ELSEVIER

Effect of Methylphenidate on Attention in Children with Attention Deficit Hyperactivity Disorder (ADHD): ERP Evidence

Glen A. Sunohara, Ph.D., Molly A. Malone, Ph.D., Joanne Rovet, Ph.D., Thomas Humphries, Ph.D., Wendy Roberts, M.D., and Margot J. Taylor, Ph.D.

Methylphenidate is the most common treatment for attention deficit hyperactivity disorder (ADHD) and has been shown to improve attention and behaviour. However, the precise nature of methylphenidate on specific aspects of attention at different dose levels remains unclear. We studied methylphenidate effects in ADHD from a neurophysiological perspective, recording event-related potentials (ERPs) during attention task performance in normal controls and children with ADHD under different dose conditions. Twenty children with ADHD and 20 age matched controls were assessed with a continuous performance task requiring subjects to identify repeating alphabetic characters. ERPs and behavioural measures were recorded and analyzed for trials where a correct response was made. The ADHD group was assessed off drug (baseline) and on placebo, low (0.28 mg/kg) and high (0.56 mg/kg) dose levels of methylphenidate. The results showed that the ADHD group at baseline was more impulsive and inattentive than controls and had shorter P2 and N2 latencies and longer P3 latencies. Low dose methylphenidate was associated with reduced impulsivity (fewer false alarms) and decreased P3 latencies, whereas the higher dose level was associated with reduced impulsivity and less inattention (more hits), as well as increased P2 and N2 latencies and decreased P3 latencies. Amplitudes were unaffected and there were no adverse effects of the higher dose for any of the children. These results suggest differential dosage effects and a dissociation between dose levels and aspects of processing.

[Neuropsychopharmacology 21:218–228, 1999]

KEY WORDS: *ADHD; Methylphenidate; ERP; Attention*

Attention deficit hyperactivity disorder (ADHD) is the most common pediatric psychiatric disorder (Swanson et al. 1995), with an estimated childhood prevalence of 9% in boys and 3% in girls (Szatmari et al. 1989). Surface symptoms of inattentiveness and impulsivity (Shue and Douglas 1992; Shaywitz and Shaywitz 1988) are often, though not invariably, accompanied by hyperactivity (Gittelman and Mannuzza 1985). ADHD is highly heterogeneous with several distinct subtypes and often comorbid with learning, anxiety, and conduct problems. During childhood, ADHD is associated with greater risk of low academic achievement, grade failure, delinquency (Barkley 1997) and during adulthood, with psychiatric disorders and substance abuse (Wender 1987). Stimulant medication, primarily methylphenidate, is the most common treatment for ADHD. Because methylphenidate may be associated with altered neurotransmitter levels (Mefford and Potter 1989; Voeller 1991), several investigators have attributed ADHD to a neuro-

From the Novartis Pharmaceuticals Canada Inc., (GAS), Dorval, Quebec, Canada; and The Hospital for Sick Children, Divisions of Neurology (MAM, TH, WR, MJT) and Psychology Research (JR), Toronto, Ontario, Canada.

Address correspondence to: Dr. Molly A. Malone, Child Development Centre, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5G 1X8, Canada.

Received August 26, 1998; revised December 30, 1998; accepted February 05, 1999.

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/99/$–see front matter
PII S0893-133X(99)00023-8

chemical imbalance in catecholarnine regulation (Malone et al. 1994; McCracken 1991; Pliszka et al. 1996).

Methylphenidate effectively reduces hyperactivity, impulsivity, and inattention in 60–90% of children diagnosed with ADHD (Whalen and Henker, 1991). Improved social skills and school performance have also been documented (e.g., Swanson et al. 1995). However, the optimal dosages have not yet been established and clinical anecdotal descriptions report some children as becoming overfocused, cognitively constricted, introverted, and "zombie-like" on higher doses (Swanson et al. 1991; Thurston et al. 1979). These descriptions are not consistently substantiated by empirical studies, however, which show both linear improvements with dose (Douglas et al. 1995; Solanto and Wender 1989) and adverse effects of high dose levels (Dyme et al. 1982; Malone et al. 1988; Sprague and Sleator 1977). A recent study by Tannock and Schachar (1992) has shown opposing effects of a high dose level at different test sessions with children making more perseverative errors in the first session and fewer in the second, while another study by this same group reported that despite clinical observations of overfocusing, measured attention performance was not affected by a high dose (Tannock et al. 1989).

