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Effects of prenatal alcohol exposure on the development of white matter volume and change in executive function

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ABSTRACT

Prenatal alcohol exposure can cause a wide range of deficits in executive function that persist throughout life, but little is known about how changes in brain structure relate to cognition in affected individuals. In the current study, we predicted that the rate of white matter volumetric development would be atypical in children with fetal alcohol spectrum disorders (FASD) when compared to typically developing children, and that the rate of change in cognitive function would relate to differential white matter development between groups. Data were available for 103 subjects [49 with FASD, 54 controls, age range 6–17, mean age = 11.83] with 153 total observations. Groups were age-matched. Participants underwent structural magnetic resonance imaging (MRI) and an executive function (EF) battery. Using white matter volumes measured bilaterally for frontal and parietal regions and the corpus callosum, change was predicted by modeling the effects of age, intracranial volume, sex, and interactions with exposure status and EF measures. While both groups showed regional increases in white matter volumes and improvement in cognitive performance over time, there were significant effects of exposure status on age-related relationships between white matter increases and EF measures. Specifically, individuals with FASD consistently showed a positive relationship between improved cognitive function and increased white matter volume over time, while no such relationships were seen in controls. These novel results relating improved cognitive function with increased white matter volume in FASD suggest that better cognitive outcomes could be possible for FASD subjects through interventions that enhance white matter plasticity.

1. Introduction

Prenatal alcohol exposure may lead to a range of physical and cognitive abnormalities in children that persist into adulthood (Mattson et al., 2011; Riley et al., 2011). The range of deficiencies observed in affected individuals is collectively described as fetal alcohol spectrum disorders (FASD) (Sampson et al., 1997), with fetal alcohol syndrome (FAS) representing the most severe form. The diagnosis for FASD is based on three major domains of deficiencies: brain growth, cognitive dysmorphology, and facial dysmorphology (Jones and Smith, 1973; Hoyme et al., 2005).

Numerous structural brain abnormalities have been observed in individuals with FASD. Smaller parietal and frontal white matter volumes and smaller corpus callosum size and/or area have been specifically reported in this population (Archibald et al., 2001; Wozniak and Muetzel, 2011) and may occur in tandem with abnormal gray matter thickness observed in the parietal and frontal cortices (Sowell et al., 2002; Sowell et al., 2008). Change in white matter development over time, however, remains under-investigated in the FASD literature. In typically developing children, post-natal development of white matter is more protracted than gray matter, and continues during childhood and adolescence and into midlife (Riddle et al., 2010; Welker and Patton, 2012). Specifically, during childhood and adolescence, there are significant age-related increases in white matter volume, with peak volumes occurring between 12 and 14 years in the frontal and temporal lobes to around 20–24 years for the parietal lobes (Giedd et al., 1999; Ge et al., 2002; Gogtay et al., 2004; Tamnes et al., 2010; Raznahan et al., 2011; Tanaka et al., 2012). Increases in white matter volume are attributed to increases in myelination and potentially to changes in the size, density, and number of white matter fibers over time (Paus et al., 1999; Welker and Patton, 2012).

Cognitive deficits in FASD children also persist throughout life. Past studies have shown that those with FASD demonstrate very little improvement of cognitive function over time, and differences in cognitive ability between exposed and typically developing subjects are even more apparent during adolescence and adulthood (Streissguth

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et al., 1991). Cross-sectional relationships between gray and white matter and cognitive function have been assessed previously in this population. For instance, earlier studies from our group have shown significant positive correlations between verbal recall and frontal gray matter thickness only in those with FASD (Sowell et al., 2008a). Similarly, white matter integrity estimated with diffusion tensor imaging (DTI) and measures of fractional anisotropy (FA) in the external capsule (significant differences near the fronto-temporal region) have been found to be correlated with performance of visuomotor tasks in individuals with FASD but not in controls (Sowell et al., 2008a; Colby et al., 2012). Others have also found lower FA (Li et al., 2009) and moderate correlations between FA and math performance in individuals with FASD (Lebel et al., 2010). However, relationships between longitudinal *change* in white matter and other executive functions over time in those with FASD have not been previously assessed.

While changes in white matter volume and executive function in typically developing children remain under investigated, cross-sectional studies of typically developing cohorts using DTI show that higher FA near frontal and parietal areas is positively associated with better reading ability, lexical decision making (Nagy et al., 2004; Gold et al., 2007) and IQ (Schmithorst et al., 2005). Positive relationships have also been reported between lower reaction times and greater white matter volumes in a lifespan sample of healthy volunteers (Walhovd and Fjell, 2007). However, in typically developing children, such relationships are not consistently found, and null results have also been reported when compared with those with FASD (Lebel et al., 2010; Treit et al., 2013).

