

Altered Accuracy of Saccadic Eye Movements in Children with Fetal Alcohol Spectrum Disorder

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Background: Prenatal exposure to alcohol is a major, preventable cause of neurobehavioral dysfunction in children worldwide. The measurement and quantification of saccadic eye movements is a powerful tool for assessing sensory, motor, and cognitive function. The quality of the motor process of an eye movement is known as saccade metrics. Saccade accuracy is 1 component of metrics, which to function optimally requires several cortical brain structures as well as an intact cerebellum and brainstem. The cerebellum has frequently been reported to be damaged by prenatal alcohol exposure. This study, therefore, tested the hypothesis that children with fetal alcohol spectrum disorder (FASD) will exhibit deficits in the accuracy of saccades.

Methods: A group of children with FASD ($n = 27$) between the ages of 8 and 16 and typically developing control children ($n = 27$) matched for age and sex, completed 3 saccadic eye movement tasks of increasing difficulty. Eye movement performance during the tasks was captured using an infrared eye tracker. Saccade metrics (e.g., velocity, amplitude, accuracy) were quantified and compared between the 2 groups for the 3 different tasks.

Results: Children with FASD were more variable in saccade endpoint accuracy, which was reflected by statistically significant increases in the error of the initial saccade endpoint and the frequency of additional, corrective saccades required to achieve final fixation. This increased variability in accuracy was amplified when the cognitive demand of the tasks increased. Children with FASD also displayed a statistically significant increase in response inhibition errors.

Conclusions: These data suggest that children with FASD may have deficits in eye movement control and sensory-motor integration including cerebellar circuits, thereby impairing saccade accuracy.

Key Words: Eye Tracking, Saccade Accuracy, Biomarkers.

PRENATAL EXPOSURE TO alcohol is a major, preventable cause of neurobehavioral dysfunction in children. The full spectrum of adverse effects induced by prenatal alcohol exposure, which includes several diagnostic subgroups, is collectively referred to as fetal alcohol spectrum disorder (FASD; Chudley et al., 2005). Children with FASD often present with deficits in executive functions (i.e., response inhibition, planning, and cognitive flexibility), attention, and working memory (Kodituwakku, 2009; Mattson and Riley, 1998; Rasmussen, 2005). These deficits contribute to the negative behavioral, neuropsychiatric, and maladaptive secondary disabilities commonly observed in this population (Rasmussen et al., 2008). Previous studies (Green et al., 2007, 2009) have established that eye movement tasks can be used to characterize deficits in executive function and motor control in children with FASD.

The circuitry responsible for the efficient and accurate execution of saccadic eye movements involves multiple cortical and subcortical brain regions, and the roles that these brain regions play in controlling eye movement behaviors have been extensively investigated (for review, see Leigh and Zee, 2006; Munoz and Everling, 2004; Scudder et al., 2002). Brain disorders that affect 1 or more specific areas of the brain may be characterized by a predictable pattern of deficits in eye movement control. The measurement of saccadic eye movements is a powerful tool for assessing damage to the central nervous system, which may include deficits in the efficiency, performance, or quality of the motor process (i.e., metrics). Therefore, analysis of the metrics of eye movement behavior can also be used to assess the contribution of multiple brain structures to oculomotor control (Leigh and Zee, 2006). The current study sought to examine the accuracy component of saccade metrics in children with FASD.

Prenatal alcohol exposure is known to cause structural alterations in the brain. The most widely reported abnormalities from structural magnetic resonance (MR) imaging studies include microcephaly, corpus callosum, and cerebellar abnormalities, and reduced volume in the basal ganglia (Mattson et al., 1996; Riley et al., 1995; Sowell et al., 1996). Children with FASD also have difficulties with fine and gross motor skills which are thought to reflect cerebellar and

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Received for publication October 12, 2012; accepted January 21, 2013.

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DOI: 10.1111/acer.12119

brain-stem damage (Blackburn and Whitehurst, 2010). The cerebellar vermis has abnormalities in size and location in FASD (O'Hare et al., 2005). In monkeys, reversible lesions to the cerebellar vermis are known to produce deficits in online correction of saccade trajectory (Keller et al., 1983). The fastigial nucleus is also associated with modulation of saccade trajectory, and inactivation results in ipsilateral and contralateral perturbations of saccade trajectory (Goffart et al., 2004). Together, the cerebellar vermis and the fastigial nucleus play an important role in saccade accuracy (Robinson and Fuchs, 2001). Based on these previous findings, the current study tested the hypothesis that children with FASD will exhibit deficits in the accuracy of saccades to visual targets. Moreover, we additionally predicted that increasing the cognitive demand of the task will exacerbate deficits in saccade accuracy as more brain circuits, which are also potentially impaired, are recruited to complete the task.

