SENSORY-MOTOR DEFICITS IN CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDERS ASSESSED USING A ROBOTIC VIRTUAL REALITY PLATFORM

by

Loriann Marie Williams

A thesis submitted to the Centre for Neuroscience Studies
In conformity with the requirements for
the degree of Master of Science

Queen’s University
Kingston, Ontario, Canada
(September, 2010)

Copyright ©Loriann Marie Williams, 2010
Abstract


Background: Maternal consumption of alcohol during pregnancy can induce a range of behavioral and cognitive deficits in offspring, which are collectively termed Fetal Alcohol Spectrum Disorders (FASD). There are significant delays in motor development and sensory-motor skills in children with FASD, but the underlying neurobiological mechanisms of these deficits are poorly understood. The goal of this research project is to test the hypothesis that the Kinesiological Instrument for Normal and Altered Reaching Movements (KINARM) will serve as an effective tool for identifying and measuring specific, neurologically-based motor deficits in children with FASD. Methods: These deficits were revealed through investigation of multi-joint upper limb movements during the performance of sensory-motor tasks. Children (31 FASD; 83 controls, aged 5 to 18 years, male and female) performed: (1) a visually-guided reaching task with fingertip feedback only; and children (31 FASD; 49 controls, aged 5 to 18 years, male and female) performed: (2) an arm position-matching task in the absence of visual feedback. Results: Children with FASD differed significantly from controls in many reaching task outcome measures, specifically those measures related to the initial motor response (calculated during the first movement to target) and corrective responses (throughout the rest of the movement). In particular, large effect sizes were observed for outcome measures related to the first (initial) movement (corresponding to feedforward control; e.g., direction error; distance error), as well as for those measures related to corrective responses (corresponding to feedback control; e.g., difference between minimum and maximum hand speeds; number of speed peaks during
movement). In the position-matching task, children with FASD constricted the spatial workspace of the subject-controlled arm relative to the robot-controlled arm, in the horizontal axis. There was also observed a systematic shift between the subject- and robot-controlled arms in the XY end position, resulting in significant error. Additionally, children with FASD exhibited significantly increased trial-to-trial variability for final hand position of the subject-controlled arm, over all targets, and for which large effect sizes were observed. **Conclusion:** The results suggest that children with FASD have difficulty integrating sensory information into planned motor movements. The KINARM is a promising research tool that may be used to assess motor control deficits in children affected by prenatal exposure to alcohol. (Supported by CIHR Grant #ELA-80227 and NSERC PGS LMW).
Co-Authorship

The research described in this thesis was conducted by Loriann Williams, under the supervision of Dr. James Reynolds and in collaboration with Dr. Stephen Scott, both of whom conceived the studies described below. Loriann Williams conducted KINARM experiments with all FASD subjects and analyzed all data described in Chapters 3, 4, and 5, and wrote the first draft of each chapter in the thesis. Noreen Choe headed the collection of data from control subjects (Choe, Scott, & Pelland, 2009) with the assistance of Loriann Williams and Carla Henderson.
Acknowledgements

No one can do anything in this world alone and there is a whole host of very special people I would like to thank for being part of my team in my endeavor to complete my Master’s degree over the past two years. My graduate degree would not have been possible without the help, time, energy, and guidance of several people. First and foremost, I would like to thank my supervisor, Dr. James Reynolds, who has guided me through the entire course of this project. I would also like to thank Dr. Stephen Scott for his contributions and ideas, every step of the way. To Dr. Jim Brien, thank you for your interest in this project. To Irene Armstrong, thank you for your guidance with the data analysis. To Justin Peterson, Helen Bretzke, Kim Moore, and Troy Herter – you all have helped me in ways you might not even realize. You were the glue that kept everything together and helped my research run as smoothly as it did; I thank you sincerely for all your work on my project. Thank you to Noreen Choe and Carla Henderson for your contribution to the data collection for control subjects. A deep gratitude goes to AJ Hickey who has held my hand through the entirety of my time here at Queen’s University, encouraging me to thrive in everything I attempt. I also must thank my fiancé and my family back home: you have all stood by me from beginning to end, supporting me at every corner. My deepest thanks are to the families and children who travelled to Kingston to be part of this project and to whom this project would not have been possible without.

This research was funded by the Canadian Institutes of Health Research (CIHR). I was also the recipient of an NSERC graduate scholarship (2008/2009 and 2009/2010). Thank you for your financial support.
Table of Contents

Abstract ........................................................................................................................................... ii
Co-Authorship ................................................................................................................................. iv
Acknowledgements ......................................................................................................................... v
List of Abbreviations and Symbols ................................................................................................. xi
Chapter 1 Introduction .................................................................................................................... 1
Chapter 2 Literature Review ............................................................................................................ 3
  2.1 Neurotoxic effects of ethanol .................................................................................................... 3
    2.1.1 Prenatal brain development ............................................................................................... 3
    2.1.2 Factors influencing the effects of PAE on the developing brain ......................................... 4
  2.2 Adverse outcomes associated with FASD .............................................................................. 5
    2.2.1 Cognitive and behavioral problems in children with FASD ............................................ 5
    2.2.2 Effects of PAE on brain structure ..................................................................................... 6
  Corpus Callosum ............................................................................................................................ 7
  Cerebellum ..................................................................................................................................... 8
  Basal Ganglia ................................................................................................................................. 9
  2.3 Secondary Disabilities ............................................................................................................. 9
  2.4 Diagnosis and Challenges ........................................................................................................ 10
  2.5 FASD motor deficits and tests used to assess motor dysfunction ......................................... 12
    2.5.1 Overview of motor disabilities ......................................................................................... 12
    2.5.2 Gross and fine motor skills ............................................................................................... 13
    2.5.3 Balance and fine motor coordination ................................................................................. 13
    2.5.4 Other tests used to assess motor function in individuals with FASD ............................... 15
    2.5.5 Current direction in FASD and motor assessment research ............................................. 16
  2.6 Biomechanics .......................................................................................................................... 18
    2.6.1 The execution of reaching movements .............................................................................. 18
    2.6.2 The Internal Model ............................................................................................................ 20
    2.6.3 Pre-planning versus on-line adjustments and the role of internal models ...................... 20
    2.6.4 Reaching movements as a function of age ....................................................................... 22
    2.6.5 Importance of using reaching movements to study brain function ............................... 23
  2.7 Instrument used, rationale, hypotheses, and objectives of the current study ....................... 23
List of Figures

Figure 1: The KINARM apparatus................................................................. 28
Figure 2: Layout of the reaching task targets............................................. 34
Figure 3: Layout of the nine position-matching targets................................ 35
Figure 4: Hand path trajectories for reaching task....................................... 38
Figure 5: Effect size for reaching task outcome measures................................ 40
Figure 6: Group differences. A) Direction error and B) Hand speed differences in reaching..... 40
Figure 7: Scatterplots depicting FASD subjects falling out of 95% CI of controls........... 42
Figure 8: Detrended data - FASD subjects’ residuals from the regression line of control data.... 44
Figure 9: Group differences in residuals.......................................................... 45
Figure 10: Arm position-matching performance summary................................. 47
Figure 11: Effect size for position-matching task outcome measures.................. 49
Figure 12: Group differences in inter-trial variability during the position-matching task......... 50
List of Tables

Table 1: Participant demographics for subjects who performed the reaching task .................. 28
Table 2: Participant demographics for subjects who performed the position-matching task ....... 28
Table 3: Specific information regarding the FASD group who participated in the two tasks ...... 31
Table 4: Specific information regarding the control group who participated in the reaching task 31
Table 5: Summary of group differences in performance of reaching task ................................. 38
Table 6: Summary of group differences in residual values (from model) for reaching task ......... 45
Table 7: Summary of group differences in performance of position-matching task .................. 49
### List of Abbreviations and Symbols

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANCOVA</td>
<td>analysis of covariance</td>
</tr>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
</tr>
<tr>
<td>ARND</td>
<td>Alcohol-Related Neuro-developmental Disorder</td>
</tr>
<tr>
<td>ADHD</td>
<td>Attention Deficit/Hyperactivity Disorder</td>
</tr>
<tr>
<td>AUDIT</td>
<td>the Alcohol Use Disorders Identification Test</td>
</tr>
<tr>
<td>CC</td>
<td>corpus callosum</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>COMPS</td>
<td>Clinical Observations of Motor and Postural Skills</td>
</tr>
<tr>
<td>CP</td>
<td>Cerebral Palsy</td>
</tr>
<tr>
<td>DNCT</td>
<td>Denckla Neurological Coordination Test</td>
</tr>
<tr>
<td>DCD</td>
<td>Developmental Coordination Disorder</td>
</tr>
<tr>
<td>DTI</td>
<td>diffusion tensor imaging</td>
</tr>
<tr>
<td>EF</td>
<td>executive function</td>
</tr>
<tr>
<td>FAS</td>
<td>Fetal Alcohol Syndrome</td>
</tr>
<tr>
<td>FASD</td>
<td>Fetal Alcohol Spectrum Disorders</td>
</tr>
<tr>
<td>FMTDistErr</td>
<td>first movement distance error</td>
</tr>
<tr>
<td>FMTDistRatio</td>
<td>first movement distance ratio</td>
</tr>
<tr>
<td>FMTDirErr</td>
<td>first movement direction error</td>
</tr>
<tr>
<td>FMTMaxSP</td>
<td>first movement maximum speed</td>
</tr>
<tr>
<td>FMTMaxSPRatio</td>
<td>first movement maximum speed ratio</td>
</tr>
<tr>
<td>IM</td>
<td>internal model</td>
</tr>
<tr>
<td>IOM</td>
<td>Sciences Institute of Medicine</td>
</tr>
<tr>
<td>KINARM</td>
<td>Kinesiological Instrument for Normal and Altered Reaching Movements</td>
</tr>
<tr>
<td>M-ABC</td>
<td>Movement Assessment Battery for Children</td>
</tr>
<tr>
<td>MANCOVA</td>
<td>multivariate analysis of covariance</td>
</tr>
<tr>
<td>MANOVA</td>
<td>multivariate analysis of variance</td>
</tr>
<tr>
<td>MAST</td>
<td>the Michigan Alcohol Screening Test</td>
</tr>
<tr>
<td>MT</td>
<td>movement</td>
</tr>
<tr>
<td>MinMaxSPDiff</td>
<td>minimum/maximum speed difference</td>
</tr>
<tr>
<td>MTMaxSP</td>
<td>movement maximum speed</td>
</tr>
<tr>
<td>NumMTMaxSP</td>
<td>number of movement maximum speeds</td>
</tr>
<tr>
<td>PAE</td>
<td>prenatal alcohol exposure</td>
</tr>
<tr>
<td>PathLenRatio</td>
<td>path length ratio</td>
</tr>
<tr>
<td>PCA</td>
<td>principle component analysis</td>
</tr>
<tr>
<td>pFAS</td>
<td>partial FAS</td>
</tr>
<tr>
<td>PS</td>
<td>postural speed</td>
</tr>
<tr>
<td>RT</td>
<td>reaction time</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
</tr>
<tr>
<td>TLFB</td>
<td>the Timeline Followback Calendar</td>
</tr>
<tr>
<td>TotalMT</td>
<td>total movement time</td>
</tr>
<tr>
<td>TWEAK</td>
<td>Acronym: Tolerance, Worry, Eye-opener, Amnesia, Cut down</td>
</tr>
<tr>
<td>VABS</td>
<td>Vineland Adaptive Behavior Scales</td>
</tr>
</tbody>
</table>
Chapter 1

Introduction

Alcohol consumption during pregnancy is harmful to the developing embryo/fetus, and can have adverse effects on child development, growth, and function of the central nervous system (CNS; Chudley et al., 2005). Fetal Alcohol Spectrum Disorders (FASD) is an umbrella term introduced to capture the continuum of the teratogenic effects of ethanol in the human, ranging from full-blown Fetal Alcohol Syndrome (FAS) to Alcohol-Related Neuro-developmental Disorder (ARND; Chudley et al., 2005). FASD describes individuals who may have physical, mental, behavioral, or learning disabilities as a result of maternal alcohol consumption during pregnancy (Chudley et al., 2005). FASD is the leading cause of mental retardation worldwide and is also the foremost preventable cause of neurobehavioral and developmental abnormalities (Murthy, Kudlur, George, & Mathew, 2009; Sarkar et al., 2009).

Maternal alcohol consumption during pregnancy, and the resulting damage to her offspring, is currently one of the most pressing public health and social concerns in Canada. The prevalence of women who consume alcohol during pregnancy is staggering. For example, according to one study, the percentage of women who drank small amounts of alcohol before realizing they had conceived was found to be 25% of all pregnant Canadians (Koren, Nulman, Chudley & Loocke, 2003). At least half of all Canadian women drink socially (Floyd, Decoufle, & Hungerford, 1999) and about half of all pregnancies are unplanned, leading to an estimated quarter of all newborns (about 100,000 infants a year, in Canada) who are exposed to some alcohol during early gestation (Martin, Park, & Sutton, 2002). Indeed, approximately 20% of women report that they consume some alcohol during pregnancy (Stratton, Howe, & Battaglia,
and some studies have found that average consumption of just one drink a week can be associated with adverse outcomes in the child (Sood et al., 2001).

Health Canada (2006) estimates the rate of FASD to be 9 children per 1000 live births annually with as many as 20% of youth in one isolated Canadian Aboriginal community affected with an FASD (Robinson, Conry, & Conry, 1987). The social and economic burden is extensive, with lifetime direct tangible costs per individual, in Canada, related to health care, education, and social services, estimated to be 1.4 million dollars (Stade, Ungar, Stevens, Beyen, & Koren, 2007).

FASD is characterized by a constellation of behavioral and physiological abnormalities. The consequences of alcohol exposure in utero include structural brain anomalies, behavioral problems (with an emphasis of the current paper on motor dysfunction), and neurocognitive disabilities (see Mattson & Riley, 1998; Rasmussen, Andrew, Zwaigenbaum, & Tough, 2008; Kodituwakku, 2007 for reviews). Not surprisingly, the burden of prenatal exposure to alcohol on children and their families is profound. Children and youth with FASD have significantly lower quality of life outcomes than children and youth from the general Canadian population (Clarke & Gibbard, 2003), making detection and accurate assessment of utmost importance. However, the delineation of an overall neuropsychological profile is quite weak, partially due to lack of objective assessment tools. In the absence of obvious facial abnormalities or confirmed maternal alcohol consumption during pregnancy, the diagnosis of partial FAS (pFAS) and ARND, usually made later in childhood, is often based, in part, on motor dysfunction symptoms (Stratton et al., 1996). However, at present, specific deficits in sensory-motor function and the underlying neurobiological mechanisms have not been clearly defined.
Chapter 2

Literature Review

2.1 Neurotoxic effects of ethanol

2.1.1 Prenatal brain development

Ethanol affects the developing prenatal brain in various ways, at different stages of development, and in a dose-dependent manner, which can result in a range of FASD phenotypes. At the cellular level, ethanol disrupts basic developmental processes within the CNS, including interference with 1) cell division and proliferation; 2) cell growth; 3) differentiation and the migration of mature cells; 4) astroglia development; and 5) neuronal-glial interactions (Stratton et al., 1996; Guerri, 1998 for review).

Some potential mechanisms that underlie the neuroteratological effects of ethanol include: 1) alterations in the regulation of gene expression; 2) interference with mitogenic and growth factor responses involved in neural stem cell and glial cell proliferation; and 3) activation of molecular signalling, controlling cell survival or death (i.e. growth factors deprivation, oxidative stress, apoptotic signalling; Guerri, 1998). An impairment of several neurotransmitter systems and/or their receptors, as well as changes in the endocrine environment during brain development, are also important factors involved in the behavioral dysfunctions observed after prenatal alcohol exposure (PAE; Guerri, 1998).
2.1.2 Factors influencing the effects of PAE on the developing brain

PAE results in a variety of neuropsychological presentations leading to a high degree of individual variability depending on specific exposure characteristics and CNS vulnerability at the time of exposure (Kaemingk & Paquette, 1999); no single neuropsychological profile of FASDs accurately describes every affected individual.

