Prenatal cannabis exposure also correlated with altered PCC and left frontal, temporal, and parietal lobe connectivity [54]. *Cocaine* Infants that had experienced prenatal cocaine exposure had lower total gray matter volume and greater cerebrospinal fluid volume compared to infants without prenatal cocaine exposure [57]. Wide-spread decreased gray matter volume across the cortex, greater FA in several tracts, and greater NAA concentrations in the white matter were related to prenatal cocaine exposure [53]. Prenatal cocaine exposure correlated with hyperconnectivity between the thalamus and frontal regions [58], with functional connectivity in the supplementary motor area and medial frontal lobe [54], and between the frontal lobe and the amygdala and the insula [59]. *Opioids* Additionally, prenatal opioid exposure associated with functional connectivity in middle frontal and angular gyrus [54].

Finally, studies are beginning to examine how variations in infant brain structure and function associated with prenatal drug exposure further associated with developmental outcomes in infancy. Anatomical correlates of prenatal exposure to cannabis and cocaine associated with social communication and adaptive behavior scores on the Vineland Adaptive Behavior Scales at 12 months [53]. Infant connectivity related to various prenatal drug exposures explained a substantial amount of variance in cognitive, language, and motor outcomes at 3 months [54, 58]. Similar studies are needed to characterize how infant brain measures that are related to prenatal drug exposures lead to outcomes later in development.

Maternal medications: *In utero* exposures to maternal medications have been linked to cognitive and behavioral difficulties later in life [60, 61]. In particular, exposure to selective serotonin reuptake inhibitors (SSRIs), methadone, and anesthesia during labor and delivery have been studied with infant neuroimaging. These studies are critical as there are important

considerations regarding weighing the potential developmental consequences of using or not using the medication as the condition the medication is treating may also be harmful for brain development (e.g., maternal depression or opioid use). *SSRIs* are commonly used—even during pregnancy—to treat depression, as well as other neuropsychiatric disorders, and have been shown to impact infant brain development. For infants exposed prenatally to SSRIs, mean and radial diffusivity was greater in several white matter tracts [62] and structural connectivity was greater between the right amygdala and right insula [63]. Prenatal exposure to SSRIs associated with gray matter volume expansions in the right amygdala and right insula [63] and connectivity in the visual cortex [54]. *Methadone* is a long-acting full opioid agonist used to treat opioid use disorder. Given the recent opioid use crisis, there is great interest in understanding how treatment during pregnancy may impact offspring development. Infants experiencing prenatal methadone exposure exhibited lower gray matter volume in the frontal lobe and greater volume in the temporal lobe and the posterior cingulate [53]. Higher mean diffusivity was observed in the superior longitudinal fasciculus and other tracts of infants that had experience prenatal methadone exposure [53, 64]. *Anesthesia* during labor and delivery is another common medication that is associated with developmental disorders [65] and may impact infant brain development. Neonates exposed to maternal anesthesia had greater volumes in bilateral frontal and occipital lobes and the right posterior portion of the cingulate gyrus [66]. Further, longer durations of exposure were positively correlated with occipital lobe volumes.

There are few studies linking variations in the brain associated with maternal medication use during pregnancy to developmental outcomes. Brain regions associated with anesthesia exposures correlated with expressive language on the BSID-III at 12 months [66]. Overall,

additional work linking prenatal mediation exposure to brain and developmental outcome is needed.

Commonalities: Broadly, there are both shared and unique structural and functional associations with infant brain development for specific drug and maternal medication exposures [53, 59]. For the studies that examined multiple exposures in the study, correlations with prefrontal regions were found to be common among prenatal drug and medication exposures. Shared among several types of drug exposures were associations with thalamic connectivity [55, 58, 62, 67]. Also, several of the studies found associations in the salience network [55, 56, 63]. These findings are interesting due to the role of these networks in drug addiction, which may suggest a pathway for intergenerational transmission [68, 69].

Evidence that the infant brain mediates exposure and later outcomes.