MATERIALS AND METHODS

Participants

All experimental procedures were reviewed and approved by the Human Research Ethics Board at Queen's University. Children with FASD (average age 12 ± 1 years) were recruited through referrals from clinicians in multidisciplinary diagnostic clinics across Canada and were assessed according to the Canadian Guidelines (Chudley et al., 2005). The FASD group consisted of 13 boys and 14 girls (Table 1). Typically developing children (average age 12 ± 1 years) were recruited from the same geographical areas. The control group consisted of 12 boys and 15 girls. Control participants were excluded if they had any neurological or psychiatric disorder, were taking any psychoactive medication, or had a visual disturbance, other than requiring corrective lenses. Participants were asked to withhold any medications (Table 1) typically taken on the day of the testing session to avoid alterations in eye movements. Participants received snacks (juice and granola bars) during the sessions and were allowed breaks when necessary. Participants received a \$10 gift card for the 1 hour session.

Table 1. Descriptive Information for Children in the FASD Group

	<i>n</i> (%)
Diagnosis	
FAS	6 (22)
pFAS	2 (7)
ARND	19 (70)
Medication	
Stimulants	7 (26)
Antidepressants	5 (19)
Antipsychotics	4 (15)
Other	2 (7)
Co-morbidities	
ADHD	11 (41)
Oppositional defiant disorder	4 (15)
Anxiety	3 (11)
Depression	3 (11)
Bipolar disorder	1 (4)
Other	2 (7)

FASD, fetal alcohol spectrum disorder; FAS, fetal alcohol syndrome; pFAS, partial fetal alcohol syndrome; ARND, alcohol-related neurodevelopmental disorder; ADHD, attention deficit hyperactivity disorder.

Saccadic Eye Movement Recordings

Participants were seated comfortably in a dark, quiet room on a stable chair. Eye position was recorded using the EyeLink 1,000 eye tracking system (SR Research, Mississauga, ON). The 17" LCD monitor and mounted infrared camera were at a distance of 58 to 64 cm from the left eye. The position of the left pupil was digitized in both the vertical and horizontal axes at a sampling rate of 500 Hz. The performance of each participant was assessed in 3 tasks, in the following order: prosaccade (Fig. 1A), antisaccade (Fig. 1B), and memory-guided (Fig. 1C). Before each task, the eye movements of each participant were calibrated using 9 on screen targets (8 around the periphery and 1 central). The targets were flashed sequentially around the screen and the participant fixated on each 1. After calibration, the process was repeated to validate that the average error between fixation and target was $<2^\circ$ and that no

