Chapter 8

Review of Current Neuroimaging Studies of the Effects of Prenatal Drug Exposure: Brain Structure and Function

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Abstract

Neuroimaging tools have provided novel methods for understanding the impact of prenatal drug exposure on brain structure and function and its relation to development and behavior. Information gained from neuroimaging studies allows for the investigation of how prenatal drug exposure alters the typical developmental trajectory. The current prevalence and characteristics of prenatal drug exposure and its implications for vulnerable periods of brain development are reviewed. Structural and functional neuroimaging methods are introduced with examples of how study results from prenatal alcohol, cocaine, marijuana, and tobacco exposure further our understanding of the neurodevelopment impact of prenatal drug exposure. Prenatal drug neuroimaging studies have advanced our understanding of mechanisms and functional deficits associated with prenatal drug exposure. Studies have identified brain circuits associated with the default mode network, inhibitory control, and working memory that show differences in function as a result of prenatal drug exposure. The information gained from studies of prenatal drug exposure on brain structure and function can be used to make connections between animal models and human studies of prenatal drug exposure, identify biomarkers of documented effects of prenatal drug exposure on behavior, and inform prevention and intervention programs for young children.

Keywords: fMRI, prenatal substance exposure, alcohol, cocaine, marijuana, tobacco

1. Introduction

This chapter begins with a review of issues surrounding the assessment of the impact of prenatal drug exposure on developmental outcomes in children followed by a brief update of

current trends in prenatal drug exposure including the prevalence, patterns, and characteristics of prenatal drug use, including alcohol, tobacco, marijuana, and other illicit drugs. Then, the impact of current neuroimaging methodology on our understanding of the effects of prenatal drug exposure is explored. The review considers examples of how neuroimaging tools have increased our understanding of the often subtle and complex impact of prenatal substance exposure on child brain development and behavior. The impact of prenatal drug exposure is challenging to assess due to characteristics of maternal drug use such as poly-drug exposure and differences in the purity and legality of drugs. Developmental outcomes associated with prenatal drug exposure will also be affected by the timing, dose, and pattern of drug use during pregnancy, and the varying impact of other environmental factors such as maternal health and nutrition, access to prenatal care, and the home environment [1, 2]. For over 40 years, the impact of prenatal drug exposure has been studied in relation to growth, behavior, and cognitive outcomes using both longitudinal and cross-sectional designs, which have provided a depth of understanding. Overall, the most important outcome of decades of research has been that no safe levels of any type of prenatal drug use during pregnancy have been identified. Furthermore, the impact of prenatal drug exposure is often subtle and combined with other environmental risk factors, contributes to poor developmental outcomes for young children and adolescents.

2. Methodological Issues and Current Trends in Prevalence and Characteristics of Prenatal Drug Exposure

Prenatal drug exposure is a major public health concern for mothers and their children. In addition, society bears significant financial costs associated with social and child welfare services utilization [3, 4], neonatal intensive care unit costs, and longer hospital stays after delivery [3–8]. Children with prenatal drug exposure are also more likely to need intervention services to address medical, developmental, behavioral, academic, and socio-emotional issues [9]. Decades of research have documented the negative impact of prenatal drug exposure on child developmental outcomes including growth, emotion and behavior regulation, and cognitive function. The impact of prenatal drug exposure on the developing child has also been shown to interact with the quality of the child's environment. Given the complexities related to prenatal drug exposure and the influence of many potential external factors, the prevalence, characteristics, and effects on developmental outcomes can be difficult to assess. Difficulties arise from the dose, timing, and duration of prenatal drug exposure, the use of multiple drugs during pregnancy, methodology limitations in the ability to document prenatal drug exposure, differentiating between delayed and longer-term effects, genetic factors, and variability introduced by environmental experiences including the quality of relationships and the home environment [10]. In addition, methods used to measure prenatal drug exposure are varied, ranging from survey methods (e.g., national surveys) to prenatal interviewing (e.g., longitudinal cohort studies).

The main strategy for dealing with the complexities of research aimed at elucidating the impact and mechanisms of prenatal drug exposure on child development is to use longitudinal

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research designs that incorporate measurement of explanatory variables. Pregnant substance abusers are not studied based on whether they classify as "recreational" users or addicts. Rather, the timing (first, second, third trimester), dose, and pattern of drug use (continuous vs. binge exposure) are key variables. Among cohort studies, there are differences in sample characteristics that are important for the interpretation of any study results that suggest negative developmental outcomes associated with prenatal drug exposure. For example, some studies focus on "high- dose" exposure (e.g., Seattle Longitudinal Study of Fetal Alcohol Syndrome), whereas other studies focus on the full spectrum of exposures ranging from light-, moderate-, to high-dose exposure (e.g., Pittsburgh Maternal Health Practices and Child Development Project). Most studies have attempted to quantify the pattern of drug exposure as either continuous (e.g., average number of drinks/day) or binge (e.g., ≥4 drinks/occasion). Cross-sectional study designs are also used to study clinical populations, capturing the important characteristics of young children who have been referred for assessment and services.

