Deficits in Eye Movement Control in Children With Fetal Alcohol Spectrum Disorders

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Background: Prenatal exposure to alcohol can result in a spectrum of adverse developmental outcomes in offspring, collectively termed fetal alcohol spectrum disorders (FASD). Deficits in executive function—the psychological processes involved in controlling voluntary goal-oriented behavior—are prevalent in FASD. Oculomotor tasks have been designed as highly sensitive tools to evaluate components of executive function. Because of the extensive overlap in the brain areas controlling eye movements and those affected in FASD, we hypothesized that individuals with FASD display specific neurobehavioral abnormalities that can be quantified with eye movement testing.

Methods: Subjects (8–12 years old) were instructed to look either toward (prosaccade) or away from (antisaccade) a stimulus that appeared in the peripheral visual field. Two fixation conditions were used. In the gap condition, the central fixation point (FP) was removed before the appearance of the peripheral stimulus; in the overlap condition, the FP remained illuminated. Saccadic reaction times (SRTs, time from stimulus appearance to saccade initiation), direction errors (saccades made in the incorrect direction relative to instruction), and express saccades (short-latency: SRT = 90–140 ms) were measured to assess automatic and volitional saccade control.

Results: Compared with controls, FASD children had elongated reaction times, excessive direction errors, and no express saccades. Metric analysis of correct prosaccades revealed a trend toward increased saccadic duration and decreased saccadic velocity in FASD subjects.

Conclusion: These results reflect deficits in executive function and motor control, and are consistent with dysfunction of the frontal lobes, possibly due to disrupted inhibitory mechanisms. Therefore, eye movement tasks may be powerful and easy tools for assessing executive function deficits in FASD.

Key Words: FASD, Eye Movement, Diagnostic Tool, Saccade, Executive Function.

T HE MAJOR CONSEQUENCE of prenatal ethanol exposure is fetal alcohol syndrome (FAS) (Astley and Clarren, 2000; Chudley et al., 2005; Clarren and Smith, 1978). Fetal alcohol syndrome is characterized by growth restriction (both prenatal and postnatal), craniofacial dysmorphology (i.e., indistinct philtrum, short palpebral fissure), and central nervous system dysfunction. Recently, the term fetal alcohol spectrum disorders (FASD) has been introduced and widely adopted as an umbrella term, which includes all disorders relating to prenatal alcohol exposure (Koren et al., 2003). Although the terminology has been clarified, an accurate diagnosis still remains a significant clinical challenge due largely to the absence of objective diagnostic tools, and particularly in cases where the craniofacial dysmorphology is absent, but the cognitive deficits are still prevalent.

Executive functions consist of those capacities that enable a person to engage successfully in independent, purposive, self-serving behaviors (Funahashi, 2001; Lezak, 1995), and deficits in these functions are now recognized as a hallmark of prenatal ethanol exposure. Individuals with FASD exhibit a range of deficits in executive function, including problems with flexibility of thought, planning, impulsivity, verbal reasoning, task switching, and working memory (Rasmussen, 2005). Indeed, several studies have documented deficits in executive function in children with a history of prenatal ethanol exposure, but without the facial dysmorphology of FAS (Connor et al., 2000; Mattson et al., 1999; Schonfeld et al., 2001). This finding reinforces the view that of the 3 key diagnostic features, it is the deficits in brain function that are of primary importance (Chudley et al., 2005). Thus, further research into the specific pattern of executive function deficits in the FASD

population, using objective and consistent measurement tools, is needed (Rasmussen, 2005).

One tool that has been used extensively to study deficits in motor control, working memory, and executive function associated with various neurodevelopmental and neurode-generative disorders is saccadic eye movements (Guitton et al., 1985; Leigh and Kennard, 2004; Leigh and Zee, 1999; Munoz and Everling, 2004; Munoz et al., 2007). The underlying neural circuitry that controls saccadic eye movements is now understood to an extent that higher cognitive function can be probed using saccade paradigms, and these tests may be used to assess specific deficits in executive function in patients with FASD. Thus, oculo-motor tasks may provide a unique opportunity to probe the effects of prenatal alcohol exposure on brain and be-havior relationships in a way that other cognitive tasks cannot.

There is considerable overlap in the structures that are responsible for producing a saccade (Leigh and Kennard, 2004; Leigh and Zee, 1999; Munoz and Everling, 2004), and those that are damaged by prenatal alcohol exposure, including the frontal lobes, thalamus, basal ganglia, and cerebellum (Kopera-Frye et al., 1996; Mattson et al., 2001; Rasmussen, 2005; Sowell et al., 2002a). Damage to these structures can affect saccade production and these deficits are measurable and quantifiable.

An important feature of human behavior is the ability to respond flexibly to different environmental stimuli. These attributes can be investigated in specific oculomotor para-digms. Subjects can be instructed to look toward a visual stimulus (Fig. 1A, prosaccade task, requires automatic response) or suppress this automatic response and look away from the stimulus (Fig. 1B, antisaccade task, requires volitional response) (Hallett, 1978; Munoz and Everling, 2004). The prosaccade task assesses basic sensorimotor reflexes, as well as the ability to maintain visual fixation, whereas the antisaccade task assesses voluntary motor control; that is, the ability to suppress the automatic response toward the peripheral stimulus in favor of an alternate behavior (Munoz and Everling, 2004). In addi-tion, to gain further insight into the process of response inhibition, 2 different fixation conditions are frequently used. In the gap condition, the central fixation point (FP) is extinguished before the appearance of the per-ipheral stimulus. Subjects experience greater difficulty in inhibiting the prepotent response under the gap condition. In the overlap condition, the central FP remains illuminated while the peripheral target appears, making it easier for subjects to suppress the unwanted movement toward the peripheral stimulus. Because cogni-tive function includes the ability to voluntarily inhibit prepotent responses, guide goal-directed behavior, and use working memory, oculomotor tasks can thus be used to dissociate these different cognitive abilities.

