TOWARDS IDENTIFYING A CHARACTERISTIC NEUROPSYCHOLOGICAL PROFILE FOR FETAL ALCOHOL SPECTRUM DISORDERS
1. ANALYSIS OF THE MOTHERISK FASD CLINIC

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ABSTRACT

Objective
Children with FASD display a heterogeneous profile and may have deficits in physical, behavioural, emotional, and social functioning, as the result of prenatal alcohol exposure. The major objective of the current study was to identify if a specific pattern of neuropsychological functioning exists among children prenatally exposed to alcohol who received a diagnosis, versus exposed children who did not. We compared groups on domains of intellectual functioning, memory, attention, executive functioning, motor functioning, language/communication and achievement.

Methods
One hundred and seventy children who were seen in the clinic between 2005 and 2009 were included in this study. Out of the total 170 children seen, 109 received an FASD diagnosis.

Results
We identified a specific neuropsychological profile that typifies children diagnosed with an FASD versus those exposed prenatally to alcohol, who did not receive a diagnosis. Diagnosed children displayed a neuropsychological profile characterized by weaknesses in the areas of verbal reasoning, memory, overall language functioning, math reasoning and calculation. Groups did not differ on measures of attention or executive functioning.

Conclusion
The information gained from these analyses, are essential for informing best practices for diagnosis and treatment.

Key Words: *Fetal Alcohol Spectrum Disorder, neuropsychological profile, diagnosis*

Fetal Alcohol Spectrum Disorders (FASD) refers to the range of conditions arising from prenatal exposure to alcohol and encompasses a range of diagnoses including Alcohol Related Neurodevelopmental Disorder (ARND), Partial Fetal Alcohol Syndrome (P/FAS), Alcohol Related Birth Defects (ARBD), as well as the most severe diagnosis on the spectrum, Fetal Alcohol Syndrome (FAS). Despite the recent consensus on the terminology used to describe children with FASD, diagnosis is not simple and clinicians are required to consider several biopsychosocial factors in the diagnostic formulation. Moreover, since the condition was first identified in the literature[2] a significant amount of research has aimed to address the elusive FASD behavioural phenotype[3,4,5,] often raising more questions than answers. Despite the research attention given to FASD, prevalence rates and societal costs continue to remain high.

In the US, prevalence estimates of FASD range from 0.5-2 per 1000 births for FAS and 10 per 1000 births for ARND.[6] In Canada, estimates are comparable ranging from 1 to 6 per 1000 live births[1], although variations do exist within and between the two countries.[7] In some Canadian populations, the incidence may be as high as 10-20%.[1] Unfortunately, to date, these rates have remained unchanged. Because a large proportion of individuals with FASD require extensive mental health services throughout their lifetime, the costs associated with FASD are staggering.

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Indeed, it is estimated that in Canada $344 million are spent annually on affected youth.[8] Since incarceration and difficult-to-measure costs such as lost productivity, alcoholism, and poor quality of life, are excluded from these estimates, the actual cost of FASD is likely much higher.

Children with FASD display a heterogeneous profile and may have deficits in physical, behavioural, emotional, and social functioning, as the result of prenatal alcohol exposure.[9-12] Neuropsychological deficits may include intelligence, achievement, executive functioning, memory, attention, visual spatial, language and processing speed weaknesses.[13-16] Secondary disabilities are also often documented and include mental health problems, trouble with the law, confinement, alcohol and drug abuse and less likely to complete school.[17-19]

According to a landmark report on the long-term outcomes of individuals with fetal alcohol exposure, early diagnosis and presumably early treatment are predictive in mitigating later secondary disabilities.[17] Nevertheless a unifying diagnostic profile has not been firmly established, making it an extremely difficult condition to assess and diagnosis clinically, although several groups are currently working towards this goal.[15,20,21] In order to better understand the FASD profile it is therefore important to identify if a specific pattern of strengths and weaknesses exists for children who have been exposed prenatally to alcohol and who meet criteria for FASD, compared to children exposed prenatally to alcohol who do not meet criteria for an FASD.