Current trends suggest that while the prevalence of women using drugs during pregnancy is relatively low, maternal substance use has an impact on many children. Approximately 400,000–440,000 infants, 10–11% of all births, are prenatally exposed to alcohol, tobacco, or illicit drugs [11]. In addition, current trends in prenatal drug exposure suggest shifts in both the prevalence and patterns of maternal substance use that reflect both wide spread knowledge and perceptions of the impact of drugs of abuse in general, and prenatal drug exposure more specifically. Alcohol and tobacco are the most commonly used drugs during pregnancy, followed by marijuana, cocaine, and opioids [12]. For all types of prenatal drug exposure, the data show that reported use in pregnant women is lower compared to nonpregnant women in the same age category and that more pregnant women report use in the first trimester compared to second and third trimesters [12]. In general, a greater number of younger pregnant women (ages 18–25) report use compared to older women (ages 26–44) [12].

2.1. Current prevalence estimates of prenatal drug exposure

Recent estimates [12] show that the rates of prenatal alcohol use are approximately 9.4%, of which 2.3% of women report binge drinking and 0.4% report heavy drinking. Higher levels of drinking are reported in the first trimester compared to second and third trimesters. Patterns of alcohol use among pregnant women have changed over time. More recently, pregnant women are reported to drink more heavily and are more likely to develop an alcohol use disorder compared to earlier studies [13]. In addition, women of childbearing age have shown an increase in binge drinking, a trend that has decreased in males over time [14, 15]. Women who binge drink during pregnancy report, on average, 4.6 binge drinking episodes (nonpregnant women report 3.1 episodes) and the number of drinks consumed, while binge drinking does not differ from nonpregnant drinkers [2]. The Centers for Disease Control reports that medical record analysis shows a rate of 0.3 out of 1000 children ages 7–9 are diagnosed with fetal alcohol syndrome (FAS), while in-person assessments find higher rates (6–9 per 1000 children). Rates of fetal alcohol spectrum disorders are more difficult to ascertain, but

community based studies in both the United State and Western Europe suggest that 24–48 per 1000 school children are affected by prenatal alcohol exposure [16, 17].

Reflecting national trends, the NSDUH [12] reports that cigarette use among women has been steadily decreasing from a rate of 30.7% in 2002–2003 to 24.0% in 2012–2013. However, during the same time period, the prevalence rate of cigarette use among pregnant women did not show a similar significant reduction. Eighteen percent of pregnant women reported cigarette use during pregnancy in 2002–2003 compared to 15.4% in 2012–2013. Other studies have shown that efforts to reduce smoking prevalence among female smokers before pregnancy have not been effective; however, efforts targeting pregnant women have met some success as rates have declined during pregnancy and after delivery [18,19].

The most commonly used illicit drug is marijuana, but illicit drug use also includes cocaine, opioids, and amphetamines. Among pregnant women, the rate of any illicit drug use is 5.4% and has not changed significantly since 2010–2011 [12]. Use remains higher in younger women (14.6%, ages 18–25) compared to older women (3.2%, ages 26–44). A high proportion of women are using marijuana illegally and fail to disclose their use to their providers. A recent study showed 81 percent of providers in urban outpatient clinics are asking their pregnant patients about illicit drug use and; of the women surveyed, 11% of women disclosed current use of marijuana, while 34% tested positive for one or more substances with marijuana being the most commonly detected (27%) [20]. Women who use methamphetamine during pregnancy show decreased prevalence and frequency of use from first to third trimester and women who decreased their use were more likely to seek prenatal care during pregnancy [21].

2.2. Maternal and environmental variables

There are a number of maternal and environmental characteristics that are associated with substance use during pregnancy [22]. Prenatal substance use is associated with younger maternal age [12] and socioeconomic factors such as lower level of education, unemployment, and higher levels of poverty [1]. Physical and mental health factors such as the utilization of health care during pregnancy [23, 24], fear of criminalization and/or stigma [25], higher rates of affective disorders including depression [1], and poly-substance exposure [1] are highly prevalent in pregnant substance users. Women using drugs during pregnancy are also more likely to have had either current and/or childhood exposure to violence and/or abuse [24]. Domestic violence is also associated with a higher proportion of substance use in women [24, 26].

