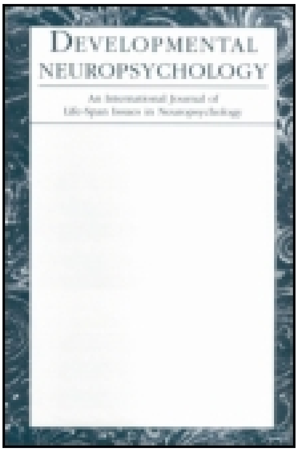

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Comparing Attentional Networks in Fetal Alcohol Spectrum Disorder and the Inattentive and Combined Subtypes of Attention Deficit Hyperactivity Disorder

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The Attention Network Test (ANT) was used to examine alerting, orienting, and executive control in fetal alcohol spectrum disorder (FASD) versus attention deficit hyperactivity disorder (ADHD). Participants were 113 children aged 7 to 10 years (31 ADHD–Combined, 16 ADHD–Primarily Inattentive, 28 FASD, 38 controls). Incongruent flanker trials triggered slower responses in both the ADHD–Combined and the FASD groups. Abnormal conflict scores in these same two groups provided additional evidence for the presence of executive function deficits. The ADHD–Primarily Inattentive group was indistinguishable from the controls on all three ANT indices, which highlights the possibility that this group constitutes a pathologically distinct entity.

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The fact that both fetal alcohol spectrum disorder (FASD) and attention deficit hyperactivity disorder (ADHD) are characterized by deficits in attention and executive functioning has fueled speculation regarding their diagnostic overlap (Doig, McLennan, & Gibbard, 2008; Mattson & Riley, 1998; Rasmussen, 2005). The problem of differential diagnosis for both disorders is important for two related reasons. Firstly, for clinicians, the diagnostic distinction between higher functioning children with FASD and children with ADHD is especially difficult to define. Secondly, misdiagnosis may lead to inappropriate treatment, as it appears that children with FASD are less likely to respond well to stimulant medication (Coles et al., 1997; Oesterheld et al., 1998). The possibility of symptom overlap between ADHD and FASD, however, has only rarely been studied by comparing both groups in a single design. Moreover, only a few of those studies were set in theoretical frameworks allowing the attention symptoms to be analyzed in terms of cognitive mechanisms and their neural correlates.

Nanson and Hiscock (1990) were among the first to compare children with fetal alcohol syndrome (FAS) to children with attention deficit disorder (ADD) on four distinct aspects of attention: sustained attention, impulsivity, arousal modulation, and instant reinforcement-seeking (Douglas, 1972). While the children with FAS were overall slower than those with ADD, their impulsivity and sustained attention problems were similar. More recently a study by Coles et al. (1997) provided another illustration of a theory-driven approach. Clinical groups were compared on neurocognitive tasks reflecting a four-factor model of attention (Mirsky, Anthony, Duncan, Ahern, & Kellam, 1991). Results showed that the children with FAS had difficulties with encoding and shifting attention, while the children with ADHD had problems with focusing and sustaining attention.

Many continuous performance task (CPT) studies have shown that ADHD and sustained attention are associated (Swanson et al., 1998), while with regard to FASD there is still ambiguity regarding the nature of the attention deficits. In our own work on FASD and ADHD, we tested children's sustained attention and inhibition abilities using CPT and Go/No-Go paradigms (Kooistra, Crawford, Gibbard, Ramage, & Kaplan, 2009). Both groups of children had similar levels of sustained attention deficits; however, their inhibition/impulsivity problems were event rate-dependent. Findings were interpreted in terms of activation regulation problems associated with the vigilance system. Children with ADHD–Combined (ADHD–C) were more affected in slow-paced conditions associated with understimulation, and children with ADHD–Primarily Inattentive (ADHD–PI) or FASD had difficulty in high-paced situations that elicit overstimulation.

