EXECUTIVE FUNCTIONING AND WORKING MEMORY DEFICITS ON THE CANTAB® AMONG CHILDREN WITH PRENATAL ALCOHOL EXPOSURE

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ABSTRACT

Background
Children with prenatal alcohol exposure (PAE) and Fetal Alcohol Spectrum Disorders (FASD) display numerous neuropsychological impairments, including deficits on measures of executive functioning (EF) and working memory.

Objectives
The goal of this project was to examine whether children with PAE and FASD demonstrate EF and working memory deficits on the CANTAB® (a computerized neuropsychological test).

Methods
Twenty-four children with PAE and 26 control children were tested on the CANTAB®.

Results
Children with PAE demonstrated deficits in the areas of executive functioning, working memory, and attention. Among the PAE group, those with FASD were specifically impaired on working memory capacity.

Conclusions
The CANTAB® is a useful tool for detecting neurobehavioral deficits in children with PAE.

Key Words: *Fetal Alcohol Spectrum Disorder (FASD); Executive function (EF); memory; CANTAB®*

Fetal Alcohol Spectrum Disorder (FASD) is an umbrella term used to describe the range of abnormalities that result from alcohol exposure during fetal development.[1] FASD occurs in approximately 9/1000 births in Canada and the U.S.[2,3] The effects of alcohol on the unborn fetus's development were first documented in 1973 in the United States.[4] The terminology used to describe the effects that result from maternal alcohol consumption during pregnancy has changed greatly over the years. The term Fetal Alcohol Syndrome (FAS) describes children with a characteristic facial phenotype, growth deficiency, and central nervous system damage (e.g., neurobehavioral deficits) whereas other terms (i.e., pFAS, ARND, FAE, neurobehavioral disorder, static encephalopathy) refer to those who lack some or all of the physical features but still have neurobehavioral deficits.[1] Previously used diagnostic categories tended to focus on the presence or absence of facial dysmorphology; however, with advances in research it became clear that not all individuals who have been exposed to alcohol display all the physical features of FAS[5,6] and the degree of neurobehavioral impairments does not necessarily differ between those with and without physical features of FAS.[7] Thus the terminology FASD was introduced, which covers a wide spectrum of abnormalities caused by alcohol. FASD-related diagnoses now focus more on the neurobehavioral deficits of these children as these are of greater functional significance than the physical features.

Children with FASD and/or prenatal alcohol exposure (PAE) display a number of neurobehavioral impairments including deficits in intellectual ability, attention, processing speed,

language, visual-spatial abilities, academics, learning, memory, and executive functioning (EF).[8]

EF, a key impairment in children and adolescents with FASD[9], refers to higher-order cognitive processes involved in thought and action under conscious control,[10] usually to achieve a goal.[11] EF involves abilities such as planning, inhibition, working memory, organized search, set-shifting, strategy employment, flexible thinking, and fluency. Prenatal exposure to alcohol negatively affects the development of the frontal cortex,[12-14] which is involved in the control of EF.[15,16]

Previous research on EF among children with FASD has documented a broad array of deficits across various standardized neuropsychological tests. For instance, children and adolescents with FASD display deficits on measures of cognitive flexibility, inhibition, verbal fluency, abstract thinking, deductive reasoning, hypothesis testing, and concept formation from the Delis-Kaplan Executive Functioning System (D-KEFS).[17] Other studies have demonstrated that children with PAE are also impaired on tests of planning[18] and nonverbal fluency from the D-KEFS[19] although there have been some mixed results across studies. Children and adolescents with FASD are impaired on the Wisconsin Card Sorting Test (WCST), which involves inhibition, set-shifting, and use of feedback. EF deficits among children with FASD have also been documented on behavioral rating measures of EF.[20,21]

One aspect of EF that appears to be particularly important is working memory. In Baddeley's theoretical model, working memory is defined as a three-component system used for short-term storage and manipulation of information required for cognitive tasks.[22,23] The visuospatial sketchpad is for holding and manipulating visual-spatial information, the phonological loop is for maintaining and rehearsing verbal information,[22] and the central executive is an attentional controlling system, is involved in planning, selective attention, set shifting, and inhibition.[24] Children with PAE have difficulties on measures of phonological working memory (i.e., the digit span task),[25,26] central executive working memory,[27] and visual-spatial working memory or visual-spatial memory.[28,29]