For nearly 20 years the Motherisk Clinic at the Hospital for Sick Children in Toronto, Ontario, Canada, has been assessing children with prenatal alcohol and drug exposures. The majority of the children are brought to this clinic by foster or adoptive parents who are concerned that their child's learning and/or behavioural problems may be caused by prenatal alcohol exposure. Since the clinic began, diagnostic procedures have evolved from the use of the Institute of Medicine Criteria[22], our own profile of strengths and weaknesses[23], to our current utilization of the Canadian diagnostic guidelines.[1] It was not until recently that a set of criteria existed that pertained specifically to a Canadian demographic and where the Motherisk clinic had enough children diagnosed using this methodology to fulfill the large sample size needed for scientific rigour.

In the current study, psychological assessment results were analyzed using the domains outlined by the Canadian Guidelines and diagnostic information will be conveyed, as per the guidelines[1] using the Washington 4-Digit code.[20] The major objective of the current study was to identify if a specific pattern of neuropsychological functioning exists among children prenatally exposed to alcohol who received a diagnosis, versus exposed children who did not. We compared groups on domains of intellectual functioning, memory, attention, executive functioning, motor functioning, language/communication and achievement. The information gained from these analyses is critical in enhancing best practices for diagnosis and treatment. Findings from this study have the potential to further refine the assessment process by identifying the key characteristics of those children receiving a diagnosis. The current study additionally adds to a similar attempt[15] by including a group of children seen in the FASD clinic because of prenatal exposure to alcohol, but ultimately not meeting diagnostic criteria, as well as using a larger sample size.

METHODS

Participants

One hundred and seventy children who were seen in the clinic between 2005 and 2009 were included in this study. Demographic characteristics of the sample are presented in Table 1. Out of the total 170 children seen, 109 received an FASD diagnosis (Dx group, mean age = 10.33, SD = 3.57, 55% male) and 61 did not receive an FASD diagnosis (Non-Dx group, mean age = 8.94, SD = 3.41, 66% male).

Materials and Procedures

The diagnostic assessments were conducted by a multidisciplinary team consisting of a psychologist, psychometrist, and neurologist, who used a combination of standardized and nonstandardized measures, rating scales, interviews, clinical observations, and developmental history. Diagnoses were made using the Canadian Guidelines and children were classified using the 4-Digit Coding system developed at the University of Washington.[20] Diagnostic expression is classified

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using a 4-point likert scale with 1 representing no evidence of the FASD profile and 4 reflecting the "classic" FAS profile. All participants in our clinic were required to have a confirmed history of prenatal exposure to alcohol either via Children's Aid's records, reported alcohol withdrawal at birth, or report from the biological mother.

With regards to the "brain" rankings used in diagnosis, Brain 1 refers to no evidence of brain damage caused by prenatal exposure to alcohol as evidenced on psychometric measures, Brain 2 refers to suspected damage, Brain 3 refers to probable brain dysfunction evidenced by psychometric measures, and Brain 4 is evidenced by damage confirmed by physical characteristics through medical examination. Children categorized by Brain 3 were required to show impairment (as classified by the Canadian Guidelines) in three or more of the following domains: sensory/motor, communication, attention, intellectual functioning, executive functioning, memory, and academic achievement. It is important to note that a Brain 4 ranking only occurs when there are "hard" medical criteria met, such as microcephly, structural abnormalities, and/or other hard neurological signs.

For the purposes of data analysis, children in the Brain 3 and 4 groups were considered diagnosed and those who received a brain score of 1 and 2 comprised the non-diagnosed group. As is importantly highlighted in the literature[24], several diagnostic centres use different nomenclature to refer to different diagnostic categories on the FASD spectrum. Therefore for clarification, a 'brain' score of 3 is similar to either an ARND or p/FAS diagnosis, while a 'brain' score of 4 similar to an FAS diagnosis. 'Brain' scores of 1 and 2 are indicative of PAE, without meeting diagnostic criteria based on the Canadian guidelines. Table 2 indicates the breakdown by brain classification and diagnosis for the sample.

