Structural, Metabolic, and Functional Brain Abnormalities as a Result of Prenatal Exposure to Drugs of Abuse: Evidence from Neuroimaging

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Abstract Prenatal exposure to alcohol and stimulants negatively affects the developing trajectory of the central nervous system in many ways. Recent advances in neuroimaging methods have allowed researchers to study the structural, metabolic, and functional abnormalities resulting from prenatal exposure to drugs of abuse in living human subjects. Here we review the neuroimaging literature of prenatal exposure to alcohol, cocaine, and methamphetamine. Neuroimaging studies of prenatal alcohol exposure have reported differences in the structure and metabolism of many brain systems, including in frontal, parietal, and temporal regions, in the cerebellum and basal ganglia, as well as in the white matter tracts that connect these brain regions. Functional imaging studies have identified significant differences in brain activation related to various cognitive domains as a result of prenatal alcohol exposure. The published literature of prenatal exposure to cocaine and methamphetamine is much smaller, but evidence is beginning to emerge suggesting that exposure to stimulant drugs in utero may be particularly toxic to dopamine-rich basal ganglia regions. Although the interpretation of such findings is somewhat limited by the problem of polysubstance abuse and by the difficulty of obtaining precise exposure histories in retrospective studies, such investigations provide important insights into the effects of drugs of abuse on the structure, function, and metabolism of the developing human brain. These insights may ultimately help clinicians develop better diagnostic tools and devise appropriate therapeutic interventions to improve the condition of children with prenatal exposure to drugs of abuse.

Keywords Neuroimaging · Prenatal exposure · Drugs of abuse · Alcohol · Fetal alcohol spectrum disorders · Cocaine · Methamphetamine · Teratogens · Brain development

Introduction

Prenatal exposure to drugs of abuse, such as alcohol and stimulants, leads to complex alterations in developing trajectory of the central nervous system. Until recently, researchers relied on animal models to study the effects of drugs of abuse on brain development. In recent years, however, important advances in neuroimaging, particularly in non-invasive Magnetic Resonance (MR)-based imaging techniques, have led to a much better understanding of the way in which prenatal exposure to drugs of abuse impact the structure, function, and metabolism of the developing human brain. Magnetic Resonance Imaging (MRI) is the most commonly used brain imaging modality in human scientific research. We will describe recent MR neuroimaging studies examining alterations in the structure, function, or metabolism of the brains of children, adoles-
cents, and young adults who were prenatally exposed to drugs of abuse; including alcohol, cocaine, methamphetamine, or a combination of these drugs. For each of these drugs, we will briefly describe the pharmacological mechanisms of action, the current theories about the mechanisms underlying teratogenic effects, and summarize the most significant findings from animal models of prenatal exposure, before reviewing the current human neuroimaging findings. Following is a description of each MR-based imaging technique which has been used as a vehicle for understanding the impact of prenatal drug exposure on the developing brain, and which comprises the literature we will discuss in the following sections.

Structural Magnetic Resonance Imaging (sMRI)

sMRI allows for high-spatial resolution in-vivo measurement of brain structure. In these studies, research participants are exposed to a high intensity magnet, which detects differences between different types of body tissue and produces data that can be reconstructed into visual images. Physical changes specific to different tissue types result in contrast between gray and white matter (Hendee and Morgan 1984). These images can later be analyzed quantitatively using computational techniques and specialized software packages. Measures such as regional volume, cortical thickness, and other measures of brain morphology can be analyzed and compared across groups.

Diffusion Tensor Imaging (DTI)

DTI also uses MRI technology, and allows measurement of the diffusion of water molecules within brain tissues, specifically white matter, in order to produce images of white matter tracts (Basser et al. 1994). Important variables derived from DTI datasets are Fractional Anisotropy (FA), Mean Diffusivity (MD), and Apparent Diffusion Coefficient (ADC). FA is a weighted measure of water diffusion, and it is believed to relate to the integrity of white matter, with higher values usually indicating increased integrity (i.e., increased myelination, increased axonal density or diameter). It is important to note that, although FA is often thought of as an indirect indication of white matter integrity, FA actually measures spatial coherence of diffusion, which can be affected by other factors besides changes in white matter integrity. Therefore, the interpretation of findings from DTI studies is not always straightforward. MD and ADC are measures of total diffusion. In some cases, higher MD suggests poorer integrity (i.e., less myelination, lower density or disorganization of axonal fibers). Despite limitations, DTI provides important information about changes occurring in white matter microstructure and microdynamics (Le Bihan 1995), during normal brain development, and in various brain pathologies. The main findings from sMRI and DTI studies of prenatal exposure to alcohol and stimulants are summarized in Table 1.

Magnetic Resonance Spectroscopy (MRS)

MRS is another MR-based neuroimaging method, which provides information about metabolic functioning in particular regions of interest. MRS capitalizes on different physical properties of chemicals in the body when they are exposed to a high magnetic field. MRS can be used to study the metabolism of various organs. This technique is particularly useful in brain research because measures of concentrations of metabolites important to the production of neurotransmitters can be detected. The application of MRS has been mostly limited to proton spectroscopy, which can resolve only a few molecules abundant in the brain. For example, concentrations of neuronal markers such as N-acetyl-containing compounds (NA) or N-acetyl aspartate (NAA) and glutamate-glutamine (GLX), glial markers such as choline (Cho) and myoinositol (MI), as well as chemicals involved in energy metabolism such as creatine (Cr) or total creatine (tCR), can be measured either in absolute concentration values or as ratios relative to each other (Ross and Bluml 2001).