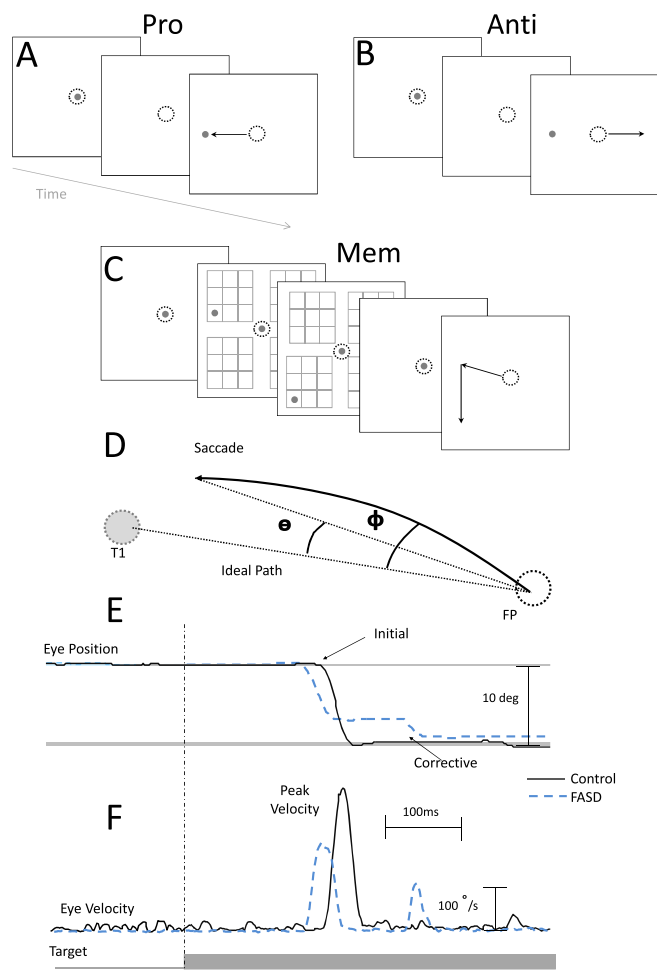


Fig. 1. (A) Prosaccade task: correct fixations (circles) and saccades (arrows). (B) Antisaccade task: correct fixations (circles) and saccades (arrows). (C) Memory-guided saccade task: correct fixations (circles) and saccades (arrows). Grid is not visible to participant. (D) Error of saccade trajectory and initial trajectory. The initial trajectory was defined as the angle between the ideal path and the path to 50% of the peak velocity (Φ). The saccade endpoint (θ) was measured as the angle ($^\circ$) between an ideal path to the target and the trajectory of the first saccade. (E) Eye trace of a control 16-year-old boy (solid line) and of a 15-year-old boy with fetal alcohol spectrum disorder (FASD; dashed line) on a prosaccade trial. (F) Velocity profiles of the above eye traces. Control 16-year-old boy with solid line and FASD 15-year-old boy with dashed line on a prosaccade trial.

loss of eye tracking occurred. This also ensured that the participants had no visual disturbances.

Behavioral Tasks

In both the prosaccade and antisaccade tasks, each trial started with illumination of a central fixation point (FP) for 800 to 1,200 ms. The FP then disappeared and, after a delay of 200 ms (gap period), a peripheral target appeared randomly at 10° to the left or right of the central FP. Participants were given 1,000 ms to initiate and complete a saccade to the correct location. In the prosaccade task, participants were instructed to look toward the target as soon as it appeared (Fig. 1A). In the antisaccade task, participants were instructed to look away from the target, toward the opposite side of the screen (Fig. 1B). No error feedback was given. One block of 60 prosaccade trials and 1 block of 60 antisaccade trials were obtained from each participant. After instructions were given, the participant repeated the instructions back to the eye tracking administrator to ensure that they understood the task instructions.

In the memory-guided saccade task, participants were instructed to maintain fixation at the central FP while 2 peripheral targets appeared. After the FP disappeared, the participants were required to make a saccade to the remembered locations (Fig. 1C). The screen was divided into 4 quadrants in which the peripheral targets could appear. Each quadrant consisted of 9 potential target locations in an invisible 3 by 3 grid centered at a 10° visual angle from the FP. The FP was illuminated for 200 to 1,000 ms before the appearance of the 2 targets. The 2 targets then appeared briefly in immediate succession for 100 ms each, within 2 of the 4 quadrants of the screen. Participants were required to fixate for an additional random time of 0, 600, 1,200, or 1,800 ms between the disappearance of the second peripheral target and the disappearance of the FP. The participants were instructed to remember the order and spatial location of the peripheral targets, and to make 2 saccades as accurately as possible to these locations in the same sequence but only after the disappearance of the FP. A single block of 72 trials was collected for this task. This task measured the ability of participants to maintain accurate memory of 2 visual targets, thereby assessing saccade accuracy after variable delay and in the absence of sensory feedback. After instructions were given, the participant repeated the instructions back to the eye tracking administrator to ensure that they understood the task instructions.

Data Analysis

Data were analyzed using custom software developed in MATLAB (Version R2009b; Mathworks, Inc., Natick, MA). Saccades were defined as having a speed of >2.5 times the standard deviation of the background noise (measured during fixation) for at least 5 sample points. Only trials where the participant was fixating on the FP at the appropriate time were used. If the participant broke fixation inappropriately (i.e., not to a target location or away from the screen), the trial was discarded from the analysis. Any trials where eye tracking was lost were removed. To be included in the analysis, each participant had to achieve >50% viable trials in each of the tasks. Two children were excluded before analysis because <50% of the trials were viable.

Saccade metrics (efficiency, performance, or quality of the motor process) for all correct trials for the 3 tasks were assessed by examining the following outcome measures: amplitude (°); peak eye velocity (°/s); the error in the initial saccade trajectory (Φ , defined as the angle between the ideal path and the actual path at 50% of the peak velocity; Fig. 1D); the error of the final saccade trajectory (θ , defined as the angle between an ideal path to the target and the trajectory of the first saccade toward the goal drawn as a straight line from the beginning to the end of the saccade; Fig. 1D); and the percentage of trials

that contained multiple saccades (more than 1 saccade generated in the direction toward the target; Fig. 1E). Saccadic reaction time (SRT) in the prosaccade and antisaccade tasks was defined as the time from the appearance of the peripheral target to the initiation of the first saccade during a correct trial. In the memory-guided saccade task, SRT of both the first and second saccades were calculated from disappearance of the central FP during a correct trial. In the memory-guided task, the accuracy of the first and final fixation was defined as the distance of the closest fixation to the actual peripheral target location, for all correct trials. Differences between the groups were analyzed for initial saccade trajectory, saccade endpoint, and corrective saccades using a 2-way repeated measures analysis of variance (ANOVA) coupled with Bonferroni post hoc tests for multiple comparisons. The variability in the saccade endpoints in the prosaccade task for each participant was quantified by: collapsing left and right endpoints, centering to 0, and then computing the principal axes of the data and their respective magnitudes using principal components analysis (PCA). The ellipse was scaled to represent 2 standard deviations of the data, and the resulting area was calculated. Effect sizes were also calculated for the dependent variables using Cohen's *d* scores (Cohen, 1988). Data are expressed as mean \pm SEM for children in the FASD ($n = 27$) and control ($n = 27$) groups, which were matched as closely as possible for age and gender (Table 1).