Clearly, model-oriented approaches in which attention is considered as a behavioral manifestation of associated cognitive and neural processes have been highly influential in studying the pathology of attention in ADHD overall, and could be equally effective in comparing the attention deficits of children with FASD, ADHD–PI and ADHD–C. Similarly, such a model-based strategy would be important in further exploring the nature of the executive function deficits in FASD versus ADHD. To date the few available relevant studies tend to support the view that, while present in both disorders, executive dysfunction in FASD signifies a more generalized neurocognitive deficit in terms of pattern and degree of symptoms (Geurts, Verté, Oosterlaan, Roeyers, & Sergeant, 2005; Rasmussen et al., 2010; Rasmussen & Bisanz, 2009; Vaurio, Riley, & Mattson, 2008)

The current study applied the Attention Network Test (ANT) (Fan, McCandliss, Sommer, Raz, & Posner, 2002) to attempt to differentiate the children with ADHD from those with FASD in terms of three attention functions: alerting, orienting, and executive control (Fan et al., 2009; Posner & Fan, 2004; Posner & Petersen, 1990). *Alerting* refers to maintaining a readiness to respond, and is associated with right prefrontal, thalamic and parietal brain areas. *Orienting* refers to the ability to direct attention toward a specific channel or stimulus while ignoring others, and is associated with the posterior parietal cortex, frontal eye fields, and the pulvinar and reticular nuclei of the thalamus. *Executive control* involves conflict monitoring and resolution through error detection and inhibition, and is linked with the anterior cingulate and dorso-lateral prefrontal areas. It is to be noted that these attention functions proposed by Posner and Petersen (1990) can be related to other more traditional concepts: the alerting function operates to establish sustained attention; orienting mediates selective attention; and executive control requires divided attention (Swanson et al., 1998).

The ANT constitutes an effective behavioral probe of these three attention functions and their associated brain areas, and has repeatedly shown its ability to differentiate between healthy controls and various patient groups with attention deficits (Posner et al., 2002; Posner et al., 2003; Sohlberg, McLaughlin, Pavese, Heidrich, & Posner, 2000). For the current study the child version of the ANT (Rueda et al., 2004) was used in which child-friendly, colorful “fish” stimuli replace the black and white arrow stimuli that typically appear in the adult ANT.

In sum, the present study sought to examine alerting, orienting and executive control in children with ADHD or FASD from a differential diagnostic perspective. While according to the limited differential data available, essentially all three functions could be affected, we expected to see the most pronounced effects in the alerting and executive components. Specifically, we predicted that the ADHD and FASD groups would show similar levels of alerting impairment (Kooistra et al., 2009), and that the FASD group would be especially defective in executive control (Rasmussen & Bisanz, 2009). A subsidiary issue addressed in the current study concerned the evaluation of the three attention functions in the children with ADHD–PI versus the children with ADHD–C.

METHOD

Participants

The study was approved by the Conjoint Health Research Ethics Board of the University of Calgary. Consent forms were signed by both parents and children. Participants ($N = 113$) were all Caucasian, aged 7 to 10 years (47 with ADHD, 28 with FASD, and 38 controls) (Table 1). The children with ADHD were recruited from one government-designated special needs school and one clinic specializing in learning and attention problems. Children seen in both locations have academic difficulties. The school principals and clinic director sent letters inviting families with children suspected of having ADHD to participate. Interested parents contacted the researchers for further details. Children had to have been diagnosed with ADHD between the ages of 5 and 7 years by a child psychiatrist or a developmental pediatrician. A three-step procedure confirmed these diagnoses. First, the Summary ADHD Checklist (Kaplan, Humphreys, Crawford, & Fisher, 1997) was completed to give an indication regarding the presence/absence of ADHD using a cutoff of at least 15/25 items with a score of 2 (“ADHD pretty much”) or 3 (“ADHD very much”). Next, the Conners’ Parent Rating Scale–Revised (Conners, 1997) was

TABLE 1
Sample Characteristics ($N = 113$)

Variable	*ADHD–C* $n = 31$	*ADHD–PI* $n = 16$	*FASD* $n = 28$	*Controls* $n = 38$
Mean age (*SD*) ($p = .232$)	9.08 (1.93)	9.71 (0.85)	8.81 (1.25)	9.13 (1.12)
Mean WISC–III FSIQ estimate (*SD*) ($p < 0.001$)	111.76 (11.43)	109.06 (13.07)	98.04 (16.03)	117.38 (10.10)
Boys/Girls	20 or 64.5% boys	12 or 75% boys	16 or 57.1% boys	20 or 52.6% boys
($p = .437$)	11 or 35.5% girls	4 or 25% girls	12 or 42.9% girls	18 or 47.4% girls
Socioeconomic status ($p = .001$):				
Low	13.3%	12.5%	42.9%	2.9%
Middle	33.3%	37.5%	35.7%	29.4%
High	53.3%	50.0%	21.4%	67.6%