Functional Magnetic Resonance Imaging (fMRI)

fMRI is one of the most frequently used techniques to study brain function in humans. This technique provides an indirect assessment of neuronal activity. It measures the dynamic regulation of blood flow in the brain, known as the hemodynamic response, which relates to brain activity. Oxygenated hemoglobin has a different MR signal than deoxygenated hemoglobin. Thus, hemodynamic events lead to transient changes in MR signal, which can be observed when nuclear magnetic resonance images of the brain are acquired in rapid succession. Determining which brain regions show an increase in MR signal intensity provides clues as to which areas are activated during a particular cognitive task. fMRI allows researchers to localize functional brain activation with an accuracy of millimeters and a temporal resolution of seconds (Cohen and Bookheimer 1994). Unlike Blood Oxygen Level-Dependent (BOLD) fMRI described above, Arterial Spin Labeling (ASL) perfusion fMRI investigates patterns of cerebral activation by using magnetically labeled arterial blood water as an endogenous tracer to provide an absolute quantification (millimeters of blood per 100 gram of tissue per minute) of Cerebral Blood Flow (CBF), which is coupled with neuronal activity (Detre et al. 1992).
Neuroimaging of Prenatal Exposure to Alcohol

Mechanism of Action and Toxicity

Alcohol is a central nervous system depressant, which decreases cortical and subcortical activity through its interactions with membrane receptors. Alcohol primarily acts as an indirect agonist at the GABA_A receptor (Ticku et al. 1986), but it also acts as an indirect antagonist at the glutamate NMDA receptor (Hoffman et al. 1989). Alcohol also facilitates dopamine transmission in the mesolimbic system (Imperato and Di Chiara 1986). Alcohol crosses the placenta and the blood-brain barrier and can exert teratogenic effects on the developing fetus through various mechanisms, including alcohol-induced hypoxia (Mitchell et al. 1998), increased embryonic oxidative stress (Pollard 2007; Ornoy

Table 1  Summary of main sMRI and DTI findings

| Alcohol | Frontal Lobes | Temporal Lobes | Parietal Lobes | Subcortical Structures | Cerebellum | Corpus Callosum |
|---------|---------------|---------------|---------------|-----------------------|------------|-----------------|
| Archibald et al. (2001) | V relatively spared | V relatively spared | ↓GM, ↓WM | ↓ V Caudate, HPC relatively spared |
| Sowell et al. (2002a) | ↓ V, ventral parts only | | ↑CT | |
| Sowell et al. (2008a) | ↑CT | ↑CT | ↑GM, ↓WM | |
| Sowell et al. (2001a) | | | ↑GM, ↓WM | |
| Sowell et al. (2002b) | | | Altered GM asymmetry | |
| Mattson et al. (1996) | | | | ↓ V BG, T, HT |
| Cortese et al. (2006) | | | | ↓ V Caudate |
| Sowell et al. (1996) | | | | ↓ A anterior VM |
| O’Hare et al. (2005) | | | | ↓ A anterior VM and DP |
| Riley et al. (1995) | | | | ↓ A or AG |
| Swayze et al. (1997) | | | | AG |
| Bookstein et al. (2001) | | | | High shape variability |
| Bookstein et al. (2002) | | | | High shape variability |
| Sowell et al. (2001b) | | | | ↓ A and DP |
| Ma et al. (2005) | | | | ↓ FA |
| Li et al. (2009) | | | | ↓ FA |
| Fryer et al. (2009) | ↓ FA | | | |
| Wozniak et al. (2006) | | ↓ FA, right | | ↓ FA |
| Sowell et al. (2008b) | | | | ↓ FA |
| Lebel et al. (2008) | ↑ MD | ↓ FA, ↑ MD | ↓ FA T, ↑ FA GP, ↑ MD GP, Put, T | ↓ FA |
| Cloak et al. (2009) | ↓ ADC | | | |
| Cocaine | Warner et al. (2006) | ↑ D_{av} | | ↓ GM | ↓ V |
| Dow-Edwards et al. (2006) | | | | | |
| Rao et al. (2007) | | | ↑ V Amygdala, ↓ V Caudate |
| Avants et al. (2007) | | | | ↓ V Caudate |
| Methamphetamine | Chang et al. (2004) | ↓ V IFG, V inferior | | ↓ V GP, Put, HPC |
| Sowell et al. (2010) | ↑ V IFG and medial | ↓ V dorsal | ↓ V Str, T |
| Cloak et al. (2009) | ↓ ADC | | | |

V Volume, A area, CT Cortical Thickness, DP Displacement, AG Agenesis, GM Gray Matter, WM White Matter, AC Anterior Cingulate, PC Posterio Cingulate, BG Basal Ganglia, Str striatum, GP Globus Pallidus, Put Putamen, HPC Hippocampus, T Thalamus, HT Hypothalamus, VM vermis, IFG Inferior Frontal Gyrus, FA Fractional Anisotropy, MD Mean Diffusivity, D_{av} Average Diffusion, ADC Average Diffusion Coefficient
Structural and Metabolic Brain Abnormalities as a Result of Prenatal Alcohol Exposure

In recent years, several neuroimaging studies have confirmed that children with heavy prenatal alcohol exposure show reductions in overall brain size (Archibald et al. 2001; Mattson et al. 1996; Swayze et al. 1997). This finding was first reported in post-mortem studies published in the 1970’s (Jones and Smith 1973; Jones et al. 1973; Clarren and Smith 1978). The advent of structural neuroimaging techniques has allowed researchers to study localized brain volume reductions and to make inferences about what brain systems are most affected by prenatal exposure to alcohol. In the next several paragraphs, we will summarize results from various neuroimaging studies of prenatal alcohol exposure. It is important to keep in mind that several of these studies used the same sample of subjects with FASD. In particular, various studies by our group relied on the same data, which was analyzed with diverse techniques in order to study different aspects of brain structure, such as brain shape abnormalities, cortical thickness, gray and white matter volumes, gray matter asymmetry, and cerebellar and callosal morphology.

Evidence of structural abnormalities in the frontal lobe as a result of prenatal alcohol exposure has been reported. Although one study found that frontal lobe volumes were relatively spared compared to other parts of the brain after controlling for overall brain size (Archibald et al. 2001), another study, which examined subregions of the frontal lobes, reported volume reductions in subjects with FASD. Specifically, children with FASD had decreased volumes of the ventral frontal lobes, most prominently in the left hemisphere, while larger dorsal frontal regions appeared somewhat spared (Sowell et al. 2002a) (Fig. 1b). A later study by the same group reported another type of structural brain abnormality in the frontal lobes. Children with FASD were found to have increased cortical thickness compared to unexposed controls in ventral and inferolateral frontal regions in the right hemisphere (Sowell et al. 2008a) (Fig. 2).