EF is assessed as part of the diagnosis of children with FASD. Obtaining an accurate diagnosis of an FASD can be very challenging because a specific profile of neurobehavioral deficits in children with FASD has not been identified.[8] The need for accurate and objective measurement tools that could assist in the identification of individuals with FASD is essential.[9] One measure of EF and working memory that has been rarely studied among children with PAE is the Cambridge Neuropsychological Test Automated Battery (CANTAB®). The CANTAB® is a computerized test, which uses a touch screen computer and visual cues to measure a variety of neuropsychological functions (visual memory, verbal memory, decision making, attention, EF, working memory, and planning). The CANTAB® has been highly researched and used in the identification of neuropsychological deficits in a number of different disorders including dementia and Alzheimer's,[30] and children with Down's Syndrome,[31] autism,[32,33] and ADHD.[34,35] The CANTAB® has many advantages over traditional neuropsychological tests including the electronic set-up which is engaging for young children, the lack of language barriers and gender differences, the wide age range (4 to 90 years), and that the CANTAB® measures a variety of neuropsychological functions in a single session.[36] Researchers[37] support the use of the CANTAB® in a variety of areas, especially for the effects of exposure to toxins. The CANTAB® is also sensitive to frontal lobe and basal ganglia dysfunction,[37,38] which are areas of the brain commonly affected in FASD.[39]

There is only one study published on the CANTAB® with children with FASD, in which researchers used the CANTAB® to detect EF and attention deficits.[40] It was found that children with FASD were impaired relative to controls in planning and working memory tasks (SOC, SWM) as well as attention tasks (RTI, MTS).[40] This study provides initial evidence for the CANTAB®'s ability to detect EF deficits in children with FASD. However, the authors only administered four of the CANTAB® subtests (two of which measured EF), thus we do not have any information on the profile of deficits that children with FASD and/or PAE display across the various subtests.

In the current study, we chose to administer eight core subtests from the CANTAB® child

battery to children with PAE. These subtests were in the domains of EF and working memory, visual memory, and attention. Administration of all three domains allowed us to examine whether children with PAE demonstrate a unique pattern of neuropsychological deficits on CANTAB® relative to control children, and to determine whether deficits were most pronounced on the EF and working memory domain. We also examined whether measures of EF and working memory on the CANTAB® were successful in differentiating between children with PAE who do and do not have an FASD diagnosis. This is important for determining whether the CANTAB® is a viable tool for assessing EF and working memory deficits in FASD.

METHODS

Participants

Fifty children ranging in age from 6 years, 1 month to 17 years, 7 months participated in this study. There were 24 children with PAE (11 females) and 26 control children (11 females). There were no significant differences in age between the PAE children (M = 9 years, 7 months, SD = 3 years 2 months) and the control children (M = 9 years 2 months, SD = 1 year, 8 months) $t(48) = .61$ $p < 0.05$. Informed consent was obtained for all participants in the control group. However, because the PAE group consisted of retrospective anonymous data, informed consent was not required (as per ethics review board). Children in the PAE group were all tested on the CANTAB® during their FASD diagnostic assessment at a hospital FASD clinic over a 1.5 year period. The CANTAB® was administered for research purposes only and the results were not used as part of the diagnostic assessment. All of the children in the PAE group had confirmed prenatal exposure to alcohol. The clinic in which this study was conducted only accepts children who have a reliable confirmation of PAE, which is validated by a social worker before the assessment. Although amounts of PAE vary in these children, drinking patterns may include binge, chronic, or mixed throughout the entire pregnancy or prior to the mother finding out she was pregnant. This documentation is obtained from extensive reviews of prenatal history, birth documents, health records, and parental interview(s).