Children with ADHD are thought to have a primary attentional deficit in inhibitory (Barkley 1994; Schachar et al. 1993) or executive control (Pennington and Ozonoff 1996) and they also show problems in selective (van der Meere and Sergeant 1987), focused (van der Meere and Sergeant 1988), and sustained attention (van der Meere et al. 1991). Given the multifaceted nature of attention (Colby 1991) and the involvement of a number of brain structures and systems in regulating attention (e.g., Mirsky et al. 1991; Posner and Cohen 1987; Stuss et al. 1995), it is possible that methylphenidate may affect certain components of attention differently. This was examined in a recent study using an information processing approach to study attention, which showed that while children with ADHD differed from controls at all stages of processing, methylphenidate had a greater effect on speed and accuracy for later (e.g., decision making, response organization) than earlier processing components (e.g., encoding; de Sonneville et al. 1994). This study also suggested the utility of a temporal approach to study attention in children with ADHD.

To assess differential effects of methylphenidate dosage, it is necessary to describe effects on brain and behaviour. One methodology that is ideally suited for investigating temporal and spatial characteristics of brain function during cognitive processing is event-related potentials (ERPs). ERPs are electrical potentials produced by discharges of large populations of neurons and are time-locked to aspects of task performance. ERP waveforms are typically designated by their wave polarity (N = negative; P = positive) and order of their occurrence (e.g., P1, N1, P2, N2, P3, etc.) or mean latency in milliseconds following stimulus presentation (e.g., P100, N100, P360, P550, etc.). These components are usually quantified in terms of the peak latency and maximum amplitude from a prestimulus baseline. The cognitive processes linked with each of these waves and their underlying, cortical sources have not been definitively identified; however, increased specificity for ERP components have been determined showing that components can reflect cognitive processes at specific neuroanatomical locations (e.g., Nobre et al. 1994). The following are the cognitive processes associated with attention-related ERP components: N1 is thought to reflect the shifting of attention to a location and is observed mostly in posterior (i.e., parietal) structures (Mangun et al. 1993; Novak et al. 1995); P2 reflects feature detection and is observed centrally and frontally (Luck and Hillyard 1994); N2 reflects target identification when it is observed at anterior locations (Breton et al. 1988); and P3, the most commonly studied component, is thought to reflect updating working memory and post decisional processes. The P3 component is largest over parietal and central regions (Picton 1992). Through systematic analysis of waveforms, one can follow attentional processing from the early stages of initial stimulus detection to subsequent mental representation and response execution.

Although there are a number of ERP studies on children with ADHD, these have dealt mainly with the P3. The findings have indicated that depending on specific task requirements, children with ADHD produce smaller P3s (Klorman et al. 1983) or longer P3 latencies (Taylor et al. 1993). Methylphenidate therapy has been observed to normalize these indices (i.e., increased amplitudes and reduced latencies, respectively) in children with ADHD. Recent work by Verbaten et al. (1994) assessing multiple ERP components during a continuous performance task has demonstrated that methylphenidate increases both N2 and P3 amplitudes, thereby suggesting medication effects for both early and later stages of attentional processing. Although this research signifies a marked advance over previous studies, it was limited by lacking a control group and investigating only a single dose level.

The present investigation aimed at identifying the specific nature of the attentional processing deficit in children with ADHD and the effects of dose of methylphenidate on attention. We compared children with ADHD to normal children on a continuous performance task requiring sustained attention. ERPs were recorded during the task. The children with ADHD were also studied under different methylphenidate dose conditions including placebo, low and high dose. We reasoned that while methylphenidate would be associated with improved performance, there may be different ef-

fects for low versus high dose levels on performance and ERPs. Based on previous findings (Taylor et al 1993), we predicted a decrease in P3 latency on medication. However, it was not evident how methylphenidate would affect the earlier components and whether there would be different optimal dose levels for early (e.g., P2, N2) versus later (e.g., P3) stages of processing.

METHOD

Participants

Twenty 10–12 years old children (16 males and 4 females, mean age = 10.5 ± 1.9 years) with a primary diagnosis of ADHD and 20 age-matched control children without ADHD (16 males and 4 females, mean age = 10.8 ± 1.8 years) participated.