A major goal of studying of prenatal exposures with infant neuroimaging is to find brain mediators of individuals differences in risk of neurodevelopmental disorders before deficits are present. Thus, studies are explicitly testing whether infant brain structure and function mediates the associations between prenatal exposures and infant developmental outcomes with promising results [19, 21, 22, 29, 34, 38, 53] (See **Figure 2** for an overview of statistical mediation). Evidence of infant brain development mediating associations between prenatal exposures and developmental outcomes has been found for maternal inflammation [19, 21]. Striatum-frontopolar connectivity mediated the relationship between SES and both externalizing symptom and behavioral inhibition at age 2 [34]. Slow cortical maturation in prefrontal regions mediated the association between multiple types of drug exposures and lower social communication and adaptive behavior scores at 12 months of age [53]. Similarly, several functional connections (particularly in the prefrontal regions) mediated the associations between prenatal drug exposure

and the language outcomes measured at 3 months of age [54]. Neonatal brain morphometry mediated the relationship between anesthesia exposures during delivery and expressive language at 12 months [66]. Testing infant brain development as a mediator of associations between prenatal exposures and developmental outcomes has the potential identify potential underlying pathways for future studies as well as potential pathways for intervention.

Sex differences.

Evidence suggests that, for some prenatal exposures, the association with brain development may be moderated by sex. These findings primarily have been found in animal studies [70-72]. However, evidence in humans is emerging, particularly suggesting the interaction effects of maternal mental health and sex on the amygdalar development. Correlations between depressive symptoms and bilateral amygdala volume was only found in males [39]. For females, higher prenatal maternal cortisol corresponded to greater amygdala functional connectivity and greater internalizing behaviors. This pattern was reversed in males [18]. Additionally, amygdala microstructure associations with prenatal maternal cortisol was only observed in males, while connectivity associations were only observed in females. Similarly, increased maternal distress related to increased FA in the stria terminalis in males, but decreased FA in females [46]. Finally, when studying prenatal drug exposure, only males exposed to methamphetamine/tobacco had lower FA and higher diffusivities in the superior and posterior corona radiate; while, only females exposures methamphetamine/tobacco or tobacco had lower FA in the anterior corona radiation [73]. These studies suggest that biological sex is an important consideration for studies of prenatal exposures and highlight the need for future studies to examine mechanisms underlying these sex-specific associations.

Multiple exposures.

Prenatal exposures do not occur in isolation. Multiple exposures are common [74, 75] and complex interactions exist among them. Effects of multiple exposures can be shared or unique. In other words, two exposures may activate the same or different mechanistic pathways to impact offspring brain. For example, inflammatory pathways can be activated by a majority of exposures discussed above. Further, there are common anatomical and functional correlates across different prenatal drug/medication exposures [53, 54]; and prenatal, maternal distress appears to commonly disrupt the development of the amygdala and hippocampus [29, 30, 36-38, 41, 49]. However, these apparent shared patterns need to be interpreted cautiously and formally tested. Many of the published analytical approaches focused on particular regions of interest (such as the amygdala and hippocampus) and, thus, may bias results to apparent similar brain alteration. Data-driven, whole-brain approaches, like [20], can mitigate biases in results caused by focusing on a single region. In addition, when explicitly tested, maternal self-report stress, depressive symptoms, and cortisol all associated with hippocampal connectivity, but each associated with a different specific functional connection to the hippocampus [29].

Effects of multiple exposures can also be viewed as additive or, even, protective. For example, maternal medication has been associated with altered brain development in offspring (such as SSRI's [63]), but these medication may protect the fetus from altered brain development associated with exposures related to maternal physical and mental health. Regarding additive effects, infants that had experienced both prenatal stress and preterm birth (also a significant stressor) showed greater reductions in amygdala-thalamus functional connectivity than those experiencing a single exposure [30]. Additionally, SSRI use during pregnancy strengthened the association between prenatal cocaine exposure and neonate functional connectivity [58].

Nevertheless, the majority of current studies only include a single exposure. To fully understand the associations between prenatal exposures and infant brain development, it will be critical to disentangle and characterize the effects of multiple prenatal exposures that occur in parallel.

Future directions.