ADHD-C = attention deficit disorder–combined; ADHD-PI = attention deficit order–primarily inattentive; FASD = fetal alcohol spectrum disorder (FASD); WISC-III = Wechsler Intelligence Scale for Children–III.

administered to confirm ADHD symptomatology using a cutoff T-score of at least 65 on the DSM-IV Total Scale. Finally, the Diagnostic Interview for Children and Adolescents–IV (Reich, Welner, & Herjanic, 1997) was used to re-confirm the diagnosis and assign ADHD subtype. In order to be included children had to meet ADHD criteria on all three measures. Further exclusion criteria were: estimated full scale Intelligence Quotient (FSIQ) $\leq$80, co-existing psychiatric disorders (e.g., oppositional defiant disorder, mood disorder), chronic medical conditions affecting cognitive function (e.g., seizures), and long acting psychiatric medication (e.g., risperidone). Of the 47 children with ADHD, 31 were ADHD–C, and 16 ADHD–PI; 43 (91%) were on stimulants. A 24-hour medication washout period was required prior to testing. Based on their school records all children with ADHD had academic problems, 24 (51%) of them had a confirmed learning disability (LD).

All families whose 7 to 10 year old children attended the FASD clinic at a pediatric hospital were invited to participate by letter from the clinic. Children had to have been identified by a pediatrician as having FASD. Their classification was based on criteria formulated by the Fetal Alcohol Syndrome Diagnostic and Prevention Network Diagnostic Guide (DPN) (Astley & Clarren, 1999). This diagnostic framework provides a 4-digit code representing the magnitude of expression (rated 1 to 4) of the four key FASD features: growth deficiency, FASD facial phenotype, brain dysfunction, and gestational alcohol exposure. Only children who fell in the categories G (sentinel physical findings/neurobehavioral disorder, alcohol exposed; $n = 6$), and H (neurobehavioral disorder, alcohol exposed; $n = 22$) were included. Alcohol exposure was deemed to be etiologically significant for all children with alcohol ranks 3 and 4. A similar three-step screening procedure as described for ADHD was used to verify co-occurring disorders in the children with FASD. These additional disorders, while recorded, were not exclusion factors. The exclusion criteria for the children with FASD were: an estimated FSIQ $\leq$ 80, a chronic medical condition affecting cognitive function, CNS-activating medication, and history of recent child abuse. Twenty-seven of the 28 children with FASD met criteria for ADHD, all the ADHD–C type. Twenty-seven of these children (96%) were on stimulant treatment and were not given medication for 24 hours preceding testing. Based on their clinical records all children with FASD struggled academically, 13 (46%) of them had a confirmed LD.

The control children were obtained from two elementary schools through posters and parents' councils. In the initial contact with parents, exclusion criteria were verified including psychiatric concerns. Next, screening instruments were administered. Only children who scored in the non-clinical range on all screening steps were accepted as controls. They were subject to the same exclusion criteria as their age peers with ADHD or FASD.

No systematic data on alcohol use during pregnancy in mothers from controls and mothers from children with ADHD were available. While both the clinic and the participating schools reported having a standard question on family alcohol problems in their screening forms, their general experience is that the alcohol question remains unanswered or is answered in line with what is socially desired. Therefore, the alcohol question was not asked upon entering the study. Instead, the non-FASD families *were told* that alcohol use during pregnancy was an exclusion criterion.

Screening Tools

Summary ADHD Checklist (SAC) (Kaplan et al., 1997). Parents completed the SAC, a DSM-IV–based 25-item checklist rated on a 4-point Likert scale ("ADHD not at all, ADHD just a little, ADHD pretty much, ADHD very much"). The SAC has adequate reliability and validity (Kaplan et al., 1997).

Conners Parent Rating Scale–Revised (Long version) (CPRS) (Conners, 1997). The CPRS is a standardized DSM-IV–based parent report checklist of a broad range of child and adolescent problems. Its 80 items, scored on a 4-point scale, represent 14 diagnostic dimensions. A profile based on *T*-scores permits comparisons with normative age and gender groups. The CPRS is among the most prominent ADHD rating scales and has sound psychometric properties (Collett, Ohan, & Myers, 2003).

