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Executive function deficits in children with fetal alcohol spectrum disorders (FASD) measured using the Cambridge Neuropsychological Tests Automated Battery (CANTAB)

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Background: Chronic prenatal alcohol exposure causes a spectrum of deleterious effects in offspring, collectively termed fetal alcohol spectrum disorders (FASD), and deficits in executive function are prevalent in FASD. The goal of this research was to test the hypothesis that children with FASD exhibit performance deficits in tasks that assess attention, planning and spatial working memory. **Methods:** Subjects (8–15 years male and female children) with a diagnosis of fetal alcohol syndrome (FAS), partial FAS (pFAS), or alcohol-related neurodevelopmental disorder (ARND), and age- and sex-matched controls, completed four tasks selected from the Cambridge Neuropsychological Tests Automated Battery (CANTAB®). **Results:** Compared with age-matched control children (n = 92), subjects with FASD (n = 89) exhibited longer reaction and decision times (effect size range; Cohen's d = .51 to .73), suggesting deficits in attention. Children with FASD demonstrated deficits in planning and spatial working memory that became more pronounced when task difficulty increased. The largest effect size in this study population (Cohen's d = 1.1) occurred in the spatial working memory task. Only one outcome measure revealed differences across the diagnostic subgroups, although all groups were different from control. **Conclusion:** This study demonstrates that deficits in multiple executive function domains, including set shifting, planning and strategy use, attention and spatial working memory, can be assessed in children with FASD using an easy to administer, brief battery of computer-based neuropsychological tasks. The tasks appear to be equally sensitive for brain injury resulting from prenatal exposure to alcohol, regardless of the presence of facial dysmorphology. **Keywords:** Fetal alcohol spectrum disorders, executive function, CANTAB®, visual search, spatial working memory. **Abbreviations:** FASD: fetal alcohol spectrum disorders; CANTAB: Cambridge Neuropsychological Tests Automated Battery; RTI: Reaction Time; MTS: Match to Sample Visual Search; SOC: Stockings of Cambridge; SWM: Spatial Working Memory.

A serious and debilitating consequence to maternal consumption of alcohol during pregnancy is fetal alcohol syndrome (FAS). FAS is characterised by growth restriction, craniofacial dysmorphology and CNS dysfunction (Astley & Clarren, 2000; Clarren & Smith, 1978). FAS represents only a fraction (10–15%) of the children affected by prenatal exposure to alcohol, as it is more common for children to present with complex behavioural and neurological dysfunction related to their exposure, but in the absence some or all of the characteristic facial features (Koren, Nulman, Chudley, & Loock, 2003). In these situations, the diagnostic terms partial FAS (pFAS) and alcohol-related neurodevelopmental disorder (ARND) have been used to describe individuals who do not meet all of the criteria for FAS (Chudley et al., 2005; Stratton, Howe, & Battaglia, 1996).

Recently, the term fetal alcohol spectrum disorders (FASD) has been widely adopted and encompasses all diagnoses and clinical presentations arising from prenatal alcohol exposure, including FAS (Koren et al., 2003; Chudley et al., 2005). Despite the various efforts to streamline diagnostic criteria, the need for accurate and objective measurement tools that could assist in the identification of individuals with prenatal exposure to alcohol is needed (Rasmussen, 2005). With early diagnosis, the appropriate clinical and therapeutic interventions could be implemented, with the goal of preventing and/or reducing the incidence of secondary disabilities (Streissguth et al., 2004).

A hallmark feature of FASD is deficits in executive function [see reviews (Rasmussen, 2005; Kodituwakku, 2007; Riley & McGee, 2005)]. Executive function is a heterogeneous term that refers to a range of abilities involved in conscious, goal-oriented behaviour (Funahashi, 2001). It has been postulated

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that a continuum exists wherein those with prenatal alcohol exposure, but without FAS, demonstrate less severe deficits compared to those with FAS. However, many research groups have failed to demonstrate differences in executive function between dysmorphic and non-dysmorphic individuals with prenatal alcohol exposure. For example, in a battery of 9 different executive function tests, Connor and colleagues found no relationship between executive function performance and facial phenotype (Connor, Sampson, Bookstein, Barr, & Streissguth, 2000). Task performance by dysmorphic and non-dysmorphic subjects was intermingled, suggesting that the presence of facial features was not predictive of performance. Similarly, both Schonfeld and colleagues (2006) and Mattson et al. (1999) failed to find significant differences in executive function among dysmorphic and non-dysmorphic subjects with a history of prenatal alcohol exposure (Schonfeld, Paley, Frankel, & O'Connor, 2006; Mattson, Goodman, Caine, Delis, & Riley, 1999).

Recently, Kodituwakku postulated a behavioural phenotype for FASD associated with the existing patterns of deficits in cognitive-behavioural functioning (Kodituwakku, 2007). These deficits contribute to a wide range of negative life outcomes that include difficulties in academic, social and emotional aspects of life. Delineating the profile for FASD is difficult as the severity of alcohol effects varies widely as a function of exposure (i.e., quantity and frequency) and maternal factors (i.e., age, body weight) (Abel, 1995; May, 1995; Jacobson, Jacobson, Sokol, & Ager, Jr., 1998; Riley & McGee, 2005). However, individuals with FASD experience greater difficulty achieving complex adaptive behaviours that involve the integration of multiple domains, and which depend on different parts of the brain; particularly the frontal lobes.