Biological and environmental factors known to influence the effects of ethanol on the developing brain include 1) dose of alcohol (and levels of ethanol reaching the fetal brain; see Bonthius & West, 1988); 2) exposure pattern (Bonthius & West, 1988; Maier & West, 2001); 3) developmental timing of exposure (strongly influences the specific brain structure affected and the magnitude of the damage; Thomas, Burchette, Dominiguez, & Riley, 2000); 4) genetic background and susceptibility of the mother and fetus, such as variations in ethanol metabolism (Abel & Hannigan, 1995); 5) social economic status, nutrition, and prenatal care (Abel & Hannigan, 1995); 6) synergistic reactions with other drugs (Abel & Hannigan, 1995); and 7) variations in the vulnerability of different brain regions (see Nayak & Murthy, 2008; O’Leary et al., 2010 for review of environmental factors).

One thing that highly determines any individual phenotype is the stage of embryological development at which exposure to ethanol occurs (Riley & McGee, 2005). Depending on the stage of brain development, ethanol triggers different patterns of neuronal deletion, and each pattern has the potential to give rise to its own unique arrangement of neurobehavioral disturbances (Olney, 2004). The first weeks after conception are the most critical, during gastrulation, where reduction of the neural progenitors pool may lead to facial dysmorphology and mental disabilities (Guerri, Bazinet, & Riley, 2009). For example, the formation of the corpus callosum (CC) and glial midline starts at around seven weeks gestation and exposure to ethanol at
this stage might disrupt the early events in callosal formation, and later on, might dysregulate axonal pruning, leading to agenesis, or hypoplasia (Guerri et al., 2009; Guerri, 1998). Alcohol exposure later in pregnancy may affect growth and may lead to cognitive impairment and learning disability (Guerri et al., 2009). Alcohol interferes with the ‘brain growth spurt’ in the 3rd trimester of human gestation, a period characterized by glial development, synaptogenesis, and development of the cerebellum and hippocampus (Guerri et al., 2009; Niccols, 2007 for review).

2.2 Adverse outcomes associated with FASD

2.2.1 Cognitive and behavioral problems in children with FASD
Common cognitive and behavioral problems in children with FASD include attention deficits; inability to predict consequences; inability to learn from previous experience; inappropriate or immature behavior; poor organizational skills; learning disabilities; poor abstract thinking, adaptability, impulse control, and judgement; in addition to speech, language, and other communication problems (see Koren et al., 2003 for review). FASD is also characterized by sensory processing impairments, affecting various daily activities and skills (Franklin, Deitz, Jirikowic, & Astley, 2008). These impairments have been associated with a wide range of neurobehavioral difficulties, including deficits in speed and efficiency of information processing, in both infancy and later in childhood (Burden, Jacobson, & Jacobson, 2005); poorer performance on complex, rather than simple, tasks, compared to typically-developing children (Aragon et al., 2008); and problems with motor coordination and visual-perceptual skills (Franklin et al., 2008). Children with FASD also have a variety of comorbidities, some of which include cardiac, skeletal, renal, ocular, and auditory problems (see Stratton et al., 1996 for review), as well as kidney, liver, and gastrointestinal birth defects (Hofer & Burd, 2009). An excess of
psychopathology is also observed, including hyperkinetic, emotional, and sleep disorders, with a strong persistence over time (Steinhausen & Spohr, 1998).

Gestational alcohol exposure is also related to a pattern of neuropsychological deficits (and the degree of CNS impairment may be independent of the presence of physical features associated with FAS; Mattson, Riley, Gramling, Delis, & Jones, 1998). Children, regardless of level of PAE, may exhibit similar neuropsychological problems, including deficits in executive functions (EF), such as response inhibition, planning, and rule learning (see Rasmussen, 2005; Rasmussen & Bisanz, 2009). Behavioral problems are commonly reported in children with FASD and can be characterized by hyperactivity, poor attention span, inattentiveness, impulsivity, and lack of inhibition (see Mattson, Schoenfeld, & Riley, 2001; Vaurio, Riley, & Mattson, 2008). Intellectual functioning is also impaired (see Steinhausen & Spohr, 1998), demonstrated by lower intelligence scores, lower academic achievement (Mattson, Riley, Gramling, Delis, & Jones, 1997), and problems with verbal and nonverbal learning (Mattson et al., 2001; Mattson, Riley, Delis, Stern, & Jones, 1996), as well as spatial memory (Mattson & Riley, 1999; Malisza et al., 2005).

2.2.2 Effects of PAE on brain structure
Brain development is a complex process that proceeds in an orderly fashion throughout the pre- and post-natal phases and continues into adulthood (Inder & Huppi, 2000). Normal brain development is altered prenatally by alcohol, leading to CNS disorganization (Spadoni, McGee, Fryer, & Riley, 2007). It is evident that brain-behavior relations are altered as a function of PAE, as abnormal neural activity or structural characteristic of any given region could affect the operation of cognitive processes that engage that region (Stevens, 2009). The devastating effects
of PAE on brain development have been documented by numerous studies (see Niccols, 2007 for review). Imaging studies show permanent structural abnormalities and atypical brain development (see Guerri et al., 2009; Autti-Ramo et al., 2002), including microcephaly (Guerri et al., 2009); decreased overall total brain volume, with growth reduction of the frontal, parietal, and temporal lobes; white matter hypoplasia; and grey matter asymmetries (Spadoni et al., 2007; Wozniak et al., 2006), in children and adolescents affected by PAE.

The toxic effects of ethanol are not uniform; the impact of PAE seems to affect certain neuro-anatomical areas and neuropsychological functions more than others. Not only are some brain regions more affected than others, but even within a given region, some cell populations are more vulnerable than others (see Bonthius & West, 1990). Some brain structures which have been associated with numerous long-term behavioral and cognitive deficits due to the neurotoxic effects of ethanol include the corpus callosum (Riley et al. 1995; Bookstein, Sampson, Streissguth, & Connor, 2001; Sowell et al., 2001), hippocampus (Autti-Ramo et al., 2002; Willoughby, Sheard, Nash, & Rovet, 2008), basal ganglia (Mattson et al., 1994; Archibald et al., 2001), and cerebellum (Mattson et al., 2001; O’Hare et al., 2005).

**Corpus Callosum**

It is believed that the CC may show increased vulnerability to gestational alcohol exposure, especially because prenatal exposure disproportionately affects midline craniofacial and brain structures (Wozniak et al., 2006). Individuals with FASD exhibit complete and partial agenesis of the CC, smaller callosal volumes, even after correcting for smaller brain size, as well as alterations and increased variability in callosal shape, especially in posterior callosal regions, such as the isthmus and splenium (Riley et al., 1995). Diffusion tensor imaging (DTI) shows decreased
white matter in the genu and splenium of the CC and diffusion differences in the isthmus, indicative of disorganized fiber tracts (Wozniak et al., 2006). Even relatively mild forms of PAE may be associated with microstructural abnormalities in the posterior CC that are detectable with DTI (Wozniak et al., 2006).

Abnormalities of the CC in those with PAE have been associated with neuropsychological and functional deficits in, for example, bimanual coordination, attention, verbal learning ability, and EF, as well as spatial and visual working memory, processes for which the CC plays a role (see Spadoni et al., 2007 for review). Certain CC anomalies in children with FASD are related to specific cognitive deficits: disruption of splenial fibers is associated with poorer visuomotor integration, while thin corpus callosum (specifically in the anterior and posterior regions) have been related to motor deficits (Spadoni et al., 2007; Sowell et al., 2001). In this case, connections within the CC may be less efficient in delivering information to the brain’s motor centers (Spadoni et al., 2007).

**Cerebellum**

The cerebellum plays a role in coordinating and executing skilled voluntary movements, and controlling muscle motor tone, posture, balance, and gait (Baillieux, Jung De Smet, Paquier, De Deyn, & Marien, 2008). It is also involved in higher cognitive functions, such as attention regulation and visuo-spatial skills (Paquier & Marien, 2005). The cerebellum is further involved in different cognitive spatial tasks, such as spatial attention and orientation, illusory space body perception, explorative behavior, and visuo-motor sequence learning (Molinari & Leggio, 2007).

The cerebellum shows a pronounced vulnerability to the deleterious effects of PAE, which is not surprising since the midline appears to be more vulnerable to the teratogenic effects...
of ethanol (O’Hare et al., 2005). Some cerebellar abnormalities noted in individuals with FASD include reductions in cerebellar volume and surface area (Olney, 2004), hypoplastic cerebellar hemispheres (Autti-Ramo et al., 2002), and vermal hypoplasia and displacement (Autti-Ramo et al., 2002). Magnetic resonance images of those heavily prenatally exposed to alcohol reveal death of Purkinje cells, with consequent disruption of cerebellar cortical structure in ways that could explain the delayed motor development and other behavioral consequences seen in humans (Bookstein, Streissguth, Connor, & Sampson, 2006). All of the above structural abnormalities may contribute to the functional deficits seen in balance, bimanual coordination, and attention.

**Basal Ganglia**

The basal ganglia, which reside deep inside the brain, are heavily connected to cortical and subcortical motor areas, and are intimately related to movement and procedural learning (Archibald et al., 2001). There has been noted a disproportionate volumetric reduction in the basal ganglia of children with FASD, even after controlling for overall brain size (Mattson et al., 1992), also possibly accounting for some of the observed neuropsychological deficits observed in the FASD population.

**2.3 Secondary Disabilities**

Primary disabilities, which reflect inherent CNS dysfunctions in cognition and behavior, can contribute to psychiatric co-morbidities and secondary disabilities. Secondary disabilities commonly reported in children, youth, and adults with FASD include: mental health problems (90%), with depression and anxiety constituting a large proportion of those problems, dependent living (80%), employment problems (80%), disruptive school experience (60%), trouble with the
law (60%), confinement (50%), inappropriate sexual behavior (50%), and alcohol or drug problems (30%; see Koren et al., 2003 for overview).

The earlier the detection and diagnosis of a child with FASD, the better the prognosis, both in terms for the patient, in preventing these debilitating secondary disabilities, and for society’s accommodation to the individual, since these disabilities are a significant economic burden to society (Stade et al., 2007).

2.4 Diagnosis and Challenges

Some of the adverse effects of PAE on children were first recognized and described in offspring born to alcoholic mothers by Lemoine, Harrousseau, Borteym, & Menuet, in 1968, and subsequently elaborated upon by Jones and Smith, in 1973. To describe the spectrum of symptoms that are seen in children with PAE, diagnostic criteria were published by a committee of the Institute of Medicine (IOM; Stratton et al., 1996). Thereafter, effects were further refined by Astley and Clarren (2000), leading to the 4-Digit Code System of diagnostic management, which was later adapted in the Hoyme Diagnostic Guidelines, in 2005 (Hoyme et al., 2005; see Astley, 2006 for comparison between the two sets of guidelines). Also in 2005, Health Canada’s National Advisory Committee on FASD published The Canadian Guidelines for Diagnosis (Chudley et al.).

The Canadian Guidelines for Diagnosis (Chudley et al., 2005) harmonizes the IOM Guidelines (Stratton et al., 1996) and the 4-Digit Diagnostic Code (Astley & Clarren, 2000) and describes four key diagnostic features in the following order: 1) growth deficiency, 2) the FAS facial phenotype, 3) CNS dysfunction, and 4) PAE, with the magnitude of expression of each
feature ranked independently on a 4-point Likert-type scale, with 1 reflecting complete absence of the FAS feature, and 4 reflecting a strong ‘classic’ presence of the FAS feature.

Diagnosis of an FASD in a child is a serious challenge, and for various reasons. The two clearest ways of determining whether or not a child may have FASD includes the presentation of facial features and confirmed maternal alcohol consumption during pregnancy, each associated with its own challenges and sometimes making a diagnosis impossible (see Chudley et al., 2005). Firstly, facial features are most evident between 8 months and 8 years of age (Koren et al., 2003); these facial signs may fade or disappear in late adolescence and adult life (or were never present to begin with), making a diagnosis, later in an individual’s life, difficult. Secondly, there may be no clear history of maternal drinking. Screening for maternal alcohol consumption relies on maternal testimony and questionnaires (AUDIT, TWEAK, MAST, and TLFB; see Russell et al., 1996; Caprara, Nash, Greenbaum, Rovet, & Koren, 2007), both with inherent threats to the reliability of a PAE history. Birth mothers may be reluctant to report that they drank during pregnancy; they may be unable to recall accurately how much they drank; or the biological mother is absent altogether (for ex., 81% of children diagnosed at Washington State FAS Diagnostic and Prevention Network clinics are in foster or adoptive care; Astley, 2006). Also lending difficulty to diagnosis is the non-specific nature of the symptoms (especially with regard to ARND); lack of a complete neuro-developmental profile; as well as lack of objective assessment tools.
2.5 FASD motor deficits and tests used to assess motor dysfunction

2.5.1 Overview of motor disabilities

Researchers are increasingly considering the importance of motor functioning of children with FASD. Although a few studies find no effect of prenatal alcohol on motor development (Chandler, Richardson, Gallagher, & Day, 1996), most studies of motor development and motor skills suggest an effect of PAE (see Mattson & Riley, 1998 for review). Early descriptions of children of chronic alcoholic mothers reported delayed motor development, noting a “nonspecific dyscoordinated motor pattern,” hemiplegia, and ataxia (Oleglrd et al., 1979). In young children with FAS, neurological signs, such as kinetic tremors, motor incoordination, weak grasp, difficulty with eye-hand coordination, seizures, hypotonia, and increased muscle tone have been observed (Spohr, Willms, & Steinhausen, 1993). Decrements in motor functioning have been reported both in studies of clinically diagnosed children and in prospective studies of the longitudinal effects of various levels of PAE in which relatively few of the subjects are diagnosable (Connor, Sampson, Streissguth, Bookstein, & Barr, 2006). Studies of motor performance in infants and children exposed prenatally to alcohol have demonstrated group mean motor performance deficits and developmental impairment of motor skills, in both gross motor and fine motor areas of motor development, in infancy, beginning in the first days of life, and persisting through the first two years of development, and often into adolescence (see Osborn, Harris, & Weinberg, 1993 for review; Autti-Ramo & Granstrom, 1991). Some of the major deficits, which will be discussed below, are with regard to gross and fine motor skills, balance, and coordination.
2.5.2 Gross and fine motor skills

Alcohol exposure during development disrupts both gross and fine motor coordination in humans, revealing developmental delays in fine and gross motor skills, believed to be related to specific neurobehavioral deficits that affect these skills (Kalberg et al., 2006).

Kalberg et al. (2006) assessed the motor development of young children with FAS to determine the presence and degree of delay in motor skills and to compare their motor development with that of children without FAS, by making use of the Vineland Adaptive Behavior Scales (VABS; Sparrow, Balla, & Cicchetti, 1984), a behavior rating scale that measures four domains of behavior (communication, daily living skills, socialization, and motor skills). Most of the young children 2-5 years of age showed clinically important delays in their motor development. There was also reported, in those with PAE, a significant discrepancy in development between fine-motor and gross-motor development, such that their fine motor skills were significantly more delayed than their gross motor skills, with no significant group differences in gross motor scores between the two groups (Kalberg et al., 2006). Forty-three percent of the children with FAS had average gross motor abilities, whereas only seven percent of the children showed average fine motor skills (Kalberg et al., 2006). Similarly, Adnams et al. (2001) failed to find a significant effect of PAE on the locomotor (gross motor) subscale used in that study, which ranged from pushing with feet and holding head erect in infancy, to jumping and skipping in middle childhood.

2.5.3 Balance and fine motor coordination

In addition, there are studies of motor performance of children with PAE showing disturbance of balance and coordination (Barr, Streissguth, Darby, & Sampson, 1990). Children with FASD (as
young as 6 to 8 years of age) show deficits on eye and hand coordination tasks related to fine motor coordination, such as drawing geometric figures and threading beads (Adnams et al., 2001), as well as deficits in complex bimanual coordination tasks (Roebuck-Spencer, Mattson, Marion, Brown, & Riley, 2004).