Saccadic eye movement experiments have been per-formed over a wide range of ages, including children (Fischer et al., 1997; Klein et al., 2003; Munoz et al., 1998; Salman et al., 2006). This technique is noninvasive and easy to administer, making it highly suitable to assess executive function in the FASD population. Furthermore, saccadic eye movement experiments have been used to characterize a variety of neuropsychological and neurode-generative diseases (Leigh and Kennard, 2004; Munoz et al., 2007), including schizophrenia (Currie et al., 1993; Zanelli et al., 2005), attention-deficit hyperactivity disor-der (ADHD; Armstrong and Munoz, 2003; Munoz et al., 2003; O'Driscoll et al., 2005), Parkinson's disease (Chan et al., 2005; Crawford et al., 1989; Kimmig et al., 2002; Le Heron et al., 2005), Tourette's syndrome (TS) (LeVasseur et al., 2001), and Alzheimer's disease (Crawford et al., 2005). The existing knowledge from these groups may assist with the identification of traits that are unique to FASD.

The aim of this study was 2-fold. The first objective was to determine whether saccades could be measured in chil-dren with FASD using prosaccade and antisaccade tasks, as these experiments have not been previously conducted in this clinical population. The second objective was to quantify the control of automatic and volitional responses using prosaccade and antisaccade tasks. It was hypothe-sized that subjects with FASD would have no trouble in performing saccadic eye movement experiments; however, based on the known deficits in frontal lobe function, these children were expected to produce saccades with increased saccadic reaction times (SRT) and make more direction errors in the antisaccade task compared with control children. In addition, because of known brainstem and cerebellar dysfunction, children with FASD were expected to produce significant deficits in saccade metrics (ampli-tude, velocity, and duration). These tasks provide an excellent method for quantifying and comparing object-ively the responses of children with FASD to those of control subjects, and may provide insight into the specific types of brain damage associated with prenatal ethanol exposure.
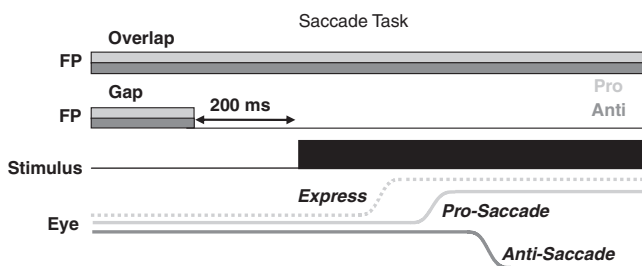
Fig. 1. In the prosaccade task, the subject was instructed to look from the central fixation point (FP) toward the eccentric stimulus. In the antisaccade task, the subject was instructed to look away from the eccentric stimulus to the opposite side. In both tasks, the state of fixation before the saccade was manipulated. In the overlap condition, the FP remained illuminated while the stimulus appeared. In the gap condition, the FP disappeared for 200 ms before the stimulus appeared. In both conditions, the saccadic reaction time was measured from the time of stimulus appearance to the initiation of the first saccade.

Preliminary versions of these data have been presented in abstract form (Green et al., 2004, 2005, 2006).

MATERIALS AND METHODS

Participants

All experimental procedures were reviewed and approved by the Queen's University Human Research Ethics Board. We selected children with FASD, as determined by a clinical geneticist and according to the 4-digit diagnostic code (Astley and Clarren, 2000). Ten children with FASD (4 males, 6 females; 9.8 ± 0.4 years of age, range 8–12 years) were recruited and compared with 12 age-matched control subjects (6 males, 6 females; 10.0 ± 0.3 years of age, range 8–12 years). Of the 10 children with FASD, 8 were medicated for behavioral symptoms relating to their comorbidities (Table 1). Children were tested off their medication, such that their last daily dose was administered the day before arriving at the lab, recognizing that for

some pharmacological agents this was not a sufficient wash-out period. Agents that were most likely to interfere with testing were stimulant medications that have a relatively short half-life ($\sim$6–12 hours) (Katzung, 1998) and for which the overnight wash-out period was sufficient. The contribution of each drug therapy could not be addressed in this study due in part to sample size, but more precisely due to the extensive differences that exist between medication regimens and treatment history. All control subjects had no known neurological, psychiatric, or visual disorders, other than requiring corrective lenses, which were worn if needed throughout the experiments. Parents and/or legal guardians were informed of the nature of the study and provided written consent on behalf of the participants. All subjects completed one, 1-hour session and were paid $10.

Saccade Task

All participants performed the saccade task (Fig. 1), consisting of 1 block of prosaccade trials, followed by 2 blocks of antisaccade

Table 1. FASD Subject Information

Subject	IOM	Sex	Age	Medication	Comorbid symptoms	Education history
1	FAE	F	10	Lithium Risperdal Prozac	Anxiety disorder Depression Bipolar mood disorder Oppositional defiant disorder	Resource help
2	ARND	F	11	Risperdal Dexedrine	ADHD	Suspension
3	ARND	M	12	Risperdal Dexedrine	ADHD Depression Oppositional defiant disorder	Suspension Learning disability Resource help Special education Special program Special class
4	ARND	F	10	Risperdal Clonidine Epival	ADHD Oppositional defiant disorder Neurological disorder	Learning disability Resource help Special education Special class
5	FAS	F	10	Concerta	ADHD	Learning disability Resource help Special education Special program
6	FAS	F	10	NA	NA	Learning disability Resource help
7	FAE	F	9	Ritalin	ADHD	Suspension Resource help Special education Special program Special class
8	ARND	M	8	Ritalin Clonidine	ADHD Conduct disorder	Suspension Learning disability Special education Special program Special class
9	FAE	M	9	Concerta Risperdal	ADHD Developmental delay	Learning disability Resource help Special education Special program Special class
10	FAS	M	9	NA	ADHD	Suspension Learning disability Resource help Special education Special program Special class

IOM, Institute of Medicine; FAE, fetal alcohol effects; ARND, alcohol-related neurodevelopmental disorder; FAS, fetal alcohol syndrome; ADHD, attention-deficit hyperactivity disorder; NA, not applicable.

trials, each block consisting of 100 trials. Subjects received breaks and refreshments between blocks. Participants were seated in a dentist chair, while in complete darkness facing the center of a translucent screen located 100 cm away. A red light-emitting diode (LED; 2.0 cd/m^2) was positioned onto the center of the screen and served as the initial FP. Red target LEDs (5.0 cd/m^2) were positioned at 20° to the right or left of the central FP. The screen was diffusely illuminated between trials to avoid dark adaptation. Each trial began with a 250-ms period of complete darkness. The FP appeared for 1,000 ms and then 1 of 2 events occurred. In the gap condition, the FP was extinguished and, after a gap period of 200 ms, the eccentric stimulus appeared in the right or left visual field. In the overlap condition, the FP remained lit when the eccentric stimulus appeared. In the prosaccade task, participants were instructed to start each trial fixated on the central FP and then look toward the stimulus as soon as it appeared. In the antisaccade task, participants were instructed to look away from the eccentric stimulus to the opposite side. The eccentric stimulus remained illuminated for 1,000 ms, after which all LEDs disappeared and the background illumination reappeared, indicating the end of that trial. Stimulus location (right or left) and fixation conditions (gap or overlap) were pseudo-randomly interleaved throughout each block of trials. Subjects were asked to repeat the instructions to the experimenter to ensure that they understood the paradigm before the onset of data collection.

