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Immediate Neural Plasticity Involving Reaction Time in a Saccadic Eye Movement Task is Intact in Children With Fetal Alcohol Spectrum Disorder

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Background: Saccades are rapid eye movements that bring an image of interest onto the retina. Previous research has found that in healthy individuals performing eye movement tasks, the location of a previous visual target can influence performance of the saccade on the next trial. This rapid behavioral adaptation represents a form of immediate neural plasticity within the saccadic circuitry. Our studies have shown that children with fetal alcohol spectrum disorder (FASD) are impaired on multiple saccade measures. We therefore investigated these previous trial effects in typically developing children and children with FASD to measure sensory neural plasticity and how these effects vary with age and pathology.

Methods: Both typically developing control children (n = 102; mean age = 10.54 ± 3.25; 48 males) and children with FASD (n = 66; mean age = 11.85 ± 3.42; 35 males) were recruited from 5 sites across Canada. Each child performed a visually guided saccade task. Reaction time and saccade amplitude were analyzed and then assessed based on the previous trial.

Results: There was a robust previous trial effect for both reaction time and amplitude, with both the control and FASD groups displaying faster reaction times and smaller saccades during alternation trials (visual target presented on the opposite side to the previous trial). Children with FASD exhibited smaller overall mean amplitude and smaller amplitude selectively on alternation trials compared with controls. The effect of the previous trial on reaction time and amplitude did not differ across childhood and adolescent development.

Conclusions: Children with FASD did not display any significant reaction time differences, despite exhibiting numerous deficits in motor and higher level cognitive control over saccades in other studies. These results suggest that this form of immediate neural plasticity in response to sensory information before saccade initiation remains intact in children with FASD. In contrast, the previous trial effect on amplitude suggests that the motor component of saccades may be affected, signifying differential vulnerability to prenatal alcohol exposure.

Key Words: Fetal Alcohol Spectrum Disorder, Neural Plasticity, Reaction Time, Amplitude, Previous Trial.

SACCADES ARE RAPID eye movements that bring an image of interest onto the fovea for further visual analysis. Saccades can be generated automatically to visual stimuli or voluntarily in the absence of any overt stimulus. Previous research has found that in healthy individuals performing eye movement tasks involving saccades toward visual targets, the location of a previous visual target or the metrics of a previous saccade can influence performance (e.g., latency, accuracy) of the saccade on the next trial, indicating that information from a previous trial leaves a residual "imprint" on the brain that goes on to affect performance on the next trial (Fecteau and Munoz, 2003). This rapid behavioral adaptation of saccades in response to the movement of the target represents a form of immediate neural plasticity (Dorris et al., 2000).

Neural plasticity is essential for learning and memory, especially during development, to refine and prune neural connections. Prenatal alcohol exposure has consistently been shown to impair neural plasticity (for a review, see Medina, 2011). Fetal alcohol spectrum disorder (FASD) is an umbrella term used to describe the full range of adverse effects induced by prenatal alcohol exposure and is characterized by central nervous system dysfunction with or without facial dysmorphology (Chudley et al., 2005). Neural plasticity impairments found in animal offspring as a consequence of prenatal alcohol exposure include deficits in long-term potentiation and depression (Izumi et al., 2005; Richardson et al., 2002), as well as

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learning and memory tests (Clements et al., 2005). This decreased neural plasticity can translate into poor adaptive functioning skills in children and adults with FASD. These individuals have deficits in the ability to monitor and adjust their behavior in changing environments. For example, children with FASD are consistently rated poorly on adaptive behavioral scales by caregivers and teachers (Fagerlund et al., 2012; Ware et al., 2014). Additionally, children with FASD show deficits on adaptive motor tasks such as matching force responses (Simmons et al., 2015). Rapid visual adaptation is a form of neural plasticity that has not been studied in this population; therefore, we sought to examine this phenomenon using a structured eye movement task in a cohort of children with FASD.

We used a simple visually guided saccade task to investigate previous trial effects in children with FASD. The task we employed requires the participant to generate a saccade to a visual target that appears to the left or right of a central fixation point. The location of the target on the previous trial has been found to influence saccadic reaction time (SRT: the time from target appearance to saccade onset) of the current trial, with SRT being slower when the target appears in the same location as the previous trial (Fecteau et al., 2004; Klein, 2000; Tanaka and Shimojo, 2000). Previous studies have demonstrated that the automatic and voluntary control of saccadic eye movements provides a reliable measure of prenatal alcohol effects and can be used to differentiate those with FASD from typically developing controls (Green et al., 2009; Paolozza et al., 2013, 2014a,b, 2015; Tseng et al., 2013). Additionally, many of the brain regions associated with eye movement control such as the prefrontal cortex (Fryer et al., 2007), basal ganglia (Mattson et al., 1996), cerebellum (O'Hare et al., 2005), and parietal cortex (Archibald et al., 2001) have been found to be damaged in individuals with FASD. Therefore, our previous findings of deficits in eye movement control in children with FASD are not surprising given the large overlap between structures involved in eye movement control and those affected by prenatal alcohol exposure.