All viable trials were analyzed for anticipatory, direction, timing, and sequence errors. Saccades generated <90 ms after the appropriate go signal were classified as anticipatory saccades (Munoz et al., 1998). Direction errors in the prosaccade and antisaccade tasks were defined as any initial saccade in the wrong direction with respect to the instruction (i.e., away from the target in the prosaccade task; toward the target in the antisaccade task). Individual trials in the memory-guided task were assigned as either correct, timing errors (saccades initiated before 90 ms after the go signal), or sequence errors (initial saccade made closer to the second peripheral target location than to the first target). These measures assessed spatial working memory, response inhibition and attention, and were examined because they are frequently reported as abnormal in children with FASD (Kodituwakku, 2009; Mattson and Riley, 1998; Rasmussen, 2005). The SRT, accuracy of both saccades, and direction and timing errors in the memory-guided task were analyzed using an unpaired *t*-test.

RESULTS

Corrective Saccades: Prosaccade and Antisaccade Tasks

Two-way repeated measures ANOVA was used to assess differences in the frequency of corrective saccades for the prosaccade and antisaccade tasks, with group (Control, FASD) as the between-subject factor and task (prosaccade, antisaccade) as the within-subject factor. This analysis revealed statistically significant main effects of group, $F(1, 52) = 7.26$, $p = 0.0095$, and task, $F(1, 52) = 24.15$, $p < 0.0001$, indicating that children with FASD often made more than 1 saccade to acquire the target (e.g., Fig. 1E dashed trace), and these corrective saccades were made more frequently in the prosaccade compared with the antisaccade task (Fig. 2A).

Initial Trajectory and Saccade Endpoint: Prosaccade and Antisaccade Tasks

Differences between the initial saccade trajectory and the saccade endpoint were examined using 2-way repeated