A study was carried out by Connor et al. (2006) to study fine motor coordination and balance in adults (mean age of 24 years) through a variety of administered tests. Motor tests included the Denckla Neurological Coordination Test (DNCT; Denckla, 1974) – a manually-administered test of unilateral and bilateral finger, hand, and foot coordination: finger tapping, finger sequencing, arm supination-pronation, toe-tapping, and heel-toe tapping. The FASD group demonstrated deficits in motor function, such that the FASD group was slower, on average, to perform finger, hand, and foot movements than controls, on the DNCT (Connor et al., 2006). Also administered was the Finger Sequencing Test (Mahurin, 1993) – a computer-administered test of two- and three-finger sequencing and bilateral alternating finger tapping. Those with FASD averaged fewer correct finger tapping sequences than did the typically-developing group of children (Connor et al., 2006). The next administered test was the Hand Steadiness Test (Matthews & Klove, 1978), which requires the subject to hold a stylus inside a series of progressively smaller openings for 15 seconds. The FASD group averaged more errors (periods of touching the side of the hole) and were slower to correct their errors than the control group. On the Dynamic Balance task (Wade & Newell, 1972), which requires the subject to maintain balance on a free moving “teeter-totter” board, the FASD group averaged less time in balance than controls. In children, exposure to alcohol during development leads to altered gait and tremor, in addition to deficits in balance and fine motor coordination (Connor et al., 2006).
Also in line with previous reports, Roebuck, Simmons, Mattson, and Riley (1998) used computerized dynamic posturegraphy and found group mean motor deficits between those with FASD and typically-developing children, in aspects of postural balance in response to balance disturbances (movements made to subjects’ support surface), indicating that those with FASD have more trouble restoring their balance.

2.5.4 Other tests used to assess motor function in individuals with FASD

Another motor test commonly used to investigate motor function in children is the Movement Assessment Battery for Children (M-ABC; Henderson & Sugden, 1992), designed to detect motor skill impairments in children aged 4-12 years. Test results are expressed in terms of a Total Impairment score, a Manual Dexterity score, a Ball Skills score, and a Balance score. The assessment battery has four age bands (4-6, 7-8, 9-10, and 11-12), with eight tasks per age band, and targets more complex motor skills. Raw scores for each task range from 0-5. Children with FASD, tested using this battery, exhibit impairment across the age range and in the various domains tested (Kooistra, et al., 2009).

The Clinical Observations of Motor and Postural Skills (COMPS; Wilson, Pollock, Kaplan, & Law, 2000) is yet another test used, designed to assess children with subtle perceptuo-motor problems, with a specific focus on cerebellar function, motor coordination, and postural control. The six motor tasks include slow movements, rapid forearm rotation, finger-nose touching, prone extension posture, asymmetrical tonic neck reflex, and supine flexion. The test typically assesses the integrity of basic motor functions served by the cerebellum. Raw scores range from 0-12 on these tasks. Basic motor control functions assessed by the COMPS are
essentially intact in the majority of children with FASD; their motor problems typically appear in tasks requiring more complex motor skills (Kooistra et al., 2009).

Dysfunctional behavior and altered motor function of children with FASD is consistent with the vulnerability of CNS motor areas to alcohol’s teratogenic effects and has, indeed, been linked to alcohol-related trauma to some of the aforementioned brain regions, including: the cerebrum, CC, and basal ganglia, all of which are involved in aspects of motor movement (see Kalberg et al., 2006). Quite often, structural and/or functional cerebellar impairment is given as a potential explanation for the observed balance deficits (Kooistra et al., 2009).

2.5.5 Current direction in FASD and motor assessment research
There is a plethora of research documenting alcohol-related decrements in motor performance in infancy and childhood, but there seems to be a lack of literature extending into late adolescence, leaving us with unanswered questions, such as, “Do motor effects, due to PAE, reported in children persist into adulthood?” The current study will help shed light on this question by including those up to 18 years of age.

Some other key differences between most of the studies discussed above and the current study are as follows: 1) the current study makes use of an objective means with which to collect data on motor performance, while some other tests, such as the DNCT, leave it up to the examiners to rate the difficulty each individual encounters in motor coordination while performing each task; 2) most studies in the literature focus on group mean differences, whereas the current study will also focus on individuals’ performances and how they compare to the norm; and 3) while reports on relations between FASD and motor impairment are relatively rare, they are largely aimed at establishing overall levels of motor competence. While agreeing on the
presence of a wide range of fine and gross motor deficiencies in children with FASD, these studies have not yet established a valid motor ability profile. The field lacks specificity regarding the type of motor problems characteristic of FASD and their underlying neurophysiological mechanisms. The current study will attempt to outline the underlying processes that contribute to sensory-motor deficits observed in the FASD population, instead of simply naming the deficits (i.e. manual dexterity/fine motor deficits).

Although many children with extensive PAE appear normal at birth, they may later be identified with many subtle neurobehavioral deficits not apparent in their early years (Koren et al., 2003); the problem lies with accurately measuring these subtle deficits. For example, for a diagnosis of ARND, one needs to be evaluated for neurological hard and soft signs, such as impaired fine motor skills, poor tandem gait, and poor hand-eye coordination (Chudley et al. 2005; Stratton et al., 1996), but the question lies with how accurately, completely, and reliably these motor skills are measured. From a clinical perspective, it is essential to have more specific information on the observed brain dysfunction.

The lack of diagnostic precision makes efforts to screen for FASD in adolescents or developmentally disabled adults very difficult, increasing our need for objective and reliable assessment/screening tools to measure alcohol-related deficits. Indeed, one of the most problematic areas of FASD research has been in the determination and quantification of the behavioral phenotype (through accurate, precise, valid, and efficient methods) and an important objective of the current paper is to determine, through a more novel and objective approach, if PAE results in a unique or clearly definable motor behavior phenotype.
2.6 Biomechanics

2.6.1 The execution of reaching movements

The development of motor functions and the acquisition of motor skills requiring the upper limbs, such as drawing, handwriting, reaching, grasping, and manipulating objects are crucial for performance in school, autonomy in everyday life, and general human development (Rueckriegel et al., 2008). Specifically, multi-segment, goal-directed movements, such as reaching, which are involved in many activities of daily life, will be discussed in further detail.

To execute arm reaching movements, coordinate transformations and initial motor commands need to be calculated (Baraduc, Guigon, & Burnod, 2001). The preparation for an arm movement toward a visual target can be described as a series of sensory-motor coordinate transformations between the retinal position of the target and arm muscle activities (Baraduc et al., 2001). The planning and execution of a simple goal-directed arm reach to a spatial target requires the integration of visual and proprioceptive information (about the location of the target and the arm in 3-dimensional space) and then the translation of this spatial information into appropriate motor commands (Lacquaniti & Caminiti, 1998). The merging of these two steps requires a series of visuomotor transformations by the nervous system, including 1) visual acquisition of the object (and its direction) on the retina, 2) coordination of multimodal proprioceptive signals (monitoring arm position in the intrinsic frame of reference of muscle, joint, and skin receptors), and ultimately, 3) the generation of appropriate muscle activity patterns to bring the hand to the spatial location of the object (Vesia, Vander, Yan, & Sergio, 2005). The end-point positions of reaching are specified by combining visuo-spatial, gaze, and arm information in a common egocentric (viewer-centered) frame of reference and the parietal cortex plays a prominent role in this process (Lacquaniti & Caminiti, 1998).
A key feature of goal-directed reaching movements is that the hand follows a fairly straight path; however, the complex mechanics of multi-limb movement (from the geometry of the multi-joint arm and the interaction torques from various forces), complicate the generation of muscle activity and forces required to make such a straight trajectory (Vesia et al., 2005). Achieving a straight hand path requires learning and accounting for the dynamic properties of the limb. The nervous system must take these biomechanical details of the limb (which will act to displace the hand away from a straight path to an object) into account when transforming a spatial sensory signal into an intrinsic pattern of joint torques for an impending reach (Vesia et al., 2005).

Studies of multi-joint arm movements have demonstrated that the nervous system anticipates and plans, prior to its initial motor output, for the mechanical effects that arise from motion of the linked limb segments, when pre-planning arm muscle activity or muscle torque, particularly for the initial motion of the arm toward a target (Sainburg, Ghez, & Kalakanis, 1999). For example, when interaction effects (generated from muscle torques) are not anticipated, errors in hand path occur, which are seen in patients following nervous system injury (Flash & Henis, 1991). The nervous system selects and adjusts muscle activities and/or torques based, in part, on predictions about the impending interaction torques (Flash & Henis, 1991).

One way in which the nervous system may predetermine movement-related limb dynamics of an impending movement (i.e. musculoskeletal and kinematic dynamics and other forces acting on the limb), in order to generate linear spatial reach trajectories, is through a representation, or internal model (IM), of the movement (Shadmehr & Mussa-Ivaldi, 1994; Thoroughman & Shadmehr, 1999).
2.6.2 The Internal Model

During practice of novel tasks, the nervous system gradually develops an internal representation (or model) of the associated environmental dynamics, which is then used to control movements made under identical or similar task conditions (Thoroughman & Shadmehr, 1999). It is believed that the CNS acquires and maintains internal models of sensory-motor mappings for different tasks and environments (Kawato, 1999; Wolpert, Ghahramani, & Jordan, 1995) and that the same general internal representation of motion is used each time a movement is about to be generated, with the spatial and temporal parameters (i.e. movement amplitude, duration, and end-point locations) chosen for that particular movement (Flash & Hogan, 1985). The acquisition of new motor skills involves learning novel mapping between motor commands and sensory signals (Klassen, Tong, & Flanagan, 2005).

Some models require a complete specification of a movement plan before its implementation (Flash & Hogan, 1985); others propose that an IM is not completely integrated into the initial stages of a movement plan, that, instead, the motor system may initially use an unpolished approximation of movement-related limb dynamics, only specifying, in advance, certain critical features of the potential movements related to the global goal of the task (i.e. target location, hand position; Wolpert & Kawato, 1998). In other words, the central neural representation of the entire detailed time course of movements may only be generated dynamically, in real time, during motor output, allowing for the refinement of the motor plan as the movement unfolds (Wolpert & Kawato, 1998).

2.6.3 Pre-planning versus on-line adjustments and the role of internal models

There are delays in sensory-motor pathways, reflecting the time when sensory information becomes available to the CNS: 30-50 ms for a short-loop feedback mechanism (Ghez & Shinoda,
1978) and about 150 ms for a long-loop mechanism (Gielen, Ramaekers, & van Zuylen, 1988). An ideal predictive feed-forward controller must possess an internal representation of how the controlled system behaves, prior to the initiation of motor output, in order to generate the appropriate outgoing motor commands, using this supposed IM of musculoskeletal dynamics and other forces acting on the limb (Vesia et al., 2005). It has been reported, however, that although a representation of the impending motor command exists prior to movement onset, the initial motor plan does not fully incorporate limb mechanics, and further, internal feedback loops relying on a forward model are integrated, in real time, into the motor commands sent to the limb (Wolpert et al., 1995). Therefore, compensation for multi-joint limb dynamics may be accounted for by an adaptive feed-forward controller that is updated by feedback loops as the movement unfolds (Sainburg et al., 1999).

One way to combine predictive neural commands with short- and long-loop sensory feedback elements of control is to incorporate both forward and inverse IMs into a limb motor control system. This limb motor control system would initially depend on a forward model, which is less sensitive to erroneous sensory data as the goal-directed motor behavior progresses, and then reacts to sensory feedback and allows the long-loop feedback pathway to make adjustments to unfolding motor behavior (Vesia et al., 2005).

To produce a desired hand trajectory, the nervous system must coordinate muscle forces with both external forces, imposed by the environment, and internal forces, that arise within the musculoskeletal system itself (Sainburg et al., 1999). Movement endpoints are achieved by a mechanism that is distinct from trajectory control; final posture is attained independently of the trajectory, by using visual information about target location and specifying motor commands to particular groups of muscles to reach the final position (Sainburg et al., 1999). It is plausible that
the final position is determined completely by feedback-mediated changes in torque. A type of combined anticipatory and postural controller is supported: Sainburg et al. (1999) indicate that intersegmental dynamics are controlled by a 3-stage control system that sequentially links anticipatory, error correction, and postural mechanisms, and is described as follows. Movements are initiated through anticipatory mechanisms based on learned representations of musculoskeletal and task-specific dynamics; later, as sensory feedback becomes available, error corrections are made; followed by positional control mechanisms that determine the final posture for the limb, all of which operate successfully to control smooth and rapid reaching movements.

2.6.4 Reaching movements as a function of age
A really coordinated behavior develops gradually, from the first manifestations of goal-directed reaches, which appear about the fourth month of life (Hofsten, 1991). Changes in arm trajectory variability in reaching occur during childhood (Sveistrup, Schneiberg, McKinley, McFadyen, & Levin, 2008). Olivier, Hay, Bard, & Fleury (2007) investigated age-related differences in the coordinative mechanism of the reach-to-grasp movement in three groups of children aged 6, 8, and 11 years, as well as in healthy adults. Results showed high variability at age 6, an age-related change between the 6 and 8 year-olds for almost all outcome measures, and a difference between the 11 year-olds and the adults, with the acquisition of an optimal coordination of the reaching and grasping commands reached only around 12 years of age (Olivier et al., 2007). One study reported that the progression of kinematic parameters for each movement domain of drawing and hand-writing tasks correlated with age (i.e. speed, number of direction changes, variability, and pressure), with the complex fine motor function reaching maturity later than basic and repetitive patterns (Rueckriegel et al., 2008).
2.6.5 Importance of using reaching movements to study brain function

Visually-guided reaching movements have become an important paradigm for studying how regions of the brain, such as primary motor cortex, are involved in the planning and control of voluntary movement (Georgopoulos, 1995) and have become important for understanding how sensory information is processed and converted into coordinated motor behavior, in both the typically-developing population, as well as in populations with neurological disorders (Scott, 2004; Coderre et al., 2010).

2.7 Instrument used, rationale, hypotheses, and objectives of the current study

Examining motor dysfunction in children with FASD is essential for understanding and defining a profile of sensory-motor deficits in the population, as well as for learning about relative strengths that could be built upon and weaknesses that may be improved with instruction, treatment, and intervention. Clinically, distinguishing children with PAE from non-exposed children is important for early and targeted intervention. Determining more specific intervention models, guided by improvements in our knowledge of specific deficits, may be effective in improving outcome and reducing the incidence of secondary disabilities. Without conducting research aiming to delineate specific and objective measures of behavioral dysfunction, such as that of sensory-motor dysfunction, through accurate, precise, and valid methods, progress in areas like screening, assessment, surveillance, and intervention will all suffer.

The Kinesiological Instrument for Normal and Altered Reaching Movements (KINARM) can address a wide range of issues related to multi-joint coordination, in addition to the integration of visual and proprioceptive information to select and guide movement. The KINARM has shown to be valuable for studying human movement, particularly in populations
exhibiting motor dysfunction, such as stroke patients (Coderre et al., 2010), and for a variety of reasons.

The KINARM is an exoskeleton that attaches to the upper arm and forearm of a subject. The mechanical linkage allows the subject to make combined flexion and extension movements of the shoulder and elbow joints to move his/her hand to targets in the horizontal plane. The KINARM eases the difficulty inherent in quantifying the mechanics of multi-joint motion, and furthermore, the movement tasks given to the participant are standardized and easily understandable, in order to avoid confusion.

The KINARM’s ability to describe hand movements and categorize performance outcome measures into specific movement domains is just one advantage that it has over classical methods of evaluating reaching. Other important advantages are the highly objective method of data acquisition, in addition to its reported high inter-rater reliability (see Coderre et al., 2010). The KINARM provides sensitive information for the detection and quantification of neurological movement disorders and this more sensitive measure of brain function may provide more exact assessment and prognosis, revealing insights into the future of a child’s abilities. The lack of appropriate tools to identify individuals with FASD causes many alcohol-exposed and affected children to go undetected, not detected until late in development, or misidentified altogether. These difficulties lead to inappropriate patient care (insufficient social, educational, and health care services), increased risk for secondary disabilities, and missed opportunities for primary prevention, in addition to inaccurate estimates of incidence and prevalence (Astley & Clarren, 2000).
Present diagnostic and clinical assessment of multi-joint motor skills rely predominantly on qualitative descriptions of movement and these assessments provide only a coarse, subjective measure of motor function, leading to the global hypothesis of the current research project:

- the KINARM will serve as an effective tool for identifying and measuring specific, neurologically-based motor deficits in children with FASD.

The KINARM may prove to be valuable for looking at deficits related to sensory-motor integration and body position sense, by its ability to measure several kinesiological variables of movement, and by producing great amounts of data to give us a comprehensive view of a child’s motor movement during the performance of two different tasks: 1) a visually-guided reaching task with fingertip feedback only and 2) an arm position-matching task in the absence of visual feedback, also expected to reveal impairments in sensory function and proprioception – areas not well researched, in this field, to date.