Here, we analyzed the effect of the first (1-back) and second (2-back) previous trials on SRT and saccade amplitude in children with FASD and control children. In previous studies with the current cohort, children with FASD were shown to have significantly poorer accuracy of visually guided saccades as indicated by more variable saccade endpoints, increases in saccade endpoint deviation, and increased frequency of additional, corrective saccades required to achieve final fixation (Paolozza et al., 2013). Moreover, children with FASD also have increased deficits in voluntary saccade control (Paolozza et al., 2014a,b) that could impact previous trial effects. Together with the deficits in neural plasticity reported in the brain as a consequence of prenatal alcohol exposure, we predicted that the previous trial effect should be significantly weaker in children with FASD compared with typically developing control children.

MATERIALS AND METHODS

Participants

Both typically developing controls and children with FASD were recruited from 5 sites across Canada including Ontario (Kingston and Ottawa), Alberta (Edmonton and Cold Lake), and Manitoba (Winnipeg). All participants were between the ages of 5 to 18 years old, and individuals with FASD ($n = 66$; mean age = 11.8 ± 3.4; 35 males) were recruited through diagnostic clinics at the participating sites and had previously been diagnosed according to the Canadian guidelines (Chudley et al., 2005). Typically developing control participants ($n = 102$; mean age = 10.5 ± 3.2; 48 males) were excluded if they had any neurological disorder, psychiatric disorder, or visual disturbance (other than corrective lenses). All experimental procedures were reviewed and approved by the Human Research Ethics Boards at Queen's University (Kingston), University of Alberta (Edmonton and Cold Lake), Children's Hospital of Eastern Ontario (Ottawa), and the University of Manitoba (Winnipeg). Written informed consent was obtained from a parent or legal guardian, and assent was obtained from each child before study participation. Socioeconomic status (SES) was calculated using Hollingshead's Four-Factor Index of Social Status (Hollingshead, 2011). Study data were collected and managed using REDCap electronic data capture tools (Harris et al., 2009). Participant characteristics are outlined in Table 1.

Saccadic Eye Movement Recordings

Participants were seated comfortably on a stationary chair in a quiet, dark room. Eye position was recorded using an Eyelink 1000

Table 1. Participant Characteristics

Characteristic	Control group ($n = 102$)	FASD group ($n = 66$)
Overall age (mean ± SD)	10.54 ± 3.25	11.85 ± 3.42
Sex *n* (% of group)		
Males	48 (47)	35 (53)
Females	54 (53)	31 (47)
SES mean ± SD	46.97 ± 9.0	42.71 ± 13.9
Subtype *n* (% of group)		
FAS	–	6 (9)
pFAS	–	14 (21)
ARND	–	46 (70)
Comorbidities *n* (% of group)		
ADHD	–	39 (59)
ODD	–	7 (11)
Anxiety	–	8 (12)
Depression	–	6 (9)
Other	–	20 (30)
Medication *n* (% of group)		
Stimulants	–	26 (39)
Antipsychotics	–	15 (23)
Antidepressant	–	9 (14)
Other	–	14 (21)
Ethnicity *n* (% of group)		
Caucasian	96 (94)	24 (36)
First Nations	2 (2)	39 (59)
Other	4 (4)	3 (5)
Age bin *n* (% group)		
5 to 9	46 (45)	16 (25)
10 to 13	38 (37)	28 (42)
14 to 18	18 (18)	22 (33)

FASD, fetal alcohol spectrum disorder; SES, socioeconomic status; FAS, fetal alcohol syndrome; pFAS, partial fetal alcohol syndrome; ARND, alcohol-related neurodevelopmental disorder; ADHD, attention-deficit hyperactivity disorder; ODD, oppositional defiant disorder.

(SR Research, Kanata, ON, Canada). A 17″ LCD monitor was kept at a distance of approximately 60 cm from the eye (left or right depending on which eye achieved the greatest accuracy during calibration) of the participant and had an infrared illuminator and camera mounted to the bottom. No head stabilization was used, and instead, a target sticker was used to track the head position and compensate for movement. The position of the pupil was digitized in both the vertical and horizontal axes at a sampling rate of 500 Hz. 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. Before each task, the eye movements of each participant were calibrated using 9 screen targets (8 around the periphery and one central) of known position. This ensured that the participants had no visual disturbances that would impair task performance as they would be unable to orient their eyes to the target positions correctly.

The session began with verbal instructions given to the participant that were then repeated back to the experimenter. Each trial started with illumination of a central fixation point (FP) for 800 to 1,200 ms. The FP then disappeared, and, after a 200-ms delay (gap period), a peripheral target appeared randomly at 10° to the left or right of the FP. The gap period was employed because it produces the shortest SRT (Dorris and Munoz, 1995). Participants were given 1,000 ms to initiate and complete a saccade toward the target. No feedback was given about performance. One block of 60 trials was obtained from each participant as part of a larger battery of eye movement and psychometric tests. The entire testing session was 2 hours, and participants were compensated with gift cards. Testing was kept to a maximum of 2 hours to minimize fatigue.

Data Analysis

Data were analyzed on custom software written in MATLAB (Mathworks, Natick, MA). Individual trials were removed from analysis if they failed to meet the following criteria: first, if the participant was not fixating on the FP at the start of the trial and/or a saccade was not made in response to the target appearing to the left or right, and second, if the participant made an error (i.e., looked to the left or right either before the target appeared or in the wrong direction of the target) on the previous 2 trials. Using these criteria, 12 control participants and 5 participants with FASD were eliminated because there were insufficient numbers of trials for quantitative analysis.

