DIAGNOSTIC SUBGROUPS AND
NEUROPSYCHOLOGICAL
ATTENTION DEFICITS
IN FETAL ALCOHOL SYNDROME

A Thesis
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in Partial Fulfillment of the Requirements
for the Degree of
Doctor of Philosophy
in the
Department of Psychology
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By
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ABSTRACT

In 1996, the Institute of Medicine made an initial step towards addressing the confusion and controversy regarding the diagnosis of fetal alcohol syndrome (FAS) by proposing a classification scheme and calling for research to evaluate its validity and clinical utility. Previous research evaluated memory, executive functions, and behaviour problems in FAS. Prior to the present study, however, there had not been an empirical evaluation of the existence of a spectrum of diagnostic subgroups or an evaluation of subgroup functioning on neuropsychological components of attention during the pre-teen and adolescent years.

Part 1 of this study used categorical data regarding diagnostic domains to determine if an a priori spectrum of four subgroups could be identified. This spectrum included FAS and three fetal alcohol effect (FAE) subgroups, which were defined using teratogenic theory, previous research findings, and logic. The sample consisted of 112 children with a confirmed history of excessive prenatal alcohol exposure.

Part 2 evaluated the continuity and comparability of the CNS dysfunction subgroups exhibited by assessing neuropsychological components of attention using models by Mirsky and Conners. The sample consisted of 30 children and subgroups were matched on age, sex, and living situation.

Results identified 3 of the 4 potential subgroups. All subgroups exhibited a clinically significant attention deficit. After adjusting for IQ, the FAS and FAE subgroups had comparable levels of functioning on all components of attention with one exception. On the sustain component, the FAE subgroups had more difficulties than the FAS subgroup in maintaining a consistent response-speed in response to changes in the length of time between targets.

This study provides empirical and theoretical support for the validity and clinical utility of a spectrum of fetal alcohol subgroups consistent with the IOM's classification. It furthers a theoretical understanding of the dose-response effects of alcohol as a teratogenic agent. It suggests that attention regulation functions are especially vulnerable to the damage caused by prenatal alcohol exposure. The findings emphasize the
importance of obtaining a history of prenatal alcohol exposure in individuals presenting with neuropsychological difficulties, and developing treatment programs for pregnant women with an alcohol addiction.
ACKNOWLEDGEMENTS

I would like to thank my advisor, Dr. Jo Nanson and members of my committee Drs. Dave Scott, Margaret McKim, and Brian Habbick for their input in this project. I would also like to thank Dr. Julie Conry for her input as an external examiner.

I would like to thank the Scottish Rite Foundation of Canada, the Royal University Hospital, and the University of Saskatchewan for their financial assistance in pursuing this degree.

I want to acknowledge the keen insights of Drs. Habbick, Zaleski, Casey, Snyder, and Nanson for identifying and following children with FAS over the past two decades. Without the diagnosis and clinical follow-up that these “clinical pioneers” provided, this study would not have been possible. Staff from the Alvin Buckwold Child Development program were also instrumental in the implementation of this research, and I am especially grateful for the support received by members of the FAS team, office staff (Joshlyn Pampu, Debby Milhomens, Rita Hirschkorn), and administration (Helen Dadiotis).

I am also grateful for having had the opportunity to discuss FAS and attention research issues with Drs. Daisy Pascualvaca and Allan Mirsky from the National Institute of Mental Health; Drs. Sarah Mattson and Ed Riley from the University of San Diego State University, and Drs. Jeane Townsend and Eric Courchesne from the University of California, San Diego. I especially want to thank Dr. Townsend and Dr. Courchesne for the opportunity to spend three days in the Neuroscience Laboratory in La Jolla, and for training me to use of their shift attention task.

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Finally, I thank Grace, Patrick and Emily. The dream of a Ph.D. led Grace and our two children on an adventure in post-secondary education spanning five Universities, seven cities and twelve homes over the past decade. I am delighted to be able to share the “mountain top experience” of completing this degree with my greatest supporters by my side. Grace’s unwavering support, Patrick’s quiet patience, and Emily’s flexibility were vital in the completion of the final stage of this research. I look forward to the adventures we will share as individuals and a family over our next decade.
DEDICATION

To adolescents with a known or unknown history of excessive prenatal alcohol exposure and their parents. My sincere hope is that this research will contribute to your quality of life, achievement, and fulfillment.
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<th>Abbreviation</th>
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<tr>
<td>ABCD</td>
<td>Alvin Buckwold Child Development Program</td>
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<tr>
<td>ADHD</td>
<td>Attention Deficit Hyperactivity Disorder</td>
</tr>
<tr>
<td>ARBD</td>
<td>Alcohol Related Birth Defects</td>
</tr>
<tr>
<td>ARND</td>
<td>Alcohol Related Neurodevelopmental Disorder</td>
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<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<tr>
<td>CPRS-R:L</td>
<td>Conners' Parent Rating Scale—Revised: Long Versions</td>
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<td>CPT</td>
<td>Continuos Performance Test</td>
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<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders — Fourth Edition</td>
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<tr>
<td>ETOH</td>
<td>Ethanol</td>
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<td>FAE</td>
<td>Fetal Alcohol Effects</td>
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<td>FAE(D)</td>
<td>Fetal Alcohol Effects with dysmorphology</td>
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<td>FAE(DX)</td>
<td>Fetal Alcohol Effect, a combined group</td>
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<tr>
<td>FAE(X)</td>
<td>Fetal Alcohol Effect with excessive exposure</td>
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<td>FAS</td>
<td>Fetal Alcohol Syndrome</td>
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<tr>
<td>IOM</td>
<td>Institute of Medicine</td>
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<tr>
<td>IQ</td>
<td>Intelligence Quotient</td>
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<tr>
<td>ISI</td>
<td>Inter-Stimulus-Interval</td>
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<tr>
<td>NIMH</td>
<td>National Institute of Mental Health</td>
</tr>
<tr>
<td>PAE</td>
<td>Prenatal Alcohol Exposure</td>
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<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>pFAS</td>
<td>partial Fetal Alcohol Syndrome</td>
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<tr>
<td>RSA</td>
<td>Research Society on Alcoholism</td>
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<tr>
<td>RT</td>
<td>Reaction Time</td>
</tr>
<tr>
<td>SDMT</td>
<td>Symbol Digit Modalities Test</td>
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<tr>
<td>SDRT</td>
<td>Standard Deviation of Reaction Time</td>
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<tr>
<td>WCST</td>
<td>Wisconsin Card Sorting Test</td>
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<tr>
<td>WRAT-R</td>
<td>Wide Range Achievement Test — Revised</td>
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AUTHOR'S NOTE

This dissertation was prepared according to guidelines for style, format, and language published by the American Psychological Association (APA, 1994) and the College of Graduate Studies and Research (1996). The Canadian Oxford Dictionary (2000) was used as the standard for spelling. This resulted in the following spellings: behaviour, fetus, and pediatrician. The following four levels of headings were used to organize the material presented:

LEVEL 1: CENTERED, FULL CAPITALS & BOLD
Level 2: Centered, Upper and Lower Case, and Bold
Level 3: Flush left, Underlined, Upper and Lower Case
Level 4: Indented, underlined, lower case paragraph heading ending with a period.
INTRODUCTION

Teratology is the study of agents capable of producing death, malformation, growth retardation, and behavioural deficits. Alcohol is the most commonly used human teratogen due to its availability, abuse potential and economic value. In 1973 Jones, Smith, Ulleland and Streissguth described a pattern of malformations in children born to mothers who were chronic alcoholics. This pattern included physical malformation (i.e., facial, limb, and cardiac anomalies), growth retardation, and developmental delay. Later that year Jones and Smith (1973) labelled this condition fetal alcohol syndrome.

Although previous studies (Lemoine, Harouseau, Borteryu, & Menuet, 1968; Ulleland, 1972) had reported high rates of abnormalities in children born to alcoholic mothers, the case studies reported by Jones and colleagues were significant because they delineated a recognizable syndrome linked to excessive prenatal alcohol exposure and they coined the term fetal alcohol syndrome (FAS). Eight years later the Fetal Alcohol Study Group of the Research Society on Alcoholism (RSA) published "preliminary" criteria for a diagnosis of FAS (Rosett, 1980). Later the same group decided that a "secure" diagnosis of FAS required signs of abnormality in each of three domains: facial dysmorphology; growth retardation; and central nervous system (CNS) dysfunction (Sokol & Clarrren, 1989).

Soon after Jones and Smith (1973) described FAS, clinicians realized that there were a large number of children who had been exposed to excessive amounts of alcohol in utero who did not exhibit anomalies in all three diagnostic domains (Aase, 1994). Initially Clarrren and Smith (1978) described these children as having "suspected fetal alcohol effects" to indicate that further proof was needed to confirm that prenatal alcohol exposure was the cause of abnormalities noted. Clinicians and researchers, however, generally omitted the term "suspected" and the term fetal alcohol effects (FAE) evolved. While FAS represents the extreme end of the continuum of physical deficits caused by
prenatal alcohol exposure, it is estimated that two-thirds of the children born to mothers
who drank excessively during pregnancy meet the criteria for FAE (Abel, 1985). These
individuals suffer from physically milder but equally debilitating conditions at social and
behavioural levels (Streissguth, Barr, Kogan, & Bookstein, 1997).

There is now widespread consensus among clinicians, parents and others (see
Streissguth & Kanter, 1997) that the most serious and life-long functional deficits
resulting from excessive prenatal alcohol exposure are the consequences of brain damage.
Furthermore, parents and researchers report that some of the social and behavioural
deficits exhibited by individuals with FAE are similar or more severe than the social and
behavioural deficits exhibited by individuals with FAS. For example, Streissguth, Barr, et
al. (1997) found that compared to individuals with FAS those with FAE had higher rates
of social and behavioural disabilities (e.g., disrupted school experience, trouble with the
law, confinement, inappropriate sexual behaviour, alcohol/drug problems). FAS and FAE
groups also had equally high levels of mental health problems (e.g., attention deficit
problems, depression, and suicide).

Attention problems were the most frequent type of mental health difficulties
reported, and were found in sixty percent of children with FAS or FAE. Surprisingly, IQ
was negatively correlated with outcome. IQ scores within the intellectually deficient
range were associated with lower rates of social and behavioural disabilities when
compared to IQ scores in the average and below average range. Streissguth, Barr, et al.
(1997) noted that the increased level of disability in the group with the higher IQ score
may be related to the fact that these individuals typically receive less specialized
developmental follow-up and intervention. Despite this knowledge, special needs funding
(e.g., educational, supportive living) and specialized developmental follow-up is generally
available only to individuals with a diagnosis of FAS. Services of this nature are often
denied to individuals with a diagnosis of FAE.

There is considerable controversy and confusion regarding the term FAE.
Although the term FAE is widely used in both research and clinical settings, a consensus
about how FAE should be defined has never been reached (Sokol & Clarren, 1989). In
1989 the RSA reached a near-consensus stating that the use of the term FAE should be strongly discouraged because there was no agreement as to how it should be defined. Sokol and Clarren also asserted that the term FAE was being incorrectly used in diagnostic, treatment, and prevention programs because it did not have an established set of diagnostic criteria. Instead of the term FAE, Sokol and Clarren recommended use of the term Alcohol Related Birth Defect (ARBD). Recently, however, Clarren and Astley (1997) revised their stance on this nomenclature issue by stating that it was not sufficient to describe patients with functional brain dysfunction of organic origin as having a birth defect. Despite the ambiguity and confusion associated with the clinical label FAE, many researchers and clinicians continue to use this term.

A general definition of FAE, however, is a history of excessive prenatal alcohol exposure and anomalies in one or two of the three diagnostic domains of FAS (Astley & Clarren, 1995; Nanson & Hiscock, 1990; Robinson, Conry, & Conry, 1987). The vagueness of this definition has resulted in FAE being defined in a variety of ways in both clinical and research settings. For example, in a study of attention deficits Nanson and Hiscock (1990) defined FAE as abnormal findings in two of three FAS diagnostic categories. In contrast, Astley and Clarren defined FAE as CNS dysfunction, with or without growth retardation, and no facial dysmorphism. Due to the lack of consensus regarding a definition of FAE, a description of how this term has been defined by researchers in previous studies was included in the Literature Review section of this project.

One explanation for multiple definitions of FAE is that there are six possible combinations of positive findings in one or two of the three diagnostic domains of FAS. The six logically possible combinations of these three diagnostic criteria are as follows: (1) dysmorphology & growth; (2) dysmorphology & CNS dysfunction; (3) growth & CNS dysfunction; (4) dysmorphology; (5) growth; (6) CNS dysfunction.

In response to the magnitude of social and behavioural disabilities associated with excessive prenatal alcohol exposure, the U.S. Congress mandated the Institute of Medicine (IOM) of the National Academy of Sciences to conduct a study of FAS and
FAE. In response to this mandate the IOM established a multi-disciplinary committee to review existing knowledge on FAS and FAE. Given the controversy and confusion regarding a definition of FAE, one of the main charges given to this committee was to evaluate existing diagnostic criteria and to formulate the best possible diagnostic guidelines (Stratton, Howe, & Battaglia, 1996). In their final report, the IOM (1996) made two key recommendations. First, additional research regarding FAS and FAE was needed to evaluate the clinical utility and validity of schemes for classification and diagnosis. Second, additional research was needed to evaluate the similarities and differences in the clinical deficits associated with FAS and FAE.

The goal of this study was to examine diagnostic, theoretical, and clinical issues associated with FAS and FAE. This was done: (1) by identifying diagnostic subgroups with a history of excessive prenatal alcohol exposure; and (2) by evaluating the specificity and magnitude of CNS dysfunction exhibited by subgroups using neuropsychological and behavioural components of attention.

Since there were no established criteria for a spectrum of diagnostic subgroups with a history of excessive prenatal alcohol exposure, a spectrum of this nature was defined for the purpose of this study using teratogenic theory, logic, and research findings. This spectrum consists of FAS and three FAE subgroups. A spectrum refers to a group of individuals with a similar medical history consisting of exposure to excessive levels of alcohol prenatally (Webster’s Collegiate Dictionary, 1985).

An FAE(D) subgroup was defined as individuals with evidence of CNS dysfunction and dysmorphology. An FAE(G) subgroup was defined as individuals with evidence of CNS dysfunction and growth retardation, and an FAE(X) subgroup was defined as individuals with evidence of CNS dysfunction and a history of excessive prenatal alcohol exposure.

Measures of attention were well suited for the task of assessing the magnitude and specificity of CNS dysfunction in a spectrum of FAS and FAE subgroups as they have consistently been found to be sensitive indicators of the brain damage resulting from in utero exposure to alcohol (Streissguth, Barr, Sampson, & Bookstein, 1994). Three
research questions were investigated in this study. First, can a spectrum of four
diagnostic subgroups with a history of excessive prenatal alcohol exposure be identified?
Second, are there similarities and differences between clinical subgroups on
neuropsychological or behavioural components of attention? Third, do all subgroups
exhibit a "clinically significant" attention deficit?

Since attention is a multifaceted construct and deficits may be present in some but
not all components, neuropsychological and behavioural models were used to provide a
assesses four clinical components of attention (i.e., Focus-Execute, Sustain, Encode, and
of Inattention and Hyperactivity-Impulsively. This provided a measure of the type of
behavioural attention deficits exhibited in everyday living situations.

The delineation of a spectrum of clinical subgroups with a history of excessive
prenatal alcohol exposure (e.g., FAS, FAE(D), FAE(G), FAE(X)) and associated
attentional strengths and weaknesses is important for the development of diagnostic,
theoretical and clinical issues. Diagnostically, it is a fundamental "next step" in the
evaluation of the clinical validity and utility of existing diagnostic classification schemes
(e.g., RSA, Sokol & Clarren, 1989; IOM, Stratton et al., 1996). Theoretically, data
regarding the spectrum of clinical subgroups and the magnitude and specificity of
associated attention deficits will further our understanding of the teratogenic nature of
excessive prenatal alcohol exposure. More specifically, does the severity of CNS
dysfunction increase when a subgroup has positive findings in one or two of the physical
diagnostic domains associated with excessive prenatal alcohol exposure (i.e., growth
retardation, and dysmorphology)? Also, are the magnitude and specificity of attention
strengths and weaknesses consistent with knowledge of differences in the extent of brain
damage associated with FAS and FAE? Clinically, information regarding the magnitude
and specificity of CNS dysfunction associated with clinical subgroups will help to predict,
understand, and habilitate neuropsychological and behavioural attention deficits.

The next major section reviews literature regarding teratology, diagnostic
subgroups, neurobehavioural and neuroanatomical deficits, and models for the assessment of attention. An overview of major findings from teratology research is presented to provide a conceptual foundation for understanding the spectrum of damage associated with prenatal alcohol exposure. A review of the clinical spectrum of diagnostic subgroups provides a brief history detailing the development and use of the terms FAS, FAE, and related terms. A discussion of neurobehavioural deficits summarizes existing empirical findings focusing on the attention deficits associated with prenatal alcohol exposure. A review of neuroanatomical damage summarizes similarities and differences in the global and regional brain damage associated with FAS and FAE. A description of the neuropsychological and behavioural models of attention by Mirsky (1989) and Conners (1997) provides information on the empirical and theoretical validity of the assessment models that were used in this study. Finally, this review concludes with a critique of methodological issues and limitations in previous research on FAS and FAE.
LITERATURE REVIEW

Teratology

The principles of teratology provide a foundation for understanding the effects of prenatal alcohol exposure. Teratology is defined as the study of agents capable of producing death, physical malformation, growth retardation, and CNS damage (Wilson, 1977). The major tenet derived from findings in teratology research is that effects are the result of dose, timing, and conditions of exposure (Streissguth, Barr, & Sampson, 1992).

Theoretical Dose-Effect Relationships

Using findings from teratology research Vorhees (1986) developed theoretical dose-effect curves to illustrate the spectrum of damage effects resulting from the exposure of a fetus to a teratogen during pregnancy. Figure 1 illustrates that as the dose of a teratogenic substance increases, more fetuses are at risk of being adversely affected, and effects become more severe, from CNS dysfunction to fetal death.

Extrapolating from this theory and assuming that conditions and timing of exposure are comparable, one would predict that an extreme dosage is likely to result in fetal death. A high dose is likely to result in findings in three domains (i.e., dysmorphology, growth retardation, and CNS dysfunction). A moderate dose is likely to produce findings in two domains (i.e., growth retardation and CNS dysfunction), and a low dose is likely only to produce CNS dysfunction.
Figure 1. Vorhees' (1986) theoretical dose-effect curves for major manifestations of teratogenesis. As the level of dose increases both the number of domains and the percentage of affected fetuses increases.
Thus, the domains of dysmorphology, growth retardation, and CNS functions have different teratogenic exposure thresholds. Furthermore, low exposure levels are more likely to produce CNS dysfunction than dysmorphology or growth retardation. Since timing, pattern, and conditions of exposure are also important mediators in teratogenic sequelae there is not a direct relationship between dose level and "affectedness". This is illustrated by Vorhees' idealized dose-effect curves where only a certain percentage of individuals are likely to be affected by a specific dose level.

Although there are a considerable number of agents known to be teratogenic to humans (e.g., anticonvulsants, benzodiazepines, thalidomide, phenylalanine), alcohol, due to its availability, abuse potential, and considerable economic value is the most devastating human teratogen (West & Goodlett, 1990). For example, in contrast to prescription drugs such as anticonvulsants, which are prescribed and monitored by a physician, blood alcohol levels that are tolerated by an addicted user are toxic to a developing fetus (Vorhees, 1989). Consequently Vorhees (1989) proposed that abuse agents such as alcohol do not possess the classical dose-effect curves presented in Figure 1. Instead, he proposed that the pattern more closely resembles that depicted in Figure 2 where CNS damage and growth retardation occur at a substantially lower dose level compared to the dose level associated with dysmorphology.
Figure 2. Vorhees' (1989) dose-effect curves for teratogenic abuse agents. In comparison to the classical pattern in Figure 1, CNS and growth deficits occur at substantially lower levels.
Figure 2 indicates that individuals who receive a diagnosis of FAS have generally been exposed to higher levels of prenatal alcohol exposure when compared to individuals with FAE. Despite differences in alcohol exposure levels, individuals with both FAS and FAE are likely to have difficulties resulting from CNS dysfunction. Since attention deficits are a common behavioural sequelae associated with CNS dysfunction, difficulties of this nature are likely to be exhibit by individuals with FAS and FAE (e.g., FAE(D), FAE(G), and FAE(X)).

One of the early goals of prenatal alcohol exposure research was to detail the extent of alcohol-induced damage on the developing brain (West, 1986), and to document the range of associated CNS deficits (e.g., mental retardation, learning disabilities, attention deficits, hyperactivity, in-coordination, behaviour problems) (Streissguth, 1986). Although progress has been made, there are important unanswered questions about the magnitude and specificity of CNS dysfunction resulting from excessive prenatal alcohol exposure on the prenatal brain. Before reviewing existing literature on attention and neuroanatomical deficits resulting from prenatal alcohol exposure, an overview of the incidence and teratogenic specificity of prenatal alcohol exposure is presented.

**Alcohol Consumption Patterns During Pregnancy**

During the first half of this century the placenta was viewed as being able to protect a fetus from the damaging effects of toxic substances such as alcohol (Coles, 1994). As a result there was little concern about alcohol consumption during pregnancy. In the 1950's and 1960's researchers discovered that exposure to toxic agents such as mercury and thalidomide had damaging effects on a fetus during the first trimester, while exposure to toxic agents during subsequent stages of prenatal development was not considered detrimental (Coles, 1994). This heightened the awareness of the vulnerability of the fetus to teratogenic agents. During the 1970's and 1980's studies reported that alcohol rapidly crosses the placenta and causes dysmorphology during the first trimester and damage to the developing brain during all three trimesters (Jones, Smith, Streissguth, & Myrianthopoulos, 1974). This knowledge led to investigations of the frequency and
damage associated with alcohol consumption during pregnancy.

In order to evaluate the frequency of alcohol consumption during pregnancy, a survey of 40,000 randomly selected women in the United States was conducted (Serdula, Williamson, Kendrick, Anda, & Byers, 1991). This study found that an alcoholic beverage had been consumed in the previous month by twenty-five percent of respondents who were pregnant at the time of the survey. Three percent met criteria for binge drinking (five or more drinks on one or more occasions during the past month), and 0.6 percent were classified as heavy drinkers (i.e., two or more drinks a day). A standard drink contains approximately 0.5 ounces of absolute alcohol (Stratton et al., 1996). Similar consumption levels were found in a stratified random sample obtained by the National Maternal Infant Health Survey in the United States by the Centre for Disease Control and Prevention (CDC, 1995). This study also reported that the likelihood of frequent drinking (i.e., six or more drinks per week during pregnancy) was significantly higher among women with annual household incomes of $10,000 or less.

**Teratogenic Specificity**

One of the first questions answered by animal teratology researchers was whether alcohol by itself could produce the constellation of damage associated with FAS (Becker, Randall, Salo, Saulnier, & Weathersby, 1994). After controlling for maternal health and nutrition factors, two laboratories independently reported that mice prenatally exposed to alcohol exhibited physical birth defects similar to those reported in children with FAS (Chernoff, 1977; Randel, Taylor, & Walker, 1977). Subsequent studies found that the structural and functional CNS deficits observed in animals prenatally exposed to alcohol were similar to those identified in children with FAS (Driscoll, Streissguth, & Riley, 1990).

Animal researchers have also investigated the damage associated with prenatal exposure to other drugs such as cocaine. Findings indicate that cocaine does not produce the severity of CNS dysfunction associated with alcohol. For example, prenatal exposure to cocaine does not result in a significant reduction in brain weight while alcohol consistently does (Chen, Andersen & West, 1994). Human studies that have controlled
for alcohol use and prenatal care have not found large effects for prenatal cocaine or nicotine exposure on CNS functioning (Day & Richardson, 1994). Although prenatal exposure to nicotine or illicit drugs such as cocaine are not good for a fetus, they do not harm the developing brain to the extent that alcohol does (Nanson, 1993). Alcohol appears to be the primary CNS teratogen in polydrug use because these women typically abuse alcohol in addition to other drugs (Brown, Bakeman, Coles, Sexson & Demi, 1998).

Fetal Brain Development and Alcohol Exposure

Fetal brain development is a complex and dynamic process that continues throughout pregnancy. Animal studies have made an invaluable contribution toward our understanding of the effects that teratogens such as alcohol have on different body structures, at different stages of development (West & Goodlett, 1990). Using animal models, researchers are able to manipulate systematically factors such as timing, dose level, and pattern of exposure and to examine the associated cellular damage using histological methods. Manipulations of this nature are obviously not possible in human studies.

Although all developing mammals pass through the same embryonic and fetal stages, the timing and duration of stages vary considerably between species. Thus, in order to generalize findings from animal to human populations, similar stages of development or trimester equivalents must be established (West, Goodlett, & Brandt, 1990). For example, in rats the first 10 days of postnatal life is equal to the human third trimester and the neocortex in rats is primitive in comparison to humans. Thus, animal studies are limited in their ability to evaluate the effects of prenatal alcohol exposure on complex cognitive functions such as the attention skills that children and adults use to learn and work efficiently in home, school, and vocational settings.

Normal Fetal Development. Approximately two weeks after conception, human embryonic cells fold to form a neural tube composed of primitive cells that will divide to form the brain and spinal cord (Kolb & Whishaw, 1990). Cells in the top half of the tube
are the precursor cells of the brain, while the rest of the neural tube contains cells that will develop into the spinal cord (Kelly & Dodd, 1991). After neurons are formed they must migrate or move to their correct location (Kolb, 1989). The process of cell formation is referred to as proliferation. The precise time of proliferation and migration of cells that will form specific body structures (e.g., brain, internal organs, and skeletal system) varies. Furthermore, cells forming a particular layer in a particular region proliferate and migrate at the same time. Thus, brief exposure to a teratogen such as alcohol can lead to the development of malformation in different body structures and substructures depending upon the precise timing of the exposure.

Like all mammals, the human brain develops from one end of the neural tube (Kolb, 1989). The hollow inside this end of the tube forms a cavity that develops into the ventricular system. Cells of the brain are generated or proliferate along the ventricular wall and then they migrate out to their proper location. As the brain develops newly formed cells migrate farther and farther to reach their destination. Once cells arrive at their final location they develop the characteristics of the cell types they are to become (e.g., pyramidal or Purkinje cells), and they grow dendrites and axons to form synapses with functionally associated cells. These two processes are referred to as differentiation and synaptogenesis. The major cellular stages in prenatal brain development, then, are proliferation, migration, differentiation and synaptogenesis.

**Critical Periods and Conditions of Exposure.** We now know that there are critical periods when specific structures of a developing fetus are particularly susceptible to the teratogenic effects of alcohol (Coles, 1994). The brain is the first body system to begin developing and it continues to develop throughout the prenatal period and beyond. Other body structures such as craniofacial features develop during the first trimester. For example, the craniofacial malformations seen in children with FAS can be replicated by exposing rats to alcohol during the first trimester while exposure during subsequent stages does not cause craniofacial dysmorphology (Sulik, Johnston, & Webb, 1981). In order to provide a conceptual framework for the variety of brain malformations seen in
children exposed to alcohol prenatally, a summary of the effects seen in animals exposed during the first, second, and third trimester is provided.

The first trimester is a critical period for the proliferation and migration of cells for major organs and bodily structures (Coles, 1994). This period is referred to as the organogenesis stage. Exposure to alcohol during this period results in gross anatomical malformations of the brain (Clarren, 1986), facial dysmorphology, internal organ defects (e.g., the heart), and skeletal or digit and limb anomalies (Becker, Randall, Salo, Saulnier, & Weathersby, 1994). Malformations of the head and face, which occur as a result of exposure during the first 8 weeks of the first trimester, are the most noticeable features of children with FAS (Jones, Smith, Streissguth, & Myrianthopoulos, 1974). Teratogenic exposure during the period of proliferation and migration also results in gross alterations in neural migration patterns and latent deficits in the establishment of functional circuitry well after exposure to alcohol has ended (Miller, 1996; West, 1986). For example, significant disruption of the timing and pattern of neuron migration results in delayed death to neuron populations after they reach their migration destination if they are unable to establish synaptic connections due to neuron loss and disturbed cell formation patterns (Miller, 1995).

The second trimester is the period of brain development that is characterized by the proliferation and migration stage for large neuron populations such as the pyramidal cells of the cerebrum and the Purkinje cells of the cerebellum (Miller, 1995; West & Goodlett, 1990). This stage is normally associated with a substantial increase in brain size. Alcohol exposure results in significant neuron loss and altered cell formation patterns in all major brain structures (i.e., cerebral cortex, basal ganglia, limbic system, diencephalon, cerebellum, brain stem), and microcephaly. Neurons that are actively proliferating and migrating during this period, such as the large pyramidal neurons from the cerebrum and the large Purkinje neurons of the cerebrum and cerebellum, are particularly vulnerable to alcohol exposure (West, 1990).

The third trimester is noted for what is referred to as the "brain growth spurt" and it involves the proliferation and migration stage of the late forming microneurons and glial
or support cells of the brain (West, 1986). Exposure during this time can result in a reduction of large maturing neuron populations such as hippocampus pyramidal and cerebellar Purkinje cells that have completed their migration before exposure to alcohol (West, 1986). Bonthius and West (1990) found that third trimester exposure to both high and low levels of alcohol significantly reduced the number of cerebellar Purkinje cells while CA1 pyramidal cells of the hippocampus were only reduced with the high dose level.

Taken together, findings from animal studies have demonstrated that alcohol exposure during any prenatal trimester can result in significant neuron loss and alterations in the migration patterns and functional circuitry of neurons in all brain regions. In addition to a general reduction in overall brain size (i.e., microcephaly), some brain regions (e.g., basal ganglia, cerebellar vermis, cerebellum) and some neuron populations (e.g., CA1 pyramidal cells, Purkinje cells) are particularly vulnerable to alcohol exposure (Hoffman, 1996). Since prenatal alcohol exposure is associated with both global and regional brain damage, one could predict that it would produce both global and specific types of functional neurobehavioural deficits. Furthermore, neurobehavioural deficits are likely to exist even when physical markers of exposure such as dysmorphology are absent.

In addition to animal studies, Coles et al. (1991) has studied the growth and CNS development in the offspring of women who drank during different stages of prenatal development. She followed the offspring of three groups of women: (1) those who drank throughout pregnancy despite educational intervention; (2) those who responded to the educational intervention and stopped drinking during the second trimester; and (3) those who never drank.

Coles et al. (1991) found that at birth, growth (i.e., height and weight) was not as reduced in infants whose mothers stopped drinking during the second trimester when compared with infants whose mothers drank throughout pregnancy (Coles, 1994). Growth measures of infants whose mothers stopped drinking during the second trimester
were reduced when compared to the growth measures of infants whose mothers never drank during pregnancy.

When these children were seen at 6 years of age, however, growth measurements for all three groups were equivalent, indicating catch-up growth. In contrast, head circumference, an estimate of brain growth, was reduced in both exposed groups and was more reduced in the group exposed throughout pregnancy.

These data indicate that growth deficits at birth are associated with drinking during the third trimester when the fetus is growing rapidly. Infants born to women who stop drinking during the second trimester, however, may have growth characteristics that are within the normal range, but show impaired brain growth over time. Furthermore, these data suggest that prenatal brain damage and the resulting neurobehavioural deficits are the most pronounced sequelae of prenatal alcohol exposure. These data also suggest that children born to women who stop drinking during the second trimester are likely to meet the diagnostic criteria of FAE(D), namely facial dysmorphology and CNS involvement but no growth retardation, despite significant exposure and functional damage.

In addition to timing of alcohol exposure, a second key factor in determining the severity of brain and physical damage is peak alcohol concentration levels. West (1986) demonstrated that a small daily dose consumed in a binge-like manner that produces higher peak blood alcohol concentration levels induces more severe damage than a larger daily dose consumed at a slower rate.

Dramatic evidence from a study conducted by Goodlett, Marcussen, and West (1991) found significant microcephaly and neuronal depletion in the cerebellum following just one day of a single short episode of alcohol consumption or binge-like exposure during the third trimester in animals. These animals appear similar to those individuals with a history of prenatal alcohol exposure, and evidence of CNS impairment, without dysmorphology or growth retardation, i.e. the group labelled FAE(X), in this study.

Several recent studies have focused on damage caused to the brain's neurochemical system and its implications for brain development and function using
animal models of prenatal alcohol exposure. For example, Shen, Hannigan, and Kapatos (1999) found prenatal alcohol exposure in a binge-like manner reduced the number of spontaneously activated dopamine neurons in subcortical structures (substantia nigra and ventral tegmental area) of a rat but not the total number of neurons. The substantia nigra and ventral tegmental area are two major subcortical regions involved in supplying dopamine to frontal cortex structures. Prenatal alcohol exposure in a binge-like manner has also been shown to significantly alter other important neurotransmitters, such as γ-aminobutyric-acid (GABA) and glutamate, which are fundamental in the autoregulation of the dopamine system (Shen et al., 1999) and are necessary for normal prenatal brain development (Ikonomidou et al., 2000).

These data also suggest that women who drink in a "binge-like" manner during any trimester cause damage to their unborn child's developing brain each time such a binge occurs, despite the fact that they are likely not considered to be heavy drinkers or alcoholic. Binge drinking is a concern as it is estimated to occur in 3% of women pregnant at a given time (Serdula et al., 1991).

In addition to maternal factors, fetal factors such as genetic vulnerability to prenatal alcohol exposure also appear to influence the severity of damage caused by prenatal alcohol exposure (Coles, 1994). For example, a study of dizygotic twins born to alcoholic mothers found substantial differences in the severity of dysmorphology and CNS dysfunction (Streissguth & Dehaene, 1993). In addition, a study of cardiac deficit in animals exposed to alcohol prenatally found that embryos have a varying capacity to repair and recover from early neural losses (Caviness & Smith, 2000). These authors concluded that genetic background strongly modulates the effects of prenatal alcohol exposure as embryos have a varying capacity to repair and recover from early neural losses. Taken together, these findings indicate that in addition to differences in the fetal environment, there are also genetically determined differences in the ability of a fetus to tolerate exposure to alcohol.
Summary

Animal studies have shown that prenatal alcohol exposure causes major damage to a developing fetus. In contrast to the dysmorphology that is a visible result of heavy first trimester exposure to alcohol, lower levels of alcohol throughout pregnancy damage the prenatal brain. There often are no externally visible markers to accompany this brain damage. Well-controlled studies have demonstrated that alcohol exposure during any prenatal trimester can result in significant neuron loss and alterations in the migration patterns and functional circuity of neurons in all brain regions. In addition, some brain regions (e.g., cerebellum) and some neuron populations (e.g., Purkinje) are particularly vulnerable to alcohol exposure, and binge drinking is more harmful than a larger dose consumed over a longer period of time. Since neuron death and altered circuitry have profound effects on brain functioning, neurobehavioural deficits are one of the most devastating consequences of prenatal alcohol exposure. This highlights the importance of further research examining the magnitude and specificity of CNS dysfunction in individuals with a history of excessive prenatal alcohol exposure.