We suggest that future directions for research on the association between prenatal exposures and infant brain development could include fetal scanning, longitudinal data, large neuroimaging datasets, and machine learning/predictive modeling.

Most existing studies of prenatal exposures measure infant brain development in neonates to attempt to mitigate postnatal factors. However, fetal neuroimaging is an emerging technique for exposure studies as it can examine brain development *in utero* [76]. To date, only prenatal lead [77], maternal BMI [78], gestational diabetes [79], and maternal distress [80, 81] exposures have been investigated with fetal neuroimaging, leaving this line of research largely unexplored.

Additionally, longitudinal studies that collect exposure information at multiple time points during pregnancy and infancy will be critical to fully characterize the impact of prenatal exposures. Exposures may have different impact depending on the gestation age of the fetus at the time of exposures. For example, 3rd—but not 2nd—trimester maternal distress correlated with infant hippocampal connectivity [29]. Additionally, exposures may not impact the brain during the new-born period, but rather the growth over the first year of life [47]. Ultimately, a better understanding of the timing effects of the exposure and the critical periods of brain development these exposures alter will be needed to inform pre and postnatal care.

While laborious and expensive to conduct—especially in infants, “big data” has the potential to answer many questions that are currently intractable [82]. Presently, most prenatal

exposures studies using infant neuroimaging data have samples with fewer than 100 participants. Given potential overlap of exposures (see **Multiple exposures.**), larger samples will be needed to disentangle common and unique brain pathways associated with different exposures. To make these larger datasets a reality, large-scale, infant neuroimaging studies, such as the Baby Connectome Project and Developing Human Connectome Project [83, 84], will help facilitate the use of "big data" in investigating the impact of prenatal exposures on the developing brain.

Using machine learning to investigate associations between prenatal exposures and infant brain development is an important future direction. Traditional approaches (e.g., correlation) tend to over-fit the data and generalize poorly to other studies [85]. This is problematic if the goal is to find brain markers of prenatal exposures that are robust across studies. Machine learning mitigate data overfitting and poor generalization using internal (i.e., cross-validation) and external validation [85, 86]. These validation steps often require larger datasets as models are typically 'trained' in one dataset (or one portion of the dataset) and 'tested' in another [87]. While these methods are increasing in popularity in neuroimaging, they are not readily used to investigate prenatal exposures.

Concluding remarks.

Across a multitude of prenatal exposures, there is strong evidence suggesting prenatal exposures shape infant brain development. Converging evidence from infant neuroimaging highlight their associations with variations in brain development as possible brain pathway underlying associations between prenatal exposures and risk for negative neurodevelopmental outcomes. Understanding these complex associations, as well as the role of multiple exposures in brain development, will be critical to guide interventions aimed at mitigating prenatal exposures and associated negative outcomes later in life.

Acknowledgements

This work was supported by the National Institute of Mental Health (grant Nos. MH093677, MH117983, and MH018268). AJD is supported by T32MH18268. We thank Corey Horien, Max Rolison, Silvia Gini, and Link Tejavibulya for their helpful comments on initial drafts of this work.

Glossary

Big data: larger, more complex data sets than typically used in a field of study.

Body mass index: (BMI) a person's weight in kilograms divided by the square of height in meters; a high BMI can be an indicator of obesity.

Connectome: a map of the brain's connections, rendered as a connectivity matrix or network [91].

C-reactive protein: (CRP): an acute phase reactant and another marker of immune activation made by the liver that is found in blood plasma. Its circulating concentrations rise in response to inflammation.

Distress: an umbrella concept encompassing multiple negative psychological states including stress, anxiety, and depression.

fMRI: (functional magnetic resonance imaging) a procedure that uses MRI (magnetic resonance imaging) technology to measure and map brain activity by detecting changes in the magnetization difference between oxy- and deoxyhaemoglobin [90].

Fractional anisotropy: (FA) is a scalar value between zero and one that describes the degree of anisotropy of a diffusion process. A value of zero means that diffusion is isotropic, i.e. it is unrestricted (or equally restricted) in all directions. FA is a common measure of white matter organization derived from diffusion weighted imaging in which values closer to 1 correspond to axonal density/higher myelination.