SRT was defined as the onset of the first saccade after the target appeared. Amplitude was defined as the size of the first saccade (degrees of eye rotation from start to end). For each measure, the trial was placed into either the repetition category (repeated trials required saccades to the same location) or the alternation category (repeated trials required saccades to the opposite location) based on where the target appeared on the previous trial (n-1), then the overall mean score was calculated. The data were then divided further into 4 categories and placed into the repetition–repetition, repetition–alternation, alternation–alternation, or alternation–repetition category based on the trial previous to the last (n-2). Due to the large sample size, we were also able to test whether developmental effects were occurring. This was accomplished by dividing the participants into 3 age bins (5 to 9, 10 to 13, and 14 to 18 years) and using repeated measures 2-way analysis of variance (ANOVA) to look for differences between age and each category of saccade. We also ran an additional 2-way ANOVA to examine group by age differences. For each measure, repeated measures 2-way analyses of covariance (ANCOVAs) were also run to look for differences between the groups and each category of saccade with age as a covariate. Finally, due to previously reported findings of sex differences between the FASD and control groups (Paolozza et al., 2015), we also ran 2-way ANCOVAs to search for any sex effects in the data, with age as a covariate.

RESULTS

Previous Trials Effects

Developmental Differences. Due to the large age range of the participants (ages 5 to 18 years), we first analyzed the data based on age to search for any developmental effects. There was a significant effect of age on SRT, with SRT decreasing with increasing age in both groups, controls: $F(2, 99) = 3.49$, $p = 0.034$; FASD: $F(2, 63) = 3.50$, $p = 0.036$. There was also a significant effect of trial, controls: $F(6, 594) = 19.56$, $p < 0.0001$; FASD: $F(6, 378) = 17.82$, $p < 0.0001$, but no interaction (Fig. 1*A*). The post hoc results revealed increased SRT for repeat trials compared to alternation trials in both groups (controls: $p < 0.0001$ in 5 to 9, $p = 0.002$ in 10 to 13, $p = 0.016$ in 14 to 18; FASD: $p = 0.003$ in 5 to 9, $p = 0.021$ in 10 to 13, $p = 0.010$ in 14 to 18). However, there was no effect of group (FASD vs. control), and no interaction between group and age for SRT.

For amplitude, there was a significant effect of age in the control group only, $F(2, 99) = 3.66$, $p = 0.029$, with amplitude increasing with increasing age, but a significant effect of trial in both groups, controls: $F(6, 594) = 3.43$, $p = 0.0024$; FASD: $F(6, 378) = 4.88$, $p < 0.0001$, with increased amplitude during repeat trials (Fig. 1*B*). There were no

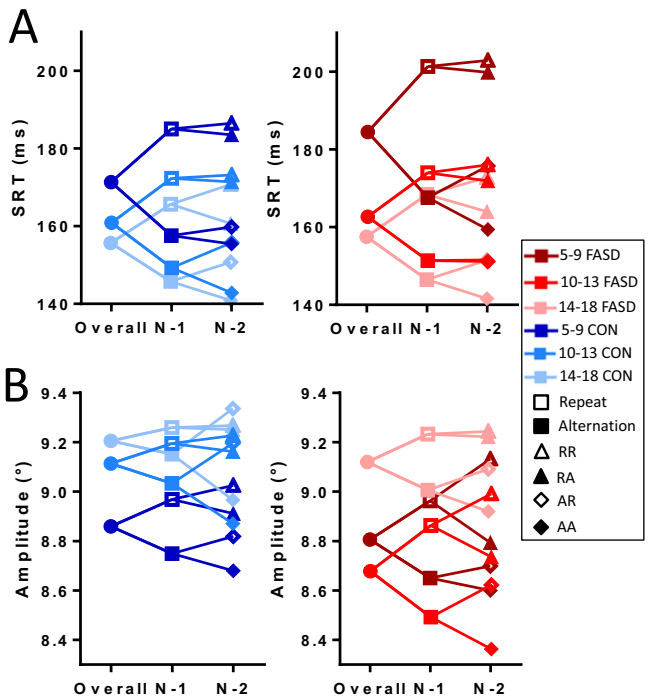

Fig. 1. Developmental Differences. Data are mean scores for the current trial (overall), the previous trial (n-1) separated into repeat and alternation, and the trial previous to that (n-2) separated into repetition–repetition (RR), repetition–alternation (RA), alternation–alternation (AA), and alternation–repetition (AR). (**A**) Saccadic reaction time (SRT) data for the control (blue) and fetal alcohol spectrum disorder (FASD; red) participants separated into 3 age groups. There was a decrease in SRT with increasing age in both groups. (**B**) Amplitude data for the control (blue) and FASD (red) participants separated into 3 age groups. There was an increase in amplitude with increasing age in the control group only.

Table 2. Group by Trial Effects

Measure	Interaction	Group	Trial	Post hocs
Saccadic reaction time	$p = 0.983$	$p = 0.388$	$p < 0.0001$	Trial: Overall Mean vs. Alternation (con: $p = 0.003$; FASD: $p = 0.035$) Overall Mean vs. Repeat (con: $p = 0.003$; FASD: $p = 0.035$) Alternation vs. Repeat (both: $p < 0.0001$)
Amplitude	$p = 0.398$	$p = 0.048$	$p < 0.0001$	Group: Overall mean ($p = 0.030$) Alternation ($p = 0.028$) Alteration–Repeat ($p = 0.019$) Trial: Alternation vs. Repeat (con: $p = 0.032$; FASD: $p = 0.0008$)

Con, controls; FASD, fetal alcohol spectrum disorder.

interactions and no statistically significant results from the post hoc tests in either group. These results indicate that the previous trial effect remained stable with development as there were no interactions found for SRT or amplitude. There was also an overall main effect of group, $F(1, 162) = 4.13$, $p = 0.044$) and age $F(2, 162) = 3.35$, $p = 0.038$, but no interaction between these variables, with amplitude increasing with increasing age and the children with FASD displaying smaller amplitudes. There were no post hoc results.