The published literature also suggests that prenatal alcohol exposure impacts the temporal lobes. Although temporal lobe volumes appear to be relatively spared compared to other brain regions after controlling for overall brain size in children with FASD (Archibald et al. 2001), subtle structural abnormalities of the temporal lobes have been reported. Specifically, children with FASD were found to have increased gray matter and decreased white matter in the temporal cortex (Sowell et al. 2001a). Another study by the same group showed that subjects with heavy prenatal alcohol exposure had increased cortical thickness in the temporal lobes, which suggests increased gray matter in these regions and corroborates the earlier report (Sowell et
al. 2008a). An additional study by this group showed that subjects with FASD have an altered pattern of gray matter asymmetry in the posterior inferior temporal lobes, with a significant reduction in asymmetry between the two hemispheres in this region, compared to unexposed controls (Sowell et al. 2002b).

It appears that the parietal lobes may be the cortical areas which are most affected by prenatal exposure to alcohol. One study reported both gray and white matter volume reductions in the parietal lobes of subjects with severe prenatal alcohol exposure (Archibald et al. 2001), whereas another study found decreased white matter but increased gray matter in the left parietal lobe of subjects with FASD (Sowell et al. 2001a). The same group later replicated their finding using different methods, and reported increased gray matter density in the inferior parietal cortex bilaterally (Sowell et al. 2002a). In a third study, the same researchers showed that children with prenatal alcohol exposure had thicker cortex in the parietal lobes compared to unexposed controls, again possibly suggesting increased gray matter in these regions (Sowell et al. 2008a), perhaps resultant from abnormal synaptic pruning or myelination. An apparent
increase in gray matter may result from incomplete synaptic pruning during neural development, but alternatively, it may be a result of unmyelinated white matter, which appears as gray matter on magnetic resonance images (Sowell et al. 2004). Brain development is a very protracted process which continues throughout the lifespan, and the trajectory of maturational effects vary extensively in different regions of the cortex (Sowell et al. 2003) (Fig. 3), with some areas myelinating early, and others continuing myelination into adulthood. In addition, the relationship between cortical thickness and cortical volumes is likely complex, and has not been well characterized in this population, which complicates the interpretation of such findings in individuals with prenatal alcohol exposure even further.

Structural brain abnormalities have also been reported in some subcortical structures in children with prenatal alcohol exposure. The published literature suggests that basal ganglia and diencephalic structures are most affected, while medial temporal lobe regions may be relatively spared. Specifically, decreased volumes of the basal ganglia have been reported, and remain significant, even after controlling for reductions in total brain volume (Mattson et al. 1996). Within the basal ganglia, the caudate appears to be most affected (Archibald et al. 2001; Cortese et al. 2006). Diencephalic structures such as the thalamus and hypothalamus also show volume reductions in children with severe prenatal alcohol exposure (Mattson et al. 1996). Hippocampal volumes, on the other hand, appear to be somewhat preserved relative to overall brain volume reduction in children exposed to alcohol in utero (Archibald et al. 2001).

Two studies have also reported structural changes in the cerebellum associated with prenatal alcohol exposure. An early study reported a significant reduction in the area of the anterior vermis, whereas posterior regions appeared relatively spared (Sowell et al. 1996). Consistent with this finding, a later investigation showed abnormalities in both the size and the location of the vermis in children with FASD. In alcohol-exposed subjects, the anterior vermis and the posterior-inferior lobe showed reduced surface area. There was also a displacement of the anterior vermis, which appeared to be shifted inferiorly and posteriorly in exposed subjects compared to unexposed controls (O’Hare et al. 2005) (Fig. 1c).

Many published studies have found abnormalities in white matter tracts in children with prenatal exposure to alcohol. The corpus callosum alone has been the object of several investigations, and several types of defects have been reported, including partial or complete agenesis and reduced size (Swayze et al. 1997; Riley et al. 1995). It has been suggested that children with FASD, unlike unexposed children, show a high level of variability in the shape of the

![Fig. 2](image-url)
corpus callosum (Bookstein et al. 2001), and that this high level of variance has also been found in adults with FASD (Bookstein et al. 2002). A study found structural abnormalities in the location and size of the corpus callosum in children, adolescents, and young adults with FASD. The inferior and anterior displacement of the corpus callosum in exposed subjects was mostly restricted to posterior splenial and isthmus regions, while the more anterior areas of the genu and mid-body appeared relatively spared. There was also a reduction in the area of the corpus callosum in subjects with FASD, mostly in the posterior region encompassing the splenium (Sowell et al. 2001b) (Fig. 1a).

Not only does the corpus callosum show morphological differences in structural MRI studies of FASD, it also reveals reductions in white matter integrity in DTI investigations. Studies have reported lower FA values in the genu and splenium (Ma et al. 2005), as well as in the isthmus (Li et al. 2009) of young adults with severe prenatal alcohol exposure, suggesting decreased integrity of white matter fibers in these callosal regions. Lower FA was observed in the body of the corpus callosum as well as in other white matter tracts, located in bilateral medial frontal and occipital regions in children and adolescents exposed to alcohol prenatally (Fryer et al. 2009). Greater MD was reported in the isthmus of children with prenatal alcohol exposure without any facial abnormalities, suggesting that exposure to alcohol in utero may be associated with microstructural abnormalities in the posterior corpus callosum even in the absence of facial dysmorphology (Wozniak et al. 2006).

In addition to the corpus callosum, abnormalities in other white matter tracts have been reported in children and adolescents with prenatal alcohol exposure. One study using a combination of DTI and structural MRI evaluated both FA, which reflects the quality of the organization of white matter microstructures, and white matter density, which is used to assess white matter macrostructure, by examining the location and amount of white matter throughout the brain. Investigators reported that FA was significantly lower in the exposed group compared to the
unexposed control group in several areas, in particular in the lateral splenium, in the deep association fibers of the right temporal lobe, and in the right internal capsule and brainstem regions. White matter density was lower in subjects with prenatal alcohol exposure in some, but not all regions where FA was affected (Sowell et al. 2008b). Another DTI study reported abnormal diffusion parameters in many areas of the brain in children with FASD. The right cingulum, bilateral inferior and superior longitudinal fasciculus, splenium of the corpus callosum and left thalamus showed FA reduction in exposed children, while increased FA was observed in the bilateral globus pallidus. Increased MD was noted in the bilateral inferior fronto-occipital fasciculus, left inferior longitudinal fasciculus, right cortico-spinal tract, globus pallidus, left putamen, and left thalamus, while MD was reduced in the genus of the corpus callosum, suggesting widespread microstructural differences between exposed subjects and unexposed controls (Lebel et al. 2008).