Children with ADHD were recruited from the Child Development Centre (CDC) at the Hospital for Sick Children, where they were assessed for problems relating to attention, hyperactivity or impulsivity by staff developmental pediatricians. All of the children were identified as meeting DSM-III-R criteria for ADHD based on clinical interview, parent and teacher questionnaire data, as well as a computerized structured diagnostic interview. Excluded from the study were subjects with a conduct disorder, internalizing disorder (e.g., anxiety), and low intelligence (IQ < 80). Children with coexisting anxiety were excluded because of the evidence that they may have a differential medication response (Pliszka 1989). A coexisting conduct disorder was used to exclude children in an attempt to reduce the heterogeneity of the sample. Children with a secondary comorbid diagnosis of oppositional defiant disorder (N = 4) or a learning disability (N = 8) identified by the clinic's psychoeducational assessment team were included in the study.

Control children were recruited through announcements posted in local community centers, libraries and schools. All were screened for psychological, neurological, psychiatric, scholastic, learning or attention disorders based on psychometric testing, parent interviews and questionnaire data. None met criteria for problems in any domain.

To assess intelligence of ADHD and control children, two subtests of the Wechsler Intelligence Scale for Children 3rd Edition (Wechsler 1991)—Vocabulary and Block Design—were given. A prorated IQ was determined on the basis of these subtests and was used in screening for subjects with IQs below 80. No subjects met this criterion.

Various rating scales and interviews were used to identify ADHD symptomatology and make a diagnosis. The CLAM (Swanson et al. 1995) is a 15-item scale completed by parents of ADHD and control children. It incorporates items from the IOWA Conners Rating Scale (Pelham et al. 1989) and the Abbreviated Conners Rating Scale (Conners 1973), both of which are commonly used to assess ADHD behaviour. The SNAP (Swanson et al. 1988) is a 23-item scale used to assess ADHD symptomatology at home and at school and was completed by parents of ADHD and control children. The Diagnostic Interview for Children and Adolescents (DICA) (Herjanic 1983) is a computerized diagnostic inventory that provides a variety of information about the child's medical history, psycho-social stressors, and presenting symptomatology for a variety of childhood and adolescent disorders (e.g., ADHD, Oppositional Disorder, conduct Disorder, Mania, etc.). This was completed by parents of ADHD children only, and used by the developmental paediatrician to augment information obtained in the clinical interview with the family.

Procedure

For the ADHD group, a double-blind, placebo-controlled cross-over trial design was used which took place over a consecutive two-day period. All subjects with ADHD were taking stimulant medication and were asked to cease this for 24 hours prior to entering the study. On the morning of the first day (baseline), participants were assessed off medication for intelligence, achievement, and attention. ERPs were recorded during the attentional testing component. Subsequently, children were assessed in the afternoon of the first day and the morning and afternoon of the second day, at which time they were randomly given placebo or a low or high dose of methylphenidate. There was a constraint on the randomization schedule such that high dose was never given in the morning of the second day to avoid possible carryover effects for the afternoon session. Medication and placebo were packaged in gelatin capsules dispensed through the hospital pharmacy. The primary investigator, who was blind to the contents of the capsule, administered the medication 90 minutes prior to attentional testing in sessions two, three and four, to ensure maximum medication effects (Swanson et al. 1978).

The original intent of the study was to compare a lower dose of 0.3 mg/kg methylphenidate directly with a higher dose of 0.7 mg/kg. However, as the CDC usually restricts maximum dose levels (with the occasional exception) to a 20 mg capsule regardless of body weight, this prevented our being able to study dose levels this high, particularly for heavier subjects. The mean for the low dose level was 0.28 mg/kg (range = 0.14 to 0.34 mg/kg) and for the high, 0.56 mg/kg (range = 0.28–0.70 mg/kg). The mean fixed low dose was 10 mg (range = 5–15 mg) and fixed high dose was 18.8 mg (range = 12.5–30 mg). We tend to use fixed doses clini-

cally, but for the study we relied on mg/kg dosing to compare our research with other studies in the literature.

Control children were assessed once only (no medications were given) for intelligence, achievement, and attention. ERPs were recorded during attention testing.

Tests and Measures

Continuous Performance Test (CPT). This task was adapted from Klee and Garfinkel's (1983) task in which subjects observe a long string of visual stimuli on the computer monitor and respond whenever a particular target stimulus appears. In the current study, a CPT-double paradigm was used, in which participants responded after seeing a repeated letter. The CPT-double version has also been used by other researchers in developmental studies (e.g., Friedman et al. 1985). Errors of omission serve as a measure of inattention, and errors of commission, while somewhat controversial, serve as a measure of impulsivity (Halperin et al. 1988).