Using the Canadian Guidelines[1] as a model, diagnostic information was ranked using the 4-Digit Diagnostic Code (Astley, 2004), which uses a 4-point Likert scale to measure growth deficiency, facial phenotype, brain dysfunction, and alcohol-use, along with prenatal (e.g., genetic conditions, exposure to other known teratogens) and postnatal (e.g., abuse, multiple placements) factors which could have impacted outcome. The diagnostic process involved assessments conducted by a multidisciplinary team (Psychologist, Speech-Language Pathologist, Occupational Therapist, Social Worker, and Developmental Pediatrician) using a combination of approaches including formal standardized and non-standardized measures, rating scales, interviews, clinical observations, photographic analysis, and information from families, caregivers, preschools, schools, community clinicians, and children's services. Each neurobehavioral domain (hard and soft neurological signs which include sensory-motor signs, brain structure, communication, attention, cognition, academic achievement, memory, executive functioning, and adaptive behavior) was assessed and ranked by the testing clinician during a team conference using a 3-point scale with the following values: 1 = within normal limits 2 = mild to moderate impairments, and 3 = significant impairments. To be considered significantly impaired on a neurobehavioral domain and receive a score of 3, test results had to fall two or more standard deviations below the mean or exhibit a difference of at least one standard deviation between sub-domains. A minimum of three of the nine neurobehavioral domains must be severely impaired for an FASD diagnosis. However, under certain conditions where clinical judgment and qualitative assessment prevail, individuals with more moderate delays can also receive the diagnosis. See Table 1 for the diagnostic results.

Of the 24 children with PAE assessed in the clinic 12 (6 females) went on to receive an FASD-related diagnosis: partial FAS (2), static encephalopathy: alcohol exposed (7), neurobehavioral disorder (3). Twelve (5 females) did not receive a diagnosis and/or were deferred

for assessment again in the future. Thus, children in the PAE group were further separated into categories of those who did and did not receive an FASD-related diagnosis. There was no significant difference in age between the children with an FASD diagnosis (M = 9 years, 6 months, SD = 3 years, 5 months) and those without a diagnosis (M = 9 years, 8 months, SD = 3 years 1 months) t(22) = .11, p <0.05. Among the FASD group 5 children were currently living with their birth parent and the rest were adopted (1), kinship arrangement (3), or in foster care (3). Among the PAE group 3 children were currently residing with their birth parent and the rest were adopted (2), kinship arrangements (4), or on foster care (3). There was no significant difference between the PAE and FASD group on whether they were currently living in their biological or non-biological home, χ^2 (1, N = 24) = 0.75, p > 0.05). The two groups also did not differ on gender, χ^2 (1, N = 24) = 0.17, p > 0.05). The control group and the PAE group were not matched for mental age because this may result in unintended unmatching on other factors, and it may also lead to results that are difficult to interpret in comparison between the two groups of participants.[41] Control children were recruited with parental permission from a local school. Parents of these children completed a screening questionnaire, and none of the children had FASD or any other neurodevelopmental disorders. All control children were living with their biological parents.

CANTAB®

Eight subtests from the child CANTAB® battery were administered measuring: 1) visual memory through the PRM (Pattern Recognition Memory), and SRM (Spatial Recognition Memory) tasks; 2) EF and working memory through the SSP (Spatial Span), SOC (Stockings of Cambridge), IED (Intra-Extra Dimensional Set Shift), and SWM (Spatial Working Memory) tasks; and 3) attention through the RTI (Reaction Time), and RVP (Rapid Visual Information Processing) tasks. A Slimbook P110 Touch ICP1.3GHZ touch screen was utilized. These tests were carried out in one session lasting about one hour unless time constraints or the child's schedule forced the remainder of the test to be conducted on a different day. The same child battery was used for all children. The CANTAB® provides both z scores and raw scores, and raw scores were used for all analyses in this study. The same room was used for the children with PAE and all children were tested by the same administrator. Control children were also all tested in the same room in their school by the same test administrator. All data was obtained in compliance with regulations of the Institutional Ethics Review Board in which the study was conducted.

Visual Memory

Pattern Recognition Memory (PRM)

The PRM test is designed to test visual memory. In this test, a series of images are shown to the participant in the centre of the screen, and then a series of images are shown in sets of two. The participant must choose the image that they think they have previously seen. The computer notifies the participant whether or not they are correct. The score that is obtained is a measure of the percent of correct responses.