Diagnostic Subgroups

Fetal alcohol syndrome represents the extreme end of the continuum of physical disability caused by excessive maternal alcohol use during pregnancy (Streissguth, Aase, Claren, Randels, LaDue, & Smith, 1991). This syndrome is associated with a constellation of physical, growth, and CNS abnormalities (Sokol & Claren, 1989). As predicted by principles of teratology there is also a large group of individuals who do not meet the full physical criteria for FAS but still suffer from significant social and behavioural deficits. These individuals have typically been given the "clinical label" of fetal alcohol effect (FAE).

Recently, the IOM (Stratton et al., 1996) proposed a revised scheme for classification and diagnosis of the spectrum of conditions related to prenatal alcohol exposure. The IOM committee recommended four major diagnostic categories: (1) fetal alcohol syndrome (FAS), with or without a confirmed history of maternal alcohol
exposure, requiring evidence of facial dysmorphology, growth retardation, and CNS
dysfunction; (2) partial FAS (pFAS) requiring a confirmed history of prenatal alcohol
exposure, facial dysmorphology, and either growth retardation or CNS abnormalities; (3)
alcohol-related neurodevelopmental disorder (ARND) requiring a confirmed history of
prenatal alcohol exposure and evidence of CNS abnormalities; and (4) alcohol-related
birth defects (ARBD) to denote the presence of congenital anomalies (e.g., cardiac,
skeletal, renal, ocular, auditory) known to be associated with a history of prenatal alcohol
exposure. A description of the history and current use of the terms FAS, FAE, pFAS,
ARND, and ARBD follows.
Fetal Alcohol Syndrome

Diagnostic Criteria. Several years after FAS was described as a recognizable birth
defect syndrome the Fetal Alcohol Study Group of the Research Society on Alcoholism
(RSA) published a preliminary definition of FAS (Rosett, 1980). Upon establishing
consensus in 1989, this group published revised diagnostic criteria for FAS that have
substantially increased the comparability of research and clinical data across sites (Sokol
& Clarren, 1989). As more clinical and research information becomes available, this type
of redefinition of criteria is common in the establishment of birth defect syndromes such
as FAS. In 1989 the Fetal Alcohol Study Group of the RSA proposed that in order to
make a diagnosis of FAS an individual must exhibit signs of abnormality in each of the
three classic teratogenic domains (i.e., physical malformations, growth deficiency, CNS
dysfunction) (Sokol & Clarren, 1989). Physical malformations were defined as facial
dysmorphology including short palpebral fissures (i.e., short eye openings), flat midface,
smooth philtrum (i.e., unusually small or flat ridges in the area between the nose and
mouth), thin upper lip, and a small jaw. Other facial features commonly found in FAS are
epicanthal folds (i.e., small fold of skin covering inner corner of eye), flat nasal bridge,
and minor ear anomalies (Streissguth et al., 1994). Criteria for growth retardation were
defined as pre- or postnatal weight and/or height below the 10th percentile. Criteria for
central nervous system involvement included neurological abnormality, developmental
delay, behavioural dysfunction or deficit, intellectual impairment and/or structural abnormalities, such as microcephaly (head circumference below the 3rd percentile) or brain malformations found on imaging or autopsy (Sokol & Clarren, 1989, p. 598).

It is now known that the severe effects of prenatal alcohol exposure that are seen in individuals with FAS, such as craniofacial deformities and mental retardation, occur only after exposure to large amounts of alcohol (Jacobson & Jacobson, 1994). For example, Sokol, Ager, and Martier (1988) estimate that at the time of conception most mothers who will go on to give birth to infants with FAS drink approximately 42 standard drinks (21 ounces of absolute alcohol) per week. Even at this high consumption level not all offspring will exhibit sufficient abnormalities to meet the criteria for FAS (Sokol et al., 1986). Similarly, Abel (1985) estimates that only one-third of children born to alcoholic mothers are FAS while the other children are often classified as FAE. The amount of alcohol that must be consumed in order to produce FAS or other alcohol related conditions is not known due to the complexity of the factors associated with timing, dose, and conditions of exposure as previously discussed (Coles, 1994).

Reliability and Validity of Dyshmorphism Criteria. Abel, Martier, Kruger, Ager, and Sokol (1993) conducted an investigation of the reliability of diagnostic criteria for facial dysmorphology. They found that both medical providers (obstetricians, pediatricians) and biomedical researchers (other clinicians and researchers specializing in the field of developmental teratology) could reliably and accurately identify the facial dysmorphism associated with FAS. Participants in this study were given photos of 64 infants whose mothers were known to have consumed a wide range of alcohol from none to large amounts. Of the 64 infants, 9 had been clinically diagnosed as having FAS using the RSA guidelines (Sokol & Clarren, 1989). Participants were asked to rate each photo using the five-point rating scale. These ratings were: (1) FAE, (2) probable FAE, (3) possible FAE, (4) unusual features but not FAE, (5) normal (Abel et al., 1993). In this scale a designation of FAE signifies that facial features are consistent with a diagnosis of FAS. The term FAS is not used because the other domains necessary for a diagnosis
were not formally assessed in this study. These data provide support for the assertion that the facial dysmorphology associated with FAS and FAE be reliably identified by professionals in this area.

In order to improve the clinical validity and consistency of the assessment of facial dysmorphology across clinical and research setting, Astley and Clarren (1995) evaluated the validity of the dysmorphology criteria of FAS using a quantitative screening tool. Astley and Clarren (1995) assert that an accurate assessment of facial dysmorphology in patients with a history of excessive prenatal alcohol exposure is best identified by a physician trained in the assessment of dysmorphology using a qualitative "gestalt approach." The purpose of their study was to derive a quantitative case definition of the "facial phenotype" associated with FAS using the gestalt diagnosis of an expert dysmorphologist as the standard of comparison. A "facial phenotype" refers to the pattern of facial characteristics that are the result of an interaction between an individual’s genetic characteristics or genotype and the conditions of their prenatal environment (e.g., exposure to excessive amount of maternal alcohol).

Astley and Clarren (1995) included all the patients 10 years of age and younger (N = 194) seen in the FAS Clinic at the University of Washington with a history of prenatal exposure to alcohol. Patients were classified into 1 of the following 4 categories. FAS was defined as reported in utero alcohol exposure, CNS dysfunction, facial dysmorphology, with or without documented growth deficiency. Atypical fetal alcohol syndrome (AFAS) was defined as reported in utero alcohol exposure, CNS dysfunction, mild facial dysmorphology, with or without documented growth retardation. Partial fetal alcohol effects (PFAE) was defined as reported in utero alcohol exposure, CNS dysfunction, absence of facial dysmorphology, with or without growth retardation. The "Other" category was defined as in utero alcohol exposure reported or suspected, but no diagnosis of FAS, AFAS, or PFAE had been made because of the absence of both dysmorphology and CNS dysfunction. There were also three patients with syndrome diagnosis not related to prenatal alcohol exposure (i.e., Marfan syndrome, William’s syndrome, and Schprintzen’s syndrome). The above classification scheme served as the
standard or true classifications from which to compare the predicted classifications generated by the screening tool.

The study population (N = 194) was divided into two groups balanced on gender, age at examination, race, diagnosis, and date of examination. Group 1 was used to identify the most differentiating feature(s), and group 2 was used to validate the differentiating capability of the feature(s). A discriminate function analysis using stepwise variable selection identified smooth philtrum, thin upper lip, and short palpebral fissures as the cluster of features that best differentiated children with FAS/AFAS from those with PFAE or the "Other" classification. Using an equation derived from this analysis a cut-off score was established to evaluate the sensitivity and specificity of the screening tool. Sensitivity refers to how accurate a procedure is in giving a positive screening result when an individual has the condition being evaluated. Specificity refers to how accurate the screening tool is in giving a negative result when the individual does not have the condition of interest. The cut-off score used by Astley and Clarren (1995) classified FAS/AFAS with 100% sensitivity (39 of 39 correctly classified as having FAS/AFAS - true positive) and 89% specificity (138 of 155 correctly classified as not having FAS/AFAS - true negatives). Seventeen of the 194 patients (9%) were classified as false positive. Twelve of the 17 false-positive classifications (71%) had a true classification of PFAE. Misclassification was not associated with race, gender, or age. All three of the patients with an identified syndrome that was not related to prenatal alcohol exposure were correctly screened as not having FAS/AFAS (Astley and Clarren, 1995).
To further test the ability of their screening tool to differentiate between FAS and other syndromes with similar facial phenotypes, Astley and Clarren (1996) conducted a discriminative analysis that included 126 individuals with FAS, AFAS, or PFAE, and 10 individuals with the following syndromes: fetal hydantoin syndrome, Bubowitz syndrome, Noonan syndrome, Turner syndrome, Bloom syndrome, Aarskog syndrome, and Opitz syndrome. Facial photos of the 10 additional subjects were obtained from syndrome diagnostic textbooks. The ages of the syndrome subjects ranged from 1 to 20 years with a distribution comparable to that of the 126 subjects with FAS, AFAS, and PFAE.

Astley and Clarren (1996) found that the quantitative screening tool correctly identified all individuals as not having the phenotype of FAS with the exception of the individual with fetal hydantoin syndrome. They concluded that their screening tool effectively separated the dysmorphic features of FAS from normal and also from many, but not necessarily all, other syndromes. Astley and Clarren also assert that although no two individuals with FAS necessarily have identical facial features, all have the overall gestalt, and to define the gestalt, one must use multivariate as opposed to a univariate approach. Although Astley and Clarren have developed a methodology that uses quantified measures of facial anomalies to discriminate children with FAS/AFAS from children with PFAE and other conditions related to prenatal alcohol exposure, a similar study evaluating the CNS dysfunction associated with FAS and alcohol related conditions is needed.

Reliability of Growth Criteria. Habbick et al. (1998) evaluated the test-retest reliability or the temporal stability of growth measures (i.e., height, weight) from early childhood (mean age = 5 years) to early adulthood (mean age = 19 years) in a group of 26 individuals with FAS. They reported no significant change in height z-scores from early childhood to early adulthood with group means being -2.16 standard deviation units [and] -2.11, respectively. There was, however, a significant change in weight z-scores over time from -2.1 to -1.14. Habbick et al. concluded that short stature could still be used as a diagnostic marker of growth retardation in early adulthood. However, the
weight gain seen in many individuals with FAS excludes a lean build as a useful diagnostic criteria in early adulthood. They did however note that generalizations of their results to the entire FAS population should be done with caution because the subgroup of 26 individuals with paired growth measurements in their sample were significantly shorter than the mean height exhibited by the full cohort of 207 patients with FAS from which their sample was drawn. Habbick et al. also noted that catch-up growth has been reported in several studies (e.g., Majewski & Goecke, 1979; Lemoine et al., 1968; Spohr, Willms, & Steinhausen, 1993) which included milder examples of FAS.

Habbick et al. (1998) also evaluated the temporal stability of head circumference measures from early childhood (mean age = 2.79 years) to early adulthood (mean age = 17.37 years) in a subgroup of 16 individuals. The mean head circumference z-scores for these two groups was -3.13 and -2.63 respectively (Habbick et al., 1998). They concluded that the mean head circumference z-score of their early adulthood sample was still well below average. They also noted that the mean head circumference of their young adult sample (z = -2.63) was substantially lower than the mean head circumference of a group of 32 adolescents with FAS (z = -1.9) reported by Streissguth et al. (1991). Habbick et al. also described the results of a 10 year follow-up study by Spohr et al. (1993) which evaluated head circumference in a group of 60 patients diagnosed as FAS in infancy and childhood. The mean age at the initial assessment was 3 years and age at follow-up was 14 years. They "found that 46 of 60 patients continued to have a head circumference below the 10th percentile, compared with 56 at initial assessment" (as cited in Habbick et al., 1998, p. 1314).

Reliability of CNS Dysfunction Criteria. Streissguth, Randel and Smith (1991) evaluated the test-retest or temporal stability of IQ measures over a 5 year period. They found the average IQ of adolescents with FAS and FAE to be stable over time. The finding of stable IQ measures from childhood to adolescents has been replicated by Spohr et al. (1994) and Nanson et al. (1995).
Fetal Alcohol Effects

FAE is a general term often used to describe individuals who have been exposed to considerable amounts of alcohol in utero but do not exhibit anomalies in all three domains required for a diagnosis of FAS. As previously discussed, the social and behavioural difficulties associated with FAE are often just as severe or worse than those associated with FAS. In contrast to FAS, which is a recognized diagnosis with an established criteria set, FAE is a clinical label without established criteria. One of the factors contributing to the existing confusion and controversy regarding the term FAE is that it is being defined by clinicians and researchers in a variety of ways. Furthermore, although Hablick et al. (1998) evaluated the reliability of growth retardation criteria in patients with FAS and Streissguth, Randels and Smith (1991) evaluated the reliability of CNS dysfunction criteria in adolescents with FAS or FAE, a study evaluating the level and specificity of CNS dysfunction criteria across clinical subgroups with a history of excessive prenatal alcohol exposure (e.g., FAS and FAE) had not been conducted prior to this study.

Institute of Medicine Diagnostic Scheme

In response to the seriousness and magnitude of the social and behavioural disabilities associated with heavy maternal alcohol consumption during pregnancy, the U.S. congress mandated that the IOM of the National Academy of Sciences conduct a study of FAS and related conditions. Given the existing controversy and confusion regarding a definition for patients affected by prenatal alcohol exposure who did not meet all the criteria for a diagnosis of FAS, one of the main charges given to this committee was to evaluate existing diagnostic criteria and to formulate the best possible diagnostic guidelines (Stratton et al., 1996). The committee recommended the four major diagnostic categories discussed above, namely, fetal alcohol syndrome (FAS), partial FAS (pFAS), alcohol-related neurodevelopmental disorder (ARND), and alcohol-related birth defects (ARBD). With the accumulation of clinical and research information this type of refinement of diagnostic categories and criteria is common in the establishment of birth defect syndromes such as Autism, Down's Syndrome, and FAS.
The Institute of Medicine committee (Stratton et al., 1996) also made several key recommendations to guide further research related to prenatal alcohol exposure conditions. They recommended that additional research be conducted (1) to evaluate the utility, reliability, and validity of their diagnostic scheme; (2) to investigate differences in the expression and specificity of behavioural and cognitive deficits in FAS and ARND; (3) to identify relationships between structural and functional brain abnormalities; and (4) to assess the clinical expression of FAS and ARND syndromes.

Summary

The purpose of a classification system is to provide an organizational scheme that will give order to clinical experience, and to orient research seeking to further our understanding of etiology, pathology, and clinical manifestation (Millon, 1991). Current diagnostic guidelines have made a significant contribution towards increasing our knowledge of the dysmorphology and growth retardation associated with FAS. More research is needed in order to establish consensus regarding diagnostic criteria for the large number of individuals that are currently given the clinical label of FAE or the diagnosis of partial FAS or ARND. In order to improve the clinical validity and consistency of the assessment of facial dysmorphology across clinical and research settings, Astley and Clareen (1995) evaluated systematically the empirical validity of the dysmorphology criteria associated with FAS and related conditions using a quantitative screening tool. A similar study evaluating the magnitude and specificity of CNS dysfunction associated with FAS and FAE subgroups was needed. Measures of attention are well suited for this task as they have been found to be sensitive indicators of the CNS dysfunction resulting from both limited and excessive prenatal alcohol exposure (Streissguth et al., 1994).

Neurobehavioural Deficits

Investigations of the neurobehavioural deficits associated with prenatal alcohol exposure are important for three major reasons: (1) they are functionally more debilitating than the difficulties associated with reduced growth or facial dysmorphology; (2) they
affect a large number of children who do not meet the full criteria for FAS; and (3) they are the most sensitive indicators of the brain damage caused by prenatal alcohol exposure. This section provides a brief overview of neuropsychological and behavioural deficits exhibited by individuals with FAS and FAE during major stages of development, and it emphasizes findings regarding neuropsychological and behavioural attention deficits.

Two major types of studies have been used to understand the long-term neurobehavioural consequences of prenatal alcohol exposure. Retrospective studies of children clinically identified as FAS and/or FAE have begun to illuminate the severity, breadth, and variability of the deficits seen at the extreme end of the "affectedness" continuum. Prospective longitudinal studies of the offspring of "social drinkers" have been used to evaluate the subtle effects of the full spectrum of prenatal alcohol exposure.

Streissguth and colleagues have published several reports summarizing findings from a prospective longitudinal study of a birth cohort of 500 offspring evaluating the effects of social drinking during pregnancy. Possible participants were identified via mid-pregnancy interviews with approximately 1500 women in Seattle Washington (Streissguth, Barr, Sampson, & Bookstein, 1994). These interviews were conducted in 1974 and 1975 when the damaging effects of prenatal alcohol exposure was not common knowledge and thus women had less reason to minimize their reported alcohol consumption than they would have in the 1990's.

The follow-up cohort of approximately 500 infants was selected at delivery based on information obtained during mid-pregnancy interviews regarding maternal drinking and smoking. This sample was stratified and over sampled for heavier maternal alcohol use and smoking. This stratification of maternal alcohol use and smoking levels facilitated the separation of the effects of alcohol from those of smoking, and it was used to include all the infants more heavily exposed to alcohol.

The self-reported alcohol consumption by mothers during a mid-pregnancy interview in 1974 and 1975 (N = 1500), before women knew that alcohol use during pregnancy was inadvisable, indicated that 80% of women used some alcohol during pregnancy. The stratified cohort contained mothers who abstained from alcohol and
mothers who were infrequent, light, moderate, and heavy drinkers. (Streissguth et al., 1994).

At mid-pregnancy interviews, 5% of the mother who drank reported alcohol consumption averaging two or more drinks per day, and 17% reported engaging in at least on instance of “binge” drinking (five or more drinks on one occasion). Fewer than 1% reported major problems with alcohol use (Carmichael-Olson, Sampson, Barr, Streissguth, & Bookstein, 1992).

The aim of the Seattle 500 study has been to detect and understand the magnitude and specificity of neurobehavioural deficits associated with alcohol consumption levels generally less than the levels necessary to cause the constellation of deficits associated with a diagnosis of FAS.

An overview follows of the neurobehavioural deficits reported in retrospective studies of children with FAS or FAE, and the deficits reported in prospective studies in the offspring of a spectrum of social drinker.

New Born and Infancy

At birth, infants with FAS are clinically described as being hypotonic (diminished muscle tone), hyperexcitable and tremulous (Driscoll, Streissguth, & Riley, 1990). They generally have feeding difficulties due to distractibility and a weak suck while drinking (Streissguth, 1986). They also tend to have difficulties with state regulation (frequent alternations between an awake and drowsy state) (Streissguth, Barr, Martin, 1983), abnormal EEG’s (Ioffe & Chernick, 1990), and reduced reaction times to novel stimuli (Jacobson, Jacobson, & Sokol, 1994). These are indicators of early CNS dysfunction that are not fully explained by the alcohol withdrawal symptoms shown by some infants heavily exposed to alcohol during the third trimester.

Studies that have evaluated infants with FAS during the first two years of life have found that they often exhibit feeding difficulties, delays in overall level of development, frequent otitis media, and cardiac problems (Stratton et al., 1996). They also often continue to exhibit regulatory difficulties, such as difficulties with the regulation of arousal and emotions.
During infancy, the development of basic emotional regulation ability is foundational for emotional and social development in general (Crockenberge & Leerkes, 2000). More specifically, an infant’s ability to regulate emotion makes an important contribution in the development of a secure attachment relationship with a caregiver. Emotional regulation also contributes to the achievement of autonomy and mastery in the second and third years of life. Difficulties in this area are also related to emotion-related behaviour problems in latter years.

In a cohort of 500 infants followed in the Seattle prospective longitudinal study (Streissguth et al., 1983), infants had similar but milder difficulties to those seen in infants with FAS, even after controlling for a wide variety of potentially confounding variables (e.g., maternal nutrition, smoking, other drug use, maternal health, and postnatal home environment). Maternal nutrition was evaluated by obtaining information at mid-pregnancy regarding nutritional intake, eating habits, and vitamin supplements taken. Drug use was evaluated by obtaining information at mid-pregnancy regarding use of cigarettes/nicotine, caffeine, aspirin, acetaminophen, valium, marijuana, and other prescription and illegal drugs. Maternal health was evaluated by obtaining information at mid-pregnancy regarding illness and infection during pregnancy, mother’s weight at delivery, and other medical conditions. Postnatal home environment was evaluated by the person to which the infant was discharged from hospital after birth.

The 500 infants from the Seattle study exhibited an increased frequency of body tremors, a higher level of activity, and poor oral sucking pressure. They also had difficulties with state regulation and habituation (the ability to tune out redundant stimuli) which are basic CNS functions for a neonate (Streissguth et al., 1983).

A longitudinal prospective study by Jacobson and colleagues examined the effects of prenatal alcohol exposure in 480 economically disadvantaged, African-American infants in Detroit, during the first year of life. Mothers were recruited during their first visit to a prenatal clinic in a large inner-city maternity hospital. At each prenatal clinic visit, mothers were interviewed regarding their drinking on a day-by-day basis during the preceding 2 weeks. Moderate and heavy drinking women were over represented in the
sample by including all women who reported alcohol consumption at conception averaging at least one alcohol drink per day.

At 6.5 months of age, Jacobson, Jacobson, and Sokol (1994) found that reaction-time impairments were associated with prenatal alcohol exposure level. At 12 months of age, information processing difficulties were noted (Jacobson, Jacobson, Sokol, Martier, & Ager, 1993). The more alcohol an infant had been exposed to prenatally, the longer they took to turn their gaze to a novel photograph.

Streissguth et al. (1983) argued that findings from studies of infants exposed to even low levels of alcohol exposure reflect CNS dysfunction. They also note that CNS dysfunction is evident prior to the impact of the postnatal environment.

Pre-School

In the pre-school years children with FAS have clinically significant intellectual deficits as measured by standardized IQ tests even after controlling for parental socio-economic status (Janzen, Nanson, & Block, 1995). In this and previous studies FAS children also exhibited verbal (Streissguth, 1986), perceptual (Aronson, Kyllerman, Sabel, Sandin, & Olegard, 1985), and fine and gross motor deficits (Kyllerman, Aronson, Sabel, Karlberg, Sandin, & Olegard, 1985).

Pre-schoolers with FAS are typically described as hyperactive, distractible, impulsive, and unresponsive to verbal cautions (Streissguth, 1986). There is often a fondness of body contact, an insatiable demand for affection, and an absence of stranger anxiety (Streissguth, 1991).

The development of age appropriate stranger anxiety is believed to be dependent upon object permanence and the ability to retain mental a image of a caregiver (Crockenberg & Leerkes, 2000). This is thought to explain the development of stranger wariness and separation protest behaviour that typically emerges between 7 and 9 months of age. It is also viewed as marking the emergence of attachment with a caregiver.

This constellation of infant-parent emotional regulation characteristics presents significant challenges for the caregivers of pre-schoolers with FAS as there is limited stranger wariness and an insatiable demand for affection. Using Ainsworth’s (as cited in
Crockenberg & Leerkes, 2000) attachment classification system, these characteristics are consistent with an ambivalent insecure attachment pattern. This pattern is classically characterized by distress at a mother’s absence. Contact seeking at her return but a failure to be fully comforted. Displaced anger and resistance may also be exhibited upon a mother’s return.

Although pre-school children of social drinkers in the Seattle prospective study obtained IQ scores that were within the normal range, increased levels of reported maternal alcohol consumption were significantly related to lower scores on IQ, attention, and fine and gross motor measures (Streissguth, Barr, Sampson, Darby, & Martin, 1989; Barr, Streissguth, Darby, & Sampson, 1990). Attention was measured using an age appropriate computerized vigilance task that assesses the ability to Sustain visual attention to a stimulus that appears infrequently (Streissguth, Martin, Barr, Sandman, Kirchner, & Darby, 1984).

School-Aged Children

School-aged children with FAS are clinically described as having attention, memory, language, learning, fine motor, and gross motor deficits (Streissguth, 1991). On a social level they often misinterpret interpersonal cues (e.g., stand too close, talk too loud); have difficulty learning from normal experience; and, despite a superficially friendly manner, they often have few friends as they grow older.

Between 6 and 13 years of age children with FAS and FAE continue to display impaired levels of global intellectual functioning with the IQ of FAS groups being significantly lower than the FAE groups (Conry, 1990). Conry defined FAE as abnormal signs in two of the three FAS diagnostic domains. In addition to IQ studies, several researchers have compared the attention abilities of a combined group of FAS/FAE children with a clinical comparison group (i.e., attention deficit and hyperactivity disorder - ADHD) or a control group.

Nanson and Hiscock (1990) compared the attention deficits of FAS/FAE (n = 20), ADHD (n = 20), and normal children (n = 20) based upon parent report, sustained attention, and reaction time tasks. FAE was defined as abnormal signs in two of three
FAS diagnostic categories. Nanson and Hiscock (1990) found that both the FAS/FAE and ADHD groups were considered by their parents to be hyperactive and inattentive, and that both groups displayed similar deficits on attention demanding tasks despite differences in IQ level.

Coles et al. (1994) compared the behavioural and neurocognitive attention deficits of FAS/FAE \( n = 23 \) and ADHD \( n = 26 \) children that were matched on IQ, SES, and race. Coles et al. did not indicate how FAE was defined in their study. Neurocognitive aspects of attention were measured using Mirsky's (1989) four factor (i.e., focus, Sustain, Encode, shift) clinical assessment model. This attention model is based upon both the results of factor analysis studies and existing knowledge of functional neuroanatomy. Using discriminant function analyses they found little overlap between these two groups on either behavioural or neurocognitive measures. The results of this study indicated that children with FAS/FAE were able to Focus and Sustain attention but had difficulties with Encode and Shift aspects. These attention factors require the ability to hold information in working memory and use new information to solve problems (Mirsky, Fantie, Tatman, 1995). In contrast, children with ADHD had difficulties with Focus and Sustained aspects of attention and the use of Ritalin helped them to maintain attention appropriately. Coles et al. (1994) concluded that the attention deficits associated with FAS/FAE might be distinct from those seen in children with ADHD.

Kodituwakku, Handmaker, Cutler, Weathersby, and Handmaker (1995) have reported similar results to those obtained by Coles et al. (1994). They compared the attention abilities of a group of high functioning FAS/FAE subjects \( n = 10 \) who did not differ from controls \( n = 10 \) on a standardized vocabulary test. FAE was defined according to the definition proposed by Rosett (1980) which is "the absence of the full FAS" (p. 119). Kodituwakku et al (1995) found that in comparison with controls the FAS/FAE group had difficulty on tasks that required the manipulation of information in working memory and planning to solve a problem, while both groups performed equally well on tasks involving rule learning and response inhibition.
The school-aged children in the Seattle prospective study had similar but milder deficits to those seen in school-aged children with FAS or FAE. During the summer following grade 1 when the children of the Seattle prospective cohort of social drinkers (n ≈ 500) were 7.5 years of age, IQ and neuropsychological functions were again significantly related to level of reported prenatal alcohol exposure using the partial least squares (PLS) multivariate technique (Streissguth, Barr, Sampson, & Bookstein, 1994). Interestingly, however, only a few of the IQ subtests (i.e., Arithmetic, Digit Span, Block Design) were significantly associated with maternal report of alcohol consumption. Furthermore, findings from a battery of neuropsychological tests indicated small but statistically significant deficits in attention and memory across both verbal and visual domains as well as difficulties with problem solving and perceptual motor functions. It is important to note that the attention deficits exhibited by pre-schoolers at 4 years of age continued to be manifested at 7 years using age appropriate tasks.

Adolescents and Adults

**Findings from FAS/FAE Studies.** Although FAS was identified as a syndrome over 20 years ago, studies have only recently focused on neurobehavioural functioning in adolescents. To a large extent this reflects the fact that relatively few clinical or research centers have followed FAS or FAE children longitudinally into adolescence. Adolescents with FAS or FAE are clinically described as having attention, memory, learning, and behaviour problems, as well as difficulties with judgement, comprehension, abstraction, and age appropriate activities of daily living (Streissguth et al., 1991).

In 1991 Streissguth, Aase, et al. published findings from the first empirical study of the long-term neurobehavioural sequelae of FAS and FAE in adolescents and adults focusing upon IQ and academic achievement. One year later Streissguth, Sampson, and Barr (1992) published an additional report on this cohort that was expanded from 42 to 82 subjects. This sample consisted of subjects between the ages of 12 and 42 years of age. FAE was defined as in utero exposure to alcohol without sufficient features for a firm diagnosis of FAS. The average IQ for the FAS group was 66 (n = 56) with a
standard deviation of 15. The average IQ for the FAE group (n = 26) was 80 with a standard deviation of 17. There was a significant difference between the IQ scores of the FAS and FAE samples, and a large range of scores within both samples.

In an evaluation of academic achievement, Streissguth, Sampson, and Barr (1989) reported that adolescents and adults with FAS (n = 67) and FAE (n = 22) have severe long-term deficits in reading, spelling, and arithmetic. They noted that, although the standardized achievement scores from the Wide Range Achievement Test - Revised (WRAT-R) for the FAS group were comparable to their average level of intellectual functioning, the arithmetic subtest score for the FAE group was lower than one would predict from their IQ score (67 versus 80, respectively). The arithmetic score of the FAE group was also comparable to that obtained by the FAS group (67 versus 62, respectively). Since arithmetic skills are heavily dependent upon basic cognitive functions such as attention, Streissguth et al. (1989) suggested that both FAS and FAE groups may have similar attention deficits. Although this is an interesting observation that has important implications, a comparison based upon direct measurement of attention would provide a much better understanding of potential similarities and differences between FAS and FAE populations. A study of this nature had not been published prior to this study.

Streissguth and colleagues have conducted several exploratory neuropsychological studies of adolescents and adults with FAS. Using norm-referenced measures, Kerns, Don, Mateer and Streissguth (1997) found that nonretarded adolescents and adults with FAS (n = 16) had difficulties on aspects of attention, memory, and executive functioning. Carmichael-Olson, Feldman, Streissguth, Sampson, and Bookstein (1998) reported marked individual diversity in the attention, memory and executive functioning profiles of nonretarded adolescents with FAS (n = 9) despite IQ scores that were within the normal range. In addition, when compared to a cohort comparison group (n = 174) that were either lightly or not exposed to alcohol prenatally, the FAS group exhibited greater intraindividual response speed variability on a CPT. Carmichael-Olson et al. (1998) interpreted this finding as a reflection of “micro-lapses in attention”. 
Conner, Streissguth, Sampson, Bookstein, and Bar (1999) evaluated auditory and visual attention in a group of nonretarded adults with FAS or FAE ($n = 11$). When compared to an age matched control group ($n = 9$), the adults with FAS/E had greater attention deficits on both auditory and visual attention tasks. The largest discrepancy between these two groups was found on the auditory attention task. Conner et al. (1999) noted that there was a subgroup of 5 FAS/E adults who exhibited exceptionally high scores on the SD of RT measure from the auditory CPT. They suggested that there likely was heterogeneity within the FAS/E subgroup in that some individuals with FAS/E have a distinct attention deficit while others do not.

Studies comparing FAS and FAE subgroups. After the research questions, hypotheses and methods for this study were finalized, Mattson and colleagues reported on a series of studies directly comparing the neuropsychological functioning of FAS and FAE subgroups. Due to confusion associated with the term FAE, these researchers used the label of prenatal exposure to alcohol (PEA) instead of FAE. PEA was defined as exposure to high levels of alcohol prenatally without meeting criteria for a diagnosis of FAS. These individuals "displayed few or none of the facial features associated with FAS and did not show evidence of growth retardation" (Mattson, Riley, Gramling, Delis, & Jones, 1998, p. 146). The definition of this PEA group is similar to the criteria for ARND established by the IOM (1996).

Mattson, Riley, Gramling, Delis, and Jones (1997) assessed the general level of intellectual functioning in FAS, PEA, and normal children 4 to 16 years of age. They found that in comparison to a normal control group ($n = 47$) both the FAS ($n = 34$) and the PEA ($n = 13$) groups displayed significant deficits in overall IQ as well as deficits on most subtest scores. Mattson, Riley, Gramling, et al. (1997) concluded that when there is a documented history of excessive prenatal alcohol exposure, absence of the physical features of FAS does not imply the absence of an intellectual deficit.

Mattson et al., (1998) assessed the general neuropsychological functioning in FAS, PAE, and normal children 5 to 16 years of age. They found that when compared to
a normal control group (n = 25), both the FAS (n = 15) and PEA (n = 10) groups were impaired on tests of confrontational naming, verbal memory and learning, and fine motor speed and dexterity. The FAS and PAE groups also had a “strikingly similar” pattern of performance across the neuropsychological domains assessed. Mattson et al. (1998) concluded that excessive prenatal alcohol exposure causes neurocognitive deficits regardless of whether or not a child exhibits the pattern of physical features associated with FAS.

Mattson, Goodman, Caine, Delis, and Riley (1999) conducted a focused assessment of executive functioning in FAS, PAE, and normal children 8 to 16 years of age. They found that when compared to a normal control group (n = 10), both the FAS (n = 10) and the PEA (n = 12) groups exhibited deficits on measures of planning ability, cognitive flexibility, selective inhibition, and conceptual reasoning. The performance of FAS and PEA groups did not differ on most measures. Mattson, and Goodman et al. (1999) concluded that executive function impairments in general are related to a history of excessive prenatal alcohol exposure, and not specifically to the dysmorphology or growth retardation features associated with a diagnosis of FAS. They also noted that their findings were consistent with parent reports of behavioural regulation deficits and a disproportional reduction in the frontal-subcortical system in children with a history of excessive prenatal alcohol exposure. Brain imaging has found the basal ganglia to be disproportionately reduced by prenatal alcohol exposure, and this structure is a major component in the frontal-subcortical circuitry involved in the modulation of executive functioning (Cummings, 1993).

Mattson and Riley (1999) conducted an assessment of implicit and explicit memory in order to assess neurocognitive functions known to be associated with subcortical dysfunction. They found that when compared to the normal control group (n = 21), children with a history of excessive prenatal alcohol exposure (FAS/PEA; n = 21) had impaired explicit memory while implicit memory was intact. Mattson and Riley (1999) suggested that this pattern of impaired explicit and intact implicit memory was consistent with subcortical dysfunction with a relative sparing of cortical functions.
In support of this position they referred to a similar pattern of known memory and brain dysfunction in patients with Huntington's disease.