Recording and Analysis of Eye Movements

Horizontal eye position was measured using DC-electrooculography (EOG). Ag–AgCl electrodes were affixed bitemporally and a grounding electrode was placed in the center of the forehead. All experimental data were digitized at 1 kHz using REX (ver 5.4; Hays et al., 1982) and analyzed off-line on a Sun Ultra 60 Sparc station.

Saccadic reaction time was defined as the time from stimulus appearance to initiation of the first saccade that exceeded 30°/s. Saccades were scored as correct if the first movement after the appearance of the eccentric stimulus was >5° in amplitude and in the correct direction (i.e., toward the stimulus in the prosaccade task, away from the stimulus in the antisaccade task). Saccades were scored as incorrect if the first saccade after the appearance of the stimulus was in the wrong direction (i.e., away from the stimulus in the prosaccade, toward the stimulus in the antisaccade task). The mean SRT in the prosaccade and antisaccade tasks was computed from trials with reaction latencies between 90 and 1,000 ms. These criteria served to eliminate anticipatory saccades and atypically long responses (Munoz et al., 1998). In addition, we measured express saccades (latency: 90–140 ms), which are the shortest latency visually triggered saccades (Dorris et al., 1997; Fischer and Ramsperger, 1984; Munoz et al., 1998). Express saccades have latencies that approach the minimal afferent and efferent conduction times for visual information to reach the oculomotor system and to be translated into a rapid eye movement (Dorris et al., 1997; Pare and Munoz, 1996). Neurons in the superior colliculus receive inputs from sensory, motor, and cognitive inputs, and these inputs contribute to establishing specific levels of excitability among populations of collicular neurons (fixation and saccade) that result in the generation of express saccades.

The following parameters were computed for each condition (gap, overlap) and direction (right, left): the mean SRT for correct trials, the coefficient of variation (CV) of SRT for correct trials [(CV = standard deviation/mean)×100], the percentage of express saccades, and the percentage of direction errors. Metric analyses for correct prosaccade trials were also carried out to determine the amplitude of the first saccade and the number of saccades made to reach the stimulus. For correct prosaccades that were restricted to 18° to 21° in amplitude, duration and peak velocity were also computed.

Data Analysis

The 2 experiments (prosaccade and antisaccade tasks) contained 2 within-subject factors: fixation state (gap vs overlap) and direction (right vs left); and 1 between-group factor: clinical pathology (FASD vs control). All dependent measures (SRT, CV, express saccades, direction errors) were analyzed using ANOVA with α set at 0.05. Two-tailed, unpaired Student's *t*-tests were conducted and corrected with Welch's approximation when the assumption for homogeneity of variance was not met. We will focus on descriptions of the relevant statistical parameters for comparisons and interactions that occurred between the control and FASD groups.

RESULTS

SRT

Figure 2 depicts the cumulative distribution of reaction times for correct responses (positive values) and direction errors (negative values) for control and FASD children in the prosaccade (Fig. 2A and 2C) and antisaccade (Fig. 2B and 2D) tasks in both the gap (Fig. 2A and 2B) and overlap (Fig. 2C and 2D) conditions. Controls were faster to react and initiate saccades in both the prosaccade and antisaccade trials (solid traces lead dashed traces). The gray boxes in Fig. 2 depict the express saccade epoch, 90 to 140 ms after stimulus appearance. In the prosaccade task, the FASD group made more direction errors and fewer express saccades compared with controls. In the antisaccade task, FASD subjects made more direction errors (although not significant); however, these errors were generated at very different times. The majority of direction errors made by controls were triggered in the express saccade range (gray box), while FASD direction errors were triggered later.

The ANOVA revealed the following for dependent measures (SRT, CV, express saccades, direction errors). FASD children had slower SRT compared with controls [$F(1, 20) = 20.9$, $p < 0.001$]. Consistent with previous studies, the mean SRT was increased for antisaccades compared with prosaccades [$F(1, 20) = 47.7$, $p < 0.001$], and in the overlap condition compared with the gap condition [$F(1, 20) = 94.2$, $p < 0.001$] for all groups. There were no significant directional effects.

Figures 3 and 4 summarize the data from the prosaccade and antisaccade tasks, respectively. In both the gap (Figs. 3A, 4A) and overlap (Figs. 3B, 4B) conditions, the mean SRT was elevated in the FASD group compared with controls in the prosaccade task [gap: $t_{(20)} = 5.8$, $p < 0.001$; overlap: $t_{(20)} = 4.6$, $p < 0.001$] and in the antisaccade task [gap: $t_{(20)} = 2.5$, $p < 0.05$; overlap: $t_{(20)} = 2.3$, $p < 0.05$]. The antieffect (antisaccade SRT–prosaccade SRT) for children with FASD was not significantly different from control children [$t_{(20)} = 0.95$, $p = 0.35$].