We attempted to classify children in this population by utilizing straight-forward sensory-motor measures of motor ability, some of which are known to be affected in individuals prenatally exposed to alcohol, with or without the facial phenotype of FAS. Additionally, by using information from multiple measures rather than any single measure, we hoped to provide a more comprehensive model for helping to detect the occurrence of FASD.

We also wanted to explore possible age-related differences in the pattern of motor performance, which would be useful for understanding how sensory-motor deficits are manifested over the course of development, with strong implications for assessment. These concepts were investigated by testing the following hypotheses:
• **Hypothesis 1a:** There is an age-dependent improvement in the performance of the visually-guided reaching task in typically-developing children over the age range of 5 to 18 years.

• **Hypothesis 1b:** Children with FASD exhibit atypical performance in a visually-guided reaching task.

• **Hypothesis 2a:** There is an age-dependent improvement in the performance of an arm position-matching task in typically-developing children over the age range of 5 to 18 years.

• **Hypothesis 2b:** Children with FASD exhibit atypical performance in an arm position-matching task.
Chapter 3

Methods

All methods and procedures for this study were reviewed and approved by the Queen’s University and Affiliated Hospitals Research Ethics Board.

3.1 Participant demographics

The study population consisted of a total of 114 children (83 typically-developing children and 31 children diagnosed with a Fetal Alcohol Spectrum Disorder) for the reaching task, and a total of 80 children (49 controls and 31 with an FASD) for the position-matching task, all between the ages of 5 and 18 years, male and female. Both groups, tested in each task, had a mean age of approximately 10 years, with no significant difference of age between the two groups who performed each task. Demographic information for the two groups of participants entered in the final analysis for the reaching task and the position-matching task are reported in Table 1 and Table 2, respectively.

3.2 Experimental Apparatus

Unloaded, center-out reaching movements (under visual guidance) and sensory matching (without any visual feedback) were performed using a robotic device called KINARM: the Kinesiological Instrument for Normal and Altered Reaching Movements (BKin Technologies Ltd., Kingston, ON; see Scott, 1999); a schematic representation of the experimental set-up is shown in Figure 1.
Table 1: Participant demographics for subjects who performed the reaching task

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>FASD</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>83</td>
<td>31</td>
</tr>
<tr>
<td>Age range (yrs)</td>
<td>5-16</td>
<td>5-18</td>
</tr>
<tr>
<td>Mean age + SD (yrs)</td>
<td>9.8 ±3.3</td>
<td>10.9±3.4</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>55% : 45%</td>
<td>65% : 35%</td>
</tr>
<tr>
<td>Dominant hand (R:L)</td>
<td>88% : 12%</td>
<td>74% : 26%</td>
</tr>
</tbody>
</table>

* n = sample size; SD = standard deviation; M = male; F = female; R = right; L = left

Table 2: Participant demographics for subjects who performed the position matching task

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>FASD</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>49</td>
<td>31</td>
</tr>
<tr>
<td>Age range (yrs)</td>
<td>5-16</td>
<td>5-18</td>
</tr>
<tr>
<td>Mean age + SD (yrs)</td>
<td>9.0 ±3.4</td>
<td>10.9±3.4</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>49% : 51%</td>
<td>65% : 35%</td>
</tr>
<tr>
<td>Dominant hand (R:L)</td>
<td>90% : 10%</td>
<td>74% : 26%</td>
</tr>
</tbody>
</table>

* n = sample size; SD = standard deviation; M = male; F = female; R = right; L = left

Figure 1: The KINARM apparatus. Characteristics include a chair, on wheels, that is adjustable, in height, for optimal position within the virtual reality platform; adjustable exoskeleton with child-sized fiber-glass troughs to support the upper and lower arms segments; and a semi-transparent mirror which displays virtual targets and finger-tip feedback for the reaching task in the (horizontal) plane of the arm. * Adapted from Choe et al., 2009.
KINARM is a bilateral exoskeleton that attaches to the upper arm and forearm of a subject and that allows one to manipulate the mechanics of movement and quantify performance. The device has a four-bar mechanical linkage that is adjustable to align its ball-bearing joints with the centers of rotation of the shoulder and elbow joints of the subject. This linkage, which is attached to the subject’s arm, allows him/her to make flexion and extension arm movements of the shoulder and elbow joints in the horizontal plane. The subject rests his/her upper- and fore-arms on custom-made fiber-glass troughs which keep all limb segments in a fixed position relative to the robotic linkage. Sensors attached to the robotic linkages measure hand displacements, as well as the kinematics and kinetics of the elbow and shoulder joints, allowing for the precise measurement of coordinated limb movement.

The KINARM is used in concert with a computer projection system that provides virtual targets in the plane of the arm after several steps of calibration to align the location of the visual display to the participant’s position in the robot and upper limb workspace. Virtual targets are reflected in the horizontal plane using a semi-transparent mirror and a projection monitor, allowing the hand to interact in the completion of a visually-guided sensory-motor task.

The software shows real-time 3-D representations of a subject’s movement and 2-D traces of hand trajectories as the task progresses, in addition to providing precise, reliable control and measurement of movement (Dexterit-E’s User Guide, 2006).

3.3 Experimental Procedures: Setting up and running a subject in the KINARM

Upon arrival at the KINARM Research Laboratory at Hotel Dieu Hospital, participants were oriented to the laboratory and to the robot, and the research goals and a description of the experimental tasks that were to be performed by the subject were outlined, in an age-appropriate
manner, and were again explained to the accompanying guardian. Each guardian and participant above 13 years of age provided written informed consent (Appendix A); children aged 13 years or younger provided written informed assent (Appendix B).

At the experimental session, the accompanying parent completed a Participant Information form detailing the child’s education, medical, and treatment history, as well as developmental history regarding physical and mental health (see Appendix C for form; Table 3 and Table 4 for specific information regarding the FASD and control groups, respectively). Eight control participants were identified as having a developmental disorder and, consequently, their data were excluded. A Modified Edinburgh Handedness Inventory (Appendix D, Oldfield, 1971) was also completed to confirm hand dominance.

To start the experimental procedures, participant’s height (cm) and weight (kg) were measured and recorded. The subject then needed to be fit to the KINARM robot so they could be wheeled up to the workspace where they would perform various tasks. To begin, the wheels were locked and the subject was seated, centered and upright, in the chair. The smallest fitting arm troughs were selected and installed. Chair height was adjusted such that the bottom of the subject’s arm (when held horizontally) was approximately in the same place as the bottom of the arm troughs.

Fitting the subject to the KINARM required 1) aligning the shoulder and elbow joint centers of rotation of the KINARM robot with that of the subject, 2) adjusting the length of the mechanical linkages so that they comfortably fit the subject and were set at equal lengths, and 3) adjusting the fit of the upper-arm, forearm, and hand troughs, so that the upper arm trough was approximately halfway between shoulder and elbow joints, supporting the center of mass, and the forearm trough was matched to the wrist joint. Shoulder alignment, elbow alignment, and linkage
Table 3: Specific information regarding the FASD group who participated in the two tasks

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross motor (upper) ability</td>
<td>6% p, 42% f, 52% g</td>
<td>5% p, 30% f, 65% g</td>
<td>9% p, 64% f, 27% g</td>
</tr>
<tr>
<td>Fine motor ability</td>
<td>38% p, 36% f, 26% g</td>
<td>45% p, 50% f, 5% g</td>
<td>27% p, 9% f, 64% g</td>
</tr>
<tr>
<td>Learning disability (Y:N)</td>
<td>87% : 13%</td>
<td>90% : 10%</td>
<td>82% : 18%</td>
</tr>
<tr>
<td>Comorbid ADHD (Y:N)</td>
<td>71% : 29%</td>
<td>85% : 15%</td>
<td>85% : 15%</td>
</tr>
<tr>
<td>Prescribed Medication (Y:N)</td>
<td>77% : 23%</td>
<td>85% : 15%</td>
<td>63% : 37%</td>
</tr>
<tr>
<td>Adopted (Y:N)</td>
<td>97% : (one missing)</td>
<td>95% : (one missing)</td>
<td>100% : 0%</td>
</tr>
</tbody>
</table>

* Motor ability: as rated by parents; p = poor; f = fair; g = good
* Y = yes; N = no
* Adopted includes living with grandparents

Table 4: Specific information regarding the control group who participated in the reaching task

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross motor (upper) ability</td>
<td>3% p, 7% f, 90% g</td>
<td>2% p, 9% f, 89% g</td>
<td>3% p, 5% f, 92% g</td>
</tr>
<tr>
<td>Fine motor ability</td>
<td>6% p, 9% f, 85% g</td>
<td>11% p, 11% f, 78% g</td>
<td>0% p, 5% f, 95% g</td>
</tr>
<tr>
<td>Learning disability (Y:N)</td>
<td>8% : 92%</td>
<td>11% : 89%</td>
<td>5% : 95%</td>
</tr>
<tr>
<td>Comorbid ADHD (Y:N)</td>
<td>2% : 98%</td>
<td>2% : 98%</td>
<td>3% : 97%</td>
</tr>
<tr>
<td>Prescribed Medication (Y:N)</td>
<td>13% : 87%</td>
<td>13% : 87%</td>
<td>14% : 86%</td>
</tr>
<tr>
<td>Adopted (Y:N)</td>
<td>2% : 98%</td>
<td>0% : 100%</td>
<td>5% : 95%</td>
</tr>
</tbody>
</table>

* Motor ability: as rated by parents; p = poor; f = fair; g = good
* Y = yes; N = no
* Adopted includes living with grandparents
lengths were then confirmed. The contra-lateral arm was then set up by repeating the previous steps.

A sticker was placed beneath the index finger, within the hand trough, to ensure the participant replaced their hand in the same position if they needed to take their arm out at any point during the testing session. Participants were wheeled up to the workstation, and the height of the chair was readjusted (if necessary) so that the projected workspace was located just below eye level and the participant had a full view of all virtual targets. A vision blocker was put in place so the subject could not see his/her arms or hands.

Once the computers and software programs were running and were connected, subject-specific information, including subject identification, weight, height, trough sizes, date of birth, gender, handedness, etc. was entered. Three calibration steps were performed, the tasks were then loaded, and data were collected.

Participants received refreshments throughout the study (juice/water and fruit, granola bar, cookies) and received a $10 gift card to Chapters/Indigo or a 10$ gift card to Cineplex Odeon for their time and contribution to the research.

3.4 Experimental Task I: Unloaded, center-out, visually-guided reaching task

Reaching movements were monitored using the KINARM. A virtual reality system displayed visual targets so that they appeared in the same (horizontal) plane as their arms. Calibration programs were used to align the limb’s endpoint with the visual display. All targets had their location defined with respect to a coordinate frame with the origin defined by shoulder and elbow angle (right arm targets relative to right shoulder and left-arm targets relative to left shoulder), and targets for both arms were defined in a right-handed coordinate frame, such that positive is
always to the right. The center target was presented in a location near the center of the arm’s workspace, defined when the subject’s hand (of the active limb) was at the given position: shoulder abducted to a 30º angle and elbow flexed to a 90º angle. Direct vision of the subject’s upper limbs was occluded with a vision blocker, akin to a bib, around the subject’s neck. Real-time visual feedback about hand position was provided as a small white dot (0.4 cm radius) representing the tip of the index finger. Raw data were collected at a sampling frequency of 1000Hz.

Subjects performed planar arm reaching movements. The goal of the task was to make reaches as ‘quickly and accurately’ as possible from a centrally-located target position (1.0 cm radius) to one of eight peripheral targets (1.0 cm radius) distributed uniformly about the circumference of a circle at 45º intervals (with a path length of 6 cm from the central target to each peripheral target; see Figure 2). The reach distance of 6 cm was selected based on previous work which showed that children (aged 5 to 7 years) were unable to reach to peripheral targets toward the body when 10 cm was used (the reach distance commonly used in adult populations; Jung et al., 2008).

Subjects began each reach trial by holding their index finger tip within the central target for 1250-1750 ms, at which point a red target light was illuminated at one of the eight peripheral target locations. Subjects were then given 3000 ms to complete the reach, or else the trial was aborted. Once the peripheral target light was extinguished, the subject was instructed to return to the central target. The central target remained illuminated during the reach trials to assure that the subject moved only when they saw the peripheral target illuminate and did not merely search in anticipation of the presentation of a new peripheral target when the central target extinguished.
Figure 2: Layout of the reaching task targets. A centrally-located target and eight peripheral targets, with a 6 cm reach trajectory to each one, are depicted (task is performed with both arms).

The eight peripheral targets were randomly presented, once each, in a random block design which included eight blocks, for a total of 64 trials. An additional ‘no-target’ trial was incorporated into each of the eight blocks to decrease the incidence of any one subject trying to guess, on a regular pace, where the next peripheral light target would appear. After completion of all trials using one arm, which was selected randomly, the same protocol was repeated using the opposite arm.

3.5 Experimental Task II: Arm position-matching task without visual feedback
Subjects were instructed to relax one arm (referred to as the robot-controlled hand) and let the robot move it to one of nine different spatial locations (or targets; Figure 3). The central target was positioned such that the shoulder was in 30° of horizontal abduction and the elbow in 90° of flexion, as in the visually-guided reaching task. The robot moved the subject’s arm to a spatial location, and when the robot stopped moving, subjects were asked to move their opposite arm
Figure 3: Layout of the nine target positions of the robot-controlled hand that each subject has to match with their opposite hand (task is performed with both arms).

(referred to as the subject-controlled hand) to the mirror location in space. Subjects then notified the experimenter when they completed each trial, at which point the next trial was triggered.

The nine target locations were randomized within a block and each subject completed six blocks, for a total of 54 trials. After completion of all trials using one arm (which was selected randomly), the same protocol was repeated with the opposite arm.

3.6 Data Analysis

From the recorded kinematics of a subject’s movement, 14 outcome measures for the reaching task and 11 outcome measures for the position-matching task were computed (see Appendix E).

Spearman’s bivariate correlations were performed among all reaching and matching task outcome measures to examine the relationship between every pair of variables. As per one of the assumptions of a multivariate analysis of variance, if dependent variables are independent of each other, then we have to sacrifice the degrees of freedom, as well as the power of analysis. Therefore, it is important that the intercorrelations, for the scores, range from moderate to high,
confirming that the variables are partially redundant (and all measure different aspects of some cohesive theme).

Linearity of the data was tested using regression analyses. Every reaching task outcome measure examined for both the control and FASD groups showed a significant linear relationship with age, $p < .05$; therefore, the General Linear Model was used. A univariate analysis of covariance (ANCOVA) or a multivariate analysis of covariance (MANCOVA) was performed (depending on the number of outcome measures within each category of performance examined), with group as the fixed variable, age as the co-variate, and each attribute or category’s outcome measures as the dependent variable(s). The multivariate test results revealed whether or not performance was significantly dependent on age or group. Univariate tests showed which specific outcome measures significantly covaried with age or were significantly dependent on group.

All of the position matching outcome measures for the control group showed a significant linear relationship with age, $p < .05$; however, none of the outcome measures for the FASD group were significant after regression analyses. Therefore, group difference for each position-matching outcome measure was investigated using a simple (one-way) analysis of variance (ANOVA).

For the analyses, the dominant and non-dominant hand performances were collapsed for each outcome measure, since there were no significant inter-limb differences in either the control or FASD group for any of the matching outcome measures, or for the majority of reaching outcome measures. Statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS Inc. Version 17.0, Chicago, IL).
Chapter 4

Results

4.1 Reaching

A total of 114 subjects were tested and entered for statistical analyses. Bivariate correlations demonstrated that almost all outcome measures were significantly related to one another, indicating that there is some relationship among the outcome measures within the performance of an individual (see Appendix F). The outcome measures for the reaching task were grouped into five attributes of sensory-motor control: Posture speed, Reaction time, Feedforward control, Feedback control, and Total movement metrics.

4.1.1 Global features

Illustrative hand trajectories from the reaching data for a typically-developing child and a child with FASD are shown in Figure 4. Overall, one can see from the plots that control subjects were able to generate relatively straighter, ‘smoother’ hand paths to all targets, compared to those with FASD. Control subjects were able to more accurately reach and stabilize within each round peripheral target, while subjects with FASD were less stable at the central target before movement onset and/or at movement offset, and produced longer path lengths to each target.

