

**NOVEL ASSESSMENT TOOL FOR FETAL ALCOHOL SPECTRUM
DISORDER (FASD) BASED ON EYE MOVEMENT BEHAVIOURS**

By

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Abstract

Fetal alcohol spectrum disorder (FASD) is the leading cause of preventable developmental disability among Canadians, affecting at least 1% of the population. Diagnosis of FASD requires collaboration from a multidisciplinary team and can be a lengthy process frequently involving long wait times. Our objective was to conduct a validation study to confirm the ability of eye tracking to efficiently and objectively identify children with FASD. In the validation study, 32 children with an FASD diagnosis and 25 typically developing control children completed three eye-tracking tasks, measuring automatic and voluntary eye movement responses, spatial working memory and visuospatial skills. Data previously collected (105 typically developing control children and 68 children with FASD) was analyzed using the same automated program, and used as the training data for the classifier. Features extracted from the eye movement control tasks were used as input to test an extreme learning machine model's ability to accurately classify children into their respective groups. Children with FASD exhibited significant differences in eye movement performance in each of the three eye-tracking tasks, including end point error, percentage of direction errors, percentage of trials with step saccades, and overall accuracy. Classification of the validation cohort participants (FASD and control) was fairly high, producing a sensitivity of 72%, a specificity of 88%, and an overall accuracy of 79%. Features recognized as important for distinguishing between the control and FASD groups were similar or related to features that were shown to differ significantly between groups. These results support the notion that eye-tracking provides information about differences in brain function between clinical and control groups that can be used to train computational models to classify

participant groups with a fairly high degree of accuracy. Measuring eye movement behaviours can help identify brain dysfunction due to prenatal alcohol exposure, providing insight into potential functional biomarkers of FASD.

Co-Authorship

The research described in this thesis was conducted by Shelby Thompson under the supervision of Dr. James Reynolds. Data for the training cohort was collected by Angelina Paolozza as part of a previous study investigating the relationship between diffusion tensor imaging and eye movement control, participants were collected throughout Canada (e.g., Kingston, Ottawa, and Alberta). Data for the validation cohort was collected by Shelby Thompson, Kennedy Denys and Katy Flannigan. All statistical analyses on both the training and validation cohort data was performed by Shelby Thompson. An automated saccade analysis program developed by Donald Brien was used to extract saccade measures used in the analysis described this thesis. Dr. Deng Wang performed the machine learning classification of the eye movement data. The first draft of the thesis was written by Shelby Thompson.

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List of Abbreviations and Symbols

| | |
|-------|--|
| ACT | Attentional Capacity Test |
| ADHD | Attention deficit/hyperactivity disorder |
| ARBD | Alcohol related birth defects |
| ARND | Alcohol related neurodevelopmental disorder |
| CNS | Central Nervous System |
| DLPFC | Dorsolateral prefrontal cortex |
| DTI | Diffusion Tensor Imaging |
| EEG | Electroencephalography |
| EF | Executive functioning |
| ELM | Extreme Learning Machine |
| FAE | Fetal Alcohol Effects |
| FAEE | Fatty acid ethyl esters |
| FAS | Fetal alcohol syndrome |
| FASD | Fetal alcohol spectrum disorder |
| FEF | Frontal eye fields |
| fMRI | Functional magnetic resonance imaging |
| FN | False Negative |
| FP | False Positive |
| FP | Fixation point |
| ILFS | Infinite Latent Feature Selection |
| IOM | Institute of Medicine |
| IQ | Intelligence quotient |
| MI | Mutual Information |
| MRI | Magnetic resonance imaging |
| PAE | Pre-natal alcohol exposure |
| PCA | Principal Component Analysis |
| p-FAS | Partial fetal alcohol syndrome |
| SRT | Saccadic reaction time |
| SEF | Supplementary eye fields |
| TN | True Negative |
| TP | True Positive |
| WRAML | Wide Range Assessment of Memory and Learning |
| > | Greater than |
| ≥ | Greater than or equal to |
| < | Less than |
| ≤ | Less than or equal to |
| ° | Degree |
| = | Equal |
| α | Alpha |

Chapter 1

Introduction

Affecting at least 1% of the population in Canada, Fetal Alcohol Spectrum Disorder (FASD) is recognized as the leading known cause of developmental disability among Canadians. Approximately 1 in every 100 children in Canada are born with FASD (Public Health Agency of Canada, modified March 28, 2012). FASD encompasses the full range of physical, behavioural, cognitive, and socio-emotional effects that can occur when children are prenatally exposed to alcohol. The extent of deficits individuals with prenatal alcohol exposure (PAE) experience depends on a number of factors, including the quantity of alcohol consumed throughout pregnancy, the frequency at which it was consumed, and the time during which it was consumed over the course of the pregnancy (Chudley et al., 2005; Enns & Taylor, 2016; Riley & McGee, 2005).

A diagnosis of FASD is made when there is evidence of pervasive brain dysfunction, which is defined as impairment in at least three of the following neurodevelopmental domains: motor skills; neuroanatomy/neurophysiology; cognition; language; academic achievement; memory; attention; executive function, including impulse control and hyperactivity; affect regulation; and adaptive behaviour, social skills or social communication (Cook et al., 2016). FASD can occur with or without the presence of sentinel facial features, common to PAE (i.e., short palpebral fissures, indistinct philtrum, thin upper lip) (Cook et al., 2016). However, it has frequently proven difficult to build an accurate profile for children thought to be prenatally exposed to alcohol as in many cases the maternal alcohol history is missing or difficult to acquire. In the absence of the sentinel facial features, confirmation of maternal drinking during pregnancy is required for an FASD diagnosis (Cook et al., 2016).

Stigma and a lack of alcohol history of biological mothers are two barriers, which can prevent children who would most benefit from an FASD diagnosis from receiving it, and thus restrict or decrease access to essential supports and services. Additional barriers include limited access to the necessary health care professionals that make up the multidisciplinary teams that carry out the assessment for FASD, and the length of time it takes for the assessment to be completed. An FASD assessment (screening, referral, admittance, and diagnosis) by a multidisciplinary team, involves a complex physical and neurodevelopmental evaluation, and can take up to 32-47 hours for one child (Cook et al., 2016; Popova et al., 2013). Since multiple health professionals are involved in the diagnostic process, this can mean the family must attend multiple appointments, often scattered over several months, to accumulate all of the necessary assessments. To combat these barriers and provide children with PAE with the best chance to succeed, several groups have investigated the utility of biomarkers as sensitive and specific screening tools for PAE and/or functional neurobehavioural outcomes in children as a consequence of PAE. One such approach investigated in this thesis is the use of eye movement behaviours as a proxy for brain injury in children with FASD.

Eye-tracking tasks measure automatic and voluntary eye movement responses, spatial working memory and visuospatial skills. These tasks have been used to characterize brain dysfunction in children with FASD (Green et al., 2009; Green, Munoz, Nikkel, & Reynolds, 2007; Paolozza, Titmen, Brien, Munoz, & Reynolds, 2013; Paolozza et al., 2014a; 2014b). These studies revealed that the performance of eye movement control tasks that examined response inhibition, working memory skills, and visuospatial skills were correlated with the individual child's performance on psychometric tests used during an FASD assessment (Paolozza et al., 2014a; 2014b). More broadly, cognitive, behavioural, and sensory-motor functions in both

typically developing populations and in many different neurological and psychiatric conditions have been explored using eye movement behaviours (Goossens & van Opstal, 1997; reviewed in Leigh & Kennard 2004; Optican & Quiaia, 2001; 2002; reviewed in Ramat, Leigh, Zee, & Optican, 2007).

The overarching goal of this project was therefore to test the hypothesis that classification of children with FASD compared to typically developing controls can be achieved using functional biomarkers of brain injury obtained from eye movement control tasks, and that the classification accuracy to differentiate children with FASD from typically developing controls will exhibit a high degree of sensitivity and specificity.

Chapter 2

Literature Review

2.1 Statement of the research problem

The prevalence of FASD in Canada is estimated to be 1 in 100, meaning that more than 330 000 individuals in Canada are affected with FASD (Cook et al., 2016). In the newest update of the Canadian FASD diagnostic guidelines, it was recommended that FASD become the diagnostic term used to describe the spectrum of disorders induced by prenatal alcohol exposure (PAE). FASD describes a range of physical, neurobehavioural and cognitive effects that can occur as a result of prenatal alcohol exposure (Cook et al., 2016). Previously, FASD encompassed a number of different disorders, which vary depending on the quantity, frequency and timing of prenatal alcohol exposure. Fetal Alcohol Syndrome (FAS), partial Fetal Alcohol Syndrome (pFAS), Alcohol-Related Neurodevelopmental Disorder (ARND), and Alcohol-Related Birth Defects (ARBD) are to be included under the umbrella term FASD according to the Canadian Diagnostic Guidelines (Cook et al., 2016; Popova et al., 2013).

Recommendations for a diagnosis of FASD are made in two instances if the specified criteria are met. Instance one includes the presence of three sentinel facial features (short palpebral fissure, smooth philtrum, thin upper lip), evidence of brain dysfunction in at least three neurodevelopmental domains, and PAE confirmed or unknown. The second instance includes evidence of impairment in three or more neurodevelopmental domains, and a confirmation of prenatal alcohol exposure (Cook et al., 2016). Cook and colleagues recommended that diagnostic categories for FASD be condensed into two designations: FASD with sentinel facial features and FASD without sentinel facial features. Diagnostic assessments are carried out by a multidisciplinary team of professionals, can be long and tedious and have been estimated to cost

between \$3.6 million to \$7.3 million annually (Popova et al., 2013). FASD is therefore a major health issue within Canada that needs to be addressed. Early screening may promote referral to a diagnostic clinic and lead to an earlier diagnosis, earlier access to support services, and overall a better quality of life (Popova et al., 2013).

2.2 FASD Diagnostic Procedure

2.2.1 Early Diagnostic Procedures.

Early research conducted in the 1970's followed three newborns born to alcoholic mothers through their first months of life (Jones & Smith, 1973). This work has influenced the diagnostic criteria used today. Jones and Smith (1973) noticed that these newborns displayed growth deficits, facial dysmorphologies, along with other health problems including deficits in fine motor skill, developmental delays, respiratory issues and microcephaly. An autopsy performed on one of the newborns demonstrated neuronal and glial disorganization and incomplete development of the brain, shown by the absence of the corpus callosum. These characteristics helped identify children with FAS.

As more research investigating the effects of PAE and FAS continued, questions arose regarding the actual cause of known symptoms. Clarren and Smith, (1978b), explored the following three questions (1) Are physical and cognitive characteristics caused by malnutrition or other substances that co-exist with alcohol? (2) Is the low IQ seen in children prenatally exposed to alcohol due to the exposure or poor parenting techniques? (3) Should children that do not exhibit the sentinel facial features associated with prenatal alcohol exposure receive a diagnosis of FAS? Investigation revealed that malnutrition did not account for the physical and cognitive characteristics of FAS, the cause of low IQ was due to prenatal alcohol exposure, and that a spectrum of deficits existed in which brain dysfunction could exist in the absence of all of

the sentinel facial features associated with PAE. Therefore, the first standardized guidelines for a diagnosis of FAS included the following: (1) delayed growth, (2) Central nervous system (CNS) dysfunction, and (3) at least two of the three sentinel facial features (Rosett, 1980).

2.2.2 Current Diagnostic Procedures.

More recent research has provided diagnostic guidelines to follow for an FASD diagnosis in Canada (Chudley et al., 2005; Cook et al., 2016). Chudley and colleagues set out to review various diagnostic and screening methods and investigate how they could be applied to aid in the diagnosis of FASD, and complications due to PAE. The diagnostic process itself has the potential to lead to recommendations of how to best manage various physical, cognitive and emotional deficits as a result of PAE, which can improve the affected individuals' quality of life. Chudley et al., (2005) suggested that a multidisciplinary approach to FASD diagnosis is best due to the range and complexity of deficits associated with prenatal alcohol exposure. This approach allows many professionals (e.g., occupational therapists, physicians, social workers) to gather information on the effects alcohol can have on an individuals' functioning and allow for the development of efficient treatment and support programs tailored to each individual's specific needs. Additionally, they recommend that the 4-digit diagnostic code developed by Astley and Clarren at the University of Washington (see below) be used to assess the presence of FASD in combination with terminology used from the Institute of Medicine.

The 4-digit diagnostic code approach uses independent measurement scales to rate the severity of deficits in four diagnostic categories; growth deficiency; FAS facial phenotype; damage or dysfunction to the central nervous system; and gestational exposure to alcohol (Astley, 2004; Astley & Clarren, 1999). The four digits in the code reflect the magnitude of the deficits in the four features listed above, in that order. The magnitude of each feature is measured

using a 4-point Likert scale, where a value of 1 represents complete absence of the feature and 4 represents the most severe manifestation of the feature. This approach has been applied to the diagnosis of FASD from newborns through to adults.

The capability to make a diagnosis of FASD early is crucial, in order to allow affected individuals to receive support services and programs earlier while reducing the likelihood or severity of secondary symptoms (e.g., criminal behaviour, aggression, depression) (Chudley et al., 2005; Popova et al., 2013). Therefore, the 4-digit diagnostic code is a frequently employed methodology as it has been shown to be a reliable and valid measure of FASD features in combination with terminology used by the Institute of Medicine (Chudley et al., 2005). However, there have been some recent changes made to the Canadian Guidelines for FASD diagnosis.

Cook and colleagues (2016) set out to update the recommendations for the diagnostic process first published by Chudley and colleagues (Chudley et al., 2005) in light of new knowledge and expertise in the field. One major change that was made to the original guidelines was the use of FASD as a diagnostic term describing the collection of effects that can result from PAE; previously FASD was not considered a diagnostic term. Additionally, the new guidelines suggest that the use of growth deficiency as a diagnostic requirement is no longer needed, special considerations for diagnosing FASD in individuals across the lifespan should be addressed, a new 'at risk' category was developed to capture individuals who do not meet the specific criteria of FASD but may still be at risk, and revision of brain areas to be assessed in the neurodevelopmental examination were proposed. The stated goal of this revision of the guidelines for diagnosing FASD was to improve the outcomes for individuals who have

been/may have been prenatally exposed to alcohol, their families and the services available to them (Cook et al., 2016).

2.3 Behavioural and Physiological Effects of Prenatal Alcohol Exposure

2.3.1 Structural Changes in the Brain.

Previous research has identified a number of structural deficits throughout the brain in individuals who have been exposed to alcohol prenatally (Archibald et al., 2001; Green et al., 2009; Green, Lebel, Rasmussen, Beaulieu, & Reynolds, 2013; Kodituwakku, 2009; Mattson et al., 1992; Mattson et al., 1996; O'Hare et al., 2005; Riley & McGee, 2005; Riley et al., 1995). There currently is no evidence demonstrating that alcohol only affects one particular brain structure, however imaging studies have shown that alcohol may have a number of effects on various brain structures, depending on the timing, frequency and severity of alcohol exposure (Archibald et al., 2001; Green et al., 2013; Mattson et al., 1992; Mattson et al., 1996; O'Hare et al., 2005; Riley & McGee, 2005). Throughout the studies mentioned above, there appear to be four main brain regions that consistently demonstrate deficits as a result of PAE.

Corpus Callosum.

The corpus callosum is a fibrous region that connects the left and right hemispheres of the brain. Riley et al., (1995) investigated the effect on the corpus callosum in 13 living children who had been prenatally exposed to high levels of alcohol, using magnetic resonance imaging (MRI) technology. They found that two of the 13 children had agenesis of the corpus callosum, while the rest of the children were shown to have a smaller corpus callosum compared to typically developing children. This evidence suggested that malformations within the corpus callosum are related to fetal exposure to high levels of alcohol.

More recent work by Wozniak and colleagues has further demonstrated the association between prenatal alcohol exposure and structural abnormalities within the corpus callosum and other white matter tracts using MRI and diffusion tensor imaging (DTI) technologies. In each of their studies, microstructural abnormalities of the corpus callosum were consistently observed in children with PAE (Wozniak & Lim, 2006; Wozniak & Muetzel, 2011). These deficits may contribute to executive functioning difficulties in children with PAE, since the corpus callosum connects the left and right hemispheres, and impaired interhemispheric connectivity could make the processing of information more difficult (Wozniak & Lim, 2006; Wozniak & Muetzel, 2011). The corpus callosum begins developing around week seven of pregnancy and is not fully developed until the 18-20th week of pregnancy. Due to the length of time for development any insults to a fetus, such as alcohol can have damaging effects on the corpus callosum (Barcovich & Norman, 1988). Barcovich and Norman, (1988) described that when insults occur to the developing corpus callosum, changes in the course of development can occur. Insults can affect structures that cause/allow axons to grow between the two developing hemispheres, causing them to grow in parallel with the interhemispheric fissure rather than growing across the midline to the opposite hemisphere. Fewer connecting axons between hemispheres has been found to be associated with deficits in executive functioning (Wozniak & Lim, 2006; Wozniak & Muetzel, 2011; Wozniak et al., 2009).

Cerebellum.

The cerebellum is involved in motor planning and cognition, this is another area of the brain that appears to be consistently affected by prenatal alcohol exposure. A study conducted to detect structural brain abnormalities using MRI technology explored the brains of 17 children exposed to heavy alcohol throughout prenatal development (Autti-Ramo et al., 2002). Heavy

alcohol exposure in this study was considered to be greater than 10 drinks per week. Results of the study revealed that the cerebellar vermis appeared to be the structure most sensitive to prenatal alcohol exposure. More than half of the children demonstrated hypoplasia of the cerebellar vermis, others had hypoplastic cerebellar hemispheres. Archibald et al., (2001) used structural MRI to obtain a more in depth look at the local pattern of hypoplasia in the brain of individuals prenatally exposed to alcohol. Similarly, they found that individuals with PAE who had an FAS diagnosis demonstrated hypoplasia in the cerebellum among other brain regions. Deficits in the cerebellum likely contribute to deficits in balance and motor development in individuals with FASD (Connor, Sampson, Streissguth, Bookstein, & Barr, 2006).

