

CHILDREN WITH ALCOHOL-RELATED  
NEURODEVELOPMENTAL DISORDER OR ATTENTION  
DEFICIT/HYPERACTIVITY DISORDER DIFFER ON  
NEUROPSYCHOLOGICAL TASKS AND MEASURES OF EYE  
MOVEMENT CONTROL

by

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## Abstract

Children with alcohol-related neurodevelopmental disorder or attention deficit/hyperactivity disorder differ on neuropsychological tasks and measures of eye movement control. M.Sc. Thesis, Queen's University, Kingston, Ontario, Canada, January, 2010.

**Background:** Alcohol-related neurodevelopmental disorder (ARND) accounts for the majority of diagnoses associated with prenatal alcohol exposure. Unfortunately, ARND frequently poses a significant clinical challenge as these patients lack the visible physical characteristics associated with alcohol teratogenicity. Moreover, the cognitive and behavioural disabilities are complex and overlap with those of attention deficit/hyperactivity disorder (ADHD). Furthermore, co-morbid ADHD is prevalent in children with prenatal alcohol exposure. While early and accurate diagnosis provides the best prognosis for those affected, there is a lack of tools for differential diagnosis between these two disorders. The goal of this study was to test the hypothesis that children with ARND exhibit different performance from children with ADHD on computer-based neuropsychological tests and eye movement tasks. **Methods:** Our study group was composed of 42 children with ARND and 31 children with ADHD aged 8-15 years, male and female. Children completed four tasks selected from the *Cambridge Neuropsychological Test Automated Battery* (CANTAB<sup>®</sup>) that provided measures of attention, planning, strategy and spatial working memory. Subjects also performed pro- and anti-saccade tasks, and eye movements were recorded using a mobile eye-tracking system. **Results:** Children with ARND demonstrated elevated decision times on a visual

matching test of attention and longer response times on a task of spatial working memory, although the two groups had similar errors scores. Also, compared to children with ADHD, children with ARND had greater anticipatory errors in both the pro- and anti-saccade tasks. **Conclusion:** This study demonstrates that there are measurable differences in executive function and eye movement control between children with ARND or ADHD. Greater deficits in visuospatial processing in ARND may underlie these differences. These findings demonstrate that the neurobehavioural phenotypes of children with ARND or ADHD have distinct features, which may be accounted for by differences in the patterns of brain injury underlying these two disorders.

## **Co-Authorship**

The research described in this thesis was conducted by Alanna Mihic in collaboration with Courtney Green under the supervision of Dr. James Reynolds, who conceived the studies described herein. Alanna Mihic conducted eye movement experiments and neuropsychological testing and analyzed all data described in Chapters 3, 4 and 5, and wrote the first draft of each chapter in the thesis. Courtney Green assisted with the collection of eye movement data and Rebecca Hakvoort-Schwerdtfeger assisted with the collection of the CANTAB® data.

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## List of Abbreviations and Symbols

AACAP	American Academy of Child and Adolescent Psychiatry
AAP	American Academy of Pediatrics
ACC	Anterior cingulate cortex
ADHD	Attention-deficit hyperactivity disorder
ANCOVA	Analysis of co-variance
ANOVA	Analysis of variance
ARND	Alcohol-related neurodevelopmental disorder
BOLD	Blood-oxygen-level dependent
CANTAB®	Cambridge Neuropsychological Test Automated Battery
CBC	Child Behaviour Checklist
CD	Caudate nucleus
cd/m <sup>2</sup>	One candelas per square meter
CN	Caudate nucleus
CNS	Central nervous system
COWAT	Controlled Oral Word Association Test
CPRS-48	Conners Parent Rating Scale
CV	Coefficient of variation
dIPFC	Dorsolateral prefrontal cortex
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision
DTI	Diffusion tensor imaging
EBN	Excitatory burst neurons
ERP	Event related potential
FABS	Fetal Alcohol Behavior Scale
FAE	(Possible/Suspected) Fetal alcohol effects
FAS	Fetal alcohol syndrome
FASD	Fetal alcohol spectrum disorders
FAS-DPN	University of Washington FAS Diagnostic and Prevention Network
FEF	Frontal eye fields
fMRI	Functional Magnetic Resonance Imaging
FP	fixation point
GABA	gamma-Aminobutyric acid
GHz	Gigahertz
GPe	External segment of the globus pallidus
Hz	Hertz
IBN	Inhibitory burst neurons
IOM	Institute of Medicine
IQ	Intelligence quotient
LGN	Lateral geniculate nucleus
LLBN	Long lead burst neuron

LED	Light-emitting diode
LIP	Lateral intraparietal area
LLBN	Long-lead burst neurons
MN	Motoneurons
MRI	Magnetic resonance imaging
ms	Millisecond
MTS	Match to Sample Visual Search
OPN	Omnipause neurons
PAE	Prenatal alcohol exposure
PEF	Parietal eye fields
PET	Positron emission tomography
pFAS	Partial fetal alcohol syndrome
PIC	Personality Inventory for Children
PPC	Poster parietal cortex
PDD-NOS	Pervasive developmental disorder – not otherwise specified
RTI	Reaction Time
s	second
SC	Superior colliculus
SCi	Intermediate layers of the superior colliculus
SCs	Superficial layers of the superior colliculus
SEF	Supplementary eye fields
SEM	Standard error of the mean
SNr	Substantia nigra pars reticulata
SOC	Stockings of Cambridge
SRT	Saccadic reaction time
SSRS	Social Skills Rating System
STN	Subthalamic nucleus.
SWM	Spatial Working Memory
T	Target
TMT	Trail Making Test
vs.	Versus
WCST	Wisconsin Card Sorting Task
UK	United Kingdom
%	percentage
\$	dollar
/	per
<	less than
~	approximately
±	plus or minus
®	registered trademark
°	degree
=	equal
α	alpha
+	plus

# **Chapter 1**

## **Introduction**

Maternal alcohol consumption during pregnancy is linked with behavioural deficits in the offspring (Olson et al., 1997), and studies demonstrate that children with prenatal exposure to alcohol have attention deficits (Streissguth et al., 1994). The diagnoses associated with prenatal alcohol exposure, including fetal alcohol syndrome (FAS), partial FAS (pFAS) and alcohol-related neurodevelopmental disorder (ARND), are grouped together under the umbrella term fetal alcohol spectrum disorders (FASD; Chudley et al., 2005), affecting as many as 2-5% of school-aged children in America (May et al., 2009). Attention deficit/hyperactivity disorder (ADHD) is characterized by hyperactivity, impulsivity and/or inattentiveness (American Psychiatric Association, 2000). ADHD occurs in the general child and adolescent population with a frequency of 3-12%, accounts for 10% of the behavioural problems seen in the general pediatric setting, and is present in 50% of child psychiatric populations (Cantwell, 1996). The disorder is even more prevalent in the FASD population (Fryer et al., 2007a). While children with FAS and pFAS display characteristic physical abnormalities which can be reliably identified and measured, children with ARND have no visible signs of prenatal alcohol exposure. Herein lays the clinical problem that engendered our experimental investigation. Since children with ARND present with ADHD-like symptoms but no physical features, there is the potential for misdiagnosis; this problem is further compounded by the recommendations of the current diagnostic guidelines and by the limitations of existing diagnostic tools. There are many adverse outcomes associated

with delayed and/or incorrect diagnosis that have significant implications for the child, family and society. The purpose of this study, therefore, was to compare performance on computer-based neuropsychological tasks and eye movement paradigms between subjects with ARND or ADHD. This work may contribute to the delineation of a neurobehavioural profile that is unique to ARND and could benefit differential diagnosis in the long-term. The ensuing literature review will describe the major issues associated with delayed and/or incorrect diagnosis of ARND, the current recommendations for ARND diagnosis, and the use of behavioural checklists and neuropsychological tests for identifying a phenotype of prenatal alcohol exposure. Similarly, the current diagnostic approaches to children with ADHD will be examined, as well as the tools used to investigate neurobehavioural performance in children with ADHD. Finally, the benefits and limitations of comparison studies involving subjects with FASD or ADHD will be reviewed.

## **Chapter 2**

### **Literature Review**

#### **2.1 Diagnosing ARND**

FASD is a non-diagnostic identification used to describe individuals with a history of prenatal alcohol exposure, who may or may not present with the characteristic diagnostic sequelae including: growth deficiencies, cranio-facial dysmorphology and central nervous system (CNS) dysfunction (Chudley et al., 2005). Although there are multiple diagnostic guidelines, there is general agreement that each diagnosis is part of a continuum, with FAS (Jones and Smith, 1975), representing the strongest physical presentation. Children with ARND lack the characteristic facial features, and this can preclude those individuals from receiving an early and accurate diagnosis. Specifically, the recommendations for assessing CNS dysfunction are often vague and the necessary CNS assessment tools are not widely available or applicable to the population. The most current clinical guidelines will now be reviewed.

##### **2.1.1 Institute of Medicine (IOM)**

The IOM guidelines were introduced to reduce confusion regarding the term fetal alcohol effects (FAE) (Stratton et al., 1996). FAE was initially used in situations where a poor birth outcome could be associated with prenatal alcohol exposure (Clarren and Smith, 1978); however, the term was inappropriately adopted as a diagnosis. The IOM proposed using ARND for some of the children with an existing FAE diagnosis.

According to the IOM, an ARND diagnosis is given when: 1) there is confirmed maternal

alcohol exposure; and 2) evidence of CNS neurodevelopmental abnormalities, such as decreased cranial size at birth, or evidence of a complex pattern of behavior/cognitive abnormalities, such as learning difficulties, poor school performance and deficits in social perception. The CNS deficits had to be inconsistent with developmental level and unrelated to familial background or environment. Clinicians were asked to adopt the terms; researchers were urged to evaluate the utility, reliability, and validity of their diagnostic schemata, and both groups were encouraged to investigate the differences in expression and specificity of behavioral and cognitive deficits in ARND.

### **2.1.2 The 4-Digit Diagnostic Code**

In 2000, Susan Astley, Sterling Clarren and the University of Washington FAS Diagnostic and Prevention Network (FAS-DPN) published the 4-Digit Diagnostic Code as a means for improving the current diagnostic approaches to FASD (Astley and Clarren, 2000). In particular, they felt the term FAE was too broad and the term ARND implied causation between alcohol exposure and CNS deficits. A multidisciplinary clinical team evaluated 1014 FAS-DPN patient records to deduce a system where each patient was given a score in the following four domains: (1) growth deficiency; 2) FAS facial phenotype; 3) brain damage/dysfunction; and 4) gestational alcohol exposure. Using a 4 point Likert scale, each domain was scored, where a '1' represented complete absence and '4' represented a classic presence of the FAS feature. A single indicator, such as a structural brain abnormality or a hard neurological sign, led to a score of '4' in the brain damage/dysfunction domain while score of 3 was given to a person presenting

with substantial deficiencies across multiple domains of brain function, including intelligence, language and neuropsychology.

### **2.1.3 The Canadian Diagnostic Guidelines**

In an attempt to unify the Canadian diagnostic approach to FASD, Health Canada's National Advisory Committee on FASD introduced a set of diagnostic guidelines (Chudley et al., 2005). The advisory committee included clinicians, FASD experts, professional interest groups, and various levels of government. The guidelines represented a harmonization of the 4-digit diagnostic code and the IOM guidelines. The recommendations included that children without facial features or growth restriction should only be referred to an FASD diagnostic clinic when there was confirmed prenatal alcohol exposure. This criterion ensures that fewer non-FASD cases are referred to the limited number of diagnostic clinics. However, considering that children in North America with behavioural issues are most commonly referred for an ADHD-assessment (Kelleher et al., 2000), the aforementioned recommendation may also decrease the likelihood that a child with ARND will receive an accurate diagnosis. In the neurological assessment component of the guidelines, at least three of the following domains must be impaired: hard and soft neurologic signs; brain structure; cognition; receptive and expressive communication; academic achievement; memory; executive functioning and abstract reasoning; attention deficit/hyperactivity; and adaptive behaviour such as social skills and social communication. Unfortunately, unlike growth deficiency, which may be evident pre- and early post-natally, and facial dysmorphology, which may be measurable at 29 weeks (Thomas et al., 1987), standardized measures for the neurological assessment

may not be applicable for children of pre-school age or available in particular regions of Canada. In these cases the guidelines recommended that a clinical judgment of “significant dysfunction” must be made or that the assessment must be delayed until the child demonstrates measurable deficits. Thus, in the case of a child with no physical deficits, an FASD assessment may be delayed or missed altogether.

#### **2.1.4 Hoyme diagnostic criteria (a clarification of the IOM criteria)**

Hoyme and colleagues (2006) introduced a set of guidelines that were intended to clarify the 1996 IOM diagnostic approaches. They recommended 1) implementing a multidisciplinary approach to diagnosis for behavioural and neuropsychological assessments; 2) confirming that the complex pattern of cognitive or behavioural abnormalities were not attributable to family characteristics or environmental influences alone; 3) differentiating between children with ARND and other developmental disorders using tests of executive function given that intelligence quotient (IQ) tests may be unreliable; and 4) collecting detailed maternal and family history. In obtaining prenatal records, the likelihood that a child with ARND will receive a definitive diagnosis increases substantially. However, this is obviously a difficult task in situations where the child is no longer with the birth parent or biological family members.

## **2.2 Assessing ARND**

In an experimental setting, researchers and clinicians study the neurobehavioural characteristics of children with prenatal alcohol exposure in order to delineate a profile for FASD, and thus improve diagnostic consistency. The tools employed in these studies have evolved from behavioural checklists to advanced measures of executive function,

and with the advent of functional neuroimaging tools, the structural and functional abnormalities that underlie these behaviours can now be explored.

### **2.2.1 Behavioural checklists**

In 1998, Streissguth and colleagues created a short, easy-to-administer *Fetal Alcohol Behavior Scale* (FABS) checklist made of thirty-two FASD-specific behavioural descriptions. The FABS could identify subjects with FASD and the FABS score was not influenced by age, sex, race, IQ, or alcohol-related diagnosis. Though promising for use in ARND, the authors urged that behavioural checklists were not appropriate as a diagnostic tool alone, but may have more potential as a screening tool.

Steinhausen and colleagues (2003) assessed whether a behavioural profile could differentiate children with FAS/FAE from those with intellectual disabilities of an unspecified diagnosis. The caregivers of each child completed the *Developmental Behaviour Checklist* and the results indicated that children with FAS/FAE scored significantly worse on measures of disruptive, self-absorbed, communicative disturbance and anxiety behaviours compared to the children with intellectual disabilities. Importantly, this study identified measurable differences between the behavioural profile of subjects with intellectual disabilities and those with FASD.

Greenbaum and colleagues (2002) tested clinic-referred children using neuropsychological tests including the *Wechsler Intelligence Scale for Children, 3<sup>rd</sup> Edition*, and on behavioural tests including the *Child Behaviour Checklist, Clinical Range*. Then the children were designated as ARND or non-ARND based on a newly developed ARND behavioural profile questionnaire. The children in the ARND group

demonstrated poorer performances on neuropsychological tests including verbal ability and auditory memory, while they had similar performance to the clinic-referred non-ARND children on the behavioural tasks, including measures of attention, impulsivity and hyperactivity. This study supports the notion that neuropsychological assessments provide greater diagnostic power than behavioural measures alone when comparing children with ARND to other clinic-referred children.

### **2.2.2 Tests of executive function**

Behavioural outcomes as measured by parent- and teacher-rated questionnaires are highly influenced by post-natal environment (Kodituwakku 2007), which questions the ability to identify a behavioural phenotype using the questionnaire method.

Anatomical studies demonstrate that prenatal alcohol exposure targets development of the frontal lobe (Sowell et al., 2002), an area associated with executive function (Stuss 2002). Thus, researchers have begun assessing the deficits in cognitive behavioural functioning in FASD using tasks of executive function. Executive functions include complex cognitive skills like planning, inhibition, working memory, set shifting, flexible thinking and strategy (Welsh and Pennington, 1988; Welsh et al., 1991), as well as emotion-related components, like the regulation of motivated and emotional behavior, and the processing of affective and non-affective stimuli (Zelazo and Müller, 2002).

In 2001, Kodituwakku and colleagues administered executive function tasks to 20 children with heavy prenatal alcohol exposure (PAE) and 20 matched controls. Emotion- and cognition-related executive functions were measured using visual learning tasks. Compared to control subjects, children with PAE demonstrated poorer performance on

both types of learning tasks. Also, the difference between group performances on the emotion-related learning task was still significant when controlling for performance deficits on the cognition-related learning task. The results demonstrated that emotion- and cognition-related executive functions are impaired in PAE and that these domains may be independent functions in this population.

Executive function tasks can also be used in combination with functional imaging technology to identify a potential locality of CNS dysfunction. O'Hare and colleagues (2009) tested 20 children and adolescents with FASD and controls in a verbal working memory task using functional Magnetic Resonance Imaging (fMRI). Subjects were presented with a lowercase letter and asked to press a button if the letter matched one of the uppercase letters from a previous visual array. There was no significant difference between groups in performance on the medium (3-letter stimulus) or hard (5-letter stimulus) conditions. Despite the similar performance, the imaging data revealed differences in brain activation patterns between the groups. The subjects with FASD demonstrated increased activation in portions of the bilateral dorsal frontal and left inferior parietal cortices compared to controls, indicating impaired fronto-parietal processing. If children with FASD demonstrate consistent processing inefficiencies during working memory tasks, then these tasks may be more sensitive in differentiating children with FASD from controls and/or other neurodevelopmental disorders.