4.1.2 Significant effect of group

ANCOVAs and MANCOVAs were conducted with group as the independent (fixed) variable, each (or set of) outcome measure(s) as the dependent variable(s), and an alpha set at .05, to test the hypothesis that the FASD group would significantly differ from the control group in reaching performance. A significant main effect of group was found (see Table 5), such that approximately
Figure 4: Hand path trajectories (6 cm) from a centrally-located target to each of eight peripheral targets, as performed with the (right) dominant hand by A) a typically-developing 14-year-old child and B) a 15-year-old child diagnosed with an FASD.

Table 5: Summary of reaching task group differences between typically-developing and FASD

<table>
<thead>
<tr>
<th>Attributes of sensory-motor control</th>
<th>Parameters measured</th>
<th>Significance, $p \leq .01$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Postural Control</strong></td>
<td>Posture speed</td>
<td>YES</td>
</tr>
<tr>
<td>-measures stability before MT</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reaction Time</strong></td>
<td>Reaction time</td>
<td>YES</td>
</tr>
<tr>
<td><strong>Feedforward Control</strong></td>
<td>First MT max speed</td>
<td>No</td>
</tr>
<tr>
<td>-characterizes the initial phase</td>
<td>First MT distance</td>
<td>YES</td>
</tr>
<tr>
<td>of each MT</td>
<td>First MT distance</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>First MT distance</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>First MT direction</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>error</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ratio of first sub-MT to total MT distance</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>Ratio of first sub-MT speed to total MT speed</td>
<td>YES</td>
</tr>
<tr>
<td><strong>Feedback Control</strong></td>
<td># of hand speed maxima</td>
<td>YES</td>
</tr>
<tr>
<td>-characterizes the corrective</td>
<td>Diff in hand speed</td>
<td>YES</td>
</tr>
<tr>
<td>response during MT</td>
<td>bw adjacent min/max</td>
<td></td>
</tr>
<tr>
<td><strong>Total MT metrics</strong></td>
<td>Total MT time</td>
<td>No</td>
</tr>
<tr>
<td>-describes global aspects of the MT</td>
<td>MT max speed</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Path length</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>Ratio of actual to optimal path length</td>
<td>YES</td>
</tr>
</tbody>
</table>
80% of the outcome measures examined for the reaching task (11/14) were significantly different between the control and FASD groups (see Appendix G for results from the univariate tests). Furthermore, almost half of the outcome measures (6/14) demonstrated a large effect size (Cohen’s $d > 0.8$; see Figure 5), with a value of 0.8 indicating a non-overlap of 47.4% in the two distributions of scores.

### 4.1.3 Group differences in feedforward and feedback control

Particularly, the greatest significant main effects of group were for two outcome measures: one related to feedforward control (which quantifies the early response of the limb, representing the internal planning of the movement) and one related to feedback control (correcting for errors during trajectory). These two outcome measures exhibited the greatest observed power and the largest effect size. For the sake of clarity, detailed analyses are shown for these two outcome measures only. There was a significant main effect of group for first movement direction error; $F(1, 109) = 70.7, p < .01$; Cohen’s $d = 1.10$ (see Figure 6A). The means indicated that subjects with FASD exhibited significantly larger direction error during the initial movement to the peripheral target (mean = 5.67º) than did the control group (mean = 3.78º). Secondly, there was a significant main effect of group for minimum-maximum hand speed difference during the reach; $F(1, 109) = 41.6, p < .01$; Cohen’s $d = 1.11$ (see Figure 6B). The means indicated that subjects with FASD exhibited significantly greater differences between each minimum and adjacent maximum hand speed during reach to each peripheral target (mean = 1.2 cm/s) than did the control group (mean = .7 cm/s).
Figure 5: Effect size. Cohen’s $d$ values are plotted for each reaching task outcome measure from large effect size (>0.8), through medium effect size (>0.5), to small effect size (>0.2). White bars denote effect sizes less than 0.2.

Figure 6: Group differences. A) Direction error (in degrees) during the initial movement to the peripheral target; B) Hand speed differences (in cm/s) between each minimum and adjacent maximum speed throughout the duration of the movement towards a peripheral target. Dots represent individuals’ dominant and non-dominant hand performances, collapsed, for both the FASD and control groups. Mean and 95% confidence interval (CI) are depicted.
4.1.4 Significant effect of age

To test the hypothesis that the performance of the FASD and control groups on the reaching task would significantly differ depending on age, all ANCOVAs and MANCOVAs were conducted with age as a covariate. The analyses revealed age as a significant covariate for every dependent variable, $p < .01$, with the exception of posture speed, $p > .05$.

The FASD and control data were plotted together, both dominant and non-dominant hand performances, as a function of age (see Figure 7). Using a model, the 95% confidence intervals (CI), for each hand, for the control data, were calculated and additionally plotted. Upon observation of Figure 7, one can discern the individual subjects with FASD who fall out of the ‘normal range’ (i.e. the 95% CI of the control data). Indeed, almost three quarters (71%) of the FASD group exhibited performance outside of the normal range in at least two of the five attributes of sensory-motor control, with more than half of the FASD group showing impairments in each feedback (58%) and feedforward (55%) control.

4.1.5 Descriptives regarding FASD subjects who fall outside the ‘normal range’

Of those subjects with FASD exhibiting performance outside the normal range (i.e. outside the 95% CI of the control data), 68% were impaired in three or more attributes; almost half (46%) were impaired in four or all five attributes; and almost a quarter (23%) were impaired in every attribute. Almost half of the group of FASD subjects (exhibiting performance outside the normal range) showed impairment, specifically, in first movement direction error, related to feedforward control (48%), and min/max hand speed difference, related to feedback control (45%). About a quarter of the group (27%) was impaired on every feedforward outcome measure; 41% were impaired on every feedback outcome measure; and 64% were impaired on outcome measures in both feedback and feedforward attributes. Most of those subjects with FASD exhibiting
Figure 7: A) Direction error (in degrees) during the first movement towards a peripheral target; and B) Minimum-maximum hand speed differences throughout a movement towards a peripheral target (in cm/s) are plotted for each individual in both the control and FASD groups, for both the dominant (dom) and non-dominant (Ndom) hands, as a function of age. The lines denote the upper bound for the 95% CI for the control data for the dominant and non-dominant hands. Data points that appear above the line are out of the ‘normal range’.
performance outside the normal range are between the ages of 5 and 13 years; subjects tested between the ages of 5 and 9 years exhibited performance outside the normal range for two or more of the 14 outcome measures examined, and those with FASD showing impairment in either four or all five attributes are all 13 years or younger, suggesting some degree of developmental delay.

4.1.6 Group effects independent of age
Age was eliminated as a factor for each outcome measure to look at the effect of group alone. This was done by calculating each individual subject’s residual from the value suggested by the regression model of the control data, at each age point. Looking at the detrended data (see Figure 8), we can see that the majority of subjects with FASD fall above the mean of the control data for both first movement direction error (Figure 8A) and minimum-maximum hand speed differences throughout movement (Figure 8B).

A multivariate analysis of variance (MANOVA), using group as the fixed variable and the (residual values of the) outcome measures as dependent variables, with an alpha set at .05, revealed significant main effects of group for all outcome measures (see Table 6 for summary of group differences using residual values). There was also observed a large effect size for 8/9 outcome measures. There was a significant main effect of group for first movement direction error; $F(1, 112) = 56.1, p < .01$ (see Figure 9A). The residual values indicated that subjects with FASD exhibited significantly larger direction error during the initial movement to the peripheral target (mean of the residuals $= 2.13^\circ$) than did the control group (mean of the residuals $= -.42^\circ$), irrespective of age. There was a significant main effect of group for minimum-maximum hand
Figure 8: Detrended data. Residuals from the regression line of the control data (line at zero) for each individual in the FASD group is plotted, across the age range. Residual = subject’s performance subtracted from the y-value of the regression line of the control data, at that subject’s age, for A) first movement direction error; and B) Minimum-maximum hand speed difference during movement to a peripheral target.
Table 6: Group differences for the residual values for each outcome measure. Mean ± SD is displayed for each group.

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Control</th>
<th>FASD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posture SP</td>
<td>.723 ± .017</td>
<td>.152 ± .028</td>
<td>.000</td>
</tr>
<tr>
<td>Reaction time</td>
<td>-.026 ± .007</td>
<td>.023 ± .012</td>
<td>.001</td>
</tr>
<tr>
<td>FMTDistErr</td>
<td>.220 ± .050</td>
<td>.443 ± .081</td>
<td>.021</td>
</tr>
<tr>
<td>FMTDirErr</td>
<td>-.415 ± .177</td>
<td>2.13 ± .290</td>
<td>.000</td>
</tr>
<tr>
<td>FMTDistRatio</td>
<td>-.019 ± .008</td>
<td>-.060 ± .014</td>
<td>.000</td>
</tr>
<tr>
<td>FMTMaxSPRatio</td>
<td>-.419 ± .012</td>
<td>-.010 ± .019</td>
<td>.000</td>
</tr>
<tr>
<td>MinMaxSPDiff</td>
<td>-.068 ± .056</td>
<td>.601 ± .092</td>
<td>.000</td>
</tr>
<tr>
<td>NumMTMaxSP</td>
<td>-.076 ± .042</td>
<td>.236 ± .069</td>
<td>.000</td>
</tr>
<tr>
<td>PathLenRatio</td>
<td>-.023 ± .011</td>
<td>.132 ± .019</td>
<td>.000</td>
</tr>
</tbody>
</table>

Figure 9: Residual values (from the regression line of the control data) are plotted for the FASD and control groups, for A) First movement direction error; and B) Difference between minimum and maximum hand speeds, throughout movement. Dots represent individual subject’s residual values from the model. Dominant and non-dominant hand performances are collapsed; mean and 95% CI are depicted.
speed difference; $F(1, 112) = 38.6, p < .01$ (see Figure 9B). The residual values indicated that subjects with FASD exhibited significantly greater differences between minimum and maximum hand speeds (mean of the residuals = .60 cm/s) than did the control group (mean of the residuals = -.068 cm/s), independent of age.

4.2 Position-Matching
A total of 80 subjects were tested and entered for statistical analyses. The outcome measures for the arm position-matching task were grouped into three different categories of matching performance: contraction/expansion of spatial area, systematic shifts between the robot- and subject-controlled hands, and trial-to-trial variability.

4.2.1 Global Features
Exemplary sensory matching performances for a typically-developing child and a child with FASD are shown in Figure 10. Generally, subjects with FASD had less sensory awareness about where their limbs were in space, illustrated by the observed shift between the robot- and subject-controlled hands’ end positions, the contraction of the subjects’ spatial area in the horizontal axis, and their increased trial-to-trial variability in end-point matching accuracy (evidenced by greater variability ellipses).
Figure 10: Sensory matching summary, with (right) dominant hand for A) a 14 year-old typically-developing subject and B) a 15 year-old subject with FASD. Mean final hand positions for each target location of the robot-controlled arm (filled shapes) and the subject-controlled arm (no fill) are plotted. PCA (principle component analysis) ellipses are computed (in m²) from the Cartesian coordinates of the (nine) end positions of the subject-controlled arm, to capture trial-to-trial variability in the plane, as well as any rotation about each target.
4.2.2 Significant effect of group

A series of ANOVAs were conducted to test the hypothesis that the FASD and control groups would significantly differ from one another on measures of arm position-matching performance. Using group as the fixed factor and an alpha set at .05, the ANOVAs revealed significant differences for several matching task outcome measures (see Appendix H for ANOVA tables). Table 7 summarizes observed group differences for all outcome measures.

4.2.3 Group differences related to trial-to-trial variability

The most pronounced main effects of group were related to trial-to-trial variability in the end positions (of the subject-controlled hand) for each of the nine targets, captured by two outcome measures related to Principle Component Analysis (PCA) ellipses, exhibiting large effect sizes (Cohen’s $d > 1.0$; see Figure 11). There was a significant main effect of group for mean area covered by the PCA variability ellipse, over all targets; $F(1, 75) = 29.6, p < .01$; Cohen’s $d = 1.14$ (see Figure 12A). The mean values indicated that subjects with FASD covered a significantly larger area over the variability ellipse (mean = .26 m$^2$) than did the control group (mean = .15 m$^2$), indicating decreased consistency and increased variability in end point accuracy for each target. Likewise, there was a significant main effect of group for the standard deviation of the mean area covered by the variability ellipse; $F (1, 75)= 34.1, p < .01$; Cohen’s $d = 1.02$ (see Figure 12B). The mean values indicated that subjects with FASD exhibited a significantly greater standard deviation of mean PCA area covered (mean = .17 m$^2$) than did the control group (mean = .086 m$^2$), over all targets.
Table 7: Group differences between typically-developing children and those with FASD

<table>
<thead>
<tr>
<th>Categories of matching performance</th>
<th>Parameters measured</th>
<th>Significance, $p \leq .01$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contraction/Expansion of overall spatial area matched by subject</td>
<td>Subject area</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Area % change</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>X range</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>Y range</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>X range % change</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Y range % change</td>
<td>No</td>
</tr>
<tr>
<td>Systematic Shifts between robot- and subject-controlled hands</td>
<td>Mean X error</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Mean Y error</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Mean XY error</td>
<td>YES</td>
</tr>
<tr>
<td>Trial-to-trial Variability in end positions for each targets</td>
<td>PCA mean area</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>PCA SD area</td>
<td>YES</td>
</tr>
</tbody>
</table>

Figure 11: Effect size. Cohen’s $d$ values are plotted for each matching task outcome measure from large effect size ($>0.8$), through medium effect size ($>0.5$), to small effect size ($>0.2$). White bar denotes an effect size less than 0.2.
Figure 12: Group differences in inter-trial variability during the position-matching task. A) Mean PCA area, in m², and B) standard deviation of the mean of the PCA area, of the variability ellipses, in m², over all targets. Dots represent individual’s dominant and non-dominant hand performances, collapsed, for both the FASD and control groups. Mean and 95% CI are depicted for each group.
4.2.4 Lack of age effects

The regression analyses performed to test for linearity of the data showed that the performance of the FASD children, on the position-matching task, does not systematically change with age as it does in the typically-developing population of children, for the same task. That is, in contrast to the visually-guided reaching task, performance in the position-matching task by children in the FASD group did not co-vary with age.
Chapter 5

Discussion

5.1 General Findings
The current study sought to investigate the potential of the KINARM to identify and measure specific, neurologically-based sensory-motor deficits in individuals with FASD. Indeed, the device was sensitive in measuring various deficits in sensory-motor control, through a range of parameters, investigated by the performance of two motor tasks: a visually-guided reaching task, and an arm position-matching task without any visual feedback.

Our results revealed significant differences between the performance of typically developing children and those with FASD on both the reaching and arm position-matching tasks. Compared to controls, who demonstrated smoother hand paths to peripheral targets, with minimal error and inter-trial variability, those with FASD had considerable problems in many attributes of sensory-motor control. Those with FASD exhibited deficits in (1) postural control, as evidenced by greater posture speed; (2) feedforward control, as demonstrated by greater direction and distance error during the initial trajectory towards a target; (3) feedback control, manifested through hand trajectories marked by phases of deceleration and acceleration (greater min-max speed differences) and greater number of speed peaks attained (as children with FASD corrected for higher magnitudes of errors in initial phase of movement); and (4) total movement metrics, attested by greater and more variable path lengths taken to each target, compared to the optimal one.

The current results regarding motor skill deficits in children with FASD are quite consistent with previous literature. Studies investigating fine motor performance in children
prenatally exposed to alcohol report increased errors and latency on fine motor tasks (Barr et al., 1990) and deficits in motor speed and precision (Mattson et al., 1998). Group mean motor deficits in eye and hand coordination tasks (Adnams et al., 2001) and complex bimanual coordination tasks (Roebuck-Spencer et al., 2004) have also been documented. In one study by Connor et al. (2006), three quarters of the subjects with FASD demonstrated deficits in motor function outside the range of comparison subjects on motor tests including unilateral and bilateral finger, hand, and foot coordination. Indeed, in the current study, almost three-quarters of the subjects (71%) exhibited motor performance outside the range of control subjects on the reaching task.

Fine motor delays in children with FASD may be related to specific brain deficits that affect fine motor skills. For example, deficits in two neural processes related to feedback and feedforward control might account for the observed deficits in reaching performance. Trajectory specification control is based largely on feedforward mechanisms (programming the ‘ballistic’ component of movements), whereas final position control is largely dependent on feedback mediated events (sensory-corrections; Winstein & Pohl, 1995). Of the subset of FASD subjects exhibiting performance outside the normal range in the current study, 64% were impaired on both feedback and feedforward measures, demonstrating a potential relationship between the disabilities in these two areas of sensory-motor control in successfully completing a reaching movement to a peripheral target.