Mattson and Riley (2000) also evaluated the parent ratings of behaviour in FAS and PAE children 4 to 16 years of age using the Child Behaviour Checklist (CBCL; Achenbach, 1991). They found that there were no differences between the FAS (n = 35) and PEA (n = 20) children on any of the eight behaviour problem scales examined. They also found that when compared to a control group matched for VIQ and SES (n = 35), a combined FAS/PEA group (n = 55) had greater difficulties on seven of the eight problem behaviour scales. Differences were not observed on the somatic complaint subscale. The severity of problem behaviours of the FAS/PEA group were within the clinically impaired range on Attention, Aggression, and Social Problems scales. Mattson and Riley (2000) concluded that the behaviour problems exhibited by children with a history of excessive prenatal alcohol exposure are not explained by intellectual level, socioeconomic factors, or the presence of physical dysmorphology.

In summary, the recent series of studies by Mattson and colleagues lead to the following two findings. First, a history of excessive prenatal alcohol exposure is associated with significant neurocognitive and neurobehavioural deficits regardless of whether or not the physical features of FAS are present. Second, FAS and PEA groups have similar patterns of performance on implicit and explicit memory, confrontational naming, executive functions, and behaviour problems. Based upon their findings, Mattson and colleagues stressed the importance of obtaining information regarding alcohol exposure during pregnancy. Given the nature and severity of the neurocognitive and neurobehavioural deficits exhibited by these children, they emphasized the importance of professional assessment at an early age in order to facilitate the implementation of habilitative strategies.

**Social, Legal and Mental Health Problems.** In 1997 Streissguth, Barr, Kogan, and Bookstein published findings from the first empirical study evaluating the social, legal, and mental health difficulties in individuals with FAS or FAE. FAS was defined
using the RSA guidelines while FAE was defined as a clear history of prenatal alcohol exposure and CNS dysfunction, without the manifestation of all the physical features of FAS. This sample included 415 subjects between 6 and 51 years of age (6 to 11 years, n = 162; 12 to 20 years, n = 163; 21 to 51 years, n = 90). Information regarding social and behavioural difficulties was gathered during interviews with available caretakers/informants using a structured interview that was developed for this study. Six major areas of social and behavioural difficulties were evaluated.

Mental Health Problems [were] defined as ever having gone to a psychotherapist or counsellor for a mental health problem or having any one of a long list of mental health problems. ... [Mental health problems were] experienced by over 90% of the full sample (6 and over).

Disrupted School Experience, defined as having been suspended or expelled from school or having dropped out of school, was experienced by 60% of the patients (12 and over).

Trouble With the Law, defined as ever having been in trouble with authorities, charged, or convicted of a crime, was experienced by 60% of the patients (12 and over).

Confinement, including inpatient treatment for mental health problems or alcohol/drug problems, or ever having been incarcerated for a crime, was experienced by about 50% of the patients (12 and over).

Inappropriate Sexual Behaviour, including having been reported to have repeated problems with one or more of 10 inappropriate sexual behaviours or ever having been sentenced to a sexual offenders' treatment program, was noted for about 50% of the patients (12 and over). (Streissguth et al., 1997, p. 33-34).

Alcohol/Drug Problems, defined as having been in treatment for an alcohol or drug problem or as having alcohol and/or drug abuse problems, was noted for about 30% of the patients (12 and over). (Streissguth et al., 1997, p. 33-34).

This study also reported that, compared to individuals with FAS, those with FAE had higher rates of disrupted school experience, trouble with the law, confinement, inappropriate sexual behaviour, and alcohol/drug problems, and comparable rates of
mental health problems. Specifics regarding the percentage of FAS and FAE individuals exhibiting these social and behavioural difficulties were not reported.

In addition to evaluating social and behavioural difficulties, Streissguth et al., (1997) also assessed risk and protective factors that might alter the rates of occurrence of social and behavioural difficulties. Risk and protective factors were evaluated in terms of odds ratios or a series of univariate logistic regressions. A low IQ score (70 and below) was found to be a protective factor for disrupted school experience, trouble with the law, confinement, and alcohol and drug problems. IQ level, however, had little relationship to mental health problems or inappropriate sexual behaviour. In addition, a diagnosis before 6 years of age was a strong protective factor for all social and behavioural difficulties except mental health problems.

In order to provide a more direct evaluation of the criminal offenses committed by individuals with FAS and FAE, Fast, Conry and Loock (1999) investigated the prevalence of FAS/FAE among youth 12 to 18 years of age who had been convicted of a criminal offense and had been sent for psychiatric and psychological assessment. Over a 1-year period they found a prevalence rate of FAS/FAE to be 23.3% in a single inpatient forensic assessment facility in British Columbia. Fast et al. (1999) concluded that youth with FAS/FAE were disproportionately represented in the juvenile justice system and that very few had been diagnosed (3%) despite the severity of associated learning and behavioural disabilities which have implications for all stages of the judicial and correctional system.

Findings from the Seattle Prospective Study. In contrast to the paucity of attention studies on adolescents with FAS or FAE, a systematic evaluation of attention was a major focus in the only existing evaluation of neurocognitive deficits in the offspring of social drinkers during adolescence (Streissguth et al., 1994). When the Seattle prospective cohort was 14 years of age, several tests measuring various components of attention and memory were administered. This data set involving 52 measures of attention and memory and 13 measures of alcohol exposure from
approximately 500 subjects. These data were analyzed using a multivariate technique referred to as a non-linear partial least squares (PLS) analysis. The multivariate analysis was developed by Streissguth and colleagues specifically to analyze data from their study.

The PLS procedure combines all the measures of alcohol exposure into one "composite dose measure," and determines which of the 52 outcome measures are most salient or influential in predicting adverse performance (Streissguth et al., 1994). The salience coefficients are proportional to correlation's between outcome variables and the composite dose measure. Streissguth et al. (1994) argued that in their study the PLS procedure was preferable to multiple regression in which adding or deleting predictor variables can substantially alter coefficients of predictors and make findings unreliable.

Data on possible confounding variables were obtained prospectively at the prenatal interview and all longitudinal assessment ages. The possible confounds assessed included multiple measures from each of the following seven categories: (1) maternal nutrition, (2) use of drugs other than alcohol during pregnancy, (3) socio-demographic and educational characteristics of the child's family, (4) mother-child interactions, (5) major life stresses in the child's household, (6) child accidents, hospitalizations and illnesses, and (7) educational experiences of the child (Streissguth et al., 1994). Given the methods used to control statistically for potential confounding variables, Streissguth et al. (1994) concluded that the neurocognitive results obtained in their study were not attributable to prenatal exposure to drugs other than alcohol (e.g., nicotine, marijuana, or other illegal drugs) or socio-demographic factors such as parental education.

Streissguth et al. (1994) found that measures of fluctuations in attention state and response inhibition had the largest association with maternal reports of prenatal alcohol exposure after covariate adjustment. Fluctuations in attentional state were observed on measures of individual reaction time variability on a tradition Continuous Performance Test (CPT). More specifically, Streissguth et al., (1994) found that the individual standard deviation of reaction time (SDRT) measure on all three conditions of the CPT (i.e., "X", "AX", and "Degraded X") were significantly associated with reported alcohol exposure (salience values were .27, .20, and .20 respectively). They suggested that the
more alcohol an adolescent was exposed to prenatally the more likely they are to exhibit a variable response rate on a Sustained attention task. Mirsky and Cardon (1962) suggested that inconsistencies in response speed are generally related to biological brain dysfunction and represent microlapses of attention.

Difficulties with response inhibition were exhibited as increased error and 'false alarm' rates on the more difficult subtests of the CPT and the Talland Letter Cancellation Test. The Talland Letter Cancellation Test requires individuals to scan rows of upper- and lower-case letters to find and cross out as many of an assigned target as possible in 60 seconds (Mirsky, Fantie, & Tatman, 1995, p. 23.). In the "Capital" condition individuals are asked to draw a line through all capital letters. In the "Space" condition individuals are asked to draw a line through the letter immediately before and after each double space while ignoring letter case. Finally, in the "Both" condition individuals are asked to draw a line through both all capital letters and the letter immediately before and after each double space (Mirsky, Fantie, & Tatman, 1995).

Streissguth et al., (1994) found that performance on the more complex "AX" condition of the CPT (i.e., false alarms) and the Both condition of the Talland Letter Cancellation Test (i.e., total correct) were highly associated with reported maternal alcohol use (.19 and -.25, respectively). They suggested that the more alcohol an adolescent was exposed to prenatally, the more difficulty they are likely to have withholding responses in the performance of tasks that require complex decision making.

A summary of IQ and attention findings from FAS, FAE, and the offspring of social drinkers are presented in Table 1.
### Table 1. Attention Deficits in FAS, FAE, and Offspring of Social Drinkers by Developmental Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>FAS &amp; FAE Retrospective</th>
<th>Offspring Social Drinkers Prospective&lt;sup&gt;9&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Infancy</td>
<td>State Regulation Diff.&lt;sup&gt;1&lt;/sup&gt; Habitation Diff.&lt;sup&gt;2&lt;/sup&gt; Hyperexcitable&lt;sup&gt;3&lt;/sup&gt; Distractable&lt;sup&gt;4&lt;/sup&gt;</td>
<td>State Regulation Diff.&lt;sup&gt;9&lt;/sup&gt; Habitation Diff.&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>Preschool</td>
<td>No Attention Studies</td>
<td>↓ Sustained Attention&lt;sup&gt;9&lt;/sup&gt;</td>
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<tr>
<td>School-Age</td>
<td>↓ Sustained Attention&lt;sup&gt;5&lt;/sup&gt; Hyperactivity&lt;sup&gt;5&lt;/sup&gt; Inattentive&lt;sup&gt;5&lt;/sup&gt; ↓ Shift Attention&lt;sup&gt;6,7&lt;/sup&gt; ↓ Encode Attention&lt;sup&gt;6,7&lt;/sup&gt;</td>
<td>↓ Sustained Attention&lt;sup&gt;9&lt;/sup&gt;</td>
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<tr>
<td>Adolescent</td>
<td>No Attention Studies</td>
<td>↓ Sustained Attention&lt;sup&gt;9&lt;/sup&gt; ↑ Response Variability ↓ Response Inhibition</td>
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1 Streissguth, Barr, & Martin (1983)  
2 Jacobson, Jacobson, & Sokol (1994)  
3 Driscoll, Streissguth, 1986)  
4 Streissguth, 1986)  
5 Nanson & Hiscock (1990)  
6 Coles et al. (1994)  
7 Kodituwakku et al. (1995)  
8 Streissguth et al. (1991)  
9 Streissguth, Barr, Sampson, & Bookstein (1994)
Summary

There is substantial evidence indicating that measures of attention are one of the most sensitive markers of the damage caused by both excessive and limited prenatal alcohol exposure (Conner et al. 1999; Streissguth et al., 1994). Clinically significant attention deficits are frequently found in individuals with FAS or FAE (Nanson & Hiscock, 1990; Mattson & Riley, 2000).

Although Mattson and colleagues evaluated memory, executive function, and behaviour problems in FAS and FAE groups, there had not been a systematic evaluation of the specific components of attention during the adolescent and pre-teen period prior to this study. This is a particularly important neurocognitive domain to understand in individuals with FAS and FAS as previous research by Streissguth and colleagues have found certain components of attention to be very sensitive to the damage caused by prenatal alcohol exposure. In addition, as FAE is generally defined by signs of abnormality in one or two of the three diagnostic domains, it is also important to evaluate if there are differences in the severity of attention deficits exhibited by FAE subgroups, as there are six possible groups of positive findings in one or two of the three diagnostic domains of FAE. Information of this nature is important in furthering our understanding of the discriminative validity of diagnostic classification systems for FAS and FAE subgroups. Information regarding the attention strengths and weaknesses of children with FAS or FAE is also important in facilitating effective early intervention and prevention of additional disability.

Neuroanatomical Damage in FAS and FAE

Neurobehavioural deficits are one of the most devastating consequences of prenatal alcohol exposure, and these difficulties are best understood as symptoms of CNS or brain dysfunction. One way of increasing understanding of the pattern of neurobehavioural strengths and weaknesses is to study brain-behaviour relationships. Existing studies of neuropathology, neuroradiology, and neuropsychology have made important contributions towards our understanding of the brain damage caused by
prenatal alcohol exposure at global, regional, and cellular levels. Before summarizing the results of previous studies an overview of major neuroanatomical structures and their function is presented.

Overview of Structural and Functional Neuroanatomy

The brain can be subdivided into three major structural regions - the brainstem, cerebellum, and cerebrum (Nolte, 1993). The brainstem plays a major role in cranial nerve functions, in conveying information to and from the cerebellum, thalamus, and basal ganglia, and in modulating autonomic processes (Nolte, 1993). The cerebellum is classically known to be involved in the subconscious modulation of posture, balance, and co-ordination. The cerebrum encompasses the largest portion of the brain including the cerebral cortex, thalamus, basal ganglia, and limbic system. Collectively, these regions are involved in controlling consciousness and complex voluntary processes (Mattson, Jernigan, & Riley, 1994).

The cerebrum can be divided into two major structural regions - the diencephalon and the cerebral hemispheres (Nolte, 1993). The diencephalon is primarily composed of the thalamus and hypothalamus. The thalamus is the major relay system for all subcortical information reaching the cortex except olfactory. It receives information regarding sight, position, movement, and memory, and acts like a filter sending this information to the appropriate cortical region for further processing. The hypothalamus is primarily involved in maintaining the body's internal environment or homeostasis.

The cerebral hemispheres can be divided into four structural regions - the cerebral cortex, the corpus callosum, the basal ganglia, and the limbic system. The cerebral cortex is commonly divided into five functional regions referred to as the frontal, parietal, temporal, occipital, and association cortices. The corpus callosum consists of a bundle of fibers connecting the brain's two hemispheres. The basal ganglia are involved in the modulation of movement and some aspects of cognition such as learning and memory, and it has extensive connections with the cerebral cortex. The limbic system contains the hippocampus and has a prominent role in verbal and spatial memory functions.
Comparative Structural Damage In FAS and FAE

Since FAS is usually not a fatal condition, only a few studies have reported on the brain abnormalities evidenced by autopsy examination. In a review of 16 reported cases, Clareen (1986) noted that heavy alcohol exposure commonly induces microcephaly (a small brain for body size), abnormal development of the cerebrum, corpus callosum, and cerebellum. These findings have been supported and extended by in vivo MRI evaluations of the brains of adolescents and children with FAS and FAE. MRI studies are particularly useful for evaluating the size of brain regions as specific brain structures can be represented in three-dimensional space and quantified using pixel counts (Mattson, Jernigan, et al., 1994).

In 1992, Mattson et al. published the first MRI evaluation of brain structures in adolescents with 2 subjects severely affected by FAS. This study focused on the question of whether or not specific brain regions were more vulnerable than others to the damaging effects of prenatal alcohol exposure. They found microcephaly, enlarged ventricles, and reduced volumes of the diencephalon, basal ganglia, and cerebellum. There were also abnormalities of the corpus callosum with complete agenesis in one case.

In order to differentiate the effects of heavy prenatal alcohol exposure from microcephaly, which is commonly associated with mental retardation, comparisons were made with Down's Syndrome (DS) and control adolescents. Cerebrum and cerebellar volumes were similarly reduced for both FAS and DS subjects, while the mean volume of basal ganglia and diencephalon structures were reduced in FAS but normal in adolescents with DS. Mattson et al. (1992) concluded that reductions of basal ganglia and diencephalon structures reflects the vulnerability of these regions to prenatal alcohol exposure, and this reduction was not fully explained by the microcephaly associated with mental retardation.

Mattson, Jernigan, and Riley's (1994) second MRI study focused on differences in the regional brain damage associated with diagnostic fetal alcohol subgroups by examining the brains of adolescents with FAS (n = 2), FAE (n = 2), and control subjects
(n = 20). FAE was defined as significant prenatal alcohol exposure but insufficient features for a confirmed diagnosis of FAS. Using non-parametric statistics both the FAS and FAE groups had significantly reduced absolute volumes of the cerebrum and cerebellum. Proportional volumes, which take into account differences in brain size, were used in comparative evaluations of specific cortical and subcortical structures. Although there were no differences in the proportional volume of cerebral or limbic cortex between FAS, FAE, and control groups, there were differences in the proportional volume of the basal ganglia and diencephalic structures. More specifically, the proportional volume of the basal ganglia was significantly reduced in comparison with controls for both the FAS and FAE groups. In contrast, proportional volume of the diencephalon for the FAE group was comparable to that of the control group, while being significantly reduced for FAS adolescents.

Although Mattson et al.'s (1994) MRI evaluation of the regional volume of limbic structures did not find differences between FAS, FAE, and control groups, this does not mean that the hippocampus and related structures are not damaged by prenatal alcohol exposure. Instead, it is more likely that the available MRI methodology was not sensitive enough to detect important damage that actually existed. This suggestion is supported by the consistent finding of a significant reduction in CA1 pyramidal cells of the hippocampus in animal FAS models with a remarkable sparing of CA3 and CA4. Thus, given the selective nature of this damage, in vivo human MRI evaluations of the hippocampus are unlikely to detect damage in individuals with FAS and FAE without a comparative evaluation of the region containing CA1 cells. A study of this nature has yet to be done.

In addition to these comparative evaluations, two studies have focused specifically on abnormalities of the corpus callosum and cerebellum. In comparison to normal age matched controls, Riley et al. (1995) found reductions in the proportional volume in three out of five regions of the corpus callosum in a group of 13 FAS/FAE subjects. FAE was defined as significant prenatal alcohol exposure but insufficient features for a confirmed diagnosis of FAS. The authors noted that similar reductions in the same corpus callosum
regions have been reported in children with attention deficit hyperactivity disorder (ADHD) (Hynd et al., 1991). This suggests that there is likely a relationship between prenatal alcohol exposure, damage to the corpus callosum, and the attention deficits exhibited by individuals with FAS and FAE (Riley et al., 1995). Individual data for FAS (n = 11) and FAE (n = 2) subgroups were not reported.

In order to further elucidate the nature of cerebellum damage associated with prenatal alcohol exposure, Sowell et al. (1996) examined the size of three regions of the cerebellar vermis in FAS/FAE (n = 9) and control subjects (n = 24). FAE was defined as significant prenatal alcohol exposure but insufficient features for a confirmed diagnosis of FAS. The cerebellar vermis represents one of four functional neuroanatomical regions of the cerebellum. Its clear morphological markers and subdivisions make it a convenient and reliable index of cerebellar abnormality (Courchesne et al., 1994).

Sowell et al. (1996) found that the anterior region of the vermis (vermal lobes I-V) was significantly reduced in the FAS/FAE group while there were no differences between groups in the volume of the posterior (vermal lobes VI-VII) and the remaining vermal region (including vermal lobes IX-X). Based on visual inspection of individually graphed data points there were also no differences between cerebellar regional volumes for FAS (n = 6) and FAE (n = 3) subgroups. The authors note that these results are consistent with animal models of FAS that have consistently found Purkinje cell loss in the early maturing vermal lobes I-V and IX-X with notable sparing of the later maturing lobes VI-VII (Goodlett et al., 1991). Taken together, the results from both animal and human studies provide convergent support for the suggestion that certain regions and cell populations of the cerebellum are particularly vulnerable to the damaging effects of prenatal alcohol exposure (Sowell et al., 1994).

Clark, Li, Conry, Conry, and Looock evaluated brain structure and function in a group of adolescents and adults with FAS (n = 19). Neuroanatomical structure was evaluated using MRI, and function was evaluated by assessing glucose metabolism using positron emission tomography (PET). Only 1 of the 19 subjects had MRI scans that were read as clinically abnormal by a radiologist. This subject had a thinned and small corpus
callosum. PET findings indicated that the FAS group had a subtle disruption in metabolism of glucose in diencephalon (thalamus) and basal ganglia (caudate and putamen) structures. Clark et al. concluded that at a neuroanatomical level these findings were consistent with subtle dysfunctional regulation of the sensory gateway to the cortex.

At a neurobehavioural level findings were viewed as being consistent with distractibility and impulsiveness.

A summary of MRI findings regarding the neuroanatomical damage associated with FAS, FAE, and Down's syndrome is provided in Table 2.
Table 2. Neuroanatomical Damage Identified using MRI in FAS, FAE, and Down’s Syndrome (DS)

<table>
<thead>
<tr>
<th></th>
<th>FAS</th>
<th>FAE</th>
<th>DS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 2)¹</td>
<td>(n = 2)²</td>
<td>(n = 2)¹</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>Microcephaly</td>
<td>Microcephaly</td>
<td></td>
</tr>
<tr>
<td>(↓ approx. 25%)</td>
<td>(↓ approx. 25%)</td>
<td>(↓ approx. 20%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 6)³</td>
<td>(n = 3)³</td>
<td></td>
</tr>
<tr>
<td>Cerebellum Vermis</td>
<td>Cerebellum Vermis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 11)⁴</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ Vol. Corpus Callosum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regions 1, 3, 5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. DS = Down’s Syndrome; ↓ = reduced; Approx. = Approximately; Prop. = Proportional; Vol. = Volume; BG = Basal Ganglia; Dien. = Diencephalon.

1 Mattson et al. (1992)
2 Mattson et al. (1994)
3 Sowell et al. (1996)
4 Riley et al. (1995)
Summary

There is now strong evidence from both animal and human studies indicating that excessive prenatal alcohol exposure produces global brain damage (e.g., microcephaly), damage to specific brain regions (e.g., basal ganglia, hippocampus, diencephalon, cerebellum, corpus callosum), and to specific cell populations (e.g., pyramidal, Purkinje). Taken together, findings suggest that there are structural brain differences between FAS and FAE subgroups. More specifically, FAS and FAE individuals exhibit significant and similar damage to basal ganglia, hippocampus and cerebellum structures while the diencephalon is remarkably spared in FAE. This suggests that in FAE certain structures and their associated neurobehavioural functions may remain relatively undisturbed while others are significantly damaged. This raises the question of whether the attention deficits of FAS and FAE groups are consistent with what would be predicted from existing knowledge of the regional neuroanatomical damage associated with FAS and FAE subgroups. One way to explore this question is to assess the attention deficits of FAS and FAE groups (i.e., FAS, FAE(D), FAE(G), FAE(X)) using assessment models with established neuroanatomical correlates. If it is possible to dissociate subgroups using measures of attention components, the findings will further our understanding of brain structure to function relationships associated with excessive prenatal alcohol exposure. A review of neuroanatomical assessment models of attention follows.

Models of Attention

One goal of neuropsychology research is to identify patterns of cognitive and behavioural strengths and weaknesses that are associated with damage to specific neuroanatomical structures. In reviews of the existing FAS literature, West et al. (1990) and Nanson (1994) argued that there was a need for studies that isolate specific cognitive processes and then relate the pattern of deficits to identified neuroanatomical damage. The advantage of using neuropsychological and cognitive tasks of attention with associated neuroanatomical correlates is that it provides a linkage between cognitive function and brain structure. More specifically, if specific brain regions in individuals
with FAS and FAE are more damaged than others (e.g., diencephalon), then attention functions mediated by these regions should also be affected differentially. Thus, the resulting pattern of strengths and weaknesses should be identified by a battery of neuropsychological, cognitive, and behavioural tasks that measure skills modulated by the brain structures of interest.

The quest to dissociate attention into basic but meaningful components presents an ongoing challenge for cognitive, behavioural and neuropsychologists. Cognitive psychologists, using highly specific tasks, have described a number of the more finely grained aspects of attention such as selectivity, focusing, sustained concentration, shifting, distractibility, coding, and rehearsal (e.g., Courchesne et al. 1994; Posner & Peterson, 1990). In contrast, neuropsychologists have grouped clinical measures of attention into conceptual categories believed to represent major components of attention in order to understand the deficits exhibited by patient populations (Mirskey, 1989; Shum, McFarland, Bain, & Humphreys, 1990; Sohlberg & Mateer, 1989). Although there are several neuropsychological assessment models of attention components, Mirsky's approach is the only one that is based upon an understanding of functional neuroanatomy. Finally, psychologists have also developed rating scales to assess the behavioural manifestation of an attention deficit (e.g., Conners, 1997).

**Mirskey's Neuropsychological Attention Model**

Mirskey's (1989) neuropsychological attention model is based on knowledge of neuroanatomical correlates from animal and human studies. The four components (i.e., Focus-Execute, Sustain, Encode, and Shift) and the specific tasks used to measure them have been validated and replicated using exploratory and confirmatory factor analyses with several different populations (e.g., children, adolescents, adults, patient and control populations; Mirsky, Fantie, & Tatman, 1995). These analyses have repeatedly found the same four factors and they have been interpreted as reflecting major components of attention that are relevant across the life span in both normal and abnormal populations.

Results from a recent evaluation of components of attention in normal aging adults using factor analysis suggests that an additional component should be added to
Mirsky's attention model (Tatman, cited in Mirsky, Yardley, Jones, Walsh, & Kendler, 1995). Tatman found that variance of reaction time measures on a CPT were factorially independent from measures of correct target responses, errors of commission (false alarms), and mean reaction time. Tatman proposed that this factor was best described as a Stability component of attention. These findings suggest that it is important to desegregate the Sustain component of attention into several subcomponents.

**Theoretical Validity.** In order to understand the degree to which a measure taps the construct it professes to measure, it is important to understand the relationship of the construct to other constructs in the domain of interest (Cronbach & Meehl, 1955). A review of the theoretical construct validity of Mirsky's model for the clinical assessment of attention was provided by Mirsky, Fantie, and Tatman (1995) and is briefly described in the following section.

The **Focus-Execute factor** is composed of two elements. The Focus element involves the ability to scan stimulus material for a target rapidly and efficiently, and the Execute element involves the ability to make a skilled manual response (e.g., Letter Cancellation Test, Digit Symbol Substitution). The function of focusing on environmental events is believed to be modulated by superior-temporal and inferior-parietal cortices as well as by structures that comprise basal ganglia corpus striatum including the caudate, putamen, and globus pallidus. The inferior-parietal and corpus-striatal regions are viewed as having a strong motor-execute function.

Once an individual has selected a stimulus for further processing, they must be able to maintain fixation on the target for as long as required. They must also resist the tendency to be distracted by competing, but irrelevant stimuli. The **Sustain factor** is measured by a continuous performance test (CPT) that requires the capacity to Sustain concentration for a period of 10 minutes. The Sustain attention component is believed to be modulated by anterior brain stem structures including the tectum, mesopontine reticular formation, and midline and reticular thalamic nucleus. These structures are
viewed as comprising the most basic and primitive components of the attention system of the brain.

In order to efficiently obtain information one must be able to monitor what is happening in the periphery, and when appropriate, terminate fixation in order to shift the focus of attention to another target. The **Shift factor** is measured using the Wisconsin Card Sorting Test. The Shift attention component is believed to be modulated by prefrontal cortex and anterior cingulate regions.

The **Encode factor** was derived from empirical and not a priori theories of attention. It is believed to embody a numerical-mnemonic quality of attention because the tasks loading on this factor (WAIS-R Digit Span and Arithmetic subtest) require the serial incorporation, cognitive manipulation, and brief retention of numeric information (Mirskey, 1989). These tasks are also commonly viewed as measures of immediate span of attention or working memory. Encode functions are believed to be supported by the hippocampus and amygdala of the limbic system. Thus, support for the theoretical validity of Mirsky's model is, in part, drawn from an understanding of functional neuroanatomy and empirical findings which suggests that specific components of attention are modulated primarily by identified brain regions.

**Construct and Factor Validity.** Support for the construct and factor validity (Kaufman, cited in Cicchetti, 1994) of Mirsky's model is drawn from consistent findings in both exploratory and confirmatory analyses (Mirskey, Anthony, Duncan, Ahearn, & Kellam, 1991; Pogge, Stokes, & Harvey, 1994). Factor analyses is a useful technique for assisting in the selection of measures and operational definitions of constructs in a clear manner. In addition, the factor structures that results from exploratory and confirmatory analyses also provide support for the construct validity of a theory-based, multi-scale test model. The factor loading values for specific measures from Mirsky et al.'s (1991) exploratory factor analysis and Pogge et al.'s (1994) confirmatory analysis are presented in Table 3. The sample used in Mirsky's study contained 126 adult neuropsychiatric patients and 76 normal controls. Using an equivalent test battery, adjusted for age, the
same four components of attention were identified in an exploratory factor analysis of 433 normal elementary school children (Mirsky et al., 1991). The sample used by Pogge et al. (1994) consisted of 278 adolescent psychiatric inpatients.
Table 3. Factor Loadings For Mirsky's Neuropsychological Model of Attention Components

<table>
<thead>
<tr>
<th></th>
<th>Focus-Execute</th>
<th>Sustain</th>
<th>Encode</th>
<th>Shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Symbol WAIS-R</td>
<td>.82 (.66)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Letter Cancellation</td>
<td>.81 (na)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPT Hits</td>
<td></td>
<td>.86 (nr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Errors</td>
<td></td>
<td>.83 (.70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction Time</td>
<td></td>
<td>.81 (.40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Span WAIS-R</td>
<td></td>
<td>.80 (.61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arithmetic WAIS-R</td>
<td></td>
<td>.72 (.78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WCST # Categories</td>
<td></td>
<td></td>
<td></td>
<td>.89 (nr)</td>
</tr>
<tr>
<td>% Correct</td>
<td></td>
<td></td>
<td></td>
<td>.83 (nr)</td>
</tr>
<tr>
<td>Errors</td>
<td></td>
<td></td>
<td></td>
<td>.81 (.40)</td>
</tr>
</tbody>
</table>

Variance Explained 31.8  30.3  27.3  15.0
In Exploratory Factor Analysis

Note. Loadings in () are from the confirmatory analysis by Pogge (1994). The other values are from Mirsky's (1991) exploratory analysis.

CPT, Continuous Performance Test; WCST, Wisconsin Card Sorting Test; na, not administered; nr, not reported.
Conners' Behavioural Attention Model

In the assessment of attentional strengths and weaknesses it is important to include an evaluation of behaviours that are reflective on an attention deficit. Conners' (1997) behavioural attention scale is a parent rating instrument that is based upon the diagnostic criteria for Attention Deficit/Hyperactivity Disorder (ADHD) of the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV).

According to the DSM-IV (APA, 1994), the central feature of ADHD is a persistent pattern of Hyperactivity-Impulsivity and/or Inattention that is developmentally inappropriate. The diagnostic criteria include 18 symptoms that are categorized into two clusters: 9 items assessing Inattentive symptoms and 9 items assessing Hyperactive-Impulsive symptoms (6 Hyperactive and 3 Impulsive). Conners (1997) created an 18-item rating scale for parents that adapts the criteria for ADHD outlined by the DSM-IV.

In a confirmatory factor analysis of two large groups of children \(n = 2,197\) and \(n = 1,661\) between 3 and 17 years of age, Conners (1997) found a two-factor model. There was one factor for the 9 Inattentive items and one factor for the 9 Hyperactive-Impulsive items. Conners (1997) points out that these results lend support for the use of the Inattentive and Hyperactive-Impulsive scales in both the DSM-IV criteria and in his rating scale. Although Nanson and Hiscock (1990) evaluated parent-report of Hyperactivity and Inattention in a group of children with FAS or FAE, before the present study there had not been a direct comparison of Hyperactivity and Inattention in FAS and FAE subgroups (e.g., FAS, FAED, FAEG, and FAEX).

Summary

Mirsky's neuroanatomical model of attention indicates that the basal ganglia is one of the primary brain regions involved in the modulation of the Focus-Execute component of attention; the thalamus is a primary region modulating the Sustain component of attention; and the hippocampus is a primary region modulating the Encoding component of attention. A summary of the neuroanatomical correlates and the tasks used to measure each component of Mirsky's model of attention is presented in Table 4. Finally, Conners behavioural attention model provides a measure of functional attention problems reported
by parents and guardians.
### Table 4. Neuroanatomical Correlates Associated with Mirsky's Clinical Model of Attention Components

<table>
<thead>
<tr>
<th>Components</th>
<th>Neuroanatomical Correlates</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FOCUS-EXECUTE</strong></td>
<td>Temporal Cortex</td>
<td>Letter Cancellation</td>
</tr>
<tr>
<td>(Perceptual/</td>
<td>Parietal Cortex</td>
<td>Digit Symbol</td>
</tr>
<tr>
<td>Motor Speed)</td>
<td>Basal Ganglia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- caudate,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- putamen,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- globus pallidus</td>
<td></td>
</tr>
<tr>
<td><strong>SUSTAIN</strong></td>
<td>Brain Stem</td>
<td>CPT</td>
</tr>
<tr>
<td>(Vigilance)</td>
<td>- tectum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- reticular formation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thalamus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- midline nucleus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- reticular nucleus</td>
<td></td>
</tr>
<tr>
<td><strong>SHIFT</strong></td>
<td>Prefrontal Cortex</td>
<td>WCST</td>
</tr>
<tr>
<td>(Flexibility)</td>
<td>Cingulate</td>
<td></td>
</tr>
<tr>
<td><strong>ENCODE</strong></td>
<td>Limbic System</td>
<td>Digit Span</td>
</tr>
<tr>
<td>(Numerical-</td>
<td>- Hippocampus</td>
<td>Spatial Span</td>
</tr>
<tr>
<td>Mnemonic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>INATTENTIVE</strong></td>
<td>-----</td>
<td>CPRS-R</td>
</tr>
<tr>
<td>**HYPERACTIVE-</td>
<td>-----</td>
<td>CPRS-R</td>
</tr>
<tr>
<td>IMPULSIVE**</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note.* CPT = Conners’ Continuous Performance Test; WCST = Wisconsin Card Sorting Test; CPRS-R, Conners’ Parent Rating Scale-R.

Terms in brackets () represent alternative descriptive labels for Mirsky’s four components of attention.
Attention measures are well suited for investigating the empirical support for
discriminative and convergent validity of FAS and related conditions due to their
demonstrated sensitivity to the deficits caused by prenatal alcohol exposure (Coles et al.,
1994; Streissguth et al., 1994) and their dependence upon brain regions and structures
that are heavily damaged in FAS and FAE (Mattson, Jernigan, et al., 1994). The
neuropsychological and behavioural models of attention by Mirsky (1989) and Conners
(1997) provide a multi-component approach for the assessment of attention with support
for theoretical and empirical validity.