The complex interactions of social, psychological, and physical variables that are at play in pregnant substance abusers also have an impact on the stability and quality of the child–parent relationship, a significant factor in healthy child development. The care that infants receive from their primary caretaker lays the foundation for the development of behavior and emotion regulation, social skills, and cognitive ability [18, 19, 27, 28], as well as physical and mental health [29, 30]. Substance abusing mothers show decreased responsivity to their infants. For example, opioid abusing mothers show a decreased ability to identify their infant's cues and to respond appropriately to them [31]. Addiction and mental illness, two factors associated with prenatal substance exposure are also associated with difficulty in forming healthy

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attachments [32]. The complex interactions of variables associated with prenatal substance exposure is important because the events that occur early in life, both in terms of the quality of relationships and environment, play a significant role in brain development. The important neural connections that support the brain circuitry that underlies emotional, social, and cognitive behavior are established early in life [33].

Prenatal drug exposures, the timing, and quality of other early experiences have a profound impact on child development because of their influence on early brain development. Early life experiences have an impact on the development of brain structure by influencing the timing and pattern of gene expression and the refinement of neural circuitry [34]. Neuroimaging methods that examine the structure and function of the brain have provided access to study the impact of prenatal drug exposure on the developing brain. Methods such as magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), and functional magnetic resonance imaging (fMRI) are noninvasive allowing for their use in children. Neuroimaging tools have been used to better understand typical patterns of structural and functional development in the brain. This information can be used to examine how prenatal drug exposure affects normal brain development and how it relates to physical and behavioral outcomes.

3. Prenatal drug exposure and brain structure

3.1. Volume, symmetry, and cortical thickness

MRI uses the inherent magnetic properties of the body to create detailed images. Short radiofrequency pulses inside a strong magnetic field create patterns of excited molecules that can be used to create an image of the structure [35]. Offering detailed structural images of the brain, MRI is an essential tool for assessing structural characteristics including global and regional brain volumes, symmetry, and cortical thickness. Structural brain differences serve as biomarkers of the impact of the prenatal drug exposure and, eventually, may aid in identification and intervention. Overall, studies of prenatal drug exposure show consistent reductions in head circumference, overall and regional reductions in brain volumes, and differential reduction in gray and white matter volumes, results which are dependent on the accumulation of polydrug exposures [36].

Recent reports are consistent with previously documented widespread changes in brain structure in children and adolescents with moderate to heavy prenatal alcohol exposure [37]. Prenatal alcohol is associated with overall reductions in global [38, 39] and regional brain volume including the hippocampus, basal ganglia, cingulate cortex, and corpus callosum [37, 40–43]. Several studies indicate that reductions in brain volume linked to prenatal alcohol exposure were associated with deficits in cognitive function and facial dsymorphology. For example, prenatal alcohol exposed is linked to reductions in caudate volume which are also associated with deficits in cognitive control and verbal learning and memory [44] as well as palpebral fissure length [45]. Moreover, reductions in brain volume increase as a function of the amount of alcohol consumed during pregnancy and the severity of diagnosis [38, 46] and were reported from early childhood through young adulthood, suggesting long-term and persistent alterations in brain structure.

Prenatal alcohol exposure was also associated with increased asymmetry in the caudate nucleus, cingulate cortex, and corpus callosum. Specific to the caudate nucleus, moderate alcohol exposure was associated with increased volume in the left caudate compared to the right [43, 47]. Asymmetry in the cingulate cortex was due to reduced volume localized to the right caudal region of the cingulate [48], which may be related to differential loss of white matter compared to gray matter in this brain region [49].

Studies have evaluated the effects of prenatal alcohol on cortical morphology by examining cortical thickness. Several studies have reported increased cortical thickness in diffuse regions across the frontal, temporal, and parietal lobes [50–52] while another study reported cortical thinning [53]. Longitudinally, children with prenatal alcohol exposure show less developmentally appropriate cortical thinning across time compared to controls [54]. When cortical thickness is examined in contrast to surface area, prenatal alcohol exposure affects global surface area to a greater degree than cortical thickness especially in the right temporal gyrus [55].

Past neuroimaging studies show that prenatal cocaine exposure was also associated with long-term changes in brain structure. Recent studies confirm overall reductions in global brain volume as well as in the caudate, corpus callosum, and right cerebellum [56–58] differences in shape and volume characteristics of the striatum [45], and cortical thickness and volume of the right prefrontal cortex [59]. In adolescence, prenatal cocaine exposure was associated with specific reductions in gray matter volumes in frontal cortical and posterior regions [60]. In one study, the structural changes were correlated with impulsivity [59]. However, the prenatal cocaine exposure-related structural changes were subtle and may lose significance when covariates including other prenatal exposures are properly controlled [36].

