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# Neuroimaging and Fetal Alcohol Spectrum Disorders

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## Abstract

The detrimental effects of prenatal alcohol exposure on the developing brain include structural brain anomalies as well as cognitive and behavioral deficits. Initial neuroimaging studies of fetal alcohol spectrum disorders (FASD) using magnetic resonance imaging (MRI) confirmed previous autopsy reports of overall reduction in brain volume and central nervous system (CNS) disorganization, with specific structural abnormalities of the corpus callosum, cerebellum, caudate, and hippocampus. Advances in neuroimaging techniques have allowed detection of regional increases in cortical thickness and gray matter volume along with decreased volume and disorganization of white matter in individuals with FASD. In addition, functional imaging studies have found functional and neurochemical differences in those prenatally exposed to alcohol. Behavioral alterations noted in individuals with FASD are consistent with the findings noted in the brain imaging studies. Continued neuroimaging studies are needed to further advance understanding of the neuroteratogenic effects of alcohol.

### Keywords

fetal alcohol syndrome; prenatal alcohol exposure; brain; magnetic resonance imaging

The devastating effects of prenatal alcohol exposure on the developing brain were first reported in a small number of autopsy studies, which documented CNS abnormalities including microcephaly and structural aberrations (e.g., corpus callosum, basal ganglia, cerebellum) [Jones and Smith, 1973, 1975; Clarren and Smith, 1978; Clarren, 1986; Coulter et al., 1993]. Defined by three criteria (CNS dysfunction, pre- and postnatal growth deficits, and specific craniofacial features) the fetal alcohol syndrome (FAS) represents the most extreme effects related to gestational alcohol exposure [Jones and Smith, 1973]. However, significant neurobehavioral impairments are described consistently in children with heavy prenatal alcohol exposure, even those lacking the facial anomalies required for a diagnosis of FAS [e.g., Mattson et al., 1997]. Currently, a broader, umbrella term, fetal alcohol spectrum disorders (FASD), is used to capture the full spectrum of individuals affected by prenatal alcohol exposure, from those with FAS to those with neurobehavioral or isolated physical birth defects resulting from gestational alcohol exposure [Bertrand et al., 2004]. The extent of cognitive difficulties observed in individuals with FASD varies, but can include lowered IQ, hyperactivity, behavioral and adaptive difficulties, and deficits in motor function, attention, verbal learning, expressive and receptive language, executive function and visuospatial skills [Mattson and Riley, 1998; Kodituwakku, 2007].

Although it is apparent that prenatal alcohol exposure results in significant and persistent cognitive and behavioral consequences, it is less clear how brain structure and function



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mediate these changes. The development of neuroimaging techniques has assisted in defining the relationship between brain and behavior by quantifying abnormalities in brain structure and function across development and the fetal alcohol spectrum.

## Structural Imaging

See Table 1 for a summary of the structural imaging studies reviewed in this section.

### Cerebral volume and shape

Among the most consistent findings in brain imaging studies of FASD is that of overall volumetric reductions [Mattson et al., 1994; Johnson et al., 1996; Swayze et al., 1997; Archibald et al., 2001; Lebel et al., 2008; Li et al., 2008; Willoughby et al., 2008]. In addition to global decreases in brain volume, studies document absolute (i.e., uncorrected for brain size) reductions in frontal, temporal, parietal, and to a lesser degree, occipital lobes, in children with FASD relative to typically developing controls [Archibald et al., 2001; Sowell et al., 2002]. The parietal lobe appears to be especially sensitive to the teratogenic effects of alcohol as parietal volume is significantly reduced even after controlling for the overall reduction in brain volume—a variable not consistently taken into account in previous findings [Archibald et al., 2001; Sowell et al., 2001b, 2002]. Another, more recent investigation has reported a disproportionate decrease in white and gray matter volumes in the occipital-temporal region [Li et al., 2008].

### Corpus callosum

In addition to analysis of the entire cortex, more focused examinations have identified specific structures that are differentially affected by prenatal alcohol exposure. Abnormalities of the corpus callosum, the major white matter tract connecting the two cerebral hemispheres, have been reported in several studies of individuals with FASD. Agenesis, or complete absence of the corpus callosum has been documented in a small number of cases of FAS [e.g., Riley et al., 1995; Swayze et al., 1997; Bhatara et al., 2002], while partial agenesis and hypoplasia have also been reported [Mattson et al., 1992; Swayze et al., 1997; Autti-Rämö et al., 2002].