Methodological Issues and Limitations in Previous Research

Empirical research examining differences and similarities between subgroups with
a history of excessive prenatal alcohol exposure is an emerging literature. Thus, it is
important to examine critically the issues addressed and methodologies employed in
previous studies. More specifically, since several of the issues addressed and methods
used in this study are relatively new to the field of psychology, an overview of the
following six topics is provided in this section: 1) continuity and comparability of
diagnostic subgroups, 2) ascertainment of a clinical sample, 3) statistical equivalency
analyses, 4) multi-component models of attention, 5) Conners’ CPT paradigm as a
measure of the Sustain component of attention, and 6) the subdivision of the Sustain
component of attention into three subcomponents.

Continuity and Comparability of Diagnostic Subgroups.

An important issue to consider in evaluating diagnostic subgroups is whether the
condition being studied is unitary or heterogeneous (i.e., with one or more subtypes).
Identifying and assessing subtypes of a general disorder is important as failure to do this
can lead to research findings that are not replicated due to unidentified or unknown
sample differences (Alloy et al., 1999). More specifically, the magnitude of the
dysfunction under evaluation may vary across subtypes. Thus, findings from any given
study will depend upon the proportion of subjects included from each subtype in the
study sample.
Issues of this nature have led to what has been termed the continuity and comparability debate in clinical and experimental research studies evaluating depression (Flett, Vredenburg, & Krames, 1997). Continuity refers to the degree of similarity among various subgroups while comparability refers to across sample comparisons (e.g., depression versus a normal control sample). The essence of a debate of this nature revolves around whether the dysfunction associated with mild or moderate forms of a condition differs in magnitude or specificity from the “full blown” syndrome.

Issues of continuity and comparability are relevant to further developing our understanding of CNS dysfunction resulting from excessive prenatal alcohol exposure as many of the previous studies have used a sample containing individuals with FAS and individuals with FAE (e.g., Coles et al., 1997; Kodituwakku et al., 1995; Nanson & Hiscock, 1990). Although several studies have compared the cognitive ability of individuals with FAS to individuals with FAE directly (e.g., Conry, 1990; Mattson et al., 1998; Streissguth, Aase, et al., 1991), there has not been a consistent definition of FAE in these studies. Furthermore, it is possible that the condition generally referred to as FAE is actually composed of several subgroups itself. This possibility is supported by the diagnostic classification scheme for FAS and related conditions proposed by the Institute of Medicine (IOM) in 1996. In essence, this scheme divides FAE into the two subgroups of partial FAS (pFAS) and Alcohol Related Neurodevelopmental Disorder (ARND).

Although the diagnostic classification scheme proposed by the IOM was a good “next step” in addressing classification issues, the authors clearly stated that further research was needed to assess the validity and clinical utility of the proposed scheme (Stratton et al., 1996). One of the weaknesses of the IOM’s classification system is that it does not account for the logically possible number of combinations of three diagnostic criteria. Thus, it is possible that one or more of the proposed diagnostic categories either contains more than one subgroup or that two or more of the proposed diagnostic categories are functionally equivalent. Another weakness is that a theoretical understanding of the damaging effects of prenatal alcohol exposure does not support the proposed diagnostic categories. The author’s study addressed the subgroup identification
limitations of previous research by deriving four clinical subgroups based on theory, research findings, and logic.

**Ascertainment of a Clinical Sample**

In clinical research, sample selection procedures have important implications for the interpretation and generalization of study findings because of characteristics of the selection process through which patients become available for inclusion (Turk & Rudy, 1990). For example, factors such as access to health care services, physician referral patterns, and responsiveness to medical and developmental follow-up can influence who is available to participate in a study using a clinical sample. Thus, in order to facilitate appropriate interpretation and generalization of study findings it is important to consider how subjects with the clinical condition of interest were identified and selected. It is also important to note that recruiting a representative clinical sample of children with a specific medical condition is a challenging task as most pediatric conditions have a low base rate. Furthermore, when a study focuses on a specific age range in order to reduce the variability associated with normal developmental processes, the number of possible participants is even more limited.

In previous FAS and FAE research, clinical samples have been selected through procedures such as population screening, clinical ascertainment, longitudinal research programs, or a combination of these approaches. Conry (1990) and Robinson, Conry, and Conry (1987) evaluated a population of children between 6 and 18 years of age “in an isolated, economically depressed, native community” in British Columbia, Canada (Conry, 1990, p. 650). Of the 123 children living in the community only seven were excluded, and 22 received a diagnosis of either FAS or FAE. Thus, 19 percent (22/116) of the children in this isolated native community met diagnostic criteria for FAS or FAE.

In the clinical sample used by Streissguth, Aase, et al. (1991) half of the participants were “clinically ascertained” from a specialized medical clinic in the Seattle, Washington area, and the rest were identified through an “FAS screening study on four Indian reservations” in the United States (p. 1961). This sample included 31 adolescents and adults with FAS and 11 with FAE. “Seventy-four percent of the sample were
American Indian, 21% were white; 5% were black; 47% lived on reservations of the Southwest and Northwest United States, 39% lived in urban areas of the Pacific Northwest, and 14% lived in rural, nonreservation areas” (p. 1962). Information regarding the total number of adolescent and adults identified with FAS or FAE as opposed to the number who participated was not described.

In the clinical sample used by Coles et al. (1997) children between 7 and 8.5 years of age were ascertained from a longitudinal study of the effect of prenatal exposure from the same inner city teaching hospital in Atlanta, Georgia. This study included 25 children classified as FAS/FAE and 62 children classified as prenatal alcohol exposure with no dysmorphology (ETOH Non-Dysmorphic). Ethanol (ETOH) is the chemical term for alcohol.

In the clinical sample used by Mattson et al. (1998) children between 5 and 16 years of age were ascertained from a medical dysmorphology clinic in San Diego, California. This study included 15 children with FAS and 10 children classified as having a history of a high level of prenatal exposure to alcohol (PAE) but did not qualify for a diagnosis of FAS. Groups were matched on age, sex, and socio-economic status. Fifty-three percent of the FAS group and 40 percent of the prenatal alcohol exposure (PAE) group were Caucasian. Information about the ethnicity of the remaining subjects was not described.

In order to reduce the selection bias and to obtain a sample that was as representative as possible of children in Saskatchewan, this study incorporated epidemiological, research, and clinical ascertainment procedures to identify children who had received a medical diagnosis of FAS or FAE. The representativeness of the samples used to recruit participants for each diagnostic subgroup was evaluated by an examination of reasons for patients being excluded from the pool used to select subjects. In order to control for the potential differences between subgroups on age, sex, ethnicity, and socio-economic status, subgroups were matched as closely as possible on these factors.

Statistical Difference, Equivalence, and Effect Size

In the last several years there has been some debate regarding the sufficiency of
statistical difference testing for the interpretation of quantitative research findings (Farrell, 1999). The outcome of psychological research has typically focused upon whether observed differences between groups represented a real or verifiable effect. In this approach, hypotheses are evaluated indirectly by ruling out or nullifying alternative explanations that could account for the findings. A null hypothesis is stated as the exact equivalence of groups (e.g., \( H_0: \mu_1 = \mu_2 \)), and an alternative hypotheses is stated as the inequivalence of groups (e.g., \( H_a: \mu_1 \neq \mu_2 \)). If there is sufficient quantitative support, the null hypothesis is rejected and the alternative hypothesis is accepted. Sufficient support is generally expressed in terms of a probability (p) level. For example, using the conventional criteria of \( p \leq .05 \) indicates that if the study was conducted an infinite number of times the likelihood that groups would differ as a result of chance would be 5 percent or less. Thus, the logic of statistical hypothesis testing requires that the hypothesis to be proven be stated as an alternative. Furthermore, if there is insufficient support for the null hypothesis to be rejected, some argue that this does not provide sufficient support for the acceptance of the null hypothesis of equivalence (Rogers, Howard, & Vessey, 1993). For example, if a comparison does not demonstrate a statistically significant difference, the lack of a verified difference between groups does not, by itself, allow one to conclude verifiable equivalence (Hatala, Holbrook, & Goldsmith, 1999).

One limitation of statistical difference testing is that there are times when a research question directly predicts and seeks to prove the null hypothesis. For example, to investigate issues of safety, cost, and patient preference, researchers have evaluated the equivalence of different forms of pharmacological treatment (Rogers et al., 1993).

The issue of equivalence testing is also relevant in an evaluation of diagnostic subgroup continuity. For example, if the neuropsychological and behavioural impairments exhibited by FAS and FAE subgroups are equivalent, then parental and educational interventions to address attention deficits that are effective for an individual with FAS will likely be effective for an individual with FAE.

Several articles have described the theory and methods involved in using
significance tests to evaluate equivalence between groups in social science research (Hatch, 1996; Rogers et al., 1993; Stegner, Bostrom, & Greenfield, 1996). There is consensus amongst these authors that using significance tests to evaluate equivalence requires reversing the nature of the traditional null and alternative hypotheses and defining an equivalence criterion (EC). This EC is defined in such a manner that any difference falling within it is deemed to be a "practically unimportant" difference. More specifically, in equivalency testing the null hypothesis states inequivalence using a defined EC and two alternative hypotheses are used to assess equivalence. These hypotheses are tested using two one-tailed equivalency tests that can be expressed in the following manner:

\[
\begin{align*}
(1) & \quad H_0: \mu_1 - \mu_2 \geq \text{EC} \quad & (2) & \quad H_0: \mu_1 - \mu_2 < \text{EC} \\
(2) & \quad H_0: \mu_1 - \mu_2 < \text{EC} \quad & H_0: \mu_1 - \mu_2 > -\text{EC}.
\end{align*}
\]

Thus, the overall alternative hypotheses for the two equivalency one-tailed tests becomes: \( H_0: \text{EC} < \mu_1 - \mu_2 < +\text{EC}. \)

It is important to note that equivalency testing does not show that \( \mu_1 = \mu_2 \), but rather, that the difference between \( \mu_1 \) and \( \mu_2 \) is small enough to be considered a "practically unimportant" difference. Thus, a confidence interval for \( \mu_1 - \mu_2 \) may not include 0, but still reflect bounds that are less than the defined EC.

Another limitation of statistical difference testing is that although it will lead to a decision to reject or accept the null hypothesis, it does not provide any indication of the magnitude of the effect or the clinical or practical significance of the effect. This is because the results of statistical significance testing are a function of the size of the difference between groups, the size of the sample, and level of within group variability. Thus, a statistically significant effect could be the result of a very large effect, a very large sample, or both (Cohen, 1990). In order to facilitate an interpretation of the magnitude of an effect researchers have used norm-referenced measures, criterion-referenced
measures, and direct measurement of effect size.

The use of norm-referenced measures facilitates an evaluation of clinical significance by providing information on the performance of a clinical sample compared to a non-clinical or normative sample. In this approach, raw scores are converted to norm-referenced standard scores that reflect relative position in the distribution of the normative sample.

The use of criterion-referenced measures facilitates an evaluation of clinical significance by providing information on the performance of a clinical sample compared to normal and abnormal performance using clinical cut-off scores or a procedure of this nature. For example, performance below the clinical cut-off score is considered to be within normal limits while performance above the cut-off score is considered to be clinically significant or abnormal.

An effect size is a direct measure or a quantification of the difference between observed group means in standard deviation units (Kendall, Butcher, & Holmbeck, 1999). For example, in a comparison of two groups, an effect size of $d = .7$ denotes that the mean of group one is $7/10^{th}$ of a standard deviation higher than the mean of group two. A guide for the interpretation of effect sizes was delineated by Cohen (1988) in small, medium, and large effect sizes ($d = .2, .5, .8$, respectively). The formula used to calculate Cohen’s effect size ($d$) is as follows: $ES = \frac{M_1 - M_2}{SD_{pooled}}$. In the present study, the limitations associated with traditional significance testing were addressed by including equivalency analyses and measures of effect size. This was done to answer specific research questions and to provide a more comprehensive description of study findings.

**Multi-Component Measurement**

Constructs that serve as the impetus for research vary in their level of specificity (Kazdin, 1999). Broad constructs such as IQ are often important beginning points for research on a particular condition. After information is acquired on how subgroups with a specified condition compare on broad constructs, such as IQ, it is then important to desegregate the construct by identifying individual components and subcomponents and
to study how they each contribute to an understanding of the condition. Specific information of this nature is often helpful in assisting parents and professionals in developing targeted and efficacious intervention plans.

Initial studies that directly compared CNS dysfunction in FAS and FAE subgroups examined the broad construct of IQ (i.e., Conry, 1990; and Streissguth, Aase, et al., 1991). Interestingly, these studies found that although the FAS group had a substantially lower IQ compared to the FAE group, the FAE group had a higher rate of social and behavioural disabilities (Streissguth et al., 1997). Attention problems were the most frequent type of mental health disorder for both groups.

Coles et al. (1997) conducted the only previous study that directly compared the performance of FAS and some form of FAE subgroup on components of attention. This study compared the performance of 25 dysmorphic FAS/FAE children with 62 children with a history of excessive prenatal alcohol (ETOH) exposure without the dysmorphic features associated with FAS (ETOH non-Dysmorphic). The sample consisted of young children between 7 and 8.5 years of age. Components of attention were assessed using Mirsky’s (1989) clinical model for the assessment of four components of attention (i.e., Focus-Execute, Encode, Shift, and Sustain). Results indicated that there were no statistically significant differences between the FAS/FAE group and the ETOH non-Dysmorphic group on these four components of attention.

In the present study, the continuity and comparability of a spectrum of four diagnostic subgroups was examined using neuropsychological and behavioural models of attention developed by Mirsky (1989) and Conners (1997). Mirsky’s neuropsychological attention model includes the following four components: Encode, Focus-Execute, Sustain, and Shift. Conners’ behavioural parent report model includes Inattentive and Hyperactive-Impulsive components.

The Traditional versus the Conners’ CPT

The Sustain component of attention was assessed in this study using Conners’ CPT instead of the CPT used in Mirsky’s attention model due to its emphasis on assessing 1) response-speed-variability and 2) the availability of norm-referenced scores.
stratified by age and sex. In order to facilitate a comparison of the measurement characteristics of the traditional and the Conner's CPT, a brief summary is provided of specific parameters used by these two measures.

The Traditional CPT Paradigm. The CPT used in Mirsky's attention model uses a modified version of the traditional CPT paradigm originally developed by Rosvold, Mirsky, Sarason, Bransome and Beck (1954). In the traditional paradigm, participants are asked to press a button when a specific letter (i.e., "X") or a specific sequence of letters (i.e., "AX") appears. The CPT used in Mirsky's attention model contained an additional stimuli presentation condition referred to as the "DX" condition. In the "DX" condition letters are "degraded" in a manner that makes it more difficult to discriminate targets. In the version for children and adolescents all three conditions use a fixed inter-stimulus-interval (ISI) of 1.5 seconds. All letters were presented for 200 milliseconds and the target letter ("X", "DX") or letter sequence ("AX") occurs infrequently (10 percent) (D. Pascualvaca, personal communication, February, 1997).

The Conners' CPT Paradigm. The Conners' (1995) CPT differs from the traditional paradigm in regard to the definition of target stimuli, the way in which task demands are manipulated, and the availability of norm-referenced scores for children and adolescents. In the Conners' CPT, target letters occur frequently (90 percent) instead of infrequently (10 percent). In the traditional CPT, subjects are asked to press a button only when the letter "X" is presented. In the Conners' CPT subjects are asked to press a button when any letter except "X" is presented. This change results in a large increase in the number of responses to target stimuli made by each subject (i.e., "all letters except X," instead of "only X").

One advantage of the frequent responding associated with the Conners' CPT is that it creates a much larger sample of reaction times (RT's) for the calculation of a subject's average RT and the variability of RT. Consequently, in comparison to the traditional version of the CPT used in Mirsky's attention model, the RT and SE of RT
scores from the Conners’ CPT are in theory statistically more reliable measures than comparable scores from a traditional CPT.

While the traditional CPT varies demand characteristics by having subjects respond to stimulus conditions of various complexities (i.e., "X", "AX", and "degraded X"), Conners’ CPT varies demand characteristics by presenting stimuli at different inter-stimulus-intervals (ISI’s). The effects of this task manipulation are assessed using measures of both speed of reaction time and the variability of reaction time speed in response to changes in the ISI.

Conners (1995) states that the sensitivity of a CPT for children with an attention deficit is increased by assessing performance in response to both short and long stimulus intervals using measures of mean reaction time and variability of reaction time. Support for this position has been provided by several studies evaluating the type of attention deficits exhibited by children with ADHD. Chee, Logan, Schachar, Lindsay, and Wachsmuth (1989) found that children with ADHD were inefficient at responding to targets when the ISI was small or large. Conners, March, Fiore, and Butcher (1993) administered a CPT to 43 individuals with ADHD. Patients were randomly assigned to treatment groups in which they received placebo, 5, 10, 15 mg of Ritalin, in a counterbalanced order. They found a clear linear effect of Ritalin dose on RT ISI Change measures. Conners et al. (1993) note that the treatment effect of Ritalin would not have been evident at any dose level if performance on a 4 second ISI condition had not been available. Conners (1995) suggested that children with ADHD may have difficulties processing information efficiently when either a fast response or a delayed response was required, and that this deficit is often responsive to treatment using a stimulant medication such as Ritalin.

Studies have also found that boys with ADHD are significantly more affected by temporal uncertainty preceding the presentation of a target stimulus compared to a normal control group, both in terms of their mean reaction time and the variability of reaction time (Sergeant & Scholten, 1985; Zahn, Kruesi, & Rapport, 1991). Thus, measuring a subject’s mean and variability of reaction time in response to changes in the
ISI, as done in the Conners’ CPT, provides a sensitive measure of some aspects of the attention deficits exhibited by children with ADHD.

Finally, the Conners’ CPT was used instead of the traditional CPT used in Mirsky’s model because normative data stratified by age and sex were available for all performance scores, including response-time variability scores. For example, the standardization sample contained between 60 and 80 children for children between 10 and 14 years of age by 2 year age increments (i.e., n = 62, 10-11 years; n = 82, 12-13 years; n = 62, 14-15 years). In comparison, the traditional CPT used in Mirsky’s attention model has primarily been used in research studies and published normative data for children and adolescents with an adequate number of children per age group was not available.

**Sustain Attention Subcomponents.**

The Sustain component of attention was assessed using coordinated accuracy, response-time, and variability of response-time scores in order to: (a) assess potential response styles involving speed-accuracy trade-offs, and (b) assess consistency of response speed on overall test performance and in response to changes in the event rate of target presentation.

It is important to assess speed-accuracy response style in an evaluation of performance on a CPT as differences in error rates between groups may be directly associated with differences in RT or variability of RT (Enns & Burack, 1997). For example, it is possible that a group may have a slower RT but make fewer errors than a comparison group as a result of a response style that emphasizes accuracy over speed – an accuracy versus speed trade off. It is also possible that a group may emphasize speed over accuracy. A coordinated evaluation of accuracy and response-speed facilitates the identification of a response style of this nature. Thus, an interpretation of RT without consideration of performance accuracy may omit important information regarding performance, and may lead to misleading interpretations. For example, Nanson and Hiscock (1990) found that children with ADD could make speed-accuracy trade-offs in favor of speed, where as children with FAS/FAE could not. They responded slowly and
inaccurately.

It is also important to assess consistency of response-speed on both overall task performance and in response to changes in the event rate of target presentation. An evaluation of this nature provides important information regarding the consistency of performance. Until recently, the variability of a subject's performance was generally viewed as a measure of dispersion or spread of scores in a given sample (Barkley, 1996). In attention research over the past decade, however, this view has been expanded by the notion that variability of RT may also be as important or even more important than mean RT in understanding performance on attention tasks (Conners, 1995).

Attention researchers have also addressed the issue regarding the type of information that can be obtained by evaluating both the mean and variance of a RT distribution of a subject's scores on CPT's. Enns and Burak (1997) proposed that if an increase in RT variability is simply a function of a corresponding increase in RT, then there is little to be gained from an analysis of both RT and variability of RT. If, however, an increase in variability of RT is independent of changes in RT, this provides information regarding consistency of RT. Thus, the inclusion of both mean RT and variability of RT allows for an evaluation of response speed variability while taking into account differences or similarities in regarding the speed of responses to targets and the consistency of RT to targets.

Variability of RT scores were of particular interest for inclusion in this study as Streissguth et al. (1994) found them to be one of the most sensitive measures of CNS dysfunction associated with prenatal alcohol exposure. Carmichael-Olson et al. (1998) reported that adolescents with FAS exhibited greater intraindividual response speed variability compared to a comparison group. They indicated that this likely reflected micro-lapses or small lapses in attention as previously suggested by Streissguth et al. (1994). Variability of RT has also been found to be a sensitive indicator of head injury (Segalowitz, Dywan & Unsal, 1997). Finally, Rovet and Cole (2000) proposed that high variability of RT scores signified "micro-lapses" of attention as a result of inconsistent neurotransmissions.
Empirical and theoretical support for the three subcomponents of the Sustain component of attention used in this study was derived from the Stability factor identified by Tatman (cited in Mirsky, et al. 1995), and from several recent advances in the refinement of CPT’s. As previously discussed, one recent development in the field of attention research is the view that response-speed-variability scores on CPT’s reflect a deficit of the Sustain component of attention that is characterized by inconsistent speed of responses to environmental events.

**Conners’ CPT Scores.** For the purpose of this study selected scores from Conners’ CPT were organized into three subcomponents guided by current theory and empirical findings discussed above. The Sustainaccuracy subcomponent was assessed using CPT scores for the number of targets to which the subject did not respond (Misses or Omission Errors), and the number of times the subject responded to a non-target (False Alarms or Commission Errors). The Sustainresponse-speed subcomponent was assessed using scores for average reaction time for responses to targets (Hit RT), and the slope of change in Hit RT over three ISI’s (Hit RT ISI Change). The Sustainresponse-speed-variability subcomponent was assessed using scores for the consistency of response times, expressed in terms of the overall SE of response time to targets (Overall Hit RT SE), and the slope of change in SE of response time to target hit over three ISI’s (Hit RT SE ISI Change). A more detailed description of CPT scores is provided in the Methods section for Part 2 of this study.

**Summary**

In order to address limitations associated with previous research, this study evaluated the continuity and comparability of a spectrum of 4 diagnostic subgroups with a history of excessive prenatal alcohol exposure. These subgroups were derived using a combination of existing diagnostic criteria, previous research findings regarding CNS dysfunction, teratogenic theory, and the number of logically possible combinations of three categorical diagnostic criteria.

In order to increase the representativeness of samples used in this study, FAS
subjects were systematically selected from a population of children identified in an epidemiological study of FAS in Saskatchewan. FAE subjects were systematically selected from information from the epidemiological study of FAS in Saskatchewan and from information in patient records in a hospital FAS/FAE diagnostic clinic at the Royal University Hospital in Saskatoon, Saskatchewan. The continuity and comparability of diagnostic subgroups with a history of excessive prenatal alcohol exposure was evaluated using neuropsychological, behavioural, and cognitive components of attention.

Given recent advances in the field of attention research, the Sustain component of attention was assessed using coordinated measures of accuracy, response-time, and variability of response-time. At a methodological level, difference analyses, equivalency analyses, and effect size measures were used to evaluate subgroup continuity and comparability.

Summary of Literature Review

Although FAS is a recognized diagnosis with established diagnostic criteria (Sokol & Clarren, 1989), FAE is a clinical label that is currently associated with several different definitions and considerable controversy and confusion. As an initial step towards addressing these nomenclature issues in 1996 the IOM committee of experts proposed a classification scheme consisting of FAS, pFAS, and ARND. In their final report, this committee also called for research to evaluate the utility and validity of the proposed classification system. One way of evaluating the clinical utility and validity of this classification system is to use existing knowledge from theory and research to construct a spectrum of diagnostic subgroups and then evaluate their existence and characteristics in a clinical sample. As predicted by teratogenic theory (Vorhees, 1986), brain dysfunction has been found to be the most sensitive indicator of the damaging effects of prenatal alcohol exposure (Streissguth et al., 1994), and it is consistently a presenting problem of individuals referred for clinical assessment (J. Nanson, personal communication, July, 1996). By making the assumption that all clinical subgroups exhibit CNS dysfunction and by using logic, the clinical continuum of prenatal alcohol effects can be represented by using FAS and three FAE subgroups (i.e., FAS, FAE(D), FAE(G),
FAE(X)). The FAE(D) subgroup is comparable to the IOM's pFAS diagnostic category, and the FAE(X) subgroup is comparable to the IOM's ARND category. The IOM's classification system does not contain a subgroup similar to the FAE(G) subgroup.

Attention measures are well suited for investigating the empirical support for continuity and comparability of FAS and FAE subgroups due to their demonstrated sensitivity to the deficits caused by prenatal alcohol exposure (Coles et al., 1994; Streissguth et al., 1994), and their dependence upon brain regions that have been found to be heavily damaged in FAS and FAE (Mattson, Jernigan, et al., 1994). The neuropsychological and behavioural models of attention deficits by Mirsky (1989) and Conners (1997) provide a multi-component approach for the assessment of attention with support for theoretical and empirical validity. Since previous research has found variability of RT to be a sensitive measure of CNS dysfunction caused by prenatal alcohol exposure, the Sustain component of attention was assessed in this study using coordinated measures of accuracy, RT, and variability of RT. Finally, in order to increase the representativeness of the samples used in this study, FAS and FAE subjects were selected from a population of children identified in an epidemiological study of FAS in Saskatchewan.
PURPOSE AND RESEARCH QUESTIONS

The purpose of this study was:

(a) **To determine** if a spectrum of diagnostic subgroups with a documented history of excessive prenatal alcohol exposure could be identified using archival information regarding dysmorphology, growth, and CNS dysfunction.

(b) **To evaluate** the continuity and comparability of existing subgroups on components of attention using neuropsychological and behavioural assessment models.

(c) **To assess** if diagnostic subgroups exhibited a “clinically significant” attention deficit using norm-referenced measures of neuropsychological and behavioural attention components.

To determine if an a priori spectrum of four diagnostic subgroups (FAS, FAE(G), FAE(D), and FAE(X)) existed in a clinical population, Part 1 used archival data regarding the three domains associated with a diagnosis of FAS or FAE. In Part 2 a sample of children from each of the identified subgroups was then used to evaluate subgroup continuity, comparability, and level of attention dysfunction on neuropsychological and behavioural components of attention. Findings are presented in two parts to facilitate conceptual clarity between medical (i.e., dysmorphology, growth, CNS dysfunction) and psychological constructs (i.e., components of attention), and to facilitate a clear linkage between research questions, methods, and findings.
PART 1: DIAGNOSTIC SUBGROUPS

Part 1 investigated whether a spectrum of diagnostic subgroups of individuals with a history of excessive prenatal alcohol exposure could be identified in a clinical population, using archival data regarding diagnostic criteria. A spectrum of medical conditions refers to a subgroup of individuals with similar characteristics associated with a specified medical history (Webster's Collegiate Dictionary, 1985). It was hypothesized that four diagnostic subgroups (i.e., FAS, FAE(G), FAE(D), and FAE(X)) would be identified using information regarding the presence or absence of facial dysmorphology, growth retardation, and CNS dysfunction.

For the purpose of this study, a diagnosis of FAS and FAE subgroups was defined using teratogenic theory, logic, and research findings. Three diagnostic subgroups were defined using Vorhees' (1989) teratogenic dose-effect theory and one subgroup was defined using a combination of logic and research findings.

Vorhees' (1989) teratogenic dose-effect theory predicts that a high level of prenatal alcohol exposure is likely to produce a subgroup of individuals with FAS who exhibit positive signs in the three diagnostic domains associated with this condition (i.e., CNS dysfunction, growth retardation, and facial dysmorphology)(see Figure 1). Vorhees' dose-effect theory also predicts that a moderate level of prenatal alcohol exposure is likely to produce a subgroup of individuals with FAE who exhibit positive signs in the domains of CNS dysfunction and growth retardation. This subgroup was given the label FAE(G). Finally, Vorhees' dose-effect theory predicts that a low level of prenatal alcohol exposure is likely to produce a subgroup of individuals with FAE who exhibit positive signs only in the domain of CNS dysfunction. This subgroup was given the label FAE(X).

A rationale for a fourth diagnostic subgroup was based upon the logical number of possible combinations of three diagnostic domains, and consistent research findings of
CNS dysfunction in children clinically referred with a history of excessive prenatal alcohol exposure. More specifically, if the assumption is made that all individuals with a history of excessive prenatal alcohol exposure exhibit CNS dysfunction, then the number of possible combinations of positive findings of three diagnostic domains drops from seven to four. Furthermore, the only resulting combination not predicted by Vorhees’ theory is a subgroup with CNS dysfunction and facial dysmorphology. This subgroup was given the label FAE(D).

Method

Design

Categorical data derived from medical and psychological assessment reports regarding the three diagnostic criteria associated with FAS and FAE were used to investigate the diagnostic subgroup hypothesis in this study. The dependent variable in this analysis was the number of cases meeting a priori criteria for each diagnostic subgroup.

Subjects

Archival data for 128 adolescent and pre-teen children between 10 and 14 years of age with an identified history of prenatal alcohol exposure were included in a file review of categorical information regarding the three diagnostic domains associated with FAS and FAE. These children had been seen for a diagnostic assessment by a pediatrician and a psychologist with expertise in assessing the damaging effects of prenatal alcohol exposure from the Alvin Buckwold Child Development (ABCD) Program. This program is part of the Royal University Hospital in Saskatoon, Saskatchewan, and it is physically located in the Kinsmen Children’s Centre. The ABCD Program is the major referral center for children with intellectual and physical handicapping conditions in central and northern Saskatchewan. This program has been diagnosing children with FAS and FAE since the early 1970s (Habbick, Zaleski, & Casey, 1979). In 1994, program staff also completed an epidemiological study of all known
cases of FAS in the province of Saskatchewan (Habbick, Nanson, Snyder, Casey, & Schulman, 1996).

Ascertainment. Archival data for children born between 1982 and 1986 with a history of excessive prenatal alcohol exposure were identified for inclusion in the file review for this study. A history of excess prenatal alcohol exposure was confirmed by the diagnosing pediatrician. However, due to difficulties associated with obtaining detailed information regarding the amount, pattern and duration of alcohol consumption during pregnancy, more detailed information regarding dose and timing of exposure was not available.

Children were identified for study inclusion using the following four patient tracking resources:

1) An epidemiological database of children with FAS in Saskatchewan (Habbick, Nanson, Snyder, Casey, & Schulman, 1996).

2) A research database of children with FAE that were identified in the process of conducting an epidemiological study of FAS in Saskatchewan (Habbick, Nanson, Snyder, Casey, & Schulman, 1996).

3) An archive of patient tracking records for children seen by the FAS team from the ABCD Program (J. Nanson, personal communication, July 1998).

4) Minutes of proceedings from the intake review committee for children referred to the ABCD program.

Minutes from proceeding of the intake review committee were used to identify children referred to the ABCD program with a reported history of prenatal alcohol exposure who had not been seen by the pediatrician in this program. This was an important source for identifying patients potentially meeting study criteria for the FAE(X) subgroup as these cases were often not included in the patient tracking documentation used by the FAS team.

Inclusion of epidemiological, clinical and research databases for subject identification is one way of reducing the selection bias often associated with clinically
referred samples and obtaining a sample that better reflects the characteristics of the population it represents (Cicchetti & Rogosch, 1999).

**Exclusion Criteria.** Patients were excluded from selection for Part 1 of this study if the diagnosing pediatrician reported that there was insufficient evidence to confirm a history of excessive maternal drinking during pregnancy. Although requiring a confirmed history of excessive prenatal alcohol exposure by a health care professional is not formally part of the criteria established by the Research Society on Alcoholism (1989), it is a logical criteria which has been included in recent studies by members of the RSA (Astley & Clarren, 1995). A history of this nature is also required for a diagnosis of pFAS and ARND using the IOM (1996) classification scheme.

**Diagnostic Subgroups Definitions**

As previously stated, the FAS subgroup was defined as children having positive findings in all three domains in accordance with RSA guidelines (Sokol & Clarren, 1989). The FAE(D) subgroup was defined as children showing evidence of CNS dysfunction and dysmorphology. The FAE(G) subgroup was defined as children showing evidence of CNS dysfunction and growth retardation, and the FAE(X) subgroup was defined as those children showing evidence of CNS dysfunction (see Table 5). As previously reviewed, the diagnostic spectrum of subgroups used in this study was developed using teratogenic theory (Vorhees, 1989), logic, and research findings (Streissguth et al., 1994).
Table 5. Diagnostic Subgroup Definitions using Categorical Criteria for CNS Dysfunction, Growth Retardation, and Dysmorphology

<table>
<thead>
<tr>
<th>Diagnostic Subgroups</th>
<th>Positive Domain Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAS</td>
<td>CNS Growth Facial Dysmorphology</td>
</tr>
<tr>
<td>FAE(D)</td>
<td>CNS - Facial Dysmorphology</td>
</tr>
<tr>
<td>FAE(G)</td>
<td>CNS Growth -</td>
</tr>
<tr>
<td>FAE(X)</td>
<td>CNS - -</td>
</tr>
</tbody>
</table>

Note. CNS = CNS Dysfunction; Growth = Growth Retardation.
Diagnostic Domain Criteria. Medical and psychological reports from the hospital chart of each of the 128 children identified for participation in this study were reviewed. This information was used to determine if each child met diagnostic study criteria for facial dysmorphology, growth retardation, and CNS dysfunction.

All children had been clinically referred by a family physician for a diagnostic assessment of a possible fetal alcohol condition, and had been seen by one of two pediatricians, Dr. R. Snyder or Dr. B. Habbick. Both these physicians have specialized expertise in the assessment of facial dysmorphology and numerous publications the field of FAS (Habbick, Zaleski, & Casey, 1970; Habbick Nanson, Snyder, Casey, & Schulman, 1996; Habbick, Nanson Snyder, & Casey, 1997; Habbick, Blakley, Houston, Snyder, Senthilselvan & Nanson, 1998).

As previously stated, children were identified for inclusion in this file review if they had an identified history of excessive prenatal alcohol exposure. Since many of these diagnostic medical assessments were conducted prior to eight years of age, and because the characteristic features of facial dysmorphology and growth retardation are the most reliably identified during this stage, information regarding diagnostic domain criteria was obtain from a file review. Children were only included in the FAS group if the diagnosing pediatrician had documented this diagnosis in a medical report.