The task was presented on a computer, programmed using the Gentask software package for the NeuroScan system (Virginia). The children were shown a total of 360 letters one at a time, 20% of which involved a repeating letter. Stimulus duration was 50 msec and the interstimulus interval was 1000 msec. The task was to make a button press as quickly as possible whenever two consecutive identical letters had appeared. Response times were measured from the onset of the target stimulus (i.e., the second, matching letter) to the onset of the bottom press. Response times less than 200 msec, reflecting premature responses, were eliminated. Three behavioural measures were recorded: hits, false alarms and reaction time. Hits provided a measure of attention and false alarms provided a measure of impulsivity. ERPs were recorded while children performed this task.

ERPs. ERPs were recorded during the CPT using an electrode cap (Electro-Cap Inc., Ohio), from 27 active electrodes (Fpz, Fpl, Fp2, FZ, F3, F4, F7, F8, Fcl, Fc2, Fc3, FC4, Cz, C3, C4, Pz, P3, P4, Pc3, Pc4, T3, T4, T5, T6, Oz, O1, and O2). A noncephalic (spinal) reference was used and the electrooculogram was monitored from the outer canthus and supraorbital ridge of the eye to enable the rejection of trials with eye movement artefact ($> \pm 100$ μV). Electrode impedance was below 5 Kohms.

ERPs were recorded with a bandpass of 0.1–30 Hz. The sweep was 800 msec and started 50 msec prior to stimulus onset. Trials that did not require a response were coded as non-target trials, whereas trials that required a response were coded as target trials. Only target rials on which a correct, behavioural response was made were analyzed.

Data Analysis

For behavioural and CPT data, the ADHD group in the baseline condition and in each of the three medication conditions (placebo, low dose, high dose) was compared with controls using t-tests. To account for the multiple comparisons on each variable, we used a Bonferonni p-correction for the accepted level of significance, which was determined to be 0.01. Within the ADHD group, repeated measures ANOVAs were used to compare medication conditions.

For the ERP data, grand averages were computed for correct trials, which served as templates for peak detection within each child's individual data. These were determined for each group and for each medication condition within the ADHD group. The N1, N2, and P2 peaks were measured within 50 msec ($\pm$ 25) of the peak's latency and the P3 peak was measured within 150 msec ($\pm$ 75) of the peak's latency in the appropriate grand average. Peak latencies and amplitudes were measured from all 27 electrode sites. The data were submitted to repeated measures ANOVAs using Greenhouse Geisser adjusted degrees of freedom (where required). The data were then analyzed as a function of hemisphere using lateral electrodes over each hemisphere and as a function of anterior/posterior location using electrodes over anterior and posterior scalp locations. Results were considered to be significant if the p-value was less than 0.01.

RESULTS

Table 1 provides the results for the two behavioural inventories completed by parents. The results show significant ($p < .001$) elevations on all scales for children with ADHD. The differences were largest for the Inattention scales of the SNAP and CLAM and the Impulsivity scale of the SNAP.

Table 1. Mean Scores for ADHD and Control Children on the SNAP and IOWA Conners

Measure	ADHD Score (s.d.)	Controls Score (s.d.)
SNAP		
Total Score	30.86[a] (8.74)	3.52 (3.02)
Hyperactivity scale	6.83[a] (4.33)	1.05 (1.10)
Inattention scale	10.81[a] (2.84)	1.26 (1.33)
Impulsivity scale	12.45[a] (3.76)	1.16 (1.30)
Peer interaction scale	9.36[a] (5.39)	1.89 (2.32)
CLAM		
Iowa Conners Scales		
Inattention/overactivity	10.70[a] (2.51)	1.10 (1.05)
Oppositional/defiant	9.21[a] (4.22)	1.68 (2.11)
Abbreviated Conners	20.08[a] (5.61)	2.26 (1.82)

[a] < 0.001.

Table 2. Performance on the CPT, Showing % Hits, % False Alarms, Mean RT, and Mean Standard Deviation in RT to Correctly Identified Targets for the Control and ADHD Groups (± SD)

		ADHD			
	Controls	**Baseline**	**Placebo**	**Lower Dose**	**Higher Dose**
% hits	71.4 (15.4)	57.9[a] (18.1)	53.6[a] (18.8)	61.4 (19.9)	66.7 (17.1)
% false alarms	3.3 (2.9)	11.7[b] (12.2)	8.3[a] (8.9)	4.8 (4.8)	4.7 (4.5)
Mean RT (msec)	577.15 (46.0)	510.20[b] (99.21)	525.76[a] (86.7)	552.85 (63.24)	546.74 (77.28)
Mean SD (msec)	131.74 (26.1)	167.69[b] (44.31)	161.39[a] (52.43)	135.22 (38.21)	133.61 (25.53)

[a] $p < .05$ for comparison of ADHD group and control group.
[b] $p < .01$ for comparison of ADHD group and control group.

