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Response inhibition deficits in children with Fetal Alcohol Spectrum Disorder: Relationship between diffusion tensor imaging of the corpus callosum and eye movement control

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ABSTRACT

Response inhibition is the ability to suppress irrelevant impulses to enable goal-directed behavior. The underlying neural mechanisms of inhibition deficits are not clearly understood, but may be related to white matter connectivity, which can be assessed using diffusion tensor imaging (DTI). The goal of this study was to investigate the relationship between response inhibition during the performance of saccadic eye movement tasks and DTI measures of the corpus callosum in children with or without Fetal Alcohol Spectrum Disorder (FASD). Participants included 43 children with an FASD diagnosis (12.3 ± 3.1 years old) and 35 typically developing children (12.5 ± 3.0 years old) both aged 7–18, assessed at three sites across Canada. Response inhibition was measured by direction errors in an antisaccade task and timing errors in a delayed memory-guided saccade task. Manual deterministic tractography was used to delineate six regions of the corpus callosum and calculate fractional anisotropy (FA), mean diffusivity (MD), parallel diffusivity, and perpendicular diffusivity. Group differences in saccade measures were assessed using t-tests, followed by partial correlations between eye movement inhibition scores and corpus callosum FA and MD, controlling for age. Children with FASD made more saccade direction errors and more timing errors, which indicates a deficit in response inhibition. The only group difference in DTI metrics was significantly higher MD of the splenium in FASD compared to controls. Notably, direction errors in the antisaccade task were correlated negatively to FA and positively to MD of the splenium in the control, but not the FASD group, which suggests that alterations in connectivity between the two hemispheres of the brain may contribute to inhibition deficits in children with FASD.

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1. Introduction

Response inhibition is the ability to suppress irrelevant stimuli or behavioral impulses to enable goal-directed behavior. Evidence from functional neuroimaging, animal models and human lesion studies indicates that the prefrontal cortex (Aron and Poldrack, 2005; Iversen and Mishkin, 1970), anterior cingulate cortex (Liddle et al., 2001), and corpus callosum (Bearden et al., 2011; Gadea et al., 2009; Stewart et al., 2003) all play a vital role in response inhibition. Eye movement control tasks have been used to measure response inhibition in typically developing children across a wide age range and have found that inhibitory skill increases with age (Hwang et al., 2010). Saccades are rapid eye movements that bring new visual targets onto the fovea of the retina and require multiple brain regions for successful execution. A number of brain regions have been associated with eye movement control, including the dorsolateral prefrontal cortex (DeSouza et al., 2003; Funahashi et al., 1993), lateral intraparietal area (Gottlieb and Goldberg, 1999; Schlag-Rey et al., 1997; Zhang and Barash, 2000), frontal eye fields (Everling and Munoz, 2000), secondary eye fields (Amador et al., 2004; Schlag-Rey et al., 1997) and superior colliculus (Everling et al., 1998, 1999). However, less is known about the role that white matter tracts play in eye movement control. Successful saccades most likely involve the corpus callosum, the largest white matter structure in the brain, which links homologous areas in the right and left hemispheres. This paper investigates the corpus callosum in terms of its relationship with eye movement control (Bruni and Montemurro, 2009). More specifically, the splenium, the most posterior sector of the corpus

Abbreviations: FASD, Fetal Alcohol Spectrum Disorder; FA, fractional anisotropy; MD, mean diffusivity; DTI, diffusion tensor imaging; FP, fixation point; SRT, saccadic reaction time; ROI, region of interest; ICC, Intraclass correlation coefficient.

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callosum, has been linked to the striate and extrastriate visual areas which are cortical targets implicated in sensorimotor processing (Putnam et al., 2010).

Eye movement control tasks have emerged as a portable and cost-effective method which can effectively measure cognitive, sensory, and motor functions in different clinical populations (Ramat et al., 2007). For example, eye movement control measures have been used to characterize deficits in executive functions and motor control in children that have prenatal alcohol exposure (Green et al., 2007, 2009; Paolozza et al., 2013, 2014a,b). Prenatal alcohol exposure induces a spectrum of adverse effects that can be categorized into several diagnostic subgroups, collectively referred to as Fetal Alcohol Spectrum Disorder (FASD) (Chudley et al., 2005). Eye movement tasks have revealed that error rates in the antisaccade task, which requires participants to suppress an automatic response towards a target and instead make a voluntary saccade in the opposite direction, are significantly elevated in children with FASD (Green et al., 2009; Paolozza et al., 2013, 2014a). Additionally, in a previous study that utilized a memory-guided saccade task which requires the participant to remember the spatial location and sequence of presentation of two visual targets (Paolozza et al., 2013, 2014b), we showed that children with FASD were unable to inhibit the automatic response and looked to the visual targets before receiving the appropriate go signal. These studies show that the suppression of automatic saccades coupled with the generation of voluntary saccades by a goal-directed plan is adversely affected in FASD.