From the performance of the arm position-matching task, results revealed that children with FASD significantly decreased their matching area (area covered by the end positions of nine targets in a 3 x 3 configuration; see Figure 3), and constricted their range in the horizontal axis, compared to typically-developing children. Children in the FASD group also demonstrated significantly increased error (in the XY coordinate frame) in the end positions of the matching
target locations, in addition to exhibiting greater trial-to-trial variability in final hand positions for each of the nine targets.

Potential mechanisms underlying differences in observed performance on the two sensory-motor tasks, between those with FASD and typically-developing children, will now be discussed in relation to what is already known about the brain structures (and functions) that are susceptible to damage by PAE.

5.2 Proposed mechanisms underlying observed motor deficits

There exists a link between developmental disorders and sensory-motor deficits (Piek & Dyck, 2004). Impairment of motor abilities can be modulated by a variety of performance components. For example, visual/spatial perception, visual-motor integration, bilateral motor integration, motor planning, and proprioception are important components that contribute to complex fine motor skills (Feder & Majnemer, 2007), and deficits in any of the aforementioned areas may be related to the observed motor deficits in the current study. Poor sensory-motor integration has long been implicated as a cause of motor problems in developmental disorders, such as Developmental Coordination Disorder (DCD), and recently ADHD and autism (Piek & Dyck, 2004). One likely mechanism underlying poorer performance, in those with FASD, on the two motor tasks investigated in the current study, and which will be discussed further, is that of inadequate sensory processing.

Effective brain function requires integration of information from segregated regions (Bashat et al., 2005). In Dunn’s (1997) “Model of Sensory Processing,” the nervous system is viewed as modulating neural responses to sensory stimuli by regulating neurological thresholds, or the amount of stimuli required for a neuron (or system of neurons) to fire, in turn, regulating
behavioral responses to sensory stimuli. “Sensory modulation” allows an individual to ignore unimportant stimuli and respond to important stimuli.

Research on difficulties within the neurocognitive domain of sensory processing, or the nervous system’s capacity to receive, organize, and understand sensory input, in children prenatally exposed to alcohol, is limited. We do know that children with FASD appear to have deficits in the encoding (Coles, Platzman, Lynch, & Freides, 2002) and processing (Burden et al., 2005) of information. In addition, sensory processing deficits in children with FASD have been shown to be two to six times greater than in typically developing children, between the ages of 2 and 19, as revealed by hyperactivity to stimuli, distractibility, and inattention (Carr, Agnihotri, & Keightley, 2010). Furthermore, studies have previously reported inefficiency in processing visual information, apparently resulting from decreased sensitivity to respond to target stimuli in the visual modality, compared to the auditory modality (Coles et al., 2002).

We also know that PAE disrupts neuronal plasticity, which is essential during development, as circuits are refined by selective pruning (Medina & Krahe, 2008). The loss of nonessential connections during pruning results in neural systems that are able to support complex computations, and enhances the capacity and speed of information processing (Luna, Velanova, & Geier, 2008). The ability to efficiently integrate information throughout the brain to support the complex computations needed for executive control of responses may be affected in those prenatally exposed to alcohol. It very well may be that prenatal exposure to alcohol alters those individuals’ processing speed and efficiency and may be an underlying factor for some of the observed deficits. Indeed, PAE has been linked to deficits in processing speed in both infancy and childhood, as evidenced by slower processing speed on several Sternberg tasks and deficits in
processing efficiency in the ‘number comparison task’ (Burden et al., 2005). The current results point to several indicators of sensory processing difficulties.

Inefficiency in sensory processing is the most likely explanation for the deficits observed in the sensory-motor tasks. Both tasks used in the current study rely on sensory information: visual and proprioceptive sensory information in the case of the reaching task and peripheral (or proprioceptive) sensory information in the case of the position matching task. Difficulties in spatial processing and integration of sensory information of multiple domains (visual and peripheral) likely underlie the motor problems, observed in the current study, in those prenatally affected by alcohol.

5.3 Brain regions likely implicated in observed performance deficits
Past studies have implicated several brain regions as possible neural underpinnings of motor deficits in subjects with FASD, including the CC, which has been shown to be affected by exposure to alcohol in utero (Sowell, Johnson, et al., 2008). Disruption of fibers in the CC in those with FASD is associated with poorer visuomotor integration (Sowell, Mattson, et al., 2008) and may explain some of the observed deficits in the reaching task. Support for the CC’s role in poorer performance in the motor tasks investigated in the current study comes from a study which found that subjects with agenesis of the CC, on an arm movement task (drawing lines through specified pathways, at different angles, using a computer cursor), performed slower and less accurately, across all angles, than typically-developing subjects, with the greatest deficits in accuracy produced by mirror-image, bimanual responding (Mueller, Marion, Paul, & Brown, 2009). Furthermore, DTI studies looking at the CC of those prenatally affected by alcohol reveal 1) lower fractional anisotropy, indicating less coherent microstructure or white matter formation.
(Spadoni et al., 2007); 2) lower white matter density, indicating less myelin or disorganized fiber tracts (Sowell, Mattson, et al., 2008); and 3) greater mean diffusivity, suggesting microstructural abnormalities (Wozniak et al., 2006), all of which have been linked to poorer performance and impairment in motor functioning and which may explain, in part, the observed deficits in reaching and in sensory matching in the current study.

In addition, altered motor function is consistent with damage to the cerebellum (Guerri et al., 2009; Bookstein et al., 2006), one of the central nervous system motor areas, which has been shown to be vulnerable to alcohol’s teratogenic effects. Firstly, the cerebellum has shown to be important for the representation of temporal information, not only for motor, but also for perceptual tasks (Paquier & Marien, 2005). Secondly, the cerebellum contributes to sensory processing with regards to movement regulation; the massive sensory input to the cerebellum is devoted to optimizing the fine regulation of voluntary movement (Restuccia, Marca, Valeriani, Leggio, & Molinari, 2007). Furthermore, the cerebellum influences processing of spatial information; cerebellar damage impairs spatial functions, leading to deficits in such tasks as reaching and grasping (Nitschke, Arp, Stavrou, Erdmann, & Heide, 2005). In fact, in one study (Bastian, Martin, Keating, & Thach, 1996), individuals with cerebellar lesions exhibited abnormal reaches, compared to controls. In particular, sensory-motor function has been localized to the anterior portion of the cerebellum (Stoodley & Schmahmann, 2009), and indeed, the observed damage in cerebellum of those with FASD has been shown to be more pronounced in the anterior lobe (O’Hare et al., 2005) and might explain the impaired performance observed in those prenatally affected by alcohol in the sensory-motor tasks used in the current study.

The observed pattern of problems in the reaching task, in those with FASD, in the current study, include: greater upper-limb instability, combined with errors in direction within the first
movement of the reach to a target, leading to more adjustive and corrective movements (consisting of more phases of acceleration and deceleration), which are often inefficient in themselves, as evidenced by longer path lengths. Although we cannot definitively differentiate the contributions of impairments in the feedback and feedforward phases from the different brain regions which might be involved, these characteristics of the individuals’ reaching movements are consistent with cerebellar damage or damage to the corpus callosum.

The cerebellum seems to be deficient in processing sensory information and in monitoring the integrity or the efficiency of the motor movement itself. It is important to note that the problems exhibited by those with FASD in the current study are not only visual; proprioceptive information is also not being used efficiently, as evidenced by the lack of sensory awareness exhibited in the arm position-matching task (or impaired sensory information), shown by lack of accuracy in matching. This proprioceptive deficit is also consistent with the idea of cerebellar damage. For the position-matching task, it could be that the cerebellum is not accurately forming an internal representation of the location of the arm, leading to errors in performance. It could also be that there is some degree of dysfunction in the transfer of information between brain hemispheres, implicating the corpus callosum as a factor in arm position-matching deficits.

5.4 Performance as a function of age

It is well known that motor maturation has an influence on kinematic parameters; the progression of kinematic parameters has been shown to be significantly correlated with age for movement domains, such as speed, direction change, and variability, of fine motor movement skills, such as drawing and handwriting (Rueckriegel et al., 2008). This progression of motor movement skills
with age is consistent with the current data showing performance on each movement domain in all five attributes of sensory-motor control, in the reaching task, to be significantly dependent on age. The maturation of neuronal networks corresponds to the maturation of fine motor skills in, for example, the planning phase of different goal trajectories (such as in handwriting or reaching; Rueckriegel et al., 2008).

Furthermore, it has been shown in collaborating labs (unpublished data) that the development of goal-directed reaching continues into late childhood and early adolescence and remains constant thereafter (Choe, et al., 2009; also see Rueckriegel et al., 2008). For example, the hand paths of younger participants, during reaching, were found to be highly variable across trials and were subdivided by phases of deceleration and acceleration as younger children corrected for greater degrees of errors in initial direction of hand trajectory. However, with age, hand paths to peripheral targets became smoother, with minimal inter-trial variability, captured by shorter (and, therefore, more direct) path lengths (Choe et al., 2009). The role of performance monitoring (related to the ability to use performance feedback for subsequent performance adjustment) is correlated with age, such that, given feedback, older subjects make fewer errors. With age, children are increasingly able to monitor their performance online, successfully using feedback cues indicating if and how performance should be adjusted (Crone, Somsen, Zanolie, & Van der Molen, 2006).

We hypothesized that children with FASD would exhibit atypical performance in these sensory-motor tasks, compared to typically-developing children, which is suggested by the current results. Children and adolescents with FASD exhibited performance outside of the normal range on reaching task outcome measures, with subjects, across the entire age range of 5 to 18 years, performing at a level closer to younger, typically-developing children, as opposed to their
age-matched counterparts. However, our data suggests that there exists some degree of developmental delay in the performance of the visually-guided reaching task, such that with age, those with FASD will attain levels of sensory-motor control and, hence, levels of performance, exhibited by typically-developing children. For example, our data showed that every individual in the youngest group of children (aged 5 to 9 years) were impaired on outcome measures in several attributes of sensory-motor control, and sometimes in all five attributes, while the older group of children (aged 10 and older) showed less severe impairment and often did not show performance outside the normal range, on any outcome measure. These findings suggest, with caution, that individuals with FASD reach normal performance, but later in their course of development. Brain injury induced by PAE seems to extend the developmental timeline of motor movement skill in the FASD population.

5.5 Clinical Relevance
Identification of sensory-motor deficits in children prenatally affected by alcohol is important for several reasons. Intrauterine exposure to alcohol can result in behavioral and cognitive impairment that limits successful life adaptation and these disabilities are often compounded by secondary emotional and behavioral disabilities. Individuals with FASD are adversely affected from the beginning of life, and when this disorder fails to be recognized, high costs are incurred to the individual, their family, and society. Despite the prevalence of the condition, this population is under-diagnosed and associated deficits are not fully understood.

Knowledge of the distribution of kinematic parameters in those with FASD, compared to healthy subjects, is crucial for the evaluation of those who suffer from motor impairment due to PAE. In terms of clinical utility, assessment of children’s motor abilities, using the KINARM,
will help to identify specific areas of weakness. The knowledge that motor development is impaired in children prenatally exposed to alcohol, and how it is impaired, may provide valuable information for families and professionals in developing new and appropriate (or ameliorating existing) programs for these children. Identification of impairment in prenatally-affected individuals could improve prognosis as it may serve to increase services and supports, and the likelihood of early placement into (developmental) intervention programs, targeting particular deficit areas, and thereby improving treatment. Research on the development of motor skills and on the identification of a consistent neurobehavioral profile in those with FASD, a topic on which there is limited research, is essential.

We attempted to identify motor deficits in children prenatally exposed to alcohol and to determine which factors are contributing to the observed motor delays. The current findings suggest some degree of motor dysfunction in almost all of the prenatally-alcohol exposed individuals tested, with great implication for the current apparatus’s potential in optimizing current assessment methods, and enabling for a better understanding of deficiencies in motor function of this patient group.

5.6 Limitations and strengths
The largest limitation in the current study is the small sample size. Due to the small sample size of FASD subjects, in particular, we were unable to investigate gender differences. Previous studies have found gender differences regarding hand movement development, apparent as early as childhood (Rueckriegel et al., 2008). For example, females tend to have lower variability (in handwriting skills) than males, while males tend to exhibit faster, but less accurate fine motor movements (Mergl, Tigges, Schroter, Moller, & Hegerl, 1999). Furthermore, due to our small
sample size, and the fact that all subjects were recruited only from Ontario, results cannot be completely generalized to the entire FASD population.

Another limitation to the current study is that it employs a sort of “snapshot approach” to looking at sensory-motor deficits within the FASD population. We were able to measure each individual’s motor abilities at one point in time, at one stage in their life cycle. This approach gives us an idea about group differences between the clinical and control populations and the extent of motor deficits within the FASD population, but it would be necessary to examine individuals’ performances at various points in their development to get an idea about if and in what manner do sensory-motor abilities change or improve across the individuals’ developmental course. Furthermore, although our sample consisted of individuals aged 5 to 18 years (a higher age range limit than most studies in the literature), it did not include adults; therefore, one cannot make conclusions regarding whether motor effects, due to PAE, are evident in adulthood.

It is also important to note that approximately 87% of the study participants with FASD presented with concomitant mental health and psychiatric diagnoses; namely, a large proportion (71% or 22/31) had a diagnosis of ADHD. Therefore, it is not clear whether the observed sensory-motor deficits reported (or the link to deficits in sensory processing) are a specific feature of FASD, other disorders, or a combination of both.

All in all, the current study does make use of a tool with high objectivity and high inter-rater reliability, and provides increased specificity regarding the type of motor problems characteristic of FASD. Furthermore, the current study contributes to an existing overall motor profile, leading a step closer in delineating a motor profile that accurately characterizes this spectrum of disorders.
5.7 Future Directions

Increasing our sample size would allow us to examine sensory-motor deficits across different FASD diagnostic categories. It is hypothesized that a continuum of interaction exists between neurological processing of sensory input and behavioral responses (Franklin et al., 2008), and so perhaps differing degrees of severity across the spectrum of fetal alcohol disorders would result in differing degrees of motor deficits. Exploring the different FASD subgroups might expose some existing vulnerability of some subgroups, to sensory-motor deficits, compared to others.

A larger sample would also allow for more individuals to be represented at each age (5 throughout 18 years); 61% of the FASD group, in the current study, is 11 years of age and younger. Increasing the number of individuals at the older end of the age spectrum would lead to more concrete insight about whether or not children with FASD actually do ‘catch up’ in motor capabilities and would let us answer questions, such as, “Do older children perform closer to their age-matched control counterparts?” The current data point towards a developmental delay in the children with FASD, in the reaching task, but without more individuals representing the older ages, one cannot be as confident.

As mentioned above, in limitations, the findings regarding motor deficits in the current study may not be specific to FASD. Future evaluation of sensory-motor control in children with other developmental disorders, such as DCD, ADHD, autism, and CP will be important for determining whether our findings point to a particular pattern of motor deficit specific to those with FASD (caused by widespread/global brain injury; i.e. various structural abnormalities; decreased overall brain volume; growth reduction of various lobes of the brain; both grey and white asymmetries) or is shared by other clinical populations, perhaps whose brain injury is different (for example, by CP, where the brain injury is caused by more discrete cortical lesions).
Further study of other neuro-developmental disorders, using the KINARM, may help delineate motor profiles for each clinical disorder and answer questions, such as, “Are the movement patterns different or distinct across developmental motor disorders, or do the patterns of performance overlap between some, if any, of the disorders?” “Are there particular patterns consistent with each type of brain injury and how do these patterns of brain injury inform us about each population?”

It is also important to note that the cognitive and behavioral profile of children with FASD can change over time. Therefore, it would also be worth conducting a longitudinal study, examining sensory-motor deficits within any one individual and how they change or stabilize over time, acting as a sort of developmental screening procedure as individuals mature. Using repeated assessments in the KINARM, over the course of several years, would help refine these individuals’ FASD brain-related assessment and would accurately capture their evolving strengths and weaknesses, perhaps allowing for the implementation of appropriate interventions.