Basal Ganglia.

The basal ganglia have important roles in both motor and cognitive control (Graybiel, 2000; Stocco, Lebiere, & Anderson, 2010). Mattson and colleagues have done extensive research investigating the effects that PAE can have on the structural integrity of the brain. Case studies, which explored the neuropsychological, MRI and EEG assessment in two children with FAS showed reductions in the basal ganglia and thalamic structures (Mattson et al., 1992). Deficits within these areas have the potential to lead to deficits within domains of executive function, such as impaired recall and poor discrimination ability (Mattson et al., 1992). Further studies using MRI and volumetric analysis also revealed that there are significant reductions in the volume of the basal ganglia, specifically the caudate nucleus along with other regions in children with FAS compared to typically developing controls (Mattson et al., 1996). A follow-up study was conducted by Archibald et al., (2001), using MRI technology, which found that within the 14 FAS participants, the basal ganglia were again smaller in size and the region most severely affected by PAE was the caudate nucleus.

Frontal Cortex.

Many studies have revealed reduced volume and/or malformation of the frontal cortex as a consequence of prenatal alcohol exposure (Burke, Palmour, Ervin, & Ptito, 2009; Riley & McGee, 2005; Wass, Persutte, & Hobbins, 2001). The frontal cortex has an important role in decision-making, critical thinking, inhibition, working memory and other areas of executive functioning. Children who have been prenatally exposed to alcohol have demonstrated difficulties or deficits in these domains of executive functioning, which is likely correlated to the effects of alcohol on the frontal cortex and developing brain in general (see Rasmussen, 2005 for review).

To attempt to investigate global or local brain abnormalities among children with various FASD's, Astley and colleagues performed a battery of neuropsychological and psychiatric assessments along with MRI, fMRI, magnetic resonance spectroscopy. Using a 3-D coronal slices and a stereological point-counting method they found that the overall volume and size of children with FAS brain's were smaller than those of control children and children with other forms of FASD (Astley et al., 2009). Previous work by Wass and colleagues investigated the size of the frontal cortex of the fetus in pregnant women. Using ultrasonographic technology, it was shown that when women consumed alcohol during their pregnancy, their fetus had a reduction in the frontal cortex, compared to women who did not consume alcohol (Wass et al., 2001).

Burke and colleagues performed a study examining neuronal reduction in the brain of offspring of St. Kitt's monkeys that voluntarily consumed alcohol during their pregnancy. They found that the offspring of pregnant monkeys that consumed alcohol exhibited a neuronal reduction in their frontal cortical neurons along with an increase in white matter neurons (dendritic processes of superficial interstitial neurons) (Burke et al., 2009). Lower numbers of

frontal cortical neurons may contribute to detrimental consequences on the frontal lobe functioning of those prenatally exposed to alcohol. Other work has shown that individuals who are prenatally exposed to alcohol show cortical thinning in areas of the bilateral middle frontal lobe. Across the lifespan, it was also shown that overall cortical thinning occurred in both individuals with FASD and typically developing controls, but the cortical thinning was seen in different areas of the brain throughout development (Zhou et al., 2011). Specifically, in children with FASD, cortical thinning was seen in left middle frontal region of the brain along with other areas, whereas the control participants demonstrated cortical thinning in the bilateral middle frontal gyrus, right inferior frontal gyrus, along with other areas. These results along with work by Treit and colleagues demonstrate the impact that PAE can have on brain development and cortical changes that are different from typical development (Treit et al., 2014; Zhou et al., 2011). It also shows that there is still more work to be done, since there is still much variation in results. Therefore, more work needs to be done in order to identify specific functional biomarkers of FASD.

2.3.2 Cognitive and Behavioural Deficits.

Alcohol has teratogenic effects on the developing brain, and this can lead to cognitive and behavioural deficits (Paolozza et al., 2014a, 2014b; Rasmussen, 2005; Rasmussen, Andrew, Zwaigenbaum, & Tough 2008). These deficits can present themselves in the form of cognitive and executive functioning difficulties, such as adaptive behaviour and social-emotional processing (Rasmussen et al., 2008). These deficits have the potential to greatly impact the quality of life of individuals with PAE, and have the potential to lead to secondary deficits such as depression and anxiety (Hellemans, Sliwowska, Verma, & Weinberg, 2010). Green and colleagues found that children with FASD tended to perform more poorly on eye movement

tasks, when comparing eye-tracking performance of children with an FASD diagnosis and typically developing controls. Children with FASD tended to make more errors during the tasks as they became more cognitively complex, indicating that children with FASD experience more difficulty on tasks that require greater cognitive effort (Green et al., 2009).

A study by Carr and colleagues examined sensory processing, adaptive behaviour, and neurocognitive functioning in individuals with varying diagnoses due to varying degrees of PAE. They found that children with a more severe diagnosis (pFAS, ARND) consistently performed worse on the domains examined compared to individuals with a less severe diagnosis (Carr, Agnihorti, & Knightley, 2010). This study demonstrated that PAE can affect many aspects of development whether intellectual or functional, therefore a broad range of standardized assessments should be done on individuals who are suspected of having PAE in order to develop a better neurodevelopmental profile.

Executive functioning (EF) and IQ of children exposed to alcohol prenatally have been examined. Connor and colleagues explored the executive functioning abilities of individuals who had been prenatally exposed to alcohol using 9 different tests of executive function. They found that although IQ and EF abilities are related, the EF deficits seen in individuals with PAE are a good reflection of damage caused by exposure to alcohol, independent of IQ and characteristic sentinel facial features (Connor, Sampson, Bookstein, Barr, & Streissguth, 2000).

Individuals with FASD can experience a number of cognitive and behavioural deficits, including poor judgement, impulse control, adaptability, and abstract thinking and demonstrate a lack of organization along with learning disabilities (see Koren, Nulman, Chudley, & Looke, 2003 for a review). These deficits can differentiate individuals with FASD from typically

developing control children and may help in the development of a cognitive and behavioural phenotype for FASD, which could aid in the screening process (Nash et al., 2006).

2.3.3 Phenotype of Cognitive and Behavioural Assessment of FASD.

Identifying and diagnosing FASD requires collaboration by a multidisciplinary team and encompasses assessment of complex physical and neurodevelopmental criteria (Cook et al., 2016). In order to develop a phenotype for FASD from cognitive and behavioural assessments, neurodevelopmental and neuropsychological tests are completed in addition to various behavioural checklists and assessments (Chudley et al., 2005). Despite the large number of tests that can help to identify cognitive and behavioural deficits, it has proven difficult to identify and develop a cognitive and behavioural phenotype for FASD. This could be due largely to the fact that characteristics of FASD overlap with other disorders seen in children and adults, such as ADHD, Autism, and learning disabilities (see Popova et al., 2016 for review). Moreover, as mentioned previously it can be difficult to determine the alcohol history of individuals thought to be exposed prenatally (Riley & McGee, 2005).

A study by Kodituwakku and colleagues in 1995 that aimed to explain behavioural learning patterns that can occur in children with FASD. They demonstrated that children with FASD performed similar to the controls on tasks such as the Story Memory and Design Memory measure from the Wide Range Assessment of Memory and Learning (WRAML). However, children with FAS/FAE performed worse than a comparable control group on tasks with increasing complexity that required manipulation of information stored in memory, such as Progressive Matrices and Attentional Capacity Test (ACT) compared to their performance on the simpler tasks. This revealed that children with FASD appear to be more impaired on tasks which

are cognitively more complex than they are on intellectually less demanding tasks (Kotiduwakku et al., 1995).

Another study that assessed cognitive functioning in children using tasks that assess both simple and complex information processing, found that children with FASD performed significantly worse on tasks that were more complex (e.g., Digit Span Backwards, Delayed Recognition Span Test of Memory, Progressive Planning Test trials 5 - 8) and required more cognitive power. This helps to develop a cognitive and behavioural phenotype among children with FASD, as it demonstrates their ability and increased difficulty with complex cognitive tasks compared to typically developing controls (Aragon et al., 2008). Controls also saw a decrease in performance on more complex tasks compared to simpler tasks, however it appeared that children with FASD were consistently below the performance of controls on the more complex tasks even though they too appeared to find the complex tasks more difficult.

2.4 Current FASD Screening Methods

It is apparent that FASD is a complex disorder to identify and diagnose due to its overlapping characteristics with other disorders along with a lack of knowledge about contributing factors. To make matters worse, many health care professionals and educators are not fully aware or informed of the attitudes and practices that should be followed with regards to consuming alcohol during pregnancy (Elliott, Payne, Haan, & Bower, 2006; Payne et al., 2005). Many health care professionals have mixed views or opinions on whether women should consume alcohol during their pregnancy and require a better knowledge base of FASD in order to best educate their clients. The same can be said with regards to teachers and educators within school systems. Many teachers are unaware of the signs and symptoms associated with FASD and as a result can assume another disorder is the cause for behavioural or learning deficits while

also failing to have resources to properly support and aid children who have been prenatally exposed to alcohol. Therefore, there is a need for collaboration and communication between scientists and the general public about FASD, the consequences of consuming alcohol during pregnancy, and a list of services should be available to individuals exposed and their families (Blackburn & Whithurst, 2010).

Thus a valid and reliable screening tool is necessary, as it could allow individuals affected to receive the necessary support and services as early as possible and reduce the risk of secondary consequences, while better educating parents, health care professionals as well as educators of the services that should and can be offered to exposed individuals (Memo, Gnoato, Caminiti, Pichini, & Tarani, 2013). Currently there are multiple screening methods that have been investigated to attempt to recognize characteristics of FASD, which can then foster further investigation and diagnostic tests.

2.4.1 Meconium and Neonatal Biomarkers.

Research has been done looking at both direct and indirect biomarkers of alcohol, both from the mother as well as the fetus (see in Joya et al., 2012 for a review; Morini et al., 2010). Direct biomarkers are those that are derivatives of alcohol, which still contain two carbon atoms from the alcohol (see Joya et al., 2012 for review), examples include non-oxidative fatty acid ethyl esters (FAEE) and ethyl glucuronide (EtG). These biomarkers can be collected from maternal and fetal hair and nail samples, as well as from meconium samples from the fetus. Both of these biomarkers can be found due to long-term, chronic alcohol use, but are not as easily found when minimal alcohol is consumed during pregnancy (see Joya et al., 2012 for review). Substances consumed by the mother (i.e., alcohol) can cross the placenta and therefore be found in meconium of the fetus. The recommended cut-off amount for FAEEs is 2nmol/g or 50ng/g of

meconium in order to reliably identify maternal alcohol use during the later half of pregnancy (Backdash et al., 2010). This method is often complex, involves many steps in sample preparation, is expensive, and requires a trained technician in order to extract and analyze the FAEEs from the meconium (Memo et al., 2013). Though, a new method of analysis has been developed by Hutson and colleagues (2011), which appears to be more efficient and cost effective. However, two limitations are that trained professionals are needed to liquefy the FAEEs from the meconium sample and FAEE's do not detect alcohol use in the first trimester since bowls are not fully developed (Clarren & Cook, 2013).

2.4.2 Facial Features.

Another method, which has been shown to be easy to use and inexpensive, is the use of a photographic screening tool. The presence of three distinct facial features is necessary for the full diagnosis of FAS. A tool, described by Astley and Clarren (1996), used frontal facial photographs of individuals who had FAS and control individuals without FAS. These computerized images were then used to measure features that are known to be characteristic of FAS (palpebral fissure length, vermilion thickness, philtrum presence). However, the computer images did not contain internal measures of scale, therefore different Likert scales and measurement techniques were used to examine the severity of facial features in individuals with FAS and those without FAS. Astley and Clarren acknowledged the lack of accuracy of using Likert scales as a form of measurement, but state that this accuracy is made up/accounted for by using measurements of pixel luminosity and circularity of main FAS facial features. A discriminant score (d-score) was calculated using individual scores on each facial feature, this d-score was then used to predict the individuals diagnostic classification. Astley and Clarren developed a number of different d-score formulas and demonstrated significant levels of

sensitivity and specificity. Overall, this technique demonstrated increased accuracy, precision and efficiency, which are key aspects needed for a reliable and effective screening tool for FASD. However, this method only applies to individuals with FAS and possibly partial FAS, therefore it misses the majority of cases of PAE.

One other method that can be used to screen individuals with FAS and partial FAS is 3D facial recognition photography. Three dimensional images can be collected using laser scanner which scans participants faces in the relaxed position. Use of the laser scanner has demonstrated the potential for 3D imaging to be used to differentiate children with FAS and the characteristic facial features from typically developing controls (Moore et al., 2007). Fang and colleagues (2008) developed a facial feature analysis technique, which was able to mathematically compare specific facial features between FAS and control groups. Three-dimensional images were developed by using a facial laser, which scanned FAS and control faces to develop a 3D image. A feature set was identified using computational algorithms and various statistical analyses. The feature set was then used to train a machine-learning algorithm to discriminate children with FAS from control children. The classification was able to accurately classify children into their respective groups using features from the 3D images, with high specificity (76.2%) and sensitivity (82.75%). This method has been shown to be a valid tool for screening individuals with FAS, however similar to the previous method, this one appears to only be able to apply to individuals with FAS and partial FAS and is expensive. This demonstrates that although this method has potential, facial characteristics may not give a full representation of underlying cognitive and emotional deficits, therefore they may not be a reliable option to consider when investigating the severity of PAE effects (Wozniak et al., 2009).

More recently, Suttie and colleagues have attempted to identify facial morphology across the spectrum of disorders that can result from PAE. Three-dimensional photographs were analyzed using dense surface modeling (heat maps) and analysis. They found that facial classification was able to accurately differentiate between the control and FAS groups very well, and fairly well between the control and partial FAS groups (Suttie et al., 2013). Therefore this method may not be appropriate for a majority of children affected by PAE, such as those with ARND since they do not need to have the sentinel facial features to receive a diagnosis.

2.4.3 Magnetic Resonance Imaging (MRI).

Another potential screening tool is MRI. MRI has the potential to provide 3D morphological information about the brain as well as acting as a quantitative assessment of which brain areas appear to be affected by PAE. MRI provides a good avenue to try to explore the connection between brain structure and function and how they are both affected by PAE (Memo et al., 2013). This technique can be combined with other screening methods in an attempt to bridge the gap between structural and functional brain deficits/changes. However, MRI is very expensive to use as a screening tool for the brain (Rauch, Carr, & Harrington, 2008) and is not easily portable to remote or rural locations, which would be a barrier for many children with FASD.

Despite all the apparent available screening tools, there is still a need for a screening tool that does not require a professional to run it, a tool that is easily interpreted and generalizable to individuals experiencing the spectrum of consequences with FASD. Additionally, a tool that has a good sensitivity and specificity when distinguishing between individuals with FASD and typically developing controls is necessary along with the ability for it to be taken to remote locations so that all populations are served and informed. Eye-tracking therefore could be the

screening tool that the field is looking for. Eye movement behaviours between children with an FASD diagnosis and typically developing control children have been shown to differ (Green et al., 2009; Green et al., 2007; Paoozza et al., 2013). Therefore, eye movement data that has been collected has the potential to act as a screening tool for FASD, while helping to identify potential functional biomarkers for FASD.

2.5 Saccadic Eye Movements

2.5.1 Saccade Neurocircuitry.

Many brain areas are involved in the production, execution, and correction of saccades. Areas that are involved include the basal ganglia, superior colliculus, cerebellum, brainstem, in addition to the frontal and parietal cortices (Quaia, Lefavre, & Optican, 1999; Robinson & Fuchs, 2001; Robinson, Straube, & Fuchs, 1993). Many of these brain regions have been shown to be experience malformations due to PAE and as a result, measuring eye movement behaviours may reveal functional deficits in the brain of individuals with FASD. The particular size of a saccade is controlled by the superior colliculus before the signal is sent to the burst generator neurons in the pontine reticular formation (Goossens & van Opstal, 2006; Quaia et al., 1999; Sparks, Holland, & Guthrie, 1976), and the cerebellar oculomotor vermis (Scudder, Kaneko, & Fuchs, 2002). It is thought that the cerebellum plays an important role in optimizing saccade accuracy and stability through stopping and steering saccades (Quaia et al., 1999). The cerebellum is able to control saccade accuracy through feedback from the motor command, which can allow for adjustments to the saccade (Chen-Harris, Joiner, Ethier, Zee, & Shadmehr, 2008; Golla et al., 2008; Xu-Wilson, Chen-Harris, Zee, & Shadmehr, 2009). Projections from cerebellar vermis Purkinje cells are sent to excitatory and inhibitory burst neurons within the brainstem, which helps control saccades (Robinson & Fuchs, 2001; Scudder et al., 2002). The

cerebellum also has many connections with the basal ganglia, which if damaged can lead to deficits in eye movement behaviours in individuals with PAE (Glickstein & Doron, 2008). Given the overlap between brain structures involved in saccade generation and control, and those known to be affected by PAE, eye movement tasks could be expected to reveal biomarkers of brain dysfunction due to PAE.

2.5.2 Saccade Tasks.

Prosaccade Task.

This saccadic eye movement task is used to measure automatic saccades made by participants when a visual target appears. The task requires participants to fixate vision on a central fixation point, and then to make a saccade to a peripheral target when it appears in either the right or left hemi-field. Participants are simply instructed to look towards the target when it appears on the screen (Figure 1(A)).

Antisaccade Task.