Diagnostic Interview for Children and Adolescents–IV, Parent version (DICA–IV) (Reich et al., 1997). The DICA-IV, a semi-structured computer-assisted diagnostic interview, was administered to parents. It branches to appropriate questions, depending on the respondents' answers, and includes a DSM-IV–based diagnostic classification module. For this study the program was configured for the assessment of ADHD, with an additional evaluation of concurrent mood, anxiety and oppositional symptomatology. The DICA–IV is widely used, has good clinical validity and moderate to high test–rest reliability (Reich, 2000).

Attention Network Test: Apparatus and Stimuli

Children were seated at a distance of 55 cm from a computer screen with both the index and middle finger of their dominant hand placed over the left and right arrow key of a computer keyboard. They were asked to fixate on a cross in the centre of the screen and make left/right direction judgments about subsequently appearing target stimuli through speeded left/right key press responses. Children were tested individually with the experimenter sitting out of the child's vision. One ANT session lasted about 25 minutes and consisted of 24 practice trials followed by 144 experimental trials distributed over three blocks of 48 trials each. In between blocks, children were allowed short breaks.

As shown in Figure 1, each trial began with a black central fixation cross displayed on a light blue background, followed by a target stimulus (i.e., a cartoon of either a single yellow fish or five yellow fish in a row). The fish had black arrow-like gills indicating their swimming direction. Depending on whether the single fish, or the central fish in the row of five, was pointing to the left or the right, the children were instructed to press the corresponding left or right arrow key. A correct response resulted in a computer-generated auditory "Woohoo" sound, together with a

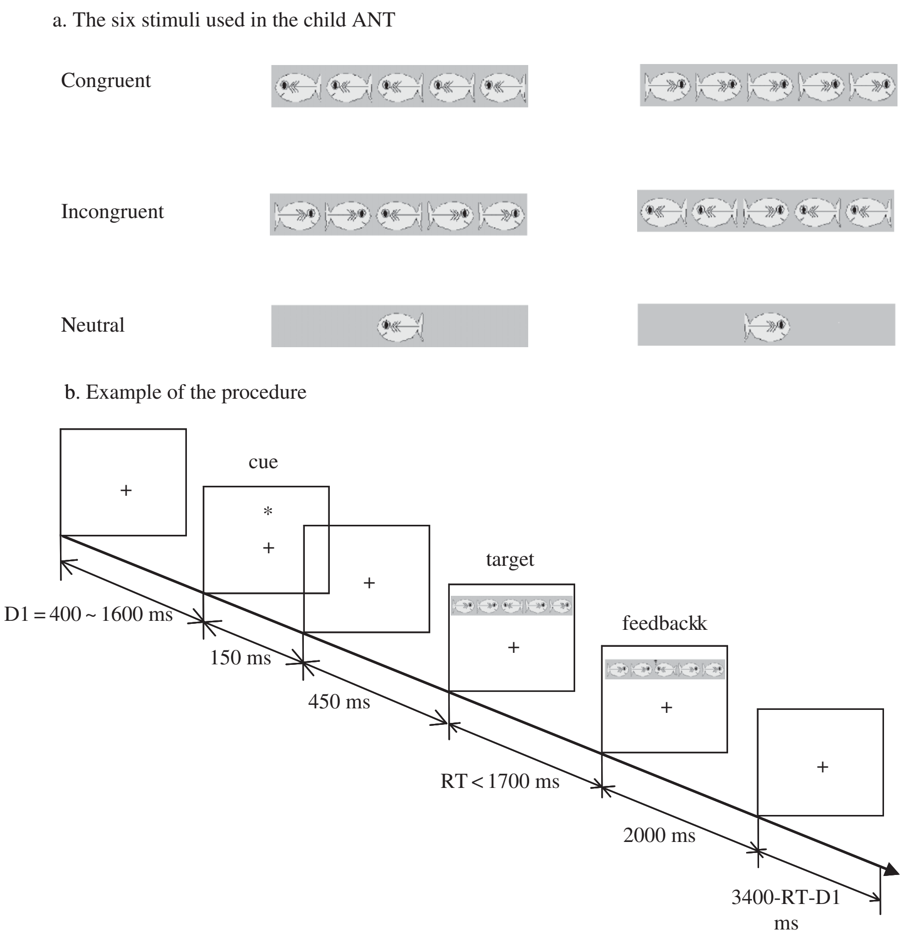

FIGURE 1 Schematic of the child version of the Attention Network Test (ANT). Although shown in block and white here, the actual task uses a background color of light blue for every display, while the fish appear in yellow.

simple animation of the target fish blowing bubbles. A mistake resulted in a monotonous "beep" without any animation.