The gap effect (overlap SRT–gap SRT) for prosaccades ranged between 19 to 95 ms for control subjects and 28 to 177 ms for FASD children, and there was no significant difference between groups [$t_{(20)} = 0.02$, $p = 0.98$]. Similarly, the gap effect for antisaccades was also not significantly different between controls and FASD [$t_{(20)} = 0.16$, $p = 0.87$], and ranged between − 2 to 75 ms and − 55 to 100 ms for control and FASD children, respectively.
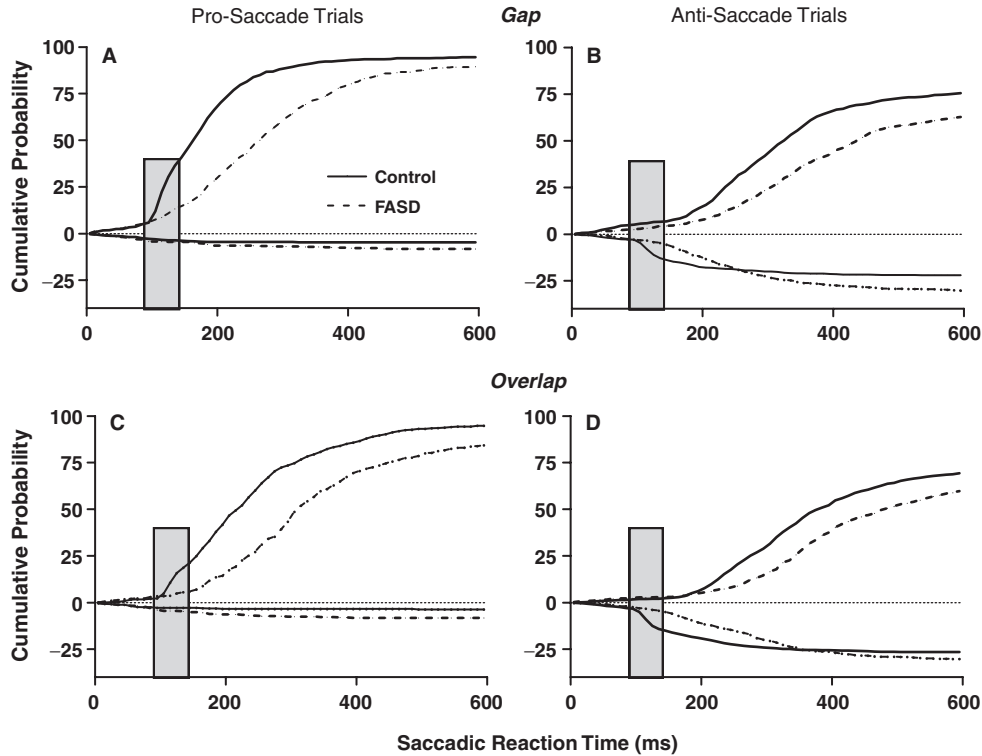
Fig. 2. Cumulative distribution of saccadic reaction times for correct responses (positive values on the ordinate) and direction errors (negative values on ordinate) for prosaccade (**A**, **C**) and antisaccade (**B**, **D**) trials in the gap (A, B) and overlap (C, D) conditions. Dashed traces, fetal alcohol spectrum disorders (FASD) data; solid traces, control data. The gray box highlights the express saccade epoch.

There was a significant interaction for group across direction and fixation condition [$F(1, 20) = 5.81$, $p < 0.05$]. In control subjects, SRT in the prosaccade task were faster for leftward saccades, whereas faster SRT in the anti-saccade task were dependent on rightward saccades. In contrast, for the FASD group, faster SRT in the prosac-cade task were dependent on rightward saccades, and direction had no effect on SRT in antisaccades.

CV

The CV normalizes for intrasubject variability in SRT. Only task was statistically significant for the CV, indicating increased variability in SRT for the antisaccade task com-pared with the prosaccade task [$F(1, 20) = 8.5$, $p < 0.01$]. There were no significant differences between group [$F(1, 20) = 2.0$, $p = 0.17$], fixation condition [$F(1, 20) = 0.9$, $p = 0.77$], or direction [$F(1, 20) = 1.0$, $p = 0.34$].

Figure 3C and 3D illustrate the intrasubject variability in SRT for prosaccades, expressed as the CV. There was no significant difference between controls and FASD in CV for the gap [$t_{(20)} = 2.3$, $p = 0.24$] and overlap [$t_{(20)} = 0.04$, $p = 0.97$] conditions (Fig. 3C and 3D). Figure 4C and 4D illustrate CV for control and FASD children in the antisaccade task. Coefficient of variation was elevated for the FASD children in the gap condition [$t_{(20)} = 2.3$, $p < 0.05$], and the same trend was present in the overlap condition [$t_{(20)} = 1.4$, $p = 0.18$].

Express Saccades

The ANOVA of dependent measures revealed significant differences between group, task, and fixation conditions in express saccades. The control group generated a higher percentage of express saccades compared with the FASD children [$F(1, 20) = 9.9$, $p < 0.01$]. A higher percentage of express saccades were also generated in the prosaccade task compared with the antisaccade task [$F(1, 20) = 21.7$, $p < 0.001$] and for the gap condition compared with the overlap condition [$F(1, 20) = 35.5$, $p < 0.001$]. There were no significant differences in direction [$F(1, 20) = 0.1$, $p = 0.78$].

There was an unexpected and significant decrease in the percentage of express saccades (Fig. 3E and 3F) by the FASD children in both the gap [$t_{(14)} = 4.0$, $p < 0.01$] and overlap [$t_{(12)} = 3.1$, $p < 0.01$] conditions. Express saccades are not generated in the antisaccade paradigm, and sac-cades with SRT latencies comparable with the express epoch represent direction errors that are made toward the stimulus (see Fig. 2B and 2D).