Interestingly, patients with FASD demonstrate clinical behaviours that resemble those for patients diagnosed with frontal lobe lesions (Connor et al., 2000); and correlation between deficits in executive function and frontal lobe damage has been evaluated in the FASD population. Functional magnetic resonance imaging (fMRI) assessed inhibitory control in children and adolescents with prenatal alcohol exposure using the blood-oxygen-level-dependent signal (Fryer et al., 2007). FASD individuals demonstrated increased activation in the prefrontal cortex during trials that required inhibition of action compared to control subjects, suggesting that greater cognitive resources were required to perform the task. Increased neocortical thickness also has been found in individuals with FASD following structural MRI analysis, particularly over large areas of the dorsolateral prefrontal lobes (Sowell et al., 2008). Neocortical thickness has been associated with functional integrity, where neocortical thinning is associated with better general intellectual functioning. This is consistent with previous observations demonstrating increased neocortical thinning from childhood to adolescence (Sowell et al., 2004; Shaw et al., 2006). The co-occurrence of a thin neocortex and better performance in control subjects was not found in the FASD group (Sowell et al., 2007), suggesting that pruning and myelination processes may not be occurring normally in children with prenatal alcohol exposure. This disorganisation of neocortical structures may result from cellular changes that occur during postnatal development and that are impacted by heavy prenatal alcohol exposure; thus, supporting the view that brain–behaviour relationships do not develop normally in these individuals.

The aim of our study was to assess executive function in children with FASD compared to age- and sex-matched controls, using the CANTAB® computerised test battery. Investigators have used CANTAB® tasks to assess executive function during typical development (Luciana & Nelson, 1998), and in other neurodegenerative (Egerhazi, Berecz, Bartok, & Degrell, 2007) and neurodevelopmental disorders (Goldberg et al., 2005). The CANTAB® has several advantages over other measures of executive function, as it provides a standardised computer-administration format that controls for variations among different examiners. It is nonverbal and provides information about direction and accuracy on screen, and employs the use of a touch-screen response that automates data acquisition. Finally, there is evidence for the involvement of prefrontal and medial temporal brain regions in the performance of the CANTAB® tasks (Luciana & Nelson, 2002). Thus, it was hypothesised that children with FASD exhibit deficits in different domains of executive function that can be quantified with the CANTAB® battery of neuropsychological tasks. Second, it was hypothesised that tasks which demand the use of spatial working memory and strategy demonstrate the most sensitivity to deficits in cognitive flexibility in children with FASD, as these functions are particularly deficient in these individuals. Finally, based on the literature, we also hypothesised that the magnitude of deficits in task performance in CANTAB® are not different among the FASD diagnostic subgroups, with and without the facial dysmorphology (i.e., FAS vs. pFAS vs. ARND).

Methods

Participants

All experimental procedures were reviewed and approved by the Human Research Ethics Boards of Queen's University, the Children's Hospital of Eastern Ontario (Ottawa subjects), and the University of Alberta (Edmonton subjects). Parents provided informed consent for participation. Children with FASD were recruited from 8 different communities across Ontario and 1 from Alberta, and were previously assessed at

Table 1 Medication history for children with FASD and controls

Medications	FASD	Control
Stimulants	38 (42.7%)	0 (0%)
Antipsychotics	29 (32.6%)	0 (0%)
Antidepressants	10 (11.2%)	0 (0%)
Anticonvulsants	3 (3.4%)	0 (0%)
Antianxiety	0 (0%)	0 (0%)
Other*	20 (22.5%)	12 (13%)

*Antihistamine, anti-asthma, oral contraceptives, melanin.

local diagnostic clinics and in accordance with the Canadian Diagnostic guidelines (Chudley et al., 2005). A total of 189 subjects were recruited into the study: 92 (40 males, 52 females; 11.2 ± .2 years of age, range 8–15 years) were control children (non-FASD) and 97 were grouped as FASD. Of the 97 subjects included in the FASD group, 89 (44 males, 45 females; 10.7 ± .2 years of age, range 8–15 years) had a diagnosis within the FASD spectrum (FAS, pFAS, ARND), while 8 were suspected and/or exposed, but had yet to receive a definitive diagnosis. All data included in the analysis for the FASD group were obtained from the 89 children who had received a diagnosis within the spectrum.

Of the 89 children with FASD, 60 were medicated (Table 1) for behavioural symptoms relating to their comorbidities (Table 2). On the test day, primary caregivers were asked to withhold stimulant medication until the testing was completed. Of the 60 children taking medications, 8 were tested on medication (87% compliance with the off-medication request), in most cases because the primary caregiver judged that the child would not be able to complete testing off medication. For the remaining 52 children, their last daily dose of stimulant medication was administered a minimum of 12 hours prior to testing.

All control subjects had no known neurological, psychiatric or visual disorders, other than requiring corrective lenses. Primary caregivers were informed of the nature of the study and provided written consent on behalf of the participants. All subjects completed one 30–45-minute neuropsychological battery. Each subject received $10 and a small gift for participating in the study.

Neuropsychological battery: CANTAB®

Subjects were asked to complete a series of 4 computerised neuropsychological tests of the Cambridge Neuropsychological Test Automated Battery (CANTAB®, Cambridge Cognition, Cambridge, UK). Subjects were seated in front of a laptop screen and were instructed to carry out the tests either by touching the screen or by pressing/releasing a press pad. Children were given short breaks whenever needed, and snacks and beverages were provided upon completion of the neuropsychological battery.