Given that there were not established criteria set for FAE subgroups, information obtain in medical reports regarding dysmorphology features and growth retardation were used to assign children to one of three subgroups [FAE(D), FAE(G), FAE(X)] when they did not meet criteria for FAS. An acknowledged limitation of this methodology is that a systematic checklist of the presence of specific facial features and the facial gestalt was not used in the original charts. Thus dysmorphic features identified in this study were limited to those described by the pediatrician in their diagnostic report. Growth measures were obtained on every visit to the pediatrician and recorded on standard pediatric growth charts.
Physical malformation was defined as signs of facial dysmorphology evidenced by one or more of the following features: (1) short palpebral fissures (short eye openings), (2) long and flattened philtrum (usually small and flat ridges between the nose and mouth), or (3) a thin upper lip. This criteria is consistent with the guidelines proposed by the RSA (Sokol & Clarren, 1989). It also includes the three features that were found by Astley and Clarren (1995) as best differentiating individuals with and without FAS using a quantitative, multivariate case definition of the facial phenotype associated with excessive prenatal alcohol exposure.

Evidence of growth retardation was defined as weight or height below the 10th percentile for the child’s age and sex at birth or when seen for a medical assessment. This criteria is consistent with the guidelines proposed by the RSA (Sokol & Clarren, 1989).

Evidence of CNS dysfunction was defined as one or more of the following: (1) microcephaly (head circumference below the 3rd percentile), (2) intellectual impairment (e.g., mental retardation, an IQ in the borderline range, a learning disability), (3) behavioural dysfunction or deficit (e.g., ADHD, behaviour problems, academic learning difficulties), (4) developmental delay (e.g., speech, fine or gross motor), or (5) neurological abnormality (e.g., seizures, small corpus callosum). This criteria is consistent with the guidelines proposed by the RSA (Sokol & Clarren, 1989).

Procedure

After obtaining approval from both the Ethics Committee of the University of Saskatchewan and the Research Office of the Saskatoon District Health Board, a list of patient names was identified from existing tracking resources at the ABCD Program. An archival file review was then conducted to determine if identified children met study criteria for facial dysmorphology, growth retardation, and CNS dysfunction. In order to answer the research question in Part 1, the only information that was required was whether or not a child met or did not meet criteria for archival evidence of facial dysmorphology, growth retardation, or CNS dysfunction.

Although a file review had previously been conducted (Habbick et al., 1996) to confirm that children in the epidemiological database met criteria for FAS, confirmation
of this nature was not available from other sources (i.e., research database, clinical patient tracking records). For example, the files for children identified as FAE needed to be reviewed to determine which combination or sole diagnostic domain criteria had been met. In order to enhance methodological consistency, the files of all identified children who had received a diagnosis of FAS were also reviewed in the same manner.

**Data Analysis**

Categorical data regarding the presence or absence of facial dysmorphism, growth retardation, and/or CNS dysfunction was used to identify the number of children meeting criteria for FAS, FAE(G), FAE(D), and FAE(X) subgroups. As previously stated, this information was obtained from medical and psychological assessment reports by clinicians with expertise in assessing the damaging effects of prenatal alcohol exposure.

**Results**

It was hypothesized that a spectrum of four diagnostic subgroups (i.e., FAS, FAE(G), FAE(D), and FAE(X)) would be identified using archival and categorical information regarding facial dysmorphism, growth retardation, and CNS dysfunction.

Three diagnostic subgroups (i.e., FAS, FAE(D), and FAE(X)) were identified, and surprisingly no cases meeting FAE(G) criteria were identified. Five cases were excluded because the diagnosing pediatrician documented that there was insufficient evidence of excessive prenatal alcohol exposure. Sixty-nine of the remaining 128 cases met study criteria for FAS (54%); 30 met criteria for FAE(D) (23%); 0 met study criteria for FAE(G) (0%); and 29 met criteria for FAE(X) (23%). Table 6a provides a summary of results from this file review.

Although no patients met study criteria for FAE(G), two came close. One subject had evidence of growth retardation and central nervous system involvement, but this child also met exclusion criteria for complicated prematurity (i.e., intraventricular hemorrhage). Another subject had growth retardation, central nervous system involvement, and “mild” facial dysmorphism (i.e., indistinct philtrum, and thin upper lip). These mild findings
meet study criteria for FAS and the subject was classified as FAS for the purpose of this study.
Table 6a. Number of Children Meeting Criteria for Diagnostic Subgroups

<table>
<thead>
<tr>
<th>Diagnostic Subgroups</th>
<th>Number of Children Identified</th>
<th>Percentage of Study Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAS</td>
<td>69</td>
<td>54%</td>
</tr>
<tr>
<td>FAE(D)</td>
<td>30</td>
<td>23%</td>
</tr>
<tr>
<td>FAE(G)</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>FAE(X)</td>
<td>29</td>
<td>23%</td>
</tr>
<tr>
<td>Total</td>
<td>128</td>
<td>100%</td>
</tr>
</tbody>
</table>
Discussion

Part 1 yielded findings pertaining to the identification of an a priori spectrum of diagnostic subgroups with a history of excessive prenatal alcohol exposure (i.e., FAS, FAE(D), FAE(G), and FAE(X). Three of the four diagnostic subgroups (i.e., FAS, FAE(D), FAE(G), and FAE(X) were identified using categorical information regarding facial dysmorphology, growth retardation, and CNS dysfunction. Surprisingly, a FAE(G) subgroup was not found in this large sample ascertained using clinical and epidemiological methods.

This was the first study to determine systematically if a spectrum of diagnostic subgroups with a history of excessive prenatal alcohol exposure could be identified using categorical data regarding the presence or absence of the three major features of the damaging effects of excessive prenatal alcohol exposure. To the author's knowledge, the absence of a FAE(G) subgroup or its equivalent has not been reported previously. Results from Part 1 of this study have implications for furthering understanding of teratogenic theory and for directing clinical research and practice. These implications will be presented in the General Discussion section of this study.

Due to the inherent limitations associated with using categorical data to evaluate diagnostic subgroups, Part 2 of this study included dimensional measures of growth retardation (i.e., height and weight) and CNS dysfunction (i.e., neuropsychological and behavioural components of attention, IQ, and head circumference). While categorical data is useful for identifying individuals with specified features associated with clinical impairment, dimensional measurement facilitates the evaluation of diagnostic characteristics on a continuum from substantially above average to substantially below average.

Dimensional measurements of growth and CNS dysfunction are routinely reported in medical reports or psychology files in the form of height, weight, head circumference measures and IQ scores. Although dimensional measurement of the dysmorphic features is possible using a computerized analysis of facial photographs, this type of information
was not available in medical charts.

Due to the importance of evaluating patient characteristics in an assessment of diagnostic subgroups, Part 2 of this study also included information on socio-economic status, race, and age at diagnosis. This was done in order to determine if diagnostic subgroups differed on demographic characteristics potentially associated with CNS dysfunction.

Part 1 of this study provided initial support for the validity of the IOM's diagnostic classification involving three diagnostic subgroups based upon the presence or absence of categorical diagnostic criteria. However, additional research was needed to evaluate the clinical validity and utility of these three subgroups using dimensional measures of CNS dysfunction. More specifically, what are the differences and similarities between these three subgroups using sensitive measures of CNS dysfunction, and do subgroups exhibit a clinically significant attention deficit? Part 2 investigated this question using neuropsychological and behavioural components of attention.
PART 2: CONTINUITY AND COMPARABILITY

Part 2 of this study examined the continuity and comparability (level of attention dysfunction) of FAS and FAE subgroups on neuropsychological and behavioural components of attention. Three hypotheses were evaluated: 1) a statistical difference hypothesis, 2) a statistical equivalence hypothesis, and 3) a clinical impairment hypothesis.

Hypotheses

Statistical Difference Hypothesis

It was hypothesized that the FAS subgroup would exhibit greater response-time variability on the Sustain component of attention (i.e., Sustain\textsubscript{response-speed-variability}) when compared to the FAE(D) and the FAE(X) subgroups, after controlling for IQ.

This hypothesis was based, in part, upon findings by Streissguth et al. (1994) who identified variability of reaction time on a sustained attention task as being correlated with levels of maternal alcohol consumption during pregnancy. It was also supported by Mattson et al.'s (1994) neuroimaging finding of diencephalon volume being significantly reduced in FAS but within normal limits in FAE. This is pertinent as the diencephalon is one of the major regions involved in the modulation of the Sustain component of attention (Mirskey et al., 1995).

Statistical Equivalency Hypothesis

After controlling for IQ, the performance of all three diagnostic subgroups (i.e., FAS, FAE(D), and FAE(X)) will be equivalent on five components (i.e., Encode, Focus-Execute, Shift, Inattention, and Hyperactivity-Impulsivity) and two subcomponents (i.e., Sustain\textsubscript{accuracy}, Sustain\textsubscript{response-speed}) of attention.

The prediction of subgroup equivalency on the Sustain\textsubscript{accuracy}, Sustain\textsubscript{response-speed} subcomponents of attention was based upon Streissguth et al.'s (1994) findings which
indicate response accuracy and response speed on a sustained attention task were not substantially correlated with maternal alcohol consumption during pregnancy.

The prediction of subgroup equivalency on Encode, Focus-Execute, and Shift components of attention was based upon research findings indicating that brain structures primarily involved in the modulation of these components of attention are damaged to a comparable extent in FAS and FAE. Mirsky et al. (1989) assert that Focus-execute, Shift, and Encode components of attention are modulated primarily by cerebral cortex (i.e., temporal, parietal, frontal), basal ganglia, and limbic system structures of the brain. Mattson et al. (1994) found that the proportional volume of the basal ganglia was significantly reduced in both FAS and FAE. Cortex and limbic system structures have also been found to be vulnerable to the damaging effects of alcohol throughout pregnancy (Guerri, 1998). The prediction of subgroup equivalency on the Hyperactive-Impulsive and Inattention components of attention was based upon findings by Nanson and Hiscock (1990), and LaDue, Streissguth and Randel (1992) which both found that parents consistently describe children with FAS or FAE as being hyperactive and inattentive.

Clinical Impairment Hypothesis

It was predicted that all diagnostic subgroups (i.e., FAS, FAE(D), and FAE(X)) would exhibit a “clinically significant attention deficit” using neuropsychological and behavioural components of attention. This hypothesis was based upon findings from previous studies which have found that children with FAS or FAE consistently exhibit significant attention related difficulties (Nanson & Hiscock, 1990; LaDue, Streissguth, & Randels, 1992). A “clinically significant attention deficit” was defined as one standardized normative score that was less than or equal to 2 standard deviations below the mean, or two or more scores that were less than or equal to 1.4 standard deviation units below the mean. IQ was not used as a covariate in these analyses as the primary focus was upon level of attention function regardless of IQ.

A summary of all hypotheses for Part 2 of this study is provided in Table 6b.
Table 6b. Summary of Attention Hypotheses

<table>
<thead>
<tr>
<th>Hypothesis Type</th>
<th>Attention Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statistical Difference</td>
<td>Sustain&lt;sub&gt;response-speed-variability&lt;/sub&gt;</td>
</tr>
<tr>
<td>Statistical Equivalence</td>
<td>Sustain&lt;sub&gt;accuracy&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td>Sustain&lt;sub&gt;response-speed&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td>Encode</td>
</tr>
<tr>
<td></td>
<td>Focus-Execute</td>
</tr>
<tr>
<td></td>
<td>Shift</td>
</tr>
<tr>
<td>Clinical Impairment</td>
<td>All Neuropsychological and</td>
</tr>
<tr>
<td></td>
<td>Behavioural Attention</td>
</tr>
<tr>
<td></td>
<td>Components and Subcomponents</td>
</tr>
</tbody>
</table>
Method

Design

This study used a quasi-experimental design in which participants were assigned to one of three clinical subgroups based upon a priori diagnostic characteristics associated with excessive prenatal alcohol exposure. A quasi-experimental design is identical to a true experiment except that it employs careful sample selection procedures and subgroup matching to control for confounds that may have influenced subgroup performance instead of random assignment (Alloy, 1999). Because there are necessary limits to experimental manipulation with human participants, random assignment of unborn children and pregnant mothers to different prenatal alcohol exposure subgroups is obviously not an option.

Sample Selection

Participants for this study were selected from the epidemiological, clinical, and research population of patients with FAS, FAE(D), or FAE(X) that was identified in Part 1. As previously reported, this population consisted of 128 adolescent and pre-teen children between 10 and 14 years of age. Ascertainment methods were detailed previously.

Exclusion Criteria. Patients were excluded from selection for possible participation in Part 2 if they met one or more of the following criteria:

1. If the patient lived in a remote area of Saskatchewan or another province. This was done due to the time and financial resources associated with families travelling to Saskatoon.

2. If a patient had a Full Scale IQ score that was less than 50. It is common practice in neuroscience research to exclude patients with extremely low IQ levels when evaluating specific aspects of cognitive functioning (E. Courchesne, personal communication, May, 1997). This is done because when general cognitive abilities are extremely low there may be multiple factors contributing to
the severity of the disability, and performance on specific aspects of cognitive functioning are likely to be uniformly low.

(3) If a patient tracking record in the ABCD Program indicated that the child had been lost to clinical follow-up.

(4) If a patient had a neurological impairment caused by a condition(s) other than prenatal alcohol exposure (e.g., severe meningitis; documented head injury; complicated prematurity such as respiratory distress syndrome, intraventricular hemorrhage, or a significant hearing loss). This was done to avoid the potential confound of findings being related to a form of brain injury other than excessive prenatal alcohol exposure.

(5) If the diagnosing pediatrician determined that there was insufficient evidence of a history of excessive prenatal alcohol exposure. This was done to ensure that all patients participating in this study were in fact exposed to excessive amount of alcohol prenatally.

(6) If medical records indicated that they were deceased. Habbick, Nanson, Snyder, and Casey (1997) found a higher rate of mortality in children with FAS compared to the general population.

There was a difference between the observed and the expected frequency of subjects excluded from the three diagnostic subgroups ($\chi^2 (2, N = 128) = 6.8$, $p = .03$). The percentage of the total number of subjects excluded by subgroup were as follows: FAS = 22%, FAE(D) = 7%; and FAE(X) = 3% (see Table 7a). Follow-up analyses indicated that a statistical difference only existed for the FAS versus FAE(X) subgroup comparison ($\chi^2 (2, N = 98) = 6.7$, $p = .01$).
Table 7a. Number of Patients Meeting Study Inclusion or Exclusion Criteria for Diagnostic Subgroups

<table>
<thead>
<tr>
<th>Criteria</th>
<th>FAS</th>
<th>FAE(D)</th>
<th>FAE(X)</th>
<th>Row Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion</td>
<td>41 (32%)</td>
<td>21 (16%)</td>
<td>25 (20%)</td>
<td>87 (68%)</td>
</tr>
<tr>
<td>Exclusion</td>
<td>28 (22%)</td>
<td>9 (7%)</td>
<td>4 (3%)</td>
<td>41 (32%)</td>
</tr>
<tr>
<td>Totals</td>
<td>69 (53%)</td>
<td>30 (23%)</td>
<td>29 (23%)</td>
<td>128 (100%)</td>
</tr>
</tbody>
</table>

Note. Tabled values represent the number of subjects per subgroup meeting subgroup inclusion or exclusion criteria.
The number of patients excluded from each of the six exclusion subcategories was
evaluated descriptively instead of using the chi-square statistic as this statistic is
inaccurate when the expected frequency in any cell is small (i.e., less than 5) (Norman &
Streiner, 1994). Two children were excluded from inclusion in the FAS subgroup as they
were deceased. No deceased children were identified in either the FAE(D) and the
FAE(X) subgroups (see Table 7b). The mortality rate in the FAS subgroup of 2.9%
(2/69) is considerably higher than what would be expected in the general population (i.e.,
1.7%, Habbick et al., 1997). This finding is also consistent with the high mortality rate in
an epidemiological study of children with FAS in Saskatchewan (Habbick et al., 1997).

A comparable percentage of subjects from each of the three subgroups were
excluded because they live in Northern Saskatchewan [FAS = 16% (16/69); FAE(D) =
13% (4/30); and FAE(X) = 10% (3/29)]. Nine percent (12/69) of FAS subjects, 2
percent of FAE(D) subjects, and no FAE(X) subjects were excluded from possible
inclusion in this study because of an IQ score less than 50. This finding is consistent with
previous reports of a lower IQ in FAS compared to FAE subgroups (Mattson et al.,
Table 7b. Number of Patients Meeting Study Criteria for Exclusion Subcategories by Diagnostic Subgroup

<table>
<thead>
<tr>
<th>Criteria</th>
<th>FAS</th>
<th>FAE(D)</th>
<th>FAE(X)</th>
<th>Row Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern Sask.</td>
<td>11</td>
<td>4</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>IQ &lt; 50</td>
<td>12</td>
<td>2</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Neurologic Comorbidity</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Deceased</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Totals</td>
<td>69</td>
<td>30</td>
<td>29</td>
<td>128</td>
</tr>
</tbody>
</table>

Note. Tabled values represent the number of subjects per subgroup meeting subgroup inclusion or exclusion criteria.
Subjects

Thirty adolescent and pre-teen children clinically referred with a history of excessive prenatal alcohol exposure participated in this study. Ten participants were selected from each of the three diagnostic subgroups identified in the previous study (i.e., FAS, FAE(D), and FAE(X)).

A parent or guardian of each child selected for possible participation in Part 2 was contacted via a letter from the medical director of the ABCD Program. This letter described the purpose and the nature of activities involved in study participation. This letter also requested a response by mail or phone indicating whether or not there was interest in study participation. Hospital staff called parents who did not respond to this letter. After hospital staff had contacted parents or guardians the names of parents and children interested in participating in this study were provided to the author. The author then called the identified parents to explain the study in more detail, answer questions, and invite participation.

Subgroup Matching

Subgroups were matched as closely as possible on age and sex. Living situation and race were evaluated retrospectively. For the purpose of this study, living situation denotes if a biological parent(s), a foster parent(s), or an adoptive parent(s) was caring for the child. Living situation was used instead of socio-economic status as many of the children clinically referred with a history of prenatal alcohol exposure are not cared for by a biological or adoptive parent, and many have a history of being cared for by a series of foster parents. Furthermore, it was important to evaluate possible confounds associated with living situation since placement in multiple foster homes during the early years can be associated with attachment and behavioural difficulties.

Subgroup characteristics regarding age, sex, living situation, and race are presented in Table 8. The average age of all three groups was very similar, between 12 and 13 years of age. There was an equal number of male (5) and female (5) participants in the FAE(D) group, but this balance was not obtained in either the FAS (male = 7; female = 3) or the FAE(X) (male = 8; female = 2) groups. One participant from each
group lived with a biological parent and all others lived with either a foster or adoptive parents. The majority of participants (73%) were of aboriginal descent. This is a common finding in studies of individuals with FAS in Canada and the Western United States.
Table 8. Matching Characteristics for Diagnostic Subgroups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FAS (n = 10)</th>
<th>FAE(D) (n = 10)</th>
<th>FAE(X) (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age At Testing (SD)</td>
<td>13.3 (1.7)</td>
<td>12.3 (1.6)</td>
<td>12.2 (1.2)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 7</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Female 3</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Living Situation</td>
<td>Biological Parent(s) 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Adoptive Parents 4</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Foster Parents 5</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Race</td>
<td>Aboriginal 7</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Caucasian 3</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

Note. Tabled values represent the number of subjects per subgroup with the exception of the age at testing characteristic.
Diagnostic Characteristics

Information regarding facial dysmorphology, growth measures, and CNS dysfunction were obtained from medical and psychological assessment reports in hospital charts. Information from the archival file review from Part 1 provided sufficient information to determine whether or not the categorical diagnostic criteria were present or absent. Thus, a second file review for the 30 children participating in this Part 1 was conducted in order to obtain more detailed information regarding diagnostic criteria exhibited. For example, in Part 1 an IQ in the borderline or impaired range was sufficient to meet diagnostic criteria for CNS dysfunction. For the purposes of Part 2, a Full Scale IQ score was required.

Facial Dysmorphology. Both the FAS and the FAE(D) group had a similar rate of the three facial dysmorphology features that were found to best differentiate children with and without FAS (Astley & Clarren, 1995) (see Table 9). These are the three features that were taken as evidence of facial dysmorphology in this study. As previously stated, since the characteristic features of facial dysmorphology are the most reliably identified during early childhood, this information was obtain from archival diagnostic medical reports by pediatricians with expertise in the assessment of dysmorphology. All children in the FAS group were clinically diagnosed as exhibiting the facial phenotype associated with this condition as were the children with FAE(D).
Table 9. Facial Dysmorphology Features Exhibited by Diagnostic Subgroups

<table>
<thead>
<tr>
<th>Features</th>
<th>FAS n = 10</th>
<th>FAE(D) n = 10</th>
<th>FAE(X) n = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short Palpebral Fissures</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Indistinct Philtrum</td>
<td>8</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Thin Upper Lip</td>
<td>7</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

Note. Tabled values do not add up to 10 per subgroup because archival medical reports indicated that some children exhibited more than one feature.
**Growth Retardation.** The growth measurements that were used in the diagnostic assessment of FAS, FAE(D), or FAE(X) are reported in Table 10 as z-scores. Z-scores were calculated using norm referenced data of a normal sample regarding height and weight by age and sex (Tanner, 1973). Generally, these measurements reflect the first time the child was seen by the FAS assessment team; however, in some cases reliable records of earlier growth measurements were available and were used by the diagnosing pediatrician.

The height of the FAS group was significantly lower than the height of either the FAE(D) or the FAE(X) groups ($M_{FAS} = -1.3$, $M_{FAE(D)} = -1.1$, $M_{FAE(X)} = .5$; $F(2,27) = 6.1$, $p = .007$). Similarly, the weight of the FAS group used in the diagnostic assessment was lower than the weight of either the FAE(D) or the FAE(X) groups ($M_{FAS} = -1.9$, $M_{FAE(D)} = .3$, $M_{FAE(X)} = .4$; $F(2,27) = 36.3$, $p < .00001$). These differences in the height and weight between the FAS and both the FAE(D) and FAE(X) groups are expected as they reflect subgroup diagnostic criteria. More specifically, evidence of growth retardation is required to meet study criteria of FAS but not of either FAE(D) or FAE(X).

It is of interest to note that the growth assessment for the FAS group occurred at an earlier age ($M_{FAS} = 2.4$) in comparisons with the age at which growth measurements were available for the FAE(D) and FAE(X) groups ($M_{FAE(D)} = 6.7$, $M_{FAE(X)} = 6.4$, $F(2,27) = 5.0$, $p = .01$). This suggests that children with FAE(D) and FAE(X) are generally seen for an initial diagnostic assessment due to complications resulting from excessive prenatal alcohol exposure at a substantially later age than children with FAS (approximately 2.5 versus 6.5 years of age for FAS and FAE subgroups respectively).
Table 10. Growth Characteristics of Diagnostic Subgroups

<table>
<thead>
<tr>
<th>Measure</th>
<th>FAS n = 10</th>
<th>FAE(D) n = 10</th>
<th>FAE(X) n = 10</th>
<th>F(2,27)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M    SD</td>
<td>M    SD</td>
<td>M    SD</td>
<td>E(2,27)</td>
<td>p</td>
</tr>
<tr>
<td>Height</td>
<td>-1.3a (1.6)</td>
<td>-0.03b (0.8)</td>
<td>0.5b (1.1)</td>
<td>6.1</td>
<td>.007</td>
</tr>
<tr>
<td>Weight</td>
<td>-1.9a (.6)</td>
<td>0.03b (.6)</td>
<td>0.4b (.7)</td>
<td>36.3</td>
<td>&lt;.00001</td>
</tr>
<tr>
<td>Age at Assessment</td>
<td>2.4a (2.3)</td>
<td>6.7b (3.1)</td>
<td>6.4b (4.4)</td>
<td>5.0</td>
<td>.002</td>
</tr>
</tbody>
</table>

Note. Growth measurements were obtained from medical records and they are reported as z-scores. Means in a row with different superscripts are significantly different (p < .05) using the Newman-Keuls test.
CNS Dysfunction. The RSA (1989) criteria for the diagnostic domain of CNS dysfunction are broadly defined. In order to examine potential patterns, subcategories of criteria for this domain were examined. CNS dysfunction measurements from the most recent assessment for each subgroup are reported in Table 11 as categorical data and Table 12 as dimensional data. Since many participants have been seen previously for a psychological assessment as part of clinical follow-up or larger multi-disciplinary study of FAS and FAE (Habbick, Nanson, Snyder, Casey, & Schulman, 1996), WISC-III scores were available for many children. If scores were not available, a WISC-III was administered as part of the study assessment. This is consistent with the procedures used by Mattson et al. (1999).

Sixty percent of FAS subjects, 30 percent of FAE(D) subjects, and 10 percent of FAE(X) subjects exhibited microcephaly. This substantial difference between diagnostic subgroups regarding the proportion of subjects meeting criteria for microcephaly (head circumference below the 3rd percentile) supports the importance of evaluating head circumference using dimensional in addition to categorical measurement methods.

In contrast to the observed subgroup categorical differences with regards to microcephaly, the number of subjects per subgroup meeting diagnostic criteria for intellectual impairment (IQ score in the Borderline or Impaired range) was similar [(FAS (n = 5) versus FAE(D) (n = 4) versus FAE(X) (n = 5)]. Finally, all subjects met diagnostic criteria for behavioural dysfunction or deficit. This category was defined as ADHD, behaviour problems, or academic learning difficulties. This was an anticipated characteristic as subjects were ascertained from a sample of patients clinically referred for an assessment of an alcohol related condition and it is the behavioural dysfunction and deficits that usually prompt a referral of this nature.
<table>
<thead>
<tr>
<th>Sub-Category</th>
<th>FAS n = 10</th>
<th>FAE(D) n = 10</th>
<th>FAE(X) n = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcephaly</td>
<td>6</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Intellectual Impairment</td>
<td>5</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Behavioural Dysfunction or Deficit</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>
Using dimensional measurement, the head circumference of the FAS and FAE(D) groups was smaller than the head circumference of the FAE(X) group ($M_{FAS} = -2.1$, $M_{FAE(D)} = -1.4$, $M_{FAE(X)} = -0.4$; $F(2, 27) = 7.6$, $p = .002$; see Table 12). Although the difference between the head circumference of the FAS and FAE(D) subgroups was substantial ($z$-score difference $= .7$), this difference did not reach statistical significance. Head circumference measurements used in these analyses were obtained generally when a child was seen for a medical assessment by the FAS team pediatrician. In some cases, however, reliable records of earlier growth measurements were available and were used by the diagnosing pediatrician.
Table 12. Dimensional CNS Dysfunction Characteristics by Diagnostic Subgroup

<table>
<thead>
<tr>
<th>Measures</th>
<th>FAS n = 10</th>
<th>FAE(D) n = 10</th>
<th>FAE(X) n = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
</tr>
<tr>
<td>Head Circumference</td>
<td>-2.1a (1.0)</td>
<td>-1.4a (1.0)</td>
<td>-0.4b (0.9)</td>
</tr>
<tr>
<td>Full Scale IQ</td>
<td>73.9 (14.8)</td>
<td>86.2 (16.2)</td>
<td>83.3 (15.4)</td>
</tr>
<tr>
<td>Age At IQ Assessment</td>
<td>11.1 (2.1)</td>
<td>9.6 (2.2)</td>
<td>11.2 (1.9)</td>
</tr>
</tbody>
</table>

Note. Head circumference is reported as z-scores (M = 1, SD = 0) and Full Scale IQ scores are reported as standard scores (M = 100, SD = 15). Means in a row with different superscripts are significantly different (p < .05) using the Newman-Keuls test.
Although the Full Scale IQ scores for the three diagnostic subgroups were not statistically different \((F(2,27) = 1.7, p = .20)\), there was a substantial difference between the FAS subgroup \(M_{FAS} \text{ IQ} = 74\) and the two FAE subgroups \(M_{FAE(D)} \text{ IQ} = 86, M_{FAE(X)} \text{ IQ} = 83\). The absence of a statistical difference between the FAS and FAE subgroups on IQ is likely a result of the relatively small subsample size \((n = 10)\) and the large within group variability of IQ scores.

This conclusion is supported by several findings from previous studies. First, this size of the difference in IQ scores between FAS and FAE groups has been consistently reported in previous studies (e.g., Streissguth et al., 1992; Mattson et al., 1997). Second, the IQ of the FAS and FAE subgroups obtained in this study are also almost identical to IQ levels reported by Mattson et al. (1997; \(M_{FAS} \text{ IQ} = 75, n = 34; M_{FAE} \text{ IQ} = 84, n = 13\)).

Finally a recent report by Streissguth (1997) also indicates that the IQ measures of FAS and FAE groups from available clinical studies are lower than the IQ scores obtained from a larger sample using broader ascertainment procedures. In this study the average IQ of a large \((n = 178)\) FAS group was 79 with scores ranging from 20 (profound mental retardation) to 120 (high average intelligence). The average IQ of the large \((n = 295)\) FAE group was 90 with scores ranging from 49 (moderate mental retardation) to 142 (superior intelligence). There was no difference between subgroups regarding the age at which an IQ assessment was conducted.

**Medications**

Many children with FAS or FAE receive pharmacological treatment for Attention Deficit Hyperactivity Disorder (ADHD). In this study, medications known to enhance attention (i.e., Ritalin and Cylert) were discontinued prior to testing. A one-day washout period was used with Ritalin because of its short half-life (2.4 hours, Compendium of Pharmaceuticals and Specialties, 1996). A two-day washout period was used with Cylert because it has a longer half-life (12 hours; Compendium of Pharmaceuticals and Specialties, 1996). This was done so that performance on measures of components of attention would not be influenced by pharmacological treatment to increase attention abilities.
Other medications (i.e., Risperidone and Clonidine) were not discontinued for medical reasons. Risperidone and Clonidine are used with this population primarily to assist with behavioural and emotional regulation. Table 13 provides a summary of patient medications.
<table>
<thead>
<tr>
<th>Type</th>
<th>FAS n = 10</th>
<th>FAE(D) n = 10</th>
<th>FAE(X) n = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritalin</td>
<td>6</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Cylert</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Risperidone</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Clonidine</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Note. Tabled values represent the number of subjects per subgroup being treated with prescription medication.
Attention Components

Attention was assessed using four neuropsychological (Mirsky (1989) and two behavioural components (Conners, 1997). The Encode component of attention was assessed using the Digit Span subtest of the WISC-III (Wechsler, 1991) and the Finger Windows subtest of the Wide Range Assessment of Memory and Learning (WRAML; Sheslow & Adams, 1990). The Focus-Execute component of attention was assessed using letter cancellation tests (Talland, 1965; Rourke, Bakker, Fisk, & Strang, 1983), and the Symbol Digit Modalities Test. The Shift component of attention was assessed using the Wisconsin Card Sorting Test (WCST; Heaton, Chelune, & Talley, 1993). The Sustain component of attention was assessed using Conners’ (1995) Continuous Performance Test. The Inattentive and Hyperactive-Impulsive components of attention were assessed using Conners’ Parent Rating Scale – Revised (CPRS-R; 1997). A brief description of each test used in this study follows.

Digit Span

This subtest requires a participant to repeat a random series of numbers in a forward and backward condition.

Finger Windows

This subtest requires participants to repeat a random series of pointing sequences demonstrated by the examiner in a forward condition. It is analogous to a visual version of the Digit Span subtest

The Finger Windows subtest was used instead of the Arithmetic subtest of the WISC-III from Mirsky’s model for two reasons. First, the performance of individuals with FAS on the Arithmetic subtest as a measure of Encode would likely be confounded by the significant difficulty they have understanding basic arithmetic concepts (Kopera-Frye, Keaheane, & Streissguth, 1994). Second, using the Finger Windows subtest provides a measure of visual attention span that is analogous to the measure of verbal attention span from the Digit Span subtest.
Letter Cancellation Tests

The letter cancellation tests used in this study included the three subtests of the Talland Letter Cancellation Test (Talland, 1965) and the Single Letter subtest from the Underlining Test (Rourke, Bakker, Fisk, & Strang, 1983). The Single Letter subtest of the Underlining Test was included in addition to the Talland Letter Cancellation Test because task completion requirements are less than those associated with the Talland Letter Cancellation Test. The decision to include this subtest in the test battery for this study was made on the basis of pilot testing data by Brock (1999) which indicated that some FAS subjects had difficulties meeting the task demands of subtests from the Talland Letter Cancellation Test. Thus, by adding the Single Letter subtest, performance on conditions of a letter cancellation test was assessed across a larger range of task complexity. However, the performance of diagnostic subgroups from the current study indicated that there were no statistically significant differences between subgroups on any of the subtests from the Talland’s or Rourke’s letter cancellation tests. Thus, for the purpose of this study subgroup performance on letter cancellation tests was reported as a single composite measure referred to as the Letter Cancellation Test. A detailed description of the three conditions from Talland’s Letter Cancellation Test and the one condition from Rourke’s Underlining test follows.

Talland Letter Cancellation Test. The Talland Letter Cancellation Test (Talland, 1965) requires individuals to scan rows of upper and lower case letters to find and cross out as many of an assigned target as possible in 60 seconds (Mirsky, Fantie, & Tatman, 1995). This test includes three conditions. In the "Capital" condition, individuals are asked to draw a line through all capital letters. In the "Space" condition, individuals are asked to draw a line through the letter immediately before and after each double space while ignoring letter case. Finally, in the "Both" condition, individuals are asked to draw a line through all capital letters and the letters immediately before and after each double space.

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Single Letter Subtest of the Underlining Test. In the Single Letter subtest of the Underlining Test (Rourke, Bakker, Fisk, & Strang, 1983) the letter "s" is interspersed among 360 randomized lower case letters. The subject is required to scan rows of lower case letters to find and cross out as many of an assigned target as possible in 30 seconds. The demands of this task are not as great as those associated with the Talland subtests because only lower case letters are used instead of lower and upper case letters, and it is an easier perceptual task because there is more space between letters and rows.

Symbol Digit Modalities Test (SDMT). The SDMT (Smith, 1982) is a paper and pencil test that presents participants with a key or sample consisting of two boxes containing meaningless geometric designs in the upper row and the numbers 1 through 9 in the lower row. The task stimuli are a series of boxes containing a meaningless symbol in the upper part and an empty space in the lower part. The participant must identify the number from the key that is paired with the appropriate stimulus symbol in both written and oral conditions.

The Symbol Digit Modalities Test (SDMT; Smith, 1982) was used instead of the Digit Symbol subtest of the WISC-III from Mirsky’s model for several reasons. Although these tests both require visual scanning, target selection, and the execution of a response, the Digit Symbol subtest requires the written transcription of nonsense symbols while the SDMT requires the transcription of numbers in both written and oral conditions. One important advantage of using the SDMT in measuring the Focus-Execute component of attention is that the transcription of numbers is a more automatized fine motor and perceptual skill than the transcription of nonsense geometric symbols. This is particularly important with samples affected by prenatal alcohol exposure as numerous studies have found significant difficulties with fine motor ability (e.g., Barr, Streissguth, Darby, & Sampson, 1990; Janzen, Nanson, & Block, 1995). Another important advantage of using the SDMT is that it contains both written and oral response conditions. This is one way to assess spatial and verbal aspects of Focus-
execute attention independent from fine motor ability.