Functional connectivity: is the temporal correlation in the high amplitude, low-frequency spontaneously generated blood oxygenation level dependent signal brain regions [92]. Regions are considered to have high functional connectivity if they have a high temporal correlation [93].

IL-6: (interleukin-6) is a proinflammatory cytokine and marker of immune activation. It helps regulate immune responses, which makes testing it potentially useful as a marker of immune system activation.

N-acetylaspartate (NAA): the second-most-concentrated molecule in the brain and a putative marker of neuronal injury

Overfitting: is a modeling error that occurs when a function is too closely fit to a limited set of data points.

Salience network: a large-scale brain network anchored in the dorsal anterior cingulate cortex, anterior insula, and amygdala involved in a variety of complex brain functions regarding filtering of salient information such as communication, social behavioral, and self-awareness [94].

Selective serotonin reuptake inhibitor: (SSRI) a type of antidepressant drug that inhibits the reabsorption of serotonin by neurons, so increasing the availability of serotonin as a neurotransmitter.

Stria terminalis: a major output pathway of the amygdala

Uncinate fasciculus: a long-range white matter association fiber tract that connects the frontal and temporal lobes; it is implicated in several neurodevelopment and psychiatric disorder including ASD, conduct disorder, and substance abuse [95].

Boxes

Box 1. Developmental programming examines how prenatal experiences may shape development. The theory of developmental programming hypothesizes that during times of rapid growth for an organism, systems are more vulnerable to disorganization influences [11, 96]. Therefore, due to its rapidity, fetal brain development may be highly vulnerable to environmental factors [11, 96-98], which in turn could have long-lasting effects on health and well-being. Fetal programming describes the process in which *in utero* conditions elicit structural and functional changes in cells, tissues, and organ systems that may have long-term consequences [11]. Fetal programming focuses on how the developing fetus senses, receives, and responds to the intrauterine environment [98]. Regarding fetal brain development, fetal programming provides a framework for understanding the complex and bidirectional interplay between an organism's genotype and early environment [11, 98]. Therefore, certain environmental conditions (such as prenatal exposures) a fetus experiences *in utero* may shape individual differences in early trajectories of brain development [11]. According to fetal programming theory, even small changes in the environment may have large consequences on the developing brain due to its vulnerability at this developmental time period. Therefore, it is critical to understand how prenatal exposures 'program' early brain developmental trajectories and how these deviations in brain development may underly increased risk for neurodevelopmental and psychiatric disorders.

Box 2. Infancy is a developmental period of rapid development of the brain's functional architecture. The human brain experiences its most rapid brain growth *in utero* and in the first 20 postnatal weeks [6]. Regarding brain function, brain activity is initially incoherent and unorganized [8]. However, by the 24th week, brain activity is more coherent and organized signals begin to emerge [99]. During this period, the brain undergoes rapid development of its large-scale networks [6, 100]. The development of the 'functional connectivity' of brain networks can be measured by temporal correlation in brain activity, generally using functional magnetic resonance imaging (fMRI) data [93, 101]. Functional connectivity increases in inter- and intra- hemispheric connectivity across gestational age and has peak increases between 24- and 31-weeks gestation [102]. Most functional brain networks are present at birth [100, 103] however they are immature and undergo developmental changes into childhood, adolescence, and adulthood. Typically, primary sensorimotor and visual networks develop first, while higher-order functional networks (such as the default mode networks) are still immature at birth and have 'scattered' connectivity patterns indicating activity that is not temporally synchronized [6, 100]. Substantial individual differences in structural and functional network development have been identified in infancy [6, 100, 103-105], as these individual differences have been linked to cognitive and behavioral outcomes later in life [7, 105]. Therefore it is critical to examine the relations between prenatal exposures, infant brain structure/function, and risk for neurodevelopmental and psychiatric disorders.