## **2.3 Issues associated with delayed and/or incorrect diagnosis**

### **2.3.1 Secondary disabilities**

Researchers have found that the secondary disabilities associated with prenatal alcohol exposure such as problems with school, drugs or alcohol can be minimized if an early (before the age of 12 years) and accurate diagnosis is obtained. A cohort of 415 subjects with FAS/FAE was assessed by the University of Washington's Fetal Alcohol and Drug Unit (Streissguth et al., 2004). Achievement and adaptive behaviour test performance was analyzed in relation to information gathered from a *Life History Interview* that evaluated the protective and harmful characteristics of personal and environmental influences. Interestingly, the life history factor 'lack of an early diagnosis' was most strongly correlated to adverse outcomes on the achievement and adaptive behaviour measures including inappropriate sexual behaviour, disrupted school experience, trouble with the law, confinement, and alcohol and drug problems. This illustrates how a late diagnosis can have lasting negative implications.

Similarly, in a twenty year follow-up study, 37 subjects with FAS/FAE were evaluated using questionnaires pertaining to academic achievement, occupational career, domestic arrangements, independent living, and emotional and behavioural problems (Spohr et al., 2007). Results indicated that only 38% graduated primary school, 13% had an "ordinary" job, and 14% lived independently. Each adverse outcome occurred in conjunction with attention problems. Interestingly, the factor that had the most protective effect was 'early diagnosis (<6 years)', further demonstrating the need for new diagnostic tools that can be used in very young children. Taken together the data suggest that

secondary disabilities are commonly associated with prenatal alcohol exposure and that early diagnosis may improve life outcomes.

### **2.3.2 Interventions**

While a delayed diagnosis poses the aforementioned problems, inappropriate interventions may also cause damage. Consider that stimulant medication is the first-line pharmacological therapy in children with ADHD (Dulcan, 1997) and that ADHD is a commonly co-diagnosed disorder in children with PAE (Fryer et al., 2007a). However, the effects of stimulants have not been adequately studied in children with PAE.

Snyder and colleagues (1997) published a blind cross-over, randomized control trial that found stimulant medication improved parent-rated measures of hyperactivity, but had no impact on sustained attention. Adverse outcomes were not addressed, the sample size was small and only children with FAS were included. Oesterheld and colleagues (1998) published a randomized double-blind placebo-controlled cross-over clinical trial to assess the efficacy and side effects of methylphenidate in 4 Native American children with FAS/FAE and co-morbid ADHD. According to traditional behavioural rating-scales, hyperactivity improved but day-dreaming did not. Also, three of the children experienced appetite-related adverse outcomes (i.e., weight loss). Together these studies reveal the need for randomized control trials that will objectively examine the effects of stimulant medication on multiple cognitive and behavioural parameters in children with FASD.

In 2000, O'Malley and colleagues (2000) published a retrospective analysis on the effects of long and short acting psychostimulant medications in 30 subjects with FASD

and co-morbid ADHD. They found that 79% of subjects who received long-acting dextroamphetamine had a positive clinical response, 29% responded well to short-acting methylphenidate and 27% had a negative reaction to methylphenidate. These findings suggest that although stimulant medication may produce benefits for some patients with FASD, the type of stimulant may need to be tailored to each individual.

Frankel and colleagues (2006) evaluated the impact of traditional stimulant and neuroleptic (antipsychotic) medications on the efficacy of a social skills training program in children with FASD. Primary caregivers and teachers completed the *Social Skills Rating System* (SSRS), which included measures pertinent to friendship, including assertion, self-control and problem behaviour. After the 12-week training program, children taking neuroleptic medication significantly improved on the three parent-reported SSRS outcomes and on one of the teacher-reported SSRS outcomes. When stimulant medication was taken alone, no improvement was found on any of the parent-reported measures. Moreover, it was associated with an increased (poorer) performance on the teacher-rated problem behaviour score.

Doig and colleagues (2008) studied the effects of ADHD-medication (i.e., dextroamphetamine and methylphenidate) in 27 children with FASD and co-morbid ADHD. Teachers were asked to complete a questionnaire pertaining to ADHD-symptoms (i.e., hyperactivity/impulsivity and inattentiveness) before and after the medication trial aimed at treating the symptoms of ADHD. After taking medication, significantly more children achieved a normal score for hyperactivity/impulsivity than for

inattentiveness, suggesting that only particular behavioural symptoms are mitigated with the use of medication.

In general, these findings suggest that aspects of hyperactivity may be ameliorated in children with FASD who receive medication; however, the frequent adverse reactions and impairments to aspects of social behaviour have long-term negative consequences. Without proper large-scale, longitudinal studies that can evaluate the impact of medication in FASD, the positive and negative outcomes cannot be fully appreciated. And unfortunately, a misdiagnosis of ADHD further compounds the problem, and places children with ARND at high risk for adverse reactions to stimulant medication.

## **2.4 Diagnosing ADHD**

The current ADHD diagnostic guidelines use subjective clinical observation and parent and teacher reports that assess the common behavioural problems associated with ADHD: inattention, impulsiveness, and hyperactivity. Recommendations have been made by the American Academy of Child and Adolescent Psychiatry (AACAP) and American Academy of Pediatrics (AAP) with respect to the existing definitions and standards of the Diagnostic and Statistical Manual of Mental Disorders-IV-TR (DSM-IV-TR) (American Psychiatric Association, 2000). According to the DSM-IV-TR, a child must have at least six of nine symptoms associated with inattention or hyperactivity-impulsivity, and these symptoms must be evident in discrete settings, persist for more than six months, and begin before seven years of age. The ADHD disorder is further divided into three subtypes: predominantly hyperactive-impulsive (ADHD-HI), predominantly inattentive (ADHD-I), and combined (ADHD-C). Children who are

predominantly hyperactive-impulsive are physically and mentally overactive; children with the predominantly inattentive subtype tend to “day-dream”; while children with the combined subtype exhibit behaviours from both categories (Castellanos, 1997).

Although the recommendations outlined below increase the likelihood that a child will receive a diagnosis of ADHD, little focus is placed on investigating prenatal alcohol exposure.

#### **2.4.1 American Academy of Child and Adolescent Psychiatry (AACAP) Guidelines**

The AACAP diagnostic guidelines (Dulcan and Benson, 1997) released their recommendations based on scientific literature and clinical opinion. The recommendations relevant to children with prenatal alcohol exposure included: 1) collecting a detailed family history, specifically parental history of drug use (i.e., over-the-counter, prescription and illicit drugs) and psychiatric/medical illnesses; 2) yielding parent and teacher information using one of many narrow-band, ADHD-specific parent and teacher rating scales; and 3) prescribing psychopharmacological agents as part of the primary treatment plan. Although the first guideline requested information pertaining to a history of drug use, alcohol was not specifically included in the recommendation. In the section describing common co-morbidities, FASD was not listed. Hence, obtaining a diagnosis of ADHD prior to an assessment for prenatal alcohol exposure does not encourage the identification of a child with FASD.

#### **2.4.2 American Academy of Pediatrics (AAP) Guidelines**

In 2001, the AAP recommended that all physicians use the DSM-IV criteria to ensure the accurate and consistent diagnosis of ADHD. However, their recommendations

had similar drawbacks to those proposed by the AACAP, which included: 1) an absence of FAS or FASD in the co-morbidity list; and 2) the use of ADHD-specific scales during evaluation. In general, the recommendations increased the likelihood of identifying a child with ADHD, but precluded the future potential of an FASD-related assessment. Therefore, both the FASD and ADHD diagnostic guidelines create barriers for children with ARND to receive an early and accurate diagnosis.

## **2.5 Assessing ADHD**

Clinically, children are typically assessed for ADHD using specific, subjective behavioural observations and checklists. Experimentally, neuropsychological tests are used to identify the components of attention and executive function that may be deficit in ADHD.

### **2.5.1 Behavioural checklists**

Behavioural checklists have been studied in experimental settings to assess differential diagnostic potential. Jensen and colleagues (1997) differentiated children with ADHD from children with pervasive developmental disorder – not otherwise specified (PDD-NOS), as these disorders have many overlapping symptoms including attention problems, impulsive behaviors, and difficulties in the classroom. Each group was assessed using the *Personality Inventory for Children* (PIC), a multi-dimensional emotional and behavioural inventory, and the *Conners' Parent Rating Scale* (CPRS-48), a behavioural rating scale. The PIC variables that greatly distinguished PDD-NOS from ADHD were those that measured unusual behaviors and cognition, poor social skills and problems in relatedness. Also, CPRS-48 scores for hyperactivity were insensitive to the

differences between children with PDD-NOS and ADHD. The authors challenged the use of brief behavioral checklists such as the CPRS-48 in making a diagnosis of ADHD in children with complex or unusual symptoms because such scales tend to emphasize primarily external behaviors and may lead to situations where children are falsely-identified as ADHD.

### **2.5.2 Neuropsychological tests of executive function**

Previous findings from anatomical and functional neuroimaging studies (Castellanos et al., 1996; Rubia et al., 1999) support the theory that people with ADHD have neurological dysfunction in components of fronto-striatal circuitry (Biederman and Faraone, 2002). As the frontal lobe is implicated in executive control (Stuss, 1992; 2002), researchers have sought to investigate executive control in children with ADHD. Children with ADHD perform worse than controls on inhibition tasks (Nigg, 1999) and working memory tasks (Karatekin and Asarnow, 1998). Some researchers have used various neuropsychological testing tools to identify the core deficits associated with ADHD for potential use in differential diagnosis. In a study by Pineda and colleagues (2007), the executive function of 249 children with ADHD and 372 control children between 6 and 11 years of age were assessed using a comprehensive battery of neuropsychological tests. Though the children with ADHD had significantly worse performance than the controls on measures of cognitive effort, auditory skills, working memory, visual-motor skills and verbal comprehension, the test scores overlapped significantly revealing no clinically relevant differences in group performance. This finding was attributed to the fact that ADHD represents a heterogeneous group with a

variety of cognitive problems that vary depending on the etiology. Future comparisons with other neurodevelopmental disorders may enable the identification of key characteristics that are specific to ADHD, and not just for general problems in attention.

## **2.6 Comparison Studies: FASD versus ADHD**

Evidence for a link between prenatal alcohol exposure and ADHD has emerged from clinical research; however, findings lack consistency. There is a clear need for novel, easy to use tools that can differentiate between children with FASD or ADHD.

### **2.6.1 Prenatal Alcohol Exposure and Attention**

Correlations between prenatal alcohol exposure and attention problems have been identified by Streissguth and colleagues (1994) in a population-based, longitudinal prospective study (n = 462). Analyses demonstrated a dose-dependent relation between prenatal alcohol exposure and attention deficits. Based on Mirsky's theory of attention, tenets of focus (i.e., to attend selectively), shift (i.e., to appropriately allocate attentional resources from task to task), sustain (i.e., to maintain alertness while perceiving a signal) and encode (i.e., to maintain information in the working memory while using this information in a cognitive process) were evaluated. Focus and sustain were most strongly correlated with prenatal alcohol exposure; however, test simplicity may have prevented observations of encode and shift impairments.

Interestingly, there was evidence that the attention problems associated with PAE were characteristically different from those seen in children with ADHD. In a longitudinal follow-up report, Brown and colleagues (1991) assessed ADHD-like symptoms in 68 children with and without PAE using the *Child Behaviour Checklist*

(CBC) and a computerized test of attention. Compared to children whose mothers did not drink, children whose mothers drank alcohol throughout pregnancy scored worse in measures of internalizing (i.e., anxiety) and externalizing (i.e. aggression) behaviours and sustained attention. However, when mother's current drinking status was controlled for, only the externalizing behaviours remained significantly worse in the alcohol-exposed group. The children with PAE did not reach clinical significance on any of the CBC measures, they exhibited deficits that were different from the usual ADHD-pattern (e.g., no evidence of impulsivity), and their performance was actually suggestive of mild neurological impairments.

### **2.6.2 Comparing attention in children with FASD or ADHD**

To further investigate differences in attention deficits among children with FASD or ADHD, Nanson and Hiscock (1990) employed computerized tests of visual attention. When selecting matching objects on a choice reaction time task, children with FAS/FAE had increased reaction times but similar error scores compared to children with ADHD or normal controls. When performing a delayed reaction time task, children with FAS/FAE or ADHD made more errors than controls, but only the FAS/FAE group had elevated reaction times. Thus, children with FAS/FAE were unable to make a normal speed-accuracy trade-off.

Unlike Nanson and Hiscock, Kooistra and colleagues (2009a) did *not* find differences in performance between children with FASD or ADHD on a measure of sustained attention. Each group completed a slow event rate continuous performance task where each child was required to fixate on a + symbol and make button-press

responses to target stimuli (but not to non-target stimuli). Both children with FASD or ADHD had increased and variable reaction times and made more errors than controls, thus indicating that problems with sustained attention are common to both clinical groups.

Coles and colleagues (1997) attempted to delineate the attention profiles of children with FAS/FAE or ADHD. Both parents and teachers completed standard behavioural checklists that reliably identified children with ADHD as ADHD; and children with FAS/FAE as not having ADHD (FAS/FAE scores were similar to controls). The neuropsychological tests identified problems in attention for both groups, but the components of the deficit were different. The children with ADHD performed less well on measures of focused and sustained attention, while children with FAS/FAE performed less well on learning new material (encoding attention) and on utilizing flexibility (shifting attention). These results demonstrate unique attention profiles for each clinical group, suggesting differences in the underlying brain deficits associated with FASD or ADHD.

Taken together, these studies illustrate that although attention deficits are commonly associated with FASD or ADHD, current clinical and experimental measures of attention do not produce consistent results that can be used to differentiate these two clinical disorders.

### **2.6.3 Novel experiments for differentiation**

Researchers have adopted novel measures of behaviour and cognition in an attempt to differentiate children with FASD or ADHD. Kooistra and colleagues (2009b)

compared children with FASD or ADHD on tests of balance, recognizing that motor deficits exist in both populations. While children with FASD or ADHD demonstrated performance deficits on tests of perceptuo-motor ability as compared to control subjects, only the children with ADHD were clinically impaired. Greenbaum and colleagues (2009) compared children with FASD or ADHD on measures of social cognition and emotion processing abilities. While both groups showed impairments, children with FASD were most impaired on the tests of social cognition and facial emotion processing, and these were strong predictors for social skills and behavioural problems. Vaurio and colleagues (2008) compared children with FASD or ADHD using standard measures of executive function: the *Wisconsin Card Sorting Task* (WCST), the *Controlled Oral Word Association Test* (COWAT), and the *Trail Making Test* (TMT). Both groups performed poorly in WCST, but ADHD performance was significantly lower than expected based on their IQ and FASD performance was significantly higher than expected based on their IQ. Also, only the FASD group demonstrated an overall letter fluency deficit on the COWAT and significant weakness in the more difficult TMT-B compared to children with ADHD. The results from these studies describe tests that are sensitive to the differences in brain dysfunction between children with FASD or ADHD and that unique neurobehavioural profiles for each group may emerge with further research. These data will be crucial for the development of reliable diagnostic tools that can differentiate these clinical groups.

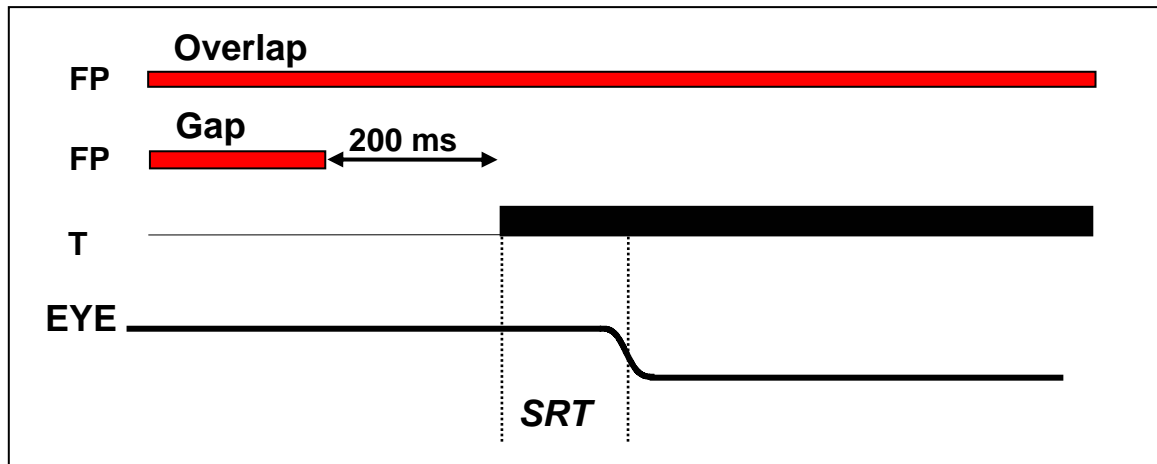
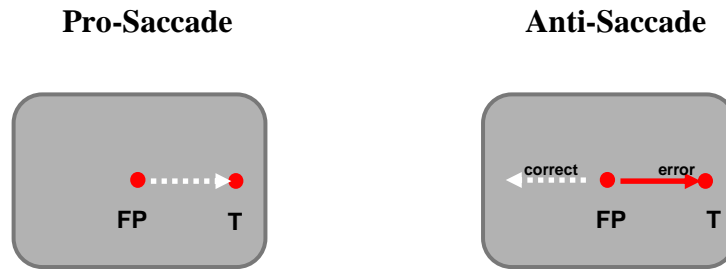
## **2.7 Saccadic eye movement experiments**

### **2.7.1 Studying saccades**

Eye movements have been used as an experimental tool in the clinical neurosciences to explore brain function and dysfunction for nearly 30 years (Leigh and Kennard, 2004). This tool is particularly useful when studying children and adolescents with developmental disorders for a number of reasons. First, the rotation of the globe within the socket is relatively simple, which allows for precise measurements. Second, novel eye tracking systems are non-invasive and produce rich and copious amounts of data for analysis. Third, eye movement paradigms can be designed to probe rudimentary sensorimotor function and higher-order cognitive abilities, like aspects of executive function. Fourth, the well-described neural circuitry for controlling eye movements is based on years of electrophysiological and lesion experiments in monkeys and behavioral imaging and clinical studies in humans. Fifth, normal and abnormal eye movement performances are unique – this allows for connections to be drawn between performance and development, disease, anatomical loci or drug interference. Sixth, eye movement studies have been carried out in various childhood and adolescent clinical populations as the tasks are easy to perform (for review see Rommelse et al., 2008). Thus, eye movement tasks may provide an objective and sensitive measure of brain dysfunction in children with ARND or ADHD, and may also provide a basis for differentiating these two groups.