**Wisconsin Card Sorting Test (WCST)**

This test requires that an individual use feedback regarding correct and incorrect card sorting responses (i.e., colour, form, and number) to find and maintain the correct response set. Then after a predetermined number of consecutive correct responses the correct response set changes without warning. Thus, the individual is required to disengage from the previous response set and shift his or her focus of attention to find and follow a new criterion.

**Conners’ Continuous Performance Test (CPT)**

**Hardware and Software Requirements.** The Conners’ (1995) CPT was administered using an IBM compatible computer that met specified hardware and software requirements to ensure the accuracy of timing and stimulus presentation mechanisms. Single letters were displayed for 250 milliseconds each and the time between letter presentations changed between 1, 2, and 4 second intervals in a systematic manner. The task took 14 minutes and 10 seconds to complete.

**Instructions.** Participants are asked to press the space bar on a keyboard when any letter is presented, except the letter “X”. Thus, the letter “X” is a non-target stimulus, and all other letters are target stimuli. In order to ensure that speed and accuracy were equally emphasized subjects were also instructed to press the space bar as quickly as they could without making mistakes.

**Block and Sub-Blocks.** Letters are grouped into 6 blocks with each block containing 3 ISI sub-blocks for a total of 18 sub-blocks. Although each block contains a 1, 2, and 4 second ISI sub-block, the order of sub-block presentation varies between the 6 blocks (see Figure 3). Each sub-block contains 18 target letters and 2 non-target letters. Thus, 90 percent of letters presented are targets. There are a total of 324 target letters and 36 nontarget letters.
Figure 3. The Conners' CPT Paradigm. Letter stimuli are grouped into 6 blocks with each block containing 3 ISI sub-blocks. Each block contains a 1, 2, and 4 second ISI sub-block, but the order of sub-block within each block varies. There are 18 target letters and 2 non-target letters in each sub-block for a total of 324 targets and 36 non-targets. It takes 14 minutes to complete.
CPT Scores. After task performance, the CPT program generates a report regarding a participant’s performance including raw and norm-referenced T-scores for a variety of accuracy, response speed, and response-speed consistency scores. A detailed description of the specific CPT scores used to measure the Sustain component of attention in this study is provided in the subsequent subsection entitled “Measures and Scores for Components of Attention”.

Data Transformations. Prior to computing reaction time test T-scores, logarithmic transformations were performed by the CPT program. This is necessary as reaction time data frequently produce a distribution that is positively skewed. An evaluation of data collected in the standardization sample indicated that although no single transformation produced approximately normal distributed data for each and every reaction time score for every sex and age group, logarithmic transformations worked well in the vast majority of cases (Conners, 1995).

The distribution of misses or omission errors also departed from normality in the standardization sample in a manner that was not easily amended via data transformation. For this variable no transformation was made. However, both the number of omission errors made and a corresponding norm-referenced percentile were reported. For the purpose of this study, percentiles were converted to T-scores so that mean subgroup performance could be calculated using scores from a scale with an interval level of measurement. The CPT program also made conversions for Hit RT scores so that a higher T-score would reflect a faster response time than a lower T-score.

Inattention and Hyperactive-Impulsive Subscales

The Inattentive and Hyperactive-Impulsive subscales from Conners’ Parent Rating Scale – Revised: Long Version (1997) were used to assess behavioural components of attention. This paper and pencil parent rating scale contains 80 items that are brief descriptions of common problems that children have. Nine interspersed items assess Inattention symptoms and 9 interspersed items assess Hyperactive-Impulsive symptoms.
Parents are asked to rate each item according to their child’s behaviour in the past month. For each item they are also asked to rate the severity of the problem on a four-point scale from “never” to “very often”.

**Reliability and Validity**

Support for the reliability and validity of tests used to assess components of attention in Mirsky’s model is drawn from studies that have found the same four factors using different factor analysis procedures (i.e., exploratory and confirmatory) with samples of different ages (i.e., adults and children) (Mirsky, Fantie, & Tatman, 1995). The measures with the highest factor loadings on each of the model’s four components of attention were chosen for use in this study with three substitutions and one addition. These modifications and the rationale supporting them were described above.

Support for the reliability and validity of measures used to assess Conners’ behavioural model of attention is drawn from two major sources. First, these two scales were developed by being based upon the diagnostic criteria for Attention Deficit/Hyperactivity Disorder (ADHD) of the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV). Second, the results of a confirmatory factor analysis by Conners (1997) using two large groups of children (\(n = 2,197\) and \(n = 1,661\)) between 3 and 17 years of age both identified a two-factor model consisting of Inattention and Hyperactive-Impulsive items groupings.

**Measures and Scores**

Since several of the attention tests used in this study provided more than one score per measure, specific scores were selected for inclusion in this study on an a priori basis. The selected scores are list below and in Table 14. The **Encode component** of attention was measured using standard scores from the Digit Span subtest from the WISC-III, and the Finger Windows subtest from the WRAML. The **Focus-Execute component** of attention was measured using standard scores from the Symbol Digit Modalities Test (oral and written conditions), and the total raw score from a Letter Cancellation Test. The **Shift component** of attention was measured using the percent preservative errors standard score from the Wisconsin Card Sorting Test.
The Sustain component of attention was measured using measures of performance accuracy, response-speed, and response-speed-variability from the Conners' CPT. Each of the three aspects of the Sustain component of attention are referred to as a subcomponent for the purpose of this study, and they were measured in the following manner.

1. The accuracy subcomponent was measured using standard scores for: (a) the total number of targets missed or Misses, and (b) the total number of false alarm responses or False Alarms.

2. The response-speed subcomponent was measured using standard scores for: (a) mean target hit reaction time for the entire test or Overall Hit RT, and (b) slope of change in mean hit reaction time over three ISI’s (1, 2, and 4 s) or Hit RT ISI Change.

3. The response-speed-variability subcomponent was measured using standard scores for: (a) standard error of response time to target hits for entire test or Overall Hit RT SE, and (b) slope of change in hit reaction time standard error over three ISI’s (1, 2, and 4 seconds) or Hit RT SE ISI Change.

An illustration of the use of linear regression to calculate a slope of change for an individual subject for Hit RT ISI Change and SE Hit RT ISI Change is provided in Figure 4. The mean values for RT and mean SE values at each ISI interval were calculated on a large number of data points (n = 108). The raw score values for slope of change measures had a possible range of +1 to −1.

The Inattention and Hyperactive-Impulsive components of attention were measured using standard scores from the Conners’ Parent Behavioural Rating Scale – Revised Edition: Long Form.

Raw scores were converted to standard scores (e.g., T-scores, z-scores) adjusted for age and sex of participant with one exception. Raw scores are reported for performance on the Letter Cancellation Test because normative data were not available for this measure.
Figure 4. Slope of change for Hit RT ISI Change (top) and SE Hit RT ISI Change (bottom) calculated using linear regression.
Table 14. Measures of Attention Components

<table>
<thead>
<tr>
<th>Component / Measure</th>
<th>Score Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encode</td>
<td></td>
</tr>
<tr>
<td>Digit Span</td>
<td>Standard Score</td>
</tr>
<tr>
<td>Finger Windows</td>
<td>Standard Score</td>
</tr>
<tr>
<td>Focus-execute</td>
<td></td>
</tr>
<tr>
<td>Symbol Digit Modalities Test</td>
<td></td>
</tr>
<tr>
<td>- Written Condition</td>
<td>Standard Score</td>
</tr>
<tr>
<td>- Oral Condition</td>
<td>Standard Score</td>
</tr>
<tr>
<td>LetterCancellation Test</td>
<td>Raw Score</td>
</tr>
<tr>
<td>Shift</td>
<td></td>
</tr>
<tr>
<td>Wisconsin Card Sorting Test</td>
<td></td>
</tr>
<tr>
<td>- Perseverative Errors</td>
<td>Standard Score</td>
</tr>
<tr>
<td>- Number Categories Completed</td>
<td>Raw Score</td>
</tr>
<tr>
<td>Sustain</td>
<td></td>
</tr>
<tr>
<td>Continuous Performance Test</td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td></td>
</tr>
<tr>
<td>- Misses</td>
<td>Raw Score</td>
</tr>
<tr>
<td>- False Alarms</td>
<td>Standard Score</td>
</tr>
<tr>
<td>Response-Speed</td>
<td></td>
</tr>
<tr>
<td>- Overall Hit RT</td>
<td>Standard Score</td>
</tr>
<tr>
<td>- Hit RT ISI Change</td>
<td>Standard Score</td>
</tr>
<tr>
<td>Response-Speed- Variability</td>
<td></td>
</tr>
<tr>
<td>- Overall Hit RT SE</td>
<td>Standard Score</td>
</tr>
<tr>
<td>- Hit RT SE ISI Change</td>
<td>Standard Score</td>
</tr>
<tr>
<td>Inattention</td>
<td></td>
</tr>
<tr>
<td>Inattention Subscale, CPRS-R:L</td>
<td>Standard Score</td>
</tr>
<tr>
<td>Hyperactivity-Impulsivity</td>
<td></td>
</tr>
<tr>
<td>Hyperactive-Impulsive Subscale</td>
<td>Standard Score</td>
</tr>
<tr>
<td>CPRS-R:L</td>
<td></td>
</tr>
</tbody>
</table>

Note. RT = reaction time; SE = standard error; ISI = interstimulus interval; CPRS-R:L = Conners’ Parent Rating Scale – Revised: Long Form.

The standard scores used in statistical difference and equivalence analyses are norm-referenced T-scores.

However, norm-referenced z-scores were used in the analysis of a "clinically significant" neuropsychological attention deficit as they are commonly used in evaluations of this nature.
Test Administration

At the time of testing, informed consent was confirmed in writing from a participating parent or guardian and ascent was obtained from the child. Participants were tested individually by the author or by a research assistant. A research assistant was trained to administer attention measures according to standardized procedures. Participants were tested in a quiet room in the Kinsmen Children's Centre. Breaks were taken as requested or as required.

Data Transformations

Norm-Referenced Scores. All scores in the statistical difference, statistical equivalence, and clinical impairment analyses were converted to norm-referenced scores (T-scores or z-scores) with two exceptions. Scores for the Letter Cancellation Test were reported as raw scores because normative data was not available for this measure. Scores for the number of misses on the Conners’ CPT and the number of categories completed on the WCST were also reported as raw scores because the distribution of responses in the test standardization sample departed from normality in a manner that was incompatible with an interval level scale (such as a T-score). As previously described, prior to computing reaction time T-scores, the Conners’ CPT computer program conducted logarithmic transformations.

Trimmed Sample. All norm-referenced scores were capped at ± 4 standard deviation units around the mean. This is a data transformation procedure called trimming which is used to reduce the influence of outliers and reduce the skewness of a sample distribution (Howell, 1997). This procedure is used by researchers (e.g., Mattson, Riley, Gramling, Delis, & Jones, 1998) and test developers to reduce the effects of extreme outliers when estimating group performance. For example, the Conners' Parent Behaviour Rating Scale – Revised (1995) capped standard scores at ± 4 standard deviation units (i.e., T-scores of 90). The Wechsler Intelligence Scale for Children - Third Edition (WISC-III; 1991) capped standard scores at ± 3.7 standard deviation units.
(i.e., standard score range from 46 to 155).

One extreme score \((z = +5)\) on the written version of the Symbol Digit Modalities Test (SDMT) required capping. After test completion this participant reported that she had quickly memorized the symbol-number reference key and had written down the vast majority of numbers from memory. Although this reflects an efficient performance strategy it is rarely seen to this degree in children, and is not representative of the typical degree of visual scanning required for accurate performance.

On the Conners' Continuous Performance Test two reaction time variables required capping (i.e., Overall Hit RT SE, \(n = 5\); Hit RT ISI Change, \(n = 8\)).

Data Screening

After data transformations and prior to conducting ANCOVA and MANCOVA procedures, all attention scores were evaluated by subgroup with regards to the assumptions of multivariate analysis. There were no univariate or multivariate outliers within subgroups. The criteria used to evaluate univariate outliers was defined as a raw subgroup standardized score greater than 3.29 (\(p < .001\), two-tailed test; Tabachnick & Fidell, 1995). A multivariate outlier was defined as a Mahalanobis distance case value with a probability level of less than .001 (Tabachnick & Fidell, 1995). This is deemed to be a conservative estimate for identifying cases with an unusual pattern of scores.

Data screening procedures also indicated that subgroup data distributions satisfied the assumptions of normality, homogeneity of variance, homogeneity of variance-covariance matrices, linearity, multicollinearity, and singularity. Univariate normality of subgroup distributions was assessed using the Shapiro-Wilks normality statistic for small samples with the conventional but conservative alpha level of .01 (Tabachnick & Fidell, 1995). Univariate homogeneity of variance was assessed using Levene’s Test. Two attention scores (i.e., Overall Hit RT SE and Hit RT ISI Change) from the Conners’ CPT were identified as having heterogeneity of subgroup variance (\(p < .05\)). Controlling for unequal subgroup variance was particularly important for the ANCOVA procedures that were used in conducting statistical equivalency analyses with these two variables (Norman & Streiner, 1997). Thus, unequal variance t-test statistics were used when
indicated by Levene’s test.

Multivariate normality and homogeneity of variance-covariance matrices was assessed using the Box M statistic. Since this test is very sensitive to departures from normality, alpha level was set at .01 (Nouri, 1988). Multicollinearity (variables that are very highly correlated - > .90) and singularity or redundancy (one variable that is a combination of two or more variables) was assessed using the procedures developed by Belsely, Kuh and Welsch (cited in Tabachnick & Fidell, 1995). The covariate (IQ) was judged to be adequately reliable for covariate analysis.
Equivalence Analysis Procedure

Since an established procedure for conducting equivalency analyses with three groups, multivariate data (two or more attention scores per component), and a covariate was not available, the following statistical formulas and procedures were used:

1) an equivalency $t$ statistic formula (Stegner, Bostrom & Greenfield, 1996):
   a) $t_1 = \frac{M_{\text{difference}} + EC}{SE_{\text{difference}}}$, and
   b) $t_2 = \frac{M_{\text{difference}} - EC}{SE_{\text{difference}}}$,

2) subgroup statistics (i.e., $M_{\text{difference}}$ and $SE_{\text{difference}}$) adjusted for IQ using the ANCOVA procedure in SPSS (Nouris, 1994),

3) the Newman-Keuls procedure to control for familywise alpha when conducting all possible pairwise comparisons (Howell, 1997), and

4) an inference of equivalence between subgroups on a component of attention was only made when all scores comprising the component were statistically equivalent using univariate analyses. A criterion for component equivalency of this nature was necessary as a multivariate equivalency procedure was not available. This is a more stringent criterion than available via MANOVA procedures as MANOVA can detect when subgroups are different on a system of variables that individually may not show significant group differences.

5) The equivalency criterion was set at 20 percent due to the exploratory nature of this research and the limited power associated with a small subsample size ($n = 10$).

A more detailed discussion of the procedures and formulas used in equivalency analyses are provided in Appendix 1.

Results

Hypotheses are repeated in this section prior to presentation of results in order to facilitate a linkage between a priori predictions and findings.

Statistical Difference

After adjusting for IQ, it was predicted that the FAS subgroup would exhibit greater response-speed-variability on the Sustain subcomponent of attention
(Sustain\textsuperscript{response-speed-variability}) when compared to the FAE(D) and the FAE(X) subgroups. A comparison of the FAS(D) and the FAE(X) subgroups was conducted on an exploratory basis.

A multivariate analysis of covariance (MANCOVA) was conducted using norm-referenced T-scores for Overall Hit RT SE and Hit RT SE ISI Change. There was not a significant overall effect for subgroup (see Table 15). Since all possible pair-wise comparisons were of interest, the omnibus F statistic from the MANCOVA was evaluated as a prerequisite to considering univariate analyses (Tabachnick & Fidell, 1995).

Scores from the Sustain\textsuperscript{response-speed-variability} component of attention were not significantly related to the covariate IQ (see Table 15). Thus, using IQ as a covariate did not result in significant adjustment of subgroup means for this analysis. Adjusted and unadjusted subgroup means are presented in Table 16a and 16b, respectively.
Table 15. MANCOVA Results for Difference Analyses with FAS, FAE(D), and FAE(X) Subgroups

<table>
<thead>
<tr>
<th>COMPONENT / Subcomponent</th>
<th>Effect</th>
<th>Wilk's Lambda</th>
<th>F</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUSTAIN Response-Speed Consistency</td>
<td>Subgroup</td>
<td>.82</td>
<td>1.28</td>
<td>4,50</td>
<td>.29</td>
</tr>
<tr>
<td></td>
<td>Covariate (IQ)</td>
<td>.86</td>
<td>2.04</td>
<td>2,25</td>
<td>.15</td>
</tr>
</tbody>
</table>

125
Table 16a. Adjusted Norm-Referenced T-scores for Difference Analyses with FAS, FAE(D), and FAE(X) Subgroups

<table>
<thead>
<tr>
<th>COMPONENT / Subcomponent</th>
<th>Measure / Score</th>
<th>FAS (n = 10)</th>
<th>FAE(D) (n = 10)</th>
<th>FAE(X) (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUSTAIN Response-Speed-Variability</td>
<td>CPT</td>
<td>M</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td></td>
<td>RT SE</td>
<td>63.8</td>
<td>73.5</td>
<td>72.9</td>
</tr>
<tr>
<td></td>
<td>RT SE ISI</td>
<td>55.4</td>
<td>69.4</td>
<td>63.6</td>
</tr>
</tbody>
</table>

Note. Means presented are adjusted for IQ.
<table>
<thead>
<tr>
<th>COMPONENT / Subcomponent</th>
<th>Measure / Score</th>
<th>FAS (n = 10)</th>
<th>FAE(D) (n = 10)</th>
<th>FAE(X) (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUSTAIN</td>
<td></td>
<td>M  SD</td>
<td>M  SD</td>
<td>M  SD</td>
</tr>
<tr>
<td>Response-Speed-Consistency</td>
<td>CPT</td>
<td>66.1 (6.3)</td>
<td>71.8 (18.8)</td>
<td>72.2 (15.2)</td>
</tr>
<tr>
<td></td>
<td>RT SE</td>
<td>56.6 (8.0)</td>
<td>68.5 (16.6)</td>
<td>63.3 (15.3)</td>
</tr>
</tbody>
</table>

Note. CPT = Conners’ Continuous Performance Test; RT = Reaction Time; SE = Standard Error; ISI = Inter-Stimulus-Interval.
**Component Equivalence**

After adjusting for IQ, it was predicted that all three subgroups (i.e., FAS, FAE(D) and FAE(X)) would be equivalent on the following seven components of attention: Sustain response-speed, Sustain accuracy, Encode, Focus-Execute, Shift, Inattention, and Hyperactive-Impulsive.

Results indicated that all three subgroups were equivalent on the Inattention component of attention, and the FAS versus the FAE(D) subgroup pair was equivalent on the Encode component (see the last column in Table 17a). As previously stated, an inference of component equivalency required all scores comprising a component to be statistically equivalent using univariate analyses. Adjusted and unadjusted subgroup means are presented in Table 17a and 17b, respectively.
Table 17a. Equivalency Results and Adjusted Means for Comparisons with FAS, FAE(D) and FAE(X) Subgroups

<table>
<thead>
<tr>
<th>COMPONENT / Subcomponent</th>
<th>Measure / Score</th>
<th>FAS (n = 10) M</th>
<th>FAE(D) (n = 10) M</th>
<th>FAE(X) (n = 10) M</th>
<th>SE diff</th>
<th>IQ Adjusted Pair-Wise Equivalency (p ≤ .05)</th>
<th>IQ Adjusted Component Equivalency ¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUSTAIN Response-Speed</td>
<td>CPT, Overall RT</td>
<td>34.1</td>
<td>37.7</td>
<td>34.4</td>
<td>5.1</td>
<td>FAS vs FAE(D)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CPT, RT ISI Change</td>
<td>62.4</td>
<td>74.5</td>
<td>74.7</td>
<td>6.4</td>
<td>FAE(D) vs FAE(X)</td>
<td></td>
</tr>
<tr>
<td>SUSTAIN Accuracy</td>
<td>CPT, Misses†</td>
<td>8.2</td>
<td>22.9</td>
<td>21.7</td>
<td>7.5</td>
<td></td>
<td>FAS vs FAE(D)</td>
</tr>
<tr>
<td></td>
<td>CPT, False Alarms</td>
<td>46.3</td>
<td>54.7</td>
<td>49.0</td>
<td>5.2</td>
<td></td>
<td>FAS vs FAE(D)</td>
</tr>
<tr>
<td>ENCODE</td>
<td>Digit Span</td>
<td>37.5</td>
<td>42.4</td>
<td>42.1</td>
<td>3.3</td>
<td>All Comparisons</td>
<td>FAS vs FAE(D)</td>
</tr>
<tr>
<td></td>
<td>Finger Windows</td>
<td>41.3</td>
<td>41.0</td>
<td>43.1</td>
<td>5.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOCUS-EXECUTE</td>
<td>SDMT Written</td>
<td>46.8</td>
<td>45.9</td>
<td>47.4</td>
<td>5.0</td>
<td>FAS vs FAE(X)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>45.0</td>
<td>44.2</td>
<td>45.9</td>
<td>6.8</td>
<td></td>
<td>FAS vs FAE(X)</td>
</tr>
<tr>
<td></td>
<td>Ltr Cancel†</td>
<td>32.0</td>
<td>32.4</td>
<td>30.9</td>
<td>4.5</td>
<td></td>
<td>FAS vs FAE(D)</td>
</tr>
<tr>
<td>SHIFT</td>
<td>WCST, Per Errors</td>
<td>42.9</td>
<td>46.2</td>
<td>51.6</td>
<td>4.7</td>
<td>FAS vs FAE(D)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WCST, Categories†</td>
<td>3.6</td>
<td>4.0</td>
<td>4.3</td>
<td>0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INATTENTION HYPERACTIVE- IMPULSIVE</td>
<td>CPRS-R:L</td>
<td>73.6</td>
<td>71.9</td>
<td>72.2</td>
<td>5.9</td>
<td>All Comparisons</td>
<td>All Comparisons</td>
</tr>
<tr>
<td></td>
<td>CPRS-R:L</td>
<td>77.1</td>
<td>75.4</td>
<td>63.6</td>
<td>6.3</td>
<td>FAS vs FAE(D)</td>
<td>FAS vs FAE(X)</td>
</tr>
</tbody>
</table>

Note. SE diff = SE of Difference; CPT = Conners' Continuous Performance Test; RT = Reaction Time; ISI = Inter-Stimulus-Interval; CPRS-R:L = Conners' Parent Rating Scale – Revised: Long Version.

(Table continues on next page)
Subgroup means were adjusted using IQ as the covariate.

Scores are presented as norm-reference T-scores with the exception of raw score values for CPT Misses, Letter Cancellation Test, and WCST Categories. Raw score values are denoted by the symbol †.

An inference of IQ adjusted component equivalency required all scores comprising a component to be statistically equivalent using a univariate equivalency analysis. Attention components with one or more equivalent subgroup comparison are presented in bold face type.
Table 17b. Unadjusted Norm-referenced T-Scores for Equivalency Analyses with FAS, FAE(D), and FAE(X) Subgroups

<table>
<thead>
<tr>
<th>COMPONENT / Subcomponent</th>
<th>Measure / Score</th>
<th>FAS (n = 10)</th>
<th>FAE(D) (n = 10)</th>
<th>FAE(X) (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
</tr>
<tr>
<td>SUSTAIN Response-Speed</td>
<td>CPT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall RT</td>
<td>33.7</td>
<td>(10.4)</td>
<td>38.1</td>
</tr>
<tr>
<td></td>
<td>RT ISI Change</td>
<td>63.6</td>
<td>(8.6)</td>
<td>73.7</td>
</tr>
<tr>
<td>SUSTAIN Accuracy</td>
<td>CPT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Misses†</td>
<td>11.7</td>
<td>(13.3)</td>
<td>20.5</td>
</tr>
<tr>
<td></td>
<td>False Alarms</td>
<td>48.6</td>
<td>(13.5)</td>
<td>53.2</td>
</tr>
<tr>
<td>ENCODE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Digit Span</td>
<td>35.7</td>
<td>(8.2)</td>
<td>43.7</td>
</tr>
<tr>
<td></td>
<td>Finger Windows</td>
<td>39.3</td>
<td>(11.3)</td>
<td>42.3</td>
</tr>
<tr>
<td>FOCUS-EXECUTE</td>
<td>SDMT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Written</td>
<td>43.9</td>
<td>(14.9)</td>
<td>48.0</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>43.6</td>
<td>(19.1)</td>
<td>45.1</td>
</tr>
<tr>
<td></td>
<td>Ltr Cancel†</td>
<td>29.0</td>
<td>(11.9)</td>
<td>34.5</td>
</tr>
<tr>
<td>SHIFT</td>
<td>WCST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Per Errors</td>
<td>39.8</td>
<td>(14.4)</td>
<td>48.3</td>
</tr>
<tr>
<td></td>
<td>Categories†</td>
<td>3.0</td>
<td>(2.7)</td>
<td>4.4</td>
</tr>
<tr>
<td>INATTENTION</td>
<td>CPRS-R:L</td>
<td>73.4</td>
<td>(11.2)</td>
<td>72.1</td>
</tr>
<tr>
<td>HYPERACTIVE-IMPULSIVE</td>
<td>CPRS-R:L</td>
<td>77.1</td>
<td>(13.5)</td>
<td>75.4</td>
</tr>
</tbody>
</table>

Note. CPT = Conners’ Continuous Performance Test; RT = Reaction Time; ISI = Inter-Stimulus-Interval.
Univariate Equivalency

Univariate equivalency analyses revealed equivalent pair-wise comparisons on 9 of the 13 attention scores from the Sustain\textsubscript{response-speed}, Sustain\textsubscript{accuracy}, Encode, Focus-Execute, Shift, Inattention and Hyperactive-Impulsive components of attention (see the second last column in Table 17a). There were also several subgroup comparisons that did not meet criteria for statistical equivalence despite comparable subgroup means. For example, although the means for the FAE(D) and FAE(X) subgroups on the Oral condition of the SDMT were comparable (44.2 and 45.9), these subgroups were not statistically equivalent. This lack of support for equivalency appears to have been related to the substantial within subgroup variability of the FAE(X) subgroup (SD = 17.3) and the relatively small subgroup size (n = 10).

Covariate Effect. Scores from the Sustain\textsubscript{accuracy}, Encode, Focus-Execute, and Shift components of attention were significantly related to the covariate IQ (see Table 18). Thus, individual regression analyses of each attention score (dependent variable, DV) were evaluated with IQ as the covariate (independent variable, IDV). Results of these analyses were used to evaluate the strength and direction of the influence that IQ had in adjusting subgroup means.

The regression coefficients for 5 of the 7 attention scores from the Encode, Focus-Execute and Shift components of attention were significantly greater than zero (β = .46 to .63; see Table 19). In contrast, the regression coefficients for both scores from the Sustain\textsubscript{accuracy} subcomponent of attention were significantly less than zero (β = -.46 and -.40). Since the FAS subgroup had a lower IQ than both the FAE(D) and FAE(X) subgroups (i.e., 74 versus 86 and 83), using IQ as a covariate resulted in a reduction of the M difference between subgroups when β was positive, and an increase in the M difference between subgroups when β was negative.
Table 18. Covariate Effects using MANCOVA and ANCOVA with FAS, FAE(D) and FAE(X) Subgroups

<table>
<thead>
<tr>
<th>Component / Subcomponent</th>
<th>Effect</th>
<th>Wilk’s Lambda</th>
<th>F</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUSTAIN Response-Speed</td>
<td>Covariate</td>
<td>.97</td>
<td>0.37</td>
<td>2,25</td>
<td>.70</td>
</tr>
<tr>
<td>SUSTAIN Accuracy</td>
<td>Covariate</td>
<td>.77</td>
<td>3.77</td>
<td>2,25</td>
<td>.04*</td>
</tr>
<tr>
<td>ENCODE</td>
<td>Covariate</td>
<td>.72</td>
<td>4.82</td>
<td>2,25</td>
<td>.02*</td>
</tr>
<tr>
<td>FOCUS-EXECUTE</td>
<td>Covariate</td>
<td>.57</td>
<td>5.95</td>
<td>3,24</td>
<td>.003*</td>
</tr>
<tr>
<td>SHIFT</td>
<td>Covariate</td>
<td>.57</td>
<td>6.06</td>
<td>3,24</td>
<td>.003*</td>
</tr>
<tr>
<td>INATTENTION</td>
<td>Covariate</td>
<td>-</td>
<td>0.04</td>
<td>1,26</td>
<td>.84</td>
</tr>
<tr>
<td>HYPERACTIVE-IMPULSIVE</td>
<td>Covariate</td>
<td>-</td>
<td>0.00</td>
<td>1,26</td>
<td>.99</td>
</tr>
</tbody>
</table>

Note. The covariate in all analyses was IQ.

Since the Inattention and the Hyperactive-Impulsive components of attention only contain a single measure, ANCOVA analyses were used and a Wilk’s Lambda value was not available.
Table 19. Regression Results for Covariate Effects in Comparisons with FAS, FAE(D) and FAE(X) Subgroups

<table>
<thead>
<tr>
<th>Component</th>
<th>Score</th>
<th>β</th>
<th>df</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUSTAIN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPT Misses</td>
<td>-.46</td>
<td>26</td>
<td></td>
<td>-2.57</td>
<td>.02*</td>
</tr>
<tr>
<td>CPT False Alarms</td>
<td>-.40</td>
<td>26</td>
<td></td>
<td>-2.11</td>
<td>.04*</td>
</tr>
<tr>
<td>ENCODE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Span</td>
<td>.46</td>
<td>26</td>
<td></td>
<td>2.80</td>
<td>.009*</td>
</tr>
<tr>
<td>Finger Windows</td>
<td>.36</td>
<td>26</td>
<td></td>
<td>1.86</td>
<td>.07</td>
</tr>
<tr>
<td>FOCUS-EXECUTE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDMT Written</td>
<td>.52</td>
<td>26</td>
<td></td>
<td>2.90</td>
<td>.007*</td>
</tr>
<tr>
<td>SDMT Oral</td>
<td>.20</td>
<td>26</td>
<td></td>
<td>0.98</td>
<td>.34</td>
</tr>
<tr>
<td>Letter Cancellation</td>
<td>.57</td>
<td>26</td>
<td></td>
<td>3.31</td>
<td>.003*</td>
</tr>
<tr>
<td>SHIFT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WCST Perseverative Errors</td>
<td>.52</td>
<td>26</td>
<td>3.27</td>
<td>.003*</td>
<td></td>
</tr>
<tr>
<td>WCST Categories Completed</td>
<td>.63</td>
<td>26</td>
<td>4.15</td>
<td>&lt;.000*</td>
<td></td>
</tr>
</tbody>
</table>

Note. β (Beta) = standard score regression coefficient.
Clinical Impairment Results

It was predicted that all diagnostic subgroups (i.e., FAS, FAE(D), and FAE(X)) would exhibit a "clinically significant attention deficit" using neuropsychological and behavioural components of attention. As previously stated, a "clinically significant attention deficit" was defined as one standardized normative score that was less than or equal to 2 standard deviations below the mean, or two or more scores that were less than or equal to 1.4 standard deviation units below the mean. IQ was not used as a covariate in these analyses as the primary focus was upon level of attention function regardless of IQ.

Results indicated that all three diagnostic subgroups exhibited a "clinically significant attention deficit". The FAS subgroup had 6 clinical attention scores equal to or below -1.4 standard deviation units; the FAE(D) subgroup had 5 clinically impaired scores; and the FAE(X) subgroup had 4 clinically impaired scores with a fifth score (i.e., Hit RT SE ISI Change $z = -1.3$) being just above the established clinical cut-off (i.e., $z = -1.4$). Subgroup performance means expressed as norm-referenced $z$-scores are presented in Table 20 and Figure 5. The graph in Figure 5a illustrates the comparable performance levels of FAE(D) and FAE(X) subgroups across 10 out of 11 attention scores. The one exception was the Hyperactive-Impulsive component on which there was a substantial difference between the FAE(D) and FAE(X) subgroups ($z = 2.5$ versus $z = 1.4$).
Table 20. Results as Normative Z-scores for Diagnostic Subgroups

<table>
<thead>
<tr>
<th>Component / Measure</th>
<th>FAS (n = 10)</th>
<th>FAE(D) (n = 10)</th>
<th>FAE(X) (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUSTAIN</td>
<td>M</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>Response-Speed-Variability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hit SE</td>
<td>1.6</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Hit RT SE ISI Change</td>
<td>.7</td>
<td>1.9</td>
<td>1.3</td>
</tr>
<tr>
<td>Response-Speed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hit RT</td>
<td>-1.6</td>
<td>-1.2</td>
<td>-1.5</td>
</tr>
<tr>
<td>Hit RT ISI Change</td>
<td>1.4</td>
<td>2.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Accuracy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>False Alarms</td>
<td>-.4</td>
<td>.3</td>
<td>-.2</td>
</tr>
<tr>
<td>ENCODE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Span</td>
<td>-1.4</td>
<td>-.6</td>
<td>-.7</td>
</tr>
<tr>
<td>Finger Windows</td>
<td>-1.1</td>
<td>-.8</td>
<td>-.6</td>
</tr>
<tr>
<td>FOCUS-EXECUTE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symbol Digit Modalities Test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Written</td>
<td>-.6</td>
<td>-.2</td>
<td>-.2</td>
</tr>
<tr>
<td>Oral</td>
<td>-.6</td>
<td>-.5</td>
<td>-.4</td>
</tr>
<tr>
<td>SHIFT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wisconsin Card Sorting Test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preservative Errors</td>
<td>-1.0</td>
<td>-.2</td>
<td>.3</td>
</tr>
<tr>
<td>INATTENTIVE</td>
<td>2.3</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>HYPERACTIVE-IMPULSIVE</td>
<td>2.7</td>
<td>2.5</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Note. RT = Reaction Time; SE = Standard Error; ISI = Inter-Stimulus-Interval. A Z-score has a \( M = 0 \), and a \( SD = 1 \). Components Z-scores \( < \) or \( = -1.4 \) are presented in bold faced type.
Figure 5. Results as normative z-scores

Note. FSIQ = Full Scale IQ; DS = Digit Span; SDMT = Symbol Digit Modalities Test – Written; Per E = perseverative errors; FA = false alarms; RT-ISI = reaction time across interstimulus intervals; SE-ISI = standard error across interstimulus intervals; Inatten = Inattention; Hyp-imp = Hyperactive-Impulsive.
EXPLORATORY ANALYSES

Method

Since results obtained in Part 2 did not support the confirmatory hypotheses, exploratory difference and equivalence analyses were conducted using the same data set. This was done to identify existing patterns of similarities and differences between diagnostic subgroups not detected by confirmatory analyses. While confirmatory analyses are designed to test for the presence of specific patterns based on a priori hypotheses, exploratory analyses attempt to discover patterns in data without relying on specific hypotheses (Farrell, 1999). Confirmatory and exploratory analyses are often used in a complimentary manner. For example, failure to find support for confirmatory hypotheses often leads to exploratory analyses. The results of exploratory analyses can then be used to generate theory and form the basis of future confirmatory studies to determine if findings can be replicated and to provide additional understanding regarding the constructs being evaluated.