Spatial Recognition Memory (SRM)

The SRM test assesses spatial recognition memory. In this test, the participant is instructed to observe the movement of a square around the screen. Then, the participant is presented with a pair of boxes, one of which is in the same location that the original square traveled to and the other which is not. The participant must successfully identify which of the boxes is in the same location as the original square's path. The score that is obtained is a measure of the percent of correct responses.

Executive Function

Spatial Span (SSP)

The SSP task measures working memory capacity. In this test, a series of squares at random locations on the screen light up in a particular path. The test participant must repeat the path that was just shown to them by touching the squares in proper order. The level of difficulty increases from 2 boxes to 9 boxes. The score that is obtained is a measure of span length (the length of the pattern the participant is able to follow).

Stockings of Cambridge (SOC)

The SOC assesses planning and motor skills. In this Tower test, the computer screen is divided into two halves. Both halves have identical visual

setups of what appear to be three hanging stockings holding three colored balls (red, green, blue) in different arrangements. The participant is instructed to arrange the balls on the bottom half of the screen to match the arrangement on the top half of the screen. On the right hand side of the screen, the participant is informed of the number of moves that the pattern can be accomplished in. If the participant exceeds a certain number of moves, the test stops and the next pattern is shown. The level of complexity and number of moves increases as the test progresses. In the second part of this test, the participant is asked to follow the pattern of movement of the balls that is seen in the top half of the screen. The scores that are obtained are a measure of the length of time taken by the participant to make the first move, the length of time taken for each subsequent move, and the number of problems solved in the minimum number of moves.

Intra-Extra Dimensional Set Shift (IED)

The IED test assesses visual discrimination and shifting attention. In this test, four large rectangles appear on the computer screen and in two of these rectangles, a set of large images appears. The participant is instructed to choose an image from the two and then make subsequent decisions based on the outcome of the first trial. If the "correct" image is chosen, the computer notifies the participant by lighting up green. Then the participant chooses from the next set of images based on information gathered from the previous trials. At a certain point, the pattern changes (i.e., a secondary shape appears next to the larger shape) and the participant must be able to detect this. The scores that are obtained are a measure of the number of stages of the task completed as well as the number of errors made.

Spatial Working Memory (SWM)

The SWM test measures spatial working memory. A series of colored boxes appear at random locations on the computer screen. By touching the boxes, the participant may or may not uncover a blue chip. Upon finding the blue chip, the participant must drag it to a meter on the right side of the screen until the meter is filled. The participant is told that once a blue chip has been uncovered, the colored box will never again be covering a blue chip. In this way, the test assesses working memory by determining whether the participant remembers which boxes have already been chosen. The level of difficulty increases as the number of boxes increases. The scores that are obtained are a measure of between errors (where the participant chooses a box under which they have already discovered a chip) and strategy (the number of boxes used for each new search).

Attention

Reaction Time (RTI)

The RTI test measures the speed of response and movement. During this test, a hand-controlled device is attached to the computer for use by the participant. A large circle appears in the centre of the screen. A small yellow circle appears in the centre of this circle when the participant pushes a button on the handheld device. The participant must then quickly touch the yellow circle on the screen. In this way, the test measures how quickly the participant is able to touch the yellow circle once it appears. In the second part of the test, the same task is performed, except now there are five circles in which the yellow circle may appear, and the participant has no way of determining which of these larger circles will contain the yellow one. The scores that are obtained are a measure of movement time and reaction time.

Rapid Visual Information Processing (RVP)

In the RVP test, visual attention is assessed. In this test, the participant is presented with a number sequence (3, 5, 7) on the screen next to a large box in which numbers appear in random order. Whenever the participant sees the 3, 5, 7 sequence, he/she must press a button on the handheld device (the same that is used in the RTI subtest). The participant must wait until the last number of the sequence is shown (i.e., the seven) before pushing the button. Initially, the participant is given visual cues such as underlined sequences or colored numbers. As the test progresses, these visual cues are removed. The score that is obtained is a measure of the number of times the participant correctly detects the pattern.