Group Differences. Due to the effects of age, we used a 2-way ANCOVA with age as a covariate to identify differences between children with FASD and typically developing controls (Table 2). For SRT, there was a significant effect of previous trial, $F(6, 996) = 49.15$, $p < 0.0001$, but no group or interaction effect (Fig. 2*A*). The post hoc results revealed significantly faster SRT in both groups between overall mean versus alternation trials (controls: $p = 0.003$; FASD: $p = 0.035$). There was also a significantly slower SRT in both groups between overall mean versus repeat trials (controls: $p = 0.003$; FASD: $p = 0.035$). Finally, alternation trials had faster SRTs when compared to repeat trials ($p < 0.0001$ in both groups). This indicates that both the control group and the FASD group displayed previous trial effects on SRT but the groups were not different.

For amplitude, there was a significant main effect of both group, $F(1, 166) = 3.96$, $p = 0.048$, and trial, $F(6, 996) = 10.88$, $p < 0.001$, but no interaction (Fig. 2*B*). Post hoc tests revealed significant differences between the groups for overall mean amplitude ($p = 0.030$), alternation amplitude ($p = 0.028$), and alteration–repeat ($p = 0.019$) with the FASD group displaying shorter amplitudes compared to controls. The post hoc tests also revealed significant differences between alternation versus repeat (controls: $p = 0.032$; FASD: $p = 0.0008$) with repeat trials displaying significantly increased amplitude. This indicates that whereas

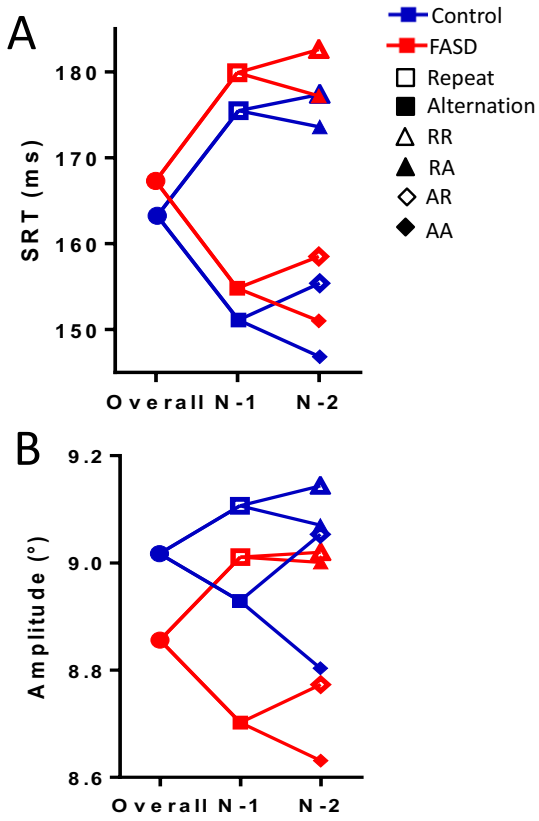

Fig. 2. Group Differences. Data are mean scores for the current trial (overall), the previous trial (n-1) separated into repeat and alternation, and the trial previous to that (n-2) separated into repetition–repetition (RR), repetition–alternation (RA), alternation–alternation (AA), and alternation–repetition (AR). (**A**) There was a strong previous trial effect for saccadic reaction time (SRT) with both control (blue) and fetal alcohol spectrum disorder (FASD; red) participants displaying faster reaction times during alternation trials with no differences between the groups. (**B**) There was also a previous trial effect for amplitude with both control (blue) and FASD (red) participants displaying smaller saccades during alternation trials. Children with FASD exhibited smaller overall mean amplitude and smaller amplitude selectively on alternation trials.

both groups displayed previous trial effects on saccade amplitude, the pattern of change was different between the groups.

Participant Characteristics

Participant characteristics from Table 1 were analyzed for group differences and as potential covariates. Age approached significance ($p = 0.068$) with the FASD group displaying an older mean age than the control group. Age was also found to be a significant covariate with both overall mean SRT ($p = 0.009$) and amplitude ($p = 0.020$); therefore, age was included as a covariate in any analysis of group differences. The ratio of males to females was not different between the 2 groups; however, due to our previous findings of sex differences in both SRT and amplitude, a separate analysis was conducted based on sex (Paolozza et al., 2015). SES was not significantly different between the 2 groups. Additionally, SES was not found to correlate to any measure; therefore, it was not included as a covariate. FASD subtype was investigated by dividing the FASD group into 2 subgroups (FAS/pFAS and ARND) and comparing these subgroups to the control group on all outcome measures using a 1-way ANOVA. ADHD comorbidity (ADHD vs. no ADHD), stimulant medication (stimulants vs. no stimulants), and ethnicity (First Nations vs. Caucasian) were investigated by grouping the children with FASD into 2 subgroups based on each of these variables, and then comparing the 2 subgroups on all measures using a *t*-test. Consistent with previous reports describing eye movement measures within the current cohort, there were no significant differences found between FASD subtype, ADHD comorbidity, medication, or ethnicity (Green et al., 2009; Paolozza et al., 2013, 2014a,b,c).