There were three trial types: one third were neutral trials in which only one fish appeared; one third were congruent trials in which the central fish was accompanied by four flanking fish all swimming in the same direction; and the remaining one third were incongruent trials in which the four flanking fish pointed in the opposite direction of the central fish.

Trials were randomly distributed over four cue conditions: central cue, double cue, spatial cue, and no cue. In the central cue condition an asterisk appeared at the location of the fixation cross, essentially functioning as an alerting signal but providing no information regarding the future location of the upcoming target. The double cue condition was similarly uninformative, as two asterisks appeared at the same time under and above the future target position. Spatial cues involved the appearance of a single asterisk at the location of the upcoming target. In the no cue condition the fixation cross remained present until target presentation.

The dependent variables collected in the ANT were median reaction time (median RT) and response accuracy (% correct responses).To obtain the alerting, orienting, and conflict scores per subject, the following subtractions were computed: alerting score = median RT for no cue trials minus median RT for double cue trials; orienting score = median RT for central cue trials minus median RT spatial cue trials; conflict score = median RT for incongruent trials minus median RT for congruent trials.

Procedure

Children were tested in a quiet room at a pediatric hospital. Testing began with a short form (15 minutes) of two subtests (block design, vocabulary) of the Wechsler Intelligence Scale for Children–III (WISC–III) to obtain an estimate of their full-scale IQ (FSIQ). Next, the ANT was administered. Total test time was approximately 45 minutes, including a 5 minute break between the WISC–III and the ANT session. Socioeconomic status (SES) was evaluated by categorizing parental employment using the Blishen index (low SES category 1–2, middle SES category 3–4, high SES category 5–6). Assessors were blind to the children's diagnostic status.

Statistical Analyses

Group comparisons on demographics were made using analysis of variance (ANOVA) for continuous variables and chi square (χ^2) tests for categorical variables. Post-hoc group comparisons were made using Fisher's LSD test.

The ANT data were analyzed using a series of separate repeated-measures MANCOVAs followed by contrast analyses using pair-wise comparisons controlling for covariates (i.e., age, gender, SES, and estimated FSIQ). The between-participants factor was group and the within-participants factors were cue condition (central cue, double cue, spatial cue, and no cue) and flanker type (congruent, incongruent and neutral). The dependent variable for the first MANCOVA was median RT. For the second MANCOVA the dependent variable was response accuracy. The final MANCOVA compared groups on the alerting, orienting and conflict effects. Only significant findings ($p < .05$) are reported.

RESULTS

As shown in Table 1, significant group differences did not emerge for age or sex, but did for estimated FSIQ ($F_{(3,106)} = 12.85$, $p < .001$; partial eta^2 = .267, power = 1.00) and SES ($\chi^2_{(6)} = 23.41$, $p = .001$, effect size, phi = .451, power = 1.00). Children with FASD had significantly lower estimated FSIQs compared to children with ADHD–C, children with ADHD–PI or control children, and children with FASD were more likely to be in the low to middle SES category (Table 1).

For median RT, groups were differentially affected by flanker type, as evidenced by a significant group by flanker interaction (Wilk's Lambda $F(6,192) = 3.05$, $p = .007$; partial eta^2 = .101, power = .917). As shown in Figure 2, additional contrast analyses showed that the RT performance of both the ADHD–C group and the FASD group was more impaired by incongruent flanker trials than congruent ones when compared to controls ($F(1,55) = 7.39$, $p = .009$, partial eta^2 = .118, power = .761; $F(1, 55) = 14.55$, $p < .001$, partial eta^2 = .209, power = .963, respectively). The ADHD–C group did not differ from the FASD group in terms of median RT, and similarly, neither did the ADHD–PI group differ from the FASD group or controls.