The goal of this research study was to assess the following four domains of executive function: attention, planning, strategy use and spatial working memory. Based on these areas of interest, the following four tests were selected as they were both age- (other tasks were considered too difficult for the younger children in our cohort) and time-appropriate (each testing session could be completed in 45 minutes or less): Reaction Time (RTI) (which was used as a measure of attention and as a simple motor screening task), Stockings of Cambridge (SOC) (assessed planning and strategy), Match to Sample Visual Search (MTS) (assessed attention) and Spatial Working Memory (SWM) (assessed spatial working memory and strategy). These tests will be described briefly, as well as the pertinent outcome measures. Some children with FASD had difficulty completing the full battery set (9 did not complete the SOC task; 2 did not complete the MTS or SWM tasks), and in one situation a computer error prevented the recording of data from one test for one control subject (SWM task).

Table 2 Comorbidities for children with FASD and controls

Comorbidities	FASD	Control
Sleeping disorders	55 (61.7%)	10 (10.9%)
Attention deficit hyperactivity disorder (ADHD)/attention deficit disorder (ADD)	53 (59.6%)	0 (0%)
Oppositional defiant disorder	19 (21.3%)	0 (0%)
Anxiety	15 (16.9%)	0 (0%)
Asthma	10 (11.2%)	12 (13.0%)
Depression	10 (11.2%)	1 (1.1%)
Neurological disorder	8 (8.9%)	0 (0%)
Bipolar	6 (6.7%)	0 (0%)
Seizure	5 (5.6%)	3* (3.3%)
Mood disorder	5 (5.6%)	0 (0%)
Conduct disorder	3 (3.4%)	0 (0%)
Astigmatism	2 (2.3%)	3 (3.3%)
Allergies	2 (2.3%)	3 (3.3%)
Autism	2 (2.3%)	0 (0%)
Asperger's disorder	2 (2.3%)	0 (0%)
Psychosis	2 (2.3%)	0 (0%)
Pre-depression	1 (1.1%)	0 (0%)
Hearing aids	1 (1.1%)	0 (0%)
Myopia	1 (1.1%)	3 (3.3%)
Reactive attachment disorder	1 (1.1%)	0 (0%)
Anger management	1 (1.1%)	0 (0%)
Chronic ear infection	1 (1.1%)	1 (1.1%)
Twisted femur	1 (1.1%)	0 (0%)
Kidney problems	1 (1.1%)	0 (0%)
Heart problems	1 (1.1%)	0 (0%)
Hepatitis C	1 (1.1%)	0 (0%)
Lactose intolerance	1 (1.1%)	0 (0%)
Tourette's	1 (1.1%)	0 (0%)
Hypotonia	1 (1.1%)	0 (0%)
Migraines	0 (0%)	1 (1.1%)
Scoliosis	0 (0%)	1 (1.1%)
Strabismus	0 (0%)	1 (1.1%)

*One time events, no diagnosis of seizure disorder/epilepsy.

Reaction Time (RTI). In the RTI task, subjects were instructed to press down on the press pad until a yellow dot appeared in the centre of either a single circle (simple) or in one of 5 different concentric circle locations (5-choice). Upon appearance of the yellow circle, the subject was instructed to release the press pad and touch the yellow circle as quickly as possible. The outcome measures were reaction time (time to release press pad after the yellow circle appeared) and movement time (time to touch the screen after releasing the press pad) for both the simple and 5-choice problem sets.

Stockings of Cambridge (SOC). The SOC task is similar to the Tower of London task, a derivative of the classic Tower of Hanoi (Shallice, 1982), with the advantage being that data collection is automated. Each problem set was comprised of three 'stockings' or socks suspended from a beam of different lengths containing different-coloured balls (green, red and blue). The computer created a problem set in the top portion of the screen and subjects were then asked to copy this same configuration by moving their coloured balls so that the two problem sets were identical. As the minimum number of moves increased, the complexity of the problems increased as well. Outcome measures included the problems solved in the minimum number of moves, the mean number of moves for each *n*-move problem (i.e., $n = 2$, 3, 4 or 5) and the initial mean thinking time for each n-move problem. The SOC task also employed two modes for evaluation; one was a *copy* mode and one was a *follow* mode. In the *copy* mode subjects were required to copy the problem set in the required number of moves, while the *follow* mode instructed subjects to follow the balls as they were moved into different stockings. The initial mean thinking time measures were determined by taking the difference between the *copy* and *follow* mode, which controlled for motor deficits.

Match to Sample Visual Search (MTS). In the MTS task, a red box appeared in the centre of the screen concentrically surrounded by 8 empty square boxes. Upon pressing down on the press pad, a pattern appeared in the centre square, and after a brief delay an array of patterns appeared in 2, 4 or 8 of the surrounding squares. Upon recognition of the matching pattern, the subject was instructed to release the press pad and touch the pattern that matched the centre pattern. The outcome measures included decision and movement times for each *n*-choice (i.e., $n = 2$, 4 or 8) problem. Decision time represented the time to release the press pad after the distracter patterns appeared, and the movement time was the time from releasing the press pad to touching the correct pattern on the screen.

Spatial Working Memory (SWM). In the SWM task subjects were presented with randomly distributed coloured boxes ranging in number from 4 to 8. Subjects were instructed to locate hidden tokens that appeared under each coloured box and move them to fill an empty panel located on the right-hand side of the screen. Once a token had been located, subjects had to recall that the computer would never hide a token in a coloured box previously found to contain one; therefore, they had to remember *not* to revisit those coloured boxes. The outcome measures analysed were total number of errors (returning to a box previously found to contain a token), errors for each *n*-box problem (i.e., $n = 4$, 6 or 8), and a strategy score, which indicated the use of a search strategy by the subject (low scores indicated good strategy use).