Figures

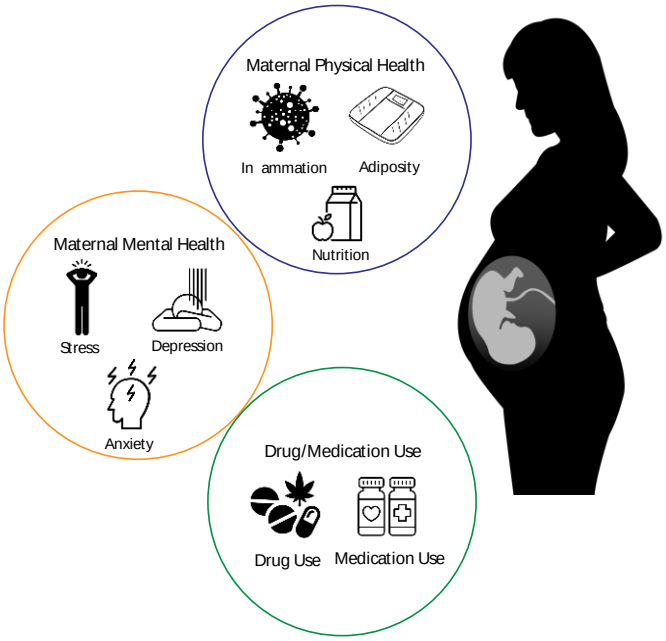

Figure 1: Clustering of exposure types. Numerous prenatal exposures have been associated with infant brain development, leading to a heterogeneous literature, often with little overlap between exposures. Yet, recent reports suggest that there may be common—along with disparate—pathways by which prenatal exposures exert their influence on the developing offspring brain through direct transfer from the mother to the fetus. As such, clustering exposures simplify the diverse exposures in the literature along with helping to identify common pathways of brain alterations. Here, we operationalize three clusters of prenatal exposures: maternal physical health, maternal mental health, and maternal drug use. For maternal physical health, exposures include measures of maternal inflammation and maternal adiposity and nutrition. For maternal mental health, exposures include measures of psychosocial stress, maternal depression, and anxiety. For maternal drug and medication use, exposures include nicotine, alcohol, cannabis, cocaine, heroin (drugs) and selective serotonin reuptake inhibitors (SSRIs), methadone, anesthesia (medications).