All children were administered a consistent series of neuropsychological measures, however due to the wide age range and children's ability to manage and cope with psychometric testing, sample sizes vary and are indicated as they pertain to each measure.

TABLE 1 Demographic Information

	FASD Diagnosed Mean (SD)	**FASD Non-Diagnosed Mean (SD)**	**p-value**
Age	10.3 (3.6)	8.9 (3.4)	p< .01
Number of placements	3.1 (1.9)	2.7 (1.5)	ns
SES	3.0 (1.2)	3.1 (1.1)	ns
Brain 1 (%)	0	34.0	n/a
Brain 2 (%)	0	66.0	n/a
Brain 3 (%)	92.9	0	n/a
Brain 4 (%)	7.1	0	n/a
Female	n=60	n=40	ns
Male	n=21	n=49	ns
Cigarette Exposure	88(%)	87(%)	ns
Cocaine Exposure	29(%)	22(%)	ns
Marijuana Exposure	40(%)	27(%)	ns
ADHD Diagnosis	61(%)	40(%)	p< .00
ODD Diagnosis	8(%)	2(%)	ns
Special Education Placement	64(%)	42(%)	p< .00
Maternal Mental Health Concerns	32(%)	18(%)	p< .04
Maternal Learning Disorder	23(%)	18(%)	ns
Paternal Substance Abuse	54(%)	56(%)	ns
Paternal Learning Disorder	19(%)	15(%)	ns
Paternal Mental Health Concerns	15(%)	4(%)	p< .03
Medication Status			
Risperidol	12(%)	9(%)	ns
Zoloft	2(%)	0	ns
Dexedrine	4(%)	0	ns

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TABLE 2 Neuropsychological Profile by Domains

Neuropsychological Domain	FASD Diagnosed Mean (SD)	FASD Non-Diagnosed Mean (SD)	p-value
Intelligence (WISC-IV)			
FSIQ	86.9 (11.5)	92.4 (13.8)	p< .01
VIQ	98.6 (8.4)	95.5 (14.1)	ns
PIQ	97.2 (8.7)	92.4 (16.4)	ns
WMI	86.2 (14.3)	87.3 (13.0)	ns
PSI	89.0 (15.2)	92.1 (18.1)	ns
Similarities	9.2 (2.7)	10.1 (2.5)	p< .05
Vocabulary	8.4 (2.4)	9.4 (2.6)	p< .01
Comprehension	8.3 (2.4)	9.1 (2.4)	p< .04
Information	7.7 (2.5)	8.9 (2.3)	p< .05
Block Design	8.3 (3.4)	8.9 (3.0)	ns
Picture Concepts	9.4 (2.9)	9.7 (2.4)	ns
Matrix Reasoning	8.1 (3.2)	8.7 (2.7)	ns
Picture Completion	9.4 (2.9)	9.7 (2.4)	ns
Digit Span	7.6 (2.9)	8.1 (2.6)	ns
Letter Number Sequencing	7.3 (3.1)	7.7 (2.5)	ns
Arithmetic	6.9 (2.4)	8.5 (2.5)	p< .00
Coding	7.9 (2.8)	8.5 (2.5)	ns
Symbol Search	8.5 (3.0)	9.1 (2.0)	ns
Cancellation	10.5 (2.5)	10.7 (2.7)	ns
Memory (CMS)			
Dot Locations Learning	8.97 (3.53)	10.0 (3.21)	p< .07
Dot Locations Total	9.44 (3.84)	10.3 (3.13)	ns
Dot Locations Long Delay	9.26 (3.24)	10.3 (2.76)	p< .04
Story Immediate	8.99 (5.81)	9.73 (2.91)	ns
Story Long Delay	9.09 (5.99)	9.56 (2.92)	ns
Story Recognition	8.77 (3.76)	9.62 (3.67)	ns
Faces Immediate	9.52 (3.71)	9.64 (3.27)	ns
Faces Long Delay	9.37 (3.44)	9.29 (3.34)	ns
Word Pairs Learning	7.71 (3.40)	7.44 (2.89)	ns
Word Pairs Total	7.67 (3.49)	7.69 (2.77)	ns
Word Pairs Long Delay	7.67 (3.33)	8.51 (3.11)	ns
Word Pairs Recognition	8.38 (4.66)	8.87 (3.36)	ns
Numbers	7.82 (7.71)	7.49 (3.13)	ns
Sequences	8.32 (4.77)	8.80 (3.07)	ns

