

**SACCADIC EYE MOVEMENT TASKS ASSESS CENTRAL
NERVOUS SYSTEM DYSFUNCTION AND COGNITIVE
IMPROVEMENTS IN CHILDREN WITH FETAL ALCOHOL
SPECTRUM DISORDERS.**

by

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Abstract

Saccadic eye movement tasks assess central nervous system dysfunction and cognitive improvements in children with fetal alcohol spectrum disorders. M.Sc. Thesis, Queen's University, Kingston, Ontario, Canada, August 2010.

Background: The central nervous system (CNS) dysfunction resulting from prenatal alcohol exposure (PAE) is the most debilitating aspect of fetal alcohol spectrum disorders (FASDs). Affected children exhibit numerous cognitive and behavioural deficits which can severely affect quality of life. As the diagnosis of FASDs often requires specially trained physicians, there is a need for sensitive and specific tools that screen PAE-related CNS dysfunction in order to identify individuals who require further consultation. Additionally, objective measures of intervention end-points are critical to assess potential treatments for this population. As saccadic eye movement behaviours reflect the integrity of multiple brain structures, a battery of oculomotor tasks may serve both these functions. This study sought to test the hypothesis that oculomotor performance in FASD would differ from typically developing children and would allow the objective measure of cognitive improvements resulting from a strength-based motor skills intervention. **Methods:** A cohort of 31 children with FASD, and 31 age- and sex-matched controls completed prosaccade, antisaccade, delayed memory-guided sequential (DMS) and predictive eye movement tasks. Additionally, a selection of these children were involved in an intervention study and therefore tested on three separate occasions using the eye movement tasks and computerized neuropsychological tests. **Results:** Compared to controls, children with FASDs elicited increased direction and anticipatory errors in the antisaccade task, increased timing and sequence errors in the DMS task, and increased anticipatory and decreased express saccades in the predictive task. The FASD group also exhibited an increase in the error of saccade trajectories in the pro- and antisaccade tasks, in addition to increased velocities of

visually-guided saccades in the predictive task. Furthermore, those involved in the intervention study improved in measures of response inhibition in the DMS task. **Conclusion:** This study indicates that frontostriatal and cerebellar dysfunction can be assessed in children with FASDs using a battery of eye movement tasks. In addition, children involved in the strength-based motor skills intervention improved in the ability to perform complex oculomotor tasks. These findings suggest that select eye movement tasks may be utilized to identify CNS dysfunction in FASD and to measure cognitive improvements resulting from behavioural interventions.

Co-Authorship

The research described in this thesis was conducted by Rebecca Titman under the supervision of Dr. James Reynolds. All eye movement data was collected and analyzed by Rebecca Titman.

The CANTAB® data was collected with the assistance of Maureen Kilmade and Bassam Khaleel and analyzed by Rebecca Titman. The first draft of this thesis was written by Rebecca Titman.

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List of Abbreviations

ADHD	Attention deficit/hyperactivity disorder
ANOVA	Analysis of variance
ARND	Alcohol related neurodevelopment disorder
BG	Basal ganglia
BOLD	Blood-oxygen level dependent
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency, Second Edition
CANTAB®	Cambridge Neuropsychological Test Automated Battery
CC	Corpus callosum
CFN	Caudal fastigial nucleus
CNS	Central nervous system
CV	Co-efficient of variation
dIPFC	Dorsolateral prefrontal cortex
DMS	Delayed memory-guided sequential
DTG	Delayed treatment group
DTI	Diffusion tensor imaging
EBN	Excitatory burst neurons
FAS	Fetal alcohol syndrome
FASD	Fetal alcohol spectrum disorder
FEF	Frontal eye fields
fMRI	Functional magnetic resonance imaging
FP	Fixation point
IBN	Inhibitory burst neurons
IOM	Institute of Medicine
IQ	Intelligence quotient
LLBN	Long-lead burst neurons
MRI	Magnetic resonance imaging
OPN	Omnipause neurons
PAE	Prenatal alcohol exposure
PEF	Parietal eye fields
PET	Positron emission tomography
pFAS	Partial fetal alcohol syndrome
PPC	Posterior parietal cortex
RTI	Reaction Time task
SCi	Intermediate layer of the superior colliculus
SEF	Supplementary eye fields
SOC	Stockings of Cambridge task
SRT	Saccadic reaction time
SSP	Spatial Span task
SWM	Spatial Working Memory task
T	Target
TG	Treatment group
TMS	Transcranial magnetic stimulation
TMT-2	Trail Making Test, Part 2

Chapter 1

Introduction

Children prenatally exposed to alcohol may present with craniofacial abnormalities, growth restrictions, and central nervous system (CNS) dysfunction, collectively referred to as fetal alcohol spectrum disorders (FASDs; Chudley et al., 2005). FASDs affect an estimated 2-5% of the population in North America, making prenatal alcohol exposure (PAE) the leading known cause of developmental delay in North America (May et al., 2009; National Institute of Alcohol Abuse and Alcoholism, 1990). Children with FASDs often present with delayed motor development and cognitive deficits in executive function (i.e., response inhibition, planning, and cognitive flexibility), attention, and working memory (Barr et al., 1990; Kodituwakku et al., 2009; Mattson et al., 1998; Rasmussen et al., 2005). These deficits, constituting only part of what may be classified as CNS dysfunction, contribute to the negative life outcomes commonly observed in this population (Streissguth et al., 1999).

In order to assess CNS dysfunction for diagnostic purposes, clinicians evaluate a variety of cognitive domains, such as working memory, attention, and executive function, using standardized neuropsychological testing tools (Chudley et al., 2005). However, these testing tools are limited due in part to the specialized training required for administration and the time that must be invested in completing them. Additionally, they are not readily accessible to all patients at risk of FASD, who may reside in rural communities. Thus, effective screening tools could be the first step in the confirmation of brain injury in order to identify which individuals require further assessment.

The measurement of eye movement control is a powerful tool for assessing sensory, motor and cognitive function, and has been in use to help assess brain function in different clinical populations for many years. Eye movements are effective measures of brain function, as the neural control spans both subcortical and cortical structures. Therefore, eye movements constitute an easily quantifiable behaviour that reflects the integrity of a large span of neural circuitry. Additionally, decades of animal electrophysiology and human imaging studies have provided significant insight into the role of each brain structure as it relates to eye movements, enabling investigators to correlate oculomotor behaviours to particular brain regions. Previous work from our laboratory has shown that children with FASDs demonstrate deficient oculomotor control when compared to typically developing children in tasks that assess sensorimotor processing and cognitive flexibility (Green et al., 2007; 2009a). The goal of this research project was to further characterize oculomotor behaviours in this population using eye movement paradigms that probed, in addition to sensorimotor processing and executive function, procedural learning and working memory abilities.

Physicians are often hesitant to diagnose FASDs due to the perception that the benefits of diagnosis do not outweigh the potential consequences (i.e., stigmatization of both the mother and child; Elliott et al., 2006). In reality, an early diagnosis is one of the strongest protective factors against the development of secondary disabilities (Streissguth et al., 2004). The lack of randomized-controlled trials examining the benefits of interventions may contribute to this knowledge gap between clinicians and researchers. Therefore, a second goal of this research was to examine the use of saccadic eye movement tasks, along with computerized neuropsychological tests, as sensitive and objective measures of cognitive improvements that result from a strength-based motor skills intervention.

Chapter 2

Literature Review

2.1 Fetal alcohol spectrum disorders

The teratogenic effects of alcohol manifest in a wide range of morphological and cognitive-behavioural outcomes. Since Jones and Smith (1973) first described fetal alcohol syndrome (FAS), significant advancements have been made to describe the effects of PAE on the developing fetus. As an umbrella term, FASD describes the craniofacial malformations, growth restriction, and CNS dysfunction resulting from PAE. Within the FASD spectrum, the current Canadian guidelines outline three diagnostic subgroups: FAS, partial FAS (pFAS), and alcohol related neurodevelopment disorder (ARND; Chudley et al., 2005). According to these guidelines, a diagnosis of FAS requires the presentation of growth restriction, the three characteristic facial anomalies (short palpebral fissure length, smooth or flattened philtrum, and thin upper lip), and CNS dysfunction (impairment in 3 or more domains of CNS function). A diagnosis of pFAS is reserved for individuals presenting with 2 of the 3 facial anomalies and CNS dysfunction. ARND is the most challenging to diagnose due to the lack of physical features; these individuals present solely with CNS dysfunction. Additionally, confirmation of maternal alcohol consumption is required for a diagnosis within the FASD spectrum, unless all the criteria for FAS are present. A recent epidemiological study based on samplings from school-aged children, estimates that 2-5% of the population qualifies for a diagnosis within the FASD spectrum, making PAE the leading known cause of mental deficiency in North America (May et al., 2009; National Institute of Alcohol Abuse and Alcoholism, 1990).

2.1.1 The diagnosis of an FASD

The Canadian diagnostic guidelines for an FASD emphasize the use of differential diagnosis; all other possible causes must be ruled out by consultation with physicians well-versed in FASD-related diagnoses, along with psychologists, occupational therapists, and social workers (Chudley et al., 2005). These recommendations represent a harmonization of the Institute of Medicine (IOM; Stratton et al., 1996) and the 4-digit diagnostic code guidelines (Astley & Clarren, 2000). When Jones and Smith (1973) first described the diagnostic term FAS, it referred to only the most severe presentation of PAE. Several decades later, the IOM developed a new set of guidelines to address patients that presented with some, but not all the diagnostic features of FAS (Stratton et al., 1996). These recommendations introduced the 3 diagnostic subgroups currently used in the Canadian guidelines. Common to all diagnoses within the spectrum are the cognitive and behavioural problems resulting from CNS dysfunction, which are not explained by developmental level, genetic mutation or environment (Kodituwakku, 2009). Subsequently, Astley and Clarren (2000) developed and adopted the 4-digit diagnostic code in an effort to improve objectivity in the assessment of possible FASD cases. They suggest that each of the 4 domains adversely affected by PAE be evaluated independently and given a score on a 4-point Likert scale, where a score of 1 indicates a complete absence of features, and a 4 indicates a strong presentation. The four domains assessed include: 1) growth deficiency, 2) facial phenotype, 3) brain damage and dysfunction, and 4) gestational alcohol exposure.

The harmonization of these methods in the creation of the Canadian guidelines combines the nomenclature of the IOM criteria with the objectivity of the 4-digit diagnostic code, while stressing a comprehensive and multidisciplinary approach (Benz et al., 2009). Although these recommendations have yet to be tested for sensitivity or specificity, they have permitted the

integration of strengths from previous diagnostic guidelines to improve and standardize the current diagnostic process (Benz et al., 2009).

2.2 The cognitive-behavioural phenotype of FASD

A substantial amount of research has been devoted to improving our understanding of the underlying neuropathology associated with FASD. However, inclusive diagnostic processes, and effective prevention and intervention strategies still pose significant clinical challenges (Rasmussen et al., 2006). Due largely to the numerous variables that influence alcohol teratogenicity, such as timing, frequency and dose of exposure, as well as maternal nutritional status, age, and genetics, the relationship between alcohol consumption and CNS dysfunction has been difficult to delineate (Riley & McGee, 2005). Following the identification of CNS damage in non-dysmorphic, alcohol-exposed individuals (Clarren et al., 1978), it became apparent that the physical manifestations of PAE were not necessarily indicative of the extent of brain insult. Since then, it has become clear that while the facial features and growth restrictions associated with a diagnosis of FAS are the most obvious markers of PAE, it is the CNS damage that is most debilitating and long-lasting (Streissguth et al., 1999). Children with FASD often present with delayed motor development, diminished information processing abilities, and abnormal visual/spatial abilities (Barr et al., 1990; Carmichael-Olsen et al., 1998). In particular, higher cognitive abilities such as executive functions (planning, cognitive flexibility, and response inhibition), working memory, and attention are significantly affected by PAE (Kodituwakku et al., 2009; Rasmussen et al., 2005). Autopsy reports and imaging studies have enabled researchers to connect behavioural outcomes to specific areas of brain injury, thus providing a wealth of knowledge relating the brain-behaviour relationship in FASD.

Early autopsies of individuals with FAS revealed widespread disorganization of the CNS, microcephaly, as well as anomalies of the corpus callosum, the basal ganglia and the cerebellum (Clarren et al., 1978). Although these studies provided insight into the types of brain injury associated with FAS, no identifiable pattern of anomalies transpired in all children with PAE. With the advent of improved neuroimaging technology, less severe cases of FASDs can now be studied, in which patterns of brain damage are emerging that are consistent with the behavioural sequelae. Subtle alterations in neuroanatomy are now being correlated with cognitive and behavioural abnormalities using these technologies (for review see: Riley & McGee, 2005). It appears that specific brain regions are particularly sensitive to PAE, including the corpus callosum, the basal ganglia, the cerebellum and regions of the cerebral cortex.

2.2.1 Corpus callosum

One of the most consistent structural changes observed in the FASD population is abnormalities of the corpus callosum (CC), which is the fibre tract that connects the two cortical hemispheres and facilitates interhemispheric communication (Riley & McGee, 2005). Early autopsy reports revealed partial or complete agenesis of the CC, which is associated with cognitive and motor coordination deficits (Clarren et al., 1978; Devinsky & D'Esposito, 2004; Jones et al., 1973). Using structural magnetic resonance imaging (MRI) technology in children with FASDs, Riley and colleagues (1995) demonstrated that the most anterior and the two most posterior portions of the CC were reduced in children with confirmed PAE compared to non-exposed children, after controlling for overall reductions in brain size. Additionally, Sowell and colleagues (2001) revealed significant displacement of the CC in alcohol-exposed subjects compared to controls, which negatively correlated with performance on a verbal learning task. Diffusion tensor imaging (DTI) studies, which allow the exploration of microstructural integrity in white matter

tracts, have also found abnormalities in regions of the CC , which have been correlated with impairments on a visual-motor integration test (Lebel et al., 2008; Ma et al., 2005; Sowell et al., 2008). Together, these studies suggest that structural abnormalities of the CC resulting from PAE may explain deficits in attention, verbal learning, and visual-motor integration in the FASD population.

2.2.2 Basal ganglia

The basal ganglia (BG) are a group of subcortical structures that have extensive connections to both cortical and subcortical motor areas and influence motor activity through a series of parallel loops connecting the frontal cortex and the thalamus (Devinsky & D'Esposito, 2004). Due to extensive connections with the frontal lobes, the BG also modulate cognitive, affective and motivational behaviour (Devinsky & D'Esposito, 2004). When compared to controls, structural MRI studies have revealed an overall reduction in the volume of the BG in alcohol-exposed children (Mattson et al., 1992; 1996); others suggest that only the caudate nucleus is affected in this population (Archibald et al., 2001). Furthermore, several studies have demonstrated that structural alterations in the BG predict cognitive deficits, including impairments in attention, verbal learning and recall, and perseverative responding in subjects with FASDs (Archibald et al., 2001; Mattson et al., 1996). Functional abnormalities were revealed in alcohol-exposed subjects using a Go/No-Go task that assesses response inhibition (Fryer et al., 2007). Despite similar behavioural performance, children with FASDs had an increased blood oxygen level dependent (BOLD) signal in the prefrontal cortex and a decreased BOLD signal in the caudate compared to controls. As the BOLD signal is an indirect measure of neural activity, the authors attribute this finding to a compensatory strategy for frontostriatal inefficiencies.

2.2.3 Cerebellum

Abnormalities in the cerebellum are consistently reported in alcohol-exposed individuals (Archibald et al., 2001; Mattson et al., 1992; 1994). The cerebellum functions to coordinate and modulate actions based on inputs from all four cortical lobes, the spinal cord, the brain stem and the thalamus (Devinsky & D'Esposito, 2004). While the cerebellum is normally associated with motor coordination, anatomical and physiological evidence suggests the structure also governs cognitive and emotional functions (Devinsky & D'Esposito, 2004). In children with FASDs, structural MRI techniques revealed a reduction in the surface area and volume of the cerebellum in children with confirmed PAE; an observation that is consistent with deficits in motor learning and balance (Autti-Ramo et al., 2002; Roebuck et al., 1998). This significant volume reduction was restricted to the anterior vermis after controlling for overall brain size (Sowell et al., 1996). Abnormalities of the cerebellar vermis may be attributed to Purkinje cell death, which is a consistent finding in animal models of PAE (Goodlett et al., 1990). Additionally, O'Hare and colleagues (2005) revealed that the greater the reduction in anterior vermal volume, the worse alcohol-exposed children performed on tests of verbal learning and memory.