Behavioural Measures

Accuracy. Table 2 presents the accuracy data for the CPT across all medication conditions. The control group produced more correct hits to targets (i.e., was more attentive) and fewer false alarms (i.e., was less impulsive) than the ADHD group in the placebo condition ($p < .01$) and showed a trend toward greater accuracy in the baseline condition ($p < .05$). The ADHD group did not differ from controls on either accuracy measure during the low or high dose conditions.

Within the ADHD group, there was a significant medication effect for false alarms, $F(3,57) = 4.82$, $p < .01$. Post hoc testing revealed that fewer false alarms were made during low and high dose conditions compared to baseline or placebo. For hits, the medication effect showed a trend only, $F(3,57) = 3.37$, $p < .05$, reflecting the higher percentage of hits in the high dose than placebo condition. These results suggest a differential effect of dose with the high dose reducing both attentive and impulsive errors and the low dose, only impulsive errors.

Reaction Time. Table 2 presents the RT data, showing that the ADHD group was significantly faster and more variable than controls in the baseline condition ($p < .01$). A trend to faster and more variable RTs than controls was observed for the placebo condition ($p < .05$). There were no differences in RTs between controls and ADHD on the low and high dose medication conditions.

Within the ADHD group, repeated measures ANOVAs were not significant for RT or standard deviation of RT.

ERPs

Figure 1 shows the grand averaged target ERPs from the ADHD children on baseline and control children; the components measured are indicated. The distribution of these peaks did not vary between groups. The N1 and P2 components measured were posteriorly located; the N2 was maximal fronto-centrally and the P3 had a centro-parietal distribution. With this task, there were no significant hemispheric asymmetries in the components.

N1. There were no significant differences between the control and ADHD groups at baseline, on placebo or on drug for N1 latency or N1 amplitude (see Table 3). However, the ADHD group on lower dose showed a trend to shorter N1 latencies ($p = .02$). Comparing the ADHD group across medication conditions, we observed a marginally significant difference ($p = .015$) between the placebo and the low dose condition, the latter having a shorter N1 latency.

P2. There were no significant differences between controls and the ADHD group in P2 amplitude or latency, although the ADHD group showed trends of shorter P2 latencies at baseline, $t(33) = 2.40$, $p = .03$, and longer P2 latencies at the high dose, $t(32) = 2.12$, $p = .04$, compared to controls.

Within the ADHD group, there was a significant medication effect for latency but not amplitude. This reflected the significantly longer P2 latencies on high dose medication ($p = .008$) and marginally longer P2 latencies on low dose ($p = .04$) than baseline (Figure 2).

N2. Compared to controls, the ADHD group showed significantly ($p < .01$) faster N2 latencies at baseline and on placebo and low dose medication, $t(31) = 4.63$, 3.41, and 6.16, respectively (see Figure 2). There was no difference in N2 latencies between the control and ADHD groups on the high medication dose. Inspection of individual data revealed that all of the N2 latencies of children with ADHD in baseline, placebo, and low-dose conditions were shorter than those of controls. There were no differences between groups in N2 amplitudes.

Within the ADHD group, there was significant medication effect for latency, reflecting longer N2 latencies on high dose versus baseline or placebo conditions ($p = .001$ for both comparisons). There were no medication effects on N2 amplitudes.