As previously stated, we recently found several sex differences when examining prosaccade metric measures in children with FASD (Paolozza et al., 2015). Therefore, we also analyzed the data for sex differences and found for SRT the 2-way ANCOVA revealed no interaction, sex, or group effect for any measure. Several group effects and interactions were found for amplitude (Fig. 3). For overall amplitude, there was a group effect, $F(1, 164) = 4.89$, $p = 0.029$, and an interaction between group and sex, $F(1, 164) = 7.90$, $p = 0.006$. The post hoc tests revealed that control females had a greater saccade amplitude compared to control males ($p = 0.042$) and females with FASD ($p = 0.022$). For alternation trials, the amplitude showed a group effect, $F(1, 164) = 5.37$, $p = 0.022$, and an interaction, $F(1, 164) = 8.10$, $p = 0.005$. The post hoc test revealed that control females had a greater saccade amplitude compared to females with FASD ($p = 0.015$). For repeat trials, the amplitude showed only an interaction, $F(1, 164) = 12.13$, $p = 0.001$. The post hoc test revealed that control females had a greater saccade amplitude compared to control males ($p = 0.022$). For alternation–alternation trials, the amplitude showed only an interaction, $F(1, 164) = 6.88$, $p = 0.01$. The post hoc test revealed that control females had a greater amplitude compared to females with FASD ($p = 0.038$). For alternation–repeat trials, the amplitude showed a group effect, $F(1, 164) = 6.09$, $p = 0.015$, and an interaction, $F(1, 164) = 5.88$, $p = 0.016$. The post hoc test again revealed that control females had a greater amplitude compared to females with FASD ($p = 0.031$). For repeat–repeat trials, the amplitude showed only an interaction, $F(1, 164) = 4.75$, $p = 0.031$. However, none of the post hoc tests were statistically significant. For repeat–alternation trials, the amplitude showed only an interaction, $F(1, 164) = 8.50$, $p = 0.004$. The post hoc test revealed that control females had a greater saccade amplitude compared to control males ($p = 0.008$).

DISCUSSION

We investigated previous trial effects in both typically developing children and children with FASD to determine the impact of prenatal alcohol exposure on rapid neural plasticity in the sensory system of the eye movement circuitry. The results of this study revealed that there was a robust

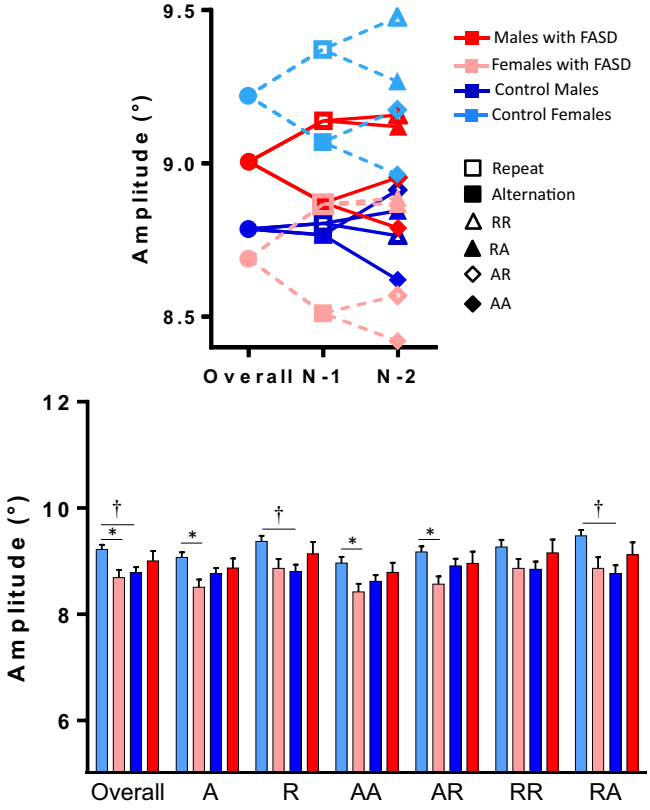

Fig. 3. Sex Differences. Amplitude data are mean scores for the current trial (overall), the previous trial (n-1) separated into repeat and alternation, and the trial previous to that (n-2) separated into repetition–repetition (RR), repetition–alternation (RA), alternation–alternation (AA), and alternation–repetition (AR). Amplitude data for the control (blue) and fetal alcohol spectrum disorder (FASD; red) participants separated by sex with females appearing in the lighter color and males appearing in the darker color. † indicates significance between the control males and females; * indicates significance between females with FASD and control females.

previous trial effect for both SRT and amplitude, with participants displaying faster reaction times and shorter saccades during alternation trials. Importantly, children with FASD displayed similar SRT characteristics in the prosaccade task compared to healthy controls. That is, for both controls and children with FASD, there was a decrease in SRT with age, and a decreased SRT for alternation trials, but no difference between controls and children with FASD for any measure of SRT. For amplitude, children with FASD had smaller saccades for several trials including overall mean amplitude and alternation trials. Additionally, mean saccade amplitude increased with age for the control group but not for the FASD group. These findings indicate that while processes triggered before the saccade is initiated (SRT) appear intact in children with FASD, control during the saccade execution itself (amplitude) appears to be damaged while completing a prosaccade. Therefore, prenatal alcohol exposure may have differential effects on the brain circuitry responsible for SRT and amplitude in children with FASD.