2.2.4 Cerebral cortex

Although total cerebral cortical volume is often reduced in the FASD population when compared to typically developing children, specific regions of the cerebral cortex appear to be disproportionately affected (Riley & McGee, 2005). Using MRI volumetrics, Archibald and colleagues (2001) found that only the parietal lobes were reduced in size after adjusting for overall brain volume. This lobe has multiple functions, and in particular serves a central role in sensorimotor integration, visual attention and perception (Devinsky & D'Esposito, 2004). Despite the fact that children with FASDs frequently exhibit deficits in frontal lobe function,

particularly in behavioural and executive control, many studies fail to find structural abnormalities using MRI volumetric and voxel-by-voxel analyses (Riley & McGee, 2005). More recently, Riley and colleagues (2004) used a novel image analysis technique that involved the creation of brain surface maps for each individual, allowing the comparison of regional abnormalities in brain size without the limitations of other analytic tools. Using this methodology, a decrease in frontal lobe surface area was found in subjects with FASD compared to controls. This reduction was more prominent in the left hemisphere suggesting altered brain symmetry, which the authors propose is associated with altered language processing and deficits in face recognition (Church & Abel, 1998; Mattson et al., 1998). Lastly, increases in cortical thickness compared to controls have been described in individuals with FASDs over areas of the lateral temporal, parietal, frontal and occipital cortices (Sowell et al., 2008). As cortical thinning occurs normally during childhood, increased cortical thickness in children with FASDs further demonstrates that PAE significantly alters normal brain development (Norman et al., 2009).

By combining the findings from imaging and behavioural studies, a pattern of brain injury associated with FASDs is emerging. This pattern is providing new insight into the neuropathology behind the FASD cognitive-behavioural phenotype. Taken together, this knowledge is useful to distinguish alcohol-exposed children from other neurodevelopmental disorders.

2.3 Assessing CNS dysfunction in FASD

CNS dysfunction in FASD has been assessed using numerous behavioural checklists and tests of executive function. Checklists used to quantify behavioural dysfunction in children with FASDs include the *Conners' Rating Scales* (Rasmussen et al., 2006) and the *Child Behaviour Checklist* (Greenbaum et al., 2002), often reporting that these children are hyperactive, disruptive

and impulsive (Riley & McGee, 2005). Intellectual ability has also been evaluated using the *Wechsler Intelligence Scale for Children, 3rd edition* for school-age children (Mattson et al., 1997) and the *Griffiths Scales Measures of Intelligence* (Adnams et al., 2001), which have revealed deficits in complex intellectual functioning in children with FASD. Checklists and rating scales have been proven useful for assessing negative life outcomes, for example academic, social and emotional problems; however, domain-specific tests of neuropsychological function are useful to define the cognitive profile of an individual (Kodituwakku 2007). In order to assess the cognitive deficits specific to PAE-related brain damage, tests of attention and information processing, executive function, memory and learning are employed.

2.3.1 Tests of attention and information processing

Attention deficits have been extensively examined in children with FASDs, as they are thought to be the most common characteristics (Kodituwakku, 2009). A *Continuous Performance Test*, in which subjects must respond to a correct stimulus and ignore distractor stimuli, may be used in pediatric populations to assess selective attention and impulsivity (Devinsky & D'Esposito, 2004). Using this test, Streissguth and colleagues (1986) found that children with prenatal alcohol exposure had performance problems on measures of vigilance, reaction time, and impulsivity. In more complex tasks of attention, for example the *Digit Span Task* where children must recall a sequence of digits that increase in length, children with FASDs perform significantly worse than the age-matched controls (Lee et al., 2004). Additionally, Burden and colleagues (2005) found that children with PAE had trouble with tasks that involved effortful processing, which requires increased attention and exertion, but not with those involving automatic processing. These results suggest that while children with FASDs may perform

similarly to controls in simple tests of attention and information processing, deficits begin to emerge as the complexity of the task increases.

2.3.2 Tests of executive function

Executive function is broadly defined as conscious, goal-directed behaviours that include planning, set-shifting, and response inhibition, and is a frontal lobe function severely impaired in children with FASDs (Kodituwakku, 2001; Rasmussen, 2005). These abilities are not only important for academic success, but also for the development of skills that are essential for independent living (i.e., management of money, maintaining employment). The *Wisconsin Card Sorting Task* is frequently used to measure cognitive flexibility, concept formation and learning (Devinsky & D'Esposito, 2004). In this task, the participant must use verbal feedback to deduce the criterion with which a set of cards are sorted (i.e., by number, colour, or shape). Once the participant determines the sorting criterion, it will change without their knowledge, except for the verbal feedback provided by the administrator. In this task, children with FASDs demonstrate difficulties in set shifting as they take longer to modify their response to match the changing criterion (Carmichael-Olsen et al., 1998). The *Trail Making Test, Part 2* (TMT-2) can also be used to evaluate set-shifting as subjects are required to draw a line through alternating numbers and letters in numeric and alphabetical order (Devinsky & D'Esposito, 2004). In children with FASDs, Connor and colleagues (2000) revealed deficient performance in both the *Wisconsin Card Sorting Task* and the TMT-2 compared to controls. To assess planning abilities and problem solving, tower tasks are commonly used in which subjects are required to move coloured balls on pegs of variable heights in order to match a predetermined pattern. In this task, children with FASDs demonstrated marked deficits in planning abilities and tended to perseverate on incorrect strategies (Mattson et al., 1998). Furthermore, even after controlling for intelligent

quotient (IQ), tests of executive function still reveal significant deficits, suggesting they are not solely the result of decreased intellectual ability (Connor et al., 2000; Kerns et al., 1997).

2.3.3 Tests of learning and memory

Learning and memory are described as the ability to recall previously presented information. Learning is distinguished from memory as information that is encoded based on repeated exposures, as opposed to on a single occasion (Devinski & D'Esposito, 2004). It has been well established from animal studies that the hippocampus is important for memory and is particularly sensitive to alcohol exposure (Riley & McGee, 2005). Tests of recall are often used to assess memory in clinical populations, as their sensitivity to hippocampal function has been well validated (Devinski & D'Esposito, 2004). In the *Smith and Milner Memory for 16 Objects* task, children with FASDs had difficulty with the delayed, but not the immediate recall of objects compared to age-matched controls (Uecker & Nadel, 1996). In a computerized version of the *Morris Water Maze* – a rodent test of memory – children with FASDs had difficulty navigating to a hidden platform despite the presence of visual cues, but not in navigating towards a visible platform compared to typically developing children (Hamilton et al., 2003). Consistent with the results from tests of attention and information processing, children with FASDs do not necessarily differ from typically developing children in simple tasks of learning and memory, but demonstrate significant difficulties as the complexity of the tasks increase.

Clinically, the accessibility of traditional neuropsychological tests is limited due to the amount of time required to complete them and the need for specially trained professionals to administer them. Therefore, there is an apparent need for novel tasks that could objectively assess cognitive function in children with FASDs using tools that are both mobile and easy to administer.

2.4 Saccadic eye movements as measures of cognitive function

Saccades are rapid, ballistic eye movements that permit the fixation of objects of interest onto the fovea, the region of the retina with the highest visual acuity (Perry & Cowey, 1985). As a result, saccades represent the integration of sensory information and internal goals that give rise to a motor response (Ramat et al., 2007). Experimentally, saccadic eye movements are an ideal tool for examining brain function. First, sensory input can be highly controlled by modifying the experimental setting enabling different aspects of sensory-motor integration to be probed (Gooding & Basso, 2008). Second, behavioural outcomes – the saccades – can be precisely measured using remote monitoring equipment that produces little to no discomfort to the participant making it an ideal tool for assessing brain function in children. Third, the mobility of the eye tracking equipment allows testing in remote communities where subjects with FASD do not have ready access to clinical supports. Finally, due to the significant overlap in the brain structures affected by PAE and those involved in eye movement control, saccadic eye movement tasks represent a suitable tool for providing insights into the CNS dysfunction associated with FASD (Green et al., 2007; 2009a).

2.4.1 Neurocircuitry of saccadic eye movements

In addition to methodological ease, saccadic eye movements are useful for the assessment of brain function as the neurophysiology has been well characterized. Saccadic neurocircuitry spans both cortical and subcortical regions of the CNS including: the parietal and frontal cortices, the basal ganglia, the thalamus, the superior colliculus, the cerebellum, and the brainstem reticular formation (Leigh & Zee, 1999). Each of these structures have specific roles in the control of eye movement behaviour, which have been elucidated from decades of electrophysiology and lesion studies, and more recently confirmed using functional MRI (fMRI)

and transcranial magnetic stimulation (TMS) experiments (Sweeney et al., 2007). Thus, eye movement paradigms can be tailored to assess specific domains of cognitive function and provide insight into the underlying neuropathology associated with different clinical populations.

Eye movements are generated by motoneurons that discharge a burst of action potentials to elicit saccades and maintain tonic discharge during fixation (Sparks, 2002). These motoneurons are under the control of excitatory and inhibitory burst neurons (EBN and IBN) which elicit bursts during saccades to produce a desired movement. Additionally, the EBN and IBN are under the influence of the excitatory long-lead burst neurons (LLBN) and the inhibitory omnipause neurons (OPN). For a saccade to be initiated, the LLBN elicit a high frequency burst activity, while the OPN inhibition must cease. The control of these premotor areas is governed by the intermediate layers of the superior colliculus (SCi), in which neurons that correspond to fixation and saccade behaviours can be found (Munoz & Fecteau, 2002).

The SCi receives inputs from the parietal and frontal cortices, the BG and the cerebellum (Leigh & Zee, 1999). The posterior parietal cortex (PPC) is involved in the generation of visually-guided saccades, and contains the parietal eye fields (PEF) which are involved in sensorimotor integration and project to the SCi (Andersen et al., 1997). Within the frontal lobe, the frontal eye fields (FEF) may act as a central point of communication due to extensive connections with other areas within the frontal lobe, the parietal lobe, the SCi, the BG, the cerebellum and the reticular formation (Pierrot-Deseilligny et al., 2004). The supplementary eye fields (SEF) and the dorsolateral prefrontal cortex (dlPFC), also found in the frontal lobe, have been shown to have roles in working memory and decision making with both areas connecting to the SCi directly and indirectly through the FEF. Further contributing to the control of saccades, the brain stem receives inputs from both the cerebellum and the BG. Projections from the

cerebellum innervate the EBN and IBN and are involved in the steering and stopping of saccades, thus influencing oculomotor accuracy (Ramat et al., 2007; Robinson & Fuchs, 2001). The BG are involved in presaccadic processing as they aid in the selection and prevention of movements, as well as the incorporation of reward (Hikosaka et al., 2000). As multiple brain structures along the neuraxis are involved in oculomotor control, brain injury affecting any of these structures can result in eye movement performance deficits observable using various saccade paradigms.

2.4.2 Saccadic eye movement tasks

As previously discussed, certain regions of the brain, namely the frontal cortex, parietal cortex, basal ganglia and cerebellum, are particularly sensitive to PAE. The overlap of brain regions affected by PAE and those involved in eye movement control suggest that saccadic eye movement behaviours may provide insight into the CNS dysfunction observed in alcohol-exposed individuals (Green et al., 2007; 2009a). In the current study, subjects performed four eye movement tasks that assessed the ability to generate different saccade types; prosaccades, antisaccades, delayed memory-guided saccades and predictive saccades.

Prosaccades are visually-guided saccades directed to a peripheral target. Due to the automatic nature of prosaccades, this task allows the quantification of sensory-motor processing. Conversely, the antisaccade task requires subjects to look away from a peripheral target. This behavior requires two processes: 1) the suppression of an automatic prosaccade towards the target and 2) the generation of an internally-driven antisaccade away from the target (Munoz & Everling, 2004). As a result of the increased cognitive demand of this task, regions of the frontal cortex and basal ganglia are recruited. Previous studies revealed deficits in cognitive control in the FASD population using the pro- and antisaccade tasks as subjects demonstrated increased

latencies, intra-subject variability and error rates when compared to age- and sex-matched controls (Green et al., 2007; 2009a).

As spatial working memory and cognitive inhibition abilities are impaired in the FASD population, a delayed memory-guided sequential (DMS) task was also used. Subjects were required to generate two memory-guided saccades to locations where peripheral targets had previously appeared. The dlPFC is chiefly involved in the response inhibition and working memory abilities necessary for this task, while the SEF are implicated in the generation of saccade sequences (Pierrot-Deseilligny et al., 2004). In a similar memory-guided saccade task, children with attention deficit/hyperactivity disorder (ADHD), and adults with Huntington's disease and Parkinson's disease demonstrated deficits in response inhibition with the frequent initiation of early responses (Chan et al., 2005; Mostofsky et al., 2001; Peltsch et al., 2008).

Lastly, to assess procedural learning in this population, a predictive task was used in which subjects follow a target alternating between two known locations in the right or left hemi-field. Learning is assessed as the ability to adjust motor responses to the predictable movement of stimuli with practice, thus reducing SRTs as the trials progress (Devinski & D'Esposito, 2004). The FEF have a key role in predictive saccade generation; both positron emission tomography (PET) and fMRI studies have revealed increased activity in these regions as predictive behaviours become apparent (O'Driscoll et al., 2000; Simo et al., 2005). It has also been suggested that this task probes aspects of spatial and temporal working memory, implicating the involvement of the dlPFC (Pierrot-Deseilligny et al., 2003). Patients with BG degeneration, including Parkinson's disease as well as those with cerebellar lesions, demonstrate difficulty generating predictive saccades, additionally implicating the basal ganglia and cerebellum in this process (Bronstein & Kennard, 1985; O'Driscoll et al., 2000)

These eye movement tasks provide an opportunity to quantify oculomotor behaviours that reflect both the automatic and higher-order cognitive abilities that are often deficient in the FASD population. Thus, objective and sensitive measures of sensory-motor processing, response inhibition, working memory, and procedural learning abilities can be obtained using these tasks.

2.5 The CANTAB® as a measure of cognitive function

The Cambridge Neuropsychological Test Automated Battery (CANTAB®) is a commercially available neuropsychological testing tool (Cambridge Cognition, Cambridge, United Kingdom). As an objective measure of cognitive function, its strengths lie largely in the computerized format and the non-verbal administration of well-validated neuropsychological tests (Lowe & Rabbitt, 1998). The computerized format allows data acquisition and scoring to be automated, which increases precision and consistency when compared to standardized pen and paper tests (Luciana, 2003). As test administration is chiefly non-verbal, experimenter bias and the effect of language proficiency is reduced. Test-retest reliability with the CANTAB® has been ineffectively studied, although these tasks have been used in intervention studies by comparing post-intervention scores to baseline measures. Furthermore, our own research group has shown performance deficits in three of the four selected CANTAB® tasks in children with FASD compared to age- and sex-matched controls (Green et al., 2009b).

In order to examine the cognitive improvements resulting from the intervention study, four tasks were selected to assess attention, spatial working memory and planning. Previous assessment of children with FASDs using the CANTAB® Reaction Time (RTI) task revealed increased reaction times in both simple and 5-choice conditions, as well as increased movement time in the simple condition (Green et al., 2009b). This study also revealed deficits in spatial working memory and planning abilities in the Spatial Working Memory (SWM) and the

Stockings of Cambridge (SOC) tasks. In the SWM task, subjects were required to remember the location of boxes in which tokens had previously been found. Children with FASDs were more likely to return to boxes in which tokens had already been found, and were less likely to use a search strategy (Green et al., 2009b). In the SOC task, subjects were required to match a target pattern of balls with their own set of balls hanging in “stockings”. This task revealed that children with FASDs were able to complete fewer trials in the minimum number of moves when compared to age- and sex-matched controls (Green et al., 2009b). In the present study, participants also performed a Spatial Span task (SSP) where the aim was to remember a sequence of flashing boxes that progressively increased in number in order to further assess spatial working memory. Although this task had not been previously administered in the FASD population, performance deficits measured as an increase in errors was documented in children with ADHD (Gau & Shang, 2010).

Both the eye movement and the CANTAB® tasks are validated measures of cognitive function in the pediatric population and have been used to assess domains of weakness in children with FASDs. This suggests the use of these tasks as sensitive and objective measures of cognitive function in the FASD population. Furthermore, these tasks may also be valuable for the evaluation of cognitive improvements resulting from a strength-based motor skills intervention.

2.6 Interventions for children with FASDs

A survey of pediatricians’ attitudes and knowledge of PAE revealed hesitations to diagnose FASD for a variety of reasons, including the perception that efficacious interventions for those affected by PAE do not exist (Elliot et al., 2006). However, the lack of a diagnosis is strongly correlated with an increased risk of adverse life outcomes (Streissguth et al., 2004). With the emergence of objective tools that can be used to assess the benefits of available

interventions, it may be possible to alter clinicians' attitudes by providing evidence of effective intervention strategies that improve quality of life.

Currently, minimal empirical evidence has been published evaluating the efficacy of interventions designed for children with FASDs. Strategies in use are often adopted from other developmental disabilities without the appropriate modifications to suit the behavioural profile of FASD (Bertrand, 2009). As the cognitive-behavioural phenotype of FASD becomes better understood, it is possible to tailor intervention strategies to better meet individual needs, while taking into account the cost, time, and lifestyle challenges of working with these children (Kodituwakku, 2009b). Intervention strategies explored in the FASD population can be grouped into three broad categories: skill-specific, pharmacological, and behavioural.