A distinct class of eye movement that is central to this thesis is the saccade - a quick coordinated movement of both eyes to redirect the line of sight to an object of interest

(Leigh and Zee, 2006). Two types of saccades that have served much experimental utility are the pro-saccade (an automatic, visually-guided saccade generated toward novel stimuli) and the anti-saccade (a volitional, goal-directed saccade generated in the opposite direction of a target) (Leigh and Kennard, 2004). In the pro-saccade task, subjects are seated in front of a visual screen and instructed to fixate on a central fixation point (FP). After a brief delay, a peripheral target (T) appears to the right or left of the FP and the subject must look toward the T (Figure 2.1). Visual and saccadic inputs from the parietal lobe to the intermediate layers of the superior colliculus (SCi) mediate these saccades (Pare and Wurtz, 1997). The speed of visual processing is measured by the saccade latency and the regulating processes of saccade initiation are gauged by the variability of the saccade latency. The anti-saccade task is considerably more difficult to execute because it requires two steps: 1) the suppression of the automatic saccade towards the T; and 2) the initiation of a voluntary saccade to an internally generated location in the opposite direction to the T (Everling & Fischer, 1998; Hallet, 1978). Anti-saccades measure voluntary control and can be used to assess executive function (Munoz and Everling, 2004). Thus, the production of the anti-saccade involves higher-order brain centers, including the frontal cortex and the basal ganglia (Gaymard et al., 1998; Hikosaka et al., 2000). This task is particularly interesting to use when studying children and/or adolescents as performance improves with age (between 5 and 15 years) and is correlated with the maturation of the frontal cortex and basal ganglia (Munoz et al., 1998;2003; Luna et al., 2001).



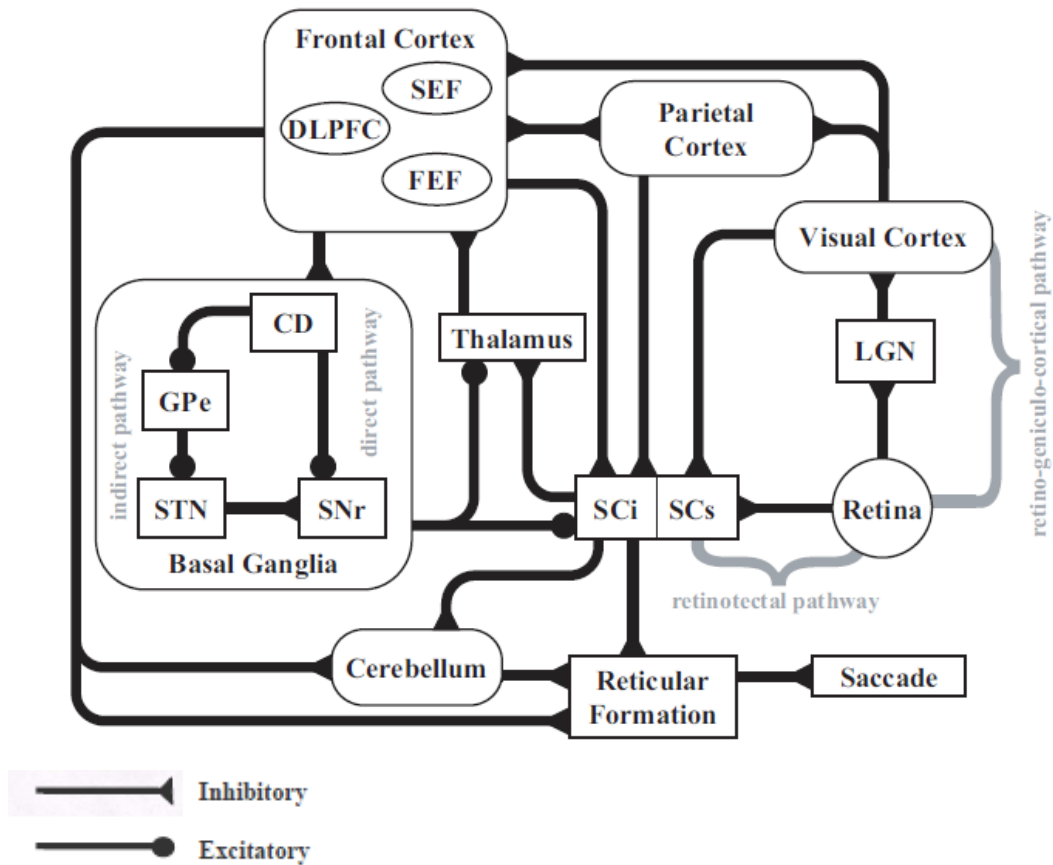
**Figure 2.1 Saccade paradigm.**

Pro-Saccade: subject looks from fixation point (FP) towards target (T). Anti-Saccade: subjects look from FP towards mirror opposite location of T. In this study, the fixation condition of the FP was manipulated in both tasks. In the overlap condition, the FP remained illuminated while the T appeared. In the gap condition, the FP disappeared 200ms prior to T onset. SRT: Saccadic reaction time. EYE: eye trace.

### **2.7.2 Neurophysiology of saccadic eye movement**

The horizontal saccade is performed through the rotation of the eye within the socket and is controlled by the lateral and medial rectus muscles. Motoneurons (MN) within the cranial nerves 3 (oculomotor) and 6 (abducens) innervate these muscles to move the eye with respect to the head. During a target-elicited saccade, the brain has the task of transforming the visual signal from the target into a motor command to move the eyes. The MN discharge a burst of action potentials during a saccade and maintain tonic discharge during fixation (Leigh and Zee, 2006). The premotor command for the MN is generated by the brainstem premotor circuitry within the reticular formation, and it includes the excitatory and inhibitory burst neurons (EBN and IBN), long-lead burst neurons (LLBN) and omnipause neurons (Sparks, 2002). EBN and IBN, which innervate the MN directly, are silent during fixation and discharge bursts of action potentials for saccades. The EBN and IBN are tonically inhibited by the OPN. Thus the OPN must be inhibited prior to a saccade (Yoshida et al., 1999) in order to allow excitatory inputs from the LLBN to innervate the EBN and IBN to initiate a saccade.

As seen in Figure 2.2, the SCi has direct projections to the premotor circuitry, and most high-level brain areas (i.e., frontal lobe, parietal lobe, basal ganglia) influence the premotor circuitry via the SCi. The neurons of the SCi with direct projections to the premotor circuitry include saccade neurons, which increase their discharge before and during saccades; and the fixation neurons, which are tonically active during visual fixation and pause during saccades (Munoz and Fecteau, 2002; Munoz et al. 2000). Cells with similar firing patterns are found within the frontal eye fields (FEF) of the frontal



**Figure 2.2 Saccade control pathways.**

Pro-saccades occur following the sudden appearance of a visual stimulus, and are controlled by the SCi, with inputs from the visual and parietal cortices. Anti-saccades are internally generated and rely on higher brain centers including the frontal cortex [Reproduced with permission (Munoz et al., 2007)]. CD: caudate nucleus; DLPFC: dorsolateral prefrontal cortex; FEF: frontal eye fields; GPe: external segment of the globus pallidus; LGN: lateral geniculate nucleus; SEF: supplementary eye fields; SCi: intermediate layers of superior colliculus; SCs: superficial layers of superior colliculus; SNr: substantia nigra pars reticulata STN: subthalamic nucleus.

lobe (Schall, 2002; Segraves and Goldberg, 1998; Sommer and Wurtz, 1998) and within cells of the posterior parietal cortex (PPC; Barash et al., 1991a;b; Wurtz et al 2001); these three areas are highly interconnected (Wurtz et al., 2001; Munoz et al., 2007). Of interest, the area of the brain involved in the sensory-motor transformation of visual signal to the saccade premotor command is the lateral intraparietal area (LIP) of the parietal lobe (Andersen et al., 1997). The frontal lobe also contains a number of fields important to saccade control: the frontal eye fields (FEF), supplementary eye fields (SEF) and dorsolateral prefrontal cortex (dlPFC), all of which project directly or indirectly (via the basal ganglia) to the SCi. The SCi sends feedback to the FEF via the thalamus (Sommer and Wurtz, 2004).

The pathways from the frontal lobe through the basal ganglia to the SCi involve multiple steps and help to involve motivation and reward activity in the planning of a saccade (Hikosaka et al. 2000; 2006). Two pathways, the direct and indirect, have been well described (Munoz et al., 2007; Hikosaka et al., 2000; 2006). In the direct pathway, frontal lobe activation causes excitation of GABAergic neurons in the caudate nucleus (CN). These inhibitory neurons synapse onto inhibitory neurons of the substantia nigra pars reticulata (SNr) which results in the disinhibition of the SCi. In the indirect pathway, the CN exerts an effect on the SNr via the external segment of the globus pallidus (GPe). GABAergic neurons in GPe project to the subthalamic nucleus (STN), which then sends excitatory projections to the SNr causing the inhibition of the SCi. In general, activation of the direct pathway leads to disinhibition of the SCi while activation of the indirect pathway causes inhibition of the SCi. Considering the multiple areas

involved in the precise control of visually triggered or volitionally generated saccades, abnormal performance on the pro- or anti-saccade task can be interpreted to indicate damage at one of many sites or connections.

### **2.7.3 Saccadic eye movements in ARND or ADHD**

To date, there are only two published studies of saccadic eye movements in children with FASD. In a small sample of children with FASD, Green and colleagues (2007) found children between the ages of 8 and 12 years to have elevated saccade latency (saccadic reaction time; SRT) and direction errors in both the pro- and anti-saccade task compared to controls. In a larger study Green and colleagues (2009a) demonstrated elevated SRT, increased variability of SRT, and an increase in direction errors in the FASD population as compared to controls. In a preliminary analysis using pro- and anti-saccade tasks, Verney and colleagues (2008) found that compared to control subjects, children and teenagers with FASD had similar pro-saccade SRT but elevated anti-saccade SRT. They suggested that difficulty with the voluntary motor command to look away from the target in the anti-saccade task is due to inhibitory dysfunction that may translate to other cognitive and behavioral problems. Willford and colleagues (2008) studied the role of motivation and reward in young adults with FASD during the pro- and anti-saccade task. While they did not report the behavioural results, preliminary analysis of fMRI imaging data demonstrated that the subjects with PAE did not show activation in brain regions associated with reward and anticipation. Also, compared to controls, subjects with PAE had more activation in the FEF during the preparatory phase before the target appears. The authors suggested variable performance in tests of

cognitive control in FASD may involve abnormal functioning of the areas responsible for reward and motivation.

There is a growing body of literature of eye movement experiments comparing children with ADHD to control subjects. Though there are some inconsistencies, the general finding is that subjects with ADHD have altered performance on pro- and anti-saccade tasks compared to typically developing controls. Pro-saccade studies reveal that children with ADHD have increased variability in pro-saccade SRT as compared to controls (Mostofsky et al. 2001; Munoz et al. 2003), which suggests deficits in the regulatory processes of saccade initiation. In the anti-saccade task, subjects with ADHD have also demonstrated increased variability of SRT (Munoz et al. 2003) and make more direction errors than controls (Klein et al., 2003; Mostofsky 2001; Munoz et al., 2003). These findings are in line with clinical evidence which demonstrates that subjects with ADHD have difficulty with cognitive control, response inhibition and working memory (Brown, 2005).

While eye movement studies provide a wealth of knowledge about control during simple and higher-order cognitive behaviours in children with FASD or ADHD, the two groups have never been directly compared.

## **2.8 Research Rationale, Hypotheses and Objectives**

Early and accurate diagnosis is a protective factor against the secondary disabilities common in people with FASD and leads to proper interventions for the best long-term outcomes. To date, much of the literature that evaluates the behavioural and neuropsychological profiles of children with FASD or ADHD has revealed inconsistent

results. Also, few studies have focused on non-dysmorphic children with prenatal alcohol exposure – those who may be most likely to face obstacles in diagnosis. The purpose of this thesis research was to investigate the use of computer-based tests of executive function and saccadic eye movement tasks in differentiating children with ARND or ADHD. The following general research hypotheses were tested:

- Children with ARND or ADHD demonstrate significant differences in executive function domains, where children with ARND reveal poorer executive control in tasks of attention, planning, strategy and spatial working memory than children with ADHD.
- Children with ARND or ADHD exhibit characteristically different eye movement profiles such that children with ARND reveal poorer oculomotor control in the pro- and anti-saccade tasks than children with ADHD.

The following research objectives were addressed:

- Elucidate specific patterns of executive function deficits that are unique to children with ARND or ADHD
- Delineate specific patterns of oculomotor control that are unique to children with ARND or ADHD using saccadic eye movement tasks

## **Chapter 3**

### **Methods**

#### **3.1 Participants**

All experimental procedures were reviewed and approved by the respective Research Ethics Boards at Queen's University, the Children's Hospital of Eastern Ontario, and the University of Alberta. At the beginning of each session, caregivers and children were toured through the laboratory and given a brief explanation of the equipment and tasks. Parental consent was obtained before testing and data collection. Subjects received refreshments (water and granola bars) during the session, and a \$10 gift card for participating in the study. The ARND cohort represents a subset of children from a large, multi-centre study that included eight testing sites across Ontario and one in Alberta, in which approximately 200 children were recruited for eye movement and neuropsychological testing, as previously described (Green et al., 2009a; Green et al., 2009b). Forty-two children between the ages of 8-15 years [ $10.8 \pm 0.3$  years, M:F 23:19] had been previously diagnosed with ARND through local diagnostic clinics and in accordance with the Canadian Diagnostic Guidelines (Chudley et al., 2005). Among these patients, 15 were medication naïve or had discontinued the use of prescribed psychoactive drugs due to lack of efficacy or adverse reaction. Sixteen of the 20 stimulant-medicated subjects refrained from taking stimulant medication on the day of testing. Thirty-one children between the ages of 9-15 years [ $11.7 \pm 0.3$  years, M:F 23:8] with a diagnosis of ADHD were recruited from the same testing sites. All had previously

received a diagnosis from their pediatrician according to the DSM-IV-TR. Among the 31 subjects, 7 were medication naïve or had discontinued prescription of psychoactive medication citing lack of efficacy or adverse reaction as the reason. Eighteen of the 22 children taking stimulant medication refrained from medication on the day of testing. Demographic information describing each subject group is presented in Table 3.1. Eye movement data from 2 subjects with ADHD were lost due to equipment failure.

### **3.2 CANTAB®**

The *Cambridge Neuropsychological Test Automated Battery* (CANTAB®, Cambridge Cognition, Cambridge, United Kingdom) is a published, experimental neuropsychological testing tool. A battery of four tests was selected to assess attention, planning, strategy and spatial working memory. In a quiet room, subjects were seated comfortably in front of a laptop screen. All tasks were completed using the touch-screen or press pad. The CANTAB® tasks were: Reaction Time (RTI), Match to Sample Visual Search (MTS), Stockings of Cambridge (SOC) and Spatial Working Memory (SWM). Four children with ARND failed the SOC practice portion and were not allowed to continue to the testing portion, so full datasets were not obtained from these subjects. Before each task, the instructor verbally explained and manually demonstrated each set of rules followed by a brief practice phase (where applicable). Test phase was initiated after successful completion of the practice phase.

In the RTI task, there were two conditions: simple and 5-choice. In the simple condition, the subject pressed down on a press pad until a yellow dot appeared in the centre of a single circle. In the 5-choice condition, the yellow dot appeared in one of

**Table 3.1 Demographics for children with ARND or ADHD**

<i>Category</i>	<i>ARND, n=42</i>	<i>ADHD, n=31</i>
Age $\pm$ SEM (years)	10.8 $\pm$ .3	11.7 $\pm$ .3
Male:Female	23:19	23:8
<b><i>Medication</i></b>	<b><i>n (%)</i></b>	<b><i>n (%)</i></b>
Stimulant	20 (48)	22 (70)
Antipsychotic	14 (33)	2 (6)
Antidepressant	5 (12)	1 (3)
Anticonvulsant	1 (2)	1 (3)
Other	8 (19)	6 (19)
<b><i>Co-morbidity</i></b>	<b><i>n (%)</i></b>	<b><i>n (%)</i></b>
Sleeping Disorders	26 (62)	8 (26)
ADHD	22 (52)	31 (100)
Oppositional defiant disorder	11 (26)	3 (10)
Anxiety	9 (21)	2 (6)
Asthma	4 (10)	2 (6)
Depression	6 (14)	0 (0)
<b><i>Guardian information</i></b>	<b><i>n (%)</i></b>	<b><i>n (%)</i></b>
Living with biological parents	12 (29)	27 (87)
Parent/Caregiver skilled employment	11 (26)	14 (45)
Parent/Caregiver level of education (mean $\pm$ SEM)	14 $\pm$ 3	15 $\pm$ 3

*Other* drugs include allergy medication and sleeping aids. Parent/Caregiver level of education refers to the number of years the parent/guardian spent in school from grade 1 to grade n years.