The antisaccade task is similar to the prosaccade task, in that participants again are required to look at a central fixation point. What differs in the antisaccade task is the instruction to the participant. The participant is told to look away from the visual target when it appears in the right or left hemi-field, and more specifically to look to the opposite location on the screen from where the visual target appears (Figure 1(B)). This task requires the participant to inhibit an automatic saccade towards the target and produce a voluntary saccade to the opposite side of the screen. As a result of this more complex task, more brain regions are recruited, such as the frontal cortex and basal ganglia (Munoz & Everling, 2004). Since this task requires inhibition of the automatic saccade it can be used as an assessment of executive functioning, specifically, response inhibition. Studies have used this task to investigate differences in eye movement

behaviour between children with FASD and typically developing controls and found that children with FASD made more direction errors – they looked toward the target instead of away from it - than control children (Green et al., 2009; Green et al., 2007; Paolozza et al., 2014a).

Memory-guided Saccade Task.

This task has been shown to be good measure of response inhibition and working memory, since participants must suppress the automatic saccade to the targets and instead wait before looking to the targets. This task requires participants to look at a central fixation point while peripheral targets (2 in the current study) flash sequentially in different locations on the screen (Figure 1(C)). Only once the fixation point disappears should the participant look to the location of the peripheral targets flashed, in the correct order that they flashed. This task has been used in a study comparing the eye movement behaviours of children with FASD and typically developing controls. Results showed that children with FASD made more errors in timing of saccades to the targets (wait for the appropriate go signal), in addition to errors accurately remembering the location of targets flashed on the screen (Paolozza et al., 2013). This demonstrates children with FASD may experience difficulties with controlling response inhibition and with spatial working memory.

2.5.3 Relationship Between Saccadic Eye Movements and Machine Learning.

Machine learning, has previously been shown to have the ability to recognize complex patterns within datasets and can learn to accurately identify different clinical populations. For example, machine learning algorithms have been used to identify children with autism from typically developing controls. Liu and colleagues (2016) used a machine-learning algorithm and a feature representative classifier, to investigate the amount of time each group (children with autism and control children) spent visually fixated on the eyes, nose and mouth during a face

recognition task. The outcomes from the task were then used to train and test the computational classifier's sensitivity (93.10%), specificity (86.21%) and overall accuracy (88.51%). Their computational classifier was shown to produce high sensitivity and specificity when differentiating between the two groups (children with FASD and controls (age and IQ matched)). Thus, the use of computational models (i.e., classifiers) has become a common tool used in biomedical sciences, specifically the field of clinical vision sciences, by providing support for clinical decision practices to improve disease detection in clinical populations (Agurto, 2011; Akram, Tariq, Khan, & Javed, 2014; see Caixinha & Nunes, 2017 for review; Medeiros, Leite, Zangwill, & Weinreb, 2011).

Tseng et al., (2013) developed a computational model of attention, which gathered information about attention and gaze control while participants watched 15 minutes of videos. Their clinical populations included individuals with attention deficit hyperactivity disorder (ADHD), Parkinson's, and individuals with FASD in addition to two control groups (healthy young adults and typically developing children). The purpose of their study was to help identify whether individuals within these respective clinical groups differed in their attention and gaze control as they watched the videos. Their findings revealed that the clinical groups focused on different features of the videos. Specifically, children with ADHD were shown to have increased sensitivity to colour, edges, and texture contrast compared to typically developing controls. Comparatively, children with FASD demonstrated differences in gaze distribution, and increased sensitivity to texture contrast compared to typically developing controls. Feature elimination was used to train and test a computational classifier, which was able to correctly differentiate children with ADHD from those with FASD. The classifier had an overall accuracy of 77.3% when discriminating between attention and gaze features of children with ADHD or FASD and

typically developing control children (chance level was 40%).

2.6 Research Rationale, Objectives, Hypotheses

This research had the goal of investigating whether eye movement behaviours can be used as input to a computational model in order to correctly categorize children into their respective clinical groups. Other screening techniques have shown either variable reliability and/or shortcomings such as the need for a trained professional to carry out the task, lack of portability, and high cost. Eye-tracking and the measurement of eye movement behaviours, in addition to being shown to be a non-invasive measure of cognitive ability in children with FASD (Green et al., 2009; Green et al., 2007; Paolozza et al., 2014a; 2014b), does not require a trained professional to run tasks, is able to be transported to more remote locations, and is relatively inexpensive to run participants. Therefore, eye movement behaviours may have the potential to be developed into a sensitive and specific screening tool.

In the current study, eye movement outcomes gathered from eye-tracking tasks were used as input into a machine-learning model. The machine-learning model used the eye movement outcomes/features to train and test the ability of a classifier to accurately differentiate children with an FASD diagnosis from typically developing control children. Previous work has demonstrated the ability of machine-learning models to be able to accurately classify children within different clinical populations into their respective groups using eye movement data (Liu et al., 2016; Tseng et al., 2013). Therefore, the results of these studies suggest that measuring eye movement behaviours hold promise as a sensitive and specific screening tool for FASD.

The aim of the current study was to assess the measurement of eye movement behaviours as a sensitive and specific screening tool for FASD, using three eye movement tasks, which

measure automatic and voluntary eye movement responses, spatial working memory and visuospatial skills. Thus the present study is designed to meet the following objective:

1. A validation study was conducted to confirm the ability of eye-tracking to rapidly and objectively identify children with FASD.

The study is designed to test the following hypotheses:

1. Eye movement tasks are a sensitive and specific screening tool that can be used to identify brain injury associated with prenatal alcohol exposure.
2. Eye movement control tasks will reveal specific functional biomarkers that will inform state-of-the-art machine-learning models to reliably and efficiently discriminate between children with FASD and typically developing control children.

Chapter 3

Materials and Methods

3.1 Participants

All experimental procedures were reviewed and approved by the Queen's University Human Research Ethics Board. Both children with an FASD diagnosis and typically developing control children between the ages of 9 and 16 were recruited from Vancouver, British Columbia and Kingston, Ontario. Children with an FASD diagnosis were assessed using Canadian Diagnostic Guidelines (Chudley et al., 2005). Preceding data collection, parents of all children provided informed consent for their child's participation in the study. Children completed a written assent form, while young children were also provided with a verbal explanation of the study proceedings. Within the control group, exclusion criteria consisted of any neurological or psychiatric disorder. Exclusion criteria for all participants included visual disturbances besides the need for corrective lenses. Corrective lenses could be worn throughout the study if necessary.

It was requested that parents or the legal guardian complete forms asking for information about their child's medical and psychological history, since many psychiatric disorders are common among children with FASD as well as the use of pharmacological agents. All participants completed one experimental session and were compensated with a \$20 gift certificate for their time. Breaks were given as needed throughout the session in addition to a snack and juice beverage. Demographic information about all participants in the validation cohort was collected (Table 1). The training cohort data was collected previously as part of a larger study (Paolozza et al., 2014). Demographic information about the training cohort can be found in Table 2.

Table 1. Demographic information for control and FASD participants in the validation cohort.

| (N=57) | Validation Control (n=25) | Validation FASD (n=32) |
|---|--|---------------------------------------|
| Age in years M (SEM) | | |
| | 12.84(0.37) | 11.47(0.39) |
| Sex N (%) | | |
| Female | 14(56) | 13(40.6) |
| Male | 11(44) | 19(59.4) |
| Comorbidities Present at Diagnosis N (%) | | |
| Attention Deficit Hyperactivity Disorder | 0 | 16(50) |
| Oppositional Defiance Disorder | 0 | 1(3.1) |
| Anxiety | 1(4) | 6(18.8) |
| Reactive Attachment Disorder | 0 | 1(3.1) |
| Post Traumatic Stress Disorder | 0 | 3(9.4) |
| Learning Disability | 0 | 11(34.4) |
| Intellectual Disability | 0 | 6(18.8) |
| Other | 1(4) | 14(43.8) |
| Medications N (%) | | |
| Acid Blockers | 1(4) | 0 |
| Stimulants | 0 | 15(46.9) |
| Antidepressants | 0 | 13(40.6) |
| Antipsychotics | 0 | 3(9.4) |
| Anticonvulsants | 0 | 1(3.1) |
| Antidyskinetics | 0 | 1(3.1) |
| Ethnicity N (%) | | |
| Caucasian | 17(68) | 22(68.8) |
| Asian | 11(44) | 0 |
| Indigenous Peoples | 0 | 13(40.6) |
| Other | 7(28) | 7(21.9) |
| Unknown | 0 | 5(15.6) |

Table 2. Demographic information for control and FASD participants in the training cohort. Modified from Paolozza et al., (2015). Individuals from this cohort that did not complete all eye-tracking tasks were eliminated from analysis.

| | Training Control (n=113) | Training FASD (n=71) |
|---|---|-------------------------------------|
| (N=184) | | |
| Age in years (\pmSD) | | |
| | 10.4 \pm 0.3 | 11.7 \pm 0.4 |
| Sex N (%) | | |
| Female | 60(53) | 32(45) |
| Male | 53(47) | 39(55) |
| Subtype (%) | 0 | |
| Fetal Alcohol Syndrome | 0 | 8(11) |
| Partial Fetal Alcohol Syndrome | 0 | 14(20) |
| Alcohol Related Neurodevelopmental Disorder | 0 | 49(69) |
| Comorbidities Present at Diagnosis N (%) | | |
| Attention Deficit Hyperactivity Disorder | 0 | 43(61) |
| Oppositional Defiance Disorder | 0 | 7(10) |
| Depression | 0 | 6(8) |
| Anxiety | 1(4) | 9(13) |
| Other | 0 | 19(26) |
| Medications N (%) | | |
| Stimulants | 0 | 31(43) |
| Antidepressants | 0 | 8(11) |
| Antipsychotics | 0 | 17(24) |
| Other | 0 | 14(19) |
| Socioeconomic Status | 47 \pm 7 | 41 \pm 14 |
| Ethnicity N (%) | | |
| Caucasian | 106(94) | 25(35) |
| First Nations/Metis | 2(2) | 43(61) |
| Other | 5(4) | 3(4) |

3.2 Experimental Setup: Eyelink 1000 Portable Eye-tracking System

Using a remote, head free portable eye-tracking system, the Eyelink 1000 (SR Research, Kanata, ON), saccadic eye movement data was obtained from all participants. Within a darkened, quiet room, children were seated in a stable chair approximately 600mm away from a 17" LED computer screen that had an infrared illuminator and infrared camera mounted on the base. A small target sticker was placed on the participants forehead or face to facilitate tracking of the selected eye. Unless difficulties were encountered in calibration, the right eye was used for all experiments. Once the pupil was located and focussed on the camera, each participant completed a nine-point calibration routine. The nine-point calibration covered the entire visual field of the computer screen, to ensure that eye movements to any part of the screen would be effectively captured. Following calibration, a validation task was completed to ensure that any error between the fixation point of the eye and the location of the nine calibration targets was $<2^\circ$. Once calibration and validation tasks were completed successfully, participants were able to begin the three eye-tracking tasks. If at any point throughout the study, participants needed a break the tasks could be paused, and calibration and validation could again be performed before continuing.

3.3 Saccade Task Paradigm

Participants performed three eye-tracking paradigms, which each explored different domains of executive functioning and sensory-motor processing. The three paradigms involved structured eye movement control tasks. All participants completed the three eye-tracking tasks in the same order of increasing difficulty (prosaccade, antisaccade, memory-guided saccade tasks).

Prosaccade Task.

This task requires participants to make an automatic saccade to a visual target that suddenly appears. Participants completed a single block of 60 trials of the prosaccade task. For this study, a gap version of the prosaccade task was used. Participants fixated on a central fixation point (FP) for 800 to 1200ms. The FP then disappeared and was followed by 200ms delay (gap period), before a peripheral target appeared 10° to the left or right of the FP on a horizontal axis. Participants were then given 1000ms to make a saccade towards the location of the peripheral target.

Antisaccade Task.

The antisaccade task requires the participant to suppress the automatic saccade to a visual target, and instead make a voluntary saccade to the opposite side of the screen from the peripheral target. Participants complete a single block of 60 trials for this task. The participant must fixate on the central FP for 800 to 1200ms. The FP then disappeared and was followed by a 200ms delay, before a peripheral target appeared either 10° to the left or right of where the FP was located. Participants were then given 1000ms to make a saccade. The correct response in this task would be a saccade to the opposite side of the screen from where the peripheral visual target appeared, and to the approximate location of where a target would appear if it was on the opposite side.

Memory-guided Saccade Task.

This task requires participants to maintain memory of the location of visual targets presented after a variable delay. Participants completed a single block of 54 or 72 trials in this task. Participants had to maintain fixation on the FP while two peripheral visual targets flashed sequentially. The targets could flash in one of four quadrants on the screen, each of which

contain 9 potential target locations on a 3-by-3 grid that is centred at 10° from the central FP (the grid is invisible during the task). The FP was illuminated for 200 to 1000ms before the peripheral targets appeared for 100ms each, in immediate sequence on the screen. Participants were instructed to only begin making saccades to remembered locations once the central FP had disappeared. After the disappearance of the final peripheral target, participants had to maintain fixation on the central FP for an additional randomly distributed time of 0, 600, or 1200ms (and 1800ms in the 72-trial version of the task) before the FP disappeared. Disappearance of the FP was the “go signal” for the participant to make saccades to the remembered location of the two peripheral targets in the same sequence in which they had appeared.

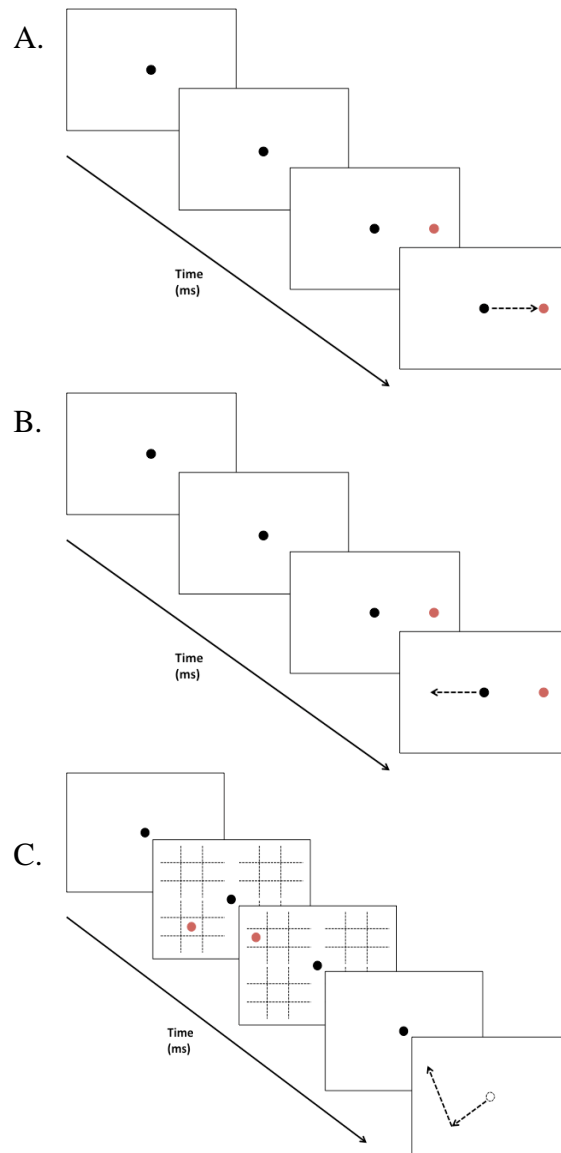


Figure 1. Structured saccadic eye movement tasks. A: Prosaccade Task: Correct fixations (black circles), peripheral target (red circles), and saccades (dashed arrows). B: Antisaccade Task: Correct fixations (black circles), peripheral target (red circles), and saccades (dashed arrows). C: Memory- Guided Saccade Task: Correct fixations (black circles), peripheral target (red circles), and saccades (dashed arrows). Participant is does not view the dashed grid lines in the memory-guided task.

3.4 Eye Movement Data Analysis

Eye movement data was collected at a sampling frequency of 500Hz, before being analyzed using custom software developed in Matlab (Version R2015b; Mathworks, Inc., Natick, MA). Saccades in the current study were defined as having a speed greater than 50°/second, while the saccadic reaction time (SRT) was defined as the time from disappearance of the central FP to the initiation of a saccade towards a target. Trials in which eye-tracking was lost, or eye movements were difficult to detect/track were not considered viable and therefore discarded. Within the block of trials in each of the tasks performed, participants needed to achieve greater than 50% viable trials in order for the data of that participant to be used in data analysis.

3.4.1 Types of Errors.

Three types of errors can occur during the pro- and antisaccade tasks: (1) Anticipation errors, these occur when a participant makes a saccade during the anticipation epoch ($\leq 89\text{ms}$) after the appearance of a peripheral target. (2) Direction errors, these are more common in the antisaccade task but can occur in the prosaccade task as well. They occur when a participant looks in the wrong direction with respect to the task instruction. The wrong direction depends on the task and the instructions given, for example during the prosaccade task a participant would make a direction error if instead of looking at the peripheral target that appeared they looked to the opposite side of the screen from where the target is presented (as you would do during the antisaccade task). A direction error occurs in the antisaccade task when instead of looking to the opposite side of the screen from where the peripheral target is presented a participant looked directly to the target that appeared (as you would do during the prosaccade task). (3) False starts, can occur when a participant makes a saccade to a target during the fixation period, then makes a saccade back to the central FP before performing the task properly. False starts are corrections of

anticipatory errors, in which the participant makes the correction in time to perform the task in response to the target. Anticipatory errors, direction errors and false starts have the potential to demonstrate deficits or difficulties in attention and inhibitory control.

There are additional errors that can occur during the memory-guided saccade task, two in particular. (1) Timing errors, which occur when a participant makes a correct motor sequence to the two targets, but they begin to make their saccades <90ms after the disappearance of the FP. (2) Sequence errors can also occur during the memory-guided saccade task. These errors occur when a participant incorrectly executes the motor sequence of the targets. This is still a sequence error even if the participant timely executes the first saccade to a target. Analysis of these errors might focus directly on deficits in working memory, depicted by errors in motor sequence. Correct trials of both the pro- and antisaccade tasks as well as the memory-guided saccade task are described as trials in which no errors were made by the participant.