2.6.1 Skill-specific interventions

As children with FASDs fail to thrive in learning environments designed for typically developing children, modified lessons that can be incorporated into normal education programs are a promising intervention strategy. It is suggested that modeling, repetition and chunking of instructions are the best way for children with FASDs to process and retain information (Paley & O'Connor, 2009; Rasmussen et al., 2006). Modified teaching methods have been utilized to teach specific skills, such as math and reading. In studies assessing the use of modified lessons to teach these skills, rehearsal strategies, modeling and the use of concrete objects to teach abstract concepts were effective at improving test scores more than a control group learning in a normal classroom setting (Adnams et al., 2007; Kable et al., 2007). This focused attention on specific skills improved children's performance in the desired domain, but not in measures of general scholastic ability. Therefore, modified teaching strategies are effective for individuals with FASDs and may be incorporated into normal classrooms to produce lasting benefits. Due to the

complex spectrum of deficits seen in FASDs however, these skill-specific approaches may be most effective in combination with other intervention strategies.

2.6.2 Pharmacological interventions

Children with PAE are often prescribed a wide variety of pharmacological agents to help mitigate the symptoms associated with FASD. Often, the medications prescribed are based on their efficacy in other neurodevelopmental disorders, such as ADHD. Clinically, there can be substantial overlap in the presentation of FASD and ADHD, though it appears the behavioural profiles may differ (Coles, 2001). Therefore, children with FASDs may react differently to the stimulant medications often prescribed to children with ADHD (Doig et al., 2008). Assessing the effects of stimulants on ADHD-like symptoms in children with FASDs, randomized-controlled trials have demonstrated that while measures of hyperactivity and opposition/defiance improved, these medications had little measurable effect on inattentiveness (Doig et al., 2008; Oesterheld et al., 1998). It is therefore likely that while pharmaceutical intervention may reduce symptoms of hyperactivity, due to the range of symptoms resulting from PAE, a multi-modal support strategy would be most effective for children with FASDs.

2.6.3 Behavioural interventions

Behavioural interventions address the behaviours that prevent children with FASDs from succeeding in academic and social environments, with the goal of transferring these improvements to other cognitive domains (i.e., academic achievement). Interventions developed to mitigate behavioural problems include *Cognitive Control Therapy* and neurocognitive habilitation, which seek to enhance self-regulation abilities in children with behavioural difficulties. Specifically, *Cognitive Control Therapy* is a method of teaching individuals how to utilize self-observation and self-regulation in order to understand their challenges and acquire

new skills (Santostefano, 1998). In an in-class intervention study, 10-months of *Cognitive Control Therapy* resulted in improvements assessed by a personal behaviours checklist, but not in neuropsychological tests or a cognitive control checklist (Adnams et al., 2003 as cited in Riley et al., 2003). Alternatively, the goal of neurocognitive habilitation is to improve executive function through the instruction of self-regulation techniques (Chasnoff et al. as cited in Bertrand, 2009 on behalf of FASD Intervention Group). Over 12 weekly sessions, children were taught how to identify and modulate their levels of arousal in order to regulate behaviour. Children involved in the neurocognitive habilitation intervention improved in measures of executive function when compared to children in a control group who were referred to standard services such as occupational therapy and community agencies. Therefore, instructing children in methods of self-regulation may allow the positive transfer of abilities to other domains (i.e., executive function).

Clearly, some effort has been devoted to the development and implementation of intervention strategies for children with FASDs. However, there is still a need for studies with improved methodologies, testing interventions that are cost- and time-effective, which can be easily incorporated into the daily lives of children regardless of home environment (Kodituwakku, 2009b). Ideally, improvements would go beyond specific skill sets and instead lead to long-term, overall changes in the quality of life.

2.6.4 Exercise interventions

The benefits of physical activity extend beyond improving health and reducing obesity. It is well established in the literature that exercise, in particular aerobic exercise, reduces the physiological measures of stress and improves overall mental health (Fox, 1999). In rodent studies, access to a running wheel has been associated with increased neuron growth, increased

blood perfusion to the brain, and an upregulation of the nerve growth factor brain-derived neurotrophic factor (Cotman & Berchtold, 2002; Kleim et al., 2002; Van Praag et al., 1999). Of particular relevance to this project, voluntary exercise in a rat model of PAE mitigated spatial memory deficits and improved synaptic plasticity compared to alcohol-exposed animals lacking access to a running wheel (Christie et al., 2005). Prospective studies in typically developing children have found positive effects of exercise on reading abilities, arithmetic scores and overall academic achievement (Hillman et al., 2008). Even moderate, acute sessions of aerobic exercise were found to result in improved academic achievement and cognitive control in pre-adolescent children (Hillman et al., 2009). While the majority of studies explore the effects of aerobic exercise on cognitive function, other interventions have focused on motor skill development. A table-tennis based motor skills program implemented in children with developmental coordination disorder revealed improvements in response inhibition in post-intervention measures, suggesting that motor skill development may positively influence performance on cognitive tasks (Tsai, 2009). Furthermore, organized physical activities, whether aerobic or anaerobic, also improve the development of social skills, improve mental health and reduce risk-taking behaviours in adolescents (Fox, 1999; Taras, 2005).

2.6.5 Novel strength-based motor skills intervention

The goal of the strength-based motor skills intervention was to provide an environment in which children with FASD would experience success, instead of focusing on their areas of weakness. Children rotated through a series of activities that focused on specific motor-skills including: fine motor precision and integration, bilateral coordination, balance, running speed and agility, upper-limb coordination, and strength. The one-on-one guidance from a Kinesiology student helper allowed the incorporation of teaching strategies deemed effective for children with

FASDs, including behaviour modeling and repetition, and the appropriate pacing of skill acquisition. As the intervention progressed, activities were modified based on individuals' improvements to ensure adequate difficulty. Measures of cognitive function were assessed before and after the intervention using both eye movement and CANTAB® tasks.

2.7 Research rationale, hypotheses and objectives

2.7.1 Saccadic eye movement tasks

The neural circuitry involved in the control of eye movements overlaps with several brain regions that are significantly affected by PAE. These include the frontal and parietal cortices, the BG, and the cerebellum. Previous studies have documented deficits in oculomotor control in children with FASDs that reflect problems with cognitive flexibility, specifically in areas of sensory-motor processing and response inhibition (Green et al 2007; 2009a). A goal of the current study was to expand the repertoire of available eye movement tasks that can be performed by children with FASD to include tasks that probe additional aspects of cognitive function, specifically spatial working memory and motor learning.

Objective:

- To assess cognitive flexibility, spatial working memory, and motor learning in children with FASDs using a remote eye tracking system.

Hypothesis:

Using a remote eye tracking system, children with FASDs will:

- Demonstrate deficits in the prosaccade and antisaccade tasks.
- Show deficits in spatial working memory and response inhibition in the DMS task on measures of accuracy and task errors.

- Exhibit deficits in motor learning in the predictive task as measured by deficient adjustment of reaction time with repetition.

2.7.2 Intervention study

As exercise has been reported to have positive effects on cognitive function in both adult and pediatric populations, we wanted to investigate the utility of implementing a strength-based motor skills intervention to improve cognitive function in subjects with FASD. Changes in cognitive performance were measured using oculomotor and CANTAB® tasks.

Objective:

- To utilize eye movement and CANTAB® tasks to assess the effects of a strength-based motor skills intervention on cognitive function.

Hypothesis:

- Children with FASDs involved in the strength-based motor skills intervention will demonstrate improvements in cognitive function in the post-intervention testing session when compared to a no-intervention control period.

Chapter 3

Materials and Methods

3.1 Oculomotor control in children with FASD

All experimental procedures were reviewed and approved by the Research Ethics Board at Queen's University. Both typically developing participants, and those with an FASD diagnosis, were recruited from the Kingston, Ontario and Abbotsford, British Columbia areas (Table 3.1; Control $n=31$, $age=10.4\pm 0.4$; FASD $n=31$, $age=10.5\pm 0.5$). Prior to the onset of data collection participants and parents/guardians were introduced to the experimental procedures and completed consent and personal information forms. Control subjects were excluded if they had any neurological, psychiatric or visual disorders, other than corrective lenses. As many children with FASDs are prescribed a variety of pharmacological agents, medication history was collected. Of the 31 children with FASD, 7 were regularly taking stimulants medications (i.e. Ritalin, Concerta), while 9 were taking other medications (i.e. antipsychotics, anticonvulsants, antidepressants). Participants were not asked to withhold any medications typically taken before the testing session as their effect on eye movement performance is unclear in this population (Green et al., 2009a). Subjects 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.

3.1.1 Saccadic eye movement recordings

During the eye movement testing sessions, participants were seated comfortably in a dark, quiet room on a stable chair. A small target sticker was placed on their forehead as part of the remote eye tracking system. Eye movement recordings were obtained using the Eyelink 1000 (SR Research, Mississauga, ON) which was positioned in front of participants so that the 17°

Table 3.1 Demographic information for control and FASD groups

Category	Control (31)	FASD (31)
Age \pm SEM	10.4 \pm 0.4	10.5 \pm 0.5
Male:female	12:19	12:19
Diagnosis		n (%)
FAS		8 (26)
pFAS		3 (10)
ARND		13 (42)
FAE		7 (22)
Medication		n (%)
Stimulants		7 (23)
Other		9 (29)
Unknown		2 (6)
Co-morbidities		n (%)
ADHD		13 (42)
Oppositional defiant disorder		4 (13)
Anxiety		3 (10)
Depression		2 (6)
Sleeping disorders		1 (3)
Bipolar disorder		1 (3)

Other drugs include antipsychotics, antidepressants, and anticonvulsants. Medication information was unavailable for two participants. None of the children in the control group were on medications or reported co-morbidities.

LCD monitor and mounted infrared camera were at a distance of 58 cm, as measured by the system from the participant's left eye. The position of the left pupil was digitized in both the vertical and horizontal axes at a sampling rate of 500 Hz. Subjects performed four tasks: prosaccade, antisaccade, delayed memory-guided sequential and predictive saccade task.

In both the pro- and antisaccade tasks, a central fixation point (FP) was illuminated for an interval randomized between 800 and 1200 ms to begin each trial. After a delay of 200 ms following the disappearance of the FP, a peripheral target (T) appeared at 10° to the left or right of the central FP. Participants were given a 1000 ms time-frame to initiate and complete a saccade. In the prosaccade task, participants were instructed to look towards the T as soon as it appeared (Fig. 3.1A); while in the antisaccade task, participants were instructed to look away from the T and towards the opposite side of the screen (Fig. 3.1B). One block of 60 trials was collected for prosaccades and another block of 60 trials of antisaccades was obtained.

For both tasks, saccadic reaction time (SRT) was defined as the time from the appearance of the peripheral T to the initiation of the first saccade that exceeded 30°/s. Intrasubject variability was assessed using the standard deviation of the SRT divided by the mean, termed the coefficient of variation (CV). Saccades initiated at 90-140 ms after T appearance were defined as express saccades, the shortest latency visually-guided saccades (Fischer et al., 1993). In separate experiments, this latency window was confirmed for this system using healthy young adults. Saccades generated less than 90 ms after the appearance of T were classified as anticipatory saccades. Direction errors were defined as any initial saccade initiated in the wrong direction with respect to the instruction (i.e., away from the T in the prosaccade task; towards the T in the antisaccade task). Additionally, the error of the saccade trajectory was measured (in degrees) as the angle between a direct path to the target and the trajectory of the first saccade.

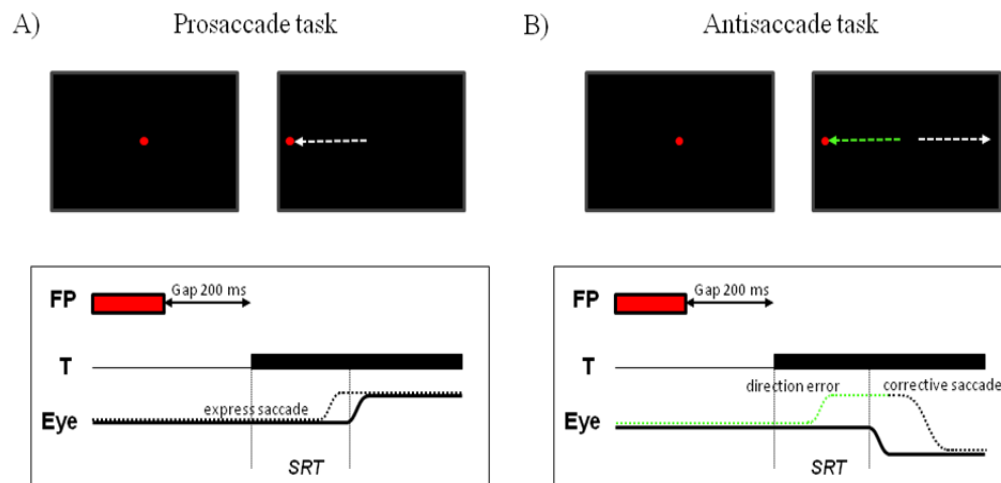


Figure 3.1 Prosaccade and antisaccade task paradigms.

(A) Prosaccade: subjects look from the fixation point (FP) to the peripheral target (T). Express saccades, as well as regular latency saccades, are often generated. (B) Antisaccade: subjects look from the FP to the opposite side of the screen to the T. Direction errors are generated when subjects look towards the T; however they are often altered by a corrective saccade.

In the DMS task, subjects were instructed to look at a central FP (time length of FP = 200 + (0-800) ms) while peripheral targets appeared. The screen was divided into four quadrants in which the peripheral T could appear. Each quadrant consisted of 9 potential T locations in a 3 by 3 grid centered at a 10° visual angle from the FP. Two targets were illuminated in succession for 100 ms each within two of the four quadrants of the screen. A delay period of 0, 600, 1200, or 1800 ms between the disappearance of the second peripheral target and the disappearance of the FP was used (Fig. 3.2). The participants were instructed to remember the order and spatial location of the peripheral targets, and to make two saccades as accurately as possible to these locations in the same sequence after the disappearance of the FP. Two blocks of 72 trials were completed in this task. Outcome measures for the DMS task included SRT of both the first and second saccade, defined as the time from the disappearance of the FP and the initiation of a saccade that exceeded 30°/s. Trials were assigned as either correct, timing errors (saccades initiated before the go signal), and sequence errors (saccades to the peripheral T locations in the incorrect order). Trials could also be combined errors where both sequence and timing errors occurred. Additionally, saccades were assessed for accuracy, measured in degrees from the closest fixation point to the actual peripheral target location.

In the predictive saccade task, a central FP (illuminated for a random interval between 1000 and 1500 ms) appeared, after which 12 peripheral T alternated between two fixed locations 10° to the right and left of the FP (Fig. 3.3). Targets alternated at either specific inter-stimulus intervals (ISIs; blocked trials) or pseudo-randomly (interleaved trials). The blocked condition of the task was comprised of 15 trials at each ISI of 750 ms and 1000 ms (total 30 trials). The interleaved condition comprised 15 trials with stimuli alternating randomly at one of

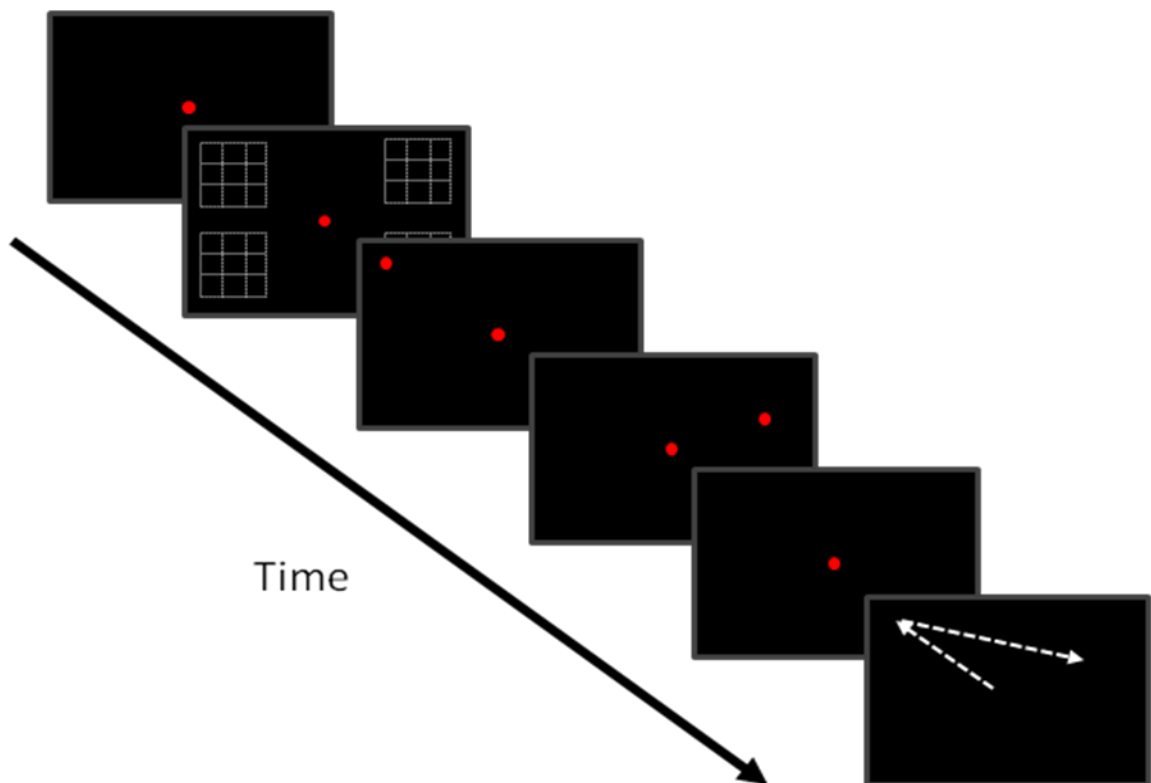


Figure 3.2 Delayed memory-guided sequential saccade paradigm.