Behavioral Findings

We found that mean SRT was significantly slower for repeat trials compared to alternation trials for both groups. While this effect has been shown many times in control populations (Fecteau and Munoz, 2003; Fecteau et al., 2004; Rafal et al., 1994), it has never been examined in children with FASD. The similar pattern between controls and children with FASD for SRT previous trial effects, mean SRT, and decreasing SRT with increasing age suggests a relative "sparing" effect in the FASD group on SRT in the eye movement circuitry responsible for this rapid adaptation to sensory input.

The previous trial effect on SRT did not differ between childhood and adolescence. Due to the large sample size in both groups, we were able to compare 3 age groups and found no interaction between trial type and age among both control and FASD groups, indicating that this effect remains stable across development from age 5 to 18. This is an important finding, as many other eye movement measures change with development, but this phenomenon appears to develop early. This finding is supported by studies which report that infants as young as 6 months of age had similar previous trial behavior compared to adults (Clohessy et al., 1991); therefore, it would likely be well established by 5 years of age. Although the effect of the previous trial did not change with development, there was a significant decrease in SRT with increasing age in both groups. This is a well-known finding in developmental research for control children (Fischer et al., 1997; Irving et al., 2006; Klein and Foerster, 2001; Luna et al., 2008; Munoz et al., 1998). It appears that children with FASD are not significantly different from controls for prosaccade SRT as they are showing a similar pattern to controls.

This is the first report of the previous trial effect on saccade amplitude in children. Due to the previous findings of differences in amplitude between children with FASD and controls, we sought to examine the impact of the previous trial on saccade amplitude. Similar to our previous studies, we found a decrease in overall mean amplitude in children with FASD. However, this effect seems to be driven by the alternation trials as only a significant difference from controls was found for alternation and not the repeat trials. This finding is further supported by the analysis of sex differences as females with FASD were found to be different from control females on trials which involved alternation, and not repeat. There was also an effect of trial found as alternation trials displayed significantly decreased amplitude compared to repeat trials in both groups. We hypothesize this is because the participant was able to more effectively "remember" the location of the target on the previous trial if it appears in the same location. This finding is supported by research in adults which has found that the amplitude was increased to previously cued locations compared to uncued locations (Ro et al., 2000).

Similar to SRT, there was no effect of age on the impact of the previous trial on saccade amplitude. That is, across all ages, the amplitude was decreased for alternation trials compared to repeat trials in both groups. There was, however, a significant effect of age in the control group: saccade amplitude increased with age, despite a constant target position. This finding is supported by previous research that has found similar results (Fioravanti et al., 1995; Munoz et al., 1998). The absence of this same pattern coupled with an overall decrease in saccade amplitude in the FASD group may point to a developmental delay due to alcohol exposure.

Neural Substrates

These findings emphasize that the oculomotor system is constantly being updated and altered by eye movement use-related experience. The superior colliculus, cerebellum, and brainstem participate in circuits necessary for saccade execution and online correction of saccade amplitude (Everling et al., 1999; Robinson and Fuchs, 2001; Sparks, 2002). Electrophysiological research in non-human primates has pointed to the superior colliculus as the source of this reversible plasticity (Dorris et al., 2000). There is considerable debate on the neurophysiology of previous trial effects on SRT. Some studies suggest top-down control arising from the oculomotor system (Klein, 2000; Rafal et al., 1989; Taylor and Klein, 1998), whereas others have postulated a sensory-based mechanism (Clohessy et al., 1991; Dorris et al., 2002; Fecteau and Munoz, 2005; Fecteau et al., 2004). Because saccadic motor deficits are common in children with FASD, but a difference in SRT between controls and children with FASD was not found, this suggests a sensory basis for the previous trial effect, and further suggests that there may be regions of the brain that are functionally relatively normal when completing an automatic stimulus driven task.

The neurophysiology of previous trial effects has not been widely studied for amplitude, therefore, less is known about

the brain structures involved. It is possible that similar patterns of response attenuation are occurring in regions involved in controlling saccade amplitude, such as the deep cerebellar nuclei and brainstem (Collins et al., 2008; Crawford and Guitton, 1997; Keller et al., 1983; Leigh and Zee, 2006). The nucleus reticularis tegmenti pontis encodes the size and direction of saccades in 3-dimensional eye displacement vectors (Van et al., 1996). It receives input from the superior colliculus and projects to the dorsal vermis and caudal fastigial nucleus of the cerebellum where the dorsal vermis is involved in modulating on-line amplitude and trajectory during a saccade (Keller et al., 1983). The developmental differences and decreased amplitude found in the FASD group may be due to damage in this circuitry caused by prenatal alcohol exposure. Previous studies have found cerebellar damage in children with FASD including abnormal size and location of the cerebellar vermis (Green et al., 2013; O'Hare et al., 2005; Spottiswoode et al., 2011). Therefore, it appears that the motor circuitry of eye movements is also involved in these previous trial effects.

Limitations

There are several limitations with the study population. There was an imbalance between the FASD and control groups on several demographic variables including ethnicity and drug therapy. The FASD population consists of just over half First Nations individuals, but the control group included only a few First Nations individuals. This imbalance needs to be corrected in future studies to properly represent the First Nations populations in the control group. Additionally, over half of the children with FASD have comorbidities and are currently on drug therapy. While this is a potential confound, it is not possible to adequately control for this imbalance as the control population by definition had to have no disorders or diagnoses to participate. Although the demographic variables discussed here were not matched between the FASD and control groups, the effect of these variables on the data was investigated for each study and no differences were found.