Volume reductions and displacement of the corpus callosum are also observed as a consequence of prenatal alcohol exposure. Riley et al. [1995] reported smaller corpus callosum areas in individuals prenatally exposed to alcohol compared to controls; the most anterior and posterior sections of the corpus callosum remained significantly smaller even after controlling for overall brain volume. In addition to a reduction in size relative to controls, the posterior section of the corpus callosum, which connects posterior temporal and inferior parietal cortices, was significantly displaced in individuals with FASD [Sowell et al., 2001a]. An increase in the variability of the corpus callosum shape relative to controls has also been reported from infants to adults exposed to alcohol prenatally [Bookstein et al., 2002a,b; Bookstein et al., 2007]. Alterations in the corpus callosum have been associated with several domains of neuropsychological function that are impaired in individuals with FASD, such as motor function [Bookstein et al., 2002b; Roebuck-Spencer et al. 2004], attention [Coles et al., 2002], verbal learning [Sowell et al., 2001a], and executive function [Bookstein et al., 2002b].

### Cerebellum

The cerebellum appears to be another specific target of alcohol teratogenesis. Decreased surface area and volume of the cerebellum have been described in studies of individuals with FAS [Mattson et al., 1992, 1994; Archibald et al., 2001], as well as in nondysmorphic children with prenatal alcohol exposure [Autti-Rämö et al., 2002]. Further, some of these

changes are localized to the anterior vermis, an early developing area in the cerebellum, which is more affected than later developing posterior regions [Sowell et al., 1996; Autti-Rämö et al., 2002]. Displacement of the anterior vermis has been reported in alcohol-exposed individuals with and without facial dysmorphology, and this displacement has been associated with greater verbal learning and memory deficits observed in persons with FASD [O'Hare et al., 2005]. Because the cerebellum is associated with motor function and attention regulation, structural anomalies in this region may be responsible for impaired balance [Roebuck et al., 1998], bi-manual coordination [Debaere et al., 2004; Roebuck-Spencer et al., 2004], and attention deficits often seen in individuals with prenatal alcohol exposure [Mattson et al., 2006]. Finally, deficits in learning a classically conditioned eye-blink response have been observed in children with FAS [Coffin et al., 2005; Jacobson et al., 2008] and are consistent with the role of the cerebellum in classical conditioning processes [Woodruff-Pak et al., 2000].

### Basal ganglia

Decreased volume of the basal ganglia, a group of subcortical nuclei, has been reported in individuals with FAS. However, further examinations accounting for overall brain volume and proportion of the total subcortical region have revealed volumetric reductions specific only to the caudate nucleus [Mattson et al., 1992, 1996b; Archibald et al., 2001]. Decreased caudate volumes, corrected for overall brain size, also have been reported in alcohol-exposed individuals without a diagnosis of FAS [Archibald et al., 2001]. Further, caudate volume has predicted performance on neuropsychological measures of inhibition and verbal learning and recall [Mattson et al., 2001]. Taken together, these findings may indicate aberrant fronto-subcortical networks in individuals with FASD, which are consistent with the behavioral changes seen in this population, including deficits in executive function [Mattson and Riley, 1998; Kodituwakku et al., 2001]. The basal ganglia also maintain connections with motor cortices [Hoover and Strick, 1993] and may be involved in deficits of fine motor control [Adnams et al., 2001; Connor et al., 2006], and bi-manual coordination [Roebuck-Spencer et al., 2004; Kraft et al., 2007] in children with FASD.

### Hippocampus

Studies using animal models of prenatal alcohol exposure [Gianoulakis, 1990; Sutherland et al., 1997; Livy et al., 2003; Klintsova et al., 2007] and reports of learning and memory impairment in children with FASD [Mattson et al., 1996a, 1998; Mattson and Roebuck, 2002; Willford et al., 2004] suggest that the hippocampus may be affected by heavy prenatal alcohol exposure, however, data are equivocal. These disparities may be due to difficulty delineating the hippocampal region, leading to inconsistent tracing techniques and demarcation of the hippocampus across studies. Some studies have documented reduced hippocampal volume in a small number of participants [Riikonen et al., 1999; Autti-Rämö et al., 2002], while others report relative sparing in these regions [Archibald et al., 2001]. A recent investigation found significant reduction of left hippocampal volume and a correlation of hippocampal volume with short and long-delay memory indices in FASD [Willoughby et al., 2008]. Despite this report, it remains unclear whether a specific pattern of hippocampal volume abnormality exists in children with FASD and conflicting findings warrant further study of the structure in this population.