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Visual Immediate	95.4 (15.2)	99.9 (15.0)	ns
Visual Delay	95.1 (14.9)	98.0 (18.7)	ns
Verbal Immediate	87.8 (16.4)	91.4 (17.2)	ns
Verbal Delay	88.3 (16.9)	93.4 (18.5)	p< .08
General Memory	88.6 (16.8)	94.8 (19.5)	p< .04
Attention/Concentration	83.1 (22.9)	83.8 (27.1)	ns
Learning	89.1 (15.9)	91.3 (18.2)	ns
Delayed Recognition			ns
Language			
PPVT	94.1 (12.8)	97.4 (13.9)	ns
EOWPVT	93.8 (12.4)	97.3 (14.2)	ns
NEPSY Language Composite	89.4 (14.6)	96.8 (13.7)	p< .04
NEPSY Phonological Processing	8.0 (3.0)	9.0 (2.5)	ns
NEPSY Speeded Naming	8.2 (3.1)	9.3 (3.0)	ns
NEPSY Comprehension of Instructions	8.6 (3.2)	9.6 (2.8)	ns
NEPSY Verbal Fluency	9.2 (3.0)	10.4 (3.1)	ns
Motor			
VMI	91.9 (13.1)	96.0 (13.6)	p< .06
WRAVMA Pegs Right Hand	93.5 (17.4)	98.6 (16.8)	p< .08
WRAVMA Pegs Left Hand	95.2 (15.3)	100.0 (16.1)	ns
Attention			
Omission			
Commission	51.0 (10.0)	51.5 (9.6)	ns
Reaction Time	53.3 (12.9)	53.0 (11.5)	ns
Attention	51.6 (9.92)	53.6 (8.65)	ns
Risk Taking	51.8 (10.3)	53.8 (12.3)	ns
Executive Functioning			
Trails A (z-score)	0.16 (1.32)	0.51 (1.71)	ns
Trails B (z-score)	0.35 (1.38)	0.82 (1.73)	ns
Achievement (WIAT)			
Word Reading	84.0 (18.8)	90.0 (20.9)	ns
Reading Comprehension	88.2 (16.7)	89.7 (20.0)	ns
Numerical Operations	77.2 (14.7)	86.0 (17.3)	p< .02
Math Reasoning	76.9 (17.7)	86.4 (18.3)	p< .03
Spelling	83.0 (22.1)	91.9 (17.6)	p< .06
Math Composite	89.0 (35.5)	89.0 (24.1)	ns

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Intelligence

Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) The WISC-IV was administered to 152 children to assess general intelligence, using Canadian norms. The composite scales have a mean of 100 and standard deviation of 15 and subtests and mean of 10 and standard deviation of 3. Standard scores ranging from 90-110 are considered to be Average, scores from 80-89 are considered Low Average and from 70-79 to be in the Borderline range.

Memory

Children's Memory Scale (CMS) The CMS was administered to 158 children to assess memory functioning across various domains. The CMS yields six index scores: visual immediate, visual delayed, verbal immediate, verbal delayed, attention/concentration, and learning. Each index score has a mean of 100 and standard deviation of 15.

Language

The Peabody Picture Vocabulary Test (PPVT-III) The PPVT-III was administered to 136 children to assess receptive word naming abilities by requiring child to select from a set of four pictures, the one best depicting a word said by the examiner. This test has a mean of 100 and standard deviation of 15.

The Expressive One Word Picture Vocabulary Test (EOWVT) The EOWPVT was administered to 151 children to assess expressive word naming abilities by requiring the child to name objects or actions depicted in a series of increasingly more complex pictures.