CONCLUSION

In conclusion, previous trial effects were observed for SRT and amplitude in both controls and children with FASD performing a prosaccade task. While there were no group differences found for SRT, there was a significant group difference found for amplitude. These results suggest that immediate neural plasticity before an automatic eye movement is initiated is relatively spared in children with FASD as their SRT was not different from controls. However, other brain regions like cerebellar and brainstem circuitry that control amplitude may be more vulnerable to prenatal alcohol exposure. Overall, these results support the notion that outcome measures obtained using eye movement control tasks may be a valuable functional biomarker of the brain injury induced by prenatal alcohol exposure.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

Archibald SL, Fennema-Notestine C, Gamst A, Riley EP, Mattson SN, Jernigan TL (2001) Brain dysmorphology in individuals with severe prenatal alcohol exposure. Dev Med Child Neurol 43:148–154.

Chudley AE, Conry J, Cook JL, Loock C, Rosales T, LeBlanc N (2005) Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. CMAJ 172:1–21.

Clements KM, Girard TA, Ellard CG, Wainwright PE (2005) Short-term memory impairment and reduced hippocampal c-Fos expression in an animal model of fetal alcohol syndrome. Alcohol Clin Exp Res 29: 1049–1059.

Clohessy AB, Posner MI, Rothbart MK, Vecera SP (1991) The development of inhibition of return in early infancy. J Cogn Neurosci 3:345–350.

Collins T, Semroud A, Orriols E, Dore-Mazars K (2008) Saccade dynamics before, during, and after saccadic adaptation in humans. Invest Ophthalmol Vis Sci 49:604–612.

Crawford JD, Guitton D (1997) Visual-motor transformations required for accurate and kinematically correct saccades. J Neurophysiol 78:1447–1467.

Dorris MC, Klein RM, Everling S, Munoz DP (2002) Contribution of the primate superior colliculus to inhibition of return. J Cogn Neurosci 14:1256–1263.

Dorris MC, Munoz DP (1995) A neural correlate for the gap effect on saccadic reaction times in monkey. J Neurophysiol 73:2558–2562.

Dorris MC, Pare M, Munoz DP (2000) Immediate neural plasticity shapes motor performance. J Neurosci 20:RC52.

Everling S, Dorris MC, Klein RM, Munoz DP (1999) Role of primate superior colliculus in preparation and execution of anti-saccades and pro-saccades. J Neurosci 19:2740–2754.

Fagerlund A, Autti-Ramo I, Kalland M, Santtila P, Hoyme HE, Mattson SN, Korkman M (2012) Adaptive behaviour in children and adolescents with foetal alcohol spectrum disorders: a comparison with specific learning disability and typical development. Eur Child Adolesc Psychiatry 21:221–231.

Fecteau JH, Au C, Armstrong IT, Munoz DP (2004) Sensory biases produce alternation advantage found in sequential saccadic eye movement tasks. Exp Brain Res 159:84–91.

Fecteau JH, Munoz DP (2003) Exploring the consequences of the previous trial. Nat Rev Neurosci 4:435–443.

Fecteau JH, Munoz DP (2005) Correlates of capture of attention and inhibition of return across stages of visual processing. J Cogn Neurosci 17:1714–1727.

Fioravanti F, Inchingolo P, Pensiero S, Spanio M (1995) Saccadic eye movement conjugation in children. Vision Res 35:3217–3228.

Fischer B, Biscaldi M, Gezeck S (1997) On the development of voluntary and reflexive components in human saccade generation. Brain Res 754:285–297.

Fryer SL, Tapert SF, Mattson SN, Paulus MP, Spadoni AD, Riley EP (2007) Prenatal alcohol exposure affects frontal-striatal BOLD response during inhibitory control. Alcohol Clin Exp Res 31:1415–1424.

Green CR, Lebel C, Rasmussen C, Beaulieu C, Reynolds JN (2013) Diffusion tensor imaging correlates of saccadic reaction time in children with fetal alcohol spectrum disorder. Alcohol Clin Exp Res 37: 1499–1507.

Green CR, Mihic AM, Brien DC, Armstrong IT, Nikkel SM, Stade BC, Rasmssen C, Munoz DP, Reynolds JN (2009) Oculomotor control in children with fetal alcohol spectrum disorders assessed using a mobile eye-tracking laboratory. Eur J Neurosci 29:1302–1309.

Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG (2009) Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 42:377–381.

Hollingshead A (2011) Four factor index of social status. Yale J Sociol 8:21–51.

Irving EL, Steinbach MJ, Lillakas L, Babu RJ, Hutchings N (2006) Horizontal saccade dynamics across the human life span. Invest Ophthalmol Vis Sci 47:2478–2484.

Izumi Y, Kitabayashi R, Funatsu M, Izumi M, Yuede C, Hartman RE, Wozniak DF, Zorumski CF (2005) A single day of ethanol exposure during development has persistent effects on bi-directional plasticity, N-methyl-D-aspartate receptor function and ethanol sensitivity. Neuroscience 136:269–279.

Keller EL, Slakey DP, Crandall WF (1983) Microstimulation of the primate cerebellar vermis during saccadic eye movements. Brain Res 288: 131–143.