Prenatal tobacco exposure was linked to overall reductions in intrauterine growth [61], which is also reflected in the brain. Prenatal tobacco exposure was associated with reductions in fetal head growth, reduced volume of the frontal lobes and cerebellum, and smaller width of the lateral ventricles [62, 63]. During childhood, prenatal tobacco exposure is associated with additional changes in brain structure including smaller total brain volume and smaller cortical gray matter volume [36, 64], cortical thinning in superior frontal and parietal cortices [64] and reduced gray matter volume in subcortical regions including the amygdala, thalamus, and pallidum [59, 65]. Increased volume in the frontal cortex with corresponding decreases in the anterior cingulate cortex was also observed [66]. Regional brain volume changes persisted into adolescence but may be explained by current adolescent tobacco use because children with prenatal tobacco exposure are at increased risk for early initiation and smoking behavior [67].

Fewer recent studies have been conducted on the impact of prenatal marijuana, methamphetamine, and opioid exposure on global and regional brain volume. But, some initial research indicates that prenatal exposure to these drugs is also associated with difference in brain structure. In contrast to other types of prenatal drug exposure, prenatal marijuana exposure was not related to reductions in global brain volume [36]. A small sample of children with prenatal opioid exposure showed reduced global brain volume as well as regional differences including reduced volume in the cerebral cortex, amygdala, nucleus accumbens, putamen, pallidum, brainstem, cerebellar cortex, cerebellar white matter, and inferior lateral

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ventricles [68]. Prenatal methamphetamine exposure was linked to regional volume reductions in both striatal and limbic structures including the caudate, anterior and posterior cingulate, inferior frontal gyrus, and ventral and lateral temporal lobes; regions that are vulnerable to the neurotoxic effects of methamphetamine in adult abusers [69]. Another study showed similar results, as well as sex-specific effects of prenatal methamphetamine exposure on brain structure, including increased volume in the striatum in males and increased cortical thickness in females [70].

3.2. Integrity of white matter tracts

DTI uses MRI to examine white matter microstructure by measuring the diffusion of water molecules in tissue and the integrity of water diffusion in one direction across a membrane. Unrestricted water molecules are capable of diffusing in any direction, however; in the presence of structural barriers such as cell membranes and myelin, water tends to diffuse in an increasingly directional manner. The degree to which water molecules are isotropic (directionally independent) versus anisotropic (directionally dependent) is determined using DTI. Anisotropy occurs in white matter tract fibers, particularly in myelinated axons [35, 71]. Functional anisotropy (FA) is used as a quantitative measure of diffusion and ranges in value from 0 (isotropic) to 1 (anisotropic) [72]. FA is highly sensitive to microstructural changes in white matter, but not to the type of change (radial or axial) [71]. Developmentally, FA undergoes the greatest amount of change during early childhood (through 5 years) [73, 74] and can be used to distinguish between stages of brain development [75]. In general, abnormal brain development or brain damage is associated with lower FA values in white matter [76]. Abnormalities in white matter that leads to decreases in FA may result from either increased radial (perpendicular and associated with changes in myelination) diffusivity and/or reduced axial (parallel and associated with axonal integrity) diffusivity [77]. Prenatal substance exposure is linked to lower FA and alterations in the structural integrity of myelin [78]. White matter microstructure, however, has been most widely studied in children with prenatal alcohol or cocaine exposure.

The impact of prenatal alcohol exposure on measures of white matter microstructure shows that effects can be detected at multiple stages of development, are associated with behavior, and fall on a continuum ranging from mild to severe Abnormalities in the corpus callosum are frequently reported, but also in anterior–posterior fiber bundles, corticospinal tracts, and the cerebellum [79–82]. Effects of prenatal alcohol exposure are linked to reduced white matter structural integrity in the cerebellum [83] and abnormalities in axial diffusivity [84] as early as infancy. In addition, subtle changes in FA have been associated with deficits in cognitive function including processing speed, math ability, executive function, and eye-blink conditioning [50, 81, 85–92] A recent study was also able to demonstrate that structural white matter changes are linked to disturbances in functional connectivity while at rest [83].