3.4.2 Marking Saccades: Automated Analysis.

An automated analysis program was used to mark the eye-tracking data since it has two major advantages, (1) it is consistent and aims to remove the experimenter bias that can occur when researchers hand mark data, and (2) many new eye movement features not previously analyzed were extracted from the data.

Prosaccade and Antisaccade Tasks.

There are a number of steps that the automated analysis followed for each trial completed by a participant, in order to gather information on saccades and saccade features made by participants. First steps of the automated marking process involve cleaning the data up so that it can be marked consistently. These steps employ algorithms which explore blink detection and removal, converting the data from pixels to a visual angle centered on the screen, velocity

calculation, and setting up saccade detection by calculating the speed threshold saccades need to overcome to be classified as a saccade.

After data cleaning, recording of saccadic eye movements are run through the automated analysis process and that is used to calculate saccade features/outcomes. The automated analysis consists of the following seven steps, which work consistently to mark eye movement behaviours and extract quantifiable outcome measures. Each consecutive step works on saccades from the previous step:

- (1) Find saccades that are well behaved (velocity < 1500 °/sec, amplitude $> 0.75^\circ$, and within -600ms to +1250ms of target onset).
- (2) Sort well behaved saccades from step one based on whether they return to fixation or not, count the number of macro saccades in the trial, and investigate whether saccades are in the direction of the target or not. Fixation saccades are defined as those that occur within a 4° rectangular window around the fixation point.
- (3) Look for the main macro saccades in the saccades from step two ($> 3^\circ$ pre-target, $> 2^\circ$ post-target, and $> 0.75^\circ$ steps).
- (4) Of saccades from step three, look at whether the saccades are in the direction of the goal (correct) or the opposite direction of the goal (error), and whether corrective saccades are made after the first saccade.
- (5) Look for false start errors in the trial.
- (6) Look for step saccades in the trial. Step saccades are defined as saccades that increase the accuracy to the goal after the main goal oriented saccade. Step saccades must occur within 400ms after the first goal oriented saccade.
- (7) Mark the onset of all macro saccades, false starts, and step saccades.

Memory-guided Saccade Task.

This task like the pro- and antisaccade tasks cleans up the data up so that it can be marked consistently. The same algorithms are used as in the pro- and antisaccade tasks, which explore blink detection and removal, converting the data from pixels to a visual angle centered on the screen, velocity calculation, and setting up saccade detection by calculating the speed threshold saccades need to overcome to be classified as a saccade.

The automated analysis for the memory-guided task (two target condition) consists of the following eleven steps.

- (1) Find saccades that are well behaved (velocity < 1500 °/sec, amplitude > 0.75°, and within -600ms to +1250ms of target onset).
- (2) Sort well behaved saccades from step one based on whether they return to fixation or not, and count the number of macro saccades in the trial. Fixation saccades are defined as those that occur within an 8° rectangular window around the fixation point.
- (3) For the saccades remaining from step one, calculate the first angle offset (the angle between the ideal target vector and the saccade vector for each target), investigate the direction of each saccade, restrict the angle each saccade is from the ideal target vector, and calculate the change in direction from one saccade to the next.
- (4) Further examine fixation oriented saccades.
- (5) Look for false starts.
- (6) Trials are marked as correct if there are at least two saccades, one preferring target 1 and a second, following the first saccade preferring target 2. There must be at least 20 milliseconds separating the two saccades.
- (7) Look for and mark sequence errors.

- (8) If no criteria in steps 6 or 7 are met, look for STOP errors (a saccade with preferred direction to target 1 is found, the participant stopped at the first target).
- (9) If no criteria in steps 6, 7, or 8 are met, look for SKIP errors (a saccade with preferred direction to target 2, the participant skipped target 1 and went to target 2).
- (10) Mark step saccades. Step saccades occur between the two goal oriented saccades as long as they are oriented towards a target.
- (11) Mark the onset of all macro saccades, error types, false starts, step saccades, and the fixation distance of the first saccade.

3.5 Linear Extreme Learning Machine (ELM) Analysis

The linear-ELM analysis was completed using Matlab (Version R2016a; Mathworks, Inc., Natick, MA). Prior to the data being used to train and test the linear-ELM classification pre-processing was conducted. Pre-processing included performing normalization calculations on all eye movement features from control and FASD groups in both the training and validation cohorts. Normalization was conducted using z-scores for all data (training and validation), producing normalized data with zero mean and unit variance. The z-scores were calculated for each eye movement feature by comparing each individual participant's performance to the average performance of the training cohort control group.

Dimensionality was reduced using principal component analysis (PCA). Principal component analysis aims to extract information from a dataset (eye-tracking features) and represent it as a new set of variables, known as principal components (Abdi & Williams, 2010). Nothing has been done to the data; it has been simplified to allow for a more clear representation of variables necessary to distinguish between FASD and control groups. There can be a number of principal components that are composed of varying weights of original variables (Bro &

Smilde, 2014). Principal component one is the component that contains the features with the greatest distinguishing power, in other words the features in component one best account for the variance between groups in the dataset (Bro & Smilde, 2014). Each consecutive component contains diverse weights of features that are still important for distinguishing but that do not account for as much variance between groups.

Following PCA, mutual information (MI) was used to select important features for distinguishing between FASD and control groups. Mutual information can be thought of as ‘pruning’ the features in a dataset so that only features that are most relevant to the output (classification) are kept and those that are not as relevant, pruned. Mutual information is able to measure subjective relationships between variables or features (Battiti, 1994). By looking at only relevant features, MI has been thought to reduce the uncertainty of one variable by considering its relation to another variable (Battiti, 1994).

The next step was ELM. In order to reduce the complexity of tuning multiple parameters, a linear kernel function, which allows for faster data analysis was used in the ELM. A 10-fold cross validation was used to divide the training dataset appropriately to train the classifier. The eye movement data from the validation cohort was then run through the ELM in order to obtain a value for overall accuracy, sensitivity and specificity of the classifier.

3.6 Statistical Analysis

All statistical analyses were performed using GraphPad Prism (Version 7.02 for Windows, GraphPad Software Inc., www.graphpad.com) and Matlab (Version R20116a; Mathworks, Inc., Natick, MA).

3.6.1 Eye-tracking Task Performance.

Throughout this thesis, unpaired, two-tailed t-tests were performed to compare the eye tracking performance between the training groups (Control and FASD). The value of α has been set to 0.05 for the following analyses and throughout this thesis, unless it has been specified to another value. All features that were shown to vary with age were age corrected using a T-score formula ($50 + 10((\text{individual (Control or FASD) performance} - \text{training Control mean performance}) / \text{standard deviation of training Control performance})$). Both raw eye movement data and T-score values from the training groups were used in the unpaired t-tests. If the variances between the two training groups (Control and FASD) significantly differed from each other, Welch's unequal variances t-test was executed, or a transformation ($Y=1/Y$, $Y=\text{Log}(Y)$, $Y=\text{Ln}(Y)$, $Y=\text{exp}(Y)$) was performed on the data in an attempt to remove the difference in variances between groups prior to performing the parametric statistical analysis.

3.6.2 Machine Learning Model (ELM) Classification.

Training and validation group data (Control and FASD) were used to train and test an extreme learning machine (ELM). The ability of the ELM to classify participants in the validation groups correctly was tested after the model was trained using the labelled training group data. Results provided from this method, include, specificity ($\text{Specificity} = \text{True Negative} / (\text{True Negative} + \text{False Positive})$), sensitivity ($\text{Sensitivity} = \text{True Positive} / (\text{True Positive} + \text{False Negative})$), and overall accuracy ($\text{Acc} = (\text{Correctly identified} + \text{correctly rejected}) / (\text{Total test number}) * 100$) of the classifier to correctly classify participants in the validation groups (Control and FASD).

3.6.3 Important Eye Movement Features.

Two-tailed correlations were conducted between the important features listed from the prosaccade, antisaccade and memory-guided tasks for the validation groups (Control and FASD) to investigate whether the features deemed important were in fact correlated with each other. Correlations were conducted using an α value of 0.05, and 95% confidence interval.

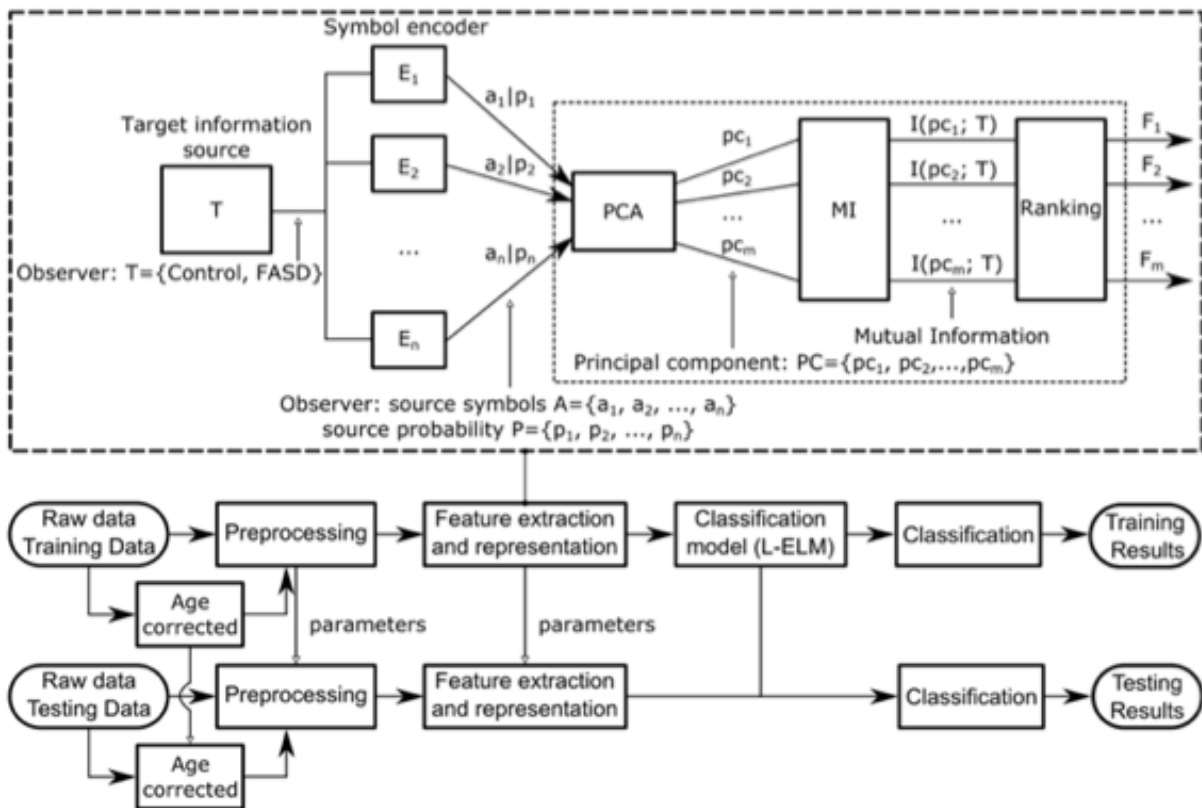


Figure 2. Summary of the computational classification procedure of eye movement behaviour data.

Chapter 4

Results

4.1 Group Differences: Saccade Performance Outcomes within the *Training Cohort*

4.1.1 Demographic Data.

The typically developing control children ($n=105$) had a mean age of 10.78(3.05), while the FASD group ($n=68$) had a mean age of 12.04(3.11). The percent of females to males in the typically developing control group was 51:49, while the percent in the FASD group was 47:53. Participants for both the typically developing control group and the FASD group were collected at multiple sites across Canada as part of a larger study (Paolozza, Munn, Munoz, & Reynolds, 2015), including Kingston, ON, Ottawa, ON, Winnipeg, MN, Edmonton, AB, and Cold Lake, AB.

4.1.2 Task Performance.

As has previously been shown, in this study it was again demonstrated that differences exist in eye-tracking performance between typically developing control children and children with FASD who were included in the training cohort for the current classification (Green et al., 2009; Green et al., 2007; Paolozza et al., 2013; Paolozza et al., 2014a,b). All data from the training cohort were subject to a new automated marking analysis, which produced new outcome measures that were not previously available.

Prosaccade Task.

Eye movement behaviour collected from the prosaccade eye-tracking task was used to investigate group differences between the typically developing control group and the group with an FASD diagnosis; both groups were part of the training cohort in this study. Selected group differences are shown in Figure 3 (as T-scores), and the full list of all eye-tracking performance

outcomes that significantly differed between participants in the training, control and FASD groups are reported in Table 3. Of the five features shown, groups only significantly differed from each other on one, endpoint error. Children in with an FASD diagnosis ($M = 56.63$, $SD = 18.05$) had a significantly greater endpoint error in the prosaccade task, compared to typically developing control children ($M = 50.01$, $SD = 10.04$), ($t(171) = 3.05$, $p = .003$, $d = 0.46$).

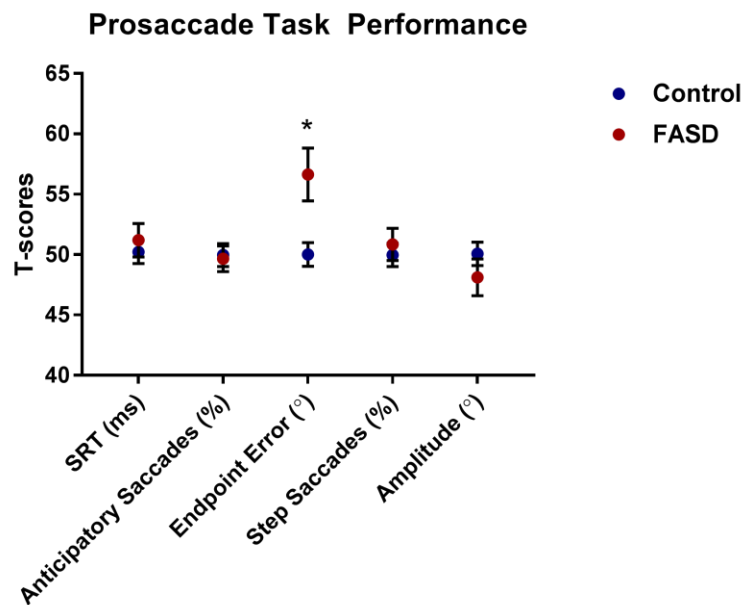


Figure 3. Training cohort eye-tracking performance on the prosaccade task (T-scores). Standardized T-score values have a mean of 50 and a standard deviation of 10. Participants with an FASD diagnosis (red circles) made less accurate saccades towards the peripheral target compared to typically developing control participants (blue circles) ($p = .003$). Error bars represent standard error.

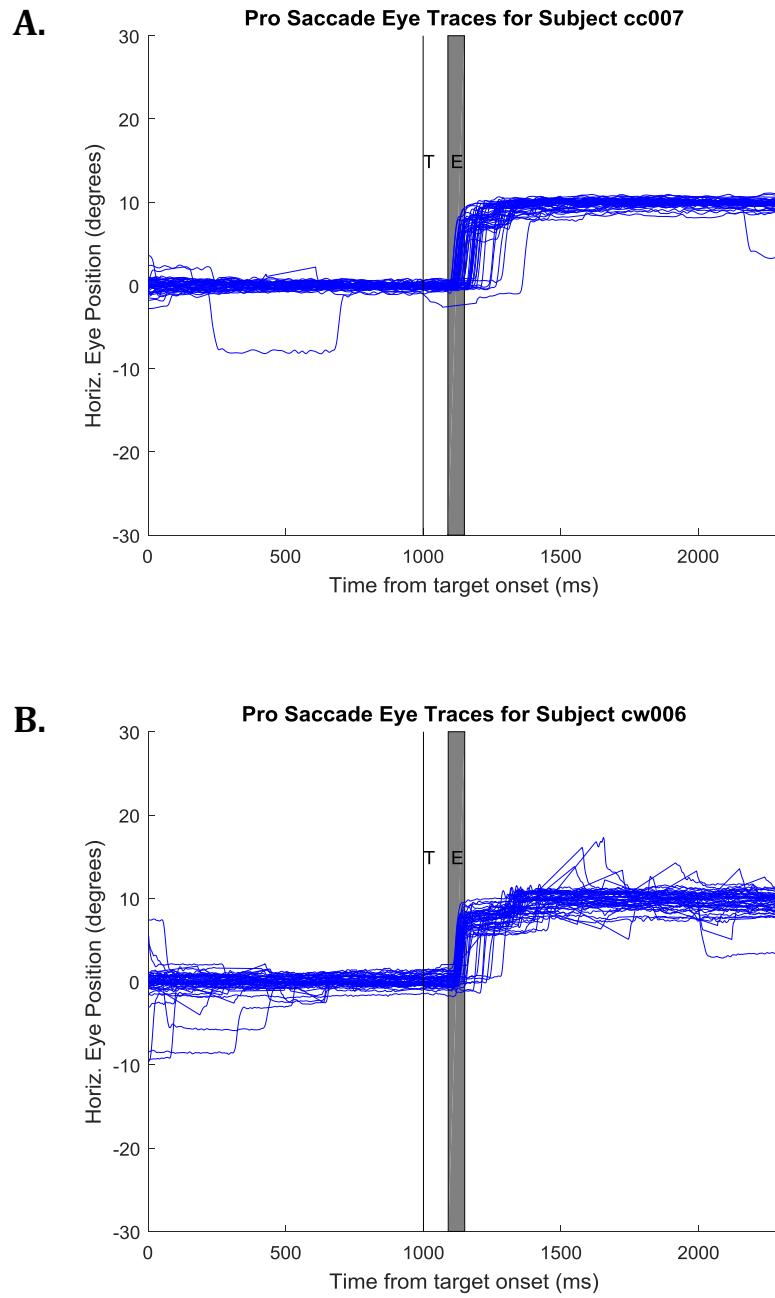


Figure 4. (A) Prosaccade eye-traces of a control participant, (B) Prosaccade eye-traces of an FASD participant.