Furthermore, the introduction of new tasks, used in concert with the KINARM, targeting different cognitive processes, such as those engaged in EF (response inhibition, spatial working memory, etc.) will further expand the repertoire of knowledge regarding this clinical population and how alcohol exposure in utero is related to adverse neuro-behavioral outcomes.
Chapter 6

Summary and Conclusion

The KINARM, together with the administration of two motor tasks (a reaching task with fingertip feedback only, and an arm position-matching task in the absence of visual feedback), is sensitive in detecting and describing brain injury resulting from prenatal alcohol exposure. Results of the reaching task revealed significant effects of PAE, across the entire age range and spectrum of fetal alcohol disorders, and indicate considerable problems in feedforward and feedback control, as evidenced by increased direction error in hand trajectory and more phases of acceleration/deceleration throughout movement, respectively. In addition, those with FASD exhibited less sensory awareness about the location of their limbs in space, manifested by increased error in matching hand position and greater trial-to-trial variability, compared to typically-developing children, in the position-matching task. Results also suggest some degree of developmental delay in motor skills in those prenatally affected by alcohol. The KINARM has shown to be a promising research tool for identifying and measuring specific, neurologically-based deficits related to sensory-motor integration and body position sense in individuals with FASD.
References


Mahurin, R. (1993). *Neurocog (Version 5.0).*


Appendix A
Consent Form

A STUDY OF MULTI-JOINT MOVEMENT COORDINATION

CONSENT FORM

Principal Investigator: Dr. S.H. Scott
Phone Number (613) 533-2855 (internal: 32855)

DETAILS OF THE STUDY:

The purpose of this study is to examine how humans coordinate multi-joint movements involving the shoulder and elbow joints. You have been asked to participate in this study because: (1) you are part of the general population with no known neurological or musculoskeletal disorders, (2) you have been diagnosed with a Fetal Alcohol Spectrum Disorder (Fetal Alcohol Syndrome, Partial Fetal Alcohol Syndrome, Alcohol Related Neurodevelopmental Disorder, or Alcohol Related Birth Defects (FASD)); or (3) you are an age-matched control subject for the FASD project.

You will be seated comfortably on a chair in front of a table. An adjustable linkage will be attached to your arm(s) using foam covered arm braces. The device allows you to move your limb in the horizontal plane. Motors attached to the linkage allow us to apply small mechanical loads to your arm.

There may be other monitoring procedures involved with your participation, they are outlined below:

Surface EMG:

☐ Will be collected, please read this section.

We would like to monitor the activity of shoulder and elbow muscles during the tasks with non-invasive surface electrodes to the skin overlying each muscle. These electrodes do not obstruct normal movements. The signals from the electrodes will be amplified using electronic equipment rated for use with humans.
Indwelling EMG:

☐ Will be collected, please read this section.

We would like to monitor the activity of shoulder and elbow muscles during the tasks with small indwelling electrodes. These are inserted into the muscle of interest using a needle. There will be some brief discomfort while the electrode is inserted but will subside as the needle is withdrawn. Once inserted you will be able to move without any pain from the electrodes.

Electrooculography:

☐ Will be collected, please read this section.

Eye movements may also be recorded using three surface electrodes. One electrode will be applied to the forehead and one lateral to each eye. Signals will be amplified using electronic equipment rated for use with humans.

Eye-tracking:

☐ Will be collected, please read this section.

Eye movements may also be recorded using a non-invasive infrared eye tracking system (ISCAN, Burlington, MA), which will be used to record the position of the pupil and compute line of gaze. The system uses a small video camera that records infrared light reflected to the eye; an infrared light source is located next to the video camera and directs the light toward the eye. The system allows the full range of vision and does not harm the eye. The infrared light emitted by the equipment is a part of the normal spectrum of light but is invisible to the naked eye.
Transcranial Magnetic Stimulation:

☐ Will be collected, please read this section.

This technique will allow us to deliver magnetic pulses to excite specific areas of the brain that are involved in controlling your arm. We will use a standard technique that has been demonstrated to be safe based on two decades of experimental research. A small paddle will be placed over the head close to the scalp to deliver a brief magnetic pulse. Mechanical loads may be applied to your arm by the robot either before or after the stimulation. Because of the magnetic pulse emitted, there are several exclusion criteria which we will need to verify:

Cochlear implants .................................................. Y or N
Cardiac pacemaker ................................................. Y or N
Metal stent ......................................................... Y or N
History of epilepsy ............................................... Y or N
Aneurysm clip ........................................................ Y or N
Any metal (other than braces and fillings) that may be in your head........ Y or N
Anything else that may exclude you? ......................... Y or N

If you have answered yes to any of the above, you will be excluded from this study.

You will be instructed to perform a number of motor tasks requiring you to maintain your hand at a spatial target or move your hand between spatial targets. These targets will be coloured lights projected onto the horizontal plane at shoulder level using a virtual reality system. In some cases, you will be required to perform these tasks when the mechanical linkage applies small loads to your arm. These small loads are harmless, but you will have to learn to compensate for these loads in order to perform the task. The duration for these experiments will be approximately 1 hour.

You may withdraw from these experiments at any time. If you have any concerns about any aspect of this study, please contact Dr. C. Graham, Head, Department of Anatomy and Cell Biology, Queen’s University (phone number: 613 533-2600, internal: 32600).

Risks:

There are a few minor risks involved in participating in this study. You may experience a temporary mild rash from the adhesive to attach the surface electrodes (EMG or EOG) to record muscle activity. This should last no more than a couple of days.

There may be some discomfort during needle EMG electrode placement but this should subside once the needle is removed. Occasionally bleeding may occur, however it is usually a small amount, which quickly clots on its own. There is a very small chance of infection at the site of electrode placement (similar to risks associated with having blood drawn by a nurse/physician.)
Some fatigue may be experienced following Transcranial Magnetic stimulation. There are no other side effects that have been reported.

**Benefits:**

Although you may not benefit directly from this study, your participation will contribute to our basic knowledge on human motor performance and motor development.

**Confidentiality:**

Only individuals in Dr. Scott’s or Dr. Reynolds’ laboratory will have access to your experimental data. All information obtained during the course of this study is strictly confidential and your anonymity will be protected at all times by using alphanumeric codes when analyzing or presenting your experimental data.

If you have concerns about your rights as a research subject, please contact:

Dr. Albert Clark, Chair of the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board at (613) 533-6081.

Dr. Stephen Scott, Principle Investigator, (613) 533-2855

Dr. James Reynolds, Collaborator, (613) 533-6946

**VOLUNTARY PARTICIPATION:**

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

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

________________________________________
Name, please print

________________________________________
Signature of subject date
INVESTIGATOR:

I, or one of my assistants, have carefully explained to the subject the nature of the above research study. I certify that, to the best of my knowledge, the subject understands the nature of the study.

__________________________________________
Signature of investigator                      date

__________________________________________
Signature of witness                           date
Dear Child:

We invite you to take part in a research project.

**What we are doing**

We are doing this study to see how some children move their arms and how they think and learn. You will be asked to do special tasks while seated with your arms attached to robot arms. You will also play some games on a computer screen. The whole procedure will take about 2 hours.

You will be given breaks whenever needed. We also will ask your parent/guardian to answer some questions on a form.

You do not have to participate and you can stop at any time. Testing will not be started if you do not want to participate. You also do not have to answer a question if you don’t want to.

Do you have any questions about the study?

Do you agree to take part in the study?
If you have any questions about the study, please contact:
Dr. Albert Clark, Chair of the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board at (613) 533-6081.

Dr. Stephen Scott, Principle Investigator, (613) 533-2855

Dr. James Reynolds, Collaborator, (613) 533-6946

Protocol ANAT-013-99, Effective Date: June 25, 2007
Appendix C
Participant Information Form

Participant Information

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

Thank you very much for helping with our study!

A. GENERAL INFORMATION

Participant’s name: __________________________________________

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

Sex (M/F): ______

Age: ______

Telephone: __________________________

Parent/Guardian (if participant is a minor): __________________________

Address: __________________________________________

Email: __________________________________________
B. EDUCATION HISTORY

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

Last school grade completed by your child: ______________________

**Complete this section if participant is a minor:**

- Has your child ever been suspended from school?  No  Yes
- Has your child ever been expelled from school?  No  Yes
- Has your child ever been diagnosed with a learning disability?  No  Yes
  
  If yes:
  
  When? ______________________

  Type?  Verbal  Non-verbal  Don’t know

- Has your child ever received resource help?  No  Yes

- Has your child ever been in a special education program?  No  Yes
  
  If yes:
  
  Number of months/years in the special program: ________________

  Currently in a special program?  No  Yes

  Was the program a special class?  No  Yes

  If yes:
  
  Describe the nature of the class (e.g. learning disabilities, emotional disorders): ____________________________________________
C. MEDICAL HISTORY

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

How would you describe your child’s health? (circle one)

- Very Poor  
- Poor    
- Fair    
- Good    
- Very Good

How would you describe your child’s hearing? (Circle one)

- Poor  
- Fair    
- Good

Has your child’s vision ever been tested?  
- No  
- Yes

If yes, what were the results? ____________________________

Is she/he colour blind?  
- No  
- Yes  
- don’t know

How would you describe your child’s speech articulation? (Circle one)

- Poor  
- Fair    
- Good

Your child’s co-ordination:

- Describe gross motor coordination (running, jumping, etc.)
  - Poor  
  - Fair    
  - Good

- Describe fine motor coordination (writing, buttoning, etc.)
  - Poor  
  - Fair    
  - Good

Has your child had any accidents resulting in the following?  
(Check all those that apply)

- Broken bones ___  
- Eye injury ___  
- Severe lacerations ___  
- Head injury ___  
- Lost teeth ___  
- Stomach pump ___  
- Severe bruises ___  
- Sutures ___  
- Other (specify) _______

How many accidents has your child experienced?  
- 1  
- 2-3  
- 4-7  
- 8-12  
- 12+

Does your child have any problems sleeping?  
- No  
- Yes

Does your child have any chronic health problems (e.g., asthma)?  
- No  
- Yes

If yes, please specify ________________________________

Have your child ever had a seizure?  
- No  
- Yes

If yes, has there been a diagnosis of seizure disorder or epilepsy?  
- No  
- Yes
(C. MEDICAL HISTORY continued)

Fetal Alcohol Spectrum Disorders (FASD)

Does your child have an existing identification of FASD? No Yes

If yes, What is the diagnosis? (please circle)

<table>
<thead>
<tr>
<th>FAS</th>
<th>ARND</th>
<th>pFAS</th>
<th>FAE</th>
<th>ARBD</th>
</tr>
</thead>
</table>

When was the diagnosis? ____________

By whom? (Check one)

___ Family Doctor ___ School Psychologist

___ Other Psychologist ___ Other

Has the diagnosis changed since the first diagnosis No Yes

If yes, what was the change and why? ________________________________

How old was your child when symptoms of FASD were noticed? __________

Has your child ever been diagnosed with any of the following? Check those that apply. If yes, indicate when the first diagnosis occurred, and whether criteria for the diagnosis are currently met.

Attention Deficit Hyperactivity Disorder (ADHD)?

Age diagnosed   Current? (No/Yes)

Tourette’s Disorder?

Age diagnosed   Current? (No/Yes)

Anxiety Disorder?

Age diagnosed   Current? (No/Yes)

Depression?

Age diagnosed   Current? (No/Yes)

Bipolar Mood Disorder?

Age diagnosed   Current? (No/Yes)

Oppositional Defiant Disorder?

Age diagnosed   Current? (No/Yes)

Conduct Disorder?

Age diagnosed   Current? (No/Yes)

Autism?

Age diagnosed   Current? (No/Yes)

Asperger’s Disorder?

Age diagnosed   Current? (No/Yes)

Psychosis?

Age diagnosed   Current? (No/Yes)
D. TREATMENT HISTORY

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

Is your child currently taking any medication?  No  Yes

If yes, Drug? ___________________ Dose/Day _____ Date started ________

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

Not effective  Somewhat effective  Effective  Very effective

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

<table>
<thead>
<tr>
<th></th>
<th>Age started</th>
<th>Age stopped</th>
<th>Reason?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritalin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexedrine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cylert</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tranquilizers</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Anticonvulsants

Antihistamines

Antidepressants

Other (specify)

E. FAMILY HISTORY

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

Is your child adopted? No Yes

Who does your child live with? (Please list each family member and his or her age)

<table>
<thead>
<tr>
<th>Relationship to child</th>
<th>Their age</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td></td>
</tr>
</tbody>
</table>

Please indicate type of employment (adults only): __________________________

Please indicate mother’s
i) type of employment: __________________________
   ii) highest grade completed, or degree: __________________________

Please indicate father’s
i) type of employment: __________________________
   ii) highest grade completed, or degree: __________________________
(E. FAMILY HISTORY continued)

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

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Family member (relation to participant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FASD:</td>
<td></td>
</tr>
<tr>
<td>ADHD or ADD:</td>
<td></td>
</tr>
<tr>
<td>Learning Disability:</td>
<td></td>
</tr>
<tr>
<td>Failed to graduate from high school:</td>
<td></td>
</tr>
<tr>
<td>Mentally challenged:</td>
<td></td>
</tr>
<tr>
<td>Psychosis or schizophrenia:</td>
<td></td>
</tr>
<tr>
<td>Depression for more than 2 weeks:</td>
<td></td>
</tr>
<tr>
<td>Bipolar mood disorder:</td>
<td></td>
</tr>
<tr>
<td>Anxiety disorder:</td>
<td></td>
</tr>
<tr>
<td>Tourette’s disorder:</td>
<td></td>
</tr>
<tr>
<td>Alcohol or substance abuse:</td>
<td></td>
</tr>
<tr>
<td>Problems with aggressiveness, defiance,</td>
<td></td>
</tr>
</tbody>
</table>
  Oppositional behaviour as a child: |                                    |
| Problems with attention, activity, and  |
  Impulse control as a child:      |                                    |
| Other (specify):                 |                                        |
Appendix D

Modified Edinburgh Handedness Inventory

Participant’s name: ________________________________________________

Parent’s name: ________________________________________________

Date of Birth: ____________________ Sex: ____________________

Signature: ____________________ Date: ____________________

Please indicate your preferences in the use of hands in the following activities by putting + in the appropriate column. Where the preference is so strong that you would never try to use the other hand unless absolutely forced to put ++. If you are indifferent put + in both columns.

Some of the activities require both hands. In these cases the part of the task or object for which hand preference is wanted is indicated in brackets.

Please try to answer all the questions and only leave a blank if you have no experience at all of the object or task.

<table>
<thead>
<tr>
<th>TASK</th>
<th>LEFT</th>
<th>RIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Writing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Drawing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Throwing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Scissors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Toothbrush</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Knife (without fork)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 Spoon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 Baseball bat or hockey stick (bottom hand)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 Turning a key</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 Opening a box (lid)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>i Which foot do you prefer to kick with?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ii Which eye do you use when using only one?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix E

Outcome Measures for the Reaching and Arm Position Matching Tasks

*Also refer to Coderre et al., 2010.

**Task 1) Visually-guided Reaching Task - Movement Outcome Measures:**

To characterize subject performance, a number of movement parameters were calculated from each individual trial. These parameters were broadly categorized into five attributes of sensory-motor control: A) postural control; B) reaction time; C) feedforward control; D) feedback control; and E) total movement metrics.

**A) Postural Control (PS):** this attribute has one measure; it characterizes a subject’s ability to keep their hand steady within the central target.

1) **postural hand speed (cm/s)** – mean hand speed for 500 ms before peripheral target illumination.

**B) Reaction Time (RT):** this attribute has one measure; it characterizes the ability of a subject to respond to a visual stimulus.

2) **reaction time (s)** – time between illumination of the peripheral target and onset of movement.

**C) Feedforward control:** this attribute has six parameters and characterizes a subject’s initial phase of movement. The time period is from movement onset to the first minimum hand speed (the first local minimum in hand speed after the first maximum hand speed).

3) **first movement distance (cm) (FMTDist)** – Estimated path length travelled during the first reaching movement.

4) **first movement distance error (cm) (FMTDistErr)** – distance between the hand position after the first movement and the peripheral target.

5) **first movement direction error (deg) (FMTDirErr)** – angular deviation between the optimal reach path and the subject’s initial reach direction.

6) **first movement distance ratio (FMTDistRatio)** – ratio of i) the distance the hand travelled during the subject’s initial movement to ii) the distance the hand travelled between movement onset and offset.

7) **first movement maximum speed (FMTMaxSP)** – maximum hand speed during the subject’s initial movement after the target light illuminated.

8) **first movement maximum hand speed ratio (FMTMaxSPRatio)** – ratio of i) maximum hand speed during the initial movement to ii) global hand speed maximum of the trial.