The subject begins at a central fixation. Each quadrant of the screen is divided into 9 possible peripheral target locations in which two peripheral targets flash sequentially, each for 100 ms. After the disappearance of the central FP, the subject must initiate two saccades to the remembered target locations in the same sequence in which they flashed.

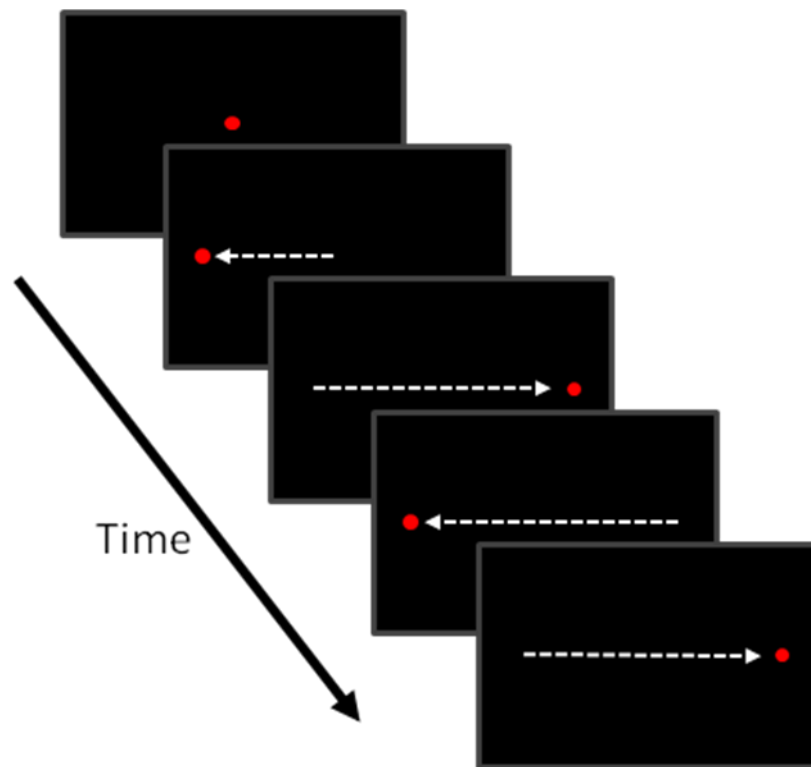


Figure 3.3 Predictive saccade task paradigm.

The subject begins at a central fixation point. The T then alternates between two fixed locations 10° from centre, for a total of 12 peripheral stimuli. Blocked trials consist of regular ISIs (either 750 ms or 1000 ms), while interleaved trials incorporate pseudo-randomized timing.

the following time intervals: 500, 750, 1000, 1250, or 1500 ms. Participants were instructed to move their eyes in time with the dots without missing any of the 12 stimuli. Outcome measures for the predictive task included the SRT of saccades made to each of the twelve stimuli. SRTs from each stimulus were collapsed and further subdivided into four different saccade categories: anticipatory (< -300 ms), predictive (-300 – 100 ms), express (100-150 ms), and regular (>150 ms). The distribution of saccade type was quantified for each individual, which allowed the analysis of velocity and amplitude by saccade type.

3.1.2 Statistical analysis of eye movement data

Differences between groups were analyzed using unpaired *t*-tests if the values passed the D'Agostino & Pearson omnibus normality test. If not, a Wilcoxon signed rank test was used. Effect sizes were also calculated for the dependent variables using Cohen's *d* scores. An effect size below 0.2 was considered small, between 0.2 and 0.8 was considered medium, and an effect size above 0.8 was considered large (Cohen, 1988). Specifically in the DMS task, two-way repeated measures analysis of variance (ANOVA) were used to examine the effect of delay on outcome measures, with the two dependent variables being group and delay. In the predictive task, two-way repeated measures ANOVAs were used to examine the effect of stimulus and group on SRT and to examine the occurrence of express saccades between groups and ISI. Additionally, Pearson correlations were used in this task to determine the relationship between the generation of express saccades and anticipatory saccades for each individual. Finally, amplitudes and velocities were analyzed across saccade category using two-way ANOVAs with Bonferroni post-hoc tests.

3.2 Intervention study

All experimental procedures were reviewed and approved by the Research Ethics Board at the University of the Fraser Valley and Queen's University. Subjects participating in the strength-based motor skills intervention study were recruited through the Fraser Valley Child Development Centre, where they received therapy for an FASD diagnosis. Children were not instructed to withhold any medications normally taken prior to testing as participants served as their own controls. Three testing sessions were attended by the intervention participants: one baseline session in October 2009, a midpoint session in December 2009 and a final session in March 2010 (Fig. 3.4). A cross-over design was employed, in which the children were divided into two groups depending on when they began the exercise intervention. Half the subjects received the 8-week intervention between the first and second testing sessions (Table 3.2; Treatment group (TG), $n=10$, $\text{age}=9.5\pm 0.8$) and the other half between the last two testing sessions (Delayed treatment group (DTG), $n=9$, $\text{age}=9.8\pm 0.7$). Nineteen children participated in the initial baseline session, 17 participated in the midpoint session and 15 returned for the final session.

3.2.1 The strength-based motor skills intervention

Children recruited for the exercise intervention study were assessed by occupational therapists at the Fraser Valley Child Development Centre using the *Bruininks-Oseretsky Test of Motor Proficiency, Second Edition* (BOT-2). This motor skill assessment consisted of a series of tasks that evaluated both gross and fine motor skills in the following 6 categories: fine motor precision and integration, bilateral coordination, balance, running speed and agility, upper-limb coordination, and strength. The BOT-2 results, along with the child's own goals for improvement, were used to develop an individualized program that focused on their areas of

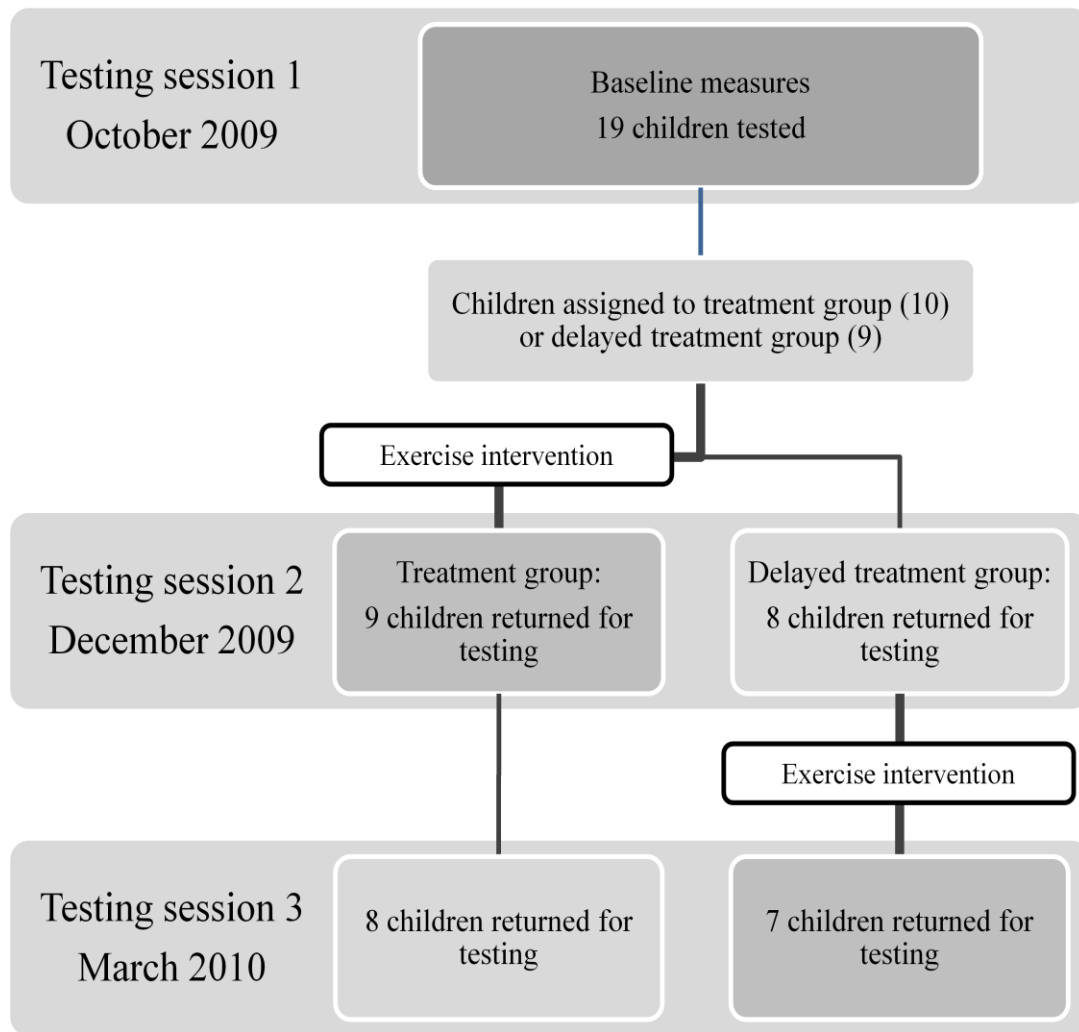


Figure 3.4 Intervention testing schedule.

Children participating in the intervention study were divided into 2 groups after baseline testing measures: a treatment group and a delayed treatment group. Pre-intervention data was collected in testing session 1 for the treatment group and in testing session 2 for the delayed treatment group. Post-intervention data was collected in testing session 2 for the treatment group and in testing session 3 for the delayed treatment group.

Table 3.2 Demographic information for the treatment and delayed treatment groups.

Category	TG (10)	DTG (9)
Age \pm SEM	9.5 \pm 0.8	9.8 \pm 0.7
Male:female	6:4	2:7
Diagnosis	n (%)	n (%)
FAS	2 (20)	2 (22)
pFAS	0 (0)	1 (11)
ARND	5 (50)	5 (56)
FAE	2(20)	1 (11)
Medication	n (%)	n (%)
Stimulants	1 (10)	5 (56)
Other	0 (0)	1 (11)
Unknown	1 (10)	0 (0)
Co-morbidities	n (%)	n (%)
ADHD	3 (30)	5 (56)

strength. Throughout the 8-week program, children attended 16 sessions (2 session per week), in which they rotated through stations that each focused on a specific skill (i.e. balance, bilateral coordination) with guidance and support from a Kinesiology student helper. Physical activity, adaptive functioning, brain function, overall stress, as well as the level of stress in the parent/guardian-child relationship were assessed before and after the exercise intervention. Our group was involved in the collection of objective measures of cognitive function using eye movement and CANTAB® tasks.

3.2.2 Saccadic eye movement tasks

All children participating in the intervention were tested using the eye movement task paradigms described in section 3.1.1. Due to the challenging nature of the DMS task, as well as the decreased ability to sustain attention in this population, not all participants were able to complete all four paradigms. Of the 19 children involved in the study, 18 performed the pro- and antisaccade tasks, 16 performed the predictive task, and 15 performed the DMS task during the initial testing session.

3.2.3 CANTAB® tasks

The CANTAB® (Cambridge Cognition, Cambridge, United Kingdom) is a highly validated, computerized neuropsychological testing tool that can be used to assess executive function. Four tests were selected in order to assess domains of executive function commonly affected by prenatal alcohol exposure. Using their dominant hand, participants utilized a touch screen and a press-pad to complete the following CANTAB® tasks: Reaction Time (RTI), Spatial Span (SSP), Spatial Working Memory (SWM), and Stockings of Cambridge (SOC) tasks. Successful completion of a practice phase was necessary before participants could continue to the test phase. Both auditory and visual feedback were provided by the CANTAB® apparatus, as

well as minimal verbal feedback from the experimenter in accordance with the provided CANTAB® scripts.

The RTI task involved a simple and a 5-choice condition. In the simple condition, a white circular outline appeared in the centre of the screen. Subjects were instructed to hold down the press pad until a yellow dot appeared within the white circle, after which they were instructed to release the press pad and touch the yellow dot as quickly as possible. In the 5-choice condition, the yellow dot would appear within one of five white circles concentrically arranged on the screen. The subject was again instructed to release the press pad upon the appearance of the yellow dot and to touch the dot as quickly as possible. Reaction time was defined as the time from the appearance of the yellow dot to the release of the press pad, while movement time was measured from the release of the press pad to the moment the screen was touched.

In the SSP task, nine white boxes were arranged randomly on the screen. One by one a sequence of boxes would flash in a different colour. Initially, only 2-box sequences appeared which sequentially increased upon the completion of correct trials. The subject was instructed to remember the pattern in which the boxes flashed and, after an auditory signal, indicate the pattern by touching the boxes in the same order. After successful completion of 2-box sequences, 3-box sequences would follow. The stages increased in difficulty up to 9-box sequences as indicated on the bottom left side of the screen. The task ended when either the subject failed to repeat a given sequence correctly on 3 successive attempts within a given stage, or after they completed the 9-box stage correctly. The colour and sequence of the flashing boxes varied throughout the task. The outcome measures of the SSP task included: span length (the longest sequence recalled), total errors (the selection of any box out of sequence) and total usage errors (the selection of a box that was not highlighted during the sequence).

In the SWM task, a random arrangement of coloured boxes was presented on the screen. Subjects were instructed to search the boxes for blue tokens, which once found were moved to an empty column on the right-hand side of the screen. Each subject was instructed to remember that once a token was found within a particular box, that box would not hold another token for the duration of that trial. The task began with a 3-box practice phase followed by the testing phase containing 4, 6 or 8 boxes. Errors were measured as the number of times a subject returned to a box in which a token was already found. Latency measures included the mean time to first response (the initiation of a search by selecting a box) and mean preparation time (the mean time taken to begin a new search after a token was found). A strategy score was also given based on the number of times the participant used a predetermined search pattern to locate tokens.

In the SOC task, the computer screen is divided into two halves. The bottom portion of the screen represents the subject's workspace where they must manipulate a set of coloured balls that are 'suspended' in stockings. The top portion of the screen represents the computer's workspace and displays the pattern of balls which the subject must copy. By touching the balls in their workspace, subjects were instructed to move their balls so the pattern matched the one presented by the computer. The task began with 2-move problems, and increased in difficulty up to 5-move problems, indicated on the right-hand side of the screen. Motor control trials occurred halfway through the testing phase and at the end of the task. In this phase, the subjects moved balls in their workspace one at a time to follow the pattern of moving balls in the computer's workspace. This controlled for motor impairments. Outcome measures in the SOC task included the number of problems solved in the mean number of moves and the mean number of moves for n-move problems (n=2-5). Mean initial thinking time was defined as the difference between the time taken to select the first ball in the copy and follow conditions. Mean subsequent thinking

time was calculated as the difference between selecting the first ball and completing the problem in the copy and follow conditions.

3.2.4 Statistical analysis of the intervention data

For both eye movement and CANTAB® tasks, pre- and post-intervention analyses were only considered for clinically relevant parameters in which a group effect was found.

Comparisons between the performance of the FASD and control groups as discussed in section 3.1 were used to determine clinically relevant parameters in the eye movement tasks. In the CANTAB® tasks, group effects were detected between FASD and control subjects using age-dependent z-scores generated by the CANTAB® database. If the values passed the D'Agostino and Pearson omnibus normality test ($p > .05$), a one sample *t*-test was used to detect deviations from the theoretical mean of 0. In cases where the data lacked normal distribution, a Wilcoxon signed rank test was administered.

In order to assess the effect of the intervention in both eye movement and CANTAB® tasks, pre- and post-intervention data was compared for all participants using a paired *t*-test if the data was parametric, and a Wilcoxon matched pairs test if the data was non-parametric. To distinguish the effect of intervention from the effects of development or practice, data from the first and second testing sessions were compared between the TG and DTG.