Antisaccade Task.

Eye movement behaviour collected from the antisaccade eye-tracking task was used to examine group differences between the typically developing control group and the group with an FASD diagnosis. Selected group differences are shown in Figure 5 and the full list of all eye-tracking performance outcomes that significantly differed between participants in both the control and FASD groups are reported in Table 4. Of the five features shown, groups differed from each other on four, SRT, Anticipatory Errors, Direction Errors, and Percent of Step Saccades. Children with an FASD diagnosis had a significantly greater SRT ($M = 57.04$, $SD = 16.58$), and made more Anticipatory Errors ($M = 55.06$, $SD = 15.03$), and Direction Errors ($M = 53.8$, $SD = 10.47$) in the antisaccade task, compared to typically developing control children ($M_{SRT} = 50.17$, $SD_{SRT} = 9.532$), ($t(94) = 3.079$, $p = .003$, $d = 0.51$), ($M_{AE} = 50.13$, $SD_{AE} = 10.06$), ($t(105) = 2.377$, $p = .019$, $d = 0.39$), ($M_{DE} = 50.17$, $SD_{DE} = 9.878$) ($t(171) = 2.306$, $p = .022$, $d = 0.36$). Whereas children with an FASD diagnosis were less likely to make step saccades in trials ($M = 45.55$, $SD = 7.92$) compared to the typically developing controls ($M = 50.04$, $SD = 10.14$), $t(171) = 3.086$, $p = .002$, $d = 0.48$)

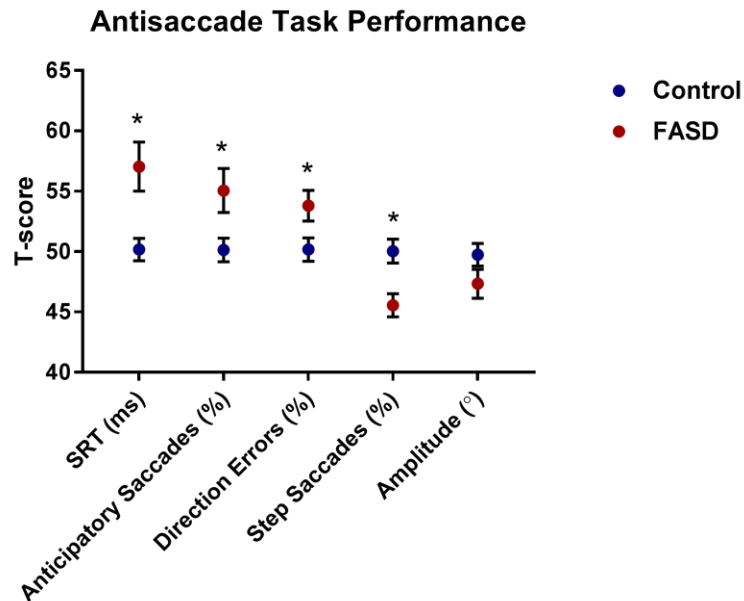


Figure 5. Training cohort eye-tracking performance on the antisaccade task (T-scores). Standardized T-score values have a mean of 50 and a standard deviation of 10. Participants with an FASD diagnosis (red circles) had greater SRT's ($p = .012$), more anticipatory errors ($p = .019$), and more direction errors than control participants ($p = .022$) (blue circles) but made step saccades in less trials than typically developing controls ($p = .002$). Error bars represent standard error.

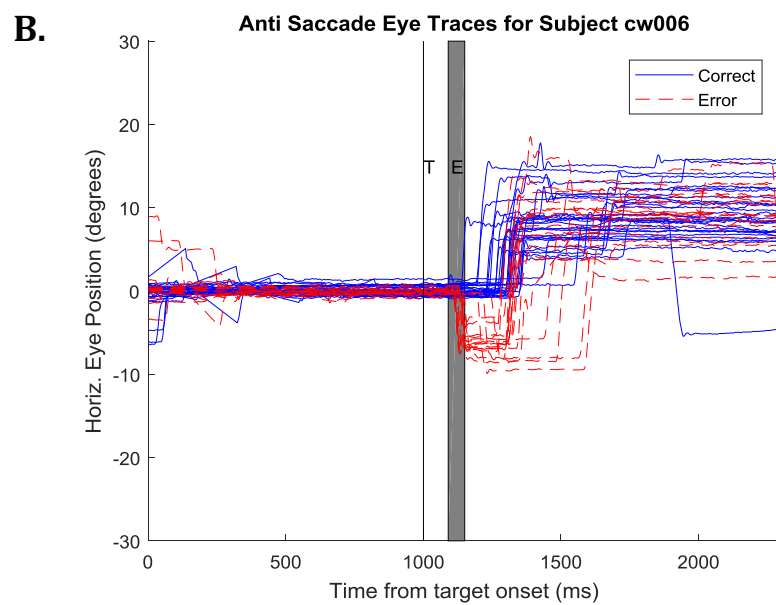
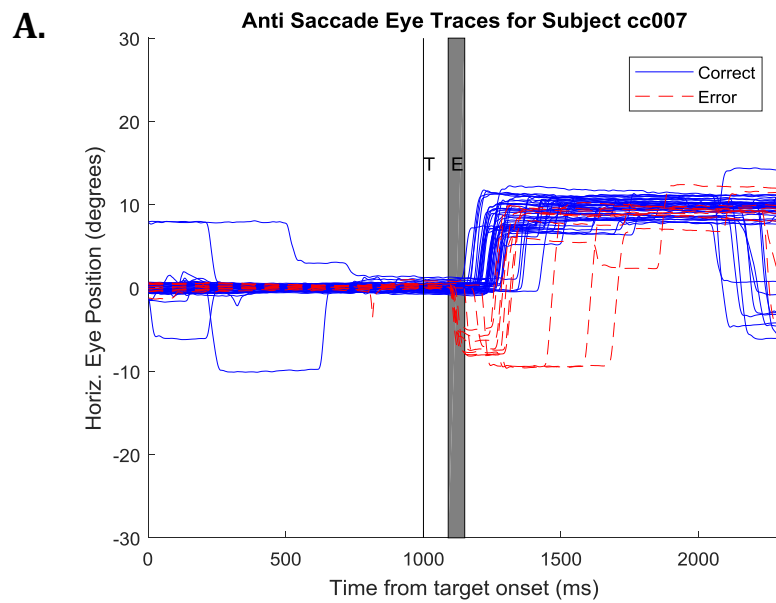


Figure 6. (A) Antisaccade eye-traces of a control participant, (B) Antisaccade eye-traces of an FASD participant.

Memory-guided Saccade Task.

Eye movement behaviour collected from the 2-target memory-guided eye-tracking task was used to investigate group differences between the typically developing control group and the group with an FASD diagnosis. Selected group differences are shown in Figure 7, and the full list of eye-tracking performance outcomes that differed significantly between both the control and FASD groups are reported in Table 5. Of the five features shown, groups differed from each other on three, Sequence Errors that include other errors (ALL), Overall Accuracy, and Path Length Accuracy. Children with an FASD diagnosis made a significantly greater percent of sequence errors (ALL) ($M = 55.98$, $SD = 9.773$), were a greater number of degrees from the target after completing their final saccade ($M = 59.72$, $SD = 18.36$) and from the optimal saccade path ($M = 55.8$, $SD = 16.68$) in the memory-guided task, compared to typically developing control children ($M_{SEQ} = 49.93$, $SD_{SEQ} = 9.811$), ($t(152) = 3.769$, $p = <.001$, $d = .62$), ($M_{OA} = 50.06$, $SD_{OA} = 9.7$), ($t(86) = 3.821$, $p = <.001$, $d = .66$), ($M_{PL} = 49.82$, $SD_{PL} = 9.603$) ($t(90) = 2.563$, $p = .012$, $d = .44$).

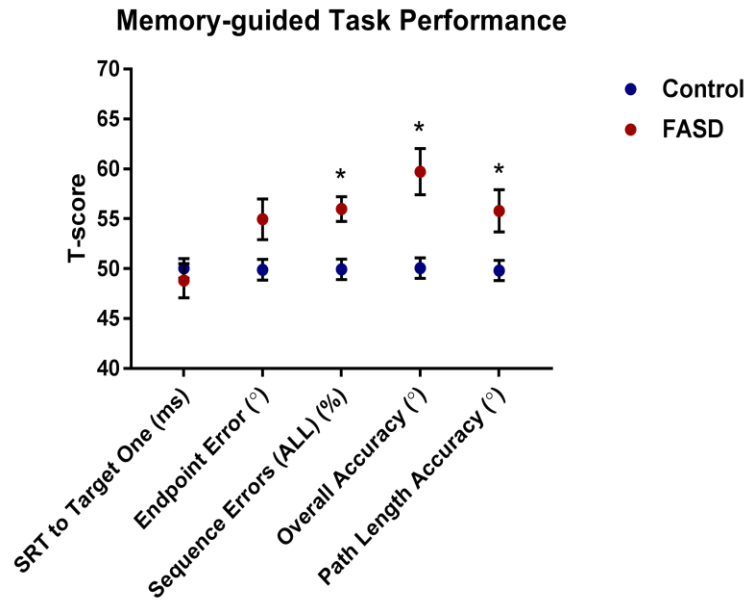


Figure 7. Training cohort eye-tracking performance on the 2-target memory-guided saccade task (T-scores). Standardized T-score values have a mean of 50 and a standard deviation of 10. Participants with an FASD diagnosis (red circles) made a significantly greater percent of sequence errors (ALL) ($p < .001$), and were a greater number of degrees from the target after completing their final saccade ($p < .001$), and from the optimal saccade path ($p = .017$) compared to typically developing control children (blue circles). Error bars represent standard error.

4.2 Eye Tracking as a Screening Tool: Classification of Eye Movement Behaviours in Validation Cohort

4.2.1 Demographic Data.

The typically developing control children group ($n=25$) had a mean age of 12.8(1.8), and the FASD group ($n=32$) had a mean age of 11.5(2.2). The percent of females to males for the typically developing control group was 56:44, compared to 41:59 for the FASD group. Two additional participants from the FASD group were removed before any analysis was conducted due to lack of eye-tracking data, and one additional control participant was removed before any analysis was conducted due to incompleteness of the participant information forms. Participants for both the control and FASD groups were collected in Vancouver, British Columbia through the Women's and Children's Hospital of British Columbia. Additional control participants were recruited and tested in Kingston, Ontario.

4.2.2 Linear-ELM Classification.

An extreme learning machine (ELM) that used a linear kernel function was used to classify eye-tracking data from the validation cohort. After performing a 10-fold cross validation on the *training* cohort, the *validation* cohort's eye-tracking data was put into the ELM. The overall accuracy, sensitivity, and specificity of the ELM's classification of the validation cohort were calculated. The accuracy of the linear-ELM was 79%, the average sensitivity was 72%, and the average specificity was 88%. Results from the test done on the validation data can be found in Figure 8. Two participants that have confirmed PAE, but currently do not have an FASD diagnosis were included in the validation cohort (but are not included in accuracy, sensitivity, and specificity results stated above). One of these participants despite lacking a confirmed FASD diagnosis was correctly classified into the FASD group. This further demonstrates the ability of

eye-tracking to help identify brain dysfunction due to PAE and further supports the idea that eye-tracking can be used as a screening tool for FASD.

| | | | |
|----------------|---------|---|---|
| TrueLabel | FASD | <p>?</p> <p>?</p> <p>9</p> <p>?</p> <p>?</p> | <p>?</p> <p>?</p> <p>23</p> <p>?</p> <p>?</p> |
| | Control | <p>?</p> <p>?</p> <p>22</p> <p>?</p> <p>?</p> | <p>?</p> <p>?</p> <p>3</p> <p>?</p> <p>?</p> |
| | | Control | FASD |
| PredictedLabel | | | |

Figure 8. ELM classification results of the validation cohort. The true label of participants is compared to their predicted label given by the ELM. Twenty-three participants with FASD were correctly classified into the FASD group (true positives) (dark red box); nine participants with an FASD diagnosis were incorrectly classified (false negatives) (light red box). Twenty-two typically developing control participants were correctly classified into the control group (true negatives) (dark blue box); three control participants were misclassified (false positives) (light blue box). This test provided a sensitivity of 72%, a specificity of 88%, and an overall accuracy of 79%.

4.2.3 Distinguishing Eye-tracking Features.

Mutual information was used to identify which eye-tracking features were most relevant for the classification of the validation cohort, control and FASD groups. Features that were shown to significantly differ between the training control and FASD groups for each task are listed in Tables 3, 4, and 5 according to their effect size. Of the features listed for each task, those that belong to principal component 12, 16, and 32 are highlighted (green, blue, and red respectively). All of the relevant features for each specific component can be found in Tables 6, 7, and 8, organized by weight or contribution to the component.

Table 3. Eye movement features (outcomes) from the prosaccade task that are significantly different between training Control and FASD participant groups, organized by effect size. Features that are part of component 12, the first of the final components with the most distinguishing power are highlighted in green.

| Prosaccade Task | | | | |
|--|--|---|-----------------------|-------------------------------|
| Eye Movement Feature | Control ($\bar{x} \pm \text{SEM}$) | FASD ($\bar{x} \pm \text{SEM}$) | <i>p</i>-value | Effect Size (<i>d</i>) |
| Second skew slope of correct saccades | 10148.51 \pm 175.35 | 9301.24 \pm 234.66 | 0 | 0.45 |
| Velocity of Saccades | 323.19 \pm 3.81 | 305.85 \pm 4.97 | 0.01 | 0.43 |
| First skew slope of correct saccades | 12762.45 \pm 222.26 | 11868.3 \pm 255.07 | 0.01 | 0.41 |
| Endpoint Error | 3.12 \pm 0.16 | 3.87 \pm 0.24 | 0.01 | 0.41 |
| Maximum acceleration of correct saccades | 22239.65 \pm 370.5 | 20779.1 \pm 434.29 | 0.01 | 0.40 |
| Duration of correct saccades | 55.26 \pm 0.4 | 56.97 \pm 0.65 | 0.03 | 0.36 |
| Initial Trajectory | 6.49 \pm 0.29 | 7.74 \pm 0.49 | 0.03 | 0.35 |
| Minimum acceleration of correct saccades | -18207.37 \pm 297.99 | -17148.8 \pm 388.68 | 0.03 | 0.34 |

Table 4. Eye movement features (outcomes) from the antisaccade task that are significantly different between training Control and FASD participant groups, organized by effect size. Features that are part of component 12, the first of the final components with the most distinguishing power are highlighted in green. Features that are part of component 16, the second of the final components with the most distinguishing power are highlighted in blue. Features that are part of component 32, the third of the final components with the most distinguishing power are highlighted in red.

| Antisaccade Task | | | | |
|--|--|---|----------------|------------------------|
| Eye Movement Feature | Control ($\bar{x} \pm \text{SEM}$) | FASD ($\bar{x} \pm \text{SEM}$) | p-value | Effect Size (d) |
| Percent of Corrective Saccades T-score | 49.98 ± 0.91 | 35.91 ± 2.9 | 0 | 0.77 |
| Number of Correct Trials T-score | 49.83 ± 0.93 | 43.81 ± 1.29 | 0 | 0.60 |
| Average degree of drift in the x dimension during fixation | 0.83 ± 0.04 | 1.3 ± 0.13 | 0 | 0.58 |
| Number of correct regular saccades T-score | 49.84 ± 0.93 | 44.38 ± 1.22 | 0 | 0.56 |
| Percent of Corrective Saccades | 89.96 ± 1.23 | 80.87 ± 2.54 | 0 | 0.53 |
| Velocity of saccades | 332.06 ± 6.35 | 300.96 ± 6.83 | 0 | 0.51 |
| SRT T-score | 50.17 ± 0.93 | 57.04 ± 2.01 | 0 | 0.51 |
| SRT of correct regular saccades T-score | 50.17 ± 0.93 | 58.44 ± 2.59 | 0 | 0.50 |
| Number of No Fixation or Target Trials | 1.81 ± 0.26 | 4.74 ± 0.98 | 0.01 | 0.49 |
| First skew slope of correct saccades | 12866.61 ± 293.27 | 11570.22 ± 301 | 0 | 0.47 |
| SRT of corrective saccades T-score | 50.23 ± 0.93 | 55.71 ± 1.68 | 0.01 | 0.46 |
| Number of Viable Trials | 57.05 ± 0.48 | 53.41 ± 1.21 | 0.01 | 0.46 |
| Number of trials with step saccades • | 11.3 ± 0.74 | 8.21 ± 0.73 | 0 | 0.45 |
| Percent of Blinks per Trial | 2.18 ± 0.21 | 3.67 ± 0.5 | 0.01 | 0.45 |
| Number of Macrosaccades per Trial | 4.81 ± 0.12 | 5.66 ± 0.32 | 0.02 | 0.41 |
| Amplitude of Saccades | 11.22 ± 0.27 | 10.25 ± 0.28 | 0.02 | 0.38 |
| Percent of Anticipation Error Saccades | 11.07 ± 0.98 | 15.61 ± 1.66 | 0.02 | 0.38 |
| Number of Step Saccades per Trial • | 0.21 ± 0.01 | 0.16 ± 0.01 | 0.02 | 0.37 |
| Percent of Trials with Step Saccades • | 19.55 ± 1.22 | 15.36 ± 1.32 | 0.02 | 0.36 |
| Percent of Direction Errors T-score | 50.17 ± 0.96 | 53.8 ± 1.27 | 0.02 | 0.36 |
| Maximum acceleration of correct saccades | 22821.75 ± 503.86 | 21069.56 ± 607.38 | 0.03 | 0.34 |
| SRT of Correct Regular Saccades | 283.18 ± 7.06 | 314.65 ± 13.92 | 0.05 | 0.33 |
| Initial Trajectory ♦♦ | 7.2 ± 0.36 | 9.05 ± 0.84 | 0.05 | 0.33 |