Finally, three MRS studies reported metabolic abnormalities in the brains of children with prenatal exposure to alcohol, but have yielded inconsistent results. One investigation found lower NAA/Cho and NAA/Cr ratios in the parietal and frontal cortices, frontal white matter, corpus callosum, thalamus, and cerebellar dentate nucleus of adolescents and young adults with FASD, compared to unexposed controls. This was due to increased intensity of the glial markers Cho and Cr, while no changes in the neuronal marker NAA were detected, suggesting that these metabolic abnormalities in subjects with FASD represent changes in glial cells rather than in neurons (Fagerlund et al. 2006). Another study, which examined children rather than adolescents, reported somewhat contradictory findings. A higher NAA/Cr ratio was observed in the caudate nucleus of exposed subjects, and this change was due to an increase in NAA alone. This suggests a lack of normal programmed cell death, dendritic pruning, or myelination in subjects with FASD (Cortese et al. 2006), perhaps consistent with the interpretation of cortical thickness increases being associated with a lack of normal synaptic pruning. A third group made observations that differed from both studies described above. Investigators reported reduced concentrations of Cho in fronto-parietal white matter regions lateral to the midsection of the corpus callosum in children with FASD. Decreased Cho concentrations were associated with reduced frontal white matter volumes and shorter length of the corpus callosum (Astley et al. 2009a).

To our knowledge, six studies have examined relationships between structural brain abnormalities and neurocognitive performance in children with prenatal alcohol exposure. One study investigated relationships between cortical thickness and two measures of cognitive functioning: verbal learning and visuospatial functioning in subjects with FASD and unexposed controls. Subjects with prenatal alcohol exposure performed more poorly than controls on both tasks. In the control group, negative correlations were reported between verbal recall performance and cortical thickness at the superior edge of the motor strip bilaterally in the left occipital lobe. In the FASD group, positive correlations were found between verbal recall scores and bilateral dorsal prefrontal regions. In the control group, negative correlations were observed between visuospatial skills and cortical thickness in bilateral parietal, left occipital, right dorsal and ventral frontal, as well as in temporal cortices. No correlations between visuospatial skills and cortical thickness were found in subjects with FASD. Taken together, these findings suggest that pruning and myelination processes as well as brain-structure-function relationships follow an altered trajectory in children with heavy prenatal alcohol exposure (Sowell et al. 2008a). Another study examined relationships between the morphology of the cerebellar vermis and verbal learning as well as visuospatial memory scores in subjects with FASD. The superior edge of the anterior vermis showed the strongest negative correlation with verbal learning performance. This region partially overlaps with the vermal region showing the greatest amount of displacement in subjects with FASD. This suggests that impaired verbal learning may be a cognitive correlate of cerebellar vermal displacement (O’Hare et al. 2005).

The remaining correlational studies examined relationships between white matter structures and cognitive performance. One study examined relationships between callosal dysmorphology, verbal learning abilities, and visuospatial skills in children, adolescents, and young adults with FASD. Results revealed that anterior displacement of the corpus callosum was strongly associated with poorer verbal learning performance. Correlations between callosal dysmorphology and visuospatial skills, on the other hand, were much weaker (Sowell et al. 2001b). Another study examined the cognitive correlates of callosal dysmorphology in children with FASD. Investigators assessed the efficiency of interhemispheric transfer of tactile information in children with FASD. Children with prenatal alcohol exposure made significantly more transfer-related errors than controls. Furthermore, there was a negative correlation between the number of transfer-related errors and the size of the isthmus and splenium, suggesting that callosal abnormalities associated with heavy prenatal alcohol exposure impair the functioning of the corpus callosum (Dodge et al. 2009).

Two additional studies investigated relationships between white matter structures and intellectual functioning. One DTI study attempted to relate white matter integrity, visuomotor integration skills, and reading abilities in...
children with FASD and unexposed controls. Correlations between reading scores and FA were not significant in any region tested. On the other hand, poorer performance on a test of visuomotor integration was significantly associated with lower FA values in the lateral splenium and parietal white matter bilaterally, in the exposed group only. These results show that some white matter microstructural abnormalities observed in children with prenatal alcohol exposure may be clinically significant (Sowell et al. 2008b) (Fig. 4). Finally, a recent DTI study examined relationships between white matter structure and mathematical skills in children with FASD. Significant correlations between math scores and FA were observed. Specifically, investigators reported two positively correlated clusters in the left parietal region, one positively-correlated cluster in the left cerebellum, and one negatively-correlated cluster in the bilateral brainstem. These findings provide additional evidence for a link between white matter microstructure and cognitive functioning in children with heavy prenatal alcohol exposure (Lebel et al. 2010) (Fig. 5).

Functional Brain Abnormalities as a Result of Prenatal Alcohol Exposure

Although a large number of studies have been published about structural brain abnormalities as a result of prenatal alcohol exposure, only six studies have investigated abnormalities in functional brain activation in subjects with FASD, four of which have examined functional brain activation during working memory. The first fMRI study, which focused on spatial working memory, reported that both children and adults with FASD showed greater activity than controls in the inferior and middle frontal cortex, suggesting improper functioning of prefrontal areas in the exposed group. Children with FASD also had greater activation than unexposed children in the parietal cortex.