Chapter 4

Results

4.1 Saccadic eye movement tasks

4.1.1 Prosaccade and antisaccade tasks

In the prosaccade task, the FASD group did not differ from the age- and sex-matched controls in measures of SRT (Fig. 4.1A; $p=.20$), CV of SRT (Fig. 4.2A; $p=.09$), or direction errors (Fig. 4.1A; $p=.15$). Differences were not observed in additional measures of saccade metrics (express saccades, amplitude, velocity) or performance (percent correct trials, percent anticipatory errors; Fig. 4.2C). Mann-Whitney analysis however, revealed greater error of saccade trajectory in the FASD group compared to controls (Fig. 4.2E; $p=.01$). Effect size analysis using the Cohen's d value, revealed a medium effect size of this parameter (Table 4.1; $d=.37$).

In the antisaccade task, the FASD group completed fewer correct trials ($p<0.01$), making more direction (Fig. 4.1B; $p=0.03$) and anticipatory errors (Fig. 4.2D; $p=.03$) compared to the control group. No differences were observed in measures of SRT, amplitude, velocity or the occurrence of express saccades. Group differences were observed however, as an increased CV of SRT in the FASD group (Fig. 4.2B; $p=.01$). Similar to the prosaccade task, the error of saccade trajectory in the antisaccade task was elevated in the FASD group (Fig.4.2F; $p<0.0001$). Effect size analyses (Table 4.1) revealed medium effect sizes in the CV of SRT ($d=.60$), percent direction errors ($d=.55$), and percent anticipatory errors ($d=.67$). Large effect sizes were observed in the analysis of the percent of correct trials ($d=-.86$) and the error of the first saccade trajectory ($d=1.10$).

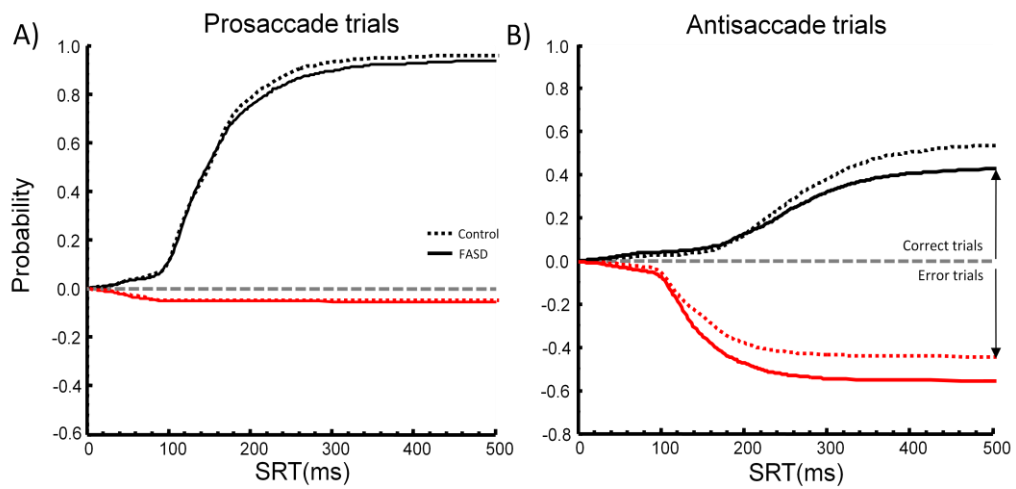


Figure 4.1 Prosaccade and antisaccade task cumulative frequencies.

Cumulative distribution of saccadic reaction times (SRTs) for correct trials (positive values) and direction errors (negative values) for the prosaccade (A) and the antisaccade (B) tasks comparing control (dashed lines) and FASD (solid lines) children.

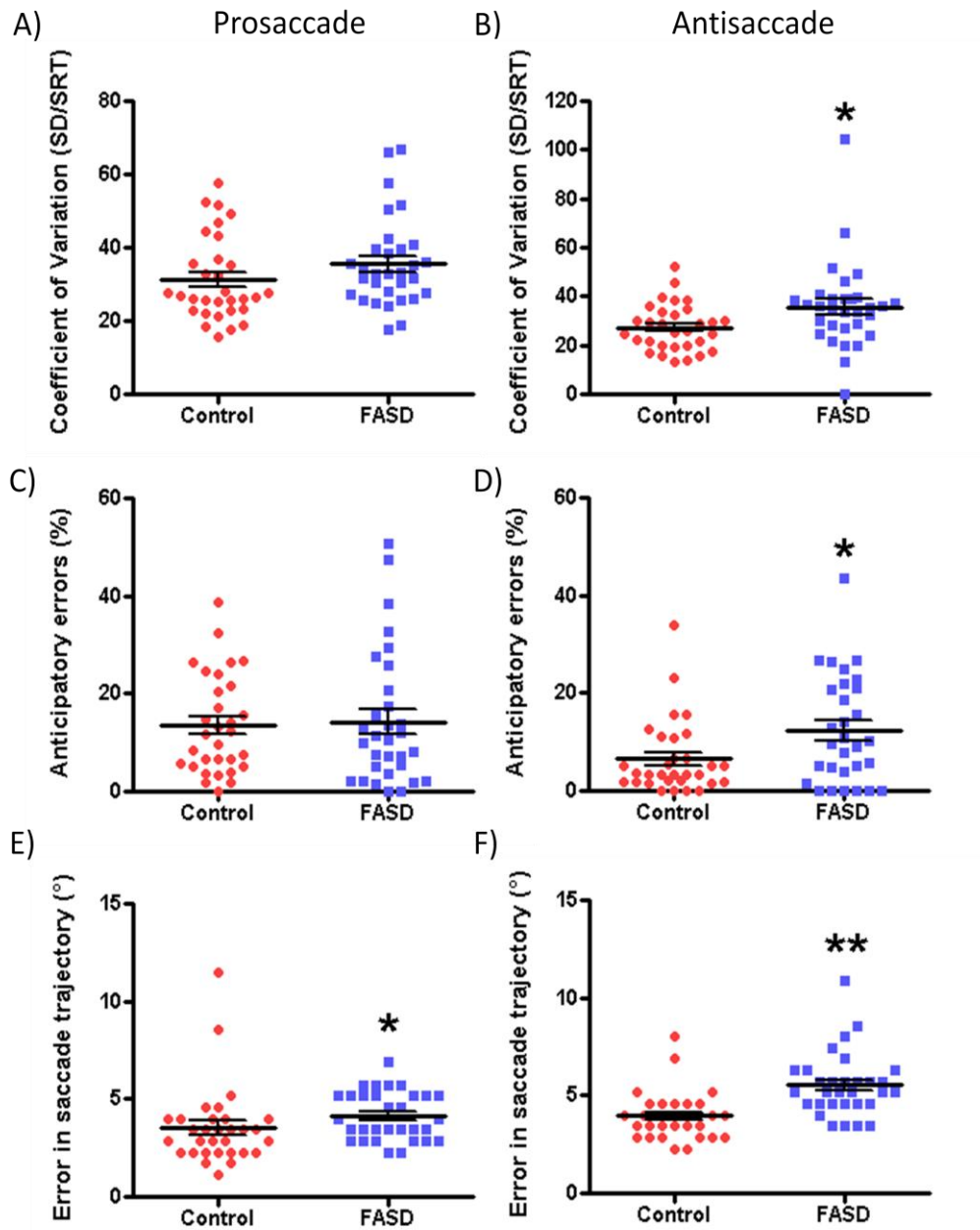


Figure 4.2 Prosaccade and antisaccade task parameters.

Comparisons between FASD and control groups in the prosaccade task included (A) CV of SRT, (C) the percent anticipatory errors, (E) the error in saccade trajectory. Parameters compared in the antisaccade task also included (B) the CV of SRT, (D) the percent anticipatory errors, and (F) the error in saccade trajectory. * $p < .05$, ** $p < .0001$

Table 4.1 Effect sizes of eye movement task parameters.

Task	Parameter	Cohen's <i>d</i>	Effect size <i>r</i>	Effect size classification
Prosaccade	Error of saccade trajectory	0.37	0.18	Medium
Antisaccade	Error of saccade trajectory	1.10	0.48	Large
	Percent correct trials	0.86	0.40	Large
	Anticipatory errors	0.67	0.32	Medium
	CV of SRT	0.60	0.29	Medium
	Direction errors	0.55	0.26	Medium
DMS	Percent correct trials	1.06	0.47	Large
	Sequence errors	0.83	0.38	Large
	Timing errors	0.80	0.37	Large
	Timing and sequence errors	0.64	0.31	Medium
Predictive	750 ms ISI – express saccades	1.24	0.05	Large
	1000 ms ISI – express saccades	1.06	0.47	Large
	Interleaved trials – anticipatory saccades	0.98	0.44	Large
	Interleaved trials – regular saccades	0.71	0.34	Medium

4.1.2 Delayed memory-guided sequential task

The percent of trials completed correctly in this task was analyzed using a two-way repeated measures ANOVA, with the dependent variables being group and delay. This analysis revealed an effect of group ($F(1,90)=8.76, p<.01$) and delay ($F(3,90)=35.43, p<.0001$) on the percent of correct trials, but not an interaction between the two variables ($F(3,90)=.68, p=.57$). When evaluating correct trials exclusively, groups did not differ in either SRTs of the first or second saccade, or in the CV of either saccade. Additionally, groups did not differ in the accuracy of correct saccades directed to either the first or second target. Children with FASDs did however, make more sequence (Fig. 4.3A) and timing (Fig. 4.3C) errors in this task. Similar to the percent of correct trials, both parameters were analyzed using two-way repeated measures ANOVAs. Sequence error analysis revealed an effect of group ($F(1,90)=5.50, p=.03$), but not of delay (Fig. 4.3B; $F(3,90)=.77, p=.51$) nor an interaction between the variables ($F(3,90)=.87, p=.46$). Conversely, timing error analysis revealed a significant effect of group ($F(1,90)=4.90, p=.03$) and delay (Fig. 4.3D; $F(3,90)=67.82, p<.0001$), but no interaction was observed between the two variables ($F(3,90)=2.02, p=.12$) as both groups elicited increased timing errors as the delay was extended. Lastly, when considering the direction of saccades elicited in trials with timing errors, the FASD group made significantly more saccades to the second target (Fig. 4.3E; $p=.02$), indicating increased combined error trials.

Effect size analyses revealed medium effect sizes of the percent of timing errors to the second target (Table 4.1; $d=-.64$), and large effect sizes in the completion of correct trials ($d=1.06$), sequence errors ($d=.83$) and timing errors ($d=.80$).

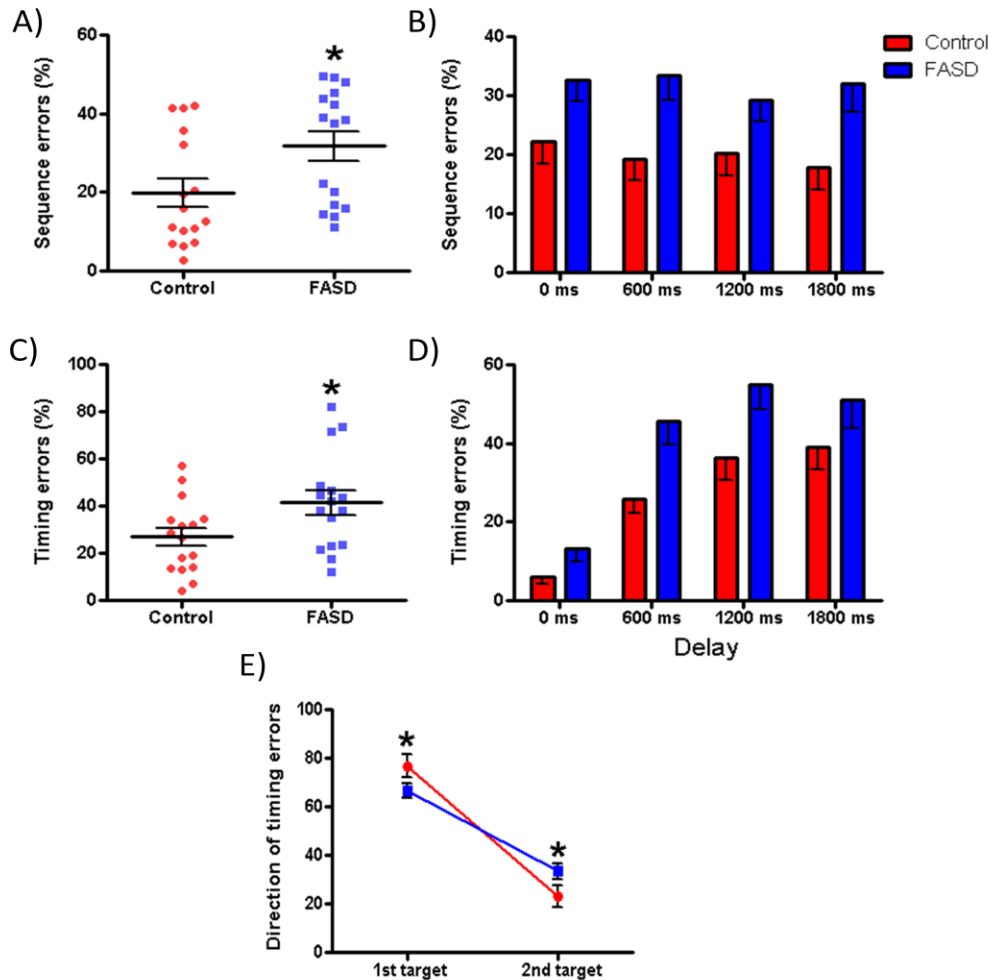


Figure 4.3 Sequence and timing errors of the DMS task.

(A) The percent sequence errors in the DMS task for all trials and (B) grouped by delay. (C) The percent timing errors for all trials and (D) grouped by delay. (E) Timing errors were further classified by the direction of the first saccade. * $p < .05$

4.1.3 Predictive saccade task

In the predictive saccade task, a two-way repeated measures ANOVA revealed that SRTs did not differ between groups in the blocked trials with ISIs of 750 ms (Fig. 4.4A; $F(1,418)=1.49$, $p=.28$) or 1000 ms (Fig. 4.4B; $F(1,418)=1.39$, $p=.25$). In contrast, for the interleaved trials, analysis revealed a significant effect of group (Fig. 4.4C; $F(1,418)=9.02$, $p<0.01$) and stimulus ($F(11,418)=10.34$, $p<.0001$) on SRTs across the twelve stimuli, as well as an interaction between the dependent variables ($F(11,418)=2.16$, $p=.02$). Both groups exhibited similar SRTs for the first two stimuli, but thereafter control children did not make predictive saccades. In contrast, children with FASD appeared to make predictive saccades to unpredictable targets. Histograms for both the control and FASD groups revealed a bimodal distribution of SRTs, in both the blocked trial conditions (Fig. 4.5). Based on the distribution of SRTs, saccades were categorized into four groups: anticipatory ($SRT < -300$ ms), predictive (-300 ms $< SRT > 100$ ms), express (100 ms $< SRT > 150$ ms), or regular ($SRT > 100$ ms). Analysis of the percent of saccades in each of these categories suggested an increased proportion of express saccades in both the blocked conditions for the control group (750 ms: Fig. 4.6A; $p<.01$, 1000 ms: Fig. 4.6B; $p=.01$). Two-way repeated measures ANOVA revealed an effect of group ($F(1,72)=9.08$, $p<.01$), and ISI ($F(2,72)=8.88$, $p<.001$) on the generation of express saccades, along with an interaction between these variables (Fig. 4.7; $F(2,72)=7.56$, $p=.001$). In the interleaved trials, both groups generated similar proportions of express saccades. In the blocked trials however, the proportion of express saccades elicited in the control group was elevated compared to both the FASD group and their own interleaved trial performance. Additionally, a negative Pearson correlation was found between the percent of express saccades and the percent of anticipatory saccades generated by each individual in both the 750 ms ISI (Fig. 4.8A; $r = -.43$, $p<0.01$) and the 1000 ms ISI (Fig. 4.8B; $r = -.56$, $p<0.001$) conditions. Due to the unpredictable nature of the interleaved trials,

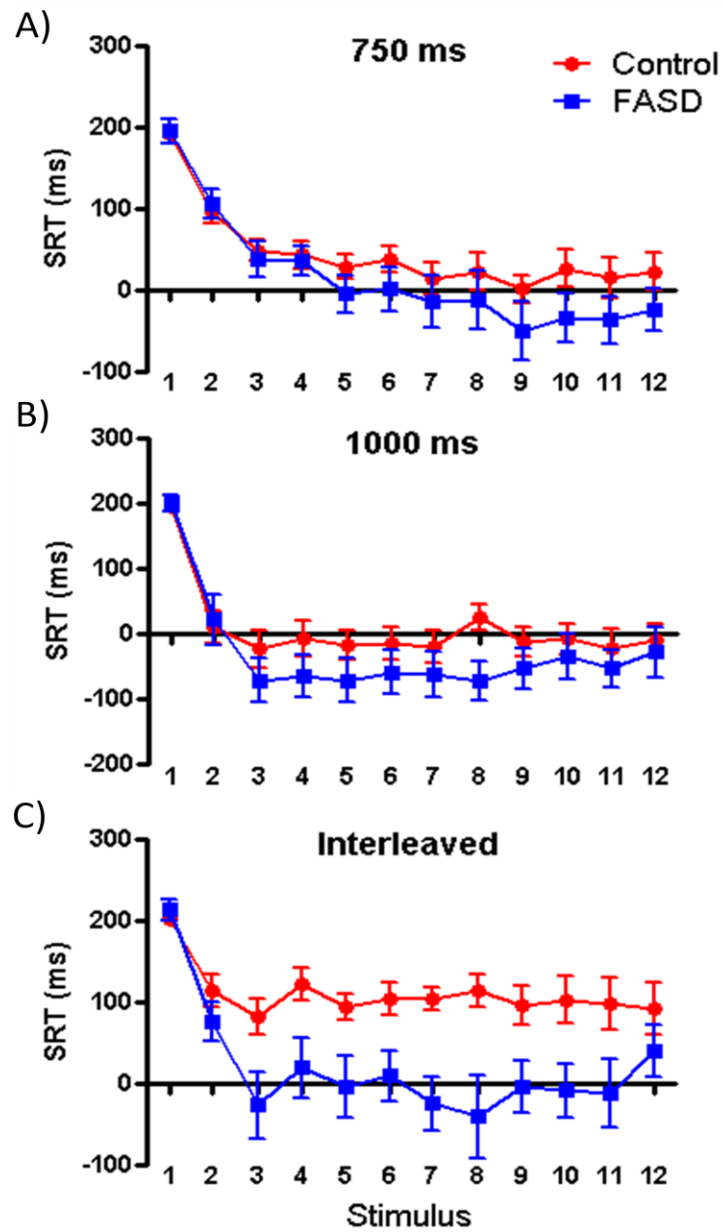


Figure 4.4 Predictive task SRT by stimulus number.