### Cortical thickness abnormalities

Whole-brain voxel and surface-based analyses of cortical structures have allowed for finer scale examination of cortical abnormalities in FASD than earlier volumetric analyses. Specifically, these studies have shown that individuals with heavy prenatal alcohol exposure have relatively more gray matter and relatively less white matter in the perisylvian cortices of the temporal and parietal regions than controls [Sowell et al., 2001b, 2002], as well as

relatively greater cortical thickness [Sowell et al., 2008b]. Sowell et al. [2008b] reported increased cortical thickness over large areas of lateral temporal, parietal, frontal, and occipital cortices in a sample of individuals with FASD relative to controls. Within the FASD group, nondysmorphic participants had fewer significant areas of increased cortical thickness compared to individuals with FAS. Increased cortical thickness in right dorsal frontal regions was associated with impaired verbal recall, and left occipital thickness was negatively associated with performance on a visuospatial measure in individuals with FAS relative to controls [Sowell et al., 2008b]. In typically developing children, the cortex generally has been shown to thin across development [Sowell et al., 2004; Shaw et al., 2008], with thinner cortex associated with more proficient performance on neuropsychological measures of verbal abilities [Sowell et al., 2004] and general intellectual function [Shaw et al., 2006]. The thicker cortices of the FASD group observed in this study may be indicative of immature brain development in these individuals. Future longitudinal studies are needed to determine whether cortical thickness differences represent a delay in the thinning and/or synaptic pruning of these regions or a permanent arrest in cortical maturation.

## Diffusion Tensor Imaging

See Table 2 for a summary of the diffusion tensor imaging (DTI) studies reviewed in this section.

DTI, a technique tracking the diffusion of water molecules, has offered a more detailed examination of white matter fibers within FASD. Relative to structural imaging, which characterizes macrostructural differences by volume, diffusion characteristics offer insight on a mircostructural level by characterizing white matter tissue organization. To examine the organization of neuronal fibers, DTI measures two types of water diffusion: (1) fractional anisotropy (FA), the degree of water diffusion in a single direction [Basser et al., 1994], and (2) mean diffusivity (MD), the average amount of diffusion, across all directions [Basser et al., 1994]. Higher values of FA and lower values of MD suggest more organized white matter. It is important to note that these two measures are not inversely related to each other, but rather signify two separate forms of water displacement.

Several studies have described alcohol-related damage to the corpus callosum at this microstructural level [Ma et al., 2005; Wozniak et al., 2006; Lebel et al., 2008; Sowell et al., 2008a; Fryer et al., 2009; Li et al., 2009]. Abnormalities of white matter structure within the posterior regions of the corpus callosum have been most consistently reported, with lower FA [Li et al., 2009] and higher MD [Wozniak et al., 2006] in the isthmus and lower FA in the splenium of individuals with FASD [Ma et al., 2005; Lebel et al., 2008; Sowell et al., 2008a]. Lower FA values in the splenium were found to be associated with impairments on the visual-motor integration test (VMI) [Sowell et al., 2008a]. Examinations of the anterior region of the corpus callosum in FASD have found a decrease of MD in the genu, the most anterior region of the corpus callosum [Lebel et al., 2008], and decreased FA in the same region [Ma et al. 2005]. Additionally, one study has reported lower FA in the body of the corpus callosum [Fryer et al., 2009]. Taken together, these studies confirm previous anatomical findings of corpus callosum abnormalities [Mattson et al., 1992; Sowell et al., 2001a; Autti-Rämö et al., 2002; Bookstein et al., 2002a,b] and suggest that this structure may be particularly affected by prenatal exposure to alcohol.

The most recent DTI studies of those prenatally exposed to alcohol have shown white matter abnormalities extend to brain regions beyond the corpus callosum. Sowell et al. [2008a] found lower FA values in the cingulate and right temporal lobes in children with FASD. Two other studies have examined whole brain diffusion using tract-based analyses. One study reported lower FA and/or higher MD in tracts with temporal connections known to

involve language and visual processing [Lebel et al., 2008]. Less efficient processing in these tracts could underlie language and visuospatial impairments reported in previous investigations [Sowell et al., 2008b; McGee et al., 2009]. A second study found the same pattern of decreased FA and/or increased MD in tracts with superior frontal connections [Fryer et al., 2009]. Less white matter organization in superior frontal regions may be related to executive dysfunction documented in individuals with FASD [Mattson et al., 1999; Kodituwakku et al., 2001; Vaurio et al., 2008]. Additionally, alcohol-exposed children had reduced FA in tracts connecting the occipital lobe with inferior frontal and parietal lobes [Fryer et al., 2009], all of which are involved in visual attention and processing [Corbetta and Shulman, 1998]. Consequently, poorer white matter integrity in these areas may be associated with deficits in visuospatial processing, attention, and spatial working memory commonly observed in individuals with FASD [Mattson and Riley, 1998].

Diffusion characteristics of gray matter also have been examined in FASD [Lebel et al., 2008]. Children with prenatal alcohol exposure display decreased FA and increased MD in the right putamen and thalamus. Conversely, alcohol-exposed children show increased FA in the globus pallidus. Few studies have examined gray matter using DTI in normal populations, but the extant literature indicates that FA increases with increasing age [Pfefferbaum et al., in press]. Lower FA in the putamen and thalamus of children with FASD relative to controls may indicate a delay in gray matter maturation consistent with previous interpretations of increased gray matter volume in children with FASD [Sowell et al., 2001b, 2002].