5 different concentric circle locations. Upon the appearance of the yellow circle, the subject was instructed to release the press pad and quickly and accurately touch the yellow circle. The monitor provided an auditory and visual feedback based on the correct or incorrect response. The outcome measures for RTI were reaction time (time to release press pad after the yellow circle appeared) and movement time (time to touch the screen after releasing the press pad).

In the MTS task, a red box appeared in the centre of the screen concentrically surrounded by 8 empty square boxes. Upon pressing down on the press pad, a pattern appeared in the centre square, and after a brief delay, patterns appeared in 2, 4 or 8 of the surrounding squares. Of the patterns, only one was a perfect match to the pattern in the middle, and upon recognition the subject was instructed to release the press pad and touch the correct pattern. The outcome measures included decision time (the time from when the surrounding patterns appeared to when the subject visually identified the matching pattern and released the press pad) and movement time (the time from when the press pad was released to when the subject selected the matching pattern on the touch screen) for each n-choice (i.e.,  $n = 2, 4$  or  $8$ ) problem, and percent of correct trials.

In the SOC task, the computer screen was divided horizontally into two; the top portion representing the computer's problem set and the bottom the subject's. Each problem set was comprised of three "stockings" of different lengths and 3 different coloured balls (green, red and blue). In the *copy* mode, the computer created a problem set in the top portion of the screen and subjects were to copy this same configuration by moving their coloured balls so that the two displays were identical. The minimum

number of moves required to solve the problem (i.e., 2 moves, 3 moves etc.) was indicated in the corner and task difficulty increased as the number of moves increased. In the *follow* mode, subjects immediately mimicked each move made by the computer using their own balls. The initial thinking time outcome measure was determined by taking the difference between the copy and follow modes, thus controlling for differences in motor function between subjects. Outcome measures included the mean number of moves for each n-move problem (i.e., n = 2, 3, 4 or 5) and the initial mean thinking time for each n-move problem and the total number of problems solved in the minimum number of moves.

In the SWM task, randomly distributed coloured boxes were presented on the screen. Subjects had to locate hidden tokens that appeared under each coloured box to fill an empty panel on the right-hand side. Once a token was located, the box closed so that it appeared identical to the other boxes. Subjects had to remember that the computer would never hide a token in a coloured box previously found to contain a token, and to therefore, *not* revisit those boxes. The task had a number of outcome measures that included total number of errors (returning to a box previously found to contain a token), mean time to the first response (the mean time between the problem being presented to the subject and the subject selecting the first box to open), mean time to the last response (the mean time between the problem being presented to the subject and the subject selecting the box with the final token for a problem), mean token preparation time (the mean time a subject takes when selecting any box to search for a token after a token has

been found) and a strategy score, which indicated the use of a search strategy (where low scores indicated good strategy use).

### **3.3 Saccadic eye movement recording**

Each participant was seated in a quiet, dark room and a head-mounted, video-based eye tracker (ISCAN Inc., Burlington, MA) was fitted comfortably on their head. To reduce movement, a chin rest was positioned at 45.8 cm from the laptop screen (Toshiba V2.10 Tecra S2 laptop LCD display). The fixation point (FP) appeared in the center of the screen and the peripheral targets (T) appeared at 15° to the right or left of the FP as red dots (luminosity of ~12.5cd/m<sup>2</sup>; and x=0.57 and y=0.32 coordinates in CIE space relative to the background lumination of ~1.0cd/m<sup>2</sup>; and x=0.34 and y=0.34 coordinates in CIE space). Each trial began with a 250 ms period of darkness followed by the appearance of the FP for 1,000 ms. In the gap condition, the FP was extinguished 200 ms before the eccentric T appeared on the opposite side of the screen. In the overlap condition, the FP remained illuminated while the eccentric T appeared. For pro-saccade blocks, the participant was instructed to look from the FP towards the T as soon as it appeared. In the anti-saccade blocks, participants were instructed to look away from the eccentric T to the opposite side of the screen. The eccentric T remained illuminated for 1,000 ms, after which all visual presentation disappeared and the background illumination reappeared, indicating the end of that trial. The visual screen was diffusely illuminated between trials to avoid dark adaptation. Target location (right or left) and fixation condition (gap or overlap) were pseudo-randomly interleaved throughout each block of trials. The task consisted of two blocks each of pro-saccade and anti-saccade

trials, with 80-trials per block. Subjects were asked to repeat and demonstrate the instructions to the experimenter to ensure that they understood the paradigm before beginning each block.

### **3.3.1 Apparatus**

Data acquisition was performed using a Dolch flexpac with a processor speed of 2.00 GHz. Eye movement paradigms were generated using E-prime software (E-Studio, Psychology Software Tools, Inc, Pittsburg, PA). The head-mounted video-based infrared eye-tracker recorded the movement of the pupil by extracting measures of horizontal eye position and size at a sampling rate of 240 Hz. Only the left eye position was digitized. Saccades were detected offline at 3 standard deviations above the background and lasted longer than 5 sample points (Matlab, custom software).

### **3.3.2 Saccadic outcome parameters**

Saccadic reaction time (SRT) was defined as the time from stimulus appearance to initiation of the first saccade that exceeded  $30^{\circ}/s$ . The mean SRT in the pro-saccade and anti-saccade task was computed from trials with reaction latencies between 90 and 1000 ms. Saccades made before 90 ms were marked as anticipatory errors (Munoz et al., 1998) and saccades between 90 and 140 ms were marked as express saccades (Fischer et al., 1993), which are the shortest latency visually triggered saccades (Fischer and Ramsperger, 1984); this express epoch was confirmed for the mobile laboratory. Saccades were scored as incorrect if the first saccade after the appearance of the stimulus was in the wrong direction relative to the instruction (i.e., away from the target in the pro-

saccade, toward the target in the anti-saccade). Corrective saccades are saccades in the correct direction but initiated after a direction error.

The following parameters were computed for each fixation condition (gap and overlap): a) for both tasks: the mean SRT for correct trials, the coefficient of variation (CV) of SRT for correct trials [ $CV = (\text{standard deviation}/\text{mean}) \times 100$ ], the percentage of anticipatory errors; b) pro-saccade task only: the percentage of express saccades; c) anti-saccade task only: the percentage of direction errors and percent of corrective saccades.

### **3.4 Data analysis**

CANTAB and oculomotor parameters were analyzed using a univariate analysis of variance (ANOVA) with  $\alpha$  set at 0.05. Univariate analysis of co-variance (ANCOVA) was performed using age as a covariate when exploratory analysis demonstrated a correlation between age and the dependent variable. Data were analysed by non-parametric Mann–Whitney tests when the conditions for normal distribution were not met.

## Chapter 4

### Results

#### 4.1 CANTAB®

##### 4.1.1 Reaction Time (RTI)

The univariate ANCOVA for RTI revealed no difference in performance between children with ARND or ADHD for reaction time in the simple choice condition ( $F(1,70)=.16, p=.69$ ). Because the conditions for homogeneity were not met, Mann-Whitney analysis was completed and revealed no difference in performance between the groups for reaction time in the five-choice ( $p=.99$ ) condition. The ANOVA found no differences for movement time in the simple choice ( $F(1,71)=3.13, p=.08$ ) or five-choice ( $F(1,71)=.48, p=.49$ ) conditions (Table 4.1).

##### 4.1.2 Match to Sample Visual Search (MTS)

The univariate ANCOVA revealed a significant difference in mean decision time between the two groups such that subjects with ARND had significantly longer decision times compared to the children with ADHD ( $F(1,69)=5.90, p=.02$ ) (Fig. 4.1A). There was no significant difference between groups with respect to mean movement time ( $F(1,70)=1.19, p=.28$ ) (Fig 4.1B) or the percent of correct trials ( $F(1,70)=.885, p=.36$ ) (Table 4.1).

##### 4.1.3 Stockings of Cambridge (SOC)

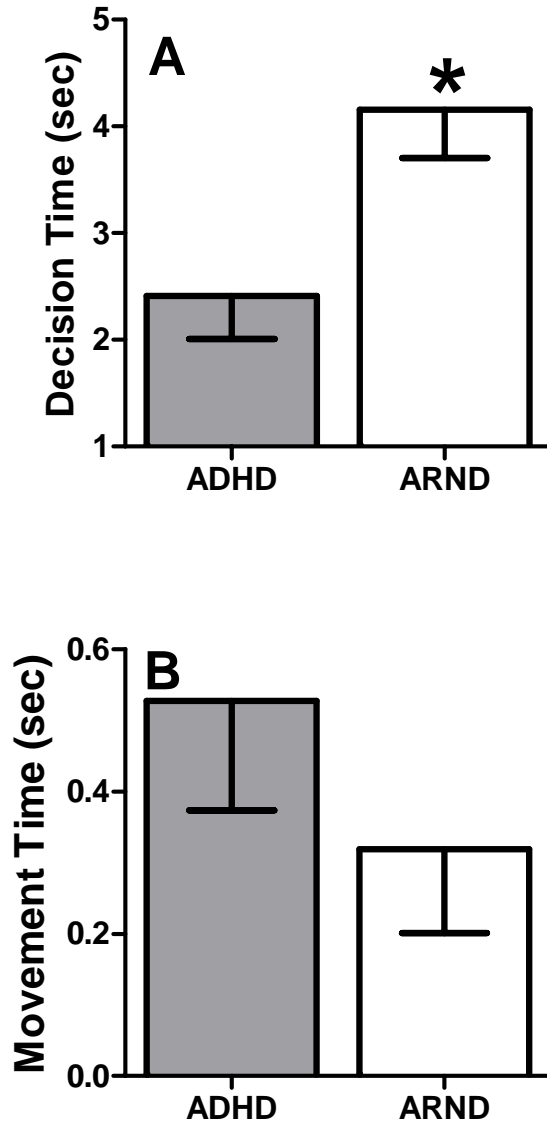
In SOC, subjects are encouraged to plan their moves before actually enacting the solution. Mean initial thinking time for n-choice problems was analyzed using the non-

**Table 4.1 Tabular results for CANTAB® outcome measures**

Data are expressed as the mean ± SEM.

<b>Task (unit)</b>	<b>condition</b>	<b>ADHD</b>	<b>ARND</b>	<b>p-value</b>
<i>RTI</i>				
Reaction time (ms)	1-choice	366±16	389±14	.69
	5-choice	388±12	399±14	.99
Movement time (ms)	1-choice	537±33	621±32	.08
	5-choice	587±26	613±27	.49
<i>MTS</i>				
Percent correct (%)		91±1	92±2	.36
<i>SOC</i>				
Mean moves (n moves)	2-ball	2.1±0.1	2.1±0.1	.57
	3-ball	3.3±0.1	3.1±0.1	.38
	4-ball	5.7±0.2	5.5±0.2	.44
	5-ball	7.4±0.2	7.3±0.2	.71
Mean thinking time (sec)	2-ball	2.5±0.3	2.2±0.4	.98
	3-ball	4.0±0.7	6.2±1.2	.30
	4-ball	3.8±0.7	5.1±0.7	.25
	5-ball	4.8±0.2	5.5±1.1	.18
Problems solved in min. moves (# of problems)		6.9±0.3	7.5±0.2	.13
<i>SWM</i>				
Strategy (strategy score)		35±0.8	36±0.7	.95
Total Errors (n errors)		40±3	43±3	.66

## Match to Sample (MTS)



**Figure 4.1 Match to Sample Visual Search (MTS)**

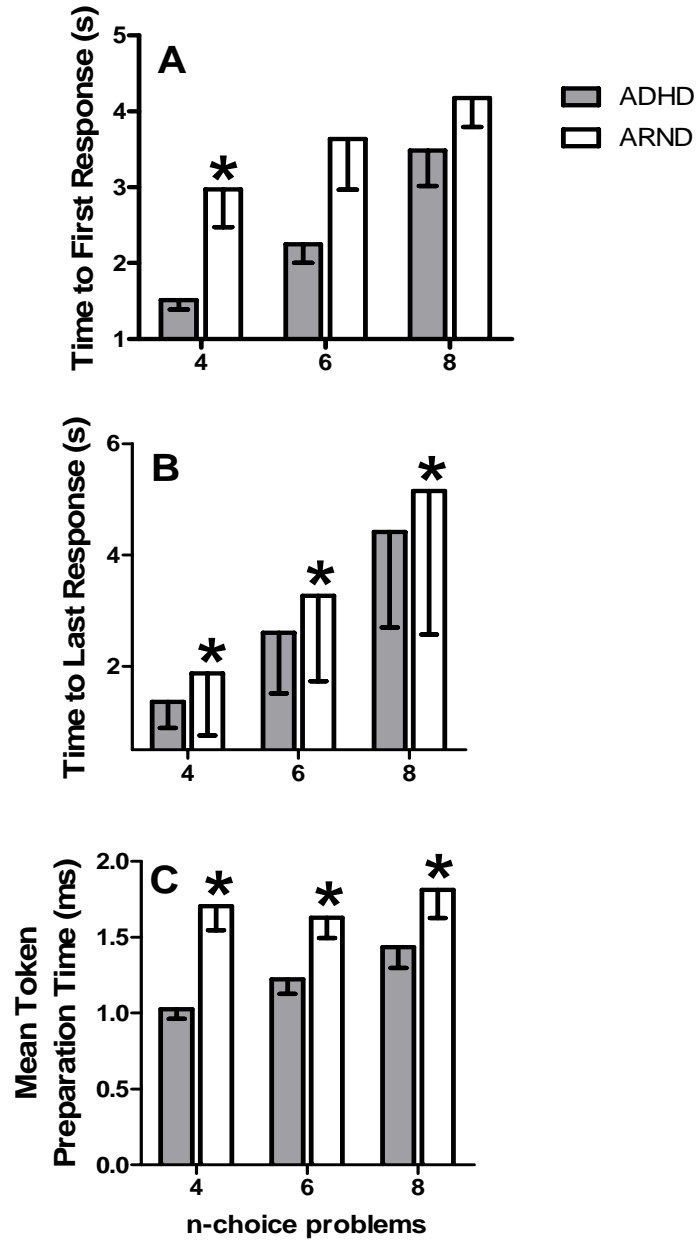
(A) Mean decision time (seconds); and (B) mean movement time (seconds) for subjects with ADHD or ARND. \* $p < 0.05$  compared to subjects with ADHD.

parametric Mann–Whitney test because the conditions for homogeneity were not met, and no significant differences between groups were found in the 2- ( $p=.98$ ), 3- ( $p=.30$ ), 4- ( $p=.25$ ) and 5-choice ( $p=.18$ ) problems, suggesting both groups took the same amount of time to plan the problem solution. The univariate ANOVA revealed no difference between groups on the mean number of moves for children to complete each n-choice problem [2-move: ( $F(1,66) = .33, p=.57$ ); 3-move ( $F(1,66) = .79, p=.38$ ); 4-move ( $F(1,66) = .62, p=.44$ ); 5-move: ( $F(1,66) = .14, p=.71$ )]; and no difference in performance on the number of problems solved in the minimum moves ( $F(1,66)=2.40, p=.13$ ) (Table 4.1).

#### **4.1.4 Spatial Working Memory (SWM)**

The ANOVA revealed no significant differences in performance between groups with respect to the total number of errors ( $F(1,71)= .20, p=.66$ ), nor did the Mann-Whitney test demonstrate differences in strategy scores between groups ( $p=.95$ ), suggesting no differences between the groups in the use of a systematic approach to solving each problem (Table 4.1). Time to first response, time to last response and mean token preparation time were analyzed using the Mann–Whitney test. Compared to subjects with ADHD, subjects with ARND took significantly longer to make their first response in the 4-box condition ( $p<.005$ ) and this trend was also present in the 6- ( $p=.08$ ) and 8-box ( $p=.08$ ) conditions (Fig. 4.2A). Compared to the children with ADHD, subjects with ARND took significantly longer to select the last box of a search pattern during the 4- ( $p<.0001$ ), 6- ( $p<.005$ ) and 8-box ( $p<.05$ ) conditions (Fig. 4.2B). Finally,

## Spatial Working Memory (SWM)



**Figure 4.2 Spatial Working Memory (SWM)**

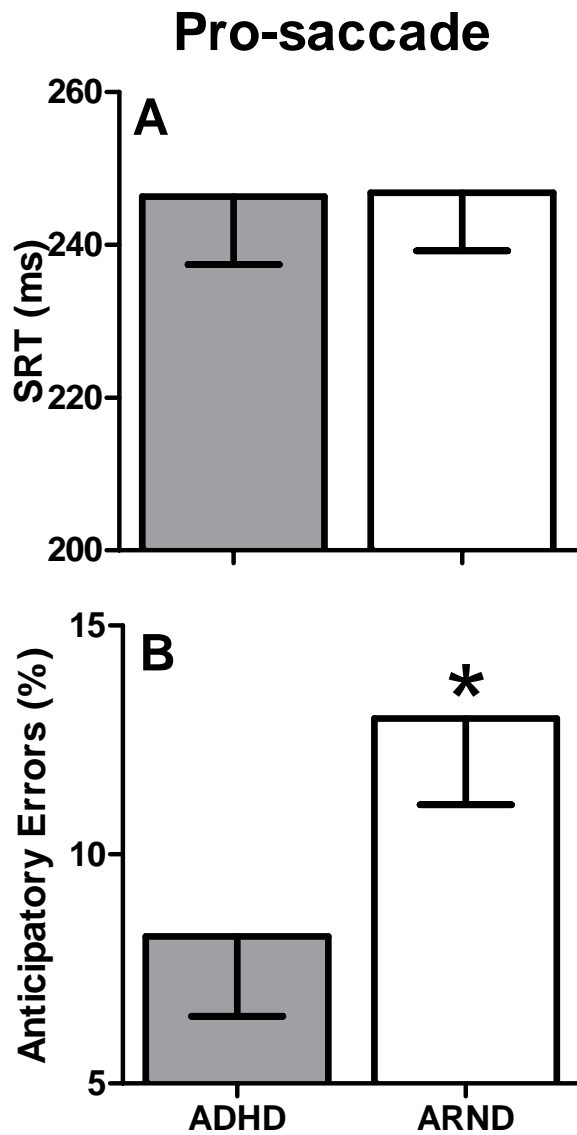
(A) Mean time to first response; (B) Mean time to last response; (C) Mean token preparation time for n-box problems. Open bars, ARND data; shaded bars, ADHD data. \* $p < 0.05$  compared with ADHD subjects.

subjects with ARND had significantly greater mean token preparation time during box selection than children with ADHD on the 4- ( $p < .0001$ ), 6- ( $p < .05$ ) and 8-box ( $p = .05$ ) conditions (Fig. 4.2C). Thus, in comparison to children with ADHD, the children with ARND were significantly delayed in response performance.