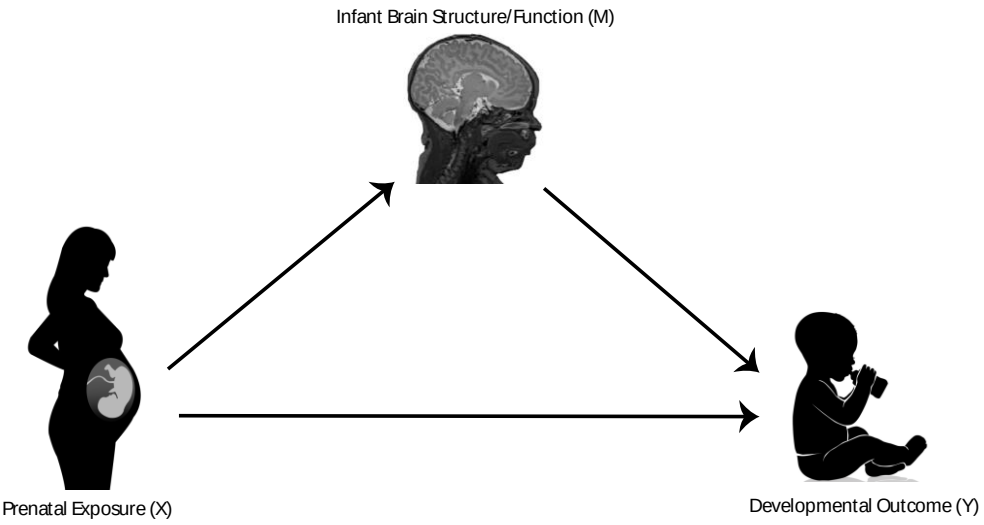

Figure 2: Statistical Mediation. A mediation model seeks to identify a mediator variable (M; infant brain structure/function) that underlies an observed association between an independent variable (X; prenatal exposure) and a dependent variable (Y; developmental outcome). To test mediation, significant correlations between all three variables (i.e., prenatal exposure, developmental outcome, infant brain structure/function) need to be present. To establish M as a mediator, the indirect effect (effect of X on Y through M) is tested and if significant it can be determined the amount of variance explained by the mediator. While prenatal exposures are linked to risk of future developmental disorders, risk alone does not capture individual differences in outcomes. Mediation analyses can test whether prenatal exposures are associated with developmental outcomes via infant brain structure and function. These brain mediators can potential act as markers of individual differences in risk of poorer developmental outcomes [13, 14] before behavioral deficits are present [15-18].

Tables

Table 1. Study, maternal exposure cluster, maternal exposure, and chronological age at the MRI scan (in weeks).

Study	Exposure Cluster	Exposure	Time of Exposure (GA weeks (SD))	Age at Scan in Weeks (SD)
Graham et al., 2018	physical	inflammation (IL-6)	21.2 (1.47)	3.79 (1.84)
Li et al., 2016	physical	BMI	~10	3.21 (0.34)
Monk et al., 2016	physical	iron intake	34-36	2.8 (1.18)
Ou et al., 2015	physical	BMI	0-10	2.15 (0.35)
Rasmussen et al., 2019	physical	inflammation (IL-6)	21.2 (1.47)	3.79 (1.84)
Rudolph et al., 2019	physical	inflammation (IL-6)	21.2 (1.47)	3.73 (1.7)
Salzwedel et al., 2019	physical	BMI	1-10	2.05 (0.24)
Spann et al., 2018	physical	inflammation (IL-6 and CRP)	34-37	3.1 (0.4)
Spann et al., 2020	physical	BMI	pre-pregnancy	3.21 (0.34)
Chen et al., 2015	mental	anxiety	26-28	1.4
Dean et al., 2018	mental	depression/anxiety	28-35	4.72
Graham et al., 2018	mental	cortisol	21.2 (1.47)	3.65 (1.72)
Humphreys et al., 2020	mental	stress	16-32	4.81 (0.93)
Lehtola et al., 2020	mental	depression/anxiety	14, 24, 34	3.74 (1.1)
Posner et al., 2016	mental	depression	34-37	5.82 (1.8)
Qiu et al., 2013	mental	anxiety	26	1.4
Qiu et al., 2015	mental	depression	26	27.98 (0.53)
Qiu et al., 2017	mental	depression	26	1.39 (0.08)
Ramphal et al., 2020	mental	stress (SES)	26-40	5.8
Rifkin-Graboi et al., 2013	mental	depression	26	1.4 (0.1)
Rifkin-Graboi et al., 2015	mental	anxiety	26-28	1.42 (0.01)

Scheinost et al., 2020	mental	stress	24-37	3.1 (0.4)
Spann et al., 2020	mental	stress (SES)	28-40	2.8 (0.7)
Stoye et al., 2019	mental	cortisol	0.5 (0.35) postnatal	3.5
Wang et al., 2018	mental	depression	26	1.4
Donald et al., 2016	drug/medication	alcohol	20-24	3.05 (0.86)
Ekblad et al., 2010	drug/medication	smoking	cigarettes per day across pregnancy	2.78
Grewen et al., 2014	drug/medication	cocaine	26-40	3.87
Grewen et al., 2015	drug/medication	cannabis	26-40	3.62
Lugo-Candelas et al., 2018	drug/medication	SSRI	19-39	3.43 (1.5)
Jha et al., 2016	drug/medication	SSRI	preconception - 12	3.7 (1.89)
Peterson et al., 2020	drug/medication	multiple drug/med.	assessed once per trimester	3.65 (3.15)
Salzwedel et al., 2016	drug/medication	cocaine	26-40	4.24
Salzwedel et al., 2020	drug/medication	multiple drug/med.	26-40	4.15 (0.41)
Spann et al., 2015	drug/medication	anesthesia	39-40	2.7 (0.7)
Walhovd et al., 2012	drug/medication	methadone	26-40	3.27 (0.94)

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