The NEPSY Subtests from the NEPSY were used to assess speeded naming (n=100), comprehension of instructions (n= 116), verbal fluency (n = 87), as well as overall language functioning (n= 73). This test has a mean of 100 and a standard deviation of 15.

Executive Functioning

Trails A & B Executive functioning was measured using the Trails A and B subtests on 137 children. Scores from this test are presented in z-scores and have a mean of 0 and standard deviation of 0.10.

Attention

K-CPT In addition to the parent and teacher reported measures of attention in our companion paper, 137 children were also administered a computerized measure of attention using a child friendly version of the Continuous Performance Test. The K-CPT provides scores for: commission errors, reaction time, overall attention score, and risk taking score.

Motor

VMI**.** The VMI was administered to 168 children to assess general visual motor precision. This test has a mean of 100 and standard deviation of 15.

WRAVMA The WRAVMA is a test that examines fine motor functioning in children's right (n=157) and left (n=138) hands using a wooden pegboard. This test has a mean of 100 and a standard deviation of 15

Achievement

Wecshler Individual Achievement Test (WIAT) Academic functioning was assessed using select subtests from the WIAT: word reading (n=85), reading comprehension (n= 111), numerical operations (n=82), math reasoning (n=81), spelling (n= 82), and the math composite (n= 72). This test has a mean of 100 and standard deviation of 15.

Data Analysis

Across each neuropsychological domain performance on each composite scale, as well as subtests, were examined to determine if a unique profile emerged for children who received a diagnosis on the FASD spectrum compared to those who did not. Additionally, for tests where differences emerged between groups, odds ratios were calculated to validate the clinical significance of the findings. Odds ratios and 95 percent confidence intervals are also presented for critical background variables associated with the sample.

RESULTS

Demographics

Odds ratio analyses, based on the variables

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presented in Table 1, indicate that compared to undiagnosed children, children diagnosed with an FASD were two times more likely to have a previous ADHD diagnosis [$p < 0.01$; odds ratio, 2.32; 95% confidence interval, 1.21 to 4.43], three times more likely to be in a special education placement [$p < 0.05$; odds ratio, 2.48; 95% confidence interval, 1.30 to 4.73], two times more likely to have a biological mother with a mental health issue [$p < 0.05$; odds ratio, 2.21; 95% confidence interval, 0.99 to 4.94], and four times more likely to have a biological father diagnosed with a mental health disorder [$p < 0.03$; odds ratio, 4.68; 95% confidence interval, 1.02 to 21.4].

Intellectual Functioning

Children diagnosed with an FASD scored significantly lower on the Similarities [$F(1, 162) = 3.80$, $p < .05$] , Vocabulary [$F(1, 164) = 6.54$, $p < .01$], Comprehension [$F(1, 162) = 4.37$, $p < .04$] Information [$F(1, 71) = 4.16$, $p < .05$], and Arithmetic subtests [$F(1, 120) = 10.89$, $p < .00$] compared to exposed children who did not meet criteria for diagnosis. Furthermore, diagnosed children were significantly 2 times more likely than undiagnosed children to have a scores in the clinical range (scaled score < 7) on the Similarities [$p < 0.05$; odds ratio, 2.724; 95% confidence interval, 0.93 to 5.56], and three times more likely to have an Arithmetic score in the clinical range [$p < 0.01$; odds ratio, 2.84; 95% confidence interval, 1.16 to 6.91] (Table 2).

Memory Functioning

Children diagnosed with FASD scored significantly lower on the Dot Locations long delay [$F(1, 156) = 4.43$, $p < .05$] and General Memory Index [$F(1, 156) = 4.36$, $p < .05$] of the CMS, compared to undiagnosed children. Furthermore, compared to undiagnosed children, those diagnosed with an FASD were found to be two times more likely to have a General Memory Index scores in the clinical range (score < 85) [$p < 0.01$; odds ratio, 2.43; 95% confidence interval, 1.15 to 5.14] (Table 2).