- Feature is also found in component 16
- ♦ Feature is also found in component 32

Table 5. Eye movement features (outcomes) from the memory-guided saccade task that are significantly different between training Control and FASD participant groups, organized by effect size. Features that are part of component 16, the second of the final components with the most distinguishing power are highlighted in blue. Features that are part of component 32, the third of the final components with the most distinguishing power are highlighted in red.

| Memory-guided (2-target) Task | | | | |
|--|---|--|---------------------|----------------------------|
| Eye Movement Feature | Control ($\bar{x} \pm$ SEM) | FASD ($\bar{x} \pm$ SEM) | p- value | Effect Size (d) |
| Target 2 Closest Saccade Accuracy T-scores | 50.04 \pm 1.01 | 60.11 \pm 2.29 | 0 | 0.69 |
| Overall Accuracy of the last Saccade T-score | 50.06 \pm 1.02 | 59.72 \pm 2.31 | 0 | 0.66 |
| Percent of 2 Target Sequence Errors that contain other errors (ALL) T-scores | 49.93 \pm 1.03 | 55.98 \pm 1.23 | 0 | 0.62 |
| Number of Correct Trials T-score | 50 \pm 1.02 | 44.63 \pm 1.04 | 0 | 0.59 |
| Number of 2 Target Sequence Errors that contain other errors (ALL) T-scores | 49.96 \pm 1.03 | 55.55 \pm 1.2 | 0 | 0.58 |
| Average degree of drift in the x dimension during fixation T-score | 50.12 \pm 1.01 | 57.69 \pm 2.29 | 0 | 0.52 |
| Percent of Blinks per Trial | 1.96 \pm 0.22 | 3.38 \pm 0.42 | 0 | 0.51 |
| Target 2 First Saccade Accuracy T-scores | 49.97 \pm 1 | 56.33 \pm 1.92 | 0 | 0.50 |
| Coefficient of Variation (CV) (in reaction time) of Target 1 | 33.76 \pm 1.11 | 39.48 \pm 1.67 | 0.01 | 0.48 |
| Fixation Distance | 1.37 \pm 0.06 | 1.77 \pm 0.13 | 0.01 | 0.48 |
| Overall Accuracy of the last Saccade | 4.11 \pm 0.21 | 5.35 \pm 0.39 | 0.01 | 0.48 |
| Percent of False Start Errors that contain other errors (ALL) | 8.47 \pm 0.69 | 11.87 \pm 1 | 0.01 | 0.47 |
| Average degree of drift in the y dimension during fixation T-score | 50.01 \pm 1.03 | 56.7 \pm 2.21 | 0.01 | 0.47 |
| Number of False Start Errors that contain other errors (ALL) | 5.98 \pm 0.48 | 8.27 \pm 0.7 | 0.01 | 0.45 |
| Target 1 Closest Saccade Accuracy T-scores | 49.87 \pm 1.05 | 56.43 \pm 2.25 | 0.01 | 0.45 |
| Path Length Accuracy of all Saccades T-scores | 49.82 \pm 1.01 | 55.8 \pm 2.1 | 0.01 | 0.44 |
| Target 2 Closest Saccade Accuracy | 3.72 \pm 0.19 | 4.56 \pm 0.28 | 0.01 | 0.42 |
| Target 1 standard deviation in reaction time T-score | 50.16 \pm 0.99 | 55.19 \pm 1.77 | 0.02 | 0.42 |
| Percent of timing errors that contain other errors (ALL) T-score | 50.08 \pm 1.02 | 55.11 \pm 1.79 | 0.02 | 0.41 |
| Number of timing errors that contain other errors (ALL) T-score | 50.09 \pm 1.02 | 54.55 \pm 1.64 | 0.02 | 0.39 |
| Number of Macrosaccades per Trial | 5.57 \pm 0.12 | 6.13 \pm 0.21 | 0.02 | 0.39 |
| Percent of 2 Target Sequence Errors that contain other errors (ALL) | 26.02 \pm 1.54 | 31.52 \pm 1.77 | 0.02 | 0.38 |
| Endpoint Error T-scores | 49.9 \pm 1.04 | 54.96 \pm 2.04 | 0.03 | 0.38 |
| Target 1 skew slope 1 for correct saccade | 9572.46 \pm 247.41 | 8744.49 \pm 259.02 | 0.02 | 0.37 |
| Duration of Saccade to Target 2 | 85.95 \pm 2.04 | 93.78 \pm 2.94 | 0.03 | 0.36 |
| Number of 2 Target Sequence Errors that contain other errors (ALL) | 18.41 \pm 1.09 | 21.89 \pm 1.21 | 0.03 | 0.35 |
| Number of Correct Trials | 30.95 \pm 1.86 | 25.38 \pm 1.99 | 0.04 | 0.33 |

Table 6. Eye movement features from all three eye-tracking tasks that contribute to component 12. Features are organized based on how much they contribute to component 12 (weight). Features highlighted in dark green contribute greater than or equal to 0.15 and features that contribute between 0.1 and 0.14 are highlighted in light green.

| Component 12 | |
|--|---------------|
| Eye Movement Feature | Weight |
| Anti_Normalized Skew Index | 0.21 |
| Pro_Average degree of drift in the y dimension during fixation | 0.18 |
| Pro_Fixation Distance | 0.17 |
| Mem_Minimum Acceleration of Saccade to Target 1 | 0.15 |
| Anti_First skew slope of correct saccades | 0.15 |
| Anti_The absolute x position of the first correct saccade | 0.15 |
| Anti_Fixation Distance | 0.14 |
| Pro_Saccade Threshold | 0.13 |
| Anti_Number of Correct Trials T-score | 0.13 |
| Anti_Number of Correct Regular Saccades | 0.12 |
| Pro_SRT of Correct Regular Saccades | 0.12 |
| Anti_Number of Trials with Step Saccades | 0.12 |
| Mem_Target 1 skew index | 0.12 |
| Anti_Amplitude of Saccades | 0.12 |
| Anti_Number of Step Saccades per Trial | 0.12 |
| Pro_Normalized Skew Index | 0.12 |
| Pro_Coefficient of Variation (CV) (in reaction time) | 0.12 |
| Anti_Percent of Trials with Step Saccades | 0.11 |
| Mem_Minimum Acceleration of Saccade to Target 2 | 0.11 |
| Pro_First skew slope of correct saccades | 0.11 |
| Anti_Velocity of Saccades | 0.11 |
| Mem_Number of 2 Target Sequence Errors Only | 0.1 |
| Pro_SRT of Corrective Saccades | 0.1 |
| Mem_Percent of 2 Target Sequence Errors Only | 0.1 |
| Anti_Number of Direction Errors T-score | -0.1 |
| Anti_Percent of Direction Errors T-score | -0.11 |
| Mem_Target 1 Duration | -0.11 |
| Anti_SRT | -0.11 |
| Anti_Standard Deviation (in reaction time) | -0.11 |
| Anti_Initial Trajectory | -0.11 |
| Mem_Target 1 Velocity | -0.11 |
| Anti_Number of Corrective Saccades T-score | -0.11 |
| Anti_SRT of Corrective Saccades T-score | -0.12 |
| Mem_Target 2 Duration | -0.12 |
| Amplitude of Saccades | -0.13 |
| Pro_The absolute x position of the first correct saccade | -0.14 |
| Anti_SRT of Correct Regular Saccades | -0.14 |
| Anti_Number of Direction Errors that were Regular Saccades T-score | -0.14 |
| Anti_SRT T-score | -0.14 |
| Pro_Duration of Saccades | -0.16 |
| Anti_SRT of Correct Regular Saccades T-score | -0.17 |

Table 7. Eye movement features from all three eye-tracking tasks that contribute to component 16. Features are organized based on how much they contribute to component 16 (weight). Features highlighted in dark green contribute greater than or equal to 0.15 and features that contribute between 0.1 and 0.14 are highlighted in light green.

| Component 16 | |
|---|---------------|
| Eye Movement Feature | Weight |
| Anti_Percent of Blinks per Trial | 0.26 |
| Anti_SRT of Direction Errors T-score | 0.19 |
| Anti_SRT of Direction Errors that were Regular Saccades | 0.19 |
| Pro_Percent of Blinks per Trial | 0.17 |
| Anti_SRT of Direction Errors | 0.15 |
| Mem_Percent of Blinks per Trial | 0.14 |
| Mem_Target 2 Saccadic Reaction Time (SRT) T-score | 0.14 |
| Anti_Average degree of drift in the x dimension during fixation | 0.13 |
| Pro_Average degree of drift in the y dimension during fixation | 0.12 |
| Mem_Target 1 Saccadic Reaction Time (SRT) T-score | 0.11 |
| Anti_Percent of Direction Errors | -0.1 |
| Pro_SRT | -0.11 |
| Anti_Number of Direction Errors that were Regular Saccades | -0.11 |
| Mem_Target 2 skew index | -0.11 |
| Anti_Number of Corrective Saccades | -0.12 |
| Pro_Coefficient of Variation (CV) (in reaction time) T-score | -0.12 |
| Mem_Amplitude of Saccade to Target 1 | -0.13 |
| Anti_Number of Direction Errors | -0.13 |
| Anti_Number of Viable Trials | -0.13 |
| Anti_Percent of Corrective Saccades T-score | -0.13 |
| Pro_Standard Deviation (in reaction time) T-score | -0.14 |
| Mem_Path Length Accuracy of all Saccades | -0.14 |
| Pro_Coefficient of Variation (CV) (in reaction time) | -0.15 |
| Pro_Standard Deviation (in reaction time) | -0.16 |
| Anti_Initial Trajectory | -0.19 |
| Anti_Percent of Trials with Step Saccades | -0.21 |
| Anti_Number of Step Saccades per Trial | -0.21 |
| Anti_Number of Trials with Step Saccades | -0.22 |

Table 8. Eye movement features from all three eye-tracking tasks that contribute to component 32. Features are organized based on how much they contribute to component 32 (weight). Features highlighted in dark green contribute greater than or equal to 0.15 and features that contribute between 0.1 and 0.14 are highlighted in light green.

| Component 32 | |
|--|---------------|
| Eye Movement Feature | Weight |
| Mem_Target 1 skew index | 0.28 |
| Anti_Percent of Correct Regular Saccades | 0.2 |
| Pro_Average degree of drift in the y dimension during fixation | 0.2 |
| Mem_Target 1 First Saccade Accuracy T-scores | 0.15 |
| Pro_Number of Macrosaccades per Trial | 0.14 |
| Mem_Maximum Acceleration of Saccade to Target 1 | 0.13 |
| Pro_Percent of Correct Regular Saccades | 0.13 |
| Mem_Target 1 Closest Saccade Accuracy T-scores | 0.12 |
| Pro_Number of Correct Regular Saccades | 0.11 |
| Anti_The absolute x position of the first correct saccade | 0.11 |
| Mem_Minimum Acceleration of Saccade to Target 2 | 0.11 |
| Anti_Number of Direction Errors that were Express Saccades | 0.1 |
| Anti_Percent of Direction Errors that were Regular Saccades | 0.1 |
| Anti_Number of Macrosaccades per Trial | 0.1 |
| Anti_SRT of Direction Errors that were Regular Saccades | 0.1 |
| Anti_SRT of Corrective Saccades T-score | 0.1 |
| Anti_Number of Direction Errors that were Regular Saccades | -0.1 |
| Anti_The absolute y position of the first correct saccade | -0.11 |
| Anti_Fixation Distance | -0.11 |
| Pro_The absolute y position of the first correct saccade | -0.12 |
| Pro_Percent of all viable trials that are Express Saccades | -0.12 |
| Pro_Percent of Correct Express Saccades | -0.13 |
| Anti_Number of Direction Errors that were Regular Saccades | -0.13 |
| Pro_Average degree of drift in the x dimension during fixation | -0.15 |
| Anti_Initial Trajectory | -0.15 |
| Pro_Normalized Skew Index | -0.16 |
| Mem_Percent of Skip Errors including other errors | -0.16 |
| Pro_Number of Correct Express Saccades | -0.16 |
| Pro_SRT of Corrective Saccades | -0.17 |
| Anti_Normalized Skew Index | -0.19 |
| Pro_Average degree of drift in the x dimension during fixation | -0.2 |

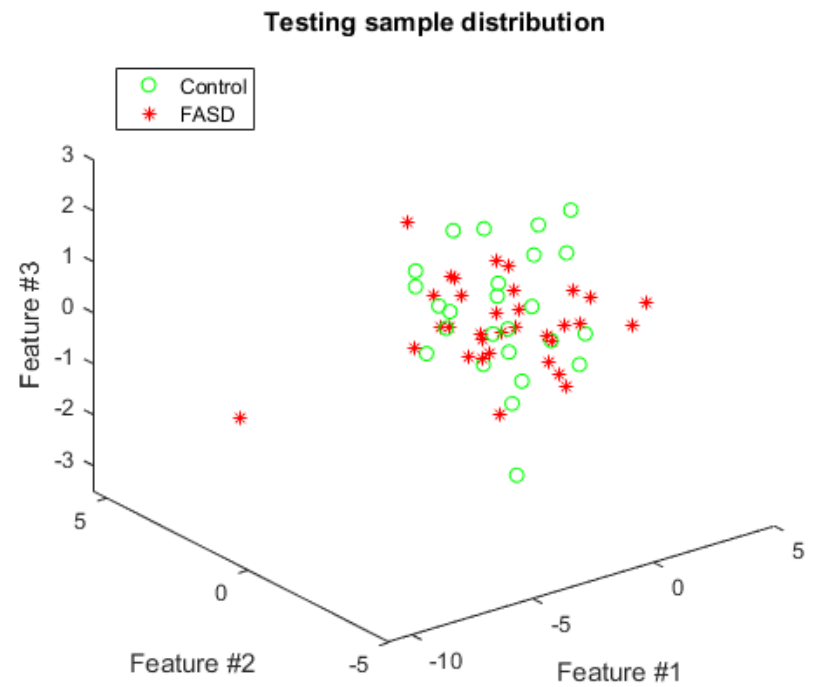
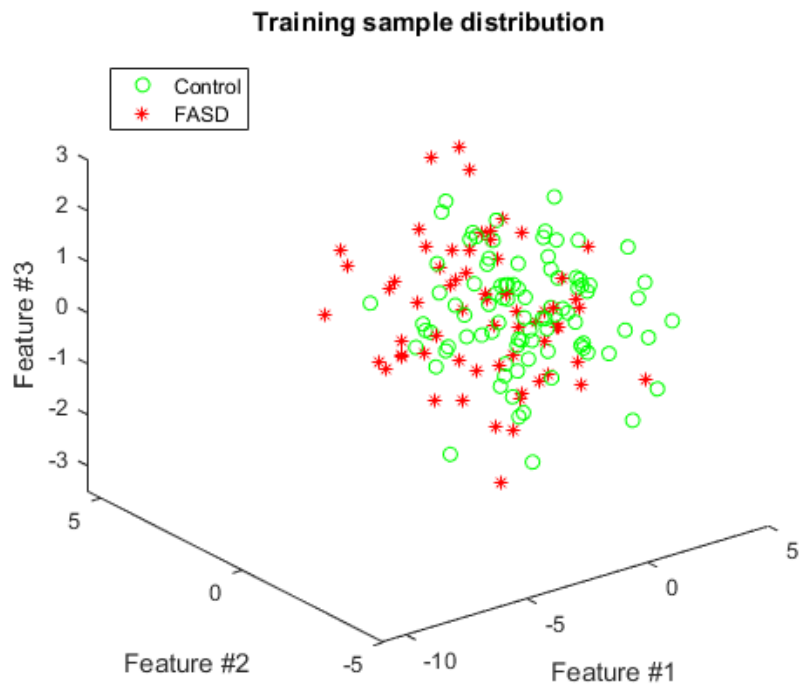


Figure 9. Visual representation of the distribution of training and testing (Validation) data using components 12 (Feature #1), 16 (Feature #2), and 32 (Feature #3).

Chapter 5

Discussion

5.1 Group Differences: Saccade Performance Outcomes within the Training Cohort

The current study set out to investigate the potential for eye-tracking technology to be used as a sensitive and specific screening tool for FASD. Participants completed three eye-tracking tasks, prosaccade, antisaccade, and the memory-guided saccade, 2-target condition, which were run using the Eyelink 1000. These tasks gather information on a number of eye movement features, which were used as input for a linear-ELM classifier that was subsequently used to classify both the typically developing control group and the FASD group from the *validation* cohort. Prior to the linear-ELM being tested on the validation cohort, it was trained using participant data from our *training* cohort. Through investigating the potential of eye-tracking to be developed into a screening tool for FASD, prospective functional biomarkers of FASD may also be identified.

There is a need for a screening tool for FASD that takes into consideration, both the behavioural characteristics of PAE and the neurodevelopmental profile (Lange, Rovet, Rehm, & Popova, 2017). Measuring eye movement behaviours with various eye-tracking tasks has the potential to be a screening tool that can account for both the behavioural characteristics of FASD, through eye movement behaviours, and the neurodevelopmental profile, again through differences in distinguishing eye movement features between the typically developing control group and the FASD group. A neurodevelopmental profile of FASD has recently been described as the outward expression of damage to the central nervous system, due to PAE. This includes outward

expressions that fall under behavioural and developmental categories (defined in Lange et al., 2017). Eye movements can inform us of the profile of FASD because there is overlap in the brain structures that are affected by PAE and those involved in the production of saccadic eye movements, such as the DLPFC, FEF, and basal ganglia. Lesions in these areas have been shown to cause a range of deficits in eye-tracking performance; such as, increases in the number of direction errors, prolonged reaction times, and difficulty with response inhibition, respectively (Munoz & Everling, 2004; Pierrot-Deseilligny et al., 2002). Therefore, eye movements may inform us about the FASD neurodevelopmental profile, since they are able to show outward behavioural and developmental expressions, that may be caused by internal damage from prenatal alcohol exposure.