There was an interaction between group and task [$F(1, 20) = 13.1$, $p < 0.01$] such that increased percentage of express saccades depended on the gap condition in the control children, whereas this relationship was virtually absent in FASD children. There was also an interaction for group across task and fixation condition [$F(1, 20) = 5.85$, $p < 0.05$], which revealed that increased express saccades in controls was dependent on prosaccades in the gap condition. While there was no evidence, an interaction
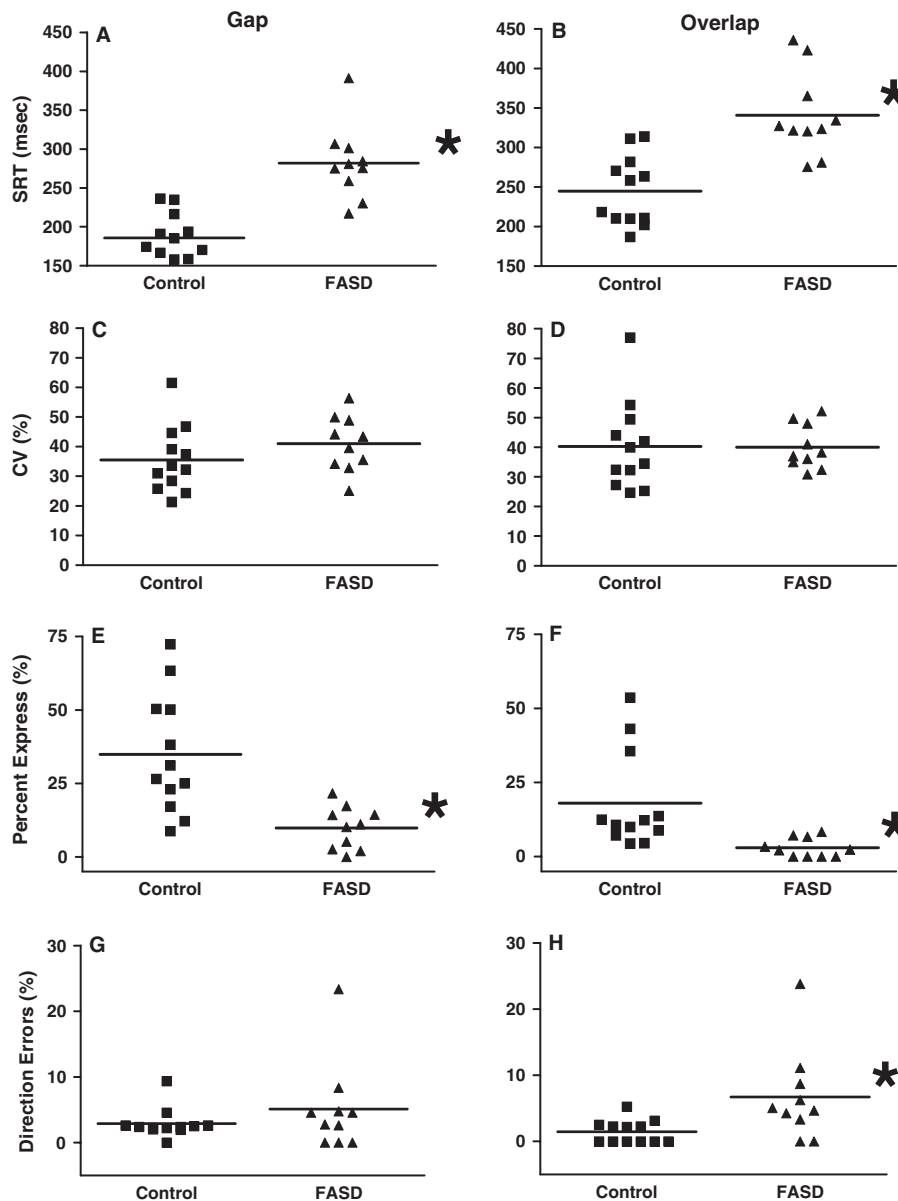
Fig. 3. Quantification of parameters in the gap (**A**, **C**, **E**, **G**) and overlap (**B**, **D**, **F**, **H**) conditions for the prosaccade task. (A and B): mean saccadic reaction times (SRTs) for correct responses. (C and D): coefficient of variation (SD of SRT/mean SRT×100%). (E and F): percentage of express saccades (SRT: 90–140 ms). (G and H): percentage of direction errors. *$p < 0.05$ compared with control subjects.

between fixation condition and group approached statistical significance [$F(1, 20) = 3.80$, $p = 0.07$].

Direction Errors

There was a statistically significant increase in the percent of direction errors in task [$F(1, 20) = 36.1$, $p < 0.001$]. Although there was no evidence for differences in group [$F(1, 20) = 3.5$, $p = 0.08$] or fixation condition [$F(1, 20)$, $p = 0.07$], both dependent measures approached statistical significance. There was no significant difference for direction [$F(1, 20) = 0.17$, $p = 0.68$].

An unexpected finding was the increase in the percent of direction errors on prosaccade trials in the overlap condition (Fig. 3H) for the FASD group compared with controls [$t_{(10)} = 2.3$, $p < 0.05$], which did not reach significance in the gap condition [$t_{(20)} = 1.0$, $p = 0.31$] (Fig. 3G). The percentage of direction errors in the antisaccade task is illustrated in Fig. 4E and 4F. Although FASD children made more direction errors in the antisaccade task, this failed to reach statistical significance [gap: $t_{(12)} = 1.5$, $p = 0.16$; overlap: $t_{(13)} = 1.2$, $p = 0.26$].

Metrics

We also investigated saccade metrics for the saccades made in the prosaccade task (Table 2). There were no differences between control and FASD subjects for amplitude of the first saccade to stimulus [$F(1, 20) = 1.69$, $p = 0.21$] or the number of saccades [$F(1, 20) = 2.37$, $p = 0.139$]. For
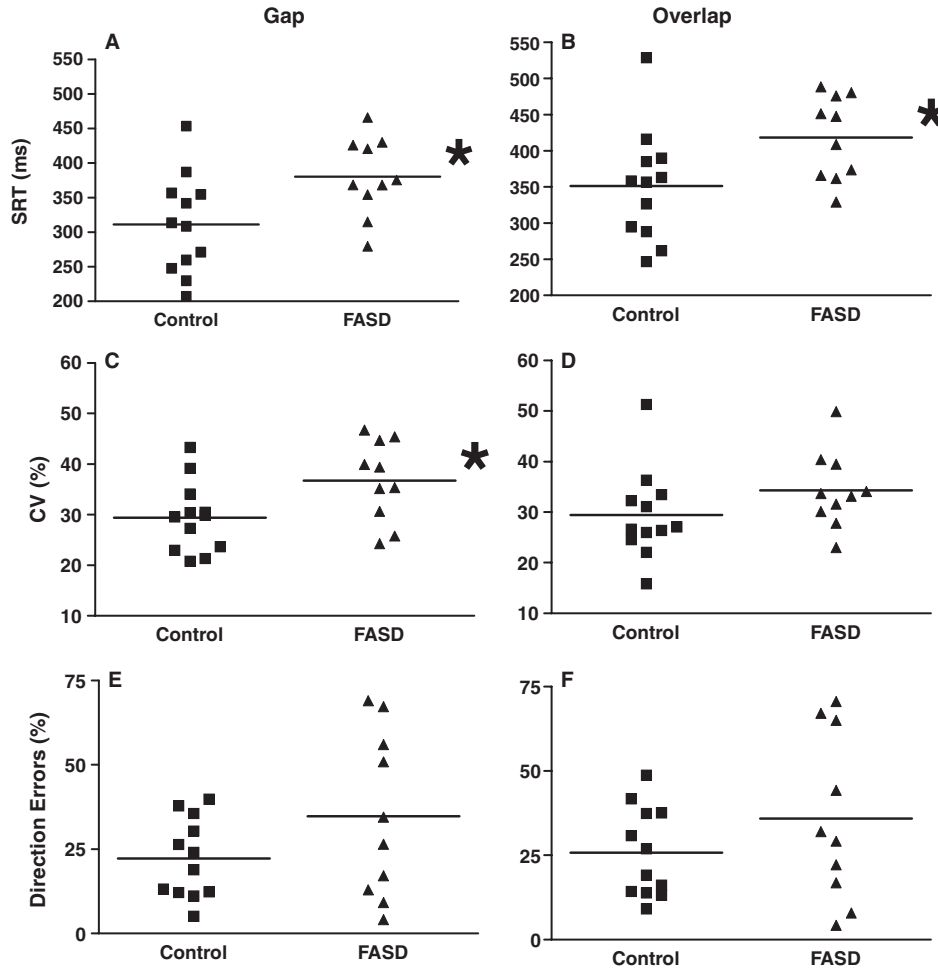
Fig. 4. Quantification of parameters in the gap (**A**, **C**, **E**) and overlap (**B**, **D**, **F**) conditions for the antisaccade task. (A and B): mean saccadic reaction times (SRTs) for correct responses. (C and D): coefficient of variation (SD of SRT/mean SRT×100%). (E and F): percentage of direction errors. *$p < 0.05$ compared with control subjects.