## Magnetic Resonance Spectroscopy

See Table 3 for a summary of the magnetic resonance spectroscopy (MRS) studies reviewed in this section.

While clear structural changes exist in the brains of alcohol-exposed individuals, studies examining brain differences in individuals with FASD also document changes in metabolite levels and ratios, cerebral blood flow (CBF), and neurotransmitters, even in the absence of structural deficits. Three studies have used MRS to examine concentration differences in the metabolites *N*-acetyl-aspartate (NAA), creatine/phosocreatine (CR) and choline compounds (CH). One study reported greater absolute NAA concentrations and increased ratios of NAA/CR in the caudate nucleus of children with FASD [Cortese et al., 2006]. NAA is thought to be a marker of neuron viability and axon integrity with loss of NAA occurring in diseases characterized by neuron loss [Ross and Bluml, 2001]. Increased NAA in FASD may suggest compensation by the caudate nucleus for low neuronal functioning in other regions [Cortese et al., 2006]. Another study of adolescents and young adults with FASD recorded minimal increases in overall NAA along with overall greater concentrations of the metabolites CR and CH [Fagerlund et al., 2006]. In the same study, decreased ratios of NAA/CR and/or NAA/CH were also found in the anterior cingulate, parietal cortex, frontal white matter, corpus callosum, and the dentate nucleus. These NAA/CR ratio differences, despite small differences in overall NAA, may reflect abnormalities in CR [Fagerlund et al., 2006], a metabolite generally thought to be associated with glial cells [Ross and Bluml, 2001]. These abnormalities suggest aberrant glial rather than neuronal cells [Fagerlund et al., 2006] and support previous reports of altered glial functioning in animal models of prenatal alcohol exposure [Guerri and Renau-Piqueras, 1997; Guerri, 2002]. The latest MRS study reported lower CH levels in a region of frontal/parietal white matter in children with FAS and partial FAS (CNS dysfunction and some craniofacial features) compared to both nondysmorphic children with FASD and controls [Astley et al., 2009b]. These lower CH concentrations were related to timing of exposure; children exposed to alcohol through the second or third trimester had lower CH concentrations than children with no exposure or exposure only in the first trimester. Additionally, across all children, lower CH levels in

frontal/parietal white matter were positively correlated with frontal white matter volume and corpus callosum length. Similarly, CH levels in the left hippocampus decreased with decreasing volume of the left hippocampus and the frontal lobe across all children. In normal populations, CH levels have been shown to be higher in white matter relative to gray matter, suggesting that the low CH concentrations seen in children with FAS and partial FAS in this study may indicate white matter deficits [Astley et al., 2009b]. Taken together, these metabolite studies provide an indication of the extent to which the two cell types, neurons and glia, contribute to structural and cognitive abnormalities.

## Functional Imaging

### Single photon emission computed tomography/positron emission tomography

See Table 3 for a summary of the single photon emission computed tomography (SPECT) and positron emission tomography (PET) studies reviewed in this section.

In addition to MRS studies, biochemical brain processes in individuals with FASD have been explored using other imaging techniques. Differences in cerebral blood flow (CBF), measured using SPECT, have been reported in the temporal [Bhatara et al., 2002], frontal, and parietal-occipital regions of the brain [Riikonen et al., 1999]. SPECT findings also suggest lower levels of serotonin transporter in the medial frontal cortex and higher levels of dopamine transporter binding in the basal ganglia [Riikonen et al., 2005]. Abnormal neurotransmitter levels may mediate behavioral problems seen in individuals with FASD, as serotonin has been linked with inhibition and impulsive aggression [Witte et al., 2009]. These implications are further supported by findings of increased levels of dopamine transporter binding in the basal ganglia in individuals with attention-deficit/hyperactivity disorder [Dougherty et al., 1999; Krause et al., 2000; Riikonen et al., 2005], which is frequently diagnosed in individuals with FASD [Steinhausen and Spohr, 1998; Bhatara et al., 2006; Fryer et al., 2007a].

Additionally, use of PET has allowed for the detection of lower levels of glucose metabolism in the caudate and thalamus of young adults with FAS, which also may be associated with inattention and hyperactivity symptoms in alcohol-exposed individuals [Clark et al., 2000].

### Functional magnetic resonance imaging

See Table 4 for a summary of the functional magnetic resonance imaging (fMRI), studies reviewed in this section.