In the current study, we investigated age-related changes in white matter volume over time within individuals with FASD, and how these changes relate to executive function change over time. The frontal and parietal regions were chosen specifically to investigate brain–behavior relationships with an executive function battery because of the following: i) these functions are known to be subserved by these cortical association regions (Smith and Jonides, 1997; Smith and Jonides, 1999; Cabeza, 2008); ii) due to the prominent attention and working memory deficits reported in FASD, these structures were hypothesized to be the most likely to be related to the deficits in function. The corpus callosum was additionally chosen as a ROI as numerous studies have previously documented abnormalities in its structure in FASD (Riley et al., 1995; Sowell et al., 2001; Astley et al., 2009), and we hypothesized that this structure would show differential volume changes in children with FASD compared to controls. Hence, we first investigated whether the rate of change in white matter volume in frontal and parietal regions differed between children and adolescents who were typically developing from those with FASD. Secondly, we investigated whether regional white matter volume changes predict the rate of change in executive functions over time and differ in children with FASD and typically developing children. We expected children with FASD to show smaller white matter volumes even after adjusting for overall brain size. Specifically, we hypothesized that volumes of frontal, parietal and total white matter would be smaller in participants with FASD than in controls independent of brain size and age. Given that previous studies have consistently found positive relationships between measures of white matter macro- and microstructure and cognitive function in FASD, we expected positive brain–behavior relationships in children with FASD, but not in controls.

2. Materials and methods

2.1. Recruitment

All participant data were obtained as part of the longitudinal Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) and included subjects from Los Angeles, California. Participants were recruited via advertisements and word-of-mouth, and alcohol exposed participants were also recruited through the Fetal Alcohol and Related Disorders Clinic at the University of California, Los Angeles. All participants received neuropsychological testing and structural brain imaging. Detailed developmental histories were also obtained from parental interviews during their visit(s).

Table 1
Demographic and cognitive variables for the control and FASD groups. Significant differences ($p<0.05$) are presented in bold.

	Controls	FASD group	*t* value	*p* value
Two time points (n)	16	25		
One time point (n)	42	27		
Scan interval (range) in years	2.36 (1.3–3.3)	2.46 (1.6–3.5)	0.272	0.788
Mean age (SD) in years	11.83 (±2.93)	11.15 (±2.81)	0.581	0.564
Age range in years	6.2–17.5	6.2–17.6		
Trail making Test A Response times (s)	40.38 (±18.78)	45.15 (±17.34)	−1.517	0.132
Trail making Test B Response times (s)	98.99 (±55.73)	122.35 (±59.28)	−2.307	**0.023**
Digit backward span	7.73 (±2.53)	6.81 (±2.14)	2.259	**0.025**
Digit forward span	8.86 (±1.99)	7.64 (±1.95)	3.559	**0.001**
CVLT-C Long recall	11.40 (±2.54)	8.86 (±3.11)	2.259	<0.001

2.2. Exposure and control status

Prenatally exposed participants were identified as those who were exposed to more than 4 drinks per occasion at least once per week or more than 13 drinks per week during pregnancy. Control subjects had none or less than 2 drinks (per week or on any one occasion) throughout pregnancy. Participants with incomplete exposure documentation were classified as alcohol exposed if they displayed the physical characteristics of fetal alcohol syndrome (FAS) as documented by an expert dysmorphologist. In the case of adoptive children, information about maternal alcohol use during pregnancy was gathered through sources other than the biological parent during the developmental history interview (Stratton, 1996; Hoyme et al., 2005). Out of the 49 FASD children in the study, only 7 children were living with their biological parents, and the rest were adopted. Detailed explanations of FASD diagnosis for CIFASD have been published previously (Jones et al., 2006; Mattson et al., 2010).

A total of 103 participants were included in the study, out of which 49 were classified as having FASD and 54 as controls. Of these, data were available for 41 participants (25 with FASD, 16 controls) for two time points. For the remaining 38 controls and 24 participants with FASD, data were available for one time point. Mean ages, scan intervals, and other demographic variables are presented in Table 1. There were no significant differences in age, sex, or severity of diagnosis between participants who did and did not return for a follow-up visit.