![Fig. 4 ROI FA analyses and brain behavior correlations. Coronal and sagittal slices of one representative subject’s brain with significant clusters from the FA and white matter density analyses. Shown in dark blue are regions where FA (but not WMD) was significantly lower in the individuals with FASD relative to control subjects (p<0.05, FDR correction for multiple comparisons). Regions in light blue are regions where WMD was lower in the FASD relative to controls (p<0.001, uncorrected) and overlapped with regions of lower FA in FASD. The y-axes for all graphs have FA values. In the top row of graphs, FA values for each subject are shown for the FASD and control groups. FA values were taken from ROIs (localized approximately at the intersection of the crosshairs in each image) of all voxels within an 8 mm sphere in the unsmoothed, white matter masked FA volume for each individual. In the bottom row, FA values from the same ROIs are shown in relation to subjects behavioral scores on the VMI. Control subjects are shown in red and FASD subjects in blue. Correlations between VMI scores and FA were highly significant in the left and right lateral splenium ROIs within the FASD, but not control subjects, and not for either group in the anterior and posterior temporal ROIs (Sowell et al. 2008)](image-url)
in one of the task conditions (Malisza et al. 2005). However, since accuracy and reaction time were poorer in exposed subjects, it is difficult to determine whether the observed differences in brain activation reflect actual group effects, or just general factors related to performance. Nonetheless, some of these findings have been replicated in a more recent fMRI study of spatial working memory in children and adolescents with FASD. Investigators reported group differences in brain activation despite equivalent performance on the task in children with prenatal alcohol exposure and controls. As in the previous study, they observed greater functional activation in exposed subjects in inferior frontal regions during spatial working memory. They also noted increased activation in other areas, including many subcortical regions, in children with FASD compared to unexposed controls (Spadoni et al. 2009). Taken together, these data suggest that prefrontal regions may be taxed to a greater degree during spatial working memory task in subjects with heavy prenatal alcohol exposure.

Two additional fMRI studies have investigated the effects of prenatal alcohol exposure on brain activation during working memory. Despite equivalent performances between groups, children and adolescents with FASD showed increased activation relative to unexposed controls in left dorsal frontal and left inferior parietal cortices, and in posterior temporal regions bilaterally during a verbal working memory task (O’Hare et al. 2009) (Fig. 6). This study relied on a sample of FASD subjects overlapping with the sample used in the DTI study that examined relationships between callosal dysmorphology, verbal learning abilities, and visuospatial skills (Sowell et al. 2008b). Interestingly, some of the areas where verbal working-memory-related abnormalities in functional activation were detected in this study, in particular posterior temporal and inferior parietal regions (O’Hare et al. 2009), had previously been reported to show structural abnormalities, specifically increased gray matter in a non-overlapping sample of individuals with FASD (Sowell et al. 2002a). The fourth functional neuroimaging study of prenatal alcohol exposure and functional brain activation during working memory focused on visual working memory. Investigators tried to determine whether fMRI could distinguish between diagnostic subclasses within the FASD spectrum. Results showed that in the harder task condition, the most severely affected children had significantly lower activation than controls in various parts of the working memory network, such as the right posterior parietal lobe, right dorsolateral prefrontal cortex, and right middle frontal regions. As one advanced across the diagnostic categories from most to least severe FASD diagnoses and then to controls, activation levels increased in these brain region (Astley et al. 2009b).
The remaining two fMRI studies examining the effects of prenatal alcohol exposure focused on inhibitory control and verbal learning. Despite the absence of group differences in performance, individuals with FASD showed increased functional activation relative to controls in the prefrontal cortex and decreased activation in the caudate nucleus during a response inhibition task. The authors suggested that this increased recruitment of prefrontal regions might mitigate decreased frontal-striatal network efficiency induced by alcohol teratogenesis (Fryer et al. 2007). On a task of verbal learning, fMRI results indicated that children with prenatal alcohol exposure showed significantly less activation than unexposed controls in the left medial and posterior temporal regions and significantly more activation in the right dorsal frontal cortex, even when group differences in IQ and memory performance were statistically controlled (Sowell et al. 2007) (Fig. 7). In this study, which relied on a sample of FASD subjects overlapping with the samples used in two other studies described above (Sowell et al. 2008b; O’Hare et al. 2009), it appears again that some of the brain regions in which children with FASD showed functional activation abnormalities had previously been shown to present structural abnormalities in a non-overlapping sample of children with heavy prenatal alcohol exposure. In particular, increased gray matter had been reported in medial temporal (Archibald et al. 2001) and posterior temporal regions (Sowell et al. 2002a) in subjects with FASD.
Consistent across all but one of these studies, there appears to be increased activation in frontal brain regions in children with FASDs compared to controls, regardless of fMRI task (Malisza et al. 2005; Spadoni et al. 2009; O’Hare et al. 2009; Fryer et al. 2007; Sowell et al. 2007). It is unclear why increased frontal activation was not reported in one of the fMRI studies (Astley et al. 2009b), as the frontal lobes are an important part of the working memory network. It is possible that differences in methodology between studies may explain this discrepancy. The study with incongruent findings examined regions of interest whereas whole brain analyses are more typically reported in the current literature.

In conclusion, the abundant neuroimaging literature of prenatal alcohol exposure suggests that most brain systems are affected by the teratogenic effects of alcohol. The functional neuroimaging studies published so far indicate that subjects with FASDs show abnormal patterns of brain activation in many cognitive domains. These human neuroimaging findings are consistent with the animal literature, which shows that prenatal alcohol exposure affects the developing nervous system through various cellular and molecular mechanisms and results in structural and metabolic abnormalities in many brain regions.

**Neuroimaging of Prenatal Exposure to Cocaine**

**Mechanism of Action and Toxicity**

Cocaine binds to and blocks the activity of monoamine transporters, including the norepinephrine (NET) and serotonin (SERT) transporters, with highest affinity for the dopamine (DAT) transporter. This results in decreased monoamine re-uptake at the synapse, and increased extracellular levels of these neurotransmitters, especially dopamine (Ritz et al. 1990; Meyer et al. 1993). Cocaine is also a potent anesthetic that blocks sodium channels in a voltage-dependent manner (Wang 1988), resulting in decreased action potentials in excitable cells. In addition, cocaine causes vasoconstriction, which could lead to reduced blood supply and oxygenation to a developing fetus, potentially resulting in chronic or intermittent hypoxia and possible ischemic injury (Koegler et al. 1991;
Because cocaine easily crosses both the placenta and the blood-brain barrier (Schenker et al. 1993), all of these mechanisms of action can exert significant teratogenic effects on the developing fetus, both directly and indirectly (Woods 1996). In addition, it has recently been proposed that cocaine may act as an intrauterine stressor, which disrupts the regulation of the neuroendocrine environment by acting on the hypothalamic-pituitary-adrenal (HPA) axis, resulting in altered genetic programming of fetal-placental development (Lester and Padbury 2009).