saccades between $18°$ and $21°$ in amplitude, there was a strong trend toward an increase in duration [$F(1, 20) = 3.76$, $p = 0.07$], and reduction in saccade velocity [$F(1, 20) = 3.08$, $p = 0.10$] for the FASD subjects compared with controls. It is expected that with a larger sample size, the latter 2 measures would reach statistical significance.

DISCUSSION

This study shows for the first time that saccadic eye movement experiments can be conducted in children with

Table 2. Saccade Metrics from the Immediate Prosaccade Task

	Amplitude (°)	Number of saccades	Duration (ms)	Peak velocity (°/s)
Gap condition				
Control	19 ± 1	1.22 ± 0.05	75 ± 5	471 ± 25
FASD	19 ± 1	1.09 ± 0.06	88 ± 5	398 ± 27
Overlap condition				
Control	19 ± 1	1.15 ± 0.04	76 ± 5	445 ± 24
FASD	20 ± 1	1.07 ± 0.05	89 ± 5	394 ± 26

FASD, fetal alcohol spectrum disorders.

FASD, and suggests that these tests may provide a sensitive indicator of the brain injury associated with FASD. Significant differences between the performance of FASD subjects and control subjects were demonstrated. Children with FASD exhibited: (1) increased reaction times; (2) a decreased ability to trigger express saccades; (3) an increase in direction errors in the prosaccade task; and (4) no significant increase in direction errors in the antisaccade task. Therefore, we conclude that these data support our initial hypothesis that eye movement experiments can be used to assess executive function in children with FASD. These data are first discussed and related to other clinical groups with developmental disabilities. We then review saccade neural circuitry and speculate about FASD pathophysiology.

Eye Movement Abnormalities in Developmental Disorders

A frequent comorbidity for individuals with FASD is ADHD (Table 1); however, differences in the neurocognitive and behavioral deficits that characterize these 2 disorders have previously been reported (Coles et al.,

1997). Several saccadic eye movement studies have been conducted in the ADHD population using prosaccade and antisaccade paradigms (Aman et al., 1998; Cairney et al., 2001; Hanisch et al., 2006; Klein et al., 2003; Mostofsky et al., 2001; Munoz et al., 2003). These studies have revealed contradictory results due largely to discrepancies in methodology. Two studies with rigorous procedural control and statistical analyses reveal that children with ADHD produce significantly more direction errors in the antisaccade task compared with controls (Klein et al., 2003; Munoz et al., 2003). However, these studies also present contrasting results regarding the occurrence of express saccades. Munoz et al. (2003) described a trend toward ADHD children producing more express saccades compared with controls. In contrast, Klein et al. (2003) found that children with ADHD exhibited a reduced proportion of express saccades in the gap condition.

Although comorbid ADHD existed in 8 of the 10 cases of FASD, the emerging profile for saccadic eye movement abnormalities in FASD is markedly different from what is observed in children with a diagnosis of ADHD (Klein et al., 2003; Munoz et al., 2003). Children with FASD failed to generate express saccades, even among direction errors in the antisaccade task (see Fig. 2). In addition, they made more direction errors in the prosaccade task, while ADHD children made more direction errors in the antisaccade task only. The increased percentage of direction errors in the prosaccade task exhibited in FASD is highly unusual and not observed in ADHD. Direction errors in the antisaccade tasks tend to be initiated immediately following target appearance, within the express epoch for both control (Munoz et al., 1998) and ADHD (Munoz et al., 2003) subjects, while FASD subjects produce direction errors with much longer latencies (see Fig. 2B and 2D). Future studies will be important for exploring the potential use of saccadic eye movement experiments for contrasting FASD and ADHD. The marked differences we report in express saccade occurrence and pattern of direction errors provide important clues and definitely suggest dramatic differences in underlying pathophysiology.

Using the same tasks described here, LeVasseur et al. (2001) demonstrated that individuals with TS have increased SRTs, no significant increase in direction errors in the antisaccade task, and a decrease in the percentage of express saccades. Although this pattern of deficits resembles the data observed in FASD, children with FASD make more direction errors in the prosaccade task, while TS subjects do not. In addition, individuals with TS display no significant differences in saccadic velocity or duration, while the amplitude of the first saccade was smaller and more saccades were generated to move to the target. These observations contrast the trends observed in FASD subjects, in which a decrease in saccadic velocity and an increase in saccadic duration approached significance. These differences between TS and FASD suggest very different patterns of pathophysiology in these 2 disorders.

Of interest, our observations on FASD are not attributable to developmental delay. The normative data generated by Munoz et al. (1998) revealed that young children (ages 5–8) initiated more express saccades than what we observed in FASD. The increase in the occurrence of express saccades among young children suggests that they have poor control over visual fixation, leading to the generation of excessive automatic (reflexive) saccades. Fixation ability improves during normal maturation. The virtual absence of express saccades in the FASD children must therefore be due to a deficit that cannot be explained simply by a delay in normal development.