Analyses for response accuracy revealed that although groups were not differentially affected by flanker type (i.e., nonsignificant group by flanker type interaction), there was a significant main effect for group ($F(3, 97) = 5.16$, $p = .002$, partial eta^2 = .138, power = .915). Posthoc contrast analyses showed that children with ADHD–C had significantly lower accuracy compared to controls ($F(1,55) = 9.16$, $p = .004$, partial eta^2 = .143, power = .845), children with ADHD–PI ($F(1, 38) = 8.05$, $p = .007$ partial eta^2 = .175, power = .789), and to children with FASD ($F(1, 50) = 4.25$, $p = .044$, partial eta^2 = .078, power = .525). No other group differences for response accuracy emerged.

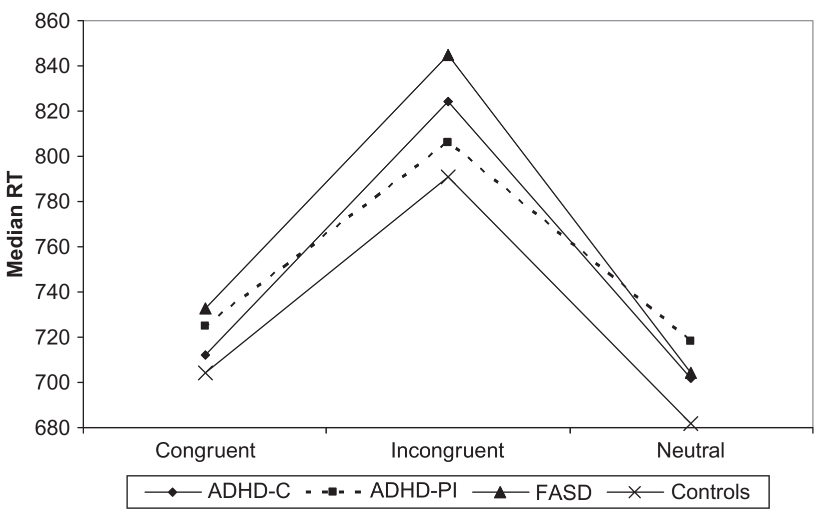

FIGURE 2 Median reaction time as a function of flanker type for the four groups of children.

TABLE 2
Attention Networks, Overall Median Reaction Time, and Overall Accuracy by Group

Variable	*ADHD-C* *n = 31*	*ADHD-PI* *n = 16*	*FASD* *n = 28*	*Controls* *n = 38*
Median RT (*SD*) (overall)	746.129 (135.9)	749.495 (82.7)	761.000 (107.3)	725.759 (158.3)
Accuracy	.929	.970	.937	.969
Attentional networks mean scores (*SD*):				
Alerting	65.68 (46.65)	66.19 (50.27)	43.39 (59.75)	59.50 (51.37)
Orienting	29.97 (59.36)	38.69 (53.18)	43.43 (43.16)	28.82 (54.07)
Conflict	111.81 (52.63)	81.13 (40.05)	111.00 (58.55)	86.50 (44.47)

ADHD-C = attention deficit disorder–combined; ADHD-PI = attention deficit order–primarily inattentive; FASD = fetal alcohol spectrum disorder (FASD); WISC-III = Wechsler Intelligence Scale for Children–III.

No significant correlations among the alerting, orienting, and conflict effects were found. As shown in Table 2, there was a significant main effect for group in the final MANCOVA (Wilk's Lambda $F(9,231) = 2.05$, $p = .035$, partial eta$^2 = .060$, power = .755). No significant between-group differences emerged for the alerting or orienting effects; however, a significant group difference did emerge for the conflict effect ($F(3, 97) = 3.87$, $p = .012$, partial eta$^2 = .107$, power = .810). Post hoc contrasts showed that both the ADHD–C and the FASD groups had significantly higher conflict scores than controls.

DISCUSSION

The purpose of this study was to attempt to differentiate children with ADHD from children with FASD in terms of attention and executive function. The study was set in a theoretical framework that emphasizes that attention is a multidimensional construct consisting of three core functions: alerting, orienting, and executive control (Posner & Petersen, 1990), which are linked to separable brain regions. Groups were differentially affected by the incongruent/congruent flanker manipulation, suggesting differences in conflict resolution. On the incongruent trials the ADHD–C and the FASD group became slower than the controls, while the ADHD–PI group performed similar to the controls. This difference in susceptibility in handling conflict between groups may constitute a differential diagnostic marker that identifies the likelihood of executive control dysfunction associated with frontal and anterior cingulate abnormalities in children with ADHD–C or FASD. It is important to emphasize that groups did not appear to be sacrificing accuracy for the sake of speed, as their performance accuracy was similarly affected by flanker manipulation. It seems, therefore, unlikely that the obtained RT differences between groups were due to bias resulting from strategy differences.