Various animal studies have suggested that abnormalities related to prenatal exposure to cocaine may result from interference with the neurotrophic functions of monoamine neurotransmitters during brain development (Levitt et al. 1997; Whitaker-Azmitia 1998; Mayes 1999; Malanga and Kosofsky 1999; Stanwood and Levitt 2004). Cocaine may also disrupt early brain development through its interactions with other neurotransmitters, such as GABA (Crandall et al. 2004) and adenosine (Kubrusly and Bhide 2010), and its secondary effects on gene expression, including transcription factor genes (Guerriero et al. 2005; Bhat and Baraban 1993), and apoptosis-related genes (Novikova et al. 2005). The precise mechanisms through which cocaine affects brain development are still debated, but animal models have clearly established that prenatal cocaine exposure results in specific cellular and molecular changes. These include altered cell proliferation (Gressens et al. 1992; Lidow and Song 2001a, b) and migration (Crandall et al. 2004; Lidow 1995; Ren et al. 2004) as well as abnormalities in dopamine D1 receptors and dysfunctions in associated G-protein signaling pathways (Friedman et al. 1996; Jones et al. 2000; Wang et al. 1995; Stanwood et al. 2005).

Structural and Metabolic Brain Abnormalities as a Result of Prenatal Cocaine Exposure

A variety of gross CNS abnormalities have been reported in children with prenatal exposure to cocaine, including cortical infarcts and neural tube defects (Heier et al. 1991), pachygyria (Gomez-Anson and Ramsey 1994), schizencephaly and interhemispheric cysts (Gieron-Korthals et al. 1994), and subependymal and periventricular cysts (Cohen et al. 1994). Regarding more subtle alterations in brain structure, human structural neuroimaging studies of prenatal cocaine exposure have yielded somewhat inconsistent results. A DTI study reported that children with prenatal cocaine exposure had higher average diffusion coefficients in the left frontal callosal and right frontal projection fibers, suggesting suboptimal white matter development due to reduced integrity and/or slower maturation of frontal brain regions (Warner et al. 2006). A study combing sMRI and MRS found no gross structural or volumetric abnormalities in exposed children and adolescents, but reported a 13% increase in right frontal white matter creatine levels, suggesting abnormal energy metabolism (Smith et al. 2001a).

One whole-brain volumetric study of children with prenatal cocaine exposure showed that exposed subjects had reduced cortical gray matter volumes, total parenchymal volumes, and head circumference. However, these effects lost statistical significance after exposure to other drugs of abuse were regressed out (Rivkin et al. 2008). On the other hand, in another volumetric study, which reported gray matter reductions in occipital and parietal lobes and white matter reductions in the volume of the corpus callosum in exposed children, the findings remained significant even after controlling for exposure to other drugs (Dow-Edwards et al. 2006). In this study, the amount of prenatal cocaine exposure predicted the total area of the corpus callosum, but reductions in gray matter volumes in the occipital and parietal lobe were not dose-dependent (Dow-Edwards et al. 2006). Regarding subcortical structures, a study reported increased gray matter volumes in the amygdala (Rao et al. 2007), and two studies reported decreased volumes in the caudate nucleus (Rao et al. 2007; Avants et al. 2007).

Among the studies published thus far, there have been two reports that changes in brain structures in children with prenatal exposure to cocaine relate to neurocognitive performance. In one study, gray matter volume reductions in the right parietal lobe at 7–8 years were significantly associated with poorer performance on tests of visual attention, visual motor precision, sensorimotor core abilities, and syntax construction at 6 years-of-age. Gray matter volume reductions in the left occipital lobe at 7–8 years were significantly associated with poorer performance on neonatal tests of visual attention, lower scores on visual recognition tests at 12 months, and decreased visuomotor performance at 6 years in children with prenatal cocaine exposure (Dow-Edwards et al. 2006). Another study reported that children exposed to cocaine in utero who showed abnormalities in frontal white matter also had poorer visuospatial and executive performance, assessed by longer completion times on a set shifting letter-number sequencing task (part B of the Trail Making Test, Warner et al. 2006).

Functional Brain Abnormalities as a Result of Prenatal Cocaine Exposure

To our knowledge, there are three published functional MRI studies of prenatal exposure to cocaine. One perfusion fMRI study reported a 10% decrease in global cerebral blood flow (CBF) in adolescents with prenatal cocaine exposure. Exposed subjects had reduced global CBF intensities in posterior and inferior brain regions and a
relative increase in CBF in anterior and superior brain regions, suggesting that compensatory mechanisms may develop during neural ontogeny (Rao et al. 2007) (Fig. 8). A BOLD fMRI study reported no significant differences in behavioral accuracy or functional brain activation between adolescents with prenatal cocaine exposure and unexposed controls during a nonspatial working memory “N-Back” task, although there was a trend for the non-exposed participants to show greater activation than exposed subjects in the left prefrontal area during the task (Hurt et al. 2008) (Fig. 9). In another BOLD fMRI study of response inhibition, there were no group differences in performance on the Go-No Go task between children with prenatal cocaine exposure and non-exposed controls, but group differences in task-related brain activation were observed. Specifically, the exposed group showed greater activation in right inferior frontal and striatal regions, whereas control subjects showed greater activation in the occipital cortex and fusiform gyrus during the task, suggesting functional differences between groups in neural systems underlying cognitive control and attention regulation (Sheinkopf et al. 2009).

In conclusion, the neuroimaging literature of prenatal exposure to cocaine is much less abundant than that of prenatal exposure to alcohol, and the results published thus far are somewhat inconsistent. Further investigations with large sample sizes will be needed in order to resolve these apparent discrepancies, and improve our understanding of the impact of prenatal cocaine exposure on the developing human brain.