Neural Circuitry

The neural circuitry underlying saccadic eye movements has been well characterized (Munoz and Everling, 2004; Munoz and Schall, 2004; Pierrot-Deseilligny et al., 2004; Schall, 2004; Scudder et al., 2002; Sparks, 2002). The dorsolateral prefrontal cortex (DLPFC) is involved in executive function, spatial working memory, and importantly, the suppression of unwanted saccades, while the frontal eye fields (FEF) play a crucial role in the execution of voluntary saccades. Punctate lesions to the DLPFC lead to increased direction errors in the antisaccade task (Gaymard et al., 1998; Guitton et al., 1985). Damage to the FEF is correlated with prolonged SRT (Rivaud et al., 1994). In the monkey, reversible inactivation of the FEF leads to increased SRT, decreased saccadic velocity, and increased saccadic duration (Dias and Segraves, 1999; Sommer and Tehovnik, 1997). Reversible inactivation of the DLPFC results in impairments in reflexive saccadic inhibition, leading to increased direction errors in the antisaccade task (Condy et al., 2007). These findings are similar to those obtained in our study, and suggest that DLPFC and FEF dysfunction may account, in part, for the oculomotor deficits observed in FASD. In FASD children, there appears to be global frontal lobe damage that may include the FEF and DLPFC, which would account for the increased SRT and excessive numbers of nonreflexive (longer-latency) direction errors in the antisaccade task.

Damage to frontal lobes has been well documented in the FASD population (Sowell et al., 2002b; Wass et al., 2001), and this has been correlated with deficits in impulsivity, response inhibition, and judgment (Rasmussen, 2005). While our study failed to reveal deficits in impulsivity (increased reflexive direction errors in the antisaccade task), it was apparent that children with FASD executed more disorganized responses that reflected increase direction errors in both the prosaccade and antisaccade tasks. Additionally, their inability to turn off the fixation mechanism in advance precluded their capacity to generate express saccades. These observations suggest that FASD

children have difficulty integrating multiple instructions into a correct sequence of actions, which is consistent with the known deficits in planning ability and/or response inhibition that are associated with FASD.

The relationship between DLPFC and express saccades has been previously investigated using single pulse transcranial magnetic stimulation (TMS) and saccadic eye movement experiments (Muri et al., 1999). The reduction in the SRT following TMS of the DLPFC was attributed to an increase in the percentage of express saccades. The authors suggested that this effect was mediated by either direct activation of the superior colliculus (Leichnetz, 1981) or disinhibition of the superior colliculus via the basal ganglia (Hikosaka et al., 2000). Thus, alterations in the pattern of signaling from DLPFC to superior colliculus may result in deficient express saccade generation. Deficits in FEF function can lead to increased latencies, which could further contribute to the increase in prosaccade duration and decrease in prosaccade velocity. Taken together, these results suggest that global deficits among regions of the frontal cortex lead to a specific pattern of eye movement behavior that is unique to the FASD population consisting of increased SRT and decreased percentage of express saccades. One plausible explanation for these observed deficits is increased inhibition within the frontal cortex. Studies conducted in experimental animal models have shown that chronic prenatal ethanol exposure induces an up-regulation in the expression of $GABA_A$ receptors in the cerebral cortex of postnatal offspring (Bailey et al., 1999, 2001), which would be expected to increase inhibitory tone.

Accumulator Model

Several models have been proposed to explain the variability of reaction time (Luce, 1986; Munoz and Schall, 2004; Nazir and Jacobs, 1991; Ratcliff, 2006; Trappenberg et al., 2001). The accumulator model is useful for interpreting the neurophysiological and behavioral data related to the initiation of saccades in clinical disorders (Munoz et al., 2007). This model is based on the supposition that to initiate movement, neural activity must grow to exceed a given threshold (Fig. 5). In the brain, this function may be represented by the presaccadic activity of saccade neurons in the FEF and superior colliculus (Munoz and Schall, 2004). These neurons can be activated in advance of target presentation, as well as activated directly by target presentation in a neuron's response field (posttarget activation). Three sources have been identified as contributors to variability in reaction time: baseline, threshold, and rate of rise (from baseline to threshold). Thus, pretarget (baseline) and posttarget (rate of rise) information processing can alter the accumulation of activity toward threshold to initiate action. In Fig. 5, the vertical gray box represents the time of the visual response on saccade neurons contralateral and ipsilateral to the side of the target. Pretarget activity (to the left of the target

appearance in Fig. 5) is influenced by fixation disengagement and target predictability (Munoz et al., 2000).

The accumulator model has been used to account for deficits in ADHD, TS, and Parkinson's disease (Munoz et al., 2007). The mean SRT was elevated in ADHD, more direction errors were generated in the antisaccade task compared with controls, and there was a trend toward more express saccades and excessive variability in SRT. These observations suggest poor control over pretarget activity. Excessive pretarget activity can combine with the phasic visual response on the contralateral side to trigger express saccades in the prosaccade task (Fig. 5A, black dashed traces) and reflexive direction errors in the antisaccade task (Fig. 5B, black dotted trace). Attention-deficit hyperactivity disorder behavior can be accounted for by deficits in managing pretarget excitability. Posttarget factors appeared somewhat normal in ADHD (Munoz et al., 2007). LeVasseur et al. (2001) suggested that the increased SRT and reduced occurrence of express saccades in TS may be due to a reduction in pretarget activity leading to delayed threshold crossing (similar to the gray traces in Fig. 5).

Recall that children with FASD exhibit increased SRT, a decreased ability to trigger express saccades, increased direction errors in the prosaccade task, and no significant increase in direction error in the antisaccade task. We speculate that FASD children have reduced excitability (reduced pretarget activity) in the saccade-generating circuit (Fig. 5, gray traces below the black traces). As a consequence, in the prosaccade task, an express saccade is never triggered, while in the antisaccade task, no direction errors are triggered at express saccade latency. Instead, the reduced pretarget baseline leads to prolonged reaction times. A striking difference between FASD and both TS and ADHD was the increase in the occurrence of direction errors in the prosaccade task. Because of poor inhibitory control in FASD, inappropriate activity is allowed to increase toward threshold on the ipsilateral side of the brain (Fig. 5A, see arrow and dotted gray trace), leading to some direction errors in the prosaccade task, which is highly abnormal.

To initiate a correct antisaccade (Fig. 5B), activity must cross threshold on the ipsilateral side of the brain. If the pretarget activity is too high, the posttarget visual response on the contralateral side can contribute to drive the system over the threshold, triggering a reflexive direction error (Fig. 5B, dotted black trace). Because of excessive inhibition in FASD, reflexive direction errors are not triggered, but longer latency direction errors can occur (Fig. 5B, see arrow and dotted gray trace).