To examine the relationship between behavior, reported abnormalities in brain structure and biochemistry in individuals with FASD, recent studies using functional magnetic resonance imaging have examined differences in spatial working memory [Malisza et al., 2005; Astley et al., 2009a] [Spadoni et al., in press], verbal memory [Sowell et al., 2007; O'Hare et al., 2009], sustained attention [Li et al., 2008], and response inhibition [Fryer et al., 2007b].

fMRI measures the blood oxygen level dependent (BOLD) signal, an indirect measure of neural activity. Three studies have examined BOLD response to spatial working memory using variations of nonverbal n-back tasks. These tasks require participants to remember the locations of previous shapes/designs and decide if the current image matches the location of an image 0, 1, or 2 screens back, depending on the specified condition. Conditions instructing one to remember two screens back (i.e., 2-back) reflect a higher cognitive load than remembering 1 screen back (i.e., 1-back), with the 0-back condition reflecting vigilance or attention.

The first study demonstrated functional differences in a 1-back spatial working memory condition in prefrontal areas in children and adults with FASD [Malisza et al., 2005]. Relative to controls, increased activation in inferior and middle frontal areas were found in all FASD individuals, with additional increased activation in the superior frontal region in adults with FASD. Children with FASD also had a pattern of decreased activity in the inferior frontal cortex with increased task difficulty, while adults with FASD and control subjects demonstrated the opposite pattern [Bookheimer and Sowell, 2005]. The second study found differences between alcohol-exposed children and controls in BOLD response to the 2-back spatial working memory condition [Astley et al., 2009a]. Here significantly lower activation was seen in children with FAS and partial FAS relative to controls in the right middle frontal region, dorsal lateral prefrontal cortex and posterior parietal lobe [Astley et al., 2009a]. BOLD response differences between children and adolescents with FASD and controls were also found in the third study of spatial working memory [Spadoni et al., in press]. Participants prenatally exposed to alcohol showed increased BOLD response in frontal, superior temporal and occipital gyri, insulae, and subcortical regions compared to controls during the 2-back condition [Spadoni et al., in press]. Together these studies confirm abnormalities within the fronto-parietal network previously shown to be involved with spatial working memory [Klingberg et al., 2002]. While all three studies have an accuracy cut-off for subject inclusion (varies by study), task performance differences during the experimental condition in the first two studies [Malisza et al., 2005; Astley et al., 2009a] and reaction times differences during the vigilance condition in the latter study [Spadoni et al., in press] suggest further investigations are needed to fully interpret these results [Bookheimer and Sowell, 2005].

Another fMRI study examined BOLD response in children and adolescents with FASD during a verbal working memory task. To ensure that BOLD response differences were not mediated by group performance differences, this study excluded less complex trials (low load trials) from the imaging analysis, where alcohol-exposed participants were significantly less accurate than controls. After accounting for overall brain volume and IQ, alcohol-exposed participants show greater BOLD response in the left dorsal lateral pre-frontal cortex, inferior parietal lobe and bilateral posterior temporal lobes relative to controls during a verbal working memory task [O'Hare et al., 2009]. Previously, individuals with FASD have shown differences relative to controls in these same regions, with increased gray matter thickness in the parietal and temporal lobes [Sowell et al., 2008b] and increased BOLD response during verbal learning in prefrontal regions [Sowell et al., 2007].

Children with FASD also exhibit functional differences in verbal learning, [Sowell et al., 2007], which is also known to be affected by prenatal alcohol exposure [Mattson et al., 1996a, 1998]. Children with FASD showed increased activation in left dorsal prefrontal regions as well as decreased activation in left medial and posterior temporal regions when compared to controls while performing a verbal learning task [Sowell et al., 2007]. Given that medial temporal and frontal areas have been shown to be involved in language processing [Saykin et al. 1999; Johnson et al., 2001], these results are consistent with behavioral findings of impaired encoding on verbal learning tasks in alcohol-exposed individuals [Mattson and Roebuck, 2002; Willford et al., 2004].

Li et al. [2008] reported differences in the occipital-temporal activation in young adults with FASD during performance on a sustained attention task. Those prenatally exposed to alcohol showed more superior occipital-temporal activation than controls. In the same occipital-temporal region, white and gray matter volume was significantly reduced in those prenatally exposed to alcohol. Despite similar levels of accuracy, reaction times were significantly greater for those prenatally exposed to alcohol, replicating reaction time differences reported

in previous visual attention investigations of alcohol-exposed individuals [Mattson et al., 2006].

Lastly, functional abnormalities were seen in alcohol-exposed subjects during a response inhibition (Go/No-Go) task [Fryer et al., 2007b]. Despite similar task performance, subjects with FASD displayed increased BOLD response in the prefrontal cortex and decreased BOLD response in the caudate nucleus relative to controls. Greater activation in the frontal regions of alcohol-exposed children may be indicative of compensatory neural effort to alleviate inefficiency of the frontal-striatal network. Alternatively, increased activation may reflect an immature pattern of frontal activation in response inhibition [Fryer et al., 2007b], as inhibitory networks become more efficient across development [Casey et al., 1997; Tamm et al., 2002]. These frontal abnormalities may contribute to impairments in response inhibition previously seen in this population [Streissguth et al., 1986; Mattson et al., 1999].