**Neuroimaging of Prenatal Exposure to Methamphetamine**

**Mechanism of Action and Toxicity**

Methamphetamine acts as a substrate for the plasma membrane dopamine and norepinephrine transporters (DAT and NET); therefore, unlike cocaine, it is transported into cells. Methamphetamine causes reverse transport, whereby the plasma membrane transporters release neurotransmitter molecules into the synapse instead of performing their normal reuptake functions, which leads to a massive increase in synaptic levels of catecholamine neurotransmitters (Sulzer et al. 2005). But methamphetamine also leads to a considerable increase in cytosolic catecholamines via at least three distinct mechanisms. Once inside the nerve terminals, methamphetamine causes the releases of dopamine and norepinephrine from vesicles by blocking the vesicular monoamine transporter (VMAT2). In addition, methamphetamine blocks the catabolism of catecholamines, by inhibiting mitochondrial monoamine oxidase (MAO). Methamphetamine also leads to increased

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**Fig. 8** Quantitative resting CBF image for the cocaine and control groups. a Mean CBF image for the cocaine group. b Mean CBF image for the control group. c Quantitative CBF differences between the two groups (cocaine—control; blue color means CBF is higher for controls, and red color means CBF is higher for cocaine-exposed subjects). Note the robust CBF decreases in the occipital and thalamus regions for the cocaine group versus the control group (Rao et al. 2007)
synthesis of dopamine and norepinephrine by stimulating the enzyme tyrosine hydroxylase (Sulzer et al. 2005). Methamphetamine has well-established neurotoxic effects (Frost and Cadet 2000), and the increase in cytosolic catecholamines via the mechanisms described above is believed to underlie most of its neurotoxicity. It leads to the loss of dopamine and norepinephrine terminals because high levels of cytosolic catecholamines are metabolized to reactive metabolites, causing the production of free radicals and leading to oxidative damage. In addition, the production of nitric oxide, p53 activation resulting in apoptosis, excitotoxicity, and mitochondrial damage may also be involved in the neurotoxicity of methamphetamine (Quinton and Yamamoto 2006).

In addition to its direct neurotoxic effects, which have been shown to alter the development of the neural circuitry (Frost and Cadet 2000), methamphetamine may exert significant teratogenic effects on the developing fetus through indirect mechanisms, such as vasoconstriction (Burchfield et al. 1991; Stek et al. 1993), potentially resulting in diminished blood flow to the fetus and fetal hypoxia (Stek et al. 1995). Like cocaine, methamphetamine could also alter the developmental trajectory of the fetus by acting on the hypothalamus-pituitary-adrenal axis, disrupting fetal placental monoamine transporter expression, and altering gene expression through epigenetic mechanisms, such as chromatin remodeling and DNA methylation (Salisbury et al. 2009). Rodent models of prenatal exposure to methamphetamine have shown widespread damage to the nervous system, including serotonergic neurotoxic effects and synaptic remodeling of axonal terminals (Weissman and Caldecott-Hazard 1995), disruptions in the levels of monoamine transmitters and altered activity of monoamine systems (Cabrera et al. 1993; Gomes-da-Silva et al. 2002), widespread deficits in the development of the visual system including the retina (Melo, Rodrigues et al. 2006) and the optic nerve (Melo, Moreno et al. 2006), and oxidative DNA damage in the brain, potentially resulting in postnatal motor abnormalities (Jeng et al. 2005).

Structural and Metabolic Brain Abnormalities as a Result of Prenatal Methamphetamine Exposure

Until recently, little was known about the effects of prenatal methamphetamine exposure in humans, but in the last few years, several large prospective studies have reported restricted fetal growth in newborn infants prenatally exposed to methamphetamine (Smith et al. 2006; Nguyen et al. 2010) along with poorer neurobehavioral outcomes, such as under-arousal and depressed movement scores (Smith et al. 2008; Lagasse et al. 2010). Three recent neuroimaging investigations have reported structural brain abnormalities in children with prenatal methamphetamine exposure. A study using sMRI showed that children exposed to methamphetamine in utero had significant regional brain volume reductions in the putamen, globus pallidus, hippocampus, and a trend-level decrease in the volume of the caudate, compared to unexposed controls (Chang et al. 2004). Some of these findings were replicated in another sMRI study aimed at differentiating the effects of prenatal methamphetamine from alcohol exposure. Volume reductions in the striatum, cingulate gyrus, and right inferior frontal gyrus were found to be more severe in children with prenatal exposure to methamphetamine than in subjects with prenatal exposure to alcohol only. These findings suggest that striatal and limbic structures may be especially vulnerable to the teratogenic effects of methamphetamine (Sowell et al. 2010) (Fig. 10). The only DTI study of prenatal methamphetamine exposure reported that exposed children had lower ADC in the frontal and parietal...
white matter compared to controls, suggesting more compact axons or greater dendritic or spine density (Cloak et al. 2009).

Two MRS studies examined metabolic changes in the brains of children with prenatal exposure to methamphetamine. In one report, exposed children had normal NA concentrations in the frontal white matter and striatum, suggesting no significant neuronal loss in these brain regions. However, they had higher Cr concentrations than controls in the striatum, which suggests that prenatal methamphetamine exposure results in abnormal energy metabolism in this region (Smith et al. 2001b). In a more recent study by the same group with a larger sample of subjects, metabolic abnormalities were detected in the frontal white matter. Compared to unexposed controls, exposed children had higher tCr, NA, and GLX concentrations in the frontal white matter, suggesting higher neuronal density or cellular compactness in this area. They also had lower MI and MI/tCr ratio in the thalamus, which suggests lower glial content in this structure. Taken together, these findings may indicate aberrant neuronal and glial development in these brain regions (Chang et al. 2009).

Among the studies described above, three have reported correlations between structural or metabolic brain abnormalities and neurocognitive performance in children with prenatal exposure to methamphetamine. Investigators showed that in exposed children, reduced MI concentrations in the thalamus were correlated with poorer performance on a visual motor integration task (Chang et al. 2009). Volume reductions in the putamen, globus pallidus, and hippocampus were found to be correlated with poorer performance on sustained attention and delayed verbal memory in children exposed to methamphetamine in utero (Chang et al. 2004). Striatal abnormalities were also shown to be associated with cognitive deficit in another study. In children with prenatal methamphetamine exposure, volume reductions in the caudate were reported to correlate with full-scale intelligence quotient (FSIQ) scores (Sowell et al. 2010).

Functional Brain Abnormalities as a Result of Prenatal Methamphetamine Exposure

To our knowledge, only one fMRI investigation of prenatal methamphetamine exposure has been published thus far. This study, which relied on a sample of subjects with prenatal exposure to methamphetamine and alcohol overlapping with the samples used in one of the sMRI studies described above (Sowell et al. 2010), examined functional brain activation during a verbal learning and memory task. Investigators reported that children with prenatal exposure to methamphetamine (most of whom had concomitant alcohol exposure) activated more diffuse brain regions, including bilateral medial temporal structures known to be important for memory, than both children with prenatal exposure to alcohol alone and unexposed controls. These findings might indicate that children with prenatal methamphetamine exposure have to recruit compensatory systems to support a weak verbal memory network. Although explanations for activation differences remain speculative, these results may suggest that prenatal meth-
amphetamine exposure affects brain networks involved in verbal memory above and beyond the effects of prenatal exposure to alcohol alone (Lu et al. 2009) (Fig. 11).