## **4.2 Saccadic eye movements**

### **4.2.1 Pro-saccade task**

All eye movement parameters were collapsed across condition as the exploratory ANOVA showed no significant interaction between group and fixation state (all  $p$ 's  $> .1$ ). For pro-saccades, the following parameters (SRT and CV) were analyzed using a univariate ANCOVA with age as the covariate. The mean SRT was not different between groups ( $F(1,66) = .002, p = .97$ ) (Fig. 4.3A). The intra-subject variance of SRT, expressed as the CV, also was not different between groups (ARND:  $45 \pm 2$ ; ADHD:  $45 \pm 2$ ; mean  $\pm$  SEM;  $F(1,66) = .585, p = .45$ ). The percent of express saccades and percent of anticipatory errors were analyzed using the non-parametric Mann–Whitney test. There was no difference in the percent of express saccades between groups (ARND:  $15 \pm 2$ ; ADHD:  $16 \pm 3$ ; mean  $\pm$  SEM;  $p = .28$ ). In contrast, the frequency of anticipatory errors did reach statistical significance such that children with ARND made more anticipatory errors compared to children with ADHD (Fig. 4.3B;  $p < .05$ ).



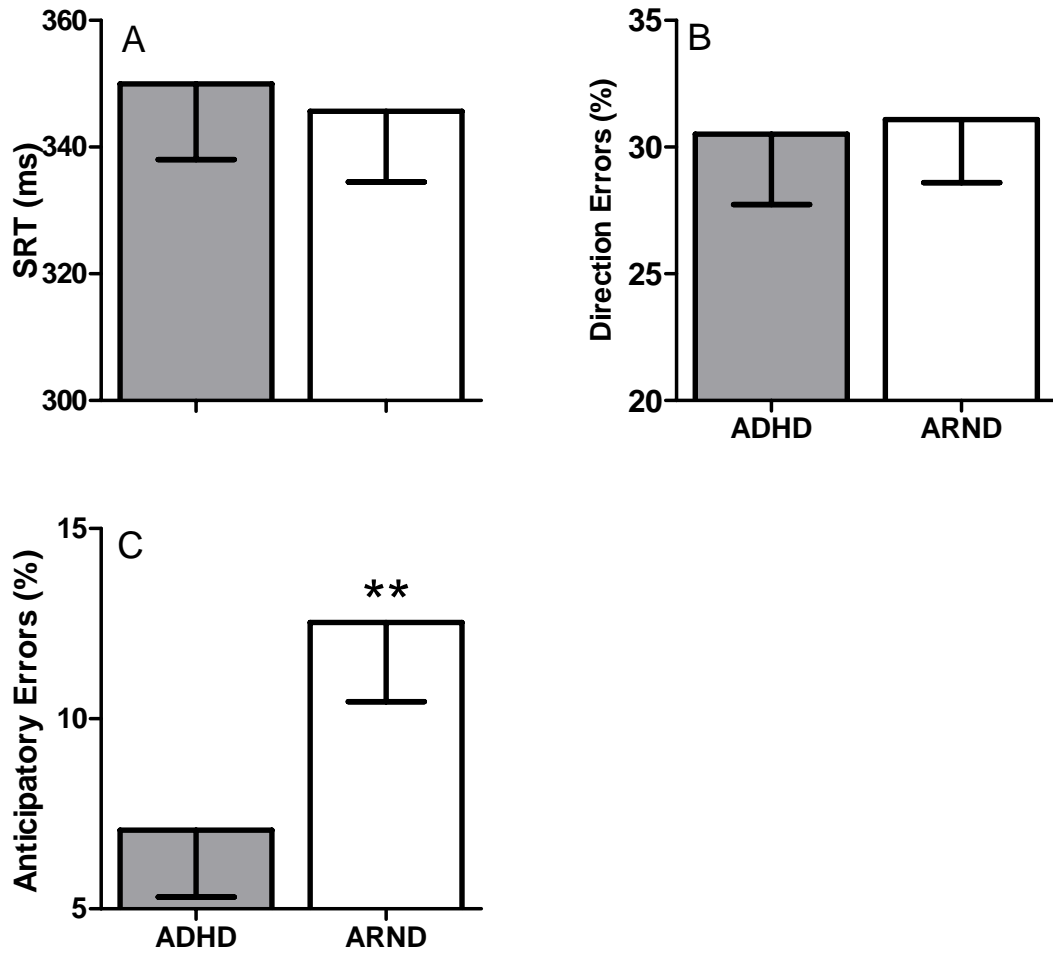
**Figure 4.3 Pro-Saccade Task.**

(A) Mean saccadic reaction time (SRT) for correct response; (B) percentage of anticipatory errors. \* $p < 0.05$  compared with ADHD subjects.

#### 4.2.2 Anti-saccade task

SRT for the anti-saccade task was analyzed using the non-parametric Mann-Whitney test and the mean SRT was not significantly different between groups ( $p=.92$ ) (Fig. 4.4A). The CV of SRT, the percent of direction errors and the percent of corrective saccades were analyzed using a univariate ANCOVA with age as the covariate. There was no difference between groups with respect to CV of SRT (ARND:  $34 \pm 1$ ; ADHD:  $36 \pm 1$ ; mean $\pm$ SEM;  $F(1,65)=.81$ ,  $p=.37$ ), nor were there differences between groups in the percent of direction errors generated ( $F(1,65)=.25$ ,  $p=.62$ ) (Fig. 4.4B) or in the percent of corrective saccades (ARND:  $57 \pm 4$ ; ADHD:  $57 \pm 4$ ; mean $\pm$ SEM;  $F(1,65)=.157$ ,  $p=.693$ ) generated. ANOVA suggested that the percentage of anticipatory errors was greater for children with ARND compared to children with ADHD ( $F(1,66)=3.64$ ,  $p=.06$ ), although the analysis failed to reach statistical significance at the  $p<.05$  level (Fig. 4.4C).

## Anti-saccade



**Figure 4.4 Anti-Saccade Task.**

(A) Mean saccadic reaction time (SRT) for correct responses; (B) percentage of direction errors; and (C) percentage of anticipatory errors. \*\* $p=0.06$  compared with ADHD subjects.

## **Chapter 5**

### **Discussion**

#### **5.1 General findings**

The current study sought to investigate whether there are measurable differences in executive function and eye movement control between subjects with ARND or ADHD. Executive function and eye movements were assessed to further delineate the neurobehavioural profiles of each group. Multiple domains of executive function were examined using a battery of tasks from the CANTAB®, and oculomotor control was investigated using pro- and anti-saccade eye tracking paradigms that objectively tested sensorimotor function and cognitive control. We hypothesized that children with ARND would demonstrate poorer performance on CANTAB® tasks of attention, planning, working memory and strategy and on the pro- and anti-saccade eye movement tasks compared to children with ADHD. Our results revealed that compared to children with ADHD, children with ARND had increased 1) decision times in the MTS task; and 2) time to first and last responses and mean token preparation time in the SWM task; and 3) anticipatory errors in the pro- and anti-saccade tasks. These findings will now be discussed as they relate to neurobehavioural performances in children with prenatal alcohol exposure or ADHD. Potential mechanisms underlying the differences in eye movement control will be discussed in relation to oculomotor neurophysiology and studies of brain structure/function in children with prenatal alcohol exposure or children with ADHD.

## **5.2 CANTAB®**

MTS measures the speed/accuracy tradeoff employed by a subject when searching for matching visual patterns. Children with ARND exhibited elevated decision time compared to subjects with ADHD, however both groups had similar movement times and error rates. Similarly, Nanson and Hiscock (1990) found children with FASD to have elevated reaction times (time from stimulus presentation to selection of the matching pattern) but similar error rates as children with ADHD on a computer-based visual matching choice reaction time task. In line with this finding, the subjects with ARND in our study may be less efficient in response execution with regard to a visuospatial task when compared to subjects with ADHD. Decision time in the MTS test includes the time spent processing the visual characteristics of the patterns and processing the spatial location of the false versus matching patterns. Mattson and colleagues (1996) found that, on a copy and recall test, children with FASD demonstrated difficulty processing the global and local features of complex visual stimuli (Mattson et al. 1996). Uecker and Nadel (1996) reported that subjects with FASD demonstrated deficits in spatial arrangement, processing and reproducing spatial information on a ‘memory for objects’ test, and showed visuospatial deficits on a test of visuomotor integration (Uecker and Nadel, 1996). It has been stated that children with FASD have general difficulties in processing speed that contribute to performance deficits (Jacobson, 1998), and Kodituwakku (2009) has recently described that the processing deficits are most apparent on tests involving complex information (Kodituwakku, 2009). Thus poor visual and

spatial processing may contribute to the elevated decision times in ARND in this study. Deficits in processing complex information could be related to a problem with interhemispheric transfer of information (Roebuck et al., 2002) since prenatal alcohol exposure damages the corpus callosum (Riley et al. 1995). Moreover, there may be a specific deficit in visual processing as opposed to other modalities, which has been previously suggested (Coles et al., 2002). Though it is not likely a basic ophthalmological defect as these are limited to children with FAS and do not extend to those who are non-dysmorphic (Flanigan et al., 2008).

Movement times in the simple choice condition of RTI were not significantly different between groups, indicating that the two groups have equivalent motor skills. Studies have shown that motor problems are present in children with FASD (Adnams et al., 2001 and with ADHD (Harvey and Reid, 2003). Compared to controls, children with FASD or ADHD demonstrated poorer performance on clinical tasks designed to detect motor skill impairments like manual dexterity and finger-nose touching (Kooistra et al., 2009b). Motor problems in FASD or ADHD may be due to cerebellar damage. The cerebellum is generally smaller in FASD (Archibald et al., 2001) and asymmetrically smaller in ADHD (Dursten et al., 2004). Distinct cerebellar impairments may underlie the differential balance problems found between the two groups (Kooistra et al., 2009b).

In the SWM task, children with ARND committed the same number of errors as the subjects with ADHD. Working memory is an important aspect of executive function; the visuospatial sketchpad is necessary for holding and manipulating visual-spatial information during spatial working memory tasks (Baddeley, 1992). Working memory is

considered a central deficit in FASD (Rasmussen 2005) and children with FASD exhibit deficits in spatial memory tasks (Kaemingk and Halverson, 2000; Uecker and Nadel, 1996). Also, animal models of prenatal alcohol exposure exhibit spatial learning deficits (Iqbal et al., 2004). However, relatively little work has been performed on *spatial working memory* tasks where children with FASD are required to hold a visual/spatial representation of information in working memory in order to successfully complete a task. Work from our lab does suggest that children with FASD are markedly impaired in visual spatial working memory (Green et al., 2009b) compared to controls. It is likely that children with ARND in this study are impaired at holding the spatial location of the box where a token was last found. One may surmise this is due to an inability to use strategy since strategy can be employed to reduce the cognitive demand on working memory capacity. Subjects with FASD can benefit from strategy if the strategy is implicit to the task (Roebuck-Spencer and Mattson, 2004). In this study, there was no difference in strategy score between subjects with ARND or ADHD, indicating that these groups can create/use strategies with the same ability. Subjects with ARND had elevated thinking times during box selection throughout SWM. Visuo-spatial processing plays a significant role in performance on SWM tasks, as processing time contributes to the degradation of information held in working memory (Jensen, 1993). In sum, subjects with ARND are more impaired than children with ADHD on tasks that require spatial working memory and the most likely cause of the performance differences is a greater visuo-spatial processing deficit in the subjects with ARND.

At the same time, children with ADHD may be responding significantly faster or impulsively compared to the ARND group on the MTS and SWM tasks. Subjects with ADHD have previously demonstrated problems with impulsivity (Losier et al., 1996) and response inhibition (Wodka et al., 2007) compared to controls. In an event-related potential (ERP) spatially shifted double-oddball visual task, children with ADHD and controls had similar ERP amplitude modulation in response to the initial target. However, subjects with ADHD exhibited a late ERP signal to the distracter stimuli that was modulated by the degree of distracter relevance (Lopez et al., 2006). The authors concluded that children with ADHD can focus immediate attention and that their flexible attention to irrelevant stimuli might allow them to respond in a rapid style. Response style on visuo-spatial tasks is differentially impaired in subjects with cerebellar lesions. Cerebellar patients were asked to assemble bi-dimensional cartoons to match one of five simultaneously presented figurines, and to complete as many trials as possible in 20 minutes. Subjects with left sided lesions completed few trials, but matched most cartoons correctly. Subjects with right cerebellar lesions completed more trials within the time limit, but most trials were incorrect (Molinari et al., 2004). Thus, the performance of the subjects with ADHD on MTS and SWM, which were equal in error but faster than the subjects with ARND, may be explained in part by right-biased cerebellar damage in ADHD (Durstun et al., 2004).

The measureable differences in executive function performance described in this thesis support the view that the executive control profile of subjects with ARND is distinct from the subjects with ADHD, and this may be indicative of differences in

patterns of brain dysfunction and damage between the two groups. The second half of this thesis research will interpret the behavioural findings from pro- and anti-saccade eye movement tasks. Since the oculomotor circuitry of eye movements is so well understood, speculations about the differences in brain dysfunction between the subjects with ARND or ADHD will be made.

### **5.3 Eye movement control**

The visuomotor circuitry controlling pro- and anti-saccades lies in many parts of the brain, including the occipital, parietal and frontal lobes, as well as, the basal ganglia, cerebellum and brainstem (Leigh and Kennard, 2004; Leigh and Zee, 2006; Munoz and Everling, 2004). Teratogenic insults and/or genetic mutations can give rise to long-term neurological dysfunction, which can lead to abnormal saccade circuitry and eye movement control. Thus, the study of abnormal eye movements can allow for hypotheses to be derived about the extent and location of injury and dysfunction. At first glance of the literature, ARND and ADHD appear to engage similar neurological coordinates for cognitive dysfunction. Prenatal alcohol exposure can cause global brain damage (Kopera-Frye et al., 1996; McGee and Riley, 2006), and the frontal cortex and basal ganglia may be specifically targeted. Currently, the most popular theory of ADHD etiology implicates fronto-striatal dysfunction as a major source for the associated deficits (Tannock 1998). However, the differences in oculomotor control and executive function reported in this study for children with ARND or ADHD suggest that variation in the underlying dysfunction may exist, and these distinctions may be exploited to further delineate the neurobehavioural profiles of these groups. Here we will discuss the

distinguishing performance deficits and possible theories as to the source of these differences between groups.

### **5.3.1 Anticipatory errors**

Subjects with ARND had increased anticipatory errors compared to children with ADHD. In assessing the implication of this finding and comparing it to previous literature, it became apparent that this parameter is not commonly investigated or reported. However, certain clinical disorders have demonstrated elevated anticipatory errors in the pro- and anti-saccade task compared to controls, such as Tourette syndrome (Farber et al., 1999) and borderline personality disorder (Grootens et al., 2008). Two studies have reported elevated anticipatory errors in ADHD compared to controls (Feifel et al., 2004; Klein et al., 2003). However, the peripheral target in these studies appeared 4 degrees from the central fixation point. As the amplitude of a target jump increases, latency also increases (Fuller 1996). Our target distance was 15 degrees from center. This discrepancy prohibits comparisons in light of this research. Unfortunately, there is no literature on anticipatory errors in FASD. Therefore, it is difficult to ascertain whether the increase in anticipatory errors observed in the ARND group compared to the ADHD group is due to a deficit in the control of internally-generated saccades or a primary failure of visual fixation, or some combination of both. There is conflicting evidence in the literature. Patients with poor endogenous fixation control, who execute significant saccades in the express epoch (90-140 ms), do not demonstrate an increase in the frequency of anticipatory errors (Biscaldi et al., 1996). This suggests that difficulty maintaining visual fixation may not underlie the significant generation of anticipatory

errors in ARND. Others have found that manipulation of the fixation condition (gap versus overlap) does not interact with anticipatory error frequency in children (10-11 years) or adults (18-26 years) but does influence anticipatory error production in very young children (6-7 years) (Klein and Foerster, 2001). Thus, it is difficult to conclude with any certainty that the increase in anticipatory errors in the ARND group results from a deficit in voluntary control rather than a deficit in fixation.