## CONCLUSION

Neuroimaging studies have only begun to advance our understanding of the vast and varying adverse effects of prenatal alcohol exposure on the developing brain. Variability in size and function of the corpus callosum and cerebellum in alcohol-exposed individuals may indicate deficient interhemispheric communication and contribute to attention and motor impairments, respectively. Likewise, difficulties with memory and learning tasks in children with FASD may be a function of structural differences of the hippocampus. Abnormalities of the frontal cortex and basal ganglia are the most consistently reported findings across structural and functional studies, suggesting an association between aberrant fronto-subcortical networks and deficits in verbal learning and recall and executive functions in those prenatally exposed to alcohol. Additionally, abnormalities of the parietal cortex and atypical temporal and occipital functioning reported across studies may contribute to impairments in language and visuospatial processing in individuals with FASD.

Together these studies have begun to elucidate the range of structural abnormalities and neuropsychological difficulties observed in individuals with FASD, but studies are limited in their sample sizes and varying methodology. Future studies should take advantage of combining imaging techniques to assess the relationship between brain structure (MRI) and function (i.e., MRS, DTI, and fMRI). Associations between cognitive domains, brain structure and function are still fairly speculative; studies should include neuropsychological measures to more concretely evaluate how brain structure and function translate into the observed behavioral profiles of individuals with FASD. In particular, subsequent DTI investigations utilizing fiber tractography analyses should examine the brain regions subserving these tracts and the associated neurocognitive domains. Additionally, with the help of expanded normal developmental studies, examinations of gray matter diffusion can support and expand the exploratory analyses reviewed here. Within the fMRI studies, behavioral differences at some or all task difficulty levels are a consistent limitation; group performance differences could be controlled by analyzing only correct trials.

These investigations include limitations that are not exclusive to neuroimaging studies, but plague all clinical research in FASD. Studies of animal model systems have shown that the timing and duration of alcohol use during pregnancy is related to specific abnormalities during neurodevelopment. Clinical studies often lack detailed information on maternal alcohol consumption, making it difficult to examine effects of dose, timing, or duration of exposure in humans [Maier and West, 2001]. Existing prospective studies, which may provide greater detail on these important factors, are limited in the number of heavily exposed individuals, resulting in smaller effects than those noted in studies of heavily exposed subjects. Future neuroimaging studies should address whether different findings

across these studies can be explained by between study differences in levels of exposure, diagnostic groups, or developmental stages studied. Finally, existing studies have focused on a relatively small number of subjects, often incorporating the same or overlapping samples between studies. Replication of existing studies in independent samples of FASD is imperative to the generalizability of the current results. In spite of these limitations, the studies reviewed herein affirm the broad and complex negative effects of prenatal alcohol exposure on the developing brain and the necessity for continued neuroimaging research to expand our current understanding of the neural underpinnings in individuals with FASD.

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**Table 1**

Structural Magnetic Resonance Imaging Findings (MRI) in Individuals with Prenatal Alcohol Exposure (ALC) Relative to Controls (CON)