5.1.1 Task Performance: Eye Movement Features.

One purpose of the training cohort, which was collected previously, was to identify differences between the typically developing control group and the FASD group performance on the eye-tracking tasks. As has been shown previously, the eye-tracker revealed performance differences between the two groups on a number of different eye-tracking features (Green et al., 2009; Green et al., 2007; Paolozza et al., 2013). Children in the FASD group differed from the control group on multiple eye-tracking features. For example, children with FASD tended to 1) make more errors in both the antisaccade and memory-guided tasks (direction, sequence), and 2) be less accurate when initiating and ending a saccade towards a visual target compared to the control group. Although, significant differences were found between groups on the features mentioned above, there were also several eye-tracking features that did not differ between the control and FASD groups (Figures 3, 4, 5).

The importance of identifying eye-tracking features that differ between the two groups is that it provides features that the linear-ELM classifier can potentially use to help train itself. That is, there are features that may be more distinguishing between the two groups, which can help the classifier recognize which group a participant from the validation cohort belongs to. The features that are distinguishing between children in the control and FASD groups, and those which are not different between the groups are important for another reason; they help to demonstrate that although children with FASD do have deficits due to PAE, they also have strengths. In a recent review, it was mentioned that neurodevelopmental assessments and standardized tests can fail to acknowledge the strengths of individuals with FASD, often focussing mainly on their weaknesses (Greenbaum, Nulman, Rovet, & Koren, 2002; Mattson et al., 2011; reviewed in Lange et al., 2017). Some of the features between the control and FASD groups did not significantly differ from each other. This demonstrates that children with FASD are able to succeed and perform well in different aspects of executive functioning tasks and can learn to improve their own lives by utilizing their strengths and not focussing on any apparent weaknesses they may have. In attempting to identify which features are able to distinguish between control and FASD groups it is important to have a reliable and consistent method, which can accurately extract features from the eye-tracking data.

5.2 Validation Classification: Linear-ELM.

Classification of the validation cohort was done using a linear-ELM, this method of classification was chosen because the use of a linear kernel function can allow for a more innate interpretation of large dataset like the one in the current study (Kim, Liu, Yeganova, & Wilbur, 2015). Results of the current classification demonstrate the ability

of eye-tracking to be used as a sensitive and specific screening tool for FASD, since the sensitivity was fairly high (72%), the specificity was high (88%) and the overall accuracy of the classification was also high (79%). Nine children from the validation FASD group ($n=32$) were incorrectly classified by the ELM. An investigation into these nine participants' performance on two of the features that made significant contributions to component 12 was conducted. It was hypothesized that if these children performed similar to control participants on these two features (within the range of control performance) they could have been incorrectly classified. Since principal component 12 was recognized as the component with the most distinguishing power between control and FASD participant groups, if children in the FASD group performed similar to children in the control group on those features that contribute significantly to the principal component, they could be incorrectly classified as belonging to the control group rather than being classified correctly in the FASD group. Two unpaired t-tests were conducted between the performance of the incorrectly classified children from the FASD group and the children in the control group, one on the percent of corrective saccades T-score and the other on the saccadic reaction time T-score in the antisaccade task. Results demonstrate that there is no significant difference in eye tracking performance on both percent of corrective saccades made and saccadic reaction between the incorrectly classified children from the FASD group ($M_{COR} = 50$, $SD_{COR} = 5.9$), ($M_{SRT} = 53.2$, $SD_{SRT} = 11.8$), and children in the control group ($M_{COR} = 50.6$, $SD_{COR} = 6.97$), ($M_{SRT} = 54.3$, $SD_{SRT} = 14.5$), ($t_{COR}(29) = 0.215$, $p = 0.83$), ($t_{SRT}(32) = 0.204$, $p = 0.84$),

Other classification methods (behavioural observations, ratings, standardized test batteries) have been used to classify binomial data and have tended to find varying results

for sensitivity (ranging from 60% to 98%) and for specificity (ranging from 42% to 100%) (see full review in Lange et al., 2017). Two common approaches that have been used to classify control and FASD groups are 1) behavioural interpretations from parents and caregivers (e.g., Child Behavior Checklist, Neurobehavioural Screening Tool), and 2) subtest scores from various neurodevelopmental test batteries.

Nash and colleagues (2006) set out to determine if children with FASD could be distinguished by a behavioural profile. Using discriminant function analysis and receiver operating characteristics they uncovered ten behavioural characteristics from the Child-Behavior Checklist (CBCL) that were effective in differentiating between children with FASD, ADHD and typically developing controls. These ten behavioural characteristics were then used to develop the neurobehavioral-screening tool (NST). The ability of the NST to be a valid screening tool for differentiating between different children with FASD and control groups has been examined many different ways and provided mixed results (Breiner et al., 2013; LaFrance et al., 2014; Nash et al., 2006; Nash et al., 2009; reviewed in Lange et al., 2017). What can be concluded from the current research is that NST is effective at correctly identifying individuals in the control groups (good specificity, 63% to 98%), but variable at correctly identifying individuals with FASD (variable sensitivity, 42% to 100%). The apparent reason for the variability in the ability of the NST to correctly identify individuals with FASD is that the NST seems to be most accurate when data has been extracted from the full CBCL, while data in the abbreviated NST alone tend to have poor predictive power. Additionally, answers from the CBCL are scored on a three-point scale, whereas the NST collapses two of the three points together (Nash, Koren, & Rovet, 2011; Nash et al., 2006).

Progress towards a neurodevelopmental profile of FASD would also aid in streamlining the diagnostic process by helping screen individuals. Mattson and colleagues, (2010), attempted to develop a neurodevelopmental profile of FASD using subject scores and performance from a number of neurodevelopmental tests administered to individuals with PAE. They performed two latent profile analyses to reveal neurodevelopmental profiles for individuals with heavy PAE, minimal PAE and typically developing controls. They found that when individuals who met criteria for FAS were compared with individuals who were not prenatally exposed to alcohol, sensitivity was 77%, and specificity was 76%, while overall accuracy was 76%. This allowed them to develop a discriminant profile of FASD, which included deficits in executive functioning, attention, and visual and spatial memory.

In a review by Lange and colleagues, the need for identification of a reliable and effective biomarker is apparent, however they recognize that currently behavioural, observational techniques and neurodevelopmental testing are the most easily accessible and appropriate to use. Using eye-tracking technology as a screening tool appears to be a reliable and effective screening method, which collects behavioural/observational data while assessing neurocognitive abilities of individuals. Results of the current linear-ELM classification of eye-tracking data revealed high sensitivity, specificity and overall accuracy, which are comparable or better than the results of other classification methods described above. Through using eye-tracking technology as a screening tool, it is proposed that individuals who would most benefit from a full diagnostic assessment for FASD, and consequently the services that are available to them, may receive them faster and earlier. Measurement of various eye-tracking features also represents a potential

functional biomarker of children with FASD. Although previous work has investigated the differences in eye-tracking performance between typically developing controls and children with FASD more work needs to be done to further investigate the likelihood of eye-movement features being a functional biomarker.

5.2.1 Distinguishing features for classification.

Using MI, components that contained the most distinguishing features were selected. A final list of 11 of the original 46 components was selected; the 11 chosen components contained the most distinguishing eye movement features. For the purposes of this study, we have focused on the top three (of the chosen 11) components, which contain eye movement features that are important for distinguishing between control and FASD participant groups. The list of features that were shown to significantly differ between the *training* FASD and Control groups on each eye-tracking (prosaccade, antisaccade, and memory-guided) task can be found in Tables 2, 3, and 4. It has been proposed that individual features are relevant if the feature is correlated or predictive of class (or group outcome), but not correlated or predictive of other chosen features (Hall, 1999). To test this idea, correlations between the different features that were important for distinguishing between groups (significantly different between FASD and Control groups) were conducted, based on task (prosaccade, antisaccade, memory-guided saccade) and group (Control, FASD). Most correlations conducted between the important features of each task were either not correlated or had a weak correlation (either positive or negative). Identifying whether these distinguishing features are correlated with one another is important since features that are correlated can result in changes in feature selection and instability of the classification model (Tolosi & Lengauer, 2011; Zhang et

al., 2014). Therefore, since most distinguishing features in the current study were not highly or even moderately correlated, it can be assumed that each feature on its own influences the classification outcome. If features were highly correlated it means that they can both have an influential role in a feature being relevant for classification, but lack certainty that each feature is important for distinguishing between groups on its own. Thus, these distinguishing features can play an important role in development of eye-tracking as a screening tool and provide valuable information about potential functional biomarkers for FASD. The eye movement behaviours, specifically the features measured from eye movements collected from the three, structured eye movement tasks have the potential to reveal patterns of dysfunction in eye movements (Green et al., 2007; Paolozza et al., 2013). If these particular patterns of dysfunction remain consistent throughout the validation FASD cohort it may demonstrate a functional deficit (biomarker) in the eye movements of children with FASD, and lend support to the use of eye movement as a screening tool for FASD.

A majority of features that significantly differ between the *training* control and FASD groups in the antisaccade task were contributing to component 12, as well as component 16, and 32 and can be recognized as having an important role in distinguishing between *validation* control and FASD groups. Additionally, there are features from both the prosaccade and memory-guided saccade task, which are significantly different between *training* control and FASD groups that contribute to each of the important components (12, 16, 32). Features that are significantly different between *training* control and FASD groups from each of the three eye-tracking tasks; prosaccade, antisaccade, and memory-guided saccade are listed in Tables 2, 3, and 4

respectively and are organized by effect size. The lowest effect size reported across the three eye-tracking tasks is 0.33, this is considered a smaller effect size but is still relevant in the current study context. Higher effect sizes that range between medium and close to large (0.5 – 0.8) are also found in the tables. This means that the features that appear to differ between the *training* control and FASD groups are important in helping to distinguish between the control and FASD groups in the *validation* cohort.

Features that contribute to each of the top three chosen components (12, 16, and 32) are recognized as being important for distinguishing between the *validation* control and FASD groups, were found to match many of the features that were shown to significantly differ between the *training* control and FASD groups. This demonstrates the potential for eye-tracking to be used as a screening tool for FASD. Eye movement behaviours from controlled eye-tracking tasks were able to identify features that significantly differed between the control and FASD participants, which may suggest underlying functional or structural damage due to PAE. This demonstrates the potential for eye-tracking technology be a screening tool that can help identify functional biomarkers of FASD.

To see if relevant, distinguishing features from each eye-tracking task were related to each other, correlations were done. Features that were important in distinguishing between groups should co-vary little with other related features. If a number of features identified as important were shown to be correlated, the classifier would not be doing a sufficient job at recognizing important features to help distinguish groups, since they would be measuring similar aspects of eye movement behaviour. Distinguishing features should not be correlated with each other in order to demonstrate

their ability to measure different aspects of eye movement behaviour gathered from the eye-tracking tasks. Correlations between features that were important for distinguishing participants were shown to either not be correlated or be very weakly correlated.

5.2.2 CNS and Brain Structures associated with Specific Eye-tracking Features.

Previous research by Paolozza and colleagues demonstrated correlations between inhibitory control, working memory and visuospatial deficits with oculomotor control in children with FASD. Results from their two studies demonstrate that children with FASD performed worse than typically developing controls on a number of eye-tracking measures as well as psychometric tests. Eye-tracking outcomes were correlated with various measures assessed by the psychometric tests, suggesting that similar domains of cognitive function are assessed by psychometric tests and eye-tracking tasks.

Additionally, results from Paolozza et al., (2014a; 2014b) suggest that psychometric tests and eye-tracking tasks assess analogous brain regions that may be damaged due to PAE.

Areas of the brain that appear to be affected by PAE are many, however much research on regions damaged by PAE has been on the corpus callosum, cerebellum, basal ganglia, and frontal cortex. All of these areas play important roles in executive functioning domains as well as eye movement behaviours. Therefore, in looking at the distinguishing eye-tracking features identified by MI, inferences can be drawn as to the brain regions that may be affected by PAE, which cause deficits in different features of eye movement behaviours.

Corrective saccades and anticipatory saccades both involve inhibitory control mechanisms. Corrective saccades are made after a direction error, which normally occur due to a lack of inhibitory control in the antisaccade task, whereas anticipatory saccades

occur when a subject looks to where they think the target will appear before it appears. Inhibitory control is required for participants to inhibit looking to where they think the target will appear before it actually appears.

The frontal cortex includes many structures that are important for controlling eye movements, frontal eye fields (FEF), supplementary eye fields (SEF), and the dorsolateral prefrontal cortex (DLPFC). The DLPFC has specifically been shown to be involved in the production of voluntary saccades that require inhibition or memory (Sweeney et al., 1996). Furthermore, studies have shown reduced volume and malformation of the frontal cortex as a consequence of prenatal alcohol exposure (Burke, Palmour, Ervin, & Pfitz, 2009; Riley & McGee, 2005; Wass, Persutte, & Hobbins, 2001). The cerebellum has been shown to play a role in controlling movement, and has been shown to influence both vertical and horizontal saccadic control (Robinson & Fuchs, 2001). Individuals with PAE and an FAS diagnosis have been shown to exhibit hypoplasia in the cerebellum (Archibald et al., 2001). Structural abnormalities have also been identified in individuals prenatally exposed to alcohol within the basal ganglia and corpus callosum (Mattson et al., 1992; Wozniak & Lim, 2006; Wozniak & Muetzel, 2011). These structures are important for executive functioning abilities and the production of purposeful eye movements (Hikosaka, Takikawa, & Kawagoe, 2000). Through exploring distinguishing eye-tracking features and the brain structures that may influence them, it seems apparent that eye-tracking could be used as a sensitive and specific screening tool for FASD. In particular, features of saccadic eye movements could represent functional biomarkers of FASD.

Generally speaking, it appears that children with FASD tend to have deficits in accuracy of saccadic eye movements while tending to make more errors throughout the three structured eye-tracking tasks. Through looking at different features of saccadic eye movements such as, initial trajectory, endpoint errors, corrective saccades and anticipatory saccades, the possibility of saccadic eye movements being a functional biomarker becomes more apparent. Saccades allow researchers to observe the eye movement behaviour of participants' while they perform a task and have been shown to be correlated to measures on various psychometric tests. Therefore, saccades appear to incorporate and measure both behaviour, and neurodevelopmental characteristics of the participants that complete the eye movement tasks. As was mentioned by Lange and colleagues, studying behavioural outcomes and neurodevelopmental profiles are two of the most appropriate ways a developmental profile of FASD can be further revealed (see full review in Lange et al., 2017). Prenatal alcohol exposure is known to impact certain structures in the brain, and these structures are important for eye movement control. Thus, specific deficits in eye movement control may serve as a functional biomarker of PAE. This is the primary question we are seeking to answer: Can deficits in eye movement control serve as an indicator that PAE occurred in an individual.

5.3 Clinical Relevance

Results of the current study suggest that eye-tracking can be used as a sensitive and specific screening tool for FASD. Using three structured eye movement tasks; prosaccade, antisaccade and memory-guided saccade 2-target condition, saccade features were extracted from the eye-tracking data to reveal differences in saccade performance between typically developing control children and children with FASD. These tasks were

chosen as they measure different aspects of eye movement control and brain function (e.g., sensory-motor integration, response inhibition, and working memory). Previous research has demonstrated deficits in performance on various eye movement features produced from each task in children with PAE. Eye-tracking tasks used can identify differences in brain function, which are shown through eye movement behaviours. Identifying differences in eye movement behaviours/features can be applied not only to FASD but other disorders where brain dysfunction is apparent, allowing for potential screening and comparison of many disorders.

Eye-tracking equipment is also easily portable and can be transported to remote locations with ease, which can facilitate screening in populations where individuals may have been prenatally exposed to alcohol but knowledge of PAE is limited or insufficient. If children and individuals who are suspected of being prenatally exposed to alcohol are able to receive support services earlier it can lead to better life outcomes and decrease secondary disabilities common to FASD (Popova et al., 2013).

5.4 Limitations

There are a few limitations for the current study that need to be discussed. First, three eye-tracking tasks were used instead of four. The free-viewing eye-tracking task, which looks at children's natural eye movements as they watch short video clips, was not included in analysis. Adding this task in addition to the other three structured eye-tracking tasks would provide more information about how children's eye movements may be affected by PAE.

A second limitation of the current study was that children in the validation FASD group were not taken off respective medications prior to coming in to complete the eye-

tracking tasks. This is a limitation because some medications that participants could be taking may improve cognitive functioning and eye movement performance. Despite this being a limitation, it did allow investigation as to whether children with FASD who were incorrectly identified by the classifier were on any medications that could have influenced better performance.

5.5 Future Directions

A few future directions for research in this field moving forward are listed below.

1. Explore the differences in eye movements between typically developing controls and children who do not yet have an FASD diagnosis. Children who are currently in the diagnostic process should complete the eye-tracking tasks so that their resulting classification based on eye-tracking features can be compared to the diagnostic conclusion reached by the multidisciplinary team. This would further demonstrate the ability of eye-tracking to be a robust screening tool for FASD.

2. Incorporate other techniques, which measure brain function and structure into the current method. By adding other assessment methods, which measure brain function or structure to the current eye-tracking tasks a larger, more in depth picture of how the brain responds to prenatal alcohol exposure could be explored. For example, having participants wear an EEG headband while completing the eye-tracking tasks would allow for direct comparison of eye movement behaviours and the associated pattern of underlying brain activity. This could further reveal information about brain dysfunction and potential functional biomarkers of FASD.

3. Lastly, adding a fourth task such as the free viewing task to the structured tasks would allow for more information regarding saccades and eye movement features to be

gathered and compared between groups. Aiding in the progress towards identifying a biomarker of FASD and adding to the idea of features of saccadic eye movements as functional biomarkers for FASD.