To further evaluate the neurophysiology of anticipatory saccades, findings from the predictive task literature will be reviewed as they relate to our results. During predictive tasks, a stimulus typically alternates between opposite positions at fixed time intervals (McDowell et al., 1996; Ross and Ross, 1987). Thus, unlike pro-saccades, which are sensory-guided, and anti-saccades, which demand cognitive inhibition and the re-mapping of the stimulus location in the opposite visual field, anticipatory saccades do not necessarily require a sensorimotor transformation. It is thought to be driven by a memory trace of the motor signal generated earlier (i.e., efference copy) and hence is considered to be a memory-guided saccade. Monkey neurophysiology demonstrates evidence for saccade-related efference copies in the FEF (Goldberg and Bruce, 1990; Umeno and Goldberg, 1997). In patients with damage to the FEF (Rivaud et al., 1994) or the cerebellum (Isotalo et al., 1995) predictive saccade performance is impaired relative to pro-saccade performance. Human functional neuroimaging studies further demonstrate that there is dissociation between predictive and sensory-guided responses. Positron emission tomography (PET) revealed greater blood flow in FEF during anticipatory saccades than during sensory-guided smooth pursuit; the cerebellum was

also preferentially activated during predictive saccades (O'Driscoll et al., 2000). A human fMRI study demonstrated that among other structures, the frontal cortex, inferior parietal lobe and cerebellum were preferentially activated during predictive saccades compared to pro-saccades (Simo et al., 2005). It has been suggested that the activity of the FEF during predictive tracking may be synchronized by the cerebellum (McDowell et al., 2008), because the cerebellum is associated with motor preparation in oculomotor control, and may coordinate the timing between motor preparation and execution (Diener et al., 1989; O'Driscoll et al., 2000). Moreover, Simo and colleagues (2005) also presented evidence that the lateral hemispheres of the cerebellum were involved in switching from sensory-driven to memory-driven behaviours, and for maintaining intact anticipatory responses. Thus, while the areas of the brain implicated in controlling the transition to, and generation of, anticipatory saccades overlap with those responsible for sensory-guided saccades, there is evidence that the degree of activation is unique to the type of saccade.

It is possible that activation differences exist between children with ARND or ADHD within the frontal cortex, cerebellum and PPC during saccadic eye movement paradigms, and this may result in differences in the frequency of anticipatory errors. There is significant evidence to support the view that children with prenatal alcohol exposure have abnormal frontal lobe activation resulting in compromised executive function. Functional activation of cortical brain areas in subjects with FASD compared to healthy controls have been examined on tasks of spatial working memory (Malisza et al., 2005; Astley et al., 2009; Spadoni et al., 2009), verbal memory (Sowell et al., 2007;

O'Hare et al., 2009) and response inhibition (Fryer et al., 2007b). With the exception of Astley and colleagues (2009), all studies found that compared to controls, subjects with FASD had a greater blood oxygen-level dependent (BOLD) response in the frontal lobe. This characteristic activation has been found even when performance differences are controlled (O'Hare et al., 2009; Fryer et al., 2007b; Sowell et al., 2007). In these cases, the increased activation in the frontal lobe may reflect a compensatory mechanism of an inefficient system that is working harder to achieve the same performance results. In contrast, there is an overwhelming amount of literature that demonstrates a reduction in frontal lobe activation in subjects with ADHD when compared to controls during tasks that measure cognitive function (Booth et al., 2005; Durston et al., 2003; 2006; Konrad et al., 2006; Pliszka et al., 2006; Durston, 2008). Taken together, these findings suggest that differences in the generation of anticipatory errors among subjects with ARND or ADHD may be due, in part, to differences in functional activity in the frontal cortices. In children with ARND, hyperactivation of the frontal cortex may initiate anticipatory behaviours, while in children with ADHD hypoactivation may lead to a decrease in anticipatory saccades. Future eye tracking studies using fMRI will be needed to further confirm or refute this interpretation.

Another possible source for the discrepancy in anticipatory errors in ARND or ADHD subjects may be the cerebellum. Many studies demonstrate a profound decrease in cerebellar volume and surface area in subjects with FAS (Mattson et al., 1992, 1994), and in non-dysmorphic subjects with prenatal alcohol exposure (Autti-Ramo et al., 2002) suggesting an enhanced sensitivity to alcohol teratogenicity. However, few studies have

evaluated functional activity in the cerebellum in subjects with FASD, instead suggesting cerebellar dysfunction as an explanation for deficits in memory (O'Hare et al., 2005) and balance (Roebuck et al., 1998). Thus, it is difficult to conclude whether damage to the cerebellum may contribute, at least in part, to the generation of anticipatory saccades. The ADHD literature is more complete with respect to cerebellar dysfunction. Structural studies reveal a reduction in cerebellar volume of young subjects with ADHD compared to controls (Castellanos et al., 1996; Berquin et al., 1998), though not necessarily in the lateral hemispheres. Durston and colleagues (2007) showed that subjects with ADHD had decreased cerebellar activity during a variation of the go/no-go task which involved a predictive aspect. This occurred together with decreased activity in prefrontal areas that are involved in the prediction of future events (Durston et al., 2007). This is consistent with our results where subjects with ADHD make less anticipatory saccades than children with ARND, which may occur because subjects with ADHD have an inability to convert sensory-driven actions to anticipatory behaviours due to hypoactivity in the cerebellum. Future examination of the functional activity of the cerebellum in children with ARND or ADHD may further characterize its contribution to the presence or absence of anticipatory saccades.

The final source for performance differences in anticipatory saccade generation that will be explored is the PPC. The lateral intraparietal area (LIP) lies at the sensory-motor interface of the PPC and projections from LIP to the SCi are involved in the sensory-motor transformations (Andersen et al. 1997) necessary for pro- and anti-saccades, but not anticipatory saccades. If the LIP is damaged or there is poor integrity

of the projections from LIP to the SCi, a compensatory mechanism may be used that relies on a previously created motor signal or efference copy. This may increase the likelihood that an anticipatory saccade will be produced. The parietal lobe is also damaged by prenatal alcohol exposure, leading to volumetric reductions, even when overall reductions in brain volume are controlled (Archibald et al., 2001). In addition, the parietal cortices of individuals with prenatal alcohol exposure have increased grey matter and decreased white matter in the perisylvian cortices (Sowell et al., 2001a, 2002) and greater cortical thickness (Sowell et al., 2008) compared to controls. Cortical thinness (low grey matter) is correlated with higher cognitive function in control subjects (Sowell et al., 2001b). Diffusion tensor imaging (DTI) – a technique that tracks the diffusion of water molecules and provides a measure of microstructural integrity of white matter (Basser et al., 1994) – studies have described damage to cortical tracts linking the occipital and parietal lobes (Fryer et al., 2009). A decrease in BOLD signal in the parietal lobe was detected on a spatial working memory task (Astley et al., 2009), while verbal working memory led to an increase in BOLD signal (O’Hare et al., 2009) in children with FASD compared to controls. Studies have also shown that children with ADHD have abnormal parietal lobe function. When performing a task of motor mapping, subjects with ADHD exhibited decreased activation of the parietal lobe compared to controls (Mostofsky et al., 2006). During no-go trials, where frontal lobe activation is correlated with successful performance in control subjects, subjects with ADHD exhibit increased BOLD signal in the inferior parietal lobule (Durstun et al., 2006), suggesting that inappropriate recruitment of additional structures is needed to

complete the task. These findings suggest that subjects with ADHD may recruit the parietal lobe to compensate for fronto-striatal deficits; an observation that is not reflected in the FASD literature. As found in subjects with FASD, abnormal white matter integrity within the right parieto-occipital region has also been found in subjects with ADHD compared to controls using DTI (Silk et al., 2009). Future DTI studies that can objectively evaluate the integrity of white matter tracts originating in the LIP and projecting to the SCi in children with ARND or ADHD are needed to further assess the contribution of the parietal lobe to anticipatory behaviours.

While the CANTAB® results indicate that there may be differences underlying the executive function deficits in children with ARND or ADHD and eye tracking suggests that there are differences in the underlying brain injury of these disorders, the neuroanatomical loci of these differences remain speculative. Considering the wide-reaching damage caused by prenatal alcohol exposure, it is unlikely that a single brain area is responsible for the behavioural differences between the two groups. Rather it is more likely that multiple areas abnormally interact to produce deficits in executive function and eye movement control in ARND and this abnormality is less severe in subjects with ADHD.

#### **5.4 Clinical relevance**

Previous eye tracking studies have revealed differences between other clinical disorders, such as schizophrenia and affective disorders (Airman et al. 1990). The anti-saccade task in particular has been used to identify deficits between groups of patients with degenerative diseases, such as progressive supranuclear palsy (PSP) and Parkinson's

disease (Rivaud-Péchoux, et al., 2007). These studies were primarily conducted in adult populations, though differences in oculomotor control have also been found in children. Despite similarities in executive and visuo-spatial dysfunction, children with Fragile X and Turner syndrome reveal performance differences using pro-, anti- and memory-guided saccade tasks (Lasker et al., 2007). Although the anti-saccade task has been criticized for lacking specificity in distinguishing eye movement dysfunction amongst various disorders, this conclusion was reached after comparing a limited number of oculomotor parameters between patient groups (Rommelse et al., 2008).

To date, several studies have attempted to characterize the differences between subjects with FASD or ADHD (Nanson and Hiscock, 1990; Coles et al., 1997; Vaurio et al., 2008; Kooistra et al., 2009a; Kooistra et al., 2009b; Greenbaum et al., 2009); however, except for Coles and colleagues (1997), these studies did not include a cohort of non-dysmorphic children with FASD. While differences were found between subjects with FASD or ADHD, it is difficult to translate these findings to the clinical situation without the inclusion of non-dysmorphic subjects. These individuals comprise the ARND diagnostic group and they may face the most obstacles to early and accurate diagnosis. Our study addressed this limitation by creating an FASD group comprised exclusively of children with a diagnosis of ARND. The results presented herein support the notion that ARND and ADHD are two separate clinical disorders, and *if* the underlying differences in neurobehavioural profiles and brain dysfunction can be fully characterized, these data may be used in future to create novel diagnostic tools that can differentiate patients with ARND from those with ADHD.

## **5.5 Limitations**

Although these results indicate that children with ARND exhibit more deficits than children with ADHD on measures of executive function and oculomotor control, these results cannot be extrapolated to the general ARND or ADHD populations; a larger scale, more randomly sampled study is warranted. As subjects selected from a clinical environment have regular access to specialists and assessments, our subjects with ARND may have been more likely to receive a co-morbid ADHD diagnosis than ARND subjects in the general population. Some studies of subjects with FASD report an ADHD co-morbidity rate as high as 95% (Fryer et al., 2007a). This is troublesome because it is unclear if the ADHD diagnosis is warranted or if it would have been negated pending a full prenatal history evaluation. However, work from our lab has demonstrated that co-morbid ADHD diagnosis does not influence eye movement performance in a large population of subjects with FASD (Green et al., 2009a).

Compared to the general ARND population, our clinical sample of subjects with ARND may represent the more severe end of the ARND spectrum and therefore one may surmise that this population of children may have had a lower IQ average. This is a concern as some executive functions are modestly related to overall intelligence function (Duncan et al., 1996). There is also evidence that men with higher IQs make less direction errors on the anti-saccade task (Evdokimidis et al., 2002), though this finding cannot necessarily be extrapolated to young children. IQ corrections could be done using post-hoc analysis however the collection of this information would require a more detailed work-up. While our ARND subject pool was completely generated from

samples of clinical subjects, our ADHD sample was not. In the general population, nearly 7% of children in North America have ADHD and boys are twice as likely to receive this diagnosis as girls (Bloom and Cohen, 2007). Thus, a random sampling from the population results in a male dominated study population and this was evident in our ADHD study population.

Unfortunately, even though most subjects refrained from medication the morning of testing, there are three ways that medication could have impacted our results. First, stimulant medication like methylphenidate has been shown to improve oculomotor control in subjects with ADHD (Klein et al., 2002). Second, medication has been shown to influence performance on tests of executive function, both in controls and children with ADHD (Langleben et al. 2006). It is possible that a 24 hour wash-out period may not have been long enough for complete drug clearance since a number of our subjects were taking long-acting stimulant medication. Third, it is possible that years of medication use alters eye movement and executive function performance in subjects. ADHD medication-naïve patients have worse performance in tasks of executive function than those who have taken medication for a prolonged period (Vance et al., 2003). This performance difference may be caused by mitigating effects of medication on the neural correlates of attention over the long term (Konrad et al., 2007). A longer wash-out period or ADHD group separation based on medication history may be warranted if medication influence cannot be accounted for in the post analysis. However, this pre-caution may not be necessary in the FASD population as previous work from our lab has demonstrated

that medication use does not have a statistical influence on eye movement performance in FASD (Green et al., 2009a).

## **5.6 Future directions**

1. Due to the small sample size, we were unable to address differences among ADHD–subtypes (i.e., hyperactive, inattentive or combined) or sexes. In subjects with ADHD, subtype and sex have been found to influence oculomotor control in pro-saccade and memory-guided saccade tasks (Mahone et al., 2009). A large-scale study would be appropriate for addressing these current limitations.
2. Based on the findings of SWM, spatial working memory deficits may be differentially impaired in subjects with ARND or ADHD. There is a well established eye movement paradigm of working memory called the memory guided saccade (MGS) task (see Leigh and Zee 2006). Subjects with ADHD have been studied using the MGS but the literature is not consistent. Some studies found that ADHD subjects made timing errors (Goto et al., 2009) while others did not (Loe et al., 2009); this may be due to differences in paradigms. Furthermore, the difference in anticipatory errors between groups warrants an investigation into anticipatory movements. The predictive saccade task is an eye movement paradigm that requires the subjects to learn and comprehend the predictability of target motion, which promotes anticipatory saccades (McDowell et al., 2008). Learning has shown to be impaired in subjects with FASD (for review see Kodituwakku 2009) or ADHD (for review see Young, 2008). Future studies involving different oculomotor paradigms like the MGS and the predictive

saccade tasks could be conducted to further characterize the deficits in eye movement control in ARND or ADHD. Furthermore, extending our cohort age from adolescent to adult would enable us to determine if the deficits we observed are long-lasting and/or persistent.

3. Using DTI and f/MRI combined with eye tracking would enable the visualization of structural and functional activation patterns during pro- and anti-saccade tasks. Based on the findings in this study, differential activation may occur in the frontal lobe, and/or parietal lobe, and/or the cerebellum. In the analysis, functional activity could be correlated with task performance to identify which structures are most related to certain aspects of performance and how these relationships differ between children with ARND or ADHD.
4. The goal of this study was to investigate whether measurable performance differences exist between children with ARND or ADHD. Future studies could evaluate the impact of various interventions to determine whether they can mitigate the deficits we found. Attention and executive function deficits can be improved in children with ADHD with training interventions (Tamm et al., 2009). Similarly, rehearsal training can improve performance in tests of executive function in FASD (Loomes et al., 2008).
5. Previous work by our lab has shown significant differences between children with FASD and their matched controls using similar oculomotor tasks and other labs have shown significant differences between children with ADHD and their matched controls using similar oculomotor tasks. These data reveal significant

differences between the ARND and ADHD groups. However, these findings may *not* be specific to these two neurodevelopmental disorders and instead be indicative of generalized frontal lobe damage. Future evaluation of oculomotor control and neuropsychological function in children with frontal lobe injury will be important for determining whether our findings are unique to ARND or ADHD, or a reflection of compromised frontal lobe function. Additionally, further study of other neurodevelopmental disorders such as velocardiofacial syndrome may further delineate the oculomotor and executive function profiles for each clinical disorder.

## **Chapter 6**

### **Summary and Conclusions**

This thesis tested the hypothesis that children with ARND would demonstrate poorer performance on CANTAB® tasks of attention, planning, working memory and strategy and on the pro- and anti-saccade eye movement tasks compared to children with ADHD.

Compared to children with ADHD, children with ARND had elevated decision times when searching for and matching complex patterns on the MTS test of attention, while both groups committed the same number of mismatches. Subjects with ARND also took significantly longer when selecting boxes to search within on the SWM test of visual spatial working memory. These times included the mean time to first response (touching a box on the screen), last response and mean token preparation time. Interestingly, the increased time taken to complete trials in the SWM task by children in the ARND group did not improve their performance, as these children demonstrated similar error rates and strategy scores as subjects with ADHD who completed the trials more quickly. These data indicate that the mechanisms underlying executive dysfunction in ARND or ADHD are distinct and that visuospatial processing deficits likely play a greater role in the poor performance of subjects with ARND than those with ADHD.

Finally, subjects with ARND made significantly more anticipatory errors in the pro- and anti-saccade tasks than subjects with ADHD. These findings support the notion

that brain injury resulting from prenatal alcohol exposure is more wide-reaching, particularly in comparison to the brain dysfunction common to ADHD. Furthermore, objective measures of brain function, such as eye movements, are sensitive to these differences. fMRI and DTI studies are necessary to identify the differential activation of structures and variation of circuit integrity between these groups.

Future studies should employ eye movement tasks related to other aspects of anticipatory behaviour and visual working memory. Such tasks may further define visuo-spatial processing, attention and working memory deficits in ARND, and will help to further delineate the neurobehavioural profile distinct to ARND. Such work is necessary for progress in screening, diagnosis and intervention in the ARND and PAE populations.