Saccadic reaction time to each peripheral stimulus for both the control (red) and FASD (blue) groups in the blocked trials (A, B) and the interleaved trials (C; effect of group, $p < .01$).

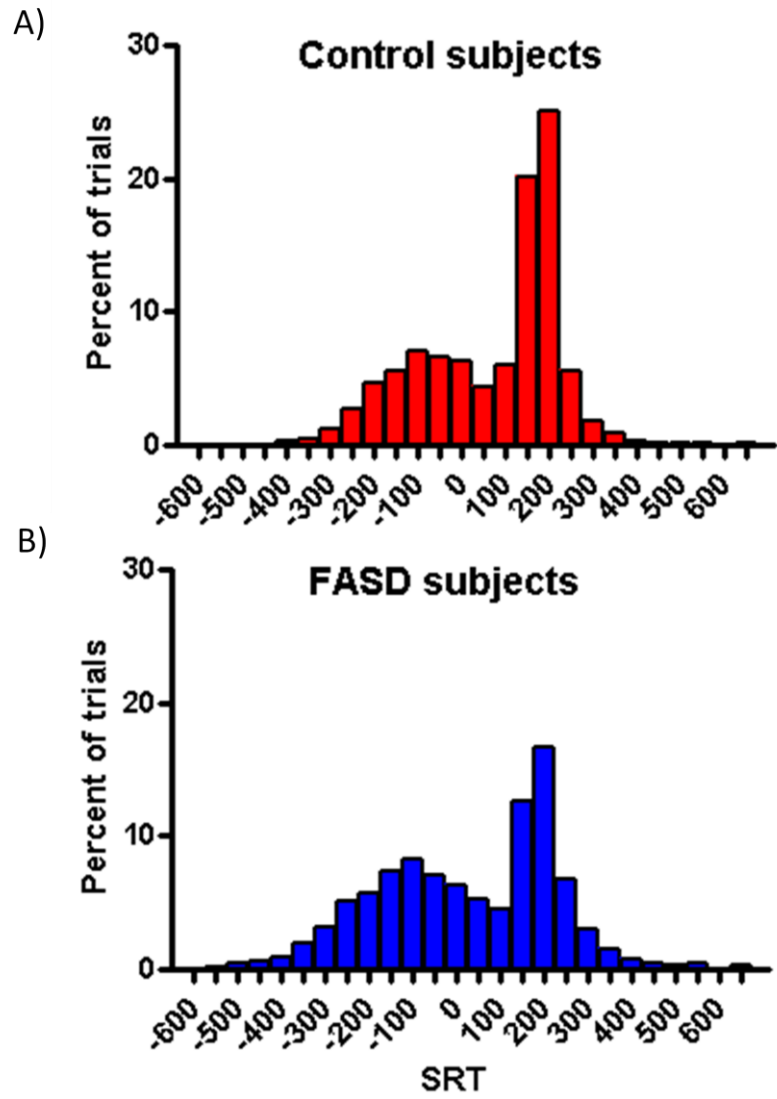


Figure 4.5 Predictive task SRT distribution.

Distributions of SRTs for the 750 ms ISI condition for both control (A) and FASD (B) groups.

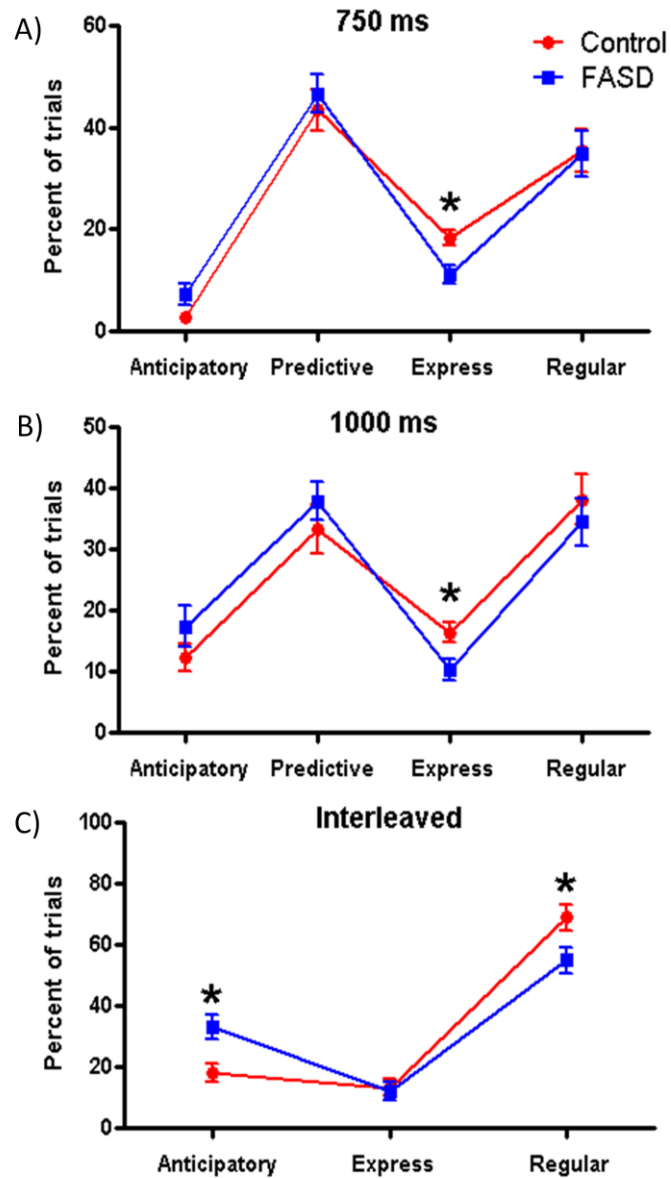


Figure 4.6 Distribution of saccade type in the predictive task.

The distribution of saccade type for the control (red) and FASD (blue) groups in the blocked (A,B) and the interleaved (C) trials. * $p < .05$

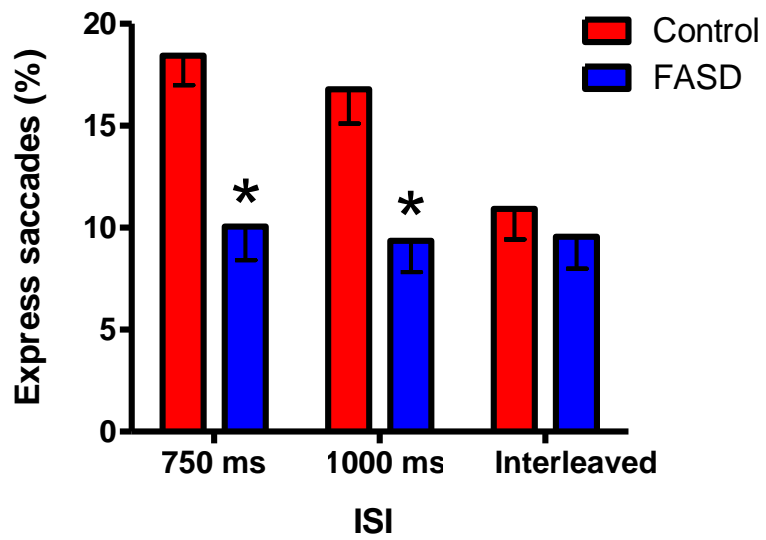


Figure 4.7 Express saccades in the predictive task.

The percent of trials in which express saccades (100-150 ms) were generated in each inter-stimulus interval (ISI) for both the control (A) and FASD (B) groups. * $p < .05$

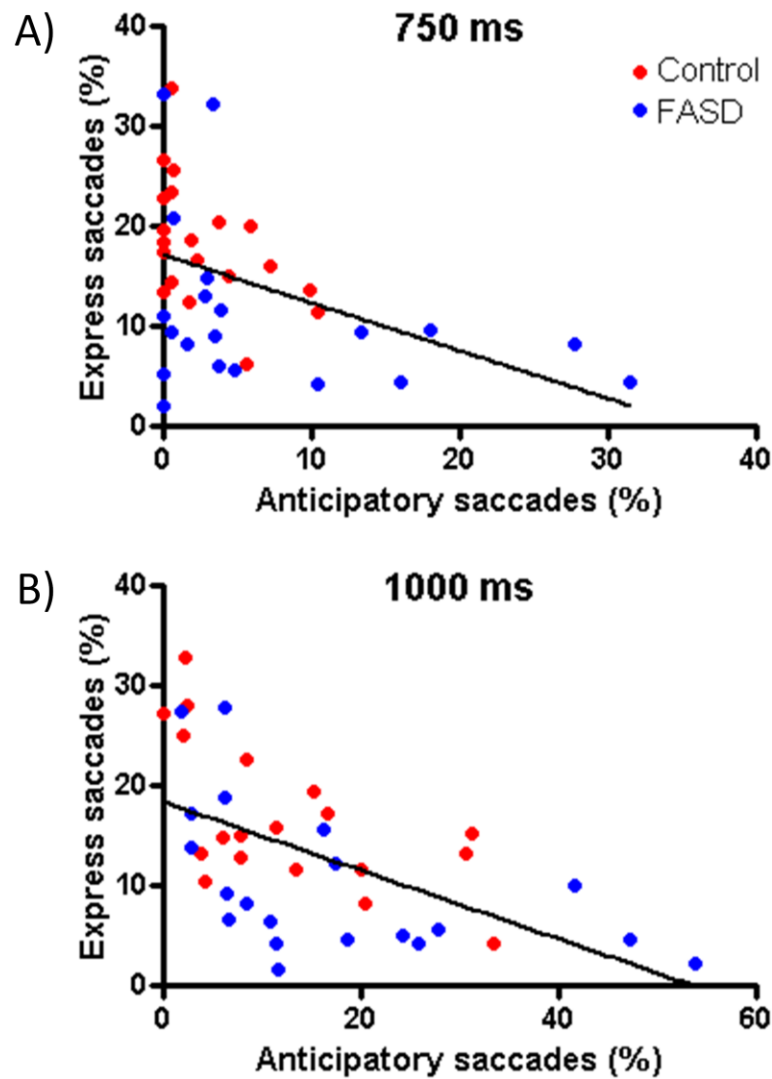


Figure 4.8 Express saccade and anticipatory saccade correlations.

The percent of trials in which individuals in the control (red) and FASD (blue) groups generate express saccades (SRT between 100 and 150 ms) is correlated with the percent of trials in which they generate anticipatory saccades (SRT < -300 ms) for both the blocked ISIs: (A) 750 ms ($r = -.43, p < .01$) and (B) 1000 ms ($r = -.56, p < .001$).

histograms of SRTs in this condition lacked the bimodal distribution observed in blocked trials. Therefore, saccades with SRTs below 100 ms were considered anticipatory in this condition. Analysis of the distribution of interleaved trials revealed that the FASD group had a greater proportion of anticipatory saccades (Fig. 4.6; $p < .05$) and fewer regular saccades ($p < .05$) compared to the control group.

In addition, cumulative frequency distributions of amplitudes for all saccades elicited by each group were separated by category. For both groups, anticipatory and predictive saccades were hypometric compared to express and regular saccades. No effect of group on saccade amplitude was revealed in the 750 ms condition (Fig. 4.9A). In the 1000 ms ISI trials, a two-way ANOVA revealed an effect of group on amplitude (Fig. 4.9B; $F(1,4470)=6.26$; $p=.01$), which was driven by longer anticipatory saccades in the FASD group ($p < .01$). In the interleaved trials, there was a significant effect of group (Fig. 4.9C; $F(1,4613)=16.07$, $p < .0001$), with the FASD group generating shorter anticipatory saccades than controls ($p < .001$).

Lastly, cumulative frequency distributions of velocity were considered within each saccade category. To control for the effect of amplitude on peak velocity, only saccades with amplitudes within the 18-21° range were included in the analysis. Two-way ANOVAs with group and saccade type as the dependent variables revealed an effect of group on peak velocities in each of the ISI conditions (Fig. 4.10; $p < .001$). Bonferroni post-hoc tests revealed that this effect was driven by an increase in velocity in the FASD group for both express and regular saccades when compared to controls ($p < .001$). Group differences in velocity were not evident in either the anticipatory or the predictive saccade categories. Further analysis confirmed that these effects were not driven by increased amplitudes in the FASD group.

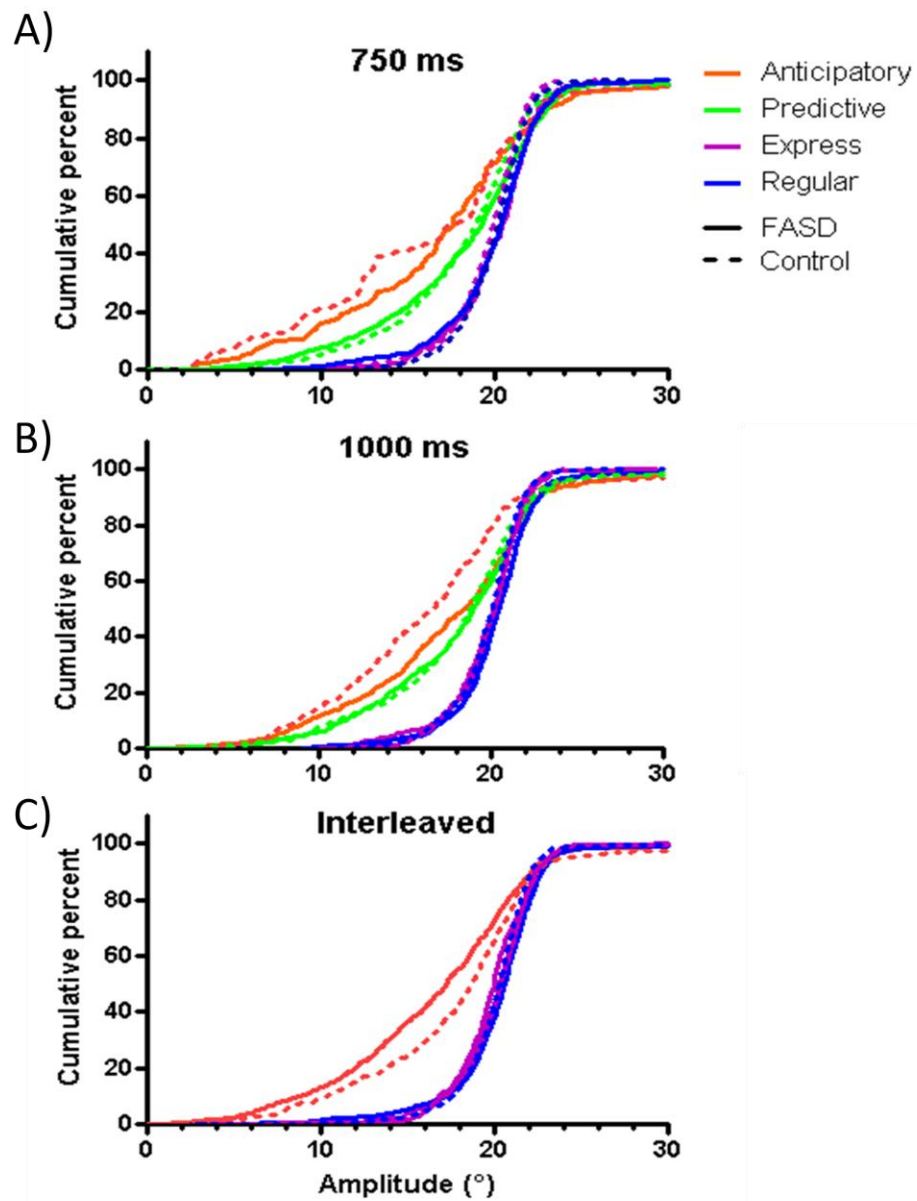


Figure 4.9 Cumulative percent distributions of amplitude by saccade type.