Language

Children diagnosed with an FASD scored significantly lower on the Language Composite of the NEPSY [$F(1, 71) = 4.55$, $p < .04$], however group differences were not observed on the PPVT or EVT. Furthermore, compared to undiagnosed children, children with FASD are three times more likely to have a NEPSY Language Composite in the clinical range [$p < 0.05$; odds ratio, 3.07; 95% confidence interval, 0.90 to 10.14] (Table 2).

Executive Functioning

No group differences were observed on the TRAILS A [$F(1, 129) = 0.535$, p = ns], or B [$F(1, 127) = 0.521$, p = ns].

Attention

Table 2 indicates results from the K-CPT. No group differences were found between diagnosed and undiagnosed children.

Motor

Table 2 indicated the results from the WRAVMA and VMI. No group differences emerged between diagnosed and undiagnosed children.

Achievement

Children diagnosed with an FASD scores significantly lower on the numerical operations [$F(1, 80) = 5.94$, $p < .02$] and math reasoning [$F(1, 79) = 5.17$, $p < .03$] compared to undiagnosed children. Furthermore, compared to undiagnosed children, children with FASD are three times more likely to have a Numerical Operations score in the clinical range [$p < 0.02$; odds ratio, 3.26; 95% confidence interval, 1.23 to 8.68] and Math Reasoning score in the clinical range [$p < 0.05$; odds ratio, 2.56; 95% confidence interval, 0.96 to 6.88]. No other significant differences emerged (Table 2).

DISCUSSION

The present study identified a specific neuropsychological profile that typifies children diagnosed with an FASD versus those exposed prenatally to alcohol, who did not receive a diagnosis. Diagnosed children displayed a neuropsychological profile characterized by weaknesses in the areas of verbal reasoning, memory, overall language functioning, math reasoning and calculation. Groups did not differ on measures of attention or executive functioning.

Present findings corroborate previous findings that children with FASD display a characteristic profile of deficits in the areas of language, memory and mathematical

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achievement.[10,15,16] Interestingly, our findings did not support a specific profile of weakness in the areas of attention and executive functioning suggested by previous studies comparing children with FASD to typically developing children.[3,19,21]

This discrepancy may occur for several reasons. First, our clinic battery of attention and executive functioning measures may not be as in depth as those administered as part of research protocols. Second, most children were taking medications for attention problems at the time of testing, which may have washed out differences that would be more apparent without medication. Thirdly, it may be that when compared to unexposed typically developing children, children with FASD display a profile characterized by weaknesses in EF and attention, but when compared to a more "clinical" comparison groups these weaknesses no longer typify the FASD profile. Lastly, as is often reported anecdotally, EF deficits may be more apparent in a "real world" context, rather than laboratory setting. It will be important for future studies to compare children with FASD to children with other behavioural diagnoses, as well as using ecologically valid measure of EF, in order to elucidate the specificity of the FASD profile.

Our findings have important implications regarding diagnostic process for FASD. In our clinic, this process is quite lengthy, often involving 4 days of assessment. One solution to reducing the assessment process would be to streamline the assessment battery for children with FASD, using an evidence-based approach, which would include only those tests found to differentiate diagnosed from undiagnosed children. Our findings suggest that important areas of inquiry might be language functioning and verbal reasoning, mathematics, and overall memory functioning, which is consistent with previous findings.[15] Reducing the time spent at the assessment stage, may lead to more efficiency at this stage and thus reduce wait-times.

This study was an attempt to better understand the neuropsychological profiles of Canadian children and adolescents with FASD, however this study is not without its limitations. Limitations include disproportionate sample sizes between diagnosed and undiagnosed children, not all children being administered every measure, and a sample based on children referred due to suspected problems. However, due to difficulties obtaining an appropriate sample, clinic referred samples are relatively common in the research on FASD.

In summary, the present study serves to identify a set of neuropsychological characteristics that typify children prenatally exposed to alcohol who received a diagnosis from alcohol exposed children who did not receive this diagnosis. While results identified language, memory, verbal reasoning and mathematics achievement as areas of concern, groups did not differ in attention and executive functioning domains. The information gained from these analyses, are essential for informing best practices for diagnosis and treatment.

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