| | | CON | ALC | | |
|---|---|---|---|---|---|
| | **Age Range (y)** | ***N* (Female)** | ***N* (Female)** | **Phenotype[a]** | **Group Differences; ALC Relative to CON** |
| Archibald et al. 2001 | 7–24 | 41 (20) | 26 (12) | FAS, other FASD, CON | Reduced cerebral and cerebellar vault, parietal lobe, caudate nucleus in FAS |
| Autti-Rämö et al. 2002[b] | 13–15 | 17 (–) | 17 (8) | FAS, other FASD, CON | Hypoplasia of corpus callosum, cerebellar vermis, reduced hippocampi |
| Bhatara et al. 2002[c] | 6–35 | 2 (1) | 5 (1) | FAS, CON | Hypoplasia and agenesis of corpus callosum |
| Bookstein et al. 2002a | 14–37 | 60 (30) | 120 (60) | FAS, other FASD, CON | Variability in corpus callosum shape |
| Bookstein et al. 2002b | 18–36 | 15 (0) | 30 (0) | FAS, other FASD, CON | Variability in corpus callosum shape |
| Bookstein et al. 2007 | Infant | 21 (16) | 23 (10) | FASD, CON | Larger angle of splenium |
| Cortese et al. 2006 | 9–12 | 4 (2) | 11 (4) | FAS, other FASD, CON | Reduced caudate nucleus |
| Johnson et al. 1996[c] | 4–20 | – | 6 (3) | FAS | Microcephaly, hypoplasia and agenesis of corpus callosum |
| Lebel et al 2008 | 5–13 | 95 (45) | 24 (11) | FASD, CON | Reduced total brain volume |
| Li et al. 2008a | 18–24 | 7 (3) | 7 (3) | FASD, CON | Reduced cerebral vault |
| Mattson et al. 1992[c] | 13–14 | 9 (–) | 2 (0) | FAS, CON, Down Syndrome | Reduced cerebral vault, cerebellar vault, basal ganglia |
| Mattson et al. 1994[c] | 16 | 20 (–) | 2 (1) | other FASD, CON | Reduced cerebral vault, cerebellar vault, basal ganglia |
| Mattson et al. 1996b | 8–19 | 7 (1) | 6 (2) | FAS, CON | Reduced cerebral vault, basal ganglia |
| Mattson et al. 2001 | 9–16 | – | 13 (7) | FAS, other FASD | Caudate volume correlated with neuropsychological measures |
| O'Hare et al. 2005 | 8–25 | 21 (12) | 21 (11) | FASD, CON | Anterior cerebellar vermis reduced, displaced, correlated with verbal learning and memory |
| Riikonen et al. 1999 | 3–23 | 6 (–) | 8 (2) | FAS, CON | Reduced left hippocampal volume in FAS (L < R) |
| Riikonen et al. 2005 | 5–16 | 10 (5) | 12 (7) | FASD, CON | Reduced left hippocampal volume in FAS (L < R) |
| Riley et al. 1995 | 8–19 | 12 (4) | 13 (4) | FAS, other FASD, CON | Reduced area of corpus callosum |
| Sowell et al 1996 | 8–24 | 24 (13) | 9 (3) | FASD, CON | Reduced cerebellar vermis I–V |
| Sowell et al. 2001a | 8–25 | 21 (12) | 20 (10) | FASD, CON | Reduced area and displacement of corpus callosum, displacement correlated with verbal learning |
| Sowell et al. 2001b | 8–25 | 21 (12) | 21 (11) | FASD, CON | Perisylvian cortices: more gray matter, less white matter |
| Sowell et al. 2002 | 8–25 | 21 (12) | 21 (11) | FASD, CON | Increased gray matter density in inferior parietal/perisylvian regions |
| Sowell et al. 2008b | 8–25 | 21 (12) | 21 (11) | FAS, other FASD, CON | Greater cortical thickness; associated with verbal recall in FAS |
| Swayze et al. 1997[c] | 4–29 | 119 (65) | 10 (4) | FAS, CON | Microcephaly, midline anomalies |
| Willoughby et al. 2008 | 9–15 | 18 (11) | 19 (5) | FASD, CON | Reduced intracranial and left hippocampal volume (FASD < CON); hippocampal volume correlated with verbal and spatial delayed recall |

[a] Other FASD may include partial FAS, prenatal alcohol exposure, prenatal exposure to alcohol, fetal alcohol effects, static encephalopathy, alcohol-related neurodevelopmental disorder; FASD also includes FAS.

[b] Prospective study.

[c] Case study.

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**Table 2**

Diffusion Tensor Imaging (DTI) Findings in Individuals with Prenatal Alcohol Exposure (ALC) Relative to Controls (CON)

| | | CON | ALC | | |
|---|---|---|---|---|---|
| | **Age Range (y)** | ***N* (Female)** | ***N* (Female)** | **Phenotype[a]** | **Group Differences; ALC Relative to CON** |
| Fryer et al. 2009 | 8–18 | 12 (6) | 15 (5) | FASD, other FASD, CON | Lower FA and/or higher MD body of corpus callosum, tracts innervating frontal and occipital regions; lower FA in corpus callosum in FAS relative to other FASD |
| Lebel et al. 2008 | 5–13 | 95 (45) | 24 (11) | FASD, CON | Lower MD genu (corpus callosum); lower FA and/or higher MD splenium (corpus callosum), temporally connected white matter tracts, putamen and thalamus; higher FA globus pallidus |
| Li et al. 2009[b] | 19–27 | 25 (13) | 57 (39) | FASD, CON | Lower FA isthmus (corpus callosum) in dysmorphic FASD |
| Ma et al. 2005[b] | 18–25 | 7 (5) | 9 (4) | FASD, CON | Lower FA genu and splenium (corpus callosum) |
| Sowell et al. 2008a | 7–15 | 19 (11) | 17 (8) | FASD, CON | Lower FA splenium (corpus callosum), cingulate, temporal lobe, lower FA in splenium (corpus callosum) associated with visual-motor skills |
| Wozniak et al. 2006 | 10–13 | 13 (7) | 14 (7) | other FASD, CON | Higher MD isthmus (corpus callosum) |

[a]Other FASD may include partial FAS, prenatal alcohol exposure, prenatal exposure to alcohol, fetal alcohol effects, static encephalopathy, alcohol-related neurodevelopmental disorder; FASD also includes FAS.