Klein RM (2000) Inhibition of return. Trends Cogn Sci 4:138–147.

Klein C, Foerster F (2001) Development of prosaccade and antisaccade task performance in participants aged 6 to 26 years. Psychophysiology 38:179–189.

Leigh RJ, Zee DS (2006) The Neurology of Eye Movements, 4th ed. Oxford University Press, New York, NY.

Luna B, Velanova K, Geier CF (2008) Development of eye-movement control. Brain Cogn 68:293–308.

Mattson SN, Riley EP, Sowell ER, Jernigan TL, Sobel DF, Jones KL (1996) A decrease in the size of the basal ganglia in children with fetal alcohol syndrome. Alcohol Clin Exp Res 20:1088–1093.

Medina AE (2011) Fetal alcohol spectrum disorders and abnormal neuronal plasticity. Neuroscientist 17:274–287.

Munoz DP, Broughton JR, Goldring JE, Armstrong IT (1998) Age-related performance of human subjects on saccadic eye movement tasks. Exp Brain Res 121:391–400.

O'Hare ED, Kan E, Yoshii J, Mattson SN, Riley EP, Thompson PM, Toga AW, Sowell ER (2005) Mapping cerebellar vermal morphology and cognitive correlates in prenatal alcohol exposure. NeuroReport 16:1285–1290.

Paolozza A, Munn R, Munoz DP, Reynolds JN (2015) Eye movements reveal sexually dimorphic deficits in children with fetal alcohol spectrum disorder. Front Neurosci 9:76.

Paolozza A, Rasmussen C, Pei J, Hanlon-Dearman A, Nikkel SM, Andrew G, McFarlane A, Samdup D, Reynolds JN (2014a) Deficits in response inhibition correlate with oculomotor control in children with fetal alcohol spectrum disorder and prenatal alcohol exposure. Behav Brain Res 259:97–105.

Paolozza A, Rasmussen C, Pei J, Hanlon-Dearman A, Nikkel SM, Andrew G, McFarlane A, Samdup D, Reynolds JN (2014b) Working memory and visuospatial deficits correlate with oculomotor control in children with fetal alcohol spectrum disorder. Behav Brain Res 263:70–79.

Paolozza A, Titman R, Brien D, Munoz DP, Reynolds JN (2013) Altered accuracy of saccadic eye movements in children with fetal alcohol spectrum disorder. Alcohol Clin Exp Res 37:1491–1498.

Paolozza A, Treit S, Beaulieu C, Reynolds JN (2014c) Response inhibition deficits in children with fetal alcohol spectrum disorder: relationship between diffusion tensor imaging of the corpus callosum and eye movement control. Neuroimage Clin 5:53–61.

Rafal RD, Calabresi PA, Brennan CW, Sciolto TK (1989) Saccade preparation inhibits reorienting to recently attended locations. J Exp Psychol Hum Percept Perform 15:673–685.

Rafal R, Egly R, Rhodes D (1994) Effects of inhibition of return on voluntary and visually guided saccades. Can J Exp Psychol 48:284–300.

Richardson DP, Byrnes ML, Brien JF, Reynolds JN, Dringenberg HC (2002) Impaired acquisition in the water maze and hippocampal long-term potentiation after chronic prenatal ethanol exposure in the guinea-pig. Eur J Neurosci 16:1593–1598.

Ro T, Pratt J, Rafal RD (2000) Inhibition of return in saccadic eye movements. Exp Brain Res 130:264–268.

Robinson FR, Fuchs AF (2001) The role of the cerebellum in voluntary eye movements. Annu Rev Neurosci 24:981–1004.

Simmons RW, Nguyen TT, Thomas JD, Riley EP (2015) The use of open- and closed-loop control during goal-directed force responses by children with heavy prenatal alcohol exposure. Alcohol Clin Exp Res 39:1814–1822.

Sparks DL (2002) The brainstem control of saccadic eye movements. Nat Rev Neurosci 3:952–964.

Spottiswoode BS, Meintjes EM, Anderson AW, Molteno CD, Stanton ME, Dodge NC, Gore JC, Peterson BS, Jacobson JL, Jacobson SW (2011) Diffusion tensor imaging of the cerebellum and eyeblink conditioning in fetal alcohol spectrum disorder. Alcohol Clin Exp Res 35:2174–2183.

Tanaka Y, Shimojo S (2000) Repetition priming reveals sustained facilitation and transient inhibition in reaction time. J Exp Psychol Hum Percept Perform 26:1421–1435.

Taylor TL, Klein RM (1998) Inhibition of return to color: a replication and nonextension of Law, Pratt, and Abrams. Percept Psychophys 60:1452–1455.

Tseng PH, Cameron IG, Pari G, Reynolds JN, Munoz DP, Itti L (2013) High-throughput classification of clinical populations from natural viewing eye movements. J Neurol 260:275–284.

Van OJ, Hepp K, Suzuki Y, Henn V (1996) Role of monkey nucleus reticularis tegmenti pontis in the stabilization of Listing's plane. J Neurosci 16:7284–7296.

Ware AL, Glass L, Crocker N, Deweese BN, Coles CD, Kable JA, May PA, Kalberg WO, Sowell ER, Jones KL, Riley EP, Mattson SN (2014) Effects of prenatal alcohol exposure and attention-deficit/hyperactivity disorder on adaptive functioning. Alcohol Clin Exp Res 38:1439–1447.