Amplitudes (in degrees) of saccades grouped by SRT as anticipatory (< -300 ms), predictive (-300 – 100 ms), express (100-150 ms), or regular (>150 ms) for the (A) 750 ms ISI, (B) 1000 ms ISI, and (C) interleaved trials.

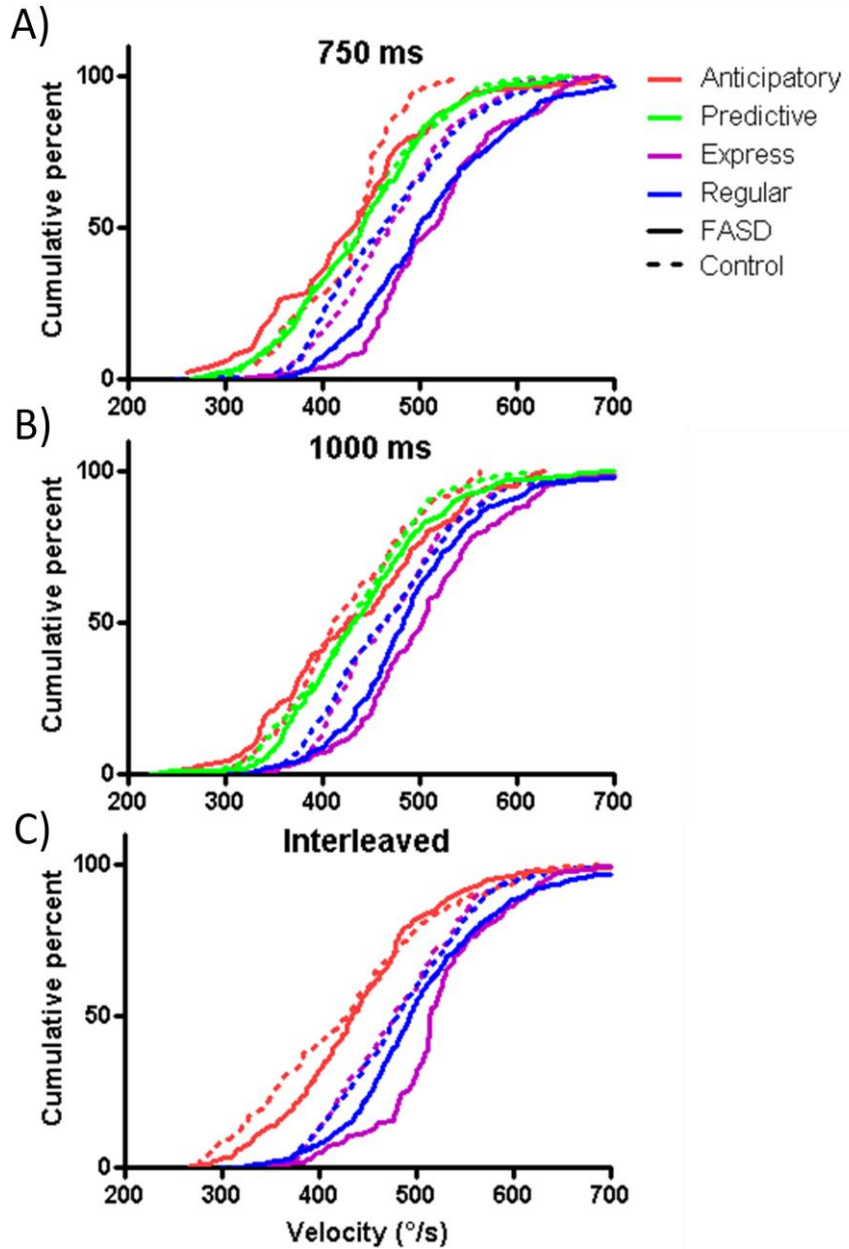


Figure 4.10 Cumulative percent distributions of velocity by saccade type.

Velocity (in °/s) of saccades grouped by SRT as anticipatory (< -300 ms), predictive (-300 – 100 ms), express (100-150 ms), or regular (>150 ms) for the (A) 750 ms ISI, (B) 1000 ms ISI, and (C) interleaved trials.

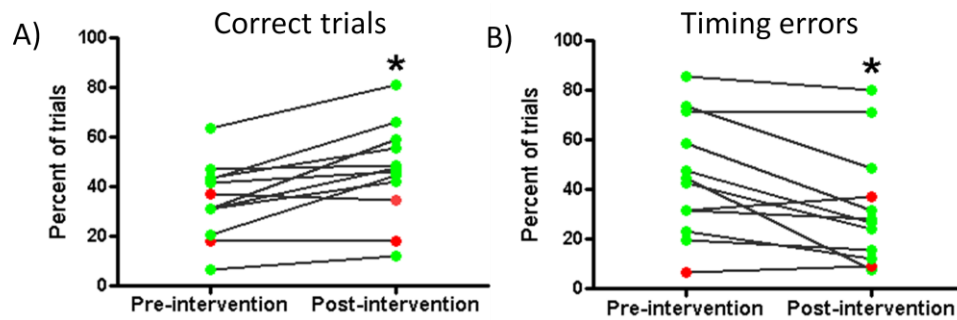
4.2 Intervention study

4.2.1 Saccadic eye movement tasks

Using paired *t*-tests comparing pre- and post-intervention data, there were no changes in the performance of either the pro- or antisaccade task parameters. In the DMS task, paired *t*-tests comparing pre- and post-intervention performance revealed that children completed more correct trials (Fig 4.11A; $p < .01$) and made fewer timing errors (4.11B; $p < .01$) after the intervention. In the control analysis using unpaired *t*-tests of the difference in performance between testing sessions 1 and 2, the treatment group (TG) improved more than the delayed treatment group (DTG) for both parameters (percent correct: Fig. 4.11C; $p = .02$, timing errors: Fig. 4.11D; $p < .01$). Conversely, improvements were not detected in the percent of sequence errors in pre- and post-intervention testing sessions ($p = .75$).

In the blocked trials of the predictive task, the percent of express saccades were compared pre- and post-intervention using a Wilcoxon signed rank test as the data was nonparametric. In the 750 ms ISI trials, participants had a greater percentage of express saccades in the post-intervention testing session (Table 4.2; $p < .01$), though this change was not evident in the 1000 ms ISI trials ($p = .22$). To control for the effects of development and practice, performance was compared between testing sessions 1 and 2, revealing that the TG did not improve more than the DTG ($p = .22$). In the interleaved trials, children made fewer anticipatory saccades (Table 4.2; $p < .01$) and more reactive saccades ($p < .01$) after the intervention as assessed by a paired *t*-test. However, the change in the percent of anticipatory and reactive saccades between sessions 1 and 2 again revealed that the TG did not improve more than the DTG ($p = .19$).

Effect of Intervention



Comparison of Session 1 and Session 2 performance

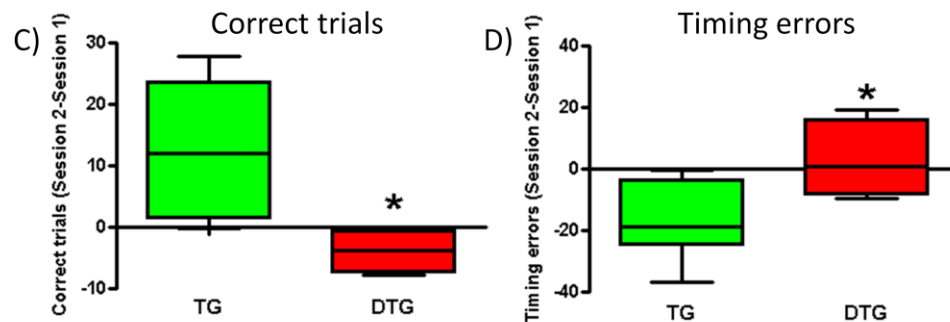


Figure 4.11 DMS task performance in the strength-based motor skills intervention.

The effect of the intervention was compared for both (A) the percent correct trials and (B) the percent timing errors where green dots indicate improved performance and red dots indicate poorer performance. (C/D) Controlling for practice and development effects, baseline performance scores were subtracted from testing session 2 data for both the treatment group (TG) and the delayed treatment group (DTG). The green box plots indicate the group that received the intervention between these testing sessions. $*p < .05$

4.2.2 CANTAB® tasks

Similar to the eye movement tasks, in order to assess clinically relevant improvements in the CANTAB® tasks resulting from the intervention, only parameters in which group differences were observed between FASD and control subjects were considered. Age-dependent z-scores generated by the CANTAB® database were used to determine if the participants' performances differed from 0 using a one sample *t*-test. In the RTI task, the participants' z-scores for reaction and movement times in both the simple and 5-choice conditions were significantly below zero ($p < .01$). Performance on the SSP task did not appear to be deficient in this group in measures of span length, total errors or total usage errors. In the SWM task, no significant deficits in performance were detected in measures of between errors, total errors or strategy use. Participants did however, have z-scores significantly above 0 in the number of within errors using a Wilcoxon signed rank test ($p < .01$). Lastly, participants solved fewer problems in the minimum number of moves in the SOC task ($p = .02$). Group differences were not observed in the mean number of moves used to solve problems at each level of difficulty, nor in the mean subsequent thinking time, excluding the 5-move problems where they performed better than the CANTAB® database control group ($p = .02$). Conversely, mean initial thinking time z-scores were above 0, suggesting that the intervention participants took longer to initiate their first move.

Individual's raw performance scores were next compared between pre- and post-intervention testing sessions. In the RTI task, improvements were observed in the reaction time of the 5-choice condition (Table 4.2; $p = .04$), as well as a trend of improvement in movement time ($p = .07$). However, when the TG and DTG scores were compared between the first and second

Table 4.2 Significant results from the strength-based motor skills intervention study.

Task	Parameter	Effect of intervention	Control analysis	Post-intervention analysis
DMS	Percent correct trials	*$p < .01$	*$p = .02$	$p = .30$
	Percent timing errors	*$p < .01$	*$p < .05$	$p = .81$
Predictive	750 ms ISI – express saccades	*$p < .01$	$p = .22$	
	Interleaved trials – anticipatory saccades	*$p < .01$	$p = .19$	
	Interleaved trials – regular saccades	*$p < .01$	$p = .19$	
CANTAB® RTI	5-Choice reaction Time	*$p = .04$	$p = .79$	

sessions, the improvements were not specific to the group TG for either reaction time or movement time scores. Deficits in performance were not observed in either the SSP or the SWM tasks, therefore analyses to determine the effects of intervention were not considered. Lastly, the number of problems solved in the minimum number of moves parameter was examined in the SOC task. Paired *t*-tests revealed that performance of participants did not improve from pre- to post-intervention testing sessions in this task.

Chapter 5

Discussion

5.1 Saccadic eye movement tasks

The current study sought to investigate the use of a battery of eye movement tasks to assess CNS dysfunction in children with FASDs. Eye movement paradigms designed to probe commonly reported deficits in this population were used. These included the prosaccade, antisaccade, delayed-memory guided sequential and predictive saccade tasks. These tasks assessed deficits in sensorimotor function, cognitive flexibility, working memory, and procedural learning. Our results suggest that: 1) the ability to generate visually-guided saccades in the FASD group did not differ from that of typically developing children, 2) performance on the antisaccade, DMS, and predictive saccade task parameters suggest injury to the prefrontal cortex and frontostriatal circuitry, and 3) prosaccade, antisaccade and predictive saccade task parameters suggest impairment in cerebellar function. From these results, it appears that this battery of saccadic eye movement tasks may be used to assess the integrity of frontostriatal structures and circuitry, and cerebellar function in the FASD population.

5.1.1 Visually-guided saccade circuitry

From the prosaccade task results, it is evident that the ability of this cohort of children to generate visually-guided saccades is relatively intact. The generation of visually-guided saccades is mediated by the SCi, along with the influence of the parietal and visual cortices (McDowell et al., 2008). In this cohort of children with FASDs, performance in the prosaccade task did not differ from age- and sex-matched controls in measures of saccade latency, intrasubject variability, or direction errors. The lack of measurable deficits in these parameters therefore suggests that the

parietal lobe and brainstem control of visually-guided saccades is largely unaffected by PAE in this population.

5.1.2 Frontostriatal structures and circuitry

The cognitive control of both visually-guided and internally-guided saccades is largely due to the prefrontal cortex and the BG (Hikosaka et al., 2000; Pierrot-Deseilligny et al., 2004). Behaviours suggesting insult to these brain regions were observed children with FASDs during the performance of the antisaccade, DMS, and predictive saccade tasks.

In order to initiate an antisaccade, an automatic, visually-guided saccade must be suppressed and an internally-guided saccade must be generated (Munoz & Everling, 2004). Upon the presentation of the visual stimulus, neuronal activity in the contralateral FEF and SCi increases. If this activity reaches a saccadic threshold, a direction error, or visually-guided prosaccade will be generated. In order to allow time for the ipsilateral brain regions to initiate an internally-guided antisaccade, this contralateral activity must be suppressed. It is thought that presaccadic activity in the FEF and SCi is inhibited by the executive control of the dlPFC and/or the substantia nigra pars reticulata of the BG. The FEF, SEF and dlPFC all project to the SCi, either directly or indirectly through the BG, and allow for the executive control over the saccadic premotor circuitry (Pierrot-Deseilligny et al., 2004). It is therefore thought that poor control of the excitability of saccade neurons of the FEF and SCi by the prefrontal cortex or BG result in increased intrasubject variability in SRT and direction errors in the antisaccade task. Children with FASD in this study had significantly greater intrasubject variability in saccade latencies and increased direction errors when compared to 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, ADHD, Huntington's

disease and Parkinson's disease (Chan et al., 2005; Green et al., 2009a; Munoz et al., 2003; Peltsch et al., 2008).

Additionally, children with FASD also generated increased anticipatory saccades in the antisaccade task. Similar to direction errors, anticipatory errors may reflect decreased inhibitory control of saccades. In contrast however, these errors reflect the disinhibition of an internally-guided, as opposed to an externally-guided, saccade. Studies have attempted with limited success to correlate the occurrence of anticipatory saccades with express saccades in the prosaccade task or direction errors in the antisaccade task (Biscaldi et al., 1996; Grootens et al., 2008). The lack of relationship suggests that anticipatory saccades are a separate type of error with different underlying neuropathology. Anticipatory saccades therefore reflect either a deficit in the inhibition of a pre-planned motor response and/or in the maintenance of fixation. An increase in anticipatory saccade generation was not observed in the FASD group during the prosaccade task, which suggests the recruitment of the frontostriatal circuitry is involved in these errors. The generation of anticipatory saccades has also been observed in the antisaccade task in ADHD and Tourette's syndrome populations (Farber et al., 1999; Feifel et al., 2004). It is therefore likely that these errors reflect deficits in executive control of the saccadic generating circuitry.

Similar to the antisaccade task, the DMS task assesses the executive control of internally-guided saccades. The difference in this task is that subjects must use previously presented sensory information to plan and initiate a motor response at the appropriate time. This task therefore requires the integration of multiple domains of cognitive function, including spatial working memory and response suppression. In the present study, children with FASDs completed fewer correct trials, indicating an inability to successfully utilize these multiple domains.

The FASD group demonstrated increased timing errors in the DMS task, reflecting deficits in either the ability to suppress and/or to inhibit saccadic responses. Previous studies have revealed increased timing errors in the ADHD, Huntington's disease and Parkinson's disease populations, implicating the frontostriatal circuitry in the successful inhibition of responses during delay (Chan et al., 2005; Mostofsky et al., 2001; Peltsch et al., 2008). The differentiation between these deficits may be elucidated by comparing the proportion of timing errors directed to the second target compared to those directed to the first target. The increase in timing errors to the second target in the FASD group suggests that this group is responding to the last presented target more than controls, indicating deficits in response inhibition.

Additionally, children in the FASD group generated increased sequence errors compared to controls, but did not exhibit deficits in saccade accuracy. Both the SEF and the dlPFC may be involved in the execution of memory-guided saccade sequences. The SEF have a role in the generation of complex oculomotor sequences (Pierrot-Deseilligny et al., 2004). For example, a TMS study in which stimulation was applied to the SEF resulted in the disruption of saccade sequence order (Tobler & Muri, 2002). Conversely, the dlPFC is implicated in both short-term spatial memory and response inhibition (Pierrot-Deseilligny et al., 2003). In humans with lesions to the dlPFC, increased variability is observed in the accuracy of memory-guided saccades, suggesting its role in the encoding of spatial information. Spatial working memory is commonly deficient in children with FASDs, although one would therefore expect deficits in both sequence order and accuracy in this task (Kodituwakku, 2009). This increase in sequence errors without deficits in saccade accuracy observed in this population could thus be attributed to a failure of the SEF to organize a sequence of motor behaviours. Additionally, as children with FASDs tend to exhibit greater deficits in tasks of increased complexity, these results may reflect an inability to

store both sequence and location. Lastly, the posterior parietal cortex has also been implicated in the accuracy of memory-guided saccades, and has projections to the dlPFC. Both TMS and lesion studies demonstrate that this region influences memory-guided saccade accuracy (Muri et al., 1996; Pierrot-Deseilligny et al., 1991). As the results from the prosaccade task suggest that PEF function is largely spared in this population, this may contribute to the sparing of saccade accuracy parameters when the ability to generate the correct saccade sequence is impaired.