Previous structural magnetic resonance imaging (MRI) and autopsy studies have reported widespread brain injury in those diagnosed with FASD in many of the aforementioned cortical gray matter regions and white matter including the corpus callosum (Autti-Ramo et al., 2002; Clarren and Smith, 1978; Riley et al., 1995; Swayze et al., 1997). Diffusion tensor imaging (DTI) can examine white matter integrity by measuring water diffusion in the brain. This method allows for the reconstruction of individual white matter pathways and provides quantitative measures, such as fractional anisotropy (FA) and mean diffusivity (MD), presumed to reflect cellular properties such as myelination and coherence/packing of axons (Beaulieu, 2002). DTI studies of the corpus callosum in FASD populations have revealed abnormalities of FA and MD in various tracts (Fryer et al., 2009; Lebel et al., 2008, 2010; Li et al., 2009; Ma et al., 2005; Sowell et al., 2008; Wozniak et al., 2006, 2009). FA measures in the corpus callosum have correlated with saccadic reaction time in two eye movement tasks in children with FASD (Green et al., 2013); however this paper had no control group and a relatively small sample size (n = 14). Additionally, it used a voxel-based analysis of the corpus callosum, which relies heavily on adequate spatial normalization that can be problematic for the corpus callosum (Snook et al., 2007). Tractography of individual white matter tracts overcomes this limitation and yields diffusion parameters averaged over an entire tract rather than individual voxels.

This paper reports the findings from the first DTI tractography study to examine white matter integrity in relation to performance on inhibition measures obtained from two eye movement control tasks, including a memory-guided saccade task, in a cohort of children with FASD recruited in the multi-site NeuroDevNet study (Reynolds et al., 2011). We hypothesized that FA and MD of the corpus callosum, as well as saccadic eye movements will be significantly different in children with FASD (n = 43, age range 7–18 years) when compared to controls (n = 35, age range 7–18 years). We also hypothesized that these measures will be related to one another.

2. Methods

2.1. Participants

Participants aged 7–18 years were recruited at three sites across Canada and had either a confirmed diagnosis of FASD (n = 47) or were typically developing control children (n = 41). Children with FASD were previously assessed and diagnosed according to the Canadian Guidelines for FASD diagnosis (Chudley et al., 2005) and were recruited through diagnostic clinics in Kingston, ON, Ottawa, ON, Edmonton, AB, Cold Lake, AB, and Winnipeg, MB, as part of a larger study funded by NeuroDevNet (Reynolds et al., 2011). The performance on a battery of psychometric tests and the link with eye movement control has been previously reported in a larger cohort from which the current subsample was extracted (Paolozza et al., 2014a,b). All experimental procedures were reviewed and approved by the Human Research Ethics Boards at Queen's University, University of Alberta, Children's Hospital of Eastern Ontario, and the University of Manitoba. Written informed consent was obtained from a parent or legal guardian and assent was obtained from each child before study participation. Due to quality control measures (movement, braces, etc.), 4 participants with FASD were excluded from analysis, leaving 43 FASD participants with adequate DTI data, scanned in either Kingston (n = 18; mean age = 12.6 ± 3.4; 9 males), Edmonton (n = 15; mean age = 11.5 ± 3.3; 8 males), or Winnipeg (n = 10; mean age = 12.9 ± 1.5; 5 males). Typically developing control children (n = 41) were recruited from the same geographical areas and 6 were excluded due to either a pre-existing disorder or failing quality control measures, leaving 35 control participants scanned in Kingston (n = 14; mean age = 13.8 ± 3.1; 8 males), Edmonton (n = 12; mean age = 11.6 ± 2.7; 3 males), and Winnipeg (n = 9; mean age = 11.1 ± 2.7; 2 males). Participant information is summarized in Table 1. Socioeconomic status (SES) was calculated using Hollingshead's Four-factor Index of Social Status for the FASD and control groups and analyzed for group differences (Hollingshead, 1975). Study data were collected and managed

Table 1
Demographic characteristics.

Diagnostic subtype n (%)	Control (n = 35)	FASD (n = 43)
FAS	–	3 (7)
pFAS	–	9 (21)
ARND	–	31 (72)
Demographics		t-Test p-value
Mean age ± SD (range)	12.5 ± 3.0 (7–18)	12.3 ± 3.1 (7–18)	0.90
Males n (%)	14 (39)	23 (53)	0.22
Right handed n (%)	35 (97)	39 (91)	0.24
Socioeconomic status	47	44	0.34
			Chi-squared p-value
Caucasian n (%)	34 (94)	16 (37)	<0.0001
First Nations n (%)	0 (0)	13 (30)	<0.0001
Other Ethnicity n (%)	2 (6)	14 (33)	<0.0001
Comorbidities n (%)			Chi-squared p-value
ADHD	0 (0)	25 (58)	<0.0001
ODD	0 (0)	5 (12)	0.0004
Anxiety	0 (0)	7 (16)	<0.0001
Depression	0 (0)	4 (9)	0.002
Other	0 (0)	16 (37)	<0.0001
Medications n (%)			Chi-squared p-value
Stimulants	0 (0)	22 (51)	<0.0001
Antipsychotics	0 (0)	11 (26)	<0.0001
Antidepressant	0 (0)	5 (12)	0.0004
Other	0 (0)	2 (5)	0.024

FASD = Fetal Alcohol Spectrum Disorder; FAS = Fetal Alcohol Syndrome; pFAS = Partial Fetal Alcohol Syndrome; SD = standard deviation; ARND = Alcohol Related Neurodevelopment Disorder; n = number; ADHD = Attention Deficit Hyperactivity Disorder; ODD = Oppositional Defiant Disorder.

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