Data analysis

All dependent measures (RTI: reaction and movement time; SOC: problems solved in the minimum number of moves and initial thinking time; MTS: movement time and decision time; and SWM: errors and strategy score) were analysed using ANOVA with α set at .05. Two-tailed, unpaired Student's *t*-tests were conducted and corrected with Welch's approximation when the assumption for homogeneity of variance was not met (SOC: initial thinking time across problem sets; MTS: movement and decision time across problem sets). Data was analysed by non-parametric Mann–Whitney tests when the conditions for normal distribution were not met. The effect of diagnosis (ARND, pFAS and FAS) also was determined by matching each subject in the FASD group (as closely as possible) to a control by age and sex. FASD and control subjects once subdivided were analysed by univariate analysis to demonstrate differences. Effect sizes were calculated from the means and standard deviations obtained for the major outcome measures (Cohen, 1988). We focus on descriptions of the relevant statistical parameters for comparisons that occurred between the control and FASD groups.

Results

We separately analysed the impact of several potential confounding variables in this study. First, 8 children in the FASD group were tested on stimulant medication. However, when the data for these children were excluded from the analysis there was no substantive change in the overall performance of the FASD group reported in this communication. Second, within the FASD group, we compared the performance of children withdrawn from stimulant medication to those children who were not taking any stimulant medication. There were no differences between these groups for any of the outcome measures reported in this communication (data not shown), suggesting that stimulant drug withdrawal had a negligible impact on performance of the CANTAB® tasks. Third, the major co-morbidity for children with FASD was attention deficit hyperactivity disorder (ADHD) (Table 2), and therefore we conducted an analysis of performance between children who were co-morbid for ADHD versus those that were not. There were no differences between these groups for any of the outcome measures reported in this communication (data not shown), suggesting that the co-morbid diagnosis of ADHD was not the major contributor to performance deficits in the CANTAB® tasks.

Reaction Time (RTI). Figure 1 depicts the four outcome measures for the RTI: Simple and 5-Choice reaction and movement times. The univariate ANOVA revealed the following for dependent measures (simple and 5-choice reaction and movement times) and between-subject measure (group). As compared to controls, children with FASD demonstrated increased reaction times in the simple choice ($F(1,169) = 14.5$, $p < .001$) and 5-choice ($F(1,169) = 16.2$, $p < .001$) tasks (Figure 1A, B), as

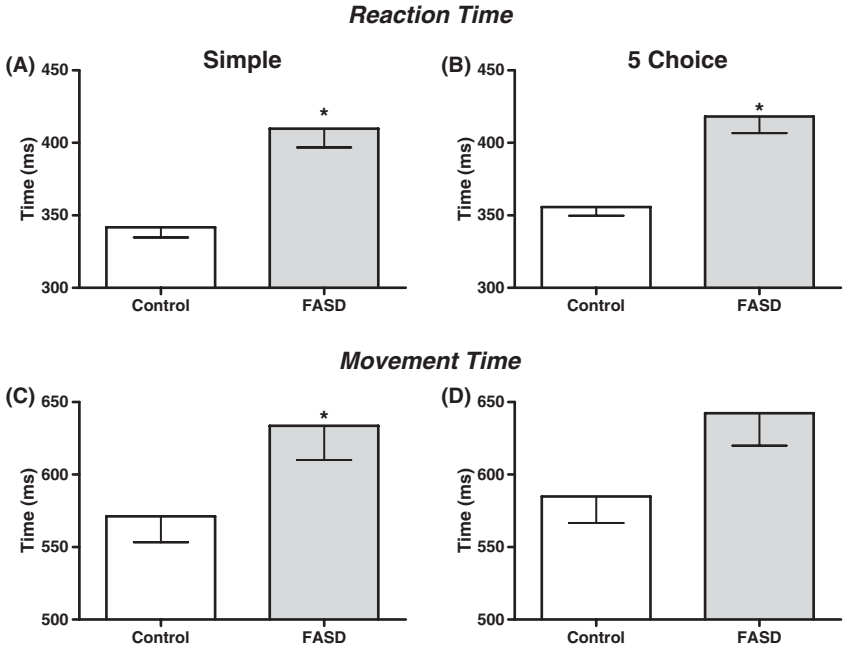

Figure 1 Quantification of parameters for reaction time (A,B) and movement time (C,D) for simple (A,C) and 5-choice (B,D) problems in the Reaction Time (RTI) task. *$p \leq .05$ compared with control subjects

well as increased movement times in the simple choice ($F(1,169) = 4.6$, $p < .05$) (Figure 1C) and a similar trend for the 5-choice ($F(1,169) = 3.0$, $p = .08$) tasks (Figure 1D).