RESULTS

Alpha was set at $\leq$ .01 for all comparisons due to the numerous analyses conducted. First, we conducted an ANCOVA (with age as the

covariate) to compare raw scores of children with PAE to control children on the CANTAB® subtests. Children with PAE scored significantly lower than the control group on the RTI reaction time, SWM (between errors and strategy), and RVP, and group differences approached significance on the SSP span length (p = .02) (*see Table 2*). In order to determine which CANTAB® subtests differentiated between children with PAE who do and do not have an FASD diagnosis, next we compared the PAE-not diagnosed group and the FASD group on all raw scores of the CANTAB® using ANCOVA (with age as the covariate) (*see Table 3*). Only the SSP span length differentiated between alcohol exposed children who do and do not have an FASD diagnosis.

TABLE 1 Percentage of children with FASD and PAE who received each score in the 4-digit diagnostic code

Score	*Growth*		*Face*		*Brain*		*Alcohol*		*Prenatal*		*Postnatal*	
	FASD	**PAE**	**FASD**	**PAE**	**FASD**	**PAE**	**FASD**	**PAE**	**FASD**	**PAE**	**FASD**	**PAE**
1	83.3	83.3	66.7	41.7	0	0	0	0	0	0	0	0
2	16.7	8.3	16.7	50	33.3	91.7	0	0	0	8.3	0	0
3	0	8.3	8.3	8.3	66.7	8.3	58.3	83.3	41.7	58.3	18.2	16.7
4	0	0	8.3	0	0	0	41.7	16.7	50	33.3	81.8	93.3

Note: Growth, Face, and Brain function scores: 1 = unlikely, 2 = possible, 3 = probable, 4 = definite. Alcohol exposure, Prenatal, and Postnatal scores: 1 = no risk, 2 = unknown risk, 3 = some risk, 4 = high risk.

TABLE 2 Raw scores (SD) of CANTAB® subtests for control and PAE groups

Domain	**CANTAB® test**	**PAE**	**Control**	**F**
Visual memory	PRM percent correct	76.8 (19.9)	83.2 (11.0)	2.35
	SRM percent correct	67.1 (17.1)	73.5 (12.1)	3.12
EF, working memory and planning	SSP span length	4.7 (1.6)	5.6 (1.4)	**5.77**
	SOC initial thinking time	4688.1 (9891.5)	4641.8 (3079.5)	0.08
	SOC sub. thinking time	2430.5 (4771.5)	1967.0 (2289.7)	0.57
	SOC problems solved in min. moves	6.9 (3.0)	6.5 (2.2)	0.00
	IED stages completed	7.7 (1.1)	7.7 (1.0)	0.45
	IED total errors	32.1 (9.4)	31.5 (12.2)	0.32
	SWM between errors	57.0 (21.3)	40.5 (17.9)	**20.68***
	SWM strategy	37.8 (3.0)	34.4 (6.3)	**9.73***
Attention	RTI movement time	422.9 (155.6)	396.6 (96.6)	.34
	RTI reaction time	481.4 (129.8)	397.1 (64.1)	**12.79***
	RVP	0.87 (0.1)	0.96 (0.0)	**22.41***

*$p < 0.01$

TABLE 3 Mean raw scores (SD) on CANTAB® subtests for the FASD and PAE-not diagnosed groups

Domain	CANTAB® subtest	FASD	PAE-not diagnosed	F
Visual memory	PRM percent correct	70.8 (21.5)	83.3 (16.5)	2.29
	SRM percent correct	66.4 (16.4)	68.0 (18.7)	0.77
EF, working memory and planning	SSP span length	4.0 (1.7)	5.5 (1.2)	**7.17***
	SOC initial thinking time	6447.8 (14341.9)	3088.5 (2156.7)	0.66
	SOC sub. thinking time	1794.0 (2263.9)	3009.1 (6336.3)	0.37
	SOC problems solved in min. moves	6.3 (3.6)	7.5 (2.5)	1.17
	IED stages completed	7.5 (1.2)	8.0 (0.9)	1.20
	IED total errors	35.3 (10.0)	28.7 (7.7)	2.69
	SWM between errors	58.3 (20.9)	55.9 (22.6)	0.20
	SWM strategy	37.6 (2.8)	37.9 (3.2)	0.05
Attention	RTI movement time	380.4 (165.7)	474.8 (132.9)	1.64
	RTI reaction time	475.1 (107.2)	489.1 (160.0)	0.17
	RVP	0.84 (0.10)	0.90 (0.06)	1.63