## References

Abel EL (1984) Prenatal effects of alcohol. *Drug Alcohol Depend* 14:1-10.

Adnams CM, Kodituwakku PW, Hay A, Molteno CD, Viljoen D, May P A (2001) Patterns of cognitive-motor development in children with fetal alcohol syndrome from a community in South Africa. *Alcoholism: Clinical and Experimental Research* 25:557–562.

Airman E, Hedeker D, Davis JM, Comaty JE, Jobe TH, Levy DL (1990) Neuropsychological test deficits are associated with smooth pursuit eye movement impairment in affective disorders but not in schizophrenia. *International Journal of Clinical Neuropsychology* 12:49-59.

American Academy of Pediatrics. Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement (2001) Clinical practice guideline: treatment of the school-aged child with attention-deficit/hyperactivity disorder. *Pediatrics* 108:1033-44.

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000.

Andersen RA, Snyder LH, Bradley DC, Xing J (1997) Multimodal representation of space in the posterior parietal cortex and its use in planning movements. *Ann Rev Neurosci* 20:303-330.

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

Astley SJ, Aylward EH, Olson HC, Kerns K, Brooks A, Coggins TE, Davies J, Dorn S, Gendler B, Jirikowic T, Kraegel P, Maravilla K, Richards T (2009). Functional magnetic resonance imaging outcomes from a comprehensive magnetic resonance study of children with fetal alcohol spectrum disorders. *J Neurodev Disord* 1:61–80.

Astley SJ, Clarren SK (2000) Diagnosing the full spectrum of fetal alcohol-exposed individuals: introducing the 4-digit diagnostic code. *Alcohol and Alcoholism* 35:400-410.

Autti-Rämö I, Autti T, Korkman M, Kettunen S, Salonen O, Valanne L (2002) MRI findings in children with school problems who had been exposed prenatally to alcohol. *Dev Med Child Neurol* 44:98–106.

- Baddeley AD (1992) Working memory. *Science* 255:556–559.
- Barkley RA (2000) Genetics of childhood disorders: XVII. ADHD, Part 1: The executive functions and ADHD. *J Am Acad Child Adolesc Psychiatry* 39:1064-8.
- Barash S, Bracewell RM, Fogassi L, Gnadt JW, Andersen RA (1991a) Saccade-related activity in the lateral intraparietal area. II. Spatial properties. *J Neurophysiol* 66:1109-1124.
- Barash S, Bracewell RM, Fogassi L, Gnadt JW, Andersen RA (1991b) Saccade-related activity in the lateral intraparietal area. I. Temporal properties; comparison with area 7a. *J Neurophysiol* 66:1095-1108.
- Basser PJ, Mattiello J, LeBihan D (1994) MR diffusion tensor spectroscopy and imaging. *Biophys J* 66:259–267.
- Berquin PC, Giedd JN, Jacobsen LK, Hamburger SD, Krain AL, Rapoport JL, Castellanos FX (1998) Cerebellum in attention-deficit hyperactivity disorder: a morphometric MRI study. *Neurology* 50:1087-1093.
- Biederman J, Faraone SV (2002) Current concepts on the neurobiology of Attention-Deficit/Hyperactivity Disorder. *J Atten Disord* 6:S7-S16.
- Biscaldi M, Fischer B, Stuhr V (1996) Human express saccade makers are impaired at suppressing visually evoked saccades. *J Neurophysiol* 76:199-214.
- Bloom B, Cohen RA (2007) Summary health statistics for U.S. children: National Health Interview Survey, 2006. *Vital Health Stat* 10 234:1-79.
- Booth JR, Burman DD, Meyer JR, Lei Z, Trommer BL, Davenport ND, Li W, Parrish TB, Gitelman DR, Mesulam MM (2005) Larger deficits in brain networks for response inhibition than for visual selective attention in attention deficit hyperactivity disorder (ADHD). *Journal of Child Psychology and Psychiatry* 46:94–111.
- Brown TE (2008) ADD/ADHD and impaired executive function in clinical practice. *Curr Psychiatry Rep* 10:407-411.
- Brown RT, Coles CD, Smith IE, Platzman KA, Silverstein J, Erickson S, Falek A (1991) Effects of prenatal alcohol exposure at school age. II. Attention and behavior. *Neurotoxicol Teratol* 13:369-76.
- Cantwell DP (1996) Attention deficit disorder: a review of the past 10 years. *J Acad Child Adolesc Psychiatry* 35:978-987

Castellanos FX (1997) Toward a pathophysiology of attention-deficit/hyperactivity disorder. *Clin Pediatr* 36:381–393.

Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Vaituzis AC, Dickstein DP, Sarfatti SE, Vauss YC, Snell JW, Lange N, Kaysen D, Krain AL, Ritchie GF, Rajapakse JC, Rapoport JL (1996) Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. *Arch Gen Psychiatry* 53:607-616.

Chudley AE, Conry J, Cook JL, Looock C, Rosales T, LeBlanc N; Public Health Agency of Canada's National Advisory Committee on Fetal Alcohol Spectrum Disorder (2005) Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. *CMAJ* 172:S1-S21.

Coe B, Tomihara K, Matsuzawa M, Hikosaka O (2002) Visual and anticipatory bias in three cortical eye fields of the monkey during an adaptive decision-making task. *J Neurosci* 22:5081-5090.

Coles CD, Platzman KA, Lynch ME, Freides D (2002) Auditory and visual sustained attention in adolescents prenatally exposed to alcohol. *Alcohol Clin Exp Res* 26:263-271.

Coles CD, Platzman KA, Raskind-Hood CL, Brown RT, Falek A, Smith IE (1997) A comparison of children affected by prenatal alcohol exposure and attention deficit, hyperactivity disorder. *Alcohol Clin Exp Res* 21:150-161.

Diener HC, Dichgans J, Guschlbauer B, Bacher M, Langenbach P (1989) Disturbances of motor preparation in basal ganglia and cerebellar disorders. *Prog Brain Res* 80:481-488

Doig J, McLennan JD, Gibbard WB (2008) Medication effects on symptoms of attention-deficit/hyperactivity disorder in children with fetal alcohol spectrum disorder. *J Child Adolesc Psychopharmacol* 18:365-371.

Dulcan M (1997) Practice parameters for the assessment and treatment of children, adolescents, and adults with attention-deficit/hyperactivity disorder. *American Academy of Child and Adolescent Psychiatry. J Am Acad Child Adolesc Psychiatry* 36:85S-121S.

Dulcan MK, Benson RS. (1997) AACAP Official Action. Summary of the practice parameters for the assessment and treatment of children, adolescents, and adults with ADHD. *J Am Acad Child Adolesc Psychiatry* 36:1311-1317

Duncan J, Emslie H, Williams P, Johnson R, Freer C (1996) Intelligence and the frontal lobe: The organization of goal-directed behavior. *Cognitive Psychology* 30:257–303.

Durston S (2008) Converging methods in studying attention-deficit/hyperactivity disorder: what can we learn from neuroimaging and genetics? *Psychopathol* 20:1133-1143.

Durston S, Davidson MC, Mulder MJ, Spicer JA, Galvan A, Tottenham N, Scheres A, Xavier Castellanos F, van Engeland H, Casey BJ (2007) Neural and behavioral correlates of expectancy violations in attention-deficit hyperactivity disorder. *J Child Psychol Psychiatry* 48:881-889.

Durston S, Hulshoff Pol HE, Schnack HG, Buitelaar JK, Steenhuis MP, Minderaa RB, Kahn RS, van Engeland H (2004) Magnetic resonance imaging of boys with attention-deficit/hyperactivity disorder and their unaffected siblings. *J Am Acad Child Adolesc Psychiatry* 43:332-340.

Durston S, Mulder M, Casey BJ, Ziermans T, van Engeland H (2006) Activation in ventral prefrontal cortex is sensitive to genetic vulnerability for attention-deficit hyperactivity disorder. *Biol Psychiatry* 60:1062-1070.

Durston S, Tottenham NT, Thomas KM, Davidson MC, Eigsti IM, Yang Y, Ulug AM, Casey BJ (2003) Differential patterns of striatal activation in young children with and without ADHD. *Biol Psychiatry* 53:871-878.

Evdokimidis I, Smyrnis N, Constantinidis TS, Stefanis NC, Avramopoulos D, Paximadis C, Theleritis C, Efstratiadis C, Kastrinakis G, Stefanis CN (2002) The antisaccade task in a sample of 2,006 young men. I. Normal population characteristics. *Exp Brain Res* 147:45-52.

Everling S, Fischer B (1998) The antisaccade: A review of basic research and clinical studies. *Neuropsychologia* 36:885-899.

Farber RH, Swerdlow NR, Clementz BA (1999) Saccadic performance characteristics and the behavioural neurology of Tourette's syndrome. *J Neurol Neurosurg Psychiatry* 66:305-312.

Feifel D, Farber RH, Clementz BA, Perry W, Anllo-Vento L (2004) Inhibitory deficits in ocular motor behavior in adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry* 56:333-339.

Fischer B, Ramsperger E (1984) Human express saccades: extremely short reaction times of goal directed eye movements. *Exp Brain Res* 57:191-195.

Fischer B, Weber H, Biscaldi M, Aiple F, Otto P, Stuhr V (1993) Separate populations of visually guided saccades in humans: reaction times and amplitudes. *Exp Brain Res* 92: 528-541.

Flanigan EY, Aros S, Bueno MF, Conley M, Troendle JF, Cassorla F, Mills JL (2008) Eye malformations in children with heavy alcohol exposure in utero. *J Pediatr* 153:391-395.

Frankel F, Paley B, Marquardt R, O'Connor M (2006) Stimulants, neuroleptics, and children's friendship training for children with fetal alcohol spectrum disorders. *J Child Adolesc Psychopharmacol* 16:777-789.

Fryer SL, McGee CL, Matt GE, Riley EP, Mattson SN (2007a) Evaluation of psychopathological conditions in children with heavy prenatal alcohol exposure. *Pediatrics* 119:e733-741.

Fryer SL, Schweinsburg BC, Bjorkquist OA, Frank LR, Mattson SN, Spadoni AD, Riley EP (2009) Characterization of white matter microstructure in fetal alcohol spectrum disorders. *Alcohol Clin Exp Res* 33:514-521.

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

Fuller JH (1996) Eye position and target amplitude effects on human visual saccadic latencies. *Exp Brain Res* 109: 457-466.

Gaymard B, Ploner CJ, Rivaud S, Vermersch AI, Pierrot-Deseilligny C (1998) Cortical control of saccades. *Experimental Brain Research* 123:159-163.

Goldberg ME, Bruce CJ (1990) Primate frontal eye fields III. Maintenance of a spatially accurate saccade signal. *Journal of Neurophysiology* 64:489-508.

Goto Y, Hatakeyama K, Kitama T, Sato Y, Kanemura H, Aoyagi K, Sugita K, Aihara M (2009) Saccade eye movements as a quantitative measure of frontostriatal network in children with ADHD. *Brain Dev* Jun 6 [Epub ahead of print].

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

Green CR, Mihic AM, Nikkel SM, Stade BC, Rasmussen C, Munoz DP, Reynolds JN (2009b) Executive function deficits in children with fetal alcohol spectrum disorders (FASD) measured using the Cambridge Neuropsychological Tests Automated Battery (CANTAB). *J Child Psychol Psychiatry* 50:688-697.

Green CR, Munoz DP, Nikkel SM, Reynolds JN (2007) Deficits in eye movement control in children with fetal alcohol spectrum disorders. *Alcohol Clin Exp Res* 31:500-511.

Greenbaum R, Nulman I, Rovet J, Koren G (2002) The Toronto experience in diagnosing alcohol-related neurodevelopmental disorder: a unique profile of deficits and assets. *Can J Clin Pharmacol* 9:215-225.

Greenbaum RL, Stevens SA, Nash K, Koren G, Rovet J (2009) Social cognitive and emotion processing abilities of children with fetal alcohol spectrum disorders: a comparison with attention deficit hyperactivity disorder. *Alcohol Clin Exp Res* 33:1656-1670.

Grootens KP, van Luijckelaar G, Buitelaar JK, van der Laan A, Hummelen JW, Verkes RJ (2008) Inhibition errors in borderline personality disorder with psychotic-like symptoms. *Prog Neuropsychopharmacol Biol Psychiatry* 32:267-273.

Hallet PE (1978) Primary and secondary saccades to goals defined by instruction. *Vision Research* 18:1279-1296.

Harvey W, Reid G (2003) Attention-deficit/hyperactivity disorder: A review of research on movement skill performance and physical fitness. *Adapted Physical Activity Quarterly* 20:1-25.

Hikosaka O, Takikawa Y, Kawagoe R (2000) Role of the basal ganglia in the control of purposive saccadic eye movements. *Physiol Rev* 80:953-978.

Hikosaka O, Nakamura K, Nakahara H (2006) Basal ganglia orient eyes to reward. *Journal of Neurophysiology* 95:567-584.

Hoyme HE, May PA, Kalberg WO, Kodituwakku P, Gossage JP, Trujillo PM, Buckley DG, Miller JH, Aragon AS, Khaole N, Viljoen DL, Jones KL, Robinson LK (2005) A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 institute of medicine criteria. *Pediatrics* 115:39-47.

Iqbal U, Dringenberg HC, Brien JF, Reynolds JN (2004) Chronic prenatal ethanol exposure alters hippocampal GABA(A) receptors and impairs spatial learning in the guinea pig. *Behav Brain Res* 150:117-125.

Isotalo E, Pyykkö I, Juhola M, Aalto H (1995) Predictable and pseudo random saccades in patients with acoustic neuroma. *Acta Otolaryngol Suppl* 520:22-24.

Jacobson SW (1998) Specificity of neurobehavioral outcomes associated with prenatal alcohol exposure. *Alcohol Clin Exp Res* 22:313-320.

- Jensen AR (1993) Why is reaction time correlated with psychometric g? *Curr Dir Psychol Sci* 2:53–56.
- Jensen VK, Larrieu JA, Mack KK (1997) Differential diagnosis between attention-deficit/hyperactivity disorder and pervasive developmental disorder--not otherwise specified. *Clin Pediatr (Phila)* 36:555-561.
- Jones KL, Smith DW (1975) The fetal alcohol syndrome. *Teratology* 12:1-10.
- Kaemingk KL, Halverson T (2000) Spatial memory following prenatal alcohol exposure: More than a material specific memory deficit. *Child Neuropsychol* 6:115–128.
- Karatekin C, Asarnow RF (1998) Working memory in childhood-onset schizophrenia and attention-deficit/hyperactivity disorder. *Psychiatry Res* 80:165-76.
- Kelleher KJ, McInerney TK, Gardner WP, Childs GE, Wasserman RC (2000) Increasing identification of psychosocial problems: 1979–1996. *Pediatrics* 105:1313–1321.
- Klein C, Jr Fischer B, Fischer B, Hartnegg K (2002) Effects of methylphenidate on saccadic responses in patients with ADHD. *Exp Brain Res* 145:121-125.
- Klein C, Foerster F (2001) Development of prosaccade and antisaccade task performance in participants aged 6 to 26 years. *Psychophysiology* 38:179-189.
- Klein CH, Raschke A, Brandenbusch A (2003) Development of pro- and antisaccades in children with attention-deficit hyperactivity disorder (ADHD) and healthy controls. *Psychophysiology* 40:17-28.
- Kodituwakku PW (2007) Defining the behavioral phenotype in children with fetal alcohol spectrum disorders: a review. *Neurosci Biobehav Rev* 31:192-201.
- Kodituwakku PW (2009) Neurocognitive profile in children with fetal alcohol spectrum disorders. *Dev Disabil Res Rev* 15:218-224.
- Kodituwakku PW, May PA, Clericuzio CL, Weers D (2001) Emotion-related learning in individuals prenatally exposed to alcohol: an investigation of the relation between set shifting, extinction of responses, and behavior. *Neuropsychologia* 39:699-708.
- Konrad K, Neufang S, Fink GR, Herpertz-Dahlmann B (2007) Long-term effects of methylphenidate on neural networks associated with executive attention in children with ADHD: results from a longitudinal functional MRI study. *J Am Acad Child Adolesc Psychiatry* 46:1633-1641.

- Konrad K, Neufang S, Hanisch C, Fink GR, Herpertz- Dahlmann, B (2006) Dysfunctional attentional networks in children with attention deficit/hyperactivity disorder, evidence from an event-related functional magnetic resonance imaging study. *Biological Psychiatry* 59:643–651.
- Kooistra L, Crawford S, Gibbard B, Ramage B, Kaplan BJ (2009a) Differentiating attention deficits in children with fetal alcohol spectrum disorder or attention-deficit-hyperactivity disorder. *Dev Med Child Neurol* Jun 22 [Epub ahead of print].
- Kooistra L, Ramage B, Crawford S, Cantell M, Wormsbecker S, Gibbard B, Kaplan BJ (2009b) Can attention deficit hyperactivity disorder and fetal alcohol spectrum disorder be differentiated by motor and balance deficits? *Hum Mov Sci* 28:529-542.
- Kopera-Frye K, Dehaene S, Streissguth AP (1996) Impairments of number processing induced by prenatal alcohol exposure. *Neuropsychologia* 34:1187–1196.
- Langleben DD, Monterosso J, Elman I, Ash B, Krikorian G, Austin G (2006) Effect of methylphenidate on Stroop Color-Word task performance in children with attention deficit hyperactivity disorder. *Psychiatry Res* 141:315-320.
- Lasker AG, Mazzocco MM, Zee DS (2007) Ocular motor indicators of executive dysfunction in fragile X and Turner syndromes. *Brain Cogn* 63:203–220.
- Leigh RJ, Kennard C (2004) Using saccades as a research tool in the clinical neurosciences. *Brain* 127:460–477.
- Leigh RJ, Zee DS (2006) *The neurology of eye movements (Book/DVD) Fourth edition* Oxford University Press, New York.
- Loe IM, Feldman HM, Yasui E, Luna B (2009) Oculomotor performance identifies underlying cognitive deficits in attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 48:431-440.
- Loomes C, Rasmussen C, Pei J, Manji S, Andrew G (2007) The effect of rehearsal training on working memory span of children with fetal alcohol spectrum disorder. *Res Dev Disabil*. 29:113-24.
- López V, López-Calderón J, Ortega R, Kreither J, Carrasco X, Rothhammer P, Rothhammer F, Rosas R, Aboitiz F (2006) Attention-deficit hyperactivity disorder involves differential cortical processing in a visual spatial attention paradigm. *Clin Neurophysiol* 117:2540-2548.