Stockings of Cambridge (SOC). Of the outcomes measures available for SOC, the problems solved in the minimum number of moves, mean moves and initial thinking time were selected for analysis (Figure 2). The univariate ANOVA for the dependent measure (problems solved in the minimum number of moves) and for between-subject effect (group) revealed that children with FASD solved fewer problems in the minimum number of moves ($F(1,160) = 10.2$, $p < .005$) (Figure 2A) than the control group. Figure 2B illustrates the breakdown in performance for children with FASD compared to controls for problem sets of increasing difficulty. These data were analysed using the non-parametric Mann–Whitney test because the conditions for normal distribution were not met. Children with FASD demonstrated poorer performance (i.e., more moves to solve a given problem) for 2-move ($p < .05$), 4-move ($p < .05$) and 5-move ($p < .05$) problems compared to control children. For initial thinking time, the ANOVA for dependent measures (choice; 2, 3, 4 or 5), revealed an effect of choice ($F(3,399) = 12.8$, $p < .001$) such that the children with FASD spent less time planning a strategy for completing the problem sets. Children with FASD demonstrated a significant decrease in their initial thinking time for 4-move ($t_{(165)} = 1.9$, $p = .05$) and 5-move ($t_{(156)} = 2.1$, $p < .05$) problem sets compared to control children, and no significant difference for 2- and 3-move problems (Figure 2C).

Match to Sample Visual Search (MTS). Figure 3 displays the outcome measures for MTS. For the univariate ANOVA of the dependent measure mean movement time for correct responses, the effect of group approached significance ($F(1,167) = 3.0$, $p = .08$); children with FASD were slower than controls (Figure 3A). For the decision time for correct responses, there was a group effect ($F(1,167) = 12.4$, $p < .005$), demonstrating that children with FASD were slower to recognise and decide which distracter pattern matched the central stimulus pattern compared to controls (Figure 3C). The movement and reaction times across problem sets of increasing difficulty are depicted in Figure 3B and D. Movement time increased with increasing difficulty (i.e., increased box number) and the ANOVA revealed for the dependent measure (boxes; 2, 4, 8) an effect of box ($F(2,332) = 29.1$, $p < .001$). The group effect approached statistical significance ($F(1,166) = 2.8$, $p = .1$); where children with FASD had slower movement times compared to control children. Decision time increased as the problem sets became more difficult (i.e., increased box number) and the ANOVA revealed a significant effect of box ($F(2,332) = 198.3$, $p < .001$). There was a group effect for decision time ($F(1,166) = 13.6$, $p < .001$); which demonstrated that children with FASD took longer to decide which distracter pattern matched the central target pattern (Figure 3C). For movement time, children with FASD demonstrated significant motor delays for both the 4- and 8-box problem sets ($t_{(99)} = 2.5$, $p < .05$ and $t_{(116)} = 2.1$, $p < .05$, respectively); and this approached significance in the 2-box problem set ($t_{(103)} = 1.8$, $p = .08$). Similarly, for decision time, children with FASD required more

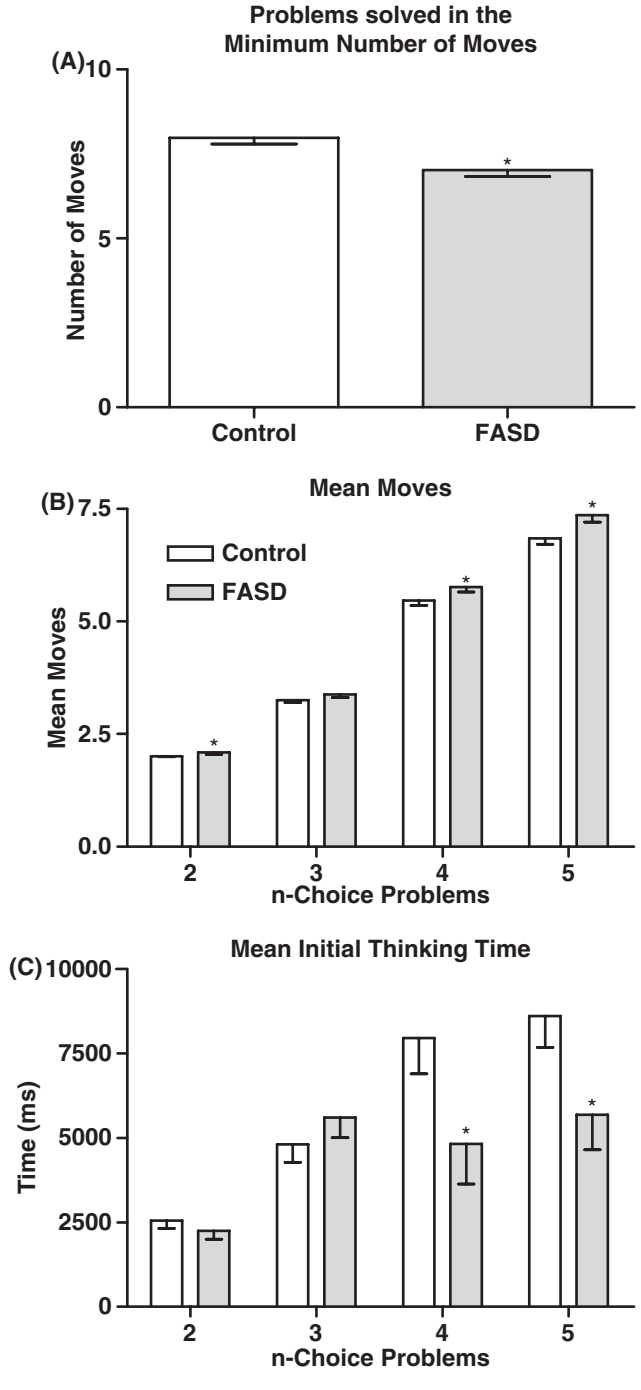

Figure 2 Quantification of parameters for the total problems solved in the minimum number of moves (A), number of moves for n-choice problems (B) and mean initial thinking time for n-choice problems (C) in the Stockings of Cambridge (SOC) task. Shaded bars, fetal alcohol spectrum disorders (FASD) data; Empty bars, control data. *$p \leq .05$ compared with control subjects

time to differentiate the matching pattern from distracters for 2-, 4- and 8-box problems sets ($t_{(136)} = 4.4$, $p < .001$, $t_{(150)} = 3.0$, $p < .005$ and $t_{(134)} = 3.1$, $p < .005$, respectively).