DISCUSSION

We examined whether children with PAE demonstrated specific EF and working memory deficits on the CANTAB® relative to control children, and, also whether EF and working memory was successful in differentiating between children with PAE who do and do not have an FASD-related diagnosis. Children with PAE scored lower than the control group on measures of executive functioning and working memory (SSP and SWM), as well as attention (RTI and RVP). These findings confirm previous research indicating that children with PAE have deficits in executive functioning and working memory[9] as well as attention.[42,43] Children with PAE were not impaired on the two other EF measures; the SOC which involves planning, and the IED which involves visual discrimination and shifting attention, indicating that these aspects of EF were relatively unimpaired in our sample. In contrast, the SSP and SWM depend heavily on intact spatial working memory, indicating spatial working memory is a significant impairment in children with FASD. Kodituawakku et al.[44] found that children with FASD were best distinguished from control children by the mechanism which enables us to manage goals in working memory in a flexible manner. Specifically, Kodituawakku et al.[44] proposed that there exists a dysfunction in the ability of children with FASD to hold and manipulate information and to manage goals in working memory as the underlying cognitive mechanism responsible for the impairments they

observed—including those traditionally attributed to attentional deficits. This could correspond with working memory theory in which the central executive is theorized to fulfill that management role.

In a separate study on the CANTAB® with children with FASD,[40] it was found that children with PAE performed worse than controls on tasks of measuring attention (RTI, MTS), planning (SOC), and spatial working memory (SWM). The findings on the RTI and SWM support our results; however, in contrast to Green et al.[40], the alcohol-exposed children in our sample were not impaired on the SOC. The lack of group differences on the SOC was somewhat unexpected given that this tower-like test measures EF and planning. Reasons for this discrepancy between studies on the SOC could be because Green at al. [40] had a larger sample size and more power to detect group's differences and in the present study, we also included children with PAE but no FASD diagnoses, thus the sample was less severely impaired. Nevertheless, another study[17] failed to find impairments on a different tower test among children with FASD and perhaps tower-tests in general may not be as sensitive to PAE. In the current study, children with PAE were not impaired in either measure of visual memory relative to controls. There is evidence that children with PAE and FASD are impaired on visual memory tasks[45] thus this finding was somewhat unexpected. Perhaps the CANTAB® may not be sensitive to the specific aspects of visual memory that may be affected in FASD.

Another goal of this study was to examine the ability of the CANTAB® to distinguish between children with PAE who do and do not have an FASD-related diagnosis. The SSP, a measure of spatial working memory capacity, was the only measure that differentiated between children with FASD and those with PAE-not diagnosed. The FASD group performed significantly lower on the SSP than the PAE-not diagnosed group, whose performance was similar to that of the controls. Thus, working memory, which is significantly impaired in children with FASD[17] may be a useful measure aiding in the diagnosis of an FASD. Spatial working memory appears to be specifically impaired in children with FASD, which may correspond to deficits in the visuospatial sketchpad of Baddeley's working memory model.[22,23]

In conclusion, the CANTAB® appears to be a useful tool for detecting EF, working memory, and attention deficits among children with PAE and FASD. However, further research is needed to assess the diagnostic utility of the CANTAB® for FASD. Future research would benefit from larger sample sizes and replication across different samples of alcohol-exposed individuals. Furthermore, longitudinal research examining the developmental trajectory of neurobehavioral deficits on the CANTAB® among children with PAE and FASD is critical. As many differences identified using this tool were in the domain of executive functioning and working memory, it would be interesting to examine if the identified differences become more pronounced in later adolescence and early adulthood, at which point there are much greater expectations for these systems. By increasing our knowledge regarding specific impairments in children prenatally exposed to alcohol, we will be better able to shape our interventions to meet the specific needs of these children. Particularly, given the CANTAB®'s interactive nature and nonverbal emphasis, it may help control for language factors and low interest that might otherwise cloud our results. Moreover, The CANTAB® may be useful for identifying areas of strength among children with PAE that could perhaps be built upon. This study provides initial evidence for the use of the CANTAB® in the assessment of children with PAE and with future research, the CANTAB® may prove to be a useful tool aiding in the diagnosis of FASD.

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