Predictive saccade tasks assess procedural learning abilities which are associated with cerebellar and BG function, but are also associated with working memory as both spatial and temporal information must be encoded to generate internally-guided saccades (Isotalo et al., 2005). Thus, the FEF and dlPFC have both been associated with the generation of internally-guided predictive saccades (Pierrot-Deseilligny et al., 2004). Results from the blocked trials of this task suggest that children with FASDs are capable of procedural learning, as internally-guided saccades are evident in the decrease of SRTs after several stimuli. The interleaved trial performance however, demonstrates that this “predictive” behaviour is also observed in an unpredictable condition. It is therefore possible that the children with FASDs are not necessarily eliciting predictive saccades, but are exhibiting inappropriate anticipatory responses. This may be attributed to deficits in temporal working memory or inhibitory control. In order to correctly generate predictive saccades, individuals must utilize both spatial and temporal information to modify their response. The observation that the control group had an increase in percent of express saccades generated in blocked trials compared to interleaved trials supports this idea. Express saccades reflect increased presaccadic activity in the FEF and SCi neurons (Fischer & Rampsberger, 1984). It is suggested from both monkey and human studies that express saccade generation is facilitated by an increase in the predictability of target location or probability of

occurrence (Dick et al., 2005; Pare & Munoz, 1996). This is thought to be modulated by the release of the fixation system in the presaccadic phase. Consequently, this increase in express saccade generation in the blocked condition may suggest that children in the control group are utilizing temporal working memory to optimize their performance. The FASD group, conversely, exhibited the same proportion of express saccades elicited in the blocked and interleaved trials, implying that this group did not utilize temporal working memory to complete this task. Consistent with this idea, Simo and colleagues (2005) observed using fMRI that the switching from visually-guided to internally-guided saccades in a predictive task activated a distributed memory system which included the frontostriatal circuitry. Additionally, the FASD group also had a decrease in amplitude of anticipatory saccades in the interleaved condition. As these saccades are generated by an internal representation of target location, they are essentially a memory-guided saccade. Therefore, the occurrence of express saccades in the control group, and the decrease of amplitude in FASD anticipatory saccades, suggest that this deficient task performance may be related to deficits in spatial working memory.

Conversely, the interleaved trial results suggest that the FASD group has deficits in inhibitory control. In this condition, the children in the control group were able to identify the unpredictable nature of stimulus timing, and therefore continued to generate visually-guided saccades as opposed to switching to internally-guided saccades. In contrast, the FASD group generated internally-guided anticipatory saccades in this task after the first few stimuli. Similar to the anticipatory saccades observed in the antisaccade task, this behaviour may be due to an inability to suppress an internally-driven motor response or to maintain fixation.

Taken together, the above parameters in the antisaccade, DMS, and predictive saccade tasks all suggests impairments in the frontostriatal circuitry and the associated oculomotor areas.

These impairments are consistent with the behavioural studies that demonstrate deficits in response inhibition/suppression and working memory in children with FASDs.

5.1.3 Cerebellar function

While the frontostriatal circuitry is largely involved in the initiation of saccades (i.e., determining when a saccade occurs), the cerebellum is associated with the stopping and steering of these rapid eye movements in order to optimize velocity, accuracy, and consistency (Quaia et al., 1999). The cerebellum receives oculomotor input from the pontine LLBN, which project mainly to the posterior lobe of the cerebellar vermis (Ramat et al., 2007). Vermal Purkinje cells then project to the caudal fastigial nucleus (CFN) which innervates the EBN, IBN and OPN of the brainstem oculomotor circuitry (Robinson & Fuchs, 2001).

Although saccade amplitude did not differ between the control and FASD groups, the error in saccade trajectory was increased in both the pro- and antisaccade tasks in children with FASD. This finding was more robust in the antisaccade task, likely due to the lack of a visual stimulus to guide the saccadic response. As cerebellar regions involved in oculomotor control receive inputs from the LLBN and send projections back to the brainstem premotor circuitry, it has been proposed that the cerebellum receives an efference copy of each saccade generated which is subsequently used to tailor the CFN output in order to keep saccades on the right trajectory and terminate them on target (Quaia et al, 1999; Ramat et al., 2007). Therefore, the increase in the error of saccade trajectory observed in both the pro- and antisaccade tasks may be an indicator of cerebellar dysfunction in the FASD population.

Lastly, the peak velocity of visually-guided saccades was elevated in the FASD group when compared to controls in both the blocked and interleaved conditions. This finding, although initially perhaps counterintuitive, may be indicative of cerebellar injury in the FASD population.

Prior to the onset of a horizontal saccade, neurons in the contralateral CFN demonstrate a burst of activity, while neurons in the ipsilateral CFN burst later during saccade execution (Fuchs et al., 1993). This timing of ipsilateral neuron activity associates the CFN neurons with the effective termination of saccades. Consistent with this theory, both animal and human studies of cerebellar lesions observe dysmetric visually-guided saccades with greater variability in both amplitude and velocity (Robinson & Fuchs, 2001). Typically, cerebellar lesions result in an overall decrease in saccadic peak velocity; fast saccades are less commonly observed in patient populations. However, increased saccade velocity may indicate poor cerebellar control over the termination of saccades (Ramat et al., 2007). Early termination of saccades for example, may result in an elevated peak velocity when accounting for the amplitude of the movement. This behaviour has been observed in patients with late-onset Tay-Sachs disease (Rucker et al., 2004). Modeling studies suggest that abnormalities in the deceleration of saccades may be due to a faulty circuit through the cerebellum thought to normally maintain the inhibition of OPNs until saccade completion. Premature termination of saccades may also be attributed to the early choking of the saccadic drive signal, which is initiated by the CFN and acts through EBNs and IBNs (Ramat et al., 2007). Thus, the increase in velocity of visually-guided saccades observed in the FASD group may result from ineffective cerebellar control of saccade termination.

Together, findings from the pro- and antisaccade, and the predictive saccade task, suggest that these eye movement paradigms may be sensitive to cerebellar dysfunction in children with FASD. This finding is unique to this study, as these parameters had not been previously examined in the FASD population.

5.1.4 Comparisons to previous oculomotor studies in FASD

Previous work from our lab revealed increased latencies, CV of SRT and direction errors in both the pro- and antisaccade tasks in a large cohort of children with FASDs (Green et al., 2007; 2009a). Conversely, the present study observed group effects in the CV of SRT and directions errors solely in the antisaccade task, while no effect of group was found in measures of latency. Several factors may have influenced these results. First, in the present study, the majority of children had diagnoses on the less severe end of the FASD spectrum, with 12 of the children having a diagnosis of ARND. Additionally, 7 children had a diagnosis of FAE, which is an older term used to describe children presenting with the CNS deficits of FAS, but lacking some or all of the physical features. Green and colleagues (2009a) observed an effect of diagnostic subtype on performance in the prosaccade task, with the FAS group having increased SRTs, CV of SRT and direction errors compared to individuals diagnosed with ARND. The performance of individuals with ARND in this task may not have differed substantially from controls, which could explain why group differences were not observed in the prosaccade task in these parameters. Second, while children in the previous study were asked to withhold medications 12 hours prior to testing, children in the present study were tested on medication. Although the effects of stimulant medications (the most commonly prescribed drug in this group) on pro- and antisaccade performance in children with FASDs is unclear, the effects of stimulant medications on eye movement performance have been studied in other pediatric patient populations (Green et al., 2009a). In children with ADHD, methylphenidate was found to decrease latencies in both the pro- and antisaccade tasks, with conflicting results concerning effects on direction errors (Klein et al., 2002; Munoz et al., 1999). Therefore, both the difference in representations of the diagnostic subgroups and the administration of medications may have contributed to discrepancies between the present and past studies of oculomotor control in FASD.

5.1.5 Clinical relevance

The present study suggests that a battery of eye movement tasks may be implemented to assess both frontostriatal and cerebellar dysfunction in children with FASDs. A lack of physicians trained in the subtleties of FASD diagnosis, especially in remote communities, results in significant waiting periods for children with suspected PAE. Thus, the development of screening tools for CNS dysfunction in FASD could allow the identification of individuals requiring further assessment. An effective screening tool must be sensitive and specific to the neurobehavioural phenotype of FASD. Therefore, the comparison of oculomotor behaviours in FASD to other disorders with similar clinical presentations must be considered.

5.1.6 Limitations

In this pilot evaluation of novel eye movement tasks in the FASD population, there are several methodological considerations must also be accounted for. In the present study, children performed four tasks in one session. While they were given breaks, the length of the testing session was bound to have detrimental effects on performance due to diminished attention. It would therefore be advantageous to administer these tasks in either separate testing sessions, or in random order to examine the effects of fatigue on performance. Furthermore, the sustained attention required for the DMS task was extremely difficult for these children, in particular at the lower age range. Since only some of the participants were able to complete this task, the results may reflect the higher functioning end of the spectrum. This also limits the use of the DMS task in a clinical setting, as children must be able to perform the task sufficiently to obtain any indications of CNS dysfunction.

5.1.7 Future directions

1. The use of these eye movement tasks in a larger population of children with FASDs would allow the evaluation of the effects of diagnostic subtype and medication on saccade performance and further assess the sensitivity of these tasks to CNS dysfunction in FASD.
2. The examination of other development disorders with similar clinical presentations would allow assessment of the specificity of these findings to the CNS dysfunction encountered in FASD.
3. The incorporation of functional and DTI imaging techniques would provide further information regarding the neuropathology underlying these behavioural deficits.

5.2 Intervention study results

The results from the strength-based motor skills intervention study suggest that children improved in some areas of cognitive control after the intervention. In a complex task that requires the integration of multiple domains of executive function – the DMS task - children completed more correct trials in the post-intervention testing session. Additionally, improvements selective to the intervention were also observed by the research group at the University of the Fraser Valley, specifically in the performance of the BOT-2 motor skills assessment, and the *Children's Trail Making Task, Part 2* (TMT-2; Keiver et al., 2010). Furthermore, these results suggest that eye movement tasks are more sensitive to cognitive improvements than the CANTAB® tasks.

5.2.1 Saccadic eye movement tasks

Post intervention, participants improved in measures of cognitive function in both the DMS and predictive tasks. However, only the improvements observed in the DMS task

(increased correct trials and decreased timing errors) were selective to the intervention group.

The correct completion of both the DMS task and the TMT-2 required the integration of multiple domains of cognitive function. While the DMS task requires inhibitory control and working memory abilities, the TMT-2 additionally necessitates set shifting (Devinsky & D'Esposito, 2004). The strength-based motor skills intervention may therefore stimulate improvement in the ability to utilize multiple cognitive domains.

The execution of complex motor skills requires the use of multiple domains of cognitive function, such as response inhibition, prediction, attention, and response selection. Tsai and colleagues (2009) implemented a table tennis training program in a group of children with developmental coordination disorder, and assessed the effects of this intervention on response inhibition. Due to the rapid pace of table tennis, the time window in which individuals can select and plan a motor response is brief. Thus, players must use sensory information to predict which response will be most appropriate and to inhibit inappropriate behavioural responses. Similarly, the activities in which children with FASDs participated during this intervention required the use of multiple cognitive domains. Throwing a basketball while standing on a balance ball for example, requires that children: 1) plan an appropriate motor response in order to accurately throw the ball into the net, 2) inhibit inappropriate responses that would alter balance, and 3) maintain attention on the goal of the task. The cognitive improvements observed in the DMS task may therefore be due to training in the use of cognitive control to successfully complete motor tasks.

This program presented several other benefits to the participants which may have produced measurable improvements in cognitive function. The positive environment and one-on-one attention during this program may have resulted in improved mental health and self-

confidence. It is believed that intellectual functioning in children is influenced not only by their understanding of factual knowledge, but also by their perceived self-efficacy, or ability to function (Bandura, 1993). Therefore, the improvements observed in the post-intervention testing sessions may not be entirely due to motor skill training.

Other improvements were observed from the pre- to post-testing sessions in the predictive task. In the blocked trials, participants elicited increased express saccades in the post-intervention testing session, while in the interleaved trials they exhibited increased regular saccades and decreased anticipatory saccades. These behaviours were more similar to the performance of typically developing children in the predictive task. However, these improvements were not specific to the intervention group, suggesting that practice and/or development effects played a role in the change in performance.

5.2.2 CANTAB® tasks

Improvements unique to the intervention group were not observed in the CANTAB® tasks. The reaction time of the 5-Choice condition in the RTI task was reduced in the post-intervention testing session, indicating improved attention. However, this may have been due to the effects of practice or development.

The test-retest reliability of CANTAB® tasks have been minimally explored in the pediatric population (Lowe & Rabbitt, 1998). Generally, tasks of executive function may by nature have reduced retest reliability. These tests assess the ability to discover and apply strategies, monitor performance and plan ahead, and thus are most effective when novel to the subject. Furthermore, children who performed worse in the pre-intervention testing session have more room to improve in the post-intervention testing session. Conversely, children who performed well in the pre-intervention testing session would not have the chance to improve in

the post-intervention session due to ceiling effects. Taken together, these findings suggest that further examination of test-retest reliability of CANAB® tasks is warranted, in order to help define which tasks are appropriate for use in future studies with multiple testing sessions.

5.2.3 Clinical relevance

The data from the present study suggest that a strength-based motor skills intervention results in improvements in cognitive performance of complex tasks. Thus, motor skill training may qualify as an effective intervention strategy that influences both motor and cognitive function in children with FASD. While we are unable to distinguish whether the cognitive improvements are solely due to motor skill training, the beneficial effects of this program are still valid. As children only participated in 16 sessions, the benefits of a longer, more intense intervention may be more robust.

5.2.4 Limitations

Due to the challenges of working with the FASD population, there were some methodological limitations to this study. First, there was a small group size due to difficulties recruiting and retaining participants, perhaps due to the time commitment. In addition, the difficulty of the DMS task also limited the number of children that were able to complete it. Thus, data was only collected from some of the participants, further reducing the group size in this task. Second, the cross-over design of this study was not optimal for the collection of baseline measures. As the long-term effects of this intervention study were unknown, it was uncertain whether the TG would serve as an adequate control group between testing sessions 2 and 3. Ideally, the TG in this study would have received an additional baseline testing session 2 months before the initiation of the intervention. Lastly, it cannot be concluded from this data that the improvements observed in the intervention session are entirely due to the strength-based

motor skills intervention. As previously discussed, other factors may have influenced cognitive improvements. After-school programs that do not incorporate forms of physical activity may be a more appropriate control in order to identify the benefits of a motor skill intervention on cognitive function.

5.2.5 Future directions

1. To introduce a longer motor skills intervention study in a larger population of children with FASD using improved randomized-controlled design.
2. To better define the specific effects of motor skill training on cognitive function by limiting the confounding factors in a control group.

Chapter 6

Summary and Conclusions

This thesis tested the hypothesis that children with FASDs would demonstrate deficits in multiple saccade paradigms, including prosaccade, antisaccade, delayed memory-guided sequential and predictive saccades. These tasks were selected in order to probe aspects of cognitive flexibility, spatial working memory, and motor learning. In addition, these eye movement tasks, along with computerized neuropsychological tests, were used to assess the effects of a strength-based motor skill intervention on cognitive function.

Compared to age- and sex-matched typically developing children, the FASD group demonstrated deficits in response inhibition and spatial working memory in the antisaccade, DMS and predictive tasks, suggesting injury to the frontostriatal circuitry and its associated structures. Additionally, results from the prosaccade, antisaccade, and predictive tasks suggest that parameters assessing velocity and saccade trajectory may probe cerebellar dysfunction in this population. Together, this battery of eye movement tasks may allow the assessment of frontostriatal and cerebellar function; regions particularly sensitive to PAE.

Furthermore, a strength-based motor skills intervention study was found to improve performance on complex tasks of cognitive control in children with FASD. Results from the DMS task revealed that children involved in the treatment group were better able to generate a sequence of memory-guided saccades after a variable delay when compared to a delayed treatment group. While this research does not conclude that these improvements were due solely to the effects of the motor skill training, the benefits of this type of intervention are evident.

Future studies should employ the use of imaging data in order to further identify the neural correlates of the behavioural deficits observed in the eye movement tasks, as well as for the cognitive improvements resulting from the intervention. In addition, large scale studies would allow the exploration of these findings in a sampling better reflecting the general population.

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