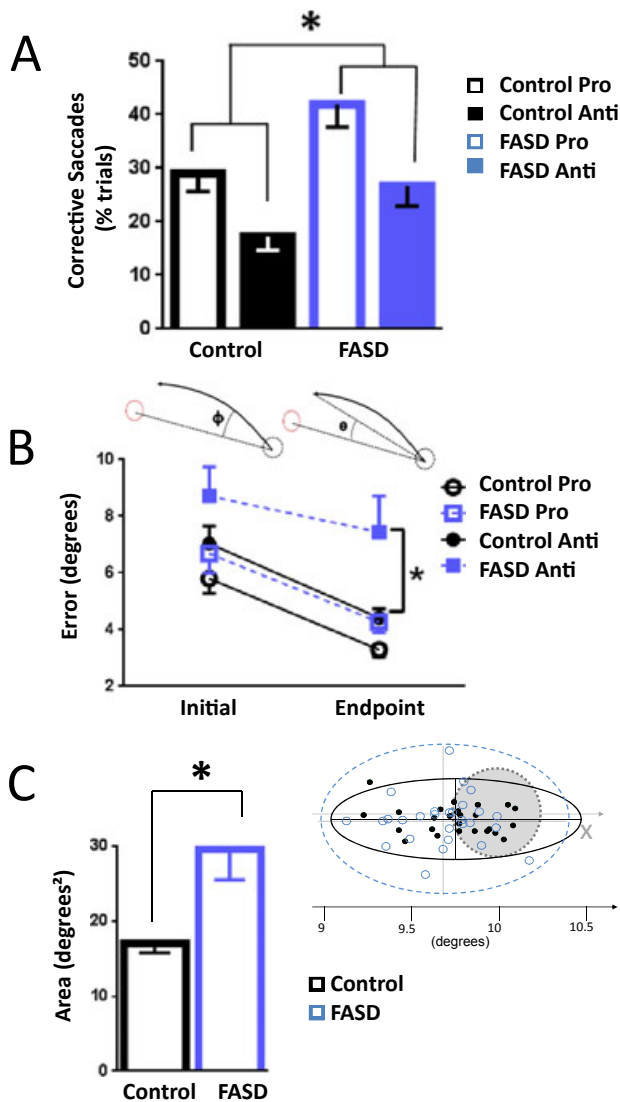


Fig. 2. Accuracy measures in the prosaccade and antisaccade task. Data are mean \pm SEM for participants in the fetal alcohol spectrum disorder (FASD; $n = 27$) and control ($n = 27$) groups. **(A)** Percentage of corrective saccades in the prosaccade task for control (open bar) and FASD (open bar) groups (left). Prosaccade effect size (d) is -0.65 . Percentage of corrective saccades in the antisaccade task for control (solid bar) and FASD (solid bar) groups (right). Antisaccade effect size (d) is -0.57 . **(B)** Accuracy of the initial trajectory toward the target and accuracy of the initial saccade endpoint toward the target. Solid line indicates control group and dashed line indicates FASD group. Performance on the prosaccade task for the control group is represented by an open circle and FASD group by an open square. Prosaccade effect size (d) is -0.59 for saccade endpoint error. Performance on the antisaccade task for the control group is represented by a solid circle and FASD group by a solid square. Antisaccade effect size (d) is -0.63 for saccade endpoint error. **(C)** The variability in the saccade endpoints in the prosaccade task for each participant quantified by principal components analysis. Effect size (d) is -0.79 . Inset: Endpoints of the initial saccade for the prosaccade task in the right direction, where the ellipses represent mean \pm 2 standard deviations for each group. Dashed ellipse and open circles is FASD population and solid ellipse and closed circles is control population. Dotted shaded circle indicates target. $*p < 0.05$ compared with control participants.

measures ANOVA with group (Control, FASD) as the between-subject factor and error (initial saccade trajectory [Φ], initial saccade endpoint [θ]) as the within-subject factor.

For the prosaccade task, there was a significant main effect of error, $F(1, 52) = 63.85, p < 0.0001$, but not group ($p > 0.05$), indicating that children in both the control and FASD groups improved their accuracy from the initial trajectory (Φ) to the saccade endpoint (θ), but that neither the initial saccade trajectory nor the initial saccade endpoint were different between the 2 groups for the prosaccade task (Fig. 2B). In contrast, 2-way ANOVA for the antisaccade task revealed significant main effects of error, $F(1, 52) = 21.25, p < 0.0001$, and group, $F(1, 51) = 4.91, p = 0.031$ (Fig. 2B). There was no interaction between error and group, but this comparison approached significance ($p = 0.14$), suggesting that the endpoint accuracy (θ) may be selectively impaired in the FASD group in the anti-saccade task (Fig. 2B).

Mapping Endpoints: Prosaccade Task

For the prosaccade task, the endpoint of the first saccade in each trial for each participant was mapped and PCA was performed. Children with FASD were significantly less accurate around the target, $t(26) = 2.9, p = 0.005$ (Fig. 2C), which further illustrates the increased variability of saccade accuracy to a visual target in children with FASD. To better visualize the variance in endpoints, ellipses were drawn around each participant's mean endpoint using the mean (center) and 2 standard deviations in x (transverse diameter) and y (conjugate diameter) directions (Fig. 2C inset; contrast dashed ellipse, FASD, to solid ellipse, Control).

Initial Trajectory and Saccade Endpoint: Memory-Guided Task

The outcome measures (Table 2) obtained for the memory-guided saccade task were first analyzed using a 2-way repeated measures ANOVA with group (FASD, Control) as the between-subject factor and delay (0 to 1,800 ms) as the within-subject factor. There was a significant main effect of delay, $F(1, 194) = 13.58, p < 0.0001$, only for the percentage of timing errors, in that both groups exhibited increased timing errors as the delay was increased (data not shown). However, there was no interaction between group and delay ($p > 0.05$), indicating that the effect of delay was not different between the 2 experimental groups. The accuracy and trajectory of saccades were also analyzed in this way but there was no main effect of delay. Thus, for simplicity of presentation, the data were collapsed across all delays for subsequent analyses. Similar to the prosaccade and antisaccade task, the children with FASD exhibited differences in saccade metrics. Two-way repeated measures ANOVA revealed significant main effects of error, $F(1, 51) = 20.42, p < 0.0001$, and group, $F(1, 51) = 4.59, p = 0.037$ (Fig. 3A). There was no interaction between these factors, suggesting that children with FASD exhibit an overall impairment of accuracy in this task. Additionally, the saccade endpoint to the second target was significantly less accurate in the FASD group compared to the control group, $t(52) = 2.8, p = 0.006$ (Fig. 3B).