[b]Prospective study.

**Table 3**

Review of Magnetic Resonance Spectroscopy (MRS), Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT) Findings in Individuals with Prenatal Alcohol Exposure (ALC) Relative to Controls (CON)

| | | CON | ALC | | |
|---|---|---|---|---|---|
| | **Age Range (y)** | ***N* (Female)** | ***N* (Female)** | **Phenotype[a]** | **Group Differences; ALC Relative to CON** |
| *MRS* | | | | | |
| Astley et al. 2009b | 8–15 | 16 (8) | 65 (28) | FAS, other FASD, CON | Lower CH frontal/parietal white matter in FAS/partial FAS, lower CH associated with timing of exposure, corpus callosum length, frontal white matter volume, left hippocampus and frontal lobes |
| Cortese et al. 2006 | 9–12 | 4 (2) | 11 (4) | FAS, other FASD, CON | Greater NAA in FAS and increased NAA/CR in caudate nucleus |
| Fagerlund et al. 2006[b] | 14–21 | 10 (9) | 10 (9) | FASD, CON | Greater CR and CH; lower NAA/Cr and/or NAA/CH anterior cingulate, parietal cortex, frontal white matter, corpus callosum, and dentate nucleus |
| *PET* | | | | | |
| Bhatara et al. 2002[c] | 6–35 | 2 (1) | 5 (1) | FAS, CON | CBF differences in temporal lobe |
| Clark et al. 2000 | 16–30 | 15 (7) | 19 (7) | FAS, CON | Decreased glucose metabolism in the caudate and thalamus |
| *SPECT* | | | | | |
| Riikonen et al. 1999 | 3–13 | – | 11 (4) | FAS | CBF differences in frontal and parietal-occipital regions |
| Riikonen et al. 2005 | 5–16 | 10 (5) | 12 (7) | FASD, CON | Lower levels of serotonin transporter in medial frontal cortex, higher levels of dopamine transporter binding in basal ganglia |

[a]Other FASD may include partial FAS, prenatal alcohol exposure, prenatal exposure to alcohol, fetal alcohol effects, static encephalopathy, alcohol-related neurodevelopmental disorder; FASD also includes FAS.

[b]Prospective study.

[c]Case study.

**Table 4**

Functional Magnetic Resonance Imaging (fMRI) in individuals with prenatal alcohol exposure (ALC) individuals relative to controls (CON)

| | | CON | ALC | | |
|---|---|---|---|---|---|
| | **Age Range (y)** | ***N* (Female)** | ***N* (Female)** | **Phenotype[a]** | **Group Differences; ALC Relative to CON** |
| *Spatial working memory* | | | | | |
| Astley et al. 2009b | 8–15 | 13 (6) | 58 (25) | FAS, other FASD, CON | Less BOLD response in middle frontal, dorsal lateral prefrontal cortex and posterior parietal areas in FAS/partial FAS |
| Malisza et al. 2005 | 7–33 | 25 (11) | 24 (13) | FASD, CON | Greater BOLD response in inferior-middle frontal in children; greater BOLD response in superior frontal regions of adults |
| Spadoni et al. 2009 | 10–18 | 12 (7) | 10 (4) | FASD, CON | Greater BOLD response in insulae, subcortical regions and frontal, superior temporal and occipital gyri |
| *Verbal working memory* | | | | | |
| O'Hare et al. 2009 | 7–15 | 20 (11) | 20 (9) | FASD, CON | Greater BOLD response in inferior parietal, posterior temporal lobe and dorsal lateral prefrontal regions |
| *Verbal learning* | | | | | |
| Sowell et al. 2007 | 7–15 | 16 (9) | 11 (2) | FASD, CON | Greater BOLD response in dorsal lateral prefrontal regions; less BOLD response in medial and posterior temporal regions |
| *Sustained attention* | | | | | |
| Li et al. 2008[b] | 18–24 | 7 (3) | 7 (3) | FASD, CON | Greater BOLD response in superior occipital-temporal region; reduced white matter and gray matter in occipital-temporal region |
| *Go/No-Go* | | | | | |
| Fryer et al. 2007 | 8–18 | 9 (5) | 13 (5) | FASD, CON | Greater BOLD response in prefrontal cortex; less BOLD response in caudate nucleus |

[a]Other FASD may include partial FAS, prenatal alcohol exposure, prenatal exposure to alcohol, fetal alcohol effects, static encephalopathy, alcohol-related neurodevelopmental disorder; FASD also includes FAS.

[b]Prospective study.