Given that the FAE(D) and FAE(X) subgroups had very similar performance levels on components of attention measured in confirmatory analyses (see Table 20 and Figure 5a), these two subgroups were combined to form a FAE(D+X) subgroup. This was done to increase the likelihood of detecting differences and equivalencies between diagnostic subgroups that actually existed as the statistical power of an analysis usually improves when sample size increases.

Support for the appropriateness of combining FAE(D) and FAE(X) subgroups is derived from subgroup definitions used in previous studies. For example, Conry (1990) and Nanson and Hiscock (1990) defined FAE as abnormal findings in two of the three domains of FAS. Streissguth, Aase, et al. (1991) defined FAE as a clear history of excessive prenatal alcohol exposure and CNS dysfunction, without the manifestation of all the physical features of FAS. Mattson et al. (1994) defined FAE as significant
prenatal alcohol exposure but insufficient features for a confirmed diagnosis of FAS. Thus, the FAE groups in these studies consisted of some individuals who would have met criteria in this for FAE(D) and some individual who would have met criteria for FAE(X).

Exploratory analyses were conducted using the sequential methodological guidelines developed by Seaman and Serlin's (1998) for assessing differences and similarities between two groups in a sequential manner. The first step entailed conducting univariate statistical difference analyses between the FAS and FAE(D+X) subgroups on all attention measures using independent t-tests. The second step involved conducting univariate equivalency analyses using the procedure detailed for confirmatory analyses. Finally, when exploratory inferential analyses were inconclusive, effect size calculations were used to describe the size of the difference between subgroups in statistical terms.

Given the exploratory nature of these analyses, IQ was used as a covariate only when it had been found to adjust subgroup means in a statically significant manner. As previously detailed (see Table 15 and Table 18), scores for the SustainAccuracy, Encode, Focus-Execute, and Shift components of attention were significantly related to the covariate IQ. Thus, IQ was used as a covariate with comparisons involving measures from these four components of attention.

Since a priori analyses found substantial differences in the variance exhibited by several subgroups, unequal variance t-tests were used as indicated by Levene's equality of variance test.

Exploratory Results

Exploratory Difference Results

The FAE(D+X) subgroup had more difficulties than the FAS subgroup on three attention scores from the CPT. Differences between these two subgroups were found on the overall measure of hit RT in response to changes in the ISI (Hit RT ISI Change, t(28) = -2.3, p = .03) and on the overall measure of hit RT SE in response to changes in the ISI (Hit RT SE ISI Change, t(28) = -2.1, p = .04; see Table 21a). Since IQ did not act as a
significant covariate for these attention scores, IQ was not used as a covariate in the above analyses.

After adjusting for IQ, the FAE(D+X) subgroup also missed more targets than the FAS subgroup on the CPT (Misses, t(28) = -2.1, p = .05), but there was not a difference between subgroups with regards to the number of false alarms responses made. As previously indicated, was used as a covariate in analysis of Miss and False Alarm scores because IQ was fond to act as a covariate.

After adjusting for IQ where indicated, there were no differences between FAS and FAE(D+X) subgroups on attention scores from Encode, Focus-Execute, Shift, Inattention, and Hyperactive-Impulsive components of attention.

Unadjusted subgroup means for FAS and FAE(D+X) subgroups are presented in Table 21a, and adjusted subgroup means are presented in Table 21b.
Table 21a. Secondary Difference Results and Unadjusted Means from Comparisons with FAS and FAE(D+X) Subgroups

<table>
<thead>
<tr>
<th>Subcomponent / Measure</th>
<th>FAS (n = 10)</th>
<th>FAED+X (n = 20)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td><strong>SUSTAIN</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>CPT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response-Speed-Variability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Hit RT SE</td>
<td>66.1</td>
<td>(6.3)</td>
<td>72.0</td>
<td>(16.6)</td>
</tr>
<tr>
<td>Hit RT SE ISI Change</td>
<td>56.6</td>
<td>(8.0)</td>
<td>65.9</td>
<td>(15.8)</td>
</tr>
<tr>
<td>Response-Speed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Hit RT</td>
<td>33.7</td>
<td>(10.4)</td>
<td>36.3</td>
<td>(11.4)</td>
</tr>
<tr>
<td>Hit RT ISI Change</td>
<td>63.6</td>
<td>(8.6)</td>
<td>74.1</td>
<td>(16.0)</td>
</tr>
<tr>
<td>Accuracy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Misses†</td>
<td>11.7</td>
<td>(13.3)</td>
<td>20.6</td>
<td>(19.6)</td>
</tr>
<tr>
<td>False Alarms</td>
<td>48.6</td>
<td>(13.5)</td>
<td>50.8</td>
<td>(11.8)</td>
</tr>
<tr>
<td><strong>ENCODE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Span</td>
<td>35.7</td>
<td>(8.2)</td>
<td>43.2</td>
<td>(8.1)</td>
</tr>
<tr>
<td>Finger Windows</td>
<td>39.3</td>
<td>(11.3)</td>
<td>43.0</td>
<td>(12.5)</td>
</tr>
<tr>
<td><strong>FOCUS-EXECUTE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symbol Digit Modalities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Written</td>
<td>43.9</td>
<td>(14.4)</td>
<td>48.1</td>
<td>(11.5)</td>
</tr>
<tr>
<td>Oral</td>
<td>43.6</td>
<td>(19.1)</td>
<td>45.7</td>
<td>(12.6)</td>
</tr>
<tr>
<td>Letter Cancellation†</td>
<td>29.0</td>
<td>(11.9)</td>
<td>33.1</td>
<td>(11.5)</td>
</tr>
<tr>
<td><strong>SHIFT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wisconsin Card Sorting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perseverative Errors</td>
<td>39.8</td>
<td>(14.4)</td>
<td>50.4</td>
<td>(11.0)</td>
</tr>
<tr>
<td>Categories Completed†</td>
<td>3.0</td>
<td>(2.7)</td>
<td>4.5</td>
<td>(1.6)</td>
</tr>
<tr>
<td><strong>INATTENTION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>73.4</td>
<td>(11.2)</td>
<td>72.2</td>
<td>(11.2)</td>
</tr>
<tr>
<td><strong>HYPERACTIVE-IMPULSIVE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>77.1</td>
<td>(13.5)</td>
<td>69.5</td>
<td>(15.5)</td>
</tr>
</tbody>
</table>

Note. # Attention scores denoted by a number sign were analyzed using ANCOVA with IQ as the covariate as one or more scores from the associated component was significantly correlated with IQ.

Statistical values for the † statistics were calculated from univariate F values ($t = \sqrt{F}$).

Unadjusted mean subgroup scores are presented in this Table and adjusted subgroup scores are presented in Table 21b.

† Raw scores are reported as a norm-referenced sample was not available.

Scores that were statistically difference are presented in bold face type.
Table 21b. Adjusted Subgroup Means for FAS versus FAE(D+X) Comparisons

| Subcomponent / Measure | FAS  
|------------------------|------------| FAED(D+X)  
|                         | M          | M          |
| **SUSTAIN**            |            |            |
| Accuracy               |            |            |
| Misses†                | 9.1        | 23.2       |
| False Alarms           | 48.6       | 50.8       |
| **ENCODE**             |            |            |
| Digit Span             | 37.1       | 41.8       |
| Finger Windows         | 40.8       | 41.6       |
| **FOCUS-EXECUTE**      |            |            |
| Symbol Digit Modalities|            |            |
| Written                | 46.1       | 45.9       |
| Oral                   | 44.6       | 44.7       |
| Letter Cancellation†   | 31.3       | 30.9       |
| **SHIFT**              |            |            |
| Wisconsin Card Sorting |            |            |
| Perseverative Errors   | 42.1       | 48.2       |
| Categories Completed†  | 3.5        | 4.0        |

Subgroup means were adjusted using IQ as the covariate.

† Raw scores are reported as a norm-referenced sample was not available.
**Hit RT ISI Change.** A comparison of norm-referenced T-scores obtained by the FAS and FAE(D+X) groups on the Hit RT ISI Change measure indicated that as the time between targets increased there was more change in the reaction time of the FAE(D+X) group than in the FAS group (M<sub>FAS</sub> = 63, M<sub>FAE(D+X)</sub> = 74; t(28) = -2.3, p = .03, see Table 21a). The difference between the FAE and FAE(D+X) groups on the Hit RT ISI Change measure was also statistically significant using raw score slope values (slope<sub>FAS</sub> = .07, slope<sub>FAE(D+X)</sub> = .13; t(28) = -3.0, p <.006, see Table 22).

As previously indicated, the raw score value for the Hit RT ISI Change score was measured as the slope of change in reaction time over three ISI’s (i.e., 1, 2, 4 s). A positive slope indicates a slowing of reaction time as the time between targets increased (Conners, 1995). The obtained average slope of change values indicates that as the time between targets increased the reaction time of the FAE(D+X) group slowed down more than the reaction time of the FAS group (slope<sub>FAE(D+X)</sub> = .13, slope<sub>FAS</sub> = .07) This is illustrated in the top panel of Figure 6.
<table>
<thead>
<tr>
<th>CPT Raw Score Slope Values</th>
<th>FAS (n = 10)</th>
<th>FAE(D+X) (n = 20)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hit RT ISI Change</td>
<td>.07 (0.2)</td>
<td>.13 (.07)</td>
<td>-3.0</td>
<td>.006</td>
</tr>
<tr>
<td>Hit RT SE ISI Change</td>
<td>.11 (.09)</td>
<td>.22 (.19)</td>
<td>-2.2</td>
<td>.04</td>
</tr>
</tbody>
</table>

Note. The possible range of raw score slope values was from +1.0 to −1.0.
Figure 6. CPT Results for Slope of Change in RT by ISI (top) and Slope of Change in SE RT by ISI (bottom) using linear regression.
Hit RT SE ISI Change. A comparison of the norm-referenced T-scores obtained by the FAS and FAE(D+X) groups indicated that as the time between targets increased there was more change in the SE of RT for the FAE(D+X) group than in the FAS group ($M_{FAS} = 56$, $M_{FAE(D+X)} = 66$; $t(28) = -2.1$, $p = .04$). The difference between the FAE and FAE(D+X) groups was also statistically significant using raw score slope values ($slope_{FAS} = .11$, $slope_{FAE(D+X)} = .22$; $t(28) = -2.2$, $p < .04$, see Table 22). The obtained average slope of change values indicates that as the time between targets increased the RT variability of the FAE(D+X) group increased more than the RT variability of the FAS group. This is illustrated in the bottom panel of Figure 6.

Exploratory Equivalence Results

The FAS and FAE(D+X) subgroups were statistically equivalent on the Inattention component ($t(28) = 2.57$, $p < .05$), and on the CPT score for Overall Hit RT and Overall Hit RT SE from the Sustain component of attention ($t(28) = 2.48$, $p < .05$; $t(28) = 1.74$, $p < .05$, respectively). Since IQ did not act as a significant covariate for these scores adjustments were not made. After adjusting for IQ the FAS and FAE(D+X) subgroups were equivalent on the number of targets missed on the CPT (Misses, $t(28) = 1.91$, $p = < .05$).

Since the FAS and the FAE(D+X) subgroups were found to be both statistically equivalent and statistically different on the CPT Misses measure, it was concluded that the mean difference between subgroups was larger than zero but smaller than a difference that would make the groups non-equivalent (Rogers, Howard & Vessey, 1993). Rogers et al. (1993) proposed that findings of this nature reflect a difference between groups that is statistically significant but clinically trivial.

An evaluation of mean raw score performance indicates that the FAS subgroup missed 11.7 out of a total of 324 targets (3.6%), and the FAE(D+X) subgroup missed 20.6 targets (6.4%). Norm-referenced T-scores are not available to evaluate subgroup performance on the Misses measure because of the non-normal distribution of scores on this measure in the standardization sample. In order to evaluate level of subgroup
functioning on this measure, norm-referenced percentiles were converted to T-scores. This transformation was necessary as the CPT only uses percentiles to compare the performance of a subject to the normal comparison group. Scores on the Misses measure were not normally distributed in the standardization sample.

When the performance of the FAS and FAE(D+X) subgroups were evaluated on the Misses score using estimated norm-referenced T-scores, results indicated neither statistical difference or equivalence. The mean performance level for both the FAS and FAE(D+X) subgroups was found to be within the average range (approximately ± 1 SD unit; estimated T-score FAS = 56.4, FAE(D+X) = 61.7). This indicates that the number of targets missed by both the FAS or FAE(D+X) subgroup was within the normal range and not reflective of inattention. Given the large number of mean target hit responses obtained for both subgroups (FAS = 312.3, FAE(D+X) = 303.4), the number of missed targets did not unduly influence the associated measure of Hit RT and Hit RT SE.

After adjusting for IQ, the FAS and FAE(D+X) subgroups were also equivalent on the written and oral conditions of the SDMT from the Focus-Execute component of attention (t(28) = 2.13, p < .05; t(28) = 1.89, p < .05, respectively), and on the Digit Span and Finger Windows subtest from the Encode component of attention (t(28) = 2.44, p < .05; and t(28) = 2.13, p < .05, respectively). A summary of equivalency results and subgroups performance means is presented in Table 23.
Table 23. Secondary Subgroup Equivalence Results and Adjusted Means for Comparisons with FAS and FAE(D+X) Subgroups

<table>
<thead>
<tr>
<th>Subcomponent / Measures</th>
<th>FAS n = 10</th>
<th>FAE(D+X) n = 20</th>
<th>Mdiff</th>
<th>SEdiff</th>
<th>EC</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SUSTAIN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response-Speed-Variability</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Hit RT SE</td>
<td>66.1</td>
<td>72.0</td>
<td>-5.9</td>
<td>4.2</td>
<td>13.2</td>
<td>1.74</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Hit RT SE ISI Change</td>
<td>56.6</td>
<td>65.9</td>
<td>-9.3</td>
<td>4.3</td>
<td>11.3</td>
<td>0.47</td>
<td>ns</td>
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<tr>
<td><strong>Response-Speed</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Hit RT</td>
<td>33.7</td>
<td>36.3</td>
<td>-2.6</td>
<td>4.3</td>
<td>13.3</td>
<td>2.48</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Hit RT ISI Change</td>
<td>63.6</td>
<td>74.1</td>
<td>-10.5</td>
<td>4.5</td>
<td>12.7</td>
<td>0.50</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Accuracy#</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Misses†</td>
<td>9.1</td>
<td>23.2</td>
<td>-14.1</td>
<td>6.4</td>
<td>1.8</td>
<td>1.91</td>
<td>&lt;.05#</td>
</tr>
<tr>
<td>False Alarms</td>
<td>47.0</td>
<td>52.4</td>
<td>-5.4</td>
<td>4.5</td>
<td>10.6</td>
<td>0.99</td>
<td>ns#</td>
</tr>
<tr>
<td><strong>ENCODE#</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Span</td>
<td>37.1</td>
<td>41.8</td>
<td>-4.7</td>
<td>3.2</td>
<td>12.6</td>
<td>2.44</td>
<td>&lt;.05#</td>
</tr>
<tr>
<td>Finger Windows</td>
<td>40.8</td>
<td>41.6</td>
<td>-0.8</td>
<td>5.2</td>
<td>11.8</td>
<td>2.13</td>
<td>&lt;.05#</td>
</tr>
<tr>
<td><strong>FOCUS-EXECUTE#</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Symbol Digit Modalities</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Written</td>
<td>46.1</td>
<td>45.9</td>
<td>.2</td>
<td>5.0</td>
<td>10.8</td>
<td>2.13</td>
<td>&lt;.05#</td>
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<tr>
<td>Oral</td>
<td>44.6</td>
<td>44.7</td>
<td>-0.1</td>
<td>6.7</td>
<td>5.8</td>
<td>1.89</td>
<td>&lt;.05#</td>
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<tr>
<td>Letter Cancellation†</td>
<td>31.3</td>
<td>30.9</td>
<td>0.4</td>
<td>3.8</td>
<td>6.2</td>
<td>1.73</td>
<td>ns#</td>
</tr>
<tr>
<td><strong>SHIFT#</strong></td>
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<td></td>
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<tr>
<td>Wisconsin Card Sorting</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perseverative Errors</td>
<td>42.1</td>
<td>48.2</td>
<td>-6.1</td>
<td>4.1</td>
<td>11.6</td>
<td>1.33</td>
<td>ns#</td>
</tr>
<tr>
<td>Categories Completed†</td>
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<td>4.0</td>
<td>-0.5</td>
<td>0.6</td>
<td>0.7</td>
<td>0.25</td>
<td>ns#</td>
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<tr>
<td><strong>INATTENTIVE</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>HYPERACTIVE-IMPULSIVE</strong></td>
<td>77.1</td>
<td>69.5</td>
<td>7.6</td>
<td>5.8</td>
<td>15.4</td>
<td>1.33</td>
<td>ns</td>
</tr>
</tbody>
</table>

Note. RT = Reaction Time; SE = Standard Error; Mdiff = Mean of difference scores; SEdiff = Standard Error of difference scores; ISI = Inter-Stimulus-Interval; EC = Equivalence Criterion.

# Attention scores denoted by a number sign were analyzed using ANCOVA with IQ as the covariate as one or more score from the associated component was significantly correlated with IQ.

Adjusted subgroup means are presented only when IQ was used as a covariate.

† Raw scores are reported as a norm-referenced sample was not available.

Scores that were statistically difference are presented in bold face type.
Summary of Exploratory Results

A summary of both statistical difference and equivalence results is provided in Table 24. Inferential conclusions were described as being inconclusive when subgroup comparison results were neither statistically equivalent nor statistically different. In order to describe the size of the difference between subgroups in statistical terms, when inferential analyses were inconclusive, effect size calculations were used. As previously indicated, an effect size is a direct measure of the difference between observed group means in standard deviation units. Cohen's general guidelines for evaluating effect size are as follows: small = .20, medium = .50, and large = .80. The obtained effect size for these comparisons ranged from .02 to .27 (see Table 24). Using Cohen's (1988) guidelines for the general interpretation of effect size the differences between subgroups on the inconclusive measures were small.
Table 24. Summary of Exploratory Difference and Equivalence Results for Comparisons with FAS and FAE(D+X) Subgroups

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>Inconclusive</th>
<th>Equivalent</th>
<th>Different</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUSTAIN Accuracy</td>
<td></td>
<td>■ ES = -.27</td>
<td></td>
</tr>
<tr>
<td>CPT Misses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPT False Alarms</td>
<td></td>
<td>■ ES = -.22</td>
<td></td>
</tr>
<tr>
<td>SUSTAIN</td>
<td></td>
<td>■</td>
<td></td>
</tr>
<tr>
<td>Response-Speed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPT Overall Hit RT</td>
<td></td>
<td>■</td>
<td></td>
</tr>
<tr>
<td>CPT Overall Hit RT ISI Change</td>
<td></td>
<td></td>
<td>■</td>
</tr>
<tr>
<td>SUSTAIN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response-Speed- Variability</td>
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<td></td>
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</tr>
<tr>
<td>CPT Overall Hit RT SE</td>
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<td>■</td>
<td></td>
</tr>
<tr>
<td>CPT Overall Hit RT SE ISI Change</td>
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<td>ENCODE</td>
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<td>■</td>
<td></td>
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<tr>
<td>Digit Span</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finger Windows</td>
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<tr>
<td>FOCUS-EXECUTE</td>
<td></td>
<td>■</td>
<td></td>
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<tr>
<td>SDMT Written</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SDMT Oral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Letter Cancellation</td>
<td></td>
<td></td>
<td>■ ES = .02</td>
</tr>
<tr>
<td>SHIFT</td>
<td></td>
<td>■</td>
<td></td>
</tr>
<tr>
<td>WCST Perseverative Errors</td>
<td></td>
<td></td>
<td>■ ES = -.27</td>
</tr>
<tr>
<td>WCST Categories Completed</td>
<td></td>
<td></td>
<td>■ ES = -.15</td>
</tr>
<tr>
<td>INATTENTIVE (CPRS-R:L)</td>
<td></td>
<td>■</td>
<td></td>
</tr>
<tr>
<td>HYPERACTIVE-IMPULSIVE (CPRS-R:L)</td>
<td></td>
<td></td>
<td>■ ES = .24</td>
</tr>
</tbody>
</table>

(Table Continues on next page)

Note. ES = effect size (M difference / SD difference).
Cohen’s (1988) generally guidelines for evaluating effect sizes are as follows: small = .20, medium = .50, and large = .80.

The term “Inconclusive” means that results were neither statistically equivalent or statistically different.

The performance of the FAE(D+X) subgroup was worse than the FAS subgroup on both the Overall Hit RT ISI Change and the Overall Hit RT SE ISI Change scores from the CPT.
Discussion

Part 2 of this study yielded findings pertaining to the continuity and comparability of diagnostic subgroups on neuropsychological and behavioural components of attention. Subgroup Continuity

Planned comparisons indicated that there were no statistical differences between the three diagnostic subgroups (i.e., FAS, FAE(D), and FAE(X)) on the Sustain,response-speed-variability subcomponent of attention. This finding was contrary to a priori prediction.

Planned comparisons indicated that the three diagnostic subgroups were equivalent on the Inattention component of attention, and after adjusting for IQ the FAE(D) and FAE(X) subgroups were equivalent on the Encode component. It had been predicted that all three subgroups would also be equivalent on Sustainaccuracy, Focus-Execute, Shift, and Hyperactive-Impulsive components of attention.

Although the FAE(D) and the FAE(X) subgroups were statistically equivalent only on the Inattention and Encode components of attention, the performance of these two groups were strikingly similar across most neuropsychological and behavioural components of attention. The lack of statistical equivalence between the FAE(D) and FAE(X) was, in part, related to a substantial degree of within subgroup variability. For example, the FAE(D) and FAE(X) subgroups were not equivalent on the RT ISI Change score from the CPT despite very comparable norm-referenced T-scores (73.7 and 74.4, respectively). Although the difference between subgroup means was small (.7), the dispersion of scores around subgroup means was large (SD = 17.6 and 15.2). In comparison, the dispersion of scores obtained by the FAS subgroup was considerably smaller (SD = 8.6). A norm-referenced T-score distribution has a SD of 10.

In order to explore the potential subject characteristics that might have been associated with this finding, FAE(D) and FAE(X) participants were assigned to a high or low variability group using a scatter plot graph. Neither IQ level nor head circumference size accounted for the finding of high variability. Thus, the presence or absence of high variability of individual performance on a Sustained attention measure in this study was not accounted for by a reduction in general level of intellectual functioning secondary to a
reduced head circumference. In children with medical conditions adversely affecting 
brain development (e.g., extremely low birth weight infants) reduced head circumference 
is often a marker of pathologically reduced brain size. However, in school-aged children 
with a medical history of extremely low birth weights, Stathis, O'Callaghan, Harvey, and 
Rogers, (1999) found that a reduction in brain size was associated with reduced general 
intellectual ability but not ADHD.

The finding of substantial variability in the severity of the attention deficit 
exhibited by individuals with FAE(D) and FAE(X) is consistent with findings from 
previous research. In an exploratory study of auditory sustained attention in adults with 
FAS/FAE, Conner et al. (1999) also found substantial heterogeneity of individual 
performance on a SD of reaction time score from a CPT.

Since the FAE(D) and FAE(X) had similar mean performance levels across most 
neuropsychological and behavioural components of attention, exploratory analyses were 
conducted comparing the performance of FAS and a combined FAE(D+X) subgroup. 
This was done to increase the likelihood of detecting similarities and differences that 
actually existed, given the difficulties associated with detecting small and medium effect 
sizes in small samples with considerable within group variability. A summary of findings 
from exploratory analyses is presented after a discussion of subgroup comparability 
results.

Subgroup Comparability

Planned comparisons indicated that all three subgroups (i.e., FAS, FAE(D), and 
FAE(X)) exhibited a clinically significant attention deficit when compared to a norm-
referenced control group. This finding was consistent with a priori prediction. More 
specifically, difficulties were exhibited by all three clinical subgroups on the Sustain, 
Inattentive, and Hyperactive-Impulsive components of attention. The finding of a 
clinically significant attention deficit in a spectrum of diagnostic subgroups (FAS, 
FAE(D), FAE(X)) provides additional empirical support for the clinical validity and 
utility of the IOM diagnostic classification system.

Difficulties on the Sustain component reflected a neuropsychological or brain-
behaviour-based deficit, and difficulties on the Inattentive and Hyperactive-Impulsive components reflected greater functional or everyday attention problems. The brain-based information processing abilities associated with the Sustain component of attention were assessed using a computerized CPT, while the functional components of attention were assessed by obtaining using a parent-report measure of child behaviour problems.

The finding of a clinically significant attention deficit in all diagnostic subgroups with a history of excessive prenatal alcohol exposure confirms findings from previous research. Nanson & Hiscock (1990) found a clinically significant attention deficit in a combined FAS/FAE group on the Hyperactivity scale from the Child Behaviour Checklist (1983). In both FAS and PEA groups, Mattson and Riley (2000) reported a clinically impaired level on the Attention scale from the Child Behaviour Checklist (1991). The PEA group in Mattson and Riley's study was comparable to the FAE(X) subgroup in this study.

The finding of a clinically significant attention deficit in all diagnostic subgroups extends findings from previous research. It does this by indicating that individuals with a history of excessive prenatal alcohol exposure are likely to exhibit an attention deficit on Sustain, Inattention, and Hyperactive-Impulsive components.

The Hyperactive-Impulsive scale was the only attention measure of the thirteen used in this study where the performance of the FAE(X) subgroup was noticeably lower than the FAE(D) subgroup. This difference between these subgroups likely reflected a parental reporting bias rather than an actual difference. This suggestion is supported by the fact that the performance of the FAE(D) and FAE(X) subgroups was comparable on all neuropsychological measures of attention components. The behaviour difficulties exhibited by children with FAE(X) may also have been viewed differently by parents because they did not meet criteria for a diagnosis of FAS or a clinical label of FAE. Before the introduction of the IOM's diagnostic criteria for ARND in 1996, there was no formal diagnosis or clinical label for individuals defined as FAE(X) in this study. It was also common for health professionals to view children who did not meet the criteria for FAS or FAE as less affected.
Exploratory Subgroup Continuity Findings

As previously stated, since the FAE(D) and FAE(X) subgroups had similar performance levels across neuropsychological and behavioural components of attention, these two subgroups were combined to form an FAE(D+X) subgroup. This was done in order to obtain additional statistical power and increase the likelihood of detecting differences and equivalencies between FAS and FAE subgroups that actually existed.

After adjusting for IQ, the performance of the FAS and FAE(D+X) subgroups were statistically equivalent or comparable (small effect size) on Inattention, Hyperactive-Impulsive, Shift, Focus-Execute, Encode, and Sustain(accuracy). The FAS and FAE(D+X) subgroups were also comparable on overall response-speed and response-speed-variability measures from the Sustain component of attention (i.e., Overall Hit RT, and Overall Hit RT SE).

Despite comparable performance levels on most neuropsychological and behavioural components of attention, the performance of FAS and FAE(D+X) subgroups were statistically different on several measures from the Sustain component of attention. These measures assessed the ability to adjust to changes in the time interval between target presentations (i.e., 1, 2, 4 s) as measured by response-speed and response-speed-variability (i.e., Hit RT ISI Change and Hit RT SE ISI Change). This indicates that the FAE(D+X) subgroup had more difficulty than the FAS subgroup maintaining a consistent response-speed when the time interval between targets changed. This relative deficit was not accounted for by differences in performance accuracy, overall response-speed, overall response-speed-variability, or IQ. Thus, when compared to the FAS subgroup, the FAE(D+X) subgroup was less adept at regulating output in response to changes in the external environment. In other words, the FAE(D+X) subgroup exhibited greater ISI response-speed-variability on both RT and SE of RT measures.

Results from exploratory analyses suggested that modifications were required to the author's initial conceptualization of subcomponents of Sustained attention using the Conners’ CPT. In a priori analyses, the Conners’ CPT was conceptualized as comprising a) Sustain(accuracy), b) Sustain(response-speed), and c) Sustain(response-speed-variability) subcomponents.
Based upon exploratory findings the Sustain component of attention was conceptualized as containing a) accuracy, b) overall-response-speed, and c) ISI response-speed-variability subcomponents. Thus, the revised conceptualization of subcomponents emphasizes the distinction between overall-response-speed scores (Overall Hit RT, Overall Hit RT SE) and changes in response-speed scores across ISI’s (Hit RT ISI Change, Hit RT SE ISI Change). For the purpose of this study, these two subcomponents are referred to as Sustain(overall-response-speed) and Sustain(ISI response-speed-variability). No modification of the Sustainaccuracy subcomponent was indicated. Table 25 lists the subcomponents and associated scores of the initial and revised conceptualizations.
Table 25. Initial and Revised Subcomponents of Sustained Attention

<table>
<thead>
<tr>
<th>Initial Subcomponents</th>
<th>Revised Subcomponents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Accuracy</strong></td>
<td><strong>Accuracy</strong></td>
</tr>
<tr>
<td>Misses</td>
<td>Misses</td>
</tr>
<tr>
<td>False Alarms</td>
<td>False Alarms</td>
</tr>
<tr>
<td><strong>Response-Speed</strong></td>
<td><strong>Overall Response-Speed</strong></td>
</tr>
<tr>
<td>Overall Hit RT</td>
<td>Overall Hit RT</td>
</tr>
<tr>
<td>Hit RT ISI Change</td>
<td>Overall Hit RT SE</td>
</tr>
<tr>
<td><strong>Response-Speed-Variability</strong></td>
<td><strong>ISI Response-Speed-Variability</strong></td>
</tr>
<tr>
<td>Overall Hit RT SE</td>
<td>Hit RT ISI Change</td>
</tr>
<tr>
<td>Hit RT SE ISI Change</td>
<td>Hit RT SE ISI Change</td>
</tr>
</tbody>
</table>
To the author's knowledge, the continuity (similarities and differences) of FAS and FAE subgroups on neuropsychological and behavioural components of attention had not been reported previously. Although Mattson et al. (1998; 1999) reported comparable verbal memory and executive function skills in FAS and PEA groups, they did not a) assess neuropsychological components of attention or b) use equivalency analyses to assess degree of comparability. This was also believed to be the first study to examine response-speed-variability in response to manipulation of the ISI on a CPT in FAS and FAE subgroups, and to identify a greater level of a specific type of attention or CNS dysfunction in FAE compared to FAS.

In a general manner, the finding of difficulties with Sustain(ISI response-speed variability) is consistent with findings from previous studies of attention deficits in ADHD. Chee et al. (1989) found that measures of response to changes in the ISI on a CPT were sensitive to the attention deficits exhibited by children with ADHD. Conners et al. (1993) found that the pharmacological treatment effect of stimulant medication (i.e., Ritalin) in children with ADHD was only evident when performance on a long ISI (i.e., 4 s) was evaluated.

Inconsistencies in response-speed on a CPT are considered to reflect brain-based information processing inefficiencies in the neural-cognitive mechanisms which support the ability to efficiently maintain a focus of attention for an extended period of time (Conners, 1995; Segalowitz, Dywn, & Unsal, 1997). At a behavioural level, these information processing inconsistencies have been described as "microlapses of attention" (Cardon & Mirsky, 1962; Streissguth et al., 1994). At a neuropsychological or brain-behaviour level, high intraindividual variability of RT's have been described as likely reflecting a deficit in the neurocognitive preparation required for efficient behavioural responding (Zahn & Mirsky, 1999). More specifically, Zahn and Mirsky suggested that momentary lapses in the level of neurocognitive preparation likely result in an increase of the variability of an individual's RT's when a response to a target stimulus is required. Neurocognitive preparation presumably involves directing the focus of attention to a particular stimulus-response or sensori-motor sequence. For example, when a visual
target letter is detected, a subject is required to make a behavioural response (e.g., press a space bar).

When neurocognitive preparation to detect a target and emit a behavioural response peak consistently at the same time as the presentation of the target stimulus, then consistency of response-speed is facilitated. If a neurocognitive preparatory state does not coincide with presentation of the target stimulus, then this preparatory neurocognitive process must be completed after the onset of a target, thus delaying a behavioural response and increasing response-variability.

In a recent conference presentation, Rovet and Cole (2000) suggested that high intraindividual variability of response-speed likely signifies "micro-lapses" of attention as a result of inconsistent neurotransmissions. This is certainly a plausible explanation as animal studies have shown that prenatal alcohol exposure is associated with alterations in the brain chemistry of the resulting offspring (Ilkonimidou et al., 2000). Response time variability and neurochemical dysfunction have also been found to be sensitive indicators of the attentional dysfunction associated with traumatic brain injury and schizophrenia (Heatherington, Stuss, & Finlayson, 1996; Segalowitz, Dywan, & Unsal, 1997; Rist & Chohen, as cited in Zahn & Mirsky, 1999).

Although a previous study of adolescents with FAS (Carmichael-Olson et al., 1998) and a study of adults with FAS/FAE (Conner et al., 1999) have reported greater intraindividual response-speed-variability than normal on a traditional CPT, the author's study was the first to evaluate this aspect of attention in FAS and FAE subgroups directly. The finding of greater Sustain(ISI response-speed-variability) in the FAE(D+X) subgroup relative to the FAS subgroup was unexpected. This subgroup difference was however confirmed using norm-referenced T-scores, slope of change values, and mean RT and SE of RT measures.

The finding of comparable Overall RT and Overall RT SE in FAS and FAE(D+X) subgroups on the Conners' CPT is consistent with results reported by Coles et al. (1997). These researchers used a traditional CPT, which requires infrequent responding, to evaluate the performance of an FAS/FAE and an ETOH non-dysmorphic group. The
performance of these two groups was comparable on measures of overall mean hit RT and overall SD of hit RT. A manipulation of the inter-stimulus-interval was not included in the traditional CPT used by Coles et al. (1997).