Losier BJ, McGrath PJ, Klein RM (1996) Error patterns on the continuous performance test in non-medicated and medicated samples of children with and without ADHD: a meta-analytic review.. *J Child Psychol Psychiatry* 37: 971-87

Luna B, Thulborn KR, Munoz DP, Merriam EP, Garver KE, Minchew NJ, Keshavan MS, Genovese CR, Eddy WF, Sweeney JA (2001) Maturation of widely distributed brain function subserves cognitive development. *Neuroimage* 13:786–793.

Mahone EM, Mostofsky SH, Lasker AG, Zee D, Denckla MB (2009) Oculomotor anomalies in attention-deficit/hyperactivity disorder: evidence for deficits in response preparation and inhibition. *J Am Acad Child Adolesc Psychiatry*48:749-756.

Malisza KL, Allman AA, Shiloff D, Jakobson L, Longstaffe S, Chudley AE (2005) Evaluation of spatial working memory function in children and adults with fetal alcohol spectrum disorders: a functional magnetic resonance imaging study. *Pediatr Res* 58:1150–1157.

Mattson SN, Gramling L, Riley EP, Delis DC, Jones KL (1996) Global — local processing in children prenatally exposed to alcohol. *Child Neuropsychol* 2:165–175.

Mattson SN, Jernigan TL, Riley EP (1994) MRI and prenatal alcohol exposure: images provide insight into FAS. *Alcohol Health Res World* 18:49–52.

Mattson SN, Riley EP, Jernigan TL, Ehlers CL, Delis DC, Jones KL, Stern C, Johnson KA, Hesselink JR, Bellugi U (1992) Fetal alcohol syndrome: a case report of neuropsychological, MRI and EEG assessment of two children. *Alcohol Clin Exp Res* 16:1001-1003.

May PA, Gossage JP, Kalberg WO, Robinson LK, Buckley D, Manning M, Hoyme HE. (2009) Prevalence and epidemiologic characteristics of FASD from various research methods with an emphasis on recent in-school studies. *Dev Disabil Res Rev* 15:176-192.

McDowell JE, Clementz BA, Wixted JT (1996) Timing and amplitude of saccades during predictive saccadic tracking in schizophrenia. *Psychophysiology* 33:93–101.

McDowell JE, Dyckman KA, Austin BP, Clementz BA (2008) Neurophysiology and neuroanatomy of reflexive and volitional saccades: evidence from studies of humans. *Brain Cogn* 68:255-270.

McGee CL, Riley EP (2006) Brain imaging and fetal alcohol spectrum disorders. *Ann Ist Super Sanita* 42:46–52.

Molinari M, Petrosini L, Misciagna S, Leggio MG (2004) Visuospatial abilities in cerebellar disorders. *J Neurol Neurosurg Psychiatry* 75:235–240.

Mostofsky SH, Lasker AG, Cutting LE, Denckla MB, Zee DS. (2001) Oculomotor abnormalities in attention deficit hyperactivity disorder: a preliminary study. *Neurology* 57:423-30.

Mostofsky SH, Rimrodt SL, Schafer JG, Boyce A, Goldberg MC, Pekar JJ, Denckla MB (2006) Atypical motor and sensory cortex activation in attention-deficit/hyperactivity disorder: a functional magnetic resonance imaging study of simple sequential finger tapping. *Biol Psychiatry* 59:48-56.

Munoz DP, Armstrong IT, Coe B. (2007) Using eye movements to probe development and dysfunction. In: *Eye movements: A window on mind and brain.* (Van Gompel RPG, Fischer MH, Murray WS, Hill RL, eds), pp 99-124. Oxford: Elsevier.

Munoz DP, Armstrong IT, Hampton KA, Moore KD (2003) Altered control of visual fixation and saccadic eye movements in attention-deficit hyperactivity disorder. *J Neurophysiol* 90:503-514.

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

Munoz DP, Dorris MC, Pare M, Everling S (2000) On your mark, get set: brainstem circuitry underlying saccadic initiation. *Can J Physiol Pharmacol* 78:934-944.

Munoz DP, Everling S (2004) Look away: the anti-saccade task and the voluntary control of eye movement. *Nat Rev Neurosci* 5:218-228.

Munoz DP, Fecteau JH (2002) Vying for dominance: dynamic interactions control visual fixation and saccadic initiation in the superior colliculus. *Prog. Brain Res* 140:3-19.

Nanson JL, Hiscock M (1990) Attention deficits in children exposed to alcohol prenatally. *Alcohol Clin Exp Res* 14:656-661.

Nigg JT (1999) The ADHD response-inhibition deficit as measured by the stop task: replication with DSM-IV combined type, extension, and qualification. *J Abnorm Child Psychol* 27:393-402.

O'Driscoll GA, Wolff AL, Benkelfat C, Florencio PS, Lal S, Evans AC (2000) Functional neuroanatomy of smooth pursuit and predictive saccades. *Neuroreport* 11:1335-1340.

Oosterheld JR, Kofoed L, Tervo R, Fogas B, Wilson A, Fiechtner H (1998) Effectiveness of methylphenidate in Native American children with fetal alcohol syndrome and

attention deficit/hyperactivity disorder: A controlled pilot study. *J Child Adolesc Psychopharmacol* 8:39–48.

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

O'Hare ED, Lu LH, Houston SM, Bookheimer SY, Mattson SN, O'Connor MJ, Sowell ER (2009) Altered frontal-parietal functioning during verbal working memory in children and adolescents with heavy prenatal alcohol exposure. *Hum Brain Mapp* 30:3200-3208.

Olson HC, Streissguth AP, Sampson PD, Barr HM, Bookstein FL, Thiede K (1997) Association of prenatal alcohol exposure with behavioral and learning problems in early adolescence. *J Am Acad Child Adolesc Psychiatry* 36:1187-1194.

O'Malley KD, Koplin B, Dohner VA (2000) Psychostimulant clinical response in fetal alcohol syndrome. *Can J Psychiatry* 45:90–91. (Letter)

Paré M, Wurtz RH (1997) Monkey posterior parietal cortex neurons antidromically activated from superior colliculus. *J Neurophysiol.* 78:3493-3497.

Pineda DA, Puerta IC, Aguirre DC, García-Barrera MA, Kamphaus RW (2007) The role of neuropsychologic tests in the diagnosis of attention deficit hyperactivity disorder. *Pediatr Neurol* 36:373-381.

Pliszka SR, Glahn DC, Semrud-Clikeman M, Franklin C, Perez R 3rd, Xiong J, Liotti M (2006) Neuroimaging of inhibitory control areas in children with attention deficit hyperactivity disorder who were treatment naive or in long-term treatment. *Am J Psychiatry* 163:1052-1060.

Rasmussen C (2005) Executive functioning and working memory in fetal alcohol spectrum disorder. *Alcohol Clin Exp Res* 29:1359–1367.

Riley EP, Mattson SN, Sowell ER, Jernigan TL, Sobel DF, Jones KL (1995) Abnormalities of the corpus callosum in children prenatally exposed to alcohol. *Alcohol Clin Exp Res* 19:1198-1202.

Rivaud S, Muri G, Gaymard B, Vermersch AI, Pierrot-Deseilligny C (1994) Eye movement disorders after frontal eye field lesions in humans. *Exp Brain Res* 102:110-120.

Rivaud-Péchoux S, Vidailhet M, Brandel JP, Gaymard B (2007) Mixing pro- and antisaccades in patients with parkinsoniansyndromes. *Brain* 130:256–264.

- Roebuck TM, Mattson SN, Riley EP (2002) Interhemispheric transfer in children with heavy prenatal alcohol exposure. *Alcohol Clin Exp Res* 26:1863–1871.
- Roebuck TM, Simmons RW, Mattson SN, Riley EP (1998) Prenatal exposure to alcohol affects the ability to maintain postural balance. *Alcohol Clin Exp Res* 22:252-258.
- Roebuck-Spencer TM, Mattson SN (2004) Implicit strategy affects learning in children with heavy prenatal alcohol exposure. *Alcohol Clin Exp Res* 28:1424-1431.
- Rommelse NN, Van der Stigchel S, Sergeant JA (2008) A review on eye movement studies in childhood and adolescent psychiatry. *Brain Cogn* 68:391-414.
- Ross SM, Ross LE (1987) Children's and adults' predictive saccades to squarewave targets. *Vision Research* 27:2177–2180.
- Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SC, Simmons A, Bullmore ET (1999) Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. *Am J Psychiatry* 156:891-896.
- Schall JD (2002) The neural selection and control of saccades by the frontal eye field. *Philos Trans R Soc Lond B Biol Sci* 357:1073-1082.
- Schall JD, Boucher L (2007) Executive control of gaze by the frontal lobes. *Cogn Affect Behav Neurosci* 7:396-412.
- Segraves MA, Goldberg ME (1987) Functional properties of corticotectal neurons in the monkey's frontal eye field. *J Neurophysiol* 58:1387-1419.
- Silk TJ, Vance A, Rinehart N, Bradshaw JL, Cunnington R (2009) White-matter abnormalities in attention deficit hyperactivity disorder: a diffusion tensor imaging study. *Hum Brain Mapp* 30:2757-2765.
- Simo LS, Krisky CM, Sweeney JA (2005) Functional neuroanatomy of anticipatory behavior: Dissociation between sensory-driven and memorydriven systems. *Cerebral Cortex* 15:1982–1991.
- Snyder J, Nanson J, Snyder R, Block G (1997) A study of stimulant medication in children with FAS. In: *The Challenge of Fetal Alcohol Syndrome: Overcoming Secondary Disabilities*. Seattle: University of Washington Press
- Sommer MA, Wurtz RH (1998) Composition and topographic organization of signals sent from the frontal eye field to the superior colliculus. *J. Neurophysiol* 83:1979–2001.

- Sommer MA, Wurtz RH (2004) What the brain stem tells the frontal cortex. I. Oculomotor signals sent from superior colliculus to frontal eye field via mediodorsal thalamus. *J Neurophysiol* 91:1381-1402.
- Sowell ER, Delis D, Stiles J, Jernigan TL (2001b) Improved memory functioning and frontal lobe maturation between childhood and adolescence: a structural MRI study. *J Int Neuropsychol Soc* 7:312–322
- Sowell ER, Lu LH, O'Hare ED, McCourt ST, Mattson SN, O'Connor MJ, Bookheimer SY (2007) Functional magnetic resonance imaging of verbal learning in children with heavy prenatal alcohol exposure. *Neuroreport* 18:635-639.
- Sowell ER, Mattson SN, Kan E, Thompson PM, Riley EP, Toga AW (2008) Abnormal cortical thickness and brain-behavior correlation patterns in individuals with heavy prenatal alcohol exposure. *Cereb Cortex* 18:136-144.
- Sowell ER, Mattson SN, Thompson PM, Jernigan TL, Riley EP, Toga AW (2001a) Mapping callosal morphology and cognitive correlates: effects of heavy prenatal alcohol exposure. *Neurology* 57:235-44.
- Sowell ER, Thompson PM, Mattson SN, Tessner KD, Jernigan TL, Riley EP, Toga AW (2002) Regional brain shape abnormalities persist into adolescence after heavy prenatal alcohol exposure. *Cereb Cortex* 12:856-865.
- Spadoni AD, Bazinet AD, Fryer SL, Tapert SF, Mattson SN, Riley EP (2009) BOLD Response During Spatial Working Memory in Youth With Heavy Prenatal Alcohol Exposure. *Alcohol Clin Exp Res* Sep 9 [Epub ahead of print].
- Sparks DL (2002) The brainstem control of saccadic eye movements. *Nature Reviews Neuroscience* 3:952-964.
- Spohr HL, Willms J, Steinhausen HC (2007) Fetal alcohol spectrum disorders in young adulthood. *J Pediatr* 150:175-179.
- Steinhausen HC, Willms J, Metzke CW, Spohr HL (2003) Behavioural phenotype in foetal alcohol syndrome and foetal alcohol effects. *Dev Med Child Neurol* 45:179-82.
- Stratton K, Howe C, Battaglia FC (1996) Fetal alcohol syndrome: diagnosis, epidemiology, prevention, and treatment. Washington, DC: Institute of Medicine and National Academy Press.
- Streissguth AP, Bookstein FL, Barr HM, Press S, Sampson PD (1998) A fetal alcohol behavior scale. *Alcohol Clin Exp Res* 22: 325-333.

Streissguth AP, Bookstein FL, Barr HM, Sampson PD, O'Malley K, Young JK (2004) Risk factors for adverse life outcomes in fetal alcohol syndrome and fetal alcohol effects. *J Dev Behav Pediatr* 25:228-238.

Streissguth AP, Sampson PD, Olson HC, Bookstein FL, Barr HM, Scott M, Feldman J, Mirsky AF (1994) Maternal drinking during pregnancy: attention and short-term memory in 14-year-old offspring--a longitudinal prospective study. *Alcohol Clin Exp Res* 18:202-218.

Stuss DT (1992) Biological and psychological development of executive functions. *Brain Cogn* 20:8-23.

Stuss DT (2002) In *Principles of Frontal Lobe Function*. Knight RT (ed). London: Oxford University Press.

Sweeney JA, Mintun MA, Kwee S, Wiseman MB, Brown DL, Rosenberg DR, Carl JR (1996) Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. *J Neurophysiol* 75:454-468.

Tamm L, Hughes C, Ames L, Pickering J, Silver CH, Stavinoha P, Castillo CL, Rintelmann J, Moore J, Foxwell A, Bolanos SG, Hines T, Nakonezny PA, Emslie G (2009) Attention Training for School-Aged Children With ADHD: Results of an Open Trial. *J Atten Disord* Oct 5. [Epub ahead of print]

Tannock R (1998) Attention deficit hyperactivity disorder: advances in cognitive, neurobiological, and genetic research. *J Child Psychol Psychiatry* 39:65-99.

Thomas IT, Gaitantzis YA, Frias JL (1987) Palpebral fissure length from 29 weeks gestation to 14 years. *J Pediatr* 111:267-268.

Uecker A, Nadel L (1996) Spatial locations gone awry: object and spatial memory deficits in children with fetal alcohol syndrome. *Neuropsychologia* 34:209-223.

Umeno MM, Goldberg ME (1997) Spatial processing in the monkey frontal eye field I. Predictive visual responses. *Journal of Neurophysiology* 78:1373-1383.

Vance AL, Maruff P, Barnett R (2003) Attention deficit hyperactivity disorder, combined type: better executive function performance with longer-term psychostimulant medication. *Aust N Z J Psychiatry* 37:570-576.

Vaurio L, Riley EP, Mattson SN (2008) Differences in executive functioning in children with heavy prenatal alcohol exposure or attention-deficit/hyperactivity disorder. *J Int Neuropsychol Soc* 14:119-129.

Verney SP, Kodituwakku P, Rodriguez E, Peña-Esparza Y, Garcia C (2008) Inhibitory and eye movement processes on the antisaccade task in children with FASD. *Alcohol Clin Exp Res* 32:232A

Welsh MC, Pennington BF (1988) Assessing frontal lobe functioning in children: Views from developmental psychology. *Dev Neuropsychol* 4:131–149.

Welsh MC, Pennington BF, Grossier DB (1991) A normative developmental study of executive function: A window of prefrontal function in children. *Dev Neuropsychol* 4:131–149.

Willford JA, Geier CF, Zeglen MJ, Cyphert NW, Kruk RD, Luna B, Day NL, (2008) Reward and Response Inhibition processing differences associated with prenatal alcohol exposure in young adults: a fast, event-related fMRI study. *Alcohol Clin Exp Res* 32:231A

Wodka EL, Mahone EM, Blankner JG, Larson JC, Fotedar S, Denckla MB, Mostofsky SH (2007) Evidence that response inhibition is a primary deficit in ADHD. *J Clin Exp Neuropsychol* 29:345-356.

Wurtz RH, Sommer MA, Paré M, Ferraina S (2001) Signal transformations from cerebral cortex to superior colliculus for the generation of saccades. *Vision Res.* 41:3399-3412.

Yoshida K, Iwamoto Y, Chimoto S, Shimazu H (1999) Saccade-related inhibitory input to pontine omnipause neurons: an intracellular study in alert cats. *J Neurophysiol* 82:1198-1208.

Young J (2008) Common comorbidities seen in adolescents with attention-deficit/hyperactivity disorder. *Adolesc Med State Art Rev* 19:216-228.

Zelazo PD, Muller U (2002) Executive function in typical and atypical development, in *Blackwell Handbook of Childhood Cognitive Development* (Goswami U, ed). pp. 445–470. Blackwell Publishers Ltd., Malden, MA.