Although the specific mechanisms remain to be determined, our suggestions of reduced pretarget activity and accumulation of activity on the wrong side (i.e., ipsilateral side for prosaccades; contralateral side for antisaccades; see arrows in Fig. 5) are unique for FASD and are dramatically different from what is proposed for ADHD
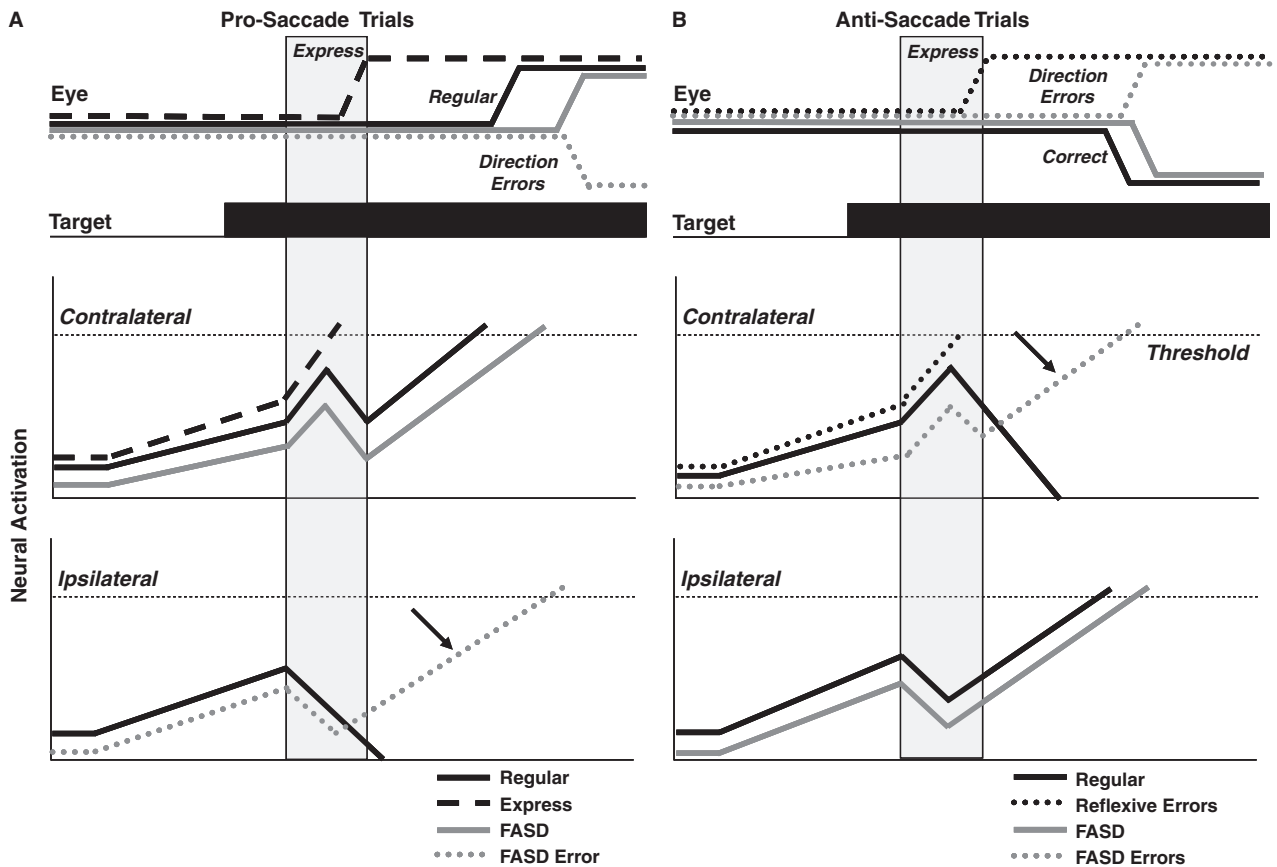
Fig. 5. Accumulator model to describe eye movement abnormalities in fetal alcohol spectrum disorders (FASD). Neural activity must grow to reach a given threshold to trigger a saccade. (**A**) In the prosaccade task, with sufficient pretarget activity, the visual response can lead to the immediate threshold crossing and trigger an express saccade (black dashed trace). Reduced pretarget activity leads to the initiation of regular-latency saccades (black solid trace). In FASD, pretarget activity is reduced, leading to delayed threshold crossing (gray solid trace). In addition, activity is allowed to increase toward the threshold on the ipsilateral side of the brain, leading to highly unusual direction errors in the prosaccade task (dotted gray trace). (**B**) To initiate a correct antisaccade, activity must cross threshold on the ipsilateral side of the brain. If the pretarget activity is too high, the posttarget visual response can contribute to drive the contralateral accumulator over the threshold, triggering a reflexive direction error (black dotted trace). In FASD, reflexive direction errors are not triggered but longer latency errors can occur (gray dotted trace).

subjects (Munoz et al., 2007). As discussed above, this may be the result of an up-regulation in the expression of $GABA_A$ receptors (Bailey et al., 1999, 2001), which would lead to increased inhibition. Such a mechanism could lead to oculomotor abnormalities, and explain the reduction in baseline activity among saccade neurons (Fig. 5). Although FASD subjects do not appear to be impaired in their ability to inhibit automatic visually triggered saccades in the antisaccade task, it is clear that they do have deficits is suppressing activity calling for inappropriate saccades (direction errors) at longer latency. The exact mechanism by which increased inhibition translates into these abnormal processes remains to be fully determined.

Study Limitations

As the sample size was small, it was not possible to confirm with any certainty the contribution that medication and/or comorbidity may have had to the findings presented here. It appears from the scatter plots that the effects reported in this study were not driven by lone sub-

jects, who were considered outliers (Figs. 3 and 4). Still, the importance of these possible confounders is noted and will be more fully investigated in future larger-scale studies.

CONCLUSION

To the best of our knowledge, this study is the first of its kind to evaluate control of saccadic eye movements in children with FASD. A preliminary report of eye movement recording in young adults with prenatal alcohol exposure reported similar effects (Willford et al., 2005). Currently, a larger-scale study is underway to characterize more fully the sensitivity and specificity of these deficits in the FASD population. The results from this pilot study suggest that measuring saccadic eye movement behavior is a promising research and diagnostic tool for evaluating the brain injury resulting from prenatal ethanol exposure.

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