Table 2. Saccade Outcome Measures

Measure	Pro: Con	Pro: FASD	Ant: Con	Ant: FASD	Mem: Con	Mem: FASD
Peak velocity (°/s)	341 ± 9	320 ± 10	357 ± 14	337 ± 13	262 ± 12	240 ± 17
Amplitude (°)	9.1 ± 0.1	8.8 ± 0.2	12.5 ± 0.7	12.1 ± 0.6	8.3 ± 0.5	7.9 ± 0.5
SRT first saccade	165 ± 6	164 ± 5	268 ± 8	278 ± 11	234 ± 9	234 ± 13
SRT second saccade	N.D.	N.D.	N.D.	N.D.	500 ± 20	439 ± 21
Anticipatory saccades (%)	12 ± 2	15 ± 2	8 ± 2	9 ± 2	N.D.	N.D.
Corrective saccades (%)	29 ± 3	42 ± 4	17 ± 3	27 ± 4	45 ± 3	50 ± 4
Direction errors (%)	0 ± 0.1	0 ± 0.2	34 ± 4	47 ± 4	N.D.	N.D.

SRT, saccadic reaction time; N.D., not determined; FASD, fetal alcohol spectrum disorder group; Con, control group.

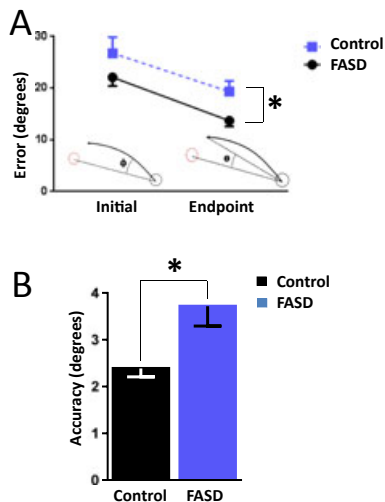


Fig. 3. Accuracy measures in the memory-guided task. Data are mean ± SEM for participants in the fetal alcohol spectrum disorder (FASD; $n = 27$) and control ($n = 27$) groups. (A) Accuracy of the initial trajectory toward the target and accuracy of the initial saccade endpoint toward the target. Solid line indicates control group and dashed line indicates FASD group. (B) Accuracy of the final fixation. The effect size (d) is -0.79 . $*p < 0.05$ compared with control participants.

Cognitive Measures

In agreement with our previous studies (Green et al., 2007, 2009), there was a statistically significant increase in the percentage of direction errors during the antisaccade task in the FASD group, $t(52) = 2.2, p = 0.029$ (Table 2). The FASD group corrected these direction errors on average 92% of the time, thereby demonstrating that they understood the task. The memory-guided task revealed significant differences between the groups on 2 new measures not previously reported in the FASD population. The SRT of the saccade to the second target was significantly faster in children with FASD, $t(52) = 2.1, p = 0.043$. As the final fixation, in relation to the second peripheral target, was significantly less accurate in the FASD group, this could reflect an inefficient speed-accuracy trade-off as the FASD group is faster to the second target but less accurate (Schouten and Bekker, 1967). There was a significant increase in the percentage of timing errors that was found in children with FASD compared to age- and sex-matched control children, $t(52) = 2.6, p = 0.011$ (Fig. 4A). Sequence errors were not different between the 2 groups (Fig. 4B).

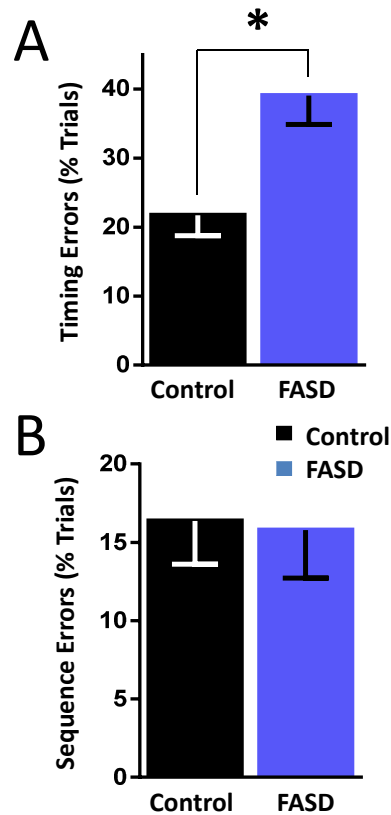


Fig. 4. Executive function measures in the memory-guided task. Data are mean ± SEM for participants in the fetal alcohol spectrum disorder (FASD; $n = 27$) and control ($n = 27$) groups. (A) Percentage of timing errors in each group. The effect size (d) is -0.92 . (B) Percentage of sequence errors in each group. $*p < 0.05$ compared with control participants.