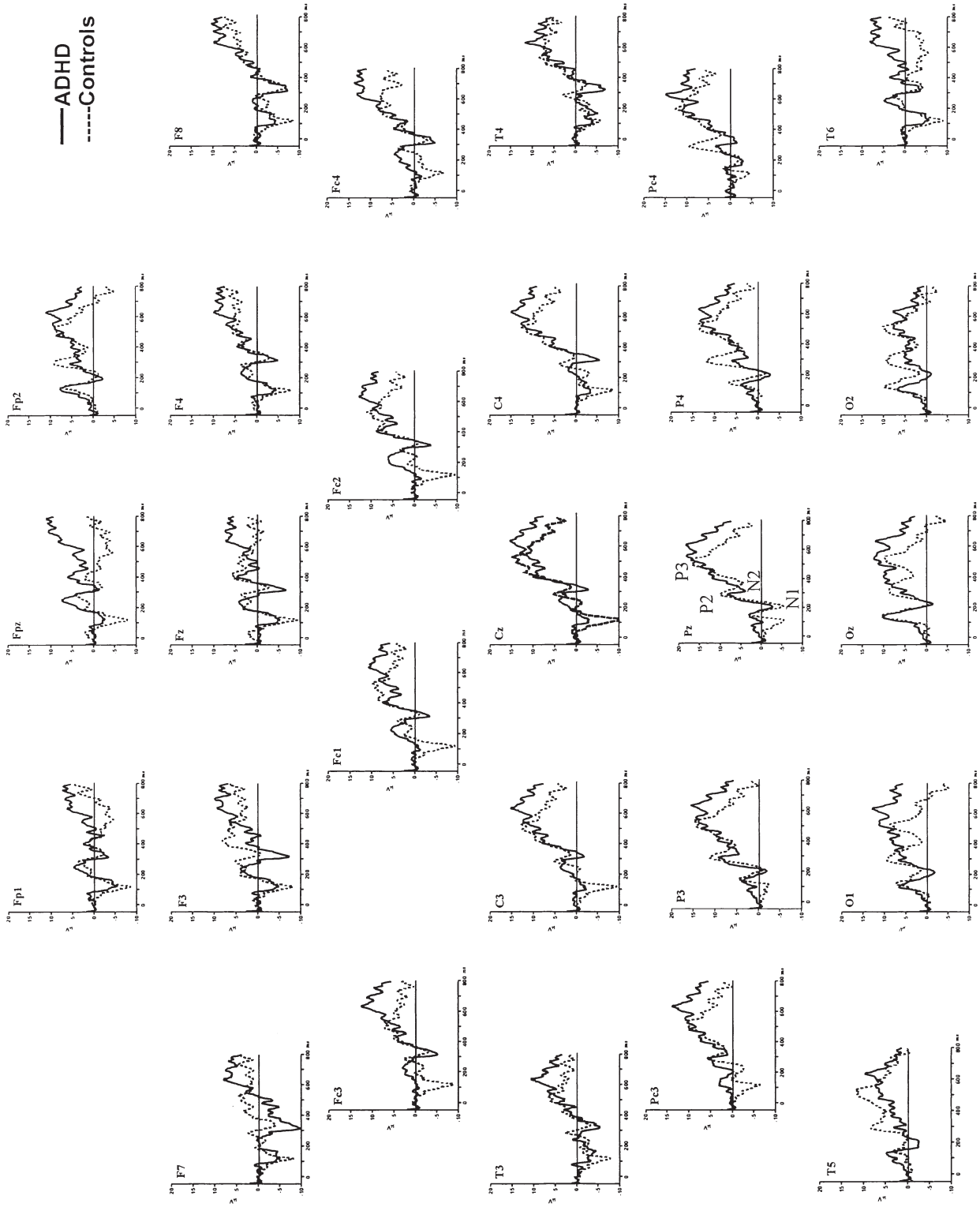

Figure 1. Grand averaged ERPs from the group of ADHD children (dark line) on baseline and the group of control children (light line) from all electrode sites. The components measured are indicated on the Pz electrode.

Table 3. Mean N1, N2, P2, and P3 Latencies (msec) and P3 Amplitude (μv) for the Control Group and ADHD Groups (± SD)

		ADHD			
	Controls	**Baseline**	**Placebo**	**Lower Dose**	**Higher Dose**
N1 latency	199.97 (8.02)	194.88 (5.57)	207.19 (8.86)	174.12[a] (8.23)	194.18 (6.21)
P2 latency	292.51 (8.07)	275.85[a] (10.21)	295.12 (2.98)	302.96[a] (6.21)	310.65[b] (5.10)
N2 latency	377.03 (16.16)	312.97[b] (11.14)	336.54[b] (8.10)	330.44[b] (13.08)	391.67 (6.41)
P3 latency	542.47 (37.52)	616.15[b] (32.69)	605.95[a] (34.92)	541.91 (32.21)	496.8 (26.56)
P3 amplitude	17.84 (3.14)	18.94 (3.84)	14.56 (2.84)	20.24 (3.40)	19.15 (4.24)

[a] $p < .05$ for comparison of ADHD and controls.
[b] $p < .01$ for comparison of ADHD and controls.