Chapter 6

Summary and Conclusions

The current thesis tested the following two hypotheses:

1. Eye movement tasks are a sensitive and specific screening tool that can be used to identify brain injury associated with prenatal alcohol exposure.
2. Eye movement control tasks will reveal specific functional biomarkers that will inform state-of-the-art machine-learning models to reliably and efficiently discriminate between children with FASD and typically developing control children.

The results of the current study suggest that eye-tracking can be used as a sensitive and specific screening tool for FASD. The Eyelink 1000 eye-tracker is able to reveal differences in eye movements between typically developing controls and children with FASD. As well, the eye-tracker is portable and can be taken to remote locations easily to screen individuals who may have been exposed to alcohol prenatally. Eye-tracking therefore appears to be a reliable tool for screening for FASD, and has the potential to be used in a number of other clinical populations who experience brain dysfunction.

Eye-tracking data was able to effectively inform a machine learning model how to adequately distinguish between typically developing control children and children with

FASD. This could largely be due to the fact that saccades and their various features have the potential to be a functional biomarker for FASD. Features of saccadic eye movements were removed from the eye-tracking data collected and used to train and test the linear-ELM used. Results of the classification reveal that the saccadic eye movement features gathered from the eye-tracking tasks were sufficient in informing the machine-learning model of differences between the two groups. The linear-ELM was able to reliably and efficiently discriminate between typically developing control and FASD groups in this study.

Future directions will aim to further explore saccadic eye movements as functional biomarkers of FASD, through additions of other technologies to eye-tracking and addition of other tasks which can help to further refine the saccadic eye movement features used for classification.

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APPENDIX A

ASSENT FORM (<12 years)

TITLE OF PROJECT: Novel assessment tool for Fetal Alcohol Spectrum Disorder (FASD) based on eye movement behaviours

Investigators: Dr. James Reynolds.

The investigator and his research team want to tell you about a study about development. They want to see if you would like to be in this study. This form tells you about the study. If there is anything you do not understand, please ask your parent, your guardian or the research team staff.

Why are they doing this study?

They want to learn more about how the brain changes as children grow up and what goes wrong when there is brain damage. They also want to see if they can measure these changes using different tests.

What will happen to you?

If you want to be in the study it should take approximately 1.5-2 hours over a single session. These things will happen:

- You will watch dots or pictures on a computer screen. A small sticker will be placed on your forehead so that the camera knows where your eyes are.
- You will be asked to wear a headset that has electrodes for measuring the electrical activity of your brain.

Will the study hurt?

The study should not hurt you at all. You may feel a little tired at times. Just let the research staff know and they will give you breaks and snacks.

Will you get better if you are in the study?

This study won't make you feel better. But the research team might find out something that will help other children like you later.

What if you have any questions?

You can ask questions any time, now or later. You can talk to the researcher: Dr. James Reynolds (613-533-6946), the Director of the Centre for Neuroscience Studies at Queen's University Dr. Doug Munoz (613-533-2111), another member of the research team, your

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family or someone else. If you have any concerns about your rights as a research participant please contact - Dr. Albert Clark, Chair, Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board at 1-844-535-2988 or clarkaf@queensu.ca.

Who will know what I did in the study?

Any information you give to the research staff will be kept private (*or secret*). Your name will not be on any study paper and no one but the research staff will know that it was you who was in the study.

Do you have to be in the study?

You do not have to be in the study. No one will be unhappy with you if you don't want to do this. If you don't want to be in this study, just say so. We will also ask your parents if they would like you to be in the study. Even if your parents want you to be in the study you can still say no. Even if you say yes now you can change your mind later. It's up to you. Saying no will not change how you are treated by anyone at Queen's University and the local hospitals.

Do you have any questions?

What questions do you have?

APPENDIX B

ASSENT FORM (12-18 years)

TITLE OF PROJECT: Novel assessment tool for Fetal Alcohol Spectrum Disorder (FASD) based on eye movement behaviours

Why are they doing this study?

You are being invited to participate in a research project because we want to study typical childhood and adolescent development; and development in children and adolescents with a developmental disability due to prenatal alcohol exposure.

The project is directed by Dr. James N. Reynolds, Professor in the Department of Biomedical and Molecular Sciences and Centre for Neuroscience Studies at Queen's University. Dr. Reynolds or a member of his research team will read through this assent form with you and describe the procedures in detail and answer any questions you may have.

What will happen to you?

If you want to be in the study it should take approximately 1.5-2 hours over a single session. These things will happen:

- Eye movements will be recorded as you watch dots or pictures on a computer screen. A small sticker will be placed on your forehead so that the camera knows where your eyes are moving (~1 hour).
- You will be asked to wear a headset that incorporates electrodes for measuring the electrical activity (electroencephalogram or EEG) of the brain both before and during the performance of the saccadic eye movement tasks (~1 hour).

Description of Tests to be performed as part of the study

Saccadic Eye Movements

Saccadic eye movements are measured using video-based eye tracking equipment. You will be seated comfortably in front of a computer screen and a small sticker will be placed on your forehead. The camera is located within the screen and will use the position of the sticker to help locate and follow your eye movements as you watch short video clips or small dots that move around the screen.

This is a non-invasive technique for recording eye movement control and should produce no discomfort. The sticker may leave a small area of redness but this should fade in a few hours.

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EEG Recording

You will be asked to wear a headset for approximately 30 minutes before and during the saccadic eye movement testing. This is a non-invasive technique for recording electrical activity in the brain and should produce no discomfort.

Will the study hurt?

There are minimal risks involved in participating in this study. You may feel tired after and/or during the tests. At any point, the tests can be paused without destroying the data collection process, and you can have a rest and snack.

Will you get better if you are in the study?

This study won't make you feel better. But the research team might find out something that will help children with a developmental disorder resulting from prenatal alcohol exposure in the future.

What if you have any questions?

You can ask questions any time, now or later. You can talk to the researchers: Dr. James Reynolds (613-533-6946), the Director of the Centre for Neuroscience Studies at Queen's University Dr. Doug Munoz (613-533-2111), another member of the research team, your family or someone else. If you have any concerns about your rights as a research participant please contact - Dr. Albert Clark, Chair, Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board at 1-844-535-2988 or clarkaf@queensu.ca.

Who will know what I did in the study?

Any information you give to the research staff will be kept private (*or secret*). Your name will not be on any study paper and no one but the research staff will know that it was you who was in the study.

Do you have to be in the study?

You do not have to be in the study. No one will be unhappy with you if you don't want to do this. If you don't want to be in this study, just say so. We will also ask your parents if they would like you to be in the study. Even if your parents want you to be in the study you can still say no. Even if you say yes now you can change your mind later. It's up to you. Saying no will not change how you are treated by anyone at Queen's University and the local hospitals.

Do you have any questions?

What questions do you have?

Assent

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Written assent if the child chooses to sign the assent.

Signature of Child Age Date

May we keep your contact information on file for potential participation in future studies?

YES _____ NO _____

I confirm that I have explained the study to the participant to the extent compatible with the participant's understanding, and that the participant has agreed to be in the study.

Printed name of Signature of Date
person obtaining assent person obtaining assent

APPENDIX C

INFORMATION/CONSENT FORM

TITLE OF PROJECT: Novel assessment tool for Fetal Alcohol Spectrum Disorder (FASD) based on eye movement behaviours

BACKGROUND INFORMATION:

Your child is being invited to participate in a research project directed by Dr. James N. Reynolds, Professor in the Department of Biomedical and Molecular Sciences and Centre for Neuroscience Studies at Queen's University.

This research study is being conducted as part of a large trans-Canadian project called *NeuroDevNet*. The aim of *NeuroDevNet* is to study typical childhood and adolescent development, and understand the changes that may occur due to brain injury. Importantly, with a better understanding of typical development, brain changes related to prenatal alcohol exposure can be measured. There is an urgent need for identification of functional biomarkers that can be used in the assessment of neurological and mental health disorders, and our previous studies suggest that tasks measuring specific eye movement behaviours may be used as an objective screening tool for brain function in clinical populations.

Dr. Reynolds or a member of the research team will read through this consent form with you and describe the procedures in detail and answer any questions you may have. This study is funded by the Networks of Centres of Excellence (NCE). This study has been reviewed for ethical compliance by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board.

DETAILS OF THE STUDY:

The purpose of this research project is to measure differences in brain function in typically developing children/youth and in children/youth with Fetal Alcohol Spectrum Disorder (FASD), a condition that occurs following exposure to alcohol in utero. These data can then be compared to give us important information about the types of brain damage associated with prenatal alcohol exposure. We anticipate recruiting a total of 100 participants from ~ 4 study centers across Canada.

Your child will be considered for this study if he/she can follow simple instructions. The experimental session will last approximately 1.5-2 hours total. Your child will be asked to perform the following:

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- Complete saccadic eye movement tests that measure how participants move their eyes to explore the visual environment (~ 1 hour)
- Participate in neuroimaging studies that involve wearing a wireless headset that incorporates electrodes for measuring the electrical activity (electroencephalogram, or EEG) of the brain both before and during the performance of the saccadic eye movement tasks (~1 hour).

In addition, to ensure that we have complete data sets from each participant, we are asking for consent to access medical (i.e., medication, co-morbidities, diagnosis if applicable) and psychological assessment records that were obtained by personnel at a diagnostic clinic, school or by a private therapist. This information is needed for us to do the appropriate statistical analyses. The personal health information collected will be kept in locked cabinets and electronic data files will be password protected and access restricted to Dr. Reynolds and members of the research team.

Description of Tests to be performed as part of the study

Saccadic Eye Movements

Saccadic eye movements are measured using video-based eye tracking equipment. Your child will be seated comfortably in front of a computer screen and a small sticker will be placed on their forehead. The camera is located within the screen and will use the position of the sticker to help locate and follow eye movements as participants watch short video clips or small dots that move around the screen. This is a non-invasive technique for recording eye movements and should produce no discomfort. The sticker may leave a small area of redness but this should fade in a few hours.

EEG Studies

Your child will be asked to wear a wireless headset that incorporates electrodes for the measurement of electrical activity in the brain (EEG). The electrodes are spring-loaded to maintain good contact with the scalp, and the headset can be adjusted to fit comfortably yet snugly on the head. This is a non-invasive procedure that records electrical activity in the brain passively, and does not produce pain or discomfort.

Risks/Side Effects

There are minimal risks involved in participating in this study. Your child may feel tired after and/or during the tests. At any point, the tests can be paused without destroying the data collection process, and participants can be given a rest and refreshments. The Avertus device uses gold-plated dry-electrodes placed on the scalp to collect EEG signals. As the Avertus headset is an investigational new device, the company has sought and obtained Investigational Testing Authorization by Health Canada, and each individual device must be certified after special investigation testing by the Canadian Standards Association (CSA) Group.

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Benefits

You and your child will not benefit directly from this study, and the information collected in this study will not be used for diagnostic or treatment purposes. However, the results from this study may improve the understanding of the changes that occur during development and as a result of limited brain function. This may in turn benefit patients with clinical disorders in the future and lead to an early and accurate diagnosis.

Exclusion

Individuals with severe developmental disabilities and/or brain injury will be excluded from the study.

Confidentiality

All information obtained during the course of this study is strictly confidential and your child's anonymity will be protected at all times. Your child will be identified using an alphanumeric code. Data will be stored in locked files and will be available only to Dr. Reynolds and his research team. Your child will not be identified in any publication or report.

Voluntary nature of study/Freedom to withdraw or participate

Your child's participation in this study is voluntary. Your child may withdraw from this study at any time and without prejudice or effects to their future care.

Withdrawal of participant by principal investigator

The principal investigator may decide to withdraw your child from this study if he feels they are unable to complete the tests appropriately.

Liability

In the event that your child is injured as a result of the study procedures, medical care will be provided to your child until resolution of the medical problem. By signing this consent form, you do not waive your child's legal rights nor release the investigator(s) from their legal and professional responsibilities.

Payment

For participants residing within the city limits of Kingston, Ontario, we will reimburse your parking expenses (upon presentation of a receipt). If you do not have access to personal transportation, other modes of transportation will be made available to you (i.e., bus tickets or taxi vouchers), if requested, on a case-by-case basis.

For participants residing outside of the city limits of Kingston, Ontario, we will attempt to coordinate a field study in your home town or city. In these cases, we will reimburse your parking expenses (upon presentation of a receipt) and coordinate transportation, if requested, on a case-by-case basis. However, in the event that participants are asked to travel to Kingston, Ontario, we will reimburse your travel expenses (i.e., train fare or mileage based on the Queen's travel policy),

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accommodation (i.e., hotel room, if needed) and meal(s) for your child and one parent/guardian. These situations will be assessed on a case-by-case basis.

APPENDIX C

PARTICIPANT STATEMENT AND SIGNATURE SECTION

I have read and understand the consent form for this study. I have had the purposes, procedures and technical language of this study explained to me. I have been given sufficient time to consider the above information and to seek advice if I chose to do so. I have had the opportunity to ask questions which have been answered to my satisfaction. I am voluntarily signing this form. I will receive a copy of this consent form for my information.

If at any time you have further questions, problems or adverse events, you can contact Dr. James Reynolds (613-533-6946), or the Director of the Centre for Neuroscience Studies, Dr. Doug Munoz (613-533-2111). If you have any concerns about your rights as a research participant please contact - Dr. Albert Clark, Chair, Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board at 1-844-535-2988 or clarkaf@queensu.ca.

By signing this consent form, I am indicating that I agree to participate in this study.

Signature of Participant

Date

Signature of Parent/Guardian

Date

Signature of Person of Conducting the Consent Discussion

Date

May we keep your contact information on file for potential participation in future studies?

YES _____ NO _____

INVESTIGATOR

I, or one of my colleagues, have carefully explained to the participant the nature of the above research study. I certify that, to the best of my knowledge, the participant understands clearly the nature of the study and demands, benefits and risks involved to participants in this study.

Signature of Principal Investigator (or delegate)

Date

APPENDIX D

Participant Information

Please answer all the questions that you can. Feel free to ask for clarification of any items. If you are completing this form on behalf of a participant in the study, please answer the questions with respect to the participant. *If, for any reason, you choose not to answer some of these questions, please skip ahead to the next question that you are willing to answer.*

Thank you very much for helping with our study!

A. GENERAL INFORMATION

Participant's name (First/Middle/Last): _____

Date of Birth: (Day/Mo/Yr): _____

Sex (M/F): _____

Age (years): _____

Telephone: (_____) _____

Parent/Guardian: _____

Address: _____

Email: _____

What is your child's ethnicity? _____

What is the parent/guardian's ethnicity? _____

What is your child's dominant hand? _____

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Other? (specify)

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C. TREATMENT HISTORY

Please answer all of the questions that you can. If you are completing this form on behalf of a participant in the study, please answer the questions with respect to the participant. Feel free to ask for clarification of any items. If, for any reason, you choose not to answer some of these questions, please skip ahead to the next question that you are willing to answer.

Is your child currently taking any medication? No Yes

If yes, Drug? _____ Dose/Day____ Date started _____

If your child is currently taking medication to reduce the symptoms of FASD, please indicate how effective it is. (Circle one)

Not effective Somewhat effective Effective Very effective

Has your child ever been prescribed any of the following prescription medication? (If yes, indicate at what age the medication was started and stopped and the reason for the prescription.)

| | Age started | Age stopped | Reason? |
|-----------------|-------------|-------------|---------|
| Ritalin | _____ | _____ | _____ |
| Dexedrine | _____ | _____ | _____ |
| Cylert | _____ | _____ | _____ |
| Tranquilizers | _____ | _____ | _____ |
| Anticonvulsants | _____ | _____ | _____ |
| Antihistamines | _____ | _____ | _____ |
| Antidepressants | _____ | _____ | _____ |
| Other (specify) | _____ | _____ | _____ |

APPENDIX D

D. FAMILY HISTORY

Please answer all of the questions that you can. If you are completing this form on behalf of a participant in the study, please answer the questions with respect to the participant. Feel free to ask for clarification of any items. *If, for any reason, you choose not to answer some of these questions, please skip ahead to the next question that you are willing to answer.*

Does the child reside with (please circle one):

Biological family Foster Care Adopted
(Please indicate relationship)

Please indicate biological mother's (if known):

i) type of employment: _____
ii) highest grade completed, or degree: _____

Please indicate biological father's (if known):

i) type of employment: _____
ii) highest grade completed, or degree: _____

Please indicate foster/adoptive mother's (if applicable):

i) type of employment: _____
ii) highest grade completed, or degree: _____

Please indicate foster/adoptive father's (if applicable):

i) type of employment: _____
ii) highest grade completed, or degree: _____

Please indicate guardian's (if applicable):

Relation to child (i.e., grandmother, aunt): _____
i) type of employment: _____
ii) highest grade completed, or degree: _____

Relation to child (i.e., grandfather, uncle): _____
i) type of employment: _____
ii) highest grade completed, or degree: _____

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E. FAMILY HISTORY (continued)

Please indicate if there is a family history of any of the following. When yes, place a check next to the item and indicate the relationship of the family member(s) to your child (e.g. maternal uncle=uncle on mother's side). Include relatives by marriage and siblings. (If child is adopted, only complete for biological family members)

| Diagnosis | Family member (relation to participant) |
|---|--|
| FASD: | _____ |
| ADHD or ADD: | _____ |
| Learning Disability: | _____ |
| Failed to graduate from high school: | _____ |
| Mentally challenged: | _____ |
| Psychosis or schizophrenia: | _____ |
| Depression for more than 2 weeks: | _____ |
| Bipolar mood disorder: | _____ |
| Anxiety disorder: | _____ |
| Tourette's disorder: | _____ |
| Alcohol or substance abuse: | _____ |
| Problems with aggressiveness, defiance, oppositional behaviour as a child: | _____ |
| Problems with attention, activity, and impulse control as a child: | _____ |
| Other (specify): | _____ |

Thank you very much for your co-operation and your time!!!