Many studies have shown that ADHD and executive function problems are associated (Barkley, 1997). Similarly, FASD has repeatedly been linked with impaired executive control (Rasmussen, 2005). Our finding of impaired conflict scores in ADHD–C and FASD, therefore, supports the claim of executive function deficits in both groups, and is not surprising given the fact that almost all of our children with FASD also met criteria for ADHD–C.

Rather more interesting, however, was our finding that the children with ADHD–PI were essentially not distinguishable from the controls in terms of alerting, orienting and executive control. Surprisingly, this result contrasts with recent findings from a similar study using the ANT where the ADHD–PI group was found to have an alerting deficit (Booth, Carlson, & Tucker, 2007). Given that Booth et al. (2007) used a nearly identical protocol to that of the current study—both in terms of task and in terms of sample characteristics—the discrepancy in results is difficult to explain, and awaits further replication with larger sample sizes, and strict control for age and learning disability.

These different findings between studies, intriguing as they are, also underline the controversies in the field concerning ADHD sub-typing. What is clear from the literature is that ADHD–C and ADHD–PI are distinct at least in terms of academic, social, and behavioral functioning (Diamond, 2005; Milich, Balentine, & Lynam, 2001). To what extent, however, that constitutes enough proof to consider both subtypes as discrete and unrelated remains open for further research, especially into the neurocognitive aspects of both groups. To date, findings from the few neurocognitive studies available are inconclusive (Baeyens, Roeyers, & Walle, 2006), with some emphasizing executive control deficits in ADHD–C (Solanto et al., 2007), and others suggesting alerting problems in ADHD–PI (Derefinko et al., 2008). As such, the discrepancy between the current study findings and those of Booth et al. (2007) reflects what has repeatedly been emphasized as a major challenge for the field (i.e., seeking improved subtype validation through neurocognitive measures of attention and executive control).

The significance of systematically identifying the neurocognitive differences between groups guided our choice for the ANT as the most appropriate paradigm to probe these differences. The ANT has gained increased recognition as an easy to administer, reliable and valid method to evaluate alerting, orienting and executive control functions in both adults and children (Fan et al., 2002). It has been successfully used in genetic, clinical and intervention studies (Posner et al., 2002; Sohlberg et al., 2000), while neuroimaging evidence is accumulating showing that each of the three postulated attention functions is independently related to specific neural networks (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Konrad et al., 2005). As such, the absence of any significant correlations among the alerting, orienting and conflict effects, is consistent with the ANT literature emphasizing the relative independence between the network scores (Fan et al., 2009).

One limitation of this study is that 27 of the 28 children with FASD also met criteria for ADHD–C. While some consider the optimal design to include a group of children with FASD *without* co-occurring ADHD, others may disagree, because the clinical reality is that essentially all children with FASD struggle with concomitant ADHD symptoms. Nevertheless, one could argue that the current study, rather than differentiating ADHD from FASD, more accurately represents a comparison between idiopathic ADHD versus ADHD from a presumed etiology (fetal alcohol exposure). Another issue relates to the relatively high IQ level of our FASD sample. By only including only those children who fell in the G and H diagnostic categories (Astley & Clarren, 1999), a deliberate choice was made for relatively high functioning children. The rationale was that for clinicians the diagnostic distinction between mildly affected children with FASD and children with ADHD is especially difficult to define and would thus require increased specificity in terms of elementary neuropsychological operations. Finally, one may also argue that the current findings should be interpreted with caution given sample size and the risk for Type I error.

In conclusion, our data demonstrate that children with ADHD–C or FASD face executive function deficits. Interestingly, finding children with ADHD–PI to be indistinguishable from controls on all three ANT indices highlights the possibility of a different pathophysiology underlying their attention problems. Replication with larger sample sizes is thus needed, since the ANT (unlike an earlier study) may not have been sensitive enough to capture the often referred to "cognitive sluggishness" in children with ADHD–PI (Carlson & Mann, 2000).

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