Spatial Working Memory (SWM). Figure 4A depicts the total number of errors (when a subject revisited a box previously found to contain a token) in the SWM task for control and FASD subjects. The univariate ANOVA for the total number of errors revealed a significant difference for group where children with FASD committed more errors compared with controls ($F(1,166) = 44.4$, $p < .001$). Figure 4B depicts the number of errors stratified by increasing task difficulty (i.e., increasing the number of boxes). As in the SOC task, the conditions for normal distribution were not met and as a consequence non-parametric analysis was conducted using the Mann–Whitney test. There was a significant difference for the 4-, 6- and 8-box problem sets ($p < .001$), indicating that the children with FASD demonstrated deficits in working memory such that they were unable to recall which boxes had been previously searched and found to contain a token. This observation was further supported by examining the strategy score, where lower scores indicate good use of strategy (Figure 4C). The univariate ANOVA revealed a significant effect of group on strategy score, such that the control children demonstrated significantly lower scores ($F(1,166) = 23.6$, $p < .001$).

Table 3 Effect size for CANTAB® outcome measures

Task	Cohen's *d*	Effect size *r*
RTI (Reaction Time-Simple)	.70	.33
RTI (Reaction Time-5 Choice)	.73	.34
RTI (Movement Time-Simple)	.31	.16
RTI (Movement Time-5 Choice)	.30	.15
MTS (Decision Time)	.51	.25
MTS (Movement Time)	.37	.18
SOC (Minimum Moves)	.55	.26
SWM (Errors)	1.08	.48
SWM (Strategy)	.75	.35

Effect size. The effect sizes were calculated for the major outcome measures obtained in the CANTAB® tasks. In the RTI task, there were moderate to strong effects in reaction times, but relatively small effects in the movement time measures (Table 3). Similarly, in the MTS task, there was a moderate effect on decision time, but a relatively small effect on movement time. In the SOC task, the number of problems solved in the minimum number of moves yielded a moderate effect (Table 3). In contrast, very strong effects were obtained in the SWM task, especially for the number of errors (searching a box previously found to contain a token) (Table 3).

Diagnostic subgroups. In the FASD group, 24 children had a diagnosis of FAS, 18 children had a diagnosis of pFAS and 40 children had a diagnosis of ARND. The control children were matched to children from 1 of 3 subgroups (paired to FAS, paired to pFAS or paired to ARND) based upon age and sex. Outcome measures for each task were then analysed and stratified by diagnosis for FASD and control children (control-FAS, control-pFAS and control-ARND to signify the match). There was no significant

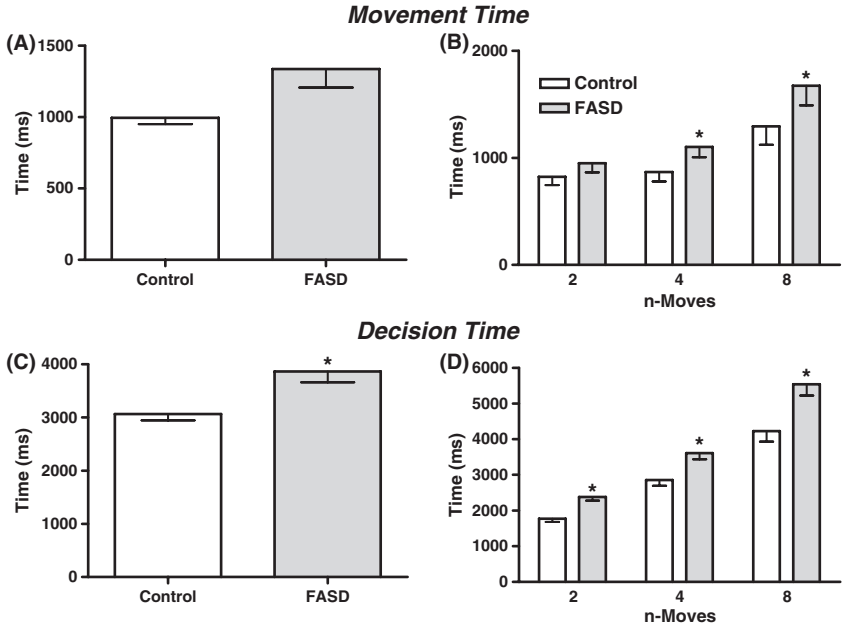

Figure 3 Quantification of parameters for the total movement time (A) and decision time (C); and the total movement time (B) and decision time (D) for n-move problems in the Match to Sample Visual Search (MTS) task. Shaded bars, fetal alcohol spectrum disorders (FASD) data; Empty bars, control data. *$p \leq .05$ compared with control subjects

difference between diagnostic subgroups for any of the outcome measures in the tasks RTI, MTS and SWM, although all diagnostic subgroups were different from controls (data not shown). In the SOC task, there was one significant difference found between children in the diagnostic subgroups ($F(2,70) = 5.2$, $p < .01$) that was not apparent for the matched control groups. Specifically, children with a diagnosis of FAS solved significantly fewer problems compared to children with a diagnosis of either pFAS ($p < .05$) or ARND ($p < .05$) (Figure 5).