In contrast, DTI studies of the impact of prenatal cocaine or methamphetamine exposure on white matter integrity are mixed. Cocaine exposure has been associated with increased diffusion in left frontal callosal and right frontal fibers [93], but do not appear to remain significant after controlling for other prenatal drug exposures [36]. Another study that

controlled carefully for other prenatal drug exposures showed that prenatal cocaine-related FA differences in fiber pathways including right cingulum, right arcuate fasciculus, left inferior longitudinal fasciculus, and splenium of the corpus callosum were associated with deficits in attention and response inhibition [94]. Only one study has reported a trend for higher FA associated with prenatal methamphetamine exposure [95]. These early studies and the lack of research on the impact of prenatal tobacco and marijuana exposure on white matter integrity indicate the need for additional research to better understand the impact of prenatal drug exposure on DTI measures.

4. Prenatal drug exposure and brain function

Neural circuits that control brain function have different patterns of activity that can be measured using fMRI. fMRI provides an indirect measure of brain function by quantifying the blood oxygen level-dependent (BOLD) response, which reflects changes in blood oxygen utilization throughout the brain. When neural circuits become active, MR signals will increase by a small amount, reflecting a signal change of approximately one percent. The ability to detect a change in MR signal depends on the different magnetic properties of oxygenated vs. deoxygenated blood and that blood flow to areas of the brain that are working are very sensitive. Different types of experimental designs are used in conjunction with fMRI methods to determine the location of brain activity. In the simplest type of experiment, patterns of brain activity are examined as a subject alternates between an experimental and control condition. The signal will increase and decrease as a function of the experimental conditions after adjusting for time. Functional neuroimaging studies produce group-averaged maps that show the level of brain activation that is associated with a specific task or in response to a specific stimulus. The group maps are then compared between conditions and/or between groups to examine the magnitude and extent of brain activation for a given response [96].

fMRI research has been used to determine if prenatal drug exposure has an impact on areas of the brain that receive more or less oxygenated blood in response to performing a cognitive task. The method has been used to demonstrate the effect of prenatal drug exposure on brain activation during a variety of cognitive behaviors. Recent work converges on three domains, the default mode network, inhibitory control, and working memory; all of which illustrate how fMRI methods can be used to better understand the impact of prenatal drug exposure on brain function. In addition, innovative functional connectivity studies have combined information from structural (MRI and DTI) with functional (fMRI) methods to understand the temporal relations between spatially distinct brain regions.

4.1. Default mode network

The default mode network (DMN) is comprised of a set of brain regions including ventral medial prefrontal cortex, posterior cingulate, inferior parietal lobe, lateral temporal cortex, dorsal medial prefrontal cortex, and the hippocampus (see **Figure 1**) [97]. This network is active when one appears to be at rest but is actually engaged in spontaneous and goal-directed mental

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tasks such as free-thinking, remembering, and making future plans [98]. In contrast, the network is inhibited while performing tasks with high-cognitive demand and increased task difficulty [99, 100]. Behaviorally, both prenatal cocaine and alcohol exposure are associated with early and persistent deficits in arousal regulation and attention deficits [101–105] and an increased risk for a diagnosis of attention-deficit/hyperactivity disorder [106, 107]. One interpretation of the results of these studies is that the dysregulation of arousal and attention, in part, explains other observable deficits in higher-cognitive function.

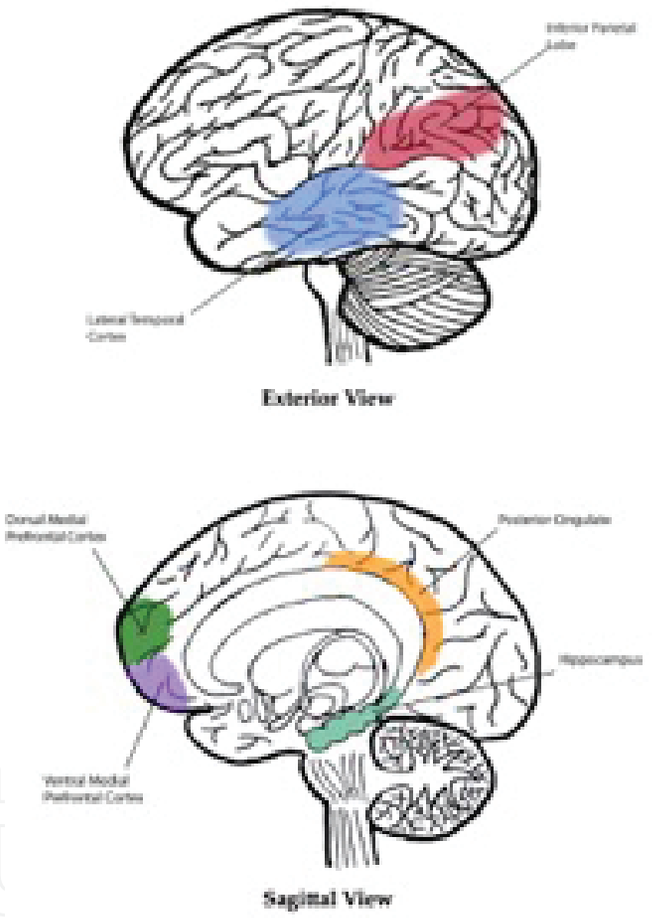

Figure 1. Key regions associated with the default mode brain network.