In general terms, the neuropsychological finding of greater Sustain(ISI response-speed-variability) in the FAE(D+X) subgroup relative to the FAS subgroup, is also consistent with Streissguth, Barr, et al.'s (1997) and Fast et al.'s (1999) report of higher rates of trouble with the law and other social and behavioural difficulties in FAE compared to FAS. This suggests that neurocognitive deficits are likely a contributing factor to the social and behavioural difficulties exhibited by many individuals with FAE.

The finding of greater Sustain(ISI response-speed-variability) in the FAE(D+X) subgroup relative to the FAS subgroup extends findings from previous research in two important ways. First, it indicates that the severity of attention deficits exhibited by individuals with FAE may be greater than the attention deficits associated with FAS. This highlights the importance of investigating the neurocognitive and neurobehavioural function of FAS and FAE subgroups separately in future research. It also emphasizes the clinical importance of identifying and treating attention deficits in individuals with either FAS or FAE.

Second, the greater response-speed-variability exhibited by the FAE(D+X) subgroup relative to the FAS subgroup was observed only when evaluating responses to a manipulation of the time interval between targets. As previously stated, this indicates that the FAE(D+X) subgroup was less adept at regulating output in response to changes in the external environment, when compared to the FAS subgroup. These difficulties were conceptualized as representing micro-lapses of attention at a behavioural level and sub-optimal neurocognitive preparation or regulation at a neuropsychological level. Thus, the relative deficit exhibited by the FAE(D+X) subgroups can be conceptualized as a deficit involving neurocognitive regulation. This is consistent with Clark et al.'s conclusion of subtle functional dysregulation of subcortical structures in individuals with FAS. This is also a fitting descriptor as difficulties with self-regulation have been previously described as a hallmark of the primary deficit exhibited by individuals with
ADHD (Barkley, 1998).

When interpreting the findings from this study within the context of previous and future research it is also important to note that differences in the level of Sustain(ISI response-speed-variability) between FAS and FAE(D+X) subgroups was not identified when overall CPT performance was evaluated (i.e., Overall Hit RT and Overall Hit RT SE). Thus, the findings from this study do not conflict with the attention results reported by Coles et al. (1997). The measures used to assess the Sustain component of attention by Coles did not include a manipulation of the time between target presentation.

The finding of relatively Sustain(ISI response-speed-variability) deficit in the FAE(D+X) subgroup has implications for furthering understanding of teratogenic theory and for directing clinical research and practice. These implications will be presented in the General Discussion.
GENERAL DISCUSSION

Diagnostic Subgroups

Part 1 of this study provided empirical and theoretical support for a spectrum of three diagnostic fetal alcohol subgroups. This was done using categorical criteria regarding the three diagnostic domains used to identify the damage caused by excessive prenatal alcohol exposure. Subgroups were defined using teratogenic theory, previous research findings, and logic.

The identified spectrum consisted of FAS, FAE(D), and FAE(X) subgroups and is comparable to the diagnostic classification proposed by the IOM in 1996. The finding of both an FAE(D) and FAE(X) subgroup in this study is consistent with the pFAS and ARND groups in the IOM’s classification system. More specifically, the definition of FAE(D) used in this study is consistent with the diagnosis of pFAS proposed by the IOM (1996). The definition of FAE(X) is consistent with the diagnosis of ARND proposed by the IOM (1996). There has been consensus regarding a definition of FAS for some time (Sokol & Clarren, 1989). Finally, in a manner consistent with findings from this study, the IOM’s diagnostic classification scheme does not include an FAE(G) subgroup.

Results from the archival file review of categorical diagnostic characteristics have implications for furthering a theoretical understanding of the teratogenic effects of excessive prenatal alcohol exposure. Contrary to what was predicted using principles from Vorhees’ teratogenic dose-effect theories (1986, 1989), the absence of an FAE(G) subgroup in this study suggested that a moderate level of prenatal alcohol exposure is not likely to produce a clinical subgroup of individuals who exhibit positive signs in the domains of CNS dysfunction and growth retardation.

These findings also suggested that if excessive prenatal alcohol exposure results in growth retardation, that individual will also likely exhibit positive signs of dysmorphism and CNS dysfunction, thus meeting criteria for FAS. This conclusion is supported by the
finding of a subgroup that exhibited signs of dysmorphology and CNS dysfunction but not growth retardation (i.e., FAE(D)), and by the fact that no FAE(G) subgroup was identified.

The application of findings from Part 1 to teratogenic theory suggest that the dose-effect relationship of excessive prenatal alcohol exposure does not completely fit the pattern for abuse agents detailed by Vorhees (1989). Vorhees postulated that with abuse agents such as alcohol, CNS dysfunction and growth retardation occur at a substantially lower dose-level compared to the dose-level associated with dysmorphology (see Figure 2). In contrast, findings from Part 1 indicate that growth retardation occurs at a higher exposure level than those associated with dysmorphology in Vorhees' teratogenic theory of abuse agents (see Figure 7).
Figure 7. Dose-effect curves for major manifestation of excessive prenatal alcohol exposure (bottom panel), based upon findings from Study 1. In comparison to Vorhees’ (1989) pattern for teratogenic abuse agents (top panel), growth retardation occurs at a higher level than that associated with dysmorphology.
In order to elaborate on the findings from Part 1, Part 2 of this study included dimensional measures of growth (height, weight) and CNS dysfunction (head circumference). Head circumference is used in diagnostic medical assessments as a measure of CNS dysfunction because it reflects brain size or brain growth.

The pattern of growth findings indicated that head circumference was significantly reduced \((z < or = -1.4)\) in subgroups with facial dysmorphology \([\text{FAS, FAE(D)}]\) and was within normal limits \((z > -1)\) in the one subgroup that did not exhibit facial dysmorphology \([\text{FAE(X)}]\). Taken together, the findings from Part 1 and Part 2 of this study indicated that reduced brain size and facial dysmorphology are more vulnerable to the toxic effects of excessive prenatal alcohol exposure than reduced somatic growth (height, weight). Microcephaly and facial dysmorphology are visible markers of pathologically reduced brain size.

Clinically these findings indicate that if head circumference is reduced, then facial dysmorphology will likely be present and a child will receive a diagnosis of FAS or pFAS. Support for this position was drawn from the finding that in the two subgroups with facial dysmorphology \([\text{FAS & FAE(D)}]\), 9 of the 20 subjects or 45 percent exhibited microcephaly. This was the positive predictive value of facial dysmorphology being present when microcephaly was exhibited.

If overall microcephaly is not exhibited, then facial dysmorphology will likely not be present and a child will receive a diagnosis of ARND. Support for this position was drawn from the finding that in the subgroup without facial dysmorphology, 9 of the 10 subjects or 90 percent did not exhibit microcephaly. This was the negative predictive value of microcephaly being present when dysmorphology was absent.

It is important to note that normal brain size does not necessarily correspond with normal brain function. Thus, the neuropsychological and behavioural functioning of diagnostic subgroups was directly assessed in Part 2 of this study.

**Continuity and Comparability on Components of Attention**

Part 2 of this study evaluated the level of functioning of a spectrum of diagnostic subgroups using dimensional norm-referenced measures of neuropsychological and
behavioural components of attention, and it yielded three major findings. First, all three diagnostic subgroups (FAS, FAE(D), FAE(X)) had a clinically significant level of CNS dysfunction in the form of neuropsychological and behavioural attention deficits. This indicated that a history of excessive prenatal alcohol exposure is predictive of clinically significant CNS dysfunction whether or not physical features of dysmorphology or growth retardation are present. The finding of a clinically significant CNS or attention deficit in FAS, FAE(D) and FAE(X) also provided support for the clinical validity of the IOM diagnostic classification scheme as it consists of three comparable diagnostic groups (FAS, pFAS, ARND).

Second, although the FAE(D) and FAE(X) subgroups had similar performance levels across all neuropsychological components of attention, individuals within both the FAE subgroups exhibited substantially greater performance variability when compared to the FAS subgroup. This variability was not accounted for by IQ or head circumference. This indicates that some but not all individuals with FAE(D) or FAE(X) have a more severe attention deficit than individuals with FAS. In clinical practice, this finding emphasizes the importance of specialized medical, psychological, and educational intervention for all individuals with a history of excessive prenatal alcohol exposure.

Third, after adjusting for IQ, the FAS and a combined FAE(D+X) subgroup had comparable levels of functioning on all components of attention with one exception. The FAS and FAE(D+X) subgroups were comparable on Inattention, Hyperactive-Impulsive, Encode, Focus-Execute, Shift, Sustain(response-speed) and Sustain(accuracy) components of attention. However, when compared to the FAS subgroup, the FAE(D+X) subgroup was more impaired on the Sustain component of attention assessing response-speed-variability with changes in the time interval between events. As previously stated, this indicated that when compared to the FAS subgroup, the FAE(D+X) subgroup was less adept at regulating behaviour in response to changes in the external environment. Inconsistencies in response-speed of this nature are believed to reflect biological brain dysfunction. At a behavioural level inconsistencies in response-speed have been described as representing "microlapses of attention" (Cardon & Mirsky,
1962; Streissguth et al., 1994). At a neuropsychological or brain-behaviour information processing level, high intraindividual variability of RT’s are thought to represent non-optimal neurocognitive preparation (Zahn & Mirsky, 1999).

The current finding of a relative Sustain(ISI response-speed-variability) deficit in FAE when compared to FAS was not consistent with predictions made regarding neuropsychological deficits based upon Mattson et al.’s (1994) report of reduced diencephalon volume in FAS but not FAE. This emphasizes the importance of understanding the damage caused by excessive prenatal alcohol exposure at multiple levels of structural and functional neuroanatomical processing. For example, although MRI studies have evaluated the proportional volume of gross-neuroanatomical structures (e.g., diencephalon, basal ganglia, cerebellum), further research is needed to assess functional brain-behaviour relationships at micro-neuroanatomical and neurochemical levels. Although Clark et al. (2000) evaluated glucose metabolism of major brain regions of adolescents and adults with FAS, a comparative study of this nature with a spectrum of diagnostic subgroups (FAS, pFAS, and ARND) is needed.

As previously stated, the diencephalon is one of the major brain structures involved in the modulation of the Sustain component of attention (Mirsky et al., 1989). It is possible then that the size of a specific brain region observed via MRI could be within normal limits, despite the fact that neurons within this region are significantly damaged and functioning at suboptimal levels due to structural and neurochemical abnormalities. This is relevant information as there is a documented relationship between neuroanatomical and neurochemical abnormalities in other conditions with attention deficits, such as ADHD (Barkley, 1998) and schizophrenia (Andreasen, 1994).

In a recent conference presentation, Rovet and Cole (2000) suggested that high variability of RT scores likely signify “micro-lapses” of attention as a result of inconsistent neurotransmissions. This is certainly a plausible contributing factor as the FAE(D+X) relative to the FAS subgroup was not consistent with current knowledge of the structural neuroanatomical damage caused by excessive prenatal alcohol exposure,
and animal studies have shown that prenatal alcohol exposure alters brain neurochemistry (Ikonomidou et al., 2000).

Findings from Part 2 of this study also have implications for furthering a theoretical understanding of the teratogenic effects of excessive prenatal alcohol exposure. When the finding of clinically impaired functioning on neuropsychological components of attention in a spectrum of diagnostic subgroups is evaluated within the context of previous studies of the neuropsychological functioning of FAS and FAE groups, three conclusions are strikingly apparent.

First, using norm-referenced measures, the severity of impairment on the Sustain component of attention in FAS, FAE(D) and FAE(X) subgroups was substantially greater than the severity of the memory deficits reported by Mattson et al. (1998) in FAS and PEA groups. For example, on the long-delay free recall condition from the California Verbal Learning Test, the performance of FAS and PEA groups were within the low average and borderline range, respectively. This comparative finding of relatively greater attention than memory deficits in FAS and FAE subgroups suggests that individuals with a history of excessive prenatal alcohol exposure are likely to exhibit both global and specific neurocognitive deficits. Furthermore, findings from this study indicate that attention functions are especially sensitive to the damaging effects of excessive prenatal alcohol exposure.

Second, the birth mothers of children with pFAS, ARND or FAE likely decreased consumption of alcohol across the trimesters of pregnancy. Many women with an alcohol addiction are able to reduce the amount of alcohol consumed while they are pregnant (Rosett, Weiner, & Edelin, 1983). The reduction or absence of alcohol exposure during the third trimester may allow catch-up growth, thus eliminating growth retardation but not the brain damage resulting from alcohol early in the pregnancy.

Third, the clinically significant attention deficits exhibited by both the FAS and FAE subgroups highlight the importance of identifying all individuals with a history of excessive prenatal alcohol exposure in order to provide specialized medical, educational and vocational services. It is especially important that children with FAS, pFAS or
ARND are diagnosed at an early age. Previous research (Streissguth, 1996) found early
diagnosis to be a key step in helping parents, children, and families adjust to the special
needs associated with FAS, pFAS and ARND.

In Saskatchewan, a diagnosis of FAS qualifies a child for special needs
educational funding in many but not all school systems. Assistance of this nature is,
however, crucial for maximizing potential and minimizing the development of additional
disabilities such as learning, social and behavioural problems, as well as depression in
individuals with FAS, pFAS, and ARND. Given that there is now empirical evidence
indicating that individuals with FAE are as severely affected at a neurobehavioural level
as individuals with FAS, there is a need for education and social policy to also qualify
individuals with FAE for special needs funding and services.

It is now well documented that FAS and FAE groups have reduced levels of
general intellectual function (Streissguth et al., 1996; Mattson et al., 1997). With regards
to specific neurocognitive functions, Mattson et al. (1998) reported that the memory
deficits in FAS and PEA groups were comparable to IQ levels. In the present study,
components of attention were found to be substantially below the IQ level of FAS,
FAE(D) and FAE(X) subgroups.

The finding of a greater Sustain(ISI response-speed-variability) deficit in the
FAE(D+X) compared to the FAS subgroup was not accounted for by the dimensional
measures of head circumference or IQ. The FAS, FAE(D) and FAE(X) subgroups had
norm-referenced head circumference (HdCir) z-scores of -2.1, -1.4, and -.4, reflecting a
substantial difference in brain size between all three subgroups. IQ was related to the
difference between the FAS and FAE(D) subgroup (HdCir = -2.1 & -1.4; IQ = 74 and
84, respectively). However, IQ was not related to the difference between the FAE(D)
and FAE(X) subgroups (HdCir = -1.4 & -0.4; IQ = 86 & 83, respectively). This indicates
that reductions in brain size caused by excessive prenatal alcohol exposure are not always
related to decreased neurocognitive functioning.

The greater Sustain(ISI response-speed-variability) deficits exhibited by the FAE
relative to the FAS subgroup was not consistent with current knowledge of the
neuroanatomical damage associated with these two conditions. As previously stated, the current finding of a relative Sustain(response-speed-variability) deficit in FAE when compared to FAS, and Mattson et al.'s (1994) finding of reduced diencephalon volume in FAS but not FAE emphasized the importance of understanding the damage caused by excessive prenatal alcohol exposure at both gross anatomical and functional neurochemical levels.

Several recent studies have focused on damage caused to the brain’s neurochemical system and its implications for brain development and function, using animal models of prenatal alcohol exposure (Shen, Hannigan, & Kapatos, 1999; Ikonomidou et al., 2000). Thus, the finding of a greater Sustain(response-speed-variability) deficit in the FAE(D+X) versus FAS subgroup in this study is likely a reflection of damage caused to the brain at microneural and neurochemical levels.
Limitations and Future Research

The relatively small sample size, substantial within subgroup variability, the quasi-experimental design, and measurement constraints limit the conclusions that can be drawn from this study.

Due to the limited population of individuals between 10 and 14 years of age who met diagnostic requirements for FAE(D) or FAE(X), the sample size is small. However, since samples were selected using a large clinical and epidemiological patient database, misrepresentation of the populations that the samples represent was minimized. The sample size (n = 10) used for FAS, FAE(D), and FAE(X) subgroups in this study is also comparable to the size of sample used in previous FAS/FAE studies (n = 6 to 10; Conner et al. 1999, Mattson et al., 1999).

Although the substantial number of analyses conducted in this study increased the possibility of Type 1 errors, alpha was set at .05 for omnibus and pairwise comparisons. This was done due to the exploratory nature of this study, the small population of children available to participate, and the ability of small samples to detect only large effect sizes. As a result of these limitations, it is important that findings be replicated, as there is a possibility that the pattern or results identified is specific to this sample.

Since this study, and all previous studies of the effects of prenatal alcohol exposure, used a quasi-experimental design that did not include random assignment to the diagnostic subgroups, this study does not support causal inferences regarding the relationships between diagnostic subgroups and attention deficits. This issue was addressed by matching subgroups on age, sex, and ethnicity. Thus, it is unlikely that the relationship between diagnostic subgroups and attention deficits found in this study were the result of differences in sample characteristics.

Given that the exact amounts and pattern of maternal alcohol consumption during pregnancy was not available it is also not appropriate to draw inferences from study findings regarding differences in the teratogenic exposure levels between subgroups. As noted by Mattson et al. (1999), due to the difficulties associated with obtain accurate reports of maternal alcohol use during pregnancy in a medical diagnostic assessment of
FAS and in a retrospective study, this is also a limitation of previous studies. However, the diagnosing pediatrician confirmed that all children in this study had a history of excessive prenatal alcohol exposure.

Another potentially confounding factor was the limited ability to control for post-natal environment. This issue was addressed by obtaining comparable living placement characteristics for all subgroups as defined by living with adoptive, foster, and biological parents. Given the sensitivity of attention functions to the effects of prenatal alcohol exposure, future research should compare the attention deficits exhibited by adolescents or adults with FAS, pFAS, and ARND who live in stable versus unstable home environments. It is possible that living in a stable and nurturing environment will modify the severity of secondary disabilities associated with excessive prenatal alcohol exposure. However, further research is needed to investigate the extent to which a good post-natal environment is able to compensate for pre-natal teratogenic exposure.

Findings from archival file review in Part 1 of this study need to be replicated using other samples of children with a confirmed history of excessive prenatal alcohol exposure from other diagnostic clinics and geographic locations. Information of this nature would help determine if there are differences in the clinical presentation of physical (e.g., facial dysmorphology) or neurobehavioral deficits in children from different races (e.g., Caucasian, Canadian-First Nations, African American). Information of this nature would also provide additional information regarding the clinical utility of the IOM (1996) diagnostic classification system.

Neuropsychological tests measure the performance of subjects on tasks that are thought to tap specific theoretical constructs, without directly measuring the cognitive processes involved. For example, in this study neuropsychological and behavioural measures of attention were used to make inferences about these neurocognitive and neurobehavioural abilities. As a result, the inferences made about abilities on components of attention are limited to the specific way in which the tasks used are thought to measure the involved processes.

Since the majority of neuropsychological and behavioural findings were based on
secondary analyses, these results need to be replicated before firm conclusions can be made regarding the magnitude and specificity of attention deficits in FAS and FAE. A study of this nature should include a CPT with an ISI manipulation, as this was the attention measure that identified more difficulties in FAE compared to FAS. If this finding can be replicated, then a follow-up functional MRI study using a CPT would be helpful in elucidating the brain-behaviour relationships behind the difficulties exhibited with response-speed-variability.

Given that the findings from several studies indicate that the neurotransmitter dopamine makes an important contribution to the attention deficits exhibited by FAS and FAE subgroups, a study of dopaminergic functioning is warranted. For example, the integrity of subcortical dopamine functioning could be evaluated in FAS, FAE(D), FAE(X), and ADHD subgroups using the positron emission topography (PET) methodology developed by Ernst, Zametkin and Matochik (1999). In an evaluation of this nature it would be informative to evaluate associations between deficits on neuropsychological components of attention and aberrant neurochemical findings.
CONCLUSION

This study provided empirical and theoretical support for the validity and clinical utility of the IOM's diagnostic classification system for medical conditions resulting from excessive prenatal alcohol exposure. This support was based upon two major findings. First, the diagnostic criteria for the three subgroups identified in this study are comparable to IOM's criteria for FAS, pFAS, and ARND. Second, support was also derived from the finding that all three subgroups exhibited a clinically significant attention deficit. To the authors' knowledge, this was the first study to evaluate and provide support for the clinical validity and utility of the IOM's (1996) diagnostic classification system.

Taken together, these findings indicate that the IOM's diagnostic classification system should be used as the current diagnostic standard in clinical practice and in research. Since the spectrum of diagnostic subgroups identified in this study was only partially consistent with a priori prediction, replication is required using similar methods with samples from another diagnostic clinic. It would also be helpful if the methodology of a study of this nature included a systematic evaluation of the medical and neurocognitive dysfunction of FAS, pFAS and ARND groups. Although findings from the author's study indicate that the neurocognitive attention deficits of FAE(D) and FAE(X) subgroups were equivalent, important differences in the medical complications exhibited by these two subgroups were not evaluated but may exist. If medical and neurocognitive functioning of pFAS and ARND subgroups are comparable, then these two subgroups should be combined.

Results from the author's study furthered a theoretical understanding of the teratogenic effects of alcohol as an abuse agent. It did this by indicating that individuals with a history of excessive prenatal alcohol exposure are likely to exhibit CNS dysfunction (in the form of an attention deficit) whether signs of dysmorphology or
growth retardation are present or absent. This conclusion was also supported by the finding of comparability in the magnitude and specificity of attention deficits exhibited by individuals with FAE(D) and FAE(X) on measures of six components of attention. Thus, the severity of the neurocognitive and neurobehavioural phenotype (CNS dysfunction) does not correspond to the severity of the physical phenotype (dysmorphology, growth retardation). On the contrary, if there is a history of excessive prenatal alcohol exposure, the neurocognitive and neurobehavioural phenotype is likely to be exhibited (in the form of an attention deficit) regardless of whether the physical phenotype is evident.

This finding emphasizes the importance of obtaining information regarding prenatal exposure to alcohol in individuals presenting with neurocognitive or neurobehavioural difficulties, to facilitate diagnosis and intervention. It also emphasizes the importance of developing a continuum of treatment programs designed to meet the needs of pregnant women with an alcohol addiction, in order to prevent fetal alcohol related conditions.

Using information regarding a history of excessive prenatal alcohol exposure to diagnose a medical condition such as ARND, in the absence of dysmorphology or growth retardation, represents a substantial change in clinical practice. For example, dysmorphologists have previously asserted that it was not possible to associate excessive prenatal alcohol exposure with CNS dysfunction in the absence of facial dysmorphology (Astley & Clarren, 1995).

Since the finding of greater Sustain(ISI response-speed-variability) exhibited by the FAE(D+X) compared to the FAS subgroup was an unexpected finding, replication and more in-depth evaluation of this finding is warranted. It would be helpful if evaluations of this nature used similar methods with a variety of patient populations (e.g., FAS, pFAS, ARND, ADHD, head injury). It would also be helpful to isolate more specifically the critical factors associated with high ISI response-speed-variability.

Since findings were not consistent with previous reports of gross structural neuroanatomical damage in FAS and FAE, additional research with more functional measures of neuroanatomical functioning are warranted. Evaluations of the
neurochemistry in FAS and FAE may be particularly informative for furthering understanding of both theoretical and clinical intervention. Finally, the comparative findings of relatively greater attention than memory or IQ deficits in FAS and FAE subgroups suggests that excessive prenatal alcohol exposure is likely to cause both global and specific neurocognitive deficits, and that basic aspects of attentional regulation functions are especially vulnerable.
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Appendix 1: Equivalency Procedures and Formulas

The statistical procedures and formulas used to conduct equivalency analyses with three subgroups and a covariate (IQ) are detailed in this Appendix. The procedures and formulas presented were programmed into a computer spreadsheet to ensure consistency and accuracy.

1) The following numerical values are required to conduct an equivalency analysis with two subgroups:
   a) the difference between group means ($M_{\text{diff}}$),
   b) the standard error of the mean difference ($SE_{\text{diff}}$), and
   c) an equivalence criterion (EC) value.

2) Mean difference ($M_{\text{diff}}$) and $SE_{\text{diff}}$ values were obtained using the one-way ANCOVA procedure with all three diagnostic subgroups and IQ as the covariate.

3) An EC was calculated by multiplying the comparison subgroup mean by .20. Twenty percent was the set equivalency criterion for this study.

4) The comparison subgroup mean was identified as the first subgroup listed in a group pair (e.g., in FAS versus FAE(D), FAS is the comparison group). Support for this decision is based on the fact that FAS is an established diagnostic criteria while there are only general guidelines for the clinical label of FAE. In comparisons involving FAE(D) versus FAE(X), FAE(D) was used as the comparison group as this group has physical features (facial dysmorphismology) that have been directly linked to excessive prenatal alcohol exposure while the FAE(X) does not exhibit physical links of this nature.

5) For the calculation of the EC value, comparison subgroup means were adjusted so that the degree to which these means differed from the normative mean value of 50 was expressed as a value above 50. Without an adjustment of this nature the EC value for performance above the normative mean of 50 would be larger than for subgroup performance that was below the normative mean. This adjustment was not applied to the one raw score subgroup comparison mean.
6) Two equivalency \( t \) statistics were calculated using the following formulas detailed by Stegner, Bostrom & Greenfield (1996): a) \( t_1 = \frac{M_{\text{diff}} + E\bar{C}}{S\text{E}_{\text{diff}}} \) and b) \( t_2 = \frac{M_{\text{diff}} - E\bar{C}}{S\text{E}_{\text{diff}}} \).

7) The smallest resulting \( t \) value was selected and compared with the appropriate \( t_{\text{critical}} \) value in order to decide if:
   a) the equivalence null hypotheses could be rejected
      (i.e., \( H_0: \mu_1 - \mu_2 \leq -E\bar{C}; H_{02}: \mu_1 - \mu_2 \geq + E\bar{C} \)), and
   b) the equivalence alternative hypotheses could be accepted
      (i.e., \( H_a: -E\bar{C} < \mu_1 - \mu_2 < +E\bar{C} \)).

   Critical values for the \( t \) statistic were obtained for a one-tailed test, and an alpha or \( p \) level of \( \leq .05 \).

The Newman-Keuls procedure (Howell, 1997) was used to conduct pairwise statistical equivalence comparisons using the following steps:

   a) Mean difference values were ordered from smallest to largest instead of from largest to smallest.

   b) For each pairwise comparison a Studentized Range Statistic (\( q \)) was calculated using the following formula:
      \( q = t \star \sqrt{2} \).

   c) The obtained \( q \) value for the pairwise comparison with the smallest \( M_{\text{diff}} \) was compared with the appropriate \( q_{\text{critical}} \) value. Critical values for the \( q \) were obtained for one-tailed tests, and the alpha level or \( p \) was set at \( \leq .05 \).

   d) Step number 3 was repeated with the next \( M_{\text{diff}} \) value in the ordered series until a subgroup pairwise comparison was found not to be equivalent.

   A priori pairwise comparisons involving three subgroups were conducted using the Newman-Keuls procedure in order to assess equivalence and control for familywise alpha. The Newman-Keuls pairwise comparison procedure was chosen for two major reasons. First, it helped answer study hypotheses, because it sorts subgroup means into homogeneous sets in the sense that they are not different from each other (Howell, 1997). Second, given the exploratory nature of this study the Newman-Keuls procedure provides
more statistical power for identifying equivalencies that actually exist when compared to other pairwise procedures such as the Tukey and Scheffe Tests.
Equivalency Testing Results for FAS vs FAEdys vs FAEexp

Equivalency Analysis with Three Groups & a Covariate (IQ)

Equivalence Criterion (EC) = 20 percent - (comparison trt mean * .20)

Sample Size (N) = 30
Subgroup Size (n) = 10

Mean difference calculated using adjusted means obtained via ANCOVA with IQ as the covariate

\[ \text{SE difference} = \sqrt{\frac{2 \times \text{MSError}}{n}} \]

\[ n \text{ refers to the number of subjects per subgroup} \]

Howell (1997), p. 370

\[ \text{SE difference} = \frac{\text{SD}}{\sqrt{n}} \]
\[ \text{SD difference} = \text{SE.diff} \times \sqrt{n} \]
\[ \text{Effect Size (ES)} = \frac{\text{Mdiff}}{\text{Sdiff}} \]

Newman-Keuls Procedure for Equivalency Testing

1) Order M diff values from smallest to largest
2) Compare the obtained q associated with the smallest M diff with q critical
3) If diff is statistically equivalent, check to see if group comparison with the next smallest M diff is equivalent
4) Proceed in this manner until a comparison is found not to be equivalent

q critical values

\[ n=30 \]

IQ as covariate
\[ df = 28 \]
\[ p = .05 \]
1-tailed

\[ r = 2, q = 2.41 \]
\[ r = 3, q = 2.90 \]
\[ r = 4, q = 3.19 \]
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Hit SE ISI 5.8 FAEdys vs FAExp  1.84  2.41 ns
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**Newman-Keuls Test**

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Note: The table provides statistical data comparing various groups, including means, standard errors, and t-values. The Newman-Keula Test indicates the comparison of means with their respective t-values and critical values.
### Parent Report

#### FAS vs FAE dys

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### Newman-Keuls Test

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| Hyper-Impul | 1.7 | FAS vs FAE dys | 3.11 | 2.41 | Equival |
| 11.9 | FAE dys vs FAE exp | 3.37 | 2.90 | Equival |
| 13.5 | FAS vs FAE exp | 0.4 | 3.19 | na |
Equivalency Testing Results for FAS (n=10) versus FAEdys/exp (n=20)

Equivalency Analysis with Two Groups, a covariate, and unequal n's per group

IQ was used as a covariate for attention scores from the following components: ENCODE, FOCUS-EXECUTE, SHIFT

IQ was used as a covariate when there was a statistically significant Multivariate Effect for covariate.

M diff values were calculated using adjusted mean obtained via ANCOVA

SE diff values were calculated using MS error values from ANCOVA

\[ \text{SEdiff} = \sqrt{\left(\text{MS error} / ni\right) + \left(\text{MS error} / nij\right)} \]

\[ = \sqrt{\left(\text{MS error} / 10\right) + \left(\text{MS error} / 20\right)} \]

SD diff = SEdiff * sqrt N

SEdiff = Sddiff / sqrt N, where N refers to the total number of subjects

EC = 20 percent (comparison treatment mean * .20)
Sample Size (N) = 30
Effect Size (ES) = M diff / SD diff

tcritical = 1.761

Equivalency Analysis with Two Groups, no covariate, and unequal n's per group

IQ was not used as a covariate for attention scores from the following components: SUSTAINresponse-speed-consistency, SUSTAINresponse-speed, SUSTAINaccuracy

IQ was not used as a covariate when the Multivariate Effect for covariate was not significant

Mdiff values were calculated using unadjusted means

SEdiff values were obtained from Independent t-test analysis

Levene's test was used when subgroup variances were unequal
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<td>2.872</td>
<td>0.633</td>
<td>-0.15</td>
<td>0.692</td>
<td>0.252</td>
<td>1.933</td>
<td>0.252</td>
</tr>
<tr>
<td><strong>Parent Report</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Inter-imp</td>
<td>75.5</td>
<td>72.22</td>
<td>3.280</td>
<td>5.248</td>
<td>0.04</td>
<td>14.800</td>
<td>3.283</td>
<td>2.574</td>
<td>2.574</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Hyper-imp</td>
<td>77.10</td>
<td>69.50</td>
<td>7.600</td>
<td>5.854</td>
<td>0.24</td>
<td>15.420</td>
<td>3.832</td>
<td>1.336</td>
<td>1.336</td>
<td>INC</td>
</tr>
</tbody>
</table>

Note: # indicates that IQ was used as a covariate.
Appendix 3: Conners’ CPT TASK PARAMETER

Task Parameters, Data Transformations, and the Calculation of Accuracy, Response-Speed, and Response-Speed-Variability Scores

1) TASK PARAMETERS:
   Overall total # target letters - 324
   Overall total # non-target letters - 26

   Total # of targets of letters collapsed by ISI (1, 2, 4 s)
   ISI = 1, - 108
   ISI = 2, - 108
   ISI = 4, - 108
       ----- 
       324

   6 letter blocks, each with 3 ISI sub-blocks (1, 2, 4 s)
   18 sub-blocks
   18 targets and 2 non-targets per sub-block
   90 percent of letters presented are targets
   10 percent of letters presented are non-targets

   Total Time to Complete Task - 14 min 10 seconds
   Time to Complete 1 block - 47 seconds

2) DATA TRANSFORMATIONS
   - All RT scores were transformed using a logarithmic transformation, as RT distributions are usually positively skewed.
   - All raw scores were converted to norm-referenced T-scores stratified by age and sex.
   - Age breakdown of the norm-referenced CPT database for age ranges included in the author’s study:

<table>
<thead>
<tr>
<th>Age</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-11</td>
<td>62</td>
</tr>
<tr>
<td>12-13</td>
<td>82</td>
</tr>
<tr>
<td>14-15</td>
<td>58</td>
</tr>
</tbody>
</table>
3) CALCULATION OF SCORES

a) Accuracy
   Misses (omission errors)
   - The total number of targets to which subject did not respond.

   False Alarms (commission errors)
   - The total number of times the subject responded to a non-target ("X").

b) Response-Time
   Overall Hit RT
   - The mean response time for all target hits in milliseconds.
   - Higher T-scores reflect faster response times.

   Hit RT ISI Change
   - The slope of change in hit reaction times over the three ISI (1, 2, 4 s).
   - A **positive slope** indicates a slowing of RT's as the ISI increased.
   - A **negative slope** indicates a faster RT's as the time between targets increased.

c) Response-Time-Variability
   Overall Hit RT SE
   - The consistency of hit response times, expressed in terms of standard error for responses to targets.

   Hit RT SE ISI Change
   - The slope of change in hit reaction time standard errors over the three ISI's (1, 2, 4 s).
   - A **positive slope** means the person's reaction times became less consistent as the time between targets increased.
   - A **negative slope** means indicates increased consistency as the time between targets increased.

205
VITA

Biographical

June, 1963
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April, 1985
Bachelor of Arts
Providence College
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University of Saskatchewan

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Psychologist
FAS, Brain Injury, Metabolic Teams
Alvin Buckwold Child Development Program
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August, 2000
Psychologist
Youth and Adult Addiction Services
Calder Centre
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Academic Research Awards

1998
Accredited Pre-Doctoral Internship, Clinical Psychology
Specialization in Clinical Neuropsychology
Hamilton Health Science Corporation, Hamilton, ON
(Formerly the Chedoke-McMaster Hospitals)

1996
Health Promotion Research Grant, Royal University Hospital, Saskatoon, SK

1994
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1992
Roehrer Institute Research Grant

1992
University of Saskatchewan, Graduate Scholarship

1991
University of Alberta, Gaul-Westfield Graduate Research Award
Publications