Discussion

Our results suggest that the computerised CANTAB® research tool provides a sensitive indicator of executive function deficits in children with FASD. Compared to controls, children with FASD exhibited: 1) longer reaction/decision time latencies in the RTI and MTS tasks; 2) a decrease in the number of problems solved in the minimum number of moves, an increase in the mean number of moves and a decrease in the initial thinking time in the SOC task; 3) increased errors and poorer use of strategy, in the spatial working memory task; and 4) little or no difference in performance across the diagnostic subgroups (FAS, pFAS, ARND). Performance in these tasks revealed deficits in attention, planning, strategy use and working memory. In this study population, the effect size for impaired performance by children with FASD was greatest for the spatial working memory task. These results support our initial hypotheses that children with FASD demonstrate deficits in executive function that can be measured experimentally, and that tasks that demand the use of spatial working memory and strategy demonstrate the most sensitivity to deficits in cognitive flexibility in children with FASD. Of the 14 outcome measures analysed across the four selected tasks, only one revealed significant differences in performance across the diagnostic subgroups (FAS, pFAS, ARND), indicating that deficits in the different domains of executive function provide sensitive indicators of brain injury resulting from prenatal exposure to alcohol, regardless of the presence of facial dysmorphology.

Our findings are consistent with previous studies in which prenatal alcohol exposure has been correlated with generalised neurocognitive performance across tasks of executive function (Rasmussen, 2005; Riley & McGee., 2005). Korkman and colleagues (Korkman, Kettunen, & Autti-Ramo, 2003) found deficits in executive function and attention, and also demonstrated deficits in other cognitive domains. Similarly, Lee et al. (2004) were able to classify alcohol-exposed children from controls with 93.3% and 90% specificity, respectively, using two common attentional outcome measures from the Wechsler Intelligence Scale for Children – Third Edition and the Attention Problems scale from the Child Behaviour Checklist (Lee, Mattson, & Riley, 2004). The selected measures for attention reliably predicted whether a child was prenatally exposed to alcohol, suggesting that attention deficits may warrant further investigation as a potential mechanism for differentiating children with FASD from other clinical populations.

The use of implicit strategy has been evaluated in children with heavy prenatal alcohol exposure to

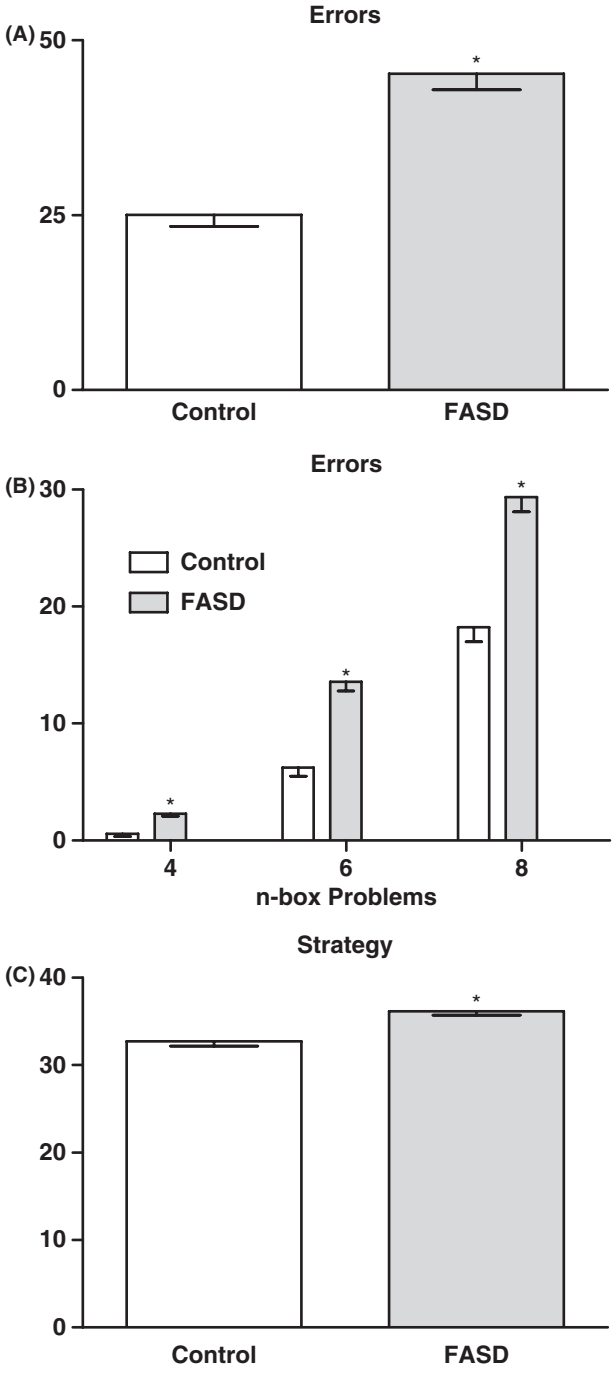

Figure 4 Quantification of parameters for the total errors (A) and errors for n-box problems (B) and the strategy score (C) in the Spatial Working Memory (SWM) task. Shaded bars, fetal alcohol spectrum disorders (FASD) data; Empty bars, control data. *$p \leq .05$ compared with control subjects

observe its effects on learning (Roebuck-Spencer & Mattson, 2004). When semantic categories were not used, children with FASD forgot more information than controls on a verbal learning test, and the greater use of semantic clustering was positively correlated with the amount of information learned and recalled. Interestingly, these observations were not driven by IQ differences between the groups, suggesting that alcohol may affect memory abilities