Current neuroimaging research suggests, however; that the underlying impact of prenatal cocaine or alcohol exposure on arousal and attention reflects changes in function of the DMN network. Results are summarized in **Table 1(A)**. Using resting-state fMRI, a recent large-scale study of neonates with prenatal cocaine exposure or polydrug exposure showed polydrug-related connectivity disruptions within frontal-amygdala, frontal-insula, and insula-sensori-motor circuits; and specific effects of prenatal cocaine exposure on the frontal-amygdala network [108]. Results showed that polydrug exposure was associated with negative connec-

tivity within these networks. Negative connectivity is interpreted as a dysregulation in excitatory and inhibitory inputs [109–111], and in this case, a failure to inhibit the amygdala response from prefrontal cortex inputs.

A number of studies indicate that the effect of prenatal cocaine exposure on functional differences within the DMN persist into childhood and adolescence. Adolescents with prenatal cocaine exposure show overall reductions in regional cerebral blood flow at rest with compensatory, relative increases in anterior and superior brain regions [112]. Additionally, while in the resting state, adolescents with prenatal cocaine exposure show increased functional connectivity in the DMN compared to controls [113], and less deactivation of the network in the DMN, while performing a working memory task with emotional distracters.

Furthermore, the effects of prenatal cocaine and alcohol exposure on the DMN can be dissociated. Similar to prenatal cocaine exposure, prenatal alcohol exposure is associated with less deactivation in the DMN while performing a cognitive task [114]. In contrast to prenatal cocaine exposure, prenatal alcohol exposure is associated with decreased functional connectivity within the DMN at rest [114]. These results suggests that the underlying mechanism for prenatal cocaine or alcohol exposure effects on cognitive ability are due, in part, to changes in baseline levels of arousal and dysregulation of excitatory and inhibitory control of neural resources allocated to perform cognitive tasks.

4.2. Inhibitory control

The ability to engage in voluntary, goal-directed behavior requires activation of neural circuitry that supports cognitive control mechanisms. Response inhibition is considered to be a key component of cognitive control and refers to the ability to inhibit a response that is no longer needed or inappropriate given a change in either internal or external states [115]. The go/no-go task is a cognitive paradigm that can be used in conjunction with fMRI to evaluate response inhibition [115, 116]. In the go/no-go task, participants are required to respond or withhold a response depending on whether they are presented with a "go" stimulus or a "no-go" stimulus, respectively.

The go/no-go task has been used to determine independent effects of prenatal alcohol, cocaine, marijuana, and tobacco on response inhibition, allowing for a comparison across studies. Results are summarized in **Table 1(B)**. Children with prenatal tobacco [117] or marijuana [118] exposure were more likely to commit commission errors while performing the go/no-go task, but children with prenatal alcohol or cocaine exposure showed no behavioral differences in task performance. Prenatal alcohol exposure was associated with increased brain activation in prefrontal regions and less activation in the caudate compared to controls [119]. A similar pattern is demonstrated in adolescents with prenatal alcohol exposure suggesting long-term changes in brain function associated with response inhibition [120]. In contrast, prenatal cocaine exposed children showed increased activation in inferior frontal cortex and caudate and less activation in temporal and occipital regions [121]. Prenatal marijuana was associated with differential activation of frontal regions including and increased BOLD response in bilateral the prefrontal cortex and right premotor cortex, and a decreased response in the cerebellum [118]. Children with prenatal tobacco exposure showed increased activation in a

more diverse set of brain regions including left frontal, right occipital, bilateral temporal, and parietal regions, and less activation in the cerebellum [117]. Young adults with prenatal tobacco exposure showed a similar pattern of results with increased activation inferior frontal, inferior parietal, basal ganglia, and cerebellum [122].