P3. The ADHD group produced significantly longer P3 latencies than controls at baseline and on placebo ($t(32) = 3.19$ and $t(30) = 2.66$, $p < .01$, respectively) but did not differ from controls in P3 latencies at either dose level. The groups also did not differ in their P3 amplitudes in any of the conditions (Figure 3).

Within the ADHD group, a significant overall medication effect was observed; for the high dose condition, P3 latencies were significantly shorter than placebo and baseline conditions, ($F(1,32) = 8.41$, $p = .001$) (see Figure 2). P3 latencies in the low dose condition were marginally shorter than for placebo or baseline ($p = .03$). There were no differences in the P3 latencies between the high or low dose conditions. Inspection of individual data revealed that regardless of dose level, methylphenidate reduced the P3 latencies from placebo for all children with ADHD. Significant changes in P3 amplitudes with medication were not observed.

Correlation between N2 and P3 Latencies. Significant correlations were obtained between N2 and P3 latencies in the baseline and placebo conditions, $r(18) = 0.86$ and 0.62, $p < .001$. The effect was marginally significant at the low dose level, $r(18) = 0.45$, $p < .05$, and disappeared at the high dose level. N2 and P3 latencies were not correlated in the control group.

ERP Distribution. Figure 1 shows the grand average ERPs at all electrode sites for the ADHD group on baseline and the control group: there were no significant differences between ADHD and control groups in the ERP components measured by hemisphere or anterior/posterior distribution. Similarly, within the ADHD group, there were no effects of the medication conditions on the topographical distributions of the components.

DISCUSSION

The results showed that the ADHD group off medication or on placebo produced fewer hits and committed more false alarms than controls on a continuous performance task, suggesting the ADHD group was less able to sustain attention and was more impulsive. Although these behavioural measures improved following methylphenidate administration, there were different effects depending on dose level. At the low dose level (0.28 mg/kg), only indices of impulsivity improved (to control group level) in children with ADHD, as indicated by a significant decrease in the false alarm rate. In contrast at the higher dose level (0.56 mg/kg), indices of both impulsivity and inattention improved. In addition, the ADHD group off drug had shorter RTs to targets than controls, while on methylphenidate, ADHD RTs became longer and the RT changes were consistent with changes in behaviour.

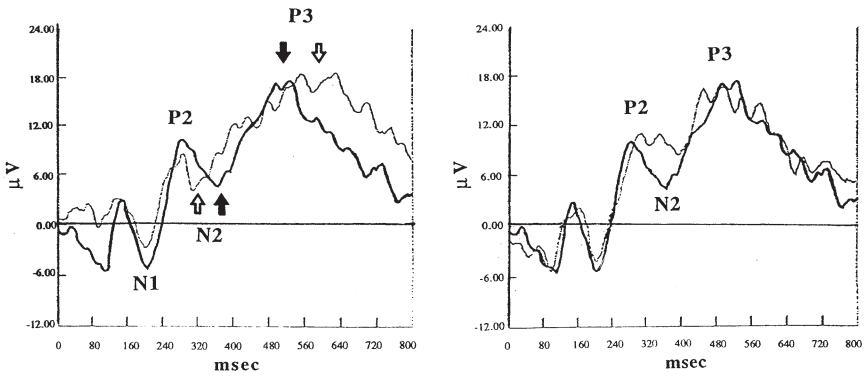

Figure 2. ERPs from Pz electrode from the control children (dark line) overplotted with the ADHD group (light line) from baseline (left side) and from the higher dose of methylphenidate conditions (right side). Note the differing latencies of the P2 and P3 off medication (dark arrows, control children; open arrows ADHD children), but the lack of significant latency differences in the ERP components with medication (right side).

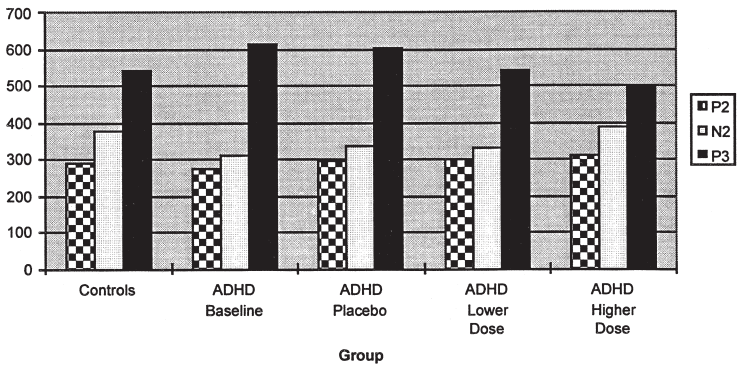

Figure 3. The mean latencies (msec) of N2, P2 and P3 for the control group and the ADHD across medication conditions are shown.