In summary, very few neuroimaging studies of prenatal exposure to methamphetamine have been published so far; thus, it may be too early to draw specific conclusions as to which brain systems are most affected by prenatal exposure to this drug in humans. The only trend that is beginning to emerge from the current literature is that methamphetamine may be particularly toxic to the striatum, which makes sense in the context of its mechanism of action on catecholamine transmitters and its known toxicity to dopamine terminals. Further investigations will be needed in order to obtain a better understanding of the impact of prenatal exposure to methamphetamine on the developing nervous system in humans.

Fig. 11 *Top Panel:* Correlation between performance and activation was significant in left medial temporal structures for the control group only. The color bar codes for Z statistics of significant clusters thresholded at \( p \leq 0.05 \). Z axis values on the bottom correspond to MNI standard space coordinates. *Bottom panel:* Group differences in the (Learning+Recall)-Rest contrast with IQ regressed out. a MA>CON, b MA>ALC, c CON>ALC. The color bars on the right code for Z statistics of significant clusters thresholded at \( p \leq 0.05 \). Z axis values on the bottom correspond to MNI standard space coordinates. MA = Methamphetamine-exposed group, ALC = Alcohol-exposed group, CON = unexposed control group (Lu et al. 2009)
Conclusions

As reviewed above, recent advances in neuroimaging techniques have helped improve our understanding of the effects of prenatal exposure to drugs of abuse on the developing human brain. However, certain drugs have been more studied than others, with most of the published literature reporting on the effects of prenatal alcohol exposure. When reviewing studies examining structural and metabolic changes in the brains of children with FASD, it appears that most brain systems are affected by the teratogenic consequences of prenatal alcohol exposure. Although early reports suggested that gross lobar regions of the brain such as the frontal and temporal lobes might be relatively spared relative to overall brain volume reduction (Archibald et al. 2001), more recent studies with enhanced spatial sensitivity suggest that these areas are also impacted, with children with FASD showing increased cortical thickness in some parts of the frontal and temporal lobes (Sowell et al. 2008a). The fMRI studies published so far suggest that subjects with heavy prenatal alcohol exposure show abnormal patterns of brain activation in many cognitive domains. Future neuroimaging studies should aim at replicating these findings in larger samples of subjects and with different methods.

The body of literature about the effects of prenatal exposure to illegal stimulant drugs is much smaller. The studies that examined the effects of prenatal exposure to cocaine have yielded inconsistent results, with some reporting regional brain volume reductions (Dow-Edwards et al. 2006) and others suggesting the absence of such volume decreases (Smith et al. 2001a), although two separate studies indicate that the striatum may be particularly affected (Rao et al. 2007; Avants et al. 2007). Results from fMRI studies are also inconclusive, with a study reporting the absence of significant differences in brain activation between exposed and non-exposed subjects (Hurt et al. 2008), and another investigation suggesting the existence of group differences in brain activation while performing a different task (Sheinkopf et al. 2009). The published studies about the effects of prenatal exposure to methamphetamine have provided more consistent findings, and suggest the existence of structural and metabolic brain abnormalities in children exposed to methamphetamine in utero in several brain regions, especially in the striatum (Chang et al. 2004; Smith et al. 2001b). Evidence for the clinical relevance of these abnormalities is also beginning to emerge (Sowell et al. 2010). Little can be said about functional brain abnormalities, however, since only one fMRI study of prenatal methamphetamine exposure has been published so far. Clearly, the study of prenatal exposure to illegal stimulants with neuroimaging is still in its infancy and further investigations with large sample sizes will be needed in order to confirm the current findings about methamphetamine and to better interpret the presently conflicting results about cocaine.

One important limitation to keep in mind when reviewing human studies of prenatal exposure to drugs of abuse is the problem of polysubstance exposure. For instance, a recent study showed that almost half of women who use methamphetamine during pregnancy also use alcohol (Smith et al. 2006). Thus, future studies should try to isolate the effects of individual drugs, and one way to achieve this is to use large samples of subjects. Large sample sizes provide more statistical power and may allow for investigators to covary the effects of a drug of interest for the effects of other drugs, provided that they have enough information about what particular combinations of drugs were used. The problem of concurrent exposure to nicotine is of particular interest here, because tobacco is often used in conjunction with alcohol and stimulants, and nicotine has been shown to induce lasting abnormalities in neurogenesis in animal models (Slotkin 1998).

The issue of polydrug exposure is further complicated by the fact that most current human studies of prenatal exposure are retrospective. Thus, accurate information of what combinations of drugs were used, in what quantities, and at what points during pregnancy is often unavailable. This is because many subjects in these studies have been removed from their biological families because of the presence of drugs of abuse in the home. Although social, medical, and legal records are often used in addition to reports from adoptive parents, it is often hard to determine precise exposure histories for these subjects. This is also the case with subjects who are still under the custody of their biological mothers, because frequencies of drug exposure are difficult to accurately recall years after the drug use, and may be compounded by the stigma of admitting to drug use during pregnancy. In order to remedy this problem, future investigations should rely on prospectively enrolled subjects, for whom more accurate exposure histories and dosages can be obtained.

Finally, future studies should aim at elucidating the relationships between structural, metabolic, and functional abnormalities and children’s actual challenges outside the scanner. For instance, in the case of prenatal alcohol exposure, future investigations should examine possible relationships between brain abnormalities and facial dysmorphology. For all drugs of abuse, relationships between brain and behavior should be further examined. Most existing studies have attempted to investigate brain-behavior relationships through correlational methods on a structure-by-structure basis. Future studies may benefit from integrating observations from different brain imaging modalities and investigating brain structure, function, and connectivity in the same children, in order to determine how these changes relate to cognitive function in various
domains, but most importantly to children’s behaviors in the “real world.” Although the interpretation of findings from such studies will be limited by the nature of correlational research, such investigations will provide important insights that may ultimately help clinicians devise appropriate interventions in order to address the specific needs of children with prenatal exposure to drugs of abuse.

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