**D) Feedback Control:** this attribute has two measures and characterizes how subjects adjust or correct their movements after their initial motor response.

9) **number of speed peaks (NumMTMaxSP)** – number of hand speed maxima between movement onset and offset.
10) differences between speed maxima and minima (cm/s) (MinMaxSPDiff) –
the mean difference between local speed peaks and minimums.

E) Total Movement Metrics: this attribute contains four measures and characterizes the
movement as a whole.
11) total movement time (s) (TotalMT) – total time elapsed from movement onset to
offset.
12) path length (cm) (PathLen) – the estimated length of the hand path during the total
movement.
13) path length ratio (PathLenRatio) – ratio of actual path length (distance travelled by
the hand between movement onset and offset) to optimal reach path length.
14) maximum hand speed (m/s) (MTMaxSP) – maximum speed that the hand travelled
among all maxima during movement.
Task 2) Arm Position-Matching Task – Movement Outcome Measures:

Outcome measures describing matching performance can be divided into three categories: A) Contraction/Expansion; B) Systematic Shifts; and C) Variability.

A) Contraction/Expansion – describes the range/area of the workspace matched by the active (subject-controlled) hand relative to the range/area of the workspace spanned by the robot-controlled hand.

1) subject area (in m²)
2) area % change (subject area/robot area)
3) x range (in m)
4) y range (in m)
5) x range % change (subject range/robot range)
6) y range % change (subject range/robot range)

B) Systematic Shifts – describe constant end position errors between the subject- and robot-controlled hands (expected end position). These are calculated by finding the mean trial-to-trial error between hands, for a mirror match for each target location, then calculating the mean of means for all target locations in the data set.

7) mean X error
8) mean Y error
9) mean XY error

C) Variability – describes trial-to-trial consistency of the subject-controlled hand. For each target location, Principle Component Analysis (PCA) ellipses (in m) are computed from the Cartesian coordinates of the end positions for all trials about any one of nine target locations. These ellipses not only capture variability in the plane, but also any rotation about each target.

10) PCA mean area: the mean area (in m²) of the PCA (variability) ellipse, covered by the subject-controlled hand, for all trials, over all nine targets.
11) PCA SD area: the standard deviation of the area of the PCA ellipse, covered by the subject-controlled hand, for all trials, over all nine targets.
Appendix F

Bivariate Correlations among variables within feedforward, feedback, and total movement metrics attributes of sensory-motor control in the reaching task

<table>
<thead>
<tr>
<th>Spearman's rho</th>
<th>FMTMaxSP</th>
<th>FMTDist</th>
<th>FMTDispErr</th>
<th>FMTDispErr</th>
<th>FMTDispRatio</th>
<th>FMTMaxSPRatio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation Coefficient</td>
<td>1.000</td>
<td>.794*</td>
<td>-.481*</td>
<td>-.229*</td>
<td>.631*</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.014</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>N</td>
<td>115</td>
<td>115</td>
<td>115</td>
<td>115</td>
<td>115</td>
<td>115</td>
</tr>
<tr>
<td>FMTDist</td>
<td>Correlation Coefficient</td>
<td>.794*</td>
<td>1.000</td>
<td>-.722*</td>
<td>-.471*</td>
<td>.857*</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>N</td>
<td>115</td>
<td>115</td>
<td>115</td>
<td>115</td>
<td>115</td>
<td>115</td>
</tr>
<tr>
<td>FMTDispErr</td>
<td>Correlation Coefficient</td>
<td>-.481*</td>
<td>-.722*</td>
<td>1.000</td>
<td>.851*</td>
<td>-.597*</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>N</td>
<td>115</td>
<td>115</td>
<td>115</td>
<td>115</td>
<td>115</td>
<td>115</td>
</tr>
<tr>
<td>FMTDispRatio</td>
<td>Correlation Coefficient</td>
<td>-.226*</td>
<td>-.471*</td>
<td>.851*</td>
<td>1.000</td>
<td>-.731*</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.014</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>N</td>
<td>115</td>
<td>115</td>
<td>115</td>
<td>115</td>
<td>115</td>
<td>115</td>
</tr>
<tr>
<td>FMTMaxSPRatio</td>
<td>Correlation Coefficient</td>
<td>.631*</td>
<td>.857*</td>
<td>-.897*</td>
<td>-.731*</td>
<td>1.000</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>N</td>
<td>115</td>
<td>115</td>
<td>115</td>
<td>115</td>
<td>115</td>
<td>115</td>
</tr>
</tbody>
</table>

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

<table>
<thead>
<tr>
<th>Spearman's rho</th>
<th>NumMTMaxSP</th>
<th>Correlation Coefficient</th>
<th>NumMTMaxSP</th>
<th>MinMaxSPDiff</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NumMTMaxSP</td>
<td>Correlation Coefficient</td>
<td>1.000</td>
<td>.638*</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>.</td>
<td>.</td>
<td>.000</td>
<td>.</td>
</tr>
<tr>
<td>N</td>
<td>115</td>
<td>115</td>
<td>115</td>
<td>115</td>
</tr>
<tr>
<td>MinMaxSPDiff</td>
<td>Correlation Coefficient</td>
<td>.638*</td>
<td>1.000</td>
<td>.</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>.</td>
<td>.</td>
<td>.000</td>
<td>.</td>
</tr>
<tr>
<td>N</td>
<td>115</td>
<td>115</td>
<td>115</td>
<td>115</td>
</tr>
</tbody>
</table>

**. Correlation is significant at the 0.01 level (2-tailed).
## Correlations

<table>
<thead>
<tr>
<th></th>
<th>TotalMTime</th>
<th>MTMaxSP</th>
<th>PathLength</th>
<th>PathLenRatio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spearman's rho</td>
<td>1.000</td>
<td>-.800&quot;</td>
<td>.107</td>
<td>.197</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.000</td>
<td>.000</td>
<td>.255</td>
<td>.034</td>
</tr>
<tr>
<td>N</td>
<td>115</td>
<td>115</td>
<td>115</td>
<td>115</td>
</tr>
<tr>
<td>MTMaxSP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correlation Coefficient</td>
<td>-.800&quot;</td>
<td>1.000</td>
<td>.368&quot;</td>
<td>.249&quot;</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.000</td>
<td>.000</td>
<td>.003</td>
<td>.007</td>
</tr>
<tr>
<td>N</td>
<td>115</td>
<td>115</td>
<td>115</td>
<td>115</td>
</tr>
<tr>
<td>PathLength</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correlation Coefficient</td>
<td>107</td>
<td>.368&quot;</td>
<td>1.000</td>
<td>.904&quot;</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>256</td>
<td>.000</td>
<td>.000</td>
<td>.000</td>
</tr>
<tr>
<td>N</td>
<td>115</td>
<td>115</td>
<td>115</td>
<td>115</td>
</tr>
<tr>
<td>PathLenRatio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correlation Coefficient</td>
<td>.197&quot;</td>
<td>.249&quot;</td>
<td>.904&quot;</td>
<td>1.000</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.034</td>
<td>.007</td>
<td>.000</td>
<td>.000</td>
</tr>
<tr>
<td>N</td>
<td>115</td>
<td>115</td>
<td>115</td>
<td>115</td>
</tr>
</tbody>
</table>

**, Correlation is significant at the 0.01 level (2-tailed).**

*, Correlation is significant at the 0.05 level (2-tailed).*
Appendix G

Univariate tests for each of five attributes of sensory-motor control in the reaching task

### Univariate Tests

**Dependent Variable: Posture_Speed**

<table>
<thead>
<tr>
<th></th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
<th>Partial Eta Squared</th>
<th>Noncent. Parameter</th>
<th>Observed Power*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast</td>
<td>5.990E-5</td>
<td>1</td>
<td>5.990E-5</td>
<td>31.767</td>
<td>.000</td>
<td>.226</td>
<td>31.767</td>
<td>1.000</td>
</tr>
<tr>
<td>Error</td>
<td>0.000</td>
<td>109</td>
<td>1.894E-6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The F tests the effect of group. This test is based on the linearly independent pairwise comparisons among the estimated marginal means.

- a. Computed using alpha = .05

**Dependent Variable: Reaction_Time**

<table>
<thead>
<tr>
<th></th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
<th>Partial Eta Squared</th>
<th>Noncent. Parameter</th>
<th>Observed Power*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast</td>
<td>0.26</td>
<td>1</td>
<td>0.026</td>
<td>6.019</td>
<td>.016</td>
<td>.052</td>
<td>6.019</td>
<td>.681</td>
</tr>
<tr>
<td>Error</td>
<td>4.75</td>
<td>109</td>
<td>0.004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The F tests the effect of group. This test is based on the linearly independent pairwise comparisons among the estimated marginal means.

- a. Computed using alpha = .05

**Dependent Variable: FMTMaxSP, FMTDist, FMTDistRatio, FMTMaxSRatio, FMTMaxSRatio**

<table>
<thead>
<tr>
<th></th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
<th>Partial Eta Squared</th>
<th>Noncent. Parameter</th>
<th>Observed Power*</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMTMaxSP Contrast</td>
<td>0.000</td>
<td>1</td>
<td>0.000</td>
<td>.183</td>
<td>.002</td>
<td>183</td>
<td>0.022</td>
<td>183</td>
</tr>
<tr>
<td>Error</td>
<td>0.000</td>
<td>109</td>
<td>3.828E-5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMTDist Contrast</td>
<td>0.000</td>
<td>1</td>
<td>0.000</td>
<td>4.212</td>
<td>.043</td>
<td>.037</td>
<td>4.212</td>
<td>0.530</td>
</tr>
<tr>
<td>Error</td>
<td>0.004</td>
<td>109</td>
<td>3.828E-5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMTDistRatio Contrast</td>
<td>0.000</td>
<td>1</td>
<td>0.000</td>
<td>37.476</td>
<td>.000</td>
<td>.256</td>
<td>37.476</td>
<td>1.000</td>
</tr>
<tr>
<td>Error</td>
<td>0.001</td>
<td>109</td>
<td>1.032E-5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMTMaxSRatio Contrast</td>
<td>0.026</td>
<td>1</td>
<td>0.026</td>
<td>70.682</td>
<td>.000</td>
<td>.393</td>
<td>70.682</td>
<td>1.000</td>
</tr>
<tr>
<td>Error</td>
<td>0.040</td>
<td>109</td>
<td>0.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMTMaxSRatio Contrast</td>
<td>0.093</td>
<td>1</td>
<td>0.093</td>
<td>21.001</td>
<td>.000</td>
<td>.162</td>
<td>21.001</td>
<td>0.995</td>
</tr>
<tr>
<td>Error</td>
<td>0.484</td>
<td>109</td>
<td>0.004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The F tests the effect of group. This test is based on the linearly independent pairwise comparisons among the estimated marginal means.

- a. Computed using alpha = .05
### Univariate Tests

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig</th>
<th>Partial Eta Squared</th>
<th>Noncent. Parameter</th>
<th>Observed Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>NumMTime</td>
<td>2.697</td>
<td>1</td>
<td>2.697</td>
<td>29.194</td>
<td>.000</td>
<td>.211</td>
<td>29.194</td>
<td>1.000</td>
</tr>
<tr>
<td>Contrasts</td>
<td>10.071</td>
<td>109</td>
<td>.092</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Error</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MinMaxSP</td>
<td>.001</td>
<td>1</td>
<td>.001</td>
<td>41.605</td>
<td>.000</td>
<td>.276</td>
<td>41.605</td>
<td>1.000</td>
</tr>
<tr>
<td>Contrasts</td>
<td>.002</td>
<td>109</td>
<td>1.392E-5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Error</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The F tests the effect of group. This test is based on the linearly independent pairwise comparisons among the estimated marginal means.

a. Computed using alpha = .05

### Univariate Tests

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig</th>
<th>Partial Eta Squared</th>
<th>Noncent. Parameter</th>
<th>Observed Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>TotalMTime</td>
<td>.047</td>
<td>1</td>
<td>.047</td>
<td>2.048</td>
<td>.155</td>
<td>.018</td>
<td>2.048</td>
<td>.294</td>
</tr>
<tr>
<td>Contrasts</td>
<td>2.521</td>
<td>109</td>
<td>.023</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Error</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTMaxSP</td>
<td>1.113E-5</td>
<td>1</td>
<td>1.113E-5</td>
<td>.012</td>
<td>.913</td>
<td>.000</td>
<td>.012</td>
<td>.051</td>
</tr>
<tr>
<td>Contrasts</td>
<td>.102</td>
<td>109</td>
<td>.011</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Error</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PathLength</td>
<td>.000</td>
<td>1</td>
<td>.000</td>
<td>28.320</td>
<td>.000</td>
<td>.206</td>
<td>28.320</td>
<td>1.000</td>
</tr>
<tr>
<td>Contrasts</td>
<td>.002</td>
<td>109</td>
<td>1.599E-5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Error</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PathLenRatio</td>
<td>.375</td>
<td>1</td>
<td>.375</td>
<td>59.291</td>
<td>.000</td>
<td>.352</td>
<td>59.291</td>
<td>1.000</td>
</tr>
<tr>
<td>Contrasts</td>
<td>.890</td>
<td>109</td>
<td>.006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The F tests the effect of group. This test is based on the linearly independent pairwise comparisons among the estimated marginal means.

a. Computed using alpha = .05

98
Appendix H
One-way ANOVAs for each outcome measure in the position matching task

<table>
<thead>
<tr>
<th>Subject</th>
<th>Area</th>
<th>Percent</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sum of Squares</td>
<td>df</td>
<td>Mean Square</td>
<td>F</td>
</tr>
<tr>
<td>Between Groups</td>
<td>.000</td>
<td>1</td>
<td>.000</td>
</tr>
<tr>
<td>Within Groups</td>
<td>.001</td>
<td>78</td>
<td>.000</td>
</tr>
<tr>
<td>Total</td>
<td>.001</td>
<td>79</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Xrange</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>.016</td>
<td>1</td>
<td>.016</td>
<td>8.559</td>
<td>.005</td>
</tr>
<tr>
<td>Within Groups</td>
<td>.147</td>
<td>78</td>
<td>.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>.163</td>
<td>79</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Yrange</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>.001</td>
<td>1</td>
<td>.001</td>
<td>2.919</td>
<td>.092</td>
</tr>
<tr>
<td>Within Groups</td>
<td>.016</td>
<td>78</td>
<td>.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>.017</td>
<td>79</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### ANOVA

#### XrangeChange

<table>
<thead>
<tr>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>.091</td>
<td>1</td>
<td>.091</td>
<td>1.596</td>
</tr>
<tr>
<td>Within Groups</td>
<td>4.464</td>
<td>78</td>
<td>.057</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4.555</td>
<td>79</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### YrangeChange

<table>
<thead>
<tr>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>.008</td>
<td>1</td>
<td>.008</td>
<td>.450</td>
</tr>
<tr>
<td>Within Groups</td>
<td>1.450</td>
<td>78</td>
<td>.019</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.459</td>
<td>79</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### MeanXerror

<table>
<thead>
<tr>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>.001</td>
<td>1</td>
<td>.001</td>
<td>1.155</td>
</tr>
<tr>
<td>Within Groups</td>
<td>.100</td>
<td>78</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>.102</td>
<td>79</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### MeanYerror

<table>
<thead>
<tr>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>.000</td>
<td>1</td>
<td>.000</td>
<td>1.155</td>
</tr>
<tr>
<td>Within Groups</td>
<td>.006</td>
<td>78</td>
<td>.000</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>.006</td>
<td>79</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### MeanXerror

<table>
<thead>
<tr>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>.005</td>
<td>1</td>
<td>.005</td>
<td>8.732</td>
</tr>
<tr>
<td>Within Groups</td>
<td>.042</td>
<td>78</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>.046</td>
<td>79</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### ANOVA

<table>
<thead>
<tr>
<th>PCAMeanArea</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>.000</td>
<td>1</td>
<td>.000</td>
<td>22.407</td>
<td>.000</td>
</tr>
<tr>
<td>Within Groups</td>
<td>.000</td>
<td>78</td>
<td>.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>.000</td>
<td>79</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PCAsdArea</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>.000</td>
<td>1</td>
<td>.000</td>
<td>28.973</td>
<td>.000</td>
</tr>
<tr>
<td>Within Groups</td>
<td>.000</td>
<td>78</td>
<td>.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>.000</td>
<td>79</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>