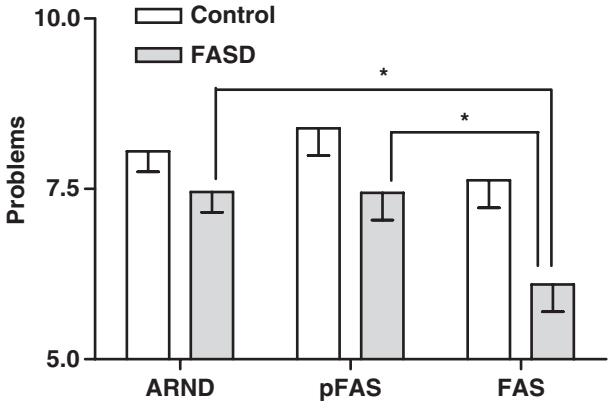

Figure 5 Quantification of the total problems solved in the minimum number of moves in the Stockings of Cambridge (SOC) task across diagnostic groups. Control subjects were matched as closely as possible to children with FAS, pFAS or ARND based on age and gender. Shaded bars, fetal alcohol spectrum disorders (FASD) data; Empty bars, control data. *$p \leq .05$ depicts statistical significance

independent of its effect on intellectual ability. The use of semantic clustering and rehearsal may be suitable strategies for optimal learning in children with FASD. Recently, rehearsal training has been evaluated in children with FASD (Loomes, Rasmussen, Pei, Manji, & Andrew, 2007). Similarly to the current study, there were difficulties in the use of strategy and working memory in the children with FASD, and these performance deficits were exacerbated with increasing task complexity. However, children who received rehearsal training performed significantly better than the control group and demonstrated the use of rehearsal strategies from their training sessions, thus improving overall memory capabilities. We did not employ rehearsal training in the current study, and thus it is possible that the poor performance for children with FASD can be attributed to their inability to effectively develop suitable strategies themselves in order to perform the tasks successfully. It is likely that the implementation of rehearsal training may help to improve these core deficits.

After reviewing the literature, it was not surprising that there was only one difference in cognitive performance among the diagnostic subgroups (FAS, pFAS and ARND). Previous studies have reported little to no differences among dysmorphic and non-dysmorphic subjects with prenatal alcohol exposure (Mattson et al., 1999; Roebuck-Spencer & Mattson, 2004; Kodituwakku, May, Clericuzio, & Weers, 2001); and this is consistent with results we obtained evaluating oculomotor control across the diagnostic subgroups (Green et al. 2008, unpublished findings). Individuals with FAS and fetal alcohol effects (FAE; describes children who do not have all the physical characteristics of FAS) do not show differences on tests of cognitive abilities,

secondary disabilities and behavioural problems (Sampson, Streissguth, Bookstein, & Barr, 2000). Furthermore, it has been suggested that central nervous system deficits in FAE may be as severe as or worse than individuals with FAS (Connor & Streissguth, 1996). Thus, it is not surprising that significant differences in performance among the three diagnostic subgroups were found only in one outcome measure.

While this study provided valuable data representative of a large sample size of children with and without FASD, there were some limitations that should be noted. First, we did not employ other neurocognitive tests in this study, which precludes the determination of the relative sensitivity of CANTAB® compared with more traditional cognitive and behavioural assessment tools. Second, data on ethnicity was not collected in this study. As this may be associated with performance, differences in performance of CANTAB® tasks by different ethnic groups should be addressed in future studies. Third, it was not possible to collect data regarding the frequency, quantity and timing of prenatal alcohol exposure for each of our subjects, as this information was unavailable, especially for children living in adoptive families or in foster care. It has proven very difficult to ascertain a dose–response relationship for alcohol exposure and outcome in offspring, as there are many factors (i.e., nutrition, genetics, ethnicity) that contribute to the severity, and for which we were unable to control. Fourth, information on alcohol and nicotine use was not quantified for our study population. It may be of interest to determine the frequency and types of drug use among children between the ages of 8 and 15 years, as this may impact on performance. Finally, as this was the first study to assess executive function in children with FASD using the CANTAB®, only a specific subset of tasks was selected. In future, tasks that probe other aspects of executive function may warrant further investigation, especially those which assess verbal learning and memory.

In conclusion, brain injury resulting from prenatal alcohol exposure can lead to significant deficits in cognitive abilities that can be quantified using an easy to administer, brief battery of computer-based neuropsychological tasks. We demonstrate herein deficits in attention, planning, strategy and working memory, revealing that the neurocognitive problems associated with FASD are widespread and generalised; though deficits in spatial working memory may be affected to the greatest extent. Prenatal alcohol exposure has been related to a decrease in the size of frontal cortex (Wass, Persutte, & Hobbins, 2001), which likely gives rise to most of these impairments regardless of the presence or absence of facial dysmorphology. Finally, by understanding the global dysfunction and comparing the subtle differences among subjects with FASD to other clinical populations, it may be possible to develop specific strategies and techniques that may mitigate the brain injury resulting from prenatal exposure to alcohol and overcome these deficits in executive function.

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Preliminary versions of these data have been presented in abstract form (Mihic et al., 2007; Green et al., 2007).

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