DISCUSSION

In the current study, we performed an in-depth analysis of saccade metrics that revealed new information relating to the quality of saccade motor movements in children with FASD. The results of this study demonstrate that children with FASD exhibit deficits in saccade accuracy in the prosaccade, antisaccade, and memory-guided saccade tasks. Specifically, during the prosaccade task, children with FASD were more variable in the endpoints of saccades to a peripheral target, which was reflected by statistically significant increases in the area bounded by the initial saccade endpoints and the frequency of additional, corrective saccades required to

achieve the peripheral target. Increasing task complexity increased both the initial and endpoint error in both groups, but children with FASD presented with a greater degree of error in the antisaccade and memory-guided saccade task compared to controls. The memory-guided task required more cognitive processing than the prosaccade task because it was necessary for the participants to remember multiple target locations. The antisaccade task required more cognitive demand than the prosaccade task because it requires top-down inhibition and sensory-motor remapping (Munoz and Everling, 2004). The pattern of deficits in eye movement control exhibited by the FASD group is discussed in the context of the brain structures known to underlie control of saccade accuracy and those implicated in FASD.

In agreement with our previous studies (Green et al., 2007, 2009), there were no differences in either amplitude or velocity of saccades in children with FASD compared with controls. However, the deficits in saccade metrics revealed in the current study may have implications for the efficiency with which children with FASD scan visual scenes. We recently reported that children with FASD exhibit differences in both bottom-up and top-down control of saccades during viewing of natural scenes (Tseng et al., 2013), and that these behavioral differences may be used to differentiate children with FASD from both control children and children with ADHD. One difference from the data reported by Green and colleagues (2009) is that there were no differences observed in SRT for either the prosaccade or antisaccade tasks in the children with FASD. This is most likely a reflection of differences in methodology and/or in the composition of the clinical group. In our previous study, we employed both gap and overlap conditions for the prosaccade and antisaccade tasks, in which the central FP either remained illuminated (overlap condition) or disappeared 200 ms before the appearance of the peripheral target (gap condition). The gap condition served as an external cue that the peripheral target was about to appear, and in this condition, both control children and children with FASD had significantly faster SRTs compared with the overlap condition (Green et al., 2009). Moreover, children with a diagnosis of alcohol-related neurodevelopmental disorder (the majority of children in the current study) exhibited minimal changes in SRT relative to control children (Green et al., 2009). Given these 2 factors, it is perhaps not surprising that no differences in SRT were observed between children with FASD and controls.

Eye Movement Circuitry

The superior colliculus, cerebellum, and brainstem participate in circuits necessary for saccade execution and online correction of saccade amplitude (Quaia et al., 1999; Robinson et al., 1993, 2002; Takagi et al., 1998). The signal generating a saccade of specific displacement comes from the superior colliculus (Goossens and Van Opstal, 2006; Quaia et al., 1999; Sparks et al., 1976) and is fed to the pontine burst generator directly (Buttner-Ennever, 2008; Rodgers

et al., 2006) and indirectly through the cerebellar oculomotor vermis (Scudder et al., 2002). The cerebellum is believed to be important for stopping and steering of saccades to optimize accuracy and consistency (Quaia et al., 1999). The cerebellum receives oculomotor input from the pontine nuclei, which project mainly to the posterior lobe of the cerebellar vermis (Scudder et al., 1996). Purkinje cells in the vermis then project to the caudal fastigial nucleus which innervates the excitatory and inhibitory burst neurons and omnipause neurons of the brainstem oculomotor circuitry that control saccades (Robinson and Fuchs, 2001; Scudder et al., 2002). The cerebellum controls saccade accuracy by monitoring motor commands via a feedback model (Quaia et al., 1999; Robinson, 1975) in which internal feedback of a motor command (efference copy) corrects for anticipated errors by rapid modifications of saccade duration (Chen-Harris et al., 2008; Golla et al., 2008; Xu-Wilson et al., 2009). Decreased volume of the cerebellum has been described in studies of individuals diagnosed with FASD (Archibald et al., 2001; Autti-Rämö et al., 2002; Mattson et al., 1992), with some of the changes localized to the anterior vermis (Autti-Rämö et al., 2002; Sowell et al., 1996). It seems likely that damage to any of these structures may underlie the behavioral and accuracy deficits observed in the present study.

Corrective Saccades

The increased percentage of corrective saccades observed in the FASD group could be the result of cerebellar dysfunction. Following dysmetric primary saccades in patients with cerebellar lesions, additional saccades are generated to try to bring the visual target to the fovea (Gaymard et al., 1994). The caudal fastigial nucleus and cerebellar oculomotor vermis are necessary for error correction and rapid adaptation of saccade amplitude (Golla et al., 2008). Injection of muscimol, a GABA_A receptor agonist, into the caudal fastigial nucleus in monkeys results in perturbations of saccade trajectory (Goffart et al., 2004). Lesions to the caudal fastigial nucleus lead to dysmetria (Quinet and Goffart, 2004; Staube et al., 2009). Children with FASD were less accurate in looking to the peripheral target in the prosaccade task, but did in fact correct for the inaccuracy detected in the initial saccades with additional saccades to the goal. The antisaccade and memory-guided tasks did not show this increase in corrective saccades, which may be attributable to the absence of a visual target.