Results across multiple studies indicate that prenatal drug exposure leads to differential activation in frontal–striatal circuits, while performing the go/no-go task. In addition, across studies, prenatal drug-related increases in activation were reported in many brain regions, which indicates an increase in the demand for cognitive resources, while performing the response inhibition task. This pattern of results is indicative of an immature brain circuitry. Across development, the typical pattern observed in neuroimaging data is that for response inhibition, there is an increase in the magnitude of activation and a decrease in the extent of activation in frontal–striatal brain regions [123, 124]. Increased efficiency of neural processing is also associated with a peak in behavioral performance. Younger children show greater activation in similar brain regions as reported in the prenatal drug imaging studies [125, 126]. Although, the data collected in each of the studies were cross-sectional, the reported effects of prenatal drug exposure in childhood, adolescence, and adulthood indicate that the changes in brain circuitry underlying response inhibition may not be due to developmental delay, but instead due to long-term changes in the activation of the circuit.

4.3. Working memory

Working memory refers to the cognitive ability to hold and manipulate information for a short period of time. Brain imaging studies have shown a load-dependent role for the prefrontal cortex in working memory [127, 128]. Using fMRI methods, prenatal drug exposure is associated with differential brain activation within the prefrontal cortex, while performing working memory tasks. Results are summarized in **Table 1(C)**. For example, children prenatally exposed to tobacco experience more activation in the inferior parietal regions of the cortex, whereas children not exposed showed activation in the bilateral inferior frontal region of the cortex [129]. Prenatal marijuana is also associated with patterns of increased activation associated with working memory including the inferior and middle frontal gyri [130].

fMRI methods have also been used to demonstrate specific effects of prenatal drug exposure in both the visual–spatial and verbal working memory domains. Prenatal alcohol exposure leads to increased activation of the frontal–parietal–cerebellar network including the left dorsal frontal and left inferior parietal cortices, and bilateral posterior temporal regions during verbal working memory compared to controls [131]. The results showed that individuals prenatally exposed to alcohol recruit a larger, more extensive neural network than their peers. Across three studies, prenatal alcohol exposure was also associated with differential patterns of activation, while performing spatial working memory tasks [132–134]. In contrast, offspring with prenatal methamphetamine exposure had less activation than their unexposed counterparts in both the frontal and striatal regions; primarily in the left hemisphere of the brain on a spatial working memory task [135], but increased activation in bilateral temporal regions in response to performing a verbal working memory task [136].

(A) Default mode network			
Drug	**Effects on network**	**Behavioral effects**	**References**
Alcohol	Increased activity in DMN during cognitive tasks	Deficits in arousal regulation	[101–107, 114]
	Decreased activation of DMN at rest	Increased risk of ADHD diagnosis	
Cocaine	Increased activity in DMN during cognitive tasks	Deficits in arousal regulation	[101–107, 113, 114]
	Increased activation of DMN at rest	Increased risk of ADHD diagnosis	
(B) Inhibitory control			
Alcohol	Increased activity in prefrontal regions	Increased effort required for response inhibition	[119]
	Decreased activity in the caudate		
Tobacco	Increased activity in left frontal, right occipital, bilateral temporal, and parietal regions	Increased effort required for response inhibition	[117]
	Decreased activity in the cerebellum	More likely to commit commission errors	
Cocaine	Increased activity in inferior frontal cortex and caudate	Increased effort required for response inhibition	[121]
	Decreased activity in temporal and occipital regions		
(C) Working memory			
Alcohol	Increased activation in bilateral dorsal frontal, bilateral posterior temporal, and left inferior parietal regions	More effort required to maintain working memory	[131, 137, 138]
Tobacco	Activation of inferior parietal cortex as opposed to bilateral inferior frontal cortex	Different mechanisms are employed to maintain working memory	[129]
Methamphetamine	Decreased activation in frontal and striatal regions, particularly in left hemisphere	Decreased working memory performance	[135]

Table 1. Summary of prenatal drug exposure effects on (A) default mode network, (B) working memory, and (C) inhibitory control.

The impact of prenatal alcohol exposure can be dissociated from other potential explanatory variables. When examined in relation to family history of alcohol use disorders, prenatal alcohol exposure independently predicted increased activation in left middle and superior frontal brain regions [137]. In a direct comparison of adolescents with prenatal alcohol exposure or ADHD, behavioral profiles were similar but the two groups showed differences in how cortical brain regions were recruited for spatial working memory [138]. Overall, prenatal alcohol exposure was associated with an increased effort to compensate in relation to increasing task demands compared to the ADHD group.

Alterations in behavioral and brain function measures of working memory extend to prenatal cocaine exposure as well. The aforementioned deficits in arousal regulation associated with prenatal cocaine exposure appear to underlie brain and behavior-related working memory function. Li et al. [139] showed differential patterns of activation as a function of emotion–memory interactions. Increased demands on memory load diminished emotion-related activation in the amygdala in controls but not in the exposed group. In contrast, the exposed group failed to show an expected decrease in activation in the prefrontal cortex as memory load decreased in the presence of emotional stimuli. Results suggest that the impact of prenatal cocaine exposure on arousal regulation acts through both the dorsal cognitive and ventral emotional systems.

Overall, multiple studies demonstrate the complexities of prenatal drug-related effects on working memory. Patterns of brain activation associated with working memory are different by type of prenatal drug exposure, are present in the absence of behavioral differences, and show more extensive networks of activation compared to controls. Specific alterations in prefrontal cortex activation in response to working memory demand suggest that these regions are taxed to a greater degree as a result of prenatal drug exposure. Furthermore, changes in activation remained after controlling for other explanatory variables such as intelligence. Collectively, studies demonstrate that the effect of prenatal drug exposure on brain activation associated with working memory is less efficient and that increased levels of activation serve to compensate for any deficits in working memory function. Compensatory action, however, may not be sufficient in real-life situations characterized by increased demands on working memory function.

4.4. Novel applications of imaging methods and statistical techniques

Recently, a number of novel applications of functional neuroimaging and statistical methods have been employed to improve upon the limitations of current methods in detecting the subtle effects of prenatal drug exposure on brain function, develop connectivity maps, and aid in diagnosis. First, a variety of model-based or data-driven methods have been employed to analyze functional neuroimaging data. General linear modeling has been used most widely because it is effective, simple, and robust [140]. However, typical approaches to the statistical analysis of fMRI data are limited in that they are not able to detect activation in heterogeneous brain regions that have the potential to play diverse roles in multiple types of task performance [141]. A recent study successfully demonstrated the advantages of group-wise sparse representation of fMRI data and statistical coefficient mapping to evaluate the effect of

prenatal alcohol exposure on functional activity. The advantages reported for this method included increased adaptability, more systematic in detecting diverse brain networks, and better able to identify commonalities and differences across subjects and groups [141].

fMRI data can also be analyzed to show how components of a neural system are working together when performing a specific task. The identification of associations between anatomically distinct time series is referred to as "functional connectivity" [140]. The ability to identify consistent, reproducible, and accurate regions of interest is the key to developing connectivity maps [142]. Using a new strategy to develop cortical landmarks (dense individualized and common connectivity-based cortical landmarks, DICCOLs), Li et al. [143] used functional connectomics signatures to identify 10 brain regions with structurally disrupted landmarks that could be used to distinctly identify prenatal cocaine exposed brains from that of controls.

Finally, a novel application of machine learning has been used to test whether brain images can be used to correctly identify prenatal cocaine-exposed young adults from socioeconomically matched controls [144]. Regional features were extracted from both structural and functional MR images, and the power of each to discriminate between prenatal cocaine exposed and control brains was accomplished through machine learning methods. The method accurately identified 91.8% of prenatally cocaine-exposed brains. The use of both structural and functional images was critical to improving the accuracy of the classification system compared to either type of image alone.

5. Conclusions

Prenatal drug exposure is a risk factor for increased vulnerability to difficulties in both behavior and cognition. Continued research to identify the structural and functional targets of prenatal drug-related neurotoxicity is important. Identifying biomarkers of prenatal drug-related changes in brain development and relating those changes to behavior, or in the case of alcohol to physical features, has the potential to inform diagnostic and treatment strategies. MRI, fMRI, and DTI neuroimaging methods provide powerful tools for visualizing the brain and, because they are noninvasive, are especially suited for research in young children. The impact of prenatal drug exposure on brain structure and function is subtle and often account for a small amount of variance that contributes to deficits in behavior regulation and cognition. These subtle effects can be explained by the complex interactions of the pattern of prenatal drug exposure both in terms of the timing and dose as well as the combination of multiple drugs, genetic, and environmental factors. Changes in brain structure and function in children and adolescents with prenatal drug exposure can be difficult to assess for a number of other reasons. To date, a neuropsychological profile for prenatal drug-related deficits in cognitive function has not been identified and there are diffuse individual differences in the expression of the impact of prenatal drug exposure on the brain and behavior. Furthermore, limitations in statistical approaches to the analysis of neuroimaging data can often lead to difficulty in detecting these subtle effects. Future studies will require large sample sizes and longitudinal research designs, and increasingly sophisticated neuroimaging and statistical

methods. A focus on connectivity measures will provide a better understanding of underlying mechanisms for the associations between brain structure and function, and behavior.

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