Saccade Endpoint Accuracy

Both the posterior parietal cortex (Wager and Smith, 2003) and the dorsolateral prefrontal cortex (Müri et al., 1996; Pierrot-Deseilligny et al., 1991) have been implicated in the accuracy of memory-guided saccades. Transcranial magnetic stimulation and lesions of the dorsolateral prefrontal cortex impairs the accuracy of memory-guided saccades (Müri et al., 1996; Pierrot-Deseilligny et al., 1991). MR imaging has shown that the parietal lobes are more affected

by prenatal alcohol exposure than the temporal and occipital lobes (Archibald et al., 2001). In the memory-guided task, the accuracy of the closest fixation to the first target was not significantly different in the FASD group but the closest fixation to the second target was less accurate in the FASD group compared to the control group. This may indicate a more rapid decline of the memory trace coding the precise location of the second target, perhaps due to a deficit in spatial working memory.

In addition, the FASD participants may have had difficulty updating the location of the second target following the first saccade. The parietal cortex plays a key role in target remapping, and the parietal lobes are involved in registering the amplitude and direction of a saccade into the contralateral field, using that information to update the representation of the location of the next saccade target (Duhamel et al., 1992).

Children in the FASD group exhibited greater deficits in saccade accuracy in the memory-guided saccade task than the simple prosaccade task. The dorsolateral prefrontal cortex is implicated in both short-term spatial memory and response inhibition and in humans with lesions to the dorsolateral prefrontal cortex, increased variability is observed in the accuracy of memory-guided saccades, suggesting its role in the encoding of spatial information (Pierrot-Deseilligny et al., 2003). Additionally, as children with FASD tend to exhibit greater deficits in tasks of increasing complexity, these results may reflect an inability to store both sequence and location.

The increase in variability in the prosaccade task and the increased deficit in saccade accuracy for the antisaccade and memory-guided saccade tasks may be due to deficits in connections between higher order brain structures and the cerebellum (Glickstein and Doron, 2008). For example, the cerebellum has indirect connections with cerebral cortex, basal ganglia, and thalamus. These pathways could participate in a more enduring resiliency of saccade trajectories due to remapping of the target (Chen-Harris et al., 2008; Soetedjo et al., 2009). A deficit in these areas seems likely as volumetric analysis of MR images showed decreased volume in the diencephalon (thalamus and hypothalamus) in children with FASD (Mattson et al., 1996).

Cognitive Measures

In this study, children with FASD had significantly increased direction errors when compared with age- and sex-matched controls. These deficits have previously been attributed to poor voluntary control over saccade generation in several clinical populations with frontostriatal circuitry impairments, including FASD (Green et al., 2007, 2009). Similar to the antisaccade task, the memory-guided task assesses the executive control of internally guided saccades. The difference in this task is that participants must use previously presented sensory information to plan and initiate a multicomponent motor response, but also wait to receive

the appropriate “go” signal before initiating the response. This task therefore requires the integration of multiple domains of cognitive function, including spatial working memory and response inhibition. In the present study, children with FASD demonstrated increased timing errors in the memory-guided task, reflecting deficits in either the ability to suppress and/or to inhibit saccadic responses. Sequence errors were not different between the groups, suggesting that, for children with FASD, remembering the sequence of 2 targets is easier to accomplish than waiting for the proper go signal.

CONCLUSIONS

Together, findings from the prosaccade, antisaccade, and memory-guided tasks reveal that the performance of these eye movement paradigms may be sensitive to cerebellar dysfunction in children with FASD. Additionally, this dysfunction is amplified when higher cortical structures, also compromised in FASD, are recruited for more complex tasks. This inaccuracy can negatively impact the everyday lives of children with FASD. Activities such as sports, reading, typing, driving, and food preparation become increasingly difficult when the initial saccade is not accurate, and additional corrective saccades must be made (Land, 2006). Therefore, it is important to better characterize these deficits to increase our understandings of the impact they have on children with FASD.

ACKNOWLEDGMENTS

We thank the participants and their families for taking part in the study. This work was supported by CIHR grant #ELA-80227 and NeuroDevNet, which is funded by the Networks of Centres of Excellence a program of the federal government to advance science and technology. DPM was supported by the Canada Research Chair Program.

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