The ERP results revealed that children with ADHD off medication and on placebo had shorter N2 latencies than controls; similar but less strong effects were observed for the P2 latencies. In contrast, P3 latencies of children with ADHD off medication were longer than controls. These effects were observed in all of the children with ADHD when individual data were examined.

When children with ADHD were treated with methylphenidate, significant changes in the ERP latencies were observed and there was a differential effect of dose level for N2 and P3 components. At the low dose level (0.28 mg/kg), only the P3 latency changed, whereas at the higher dose level, both components changed. P3 latencies became shorter at the low dose level and were comparable to the control group. At the higher dose level, P3 was further reduced while the N2 and (to a lesser degree) P2 latencies became longer and comparable to controls. This is to our knowledge the first report of a dissociation of ERP components with methylphenidate dose levels.

There was also a dissociation in the effects of the two doses of medication on the behavioural measures of task performance. Specifically, false alarms (impulsive errors) were improved with both doses and hits (attention) with the high dose only. N2 and P3 latencies were correlated in children with ADHD off medication; these components were not correlated in children with ADHD on medication or in the non-ADHD controls. This suggests a normalization on medication with the abnormally fast N2 latencies slowing down and the abnormally slow P3 latencies speeding up, resulting in reduced impulsivity and increased attention.

Consistent with several recent studies in the literature, we did not see amplitude effects on the P3 with methylphenidate, but only latency effects (Klorman et al. 1988; Taylor et al. 1993; Sunohara et al. 1997). Although earlier studies often reported an increase in amplitude with methylphenidate, this was likely partially attributable to the averaging techniques employed, in which the ERPs were averaged based on stimulus category only, rather than on both stimulus and response categories (Verbaten et al. 1994). When only hits (target stimuli with correct behavioural responses) are averaged, P3 amplitude differences are not as frequently seen. Also, our stimuli were presented very briefly and speeded responses (hence processing) were encouraged. We also saw no amplitude effects in the components earlier than the P3, either between groups, or as a function of medication. Novak et al. (1995) also found no drug or group effects on the N1, and only one of several analyses (invalidly cued right targets) produced lower P3 amplitudes in the ADHD children; the authors stated that the relevance of this finding was uncertain. Consistent with earlier visual attention studies, the distribution of the P3 did not vary as a function of group (Taylor et al. 1993; Novak et al. 1995; Sunohara et al. 1997); the ADHD children do not appear to have abnormal topographies. However, few studies with ADHD children have included a large electrode array to analyze distribution, and in future studies, or with tasks that tap other aspects of attention, such differences may emerge.

The stages of processing required for the CPT task were considered, to better link our ERP results with these stages. In the task, the subject is briefly shown (50 msec) a letter on the screen, which must be perceived and the features of which must be represented and briefly stored in memory. Then the subject must wait (1000 msec) for the second stimulus which must similarly be detected, encoded, and placed in memory, at which point the stimulus representations are compared. If they match, a response is made and both representations are deleted as the subject waits for the next stimulus series; if they do not match, a response is inhibited and the first stimulus is deleted while the second is held in memory for the next comparison.

To develop a temporal attentional processing model of this task, specific ERP components must be incorporated. As we analyzed components only when a correct response was made on a hit trial, only these processes will be considered. The P2 component is thought to reflect feature detection (Luck and Hillyard, 1994) and would occur in the present task after the second stimulus is detected. The N2 component reflects focused at-

tention to stimulus features (Breton et al. 1988). This component likely indexes the process of stimulus classification in the present task (i.e., whether the stimuli match and hence whether to respond). The P3 is frequently interpreted to reflect post decisional processing and/or the updating of working memory (Karis et al. 1984; Picton 1992). In the present task, this would involve cleaning the memory slate completely following a hit trial and preparing for the next stimulus.

In the ADHD group off medication, P2 and N2 latencies were shorter than for controls. This suggests the children with ADHD detected and represented or classified information about the second letter more rapidly or perhaps in less detail than controls. This faster processing at this stage may reflect their impulsivity, suggesting the ADHD group responded prior to adequately processing the stimulus information. In contrast, their P3 latencies were longer and may reflect their inattention as they are taking longer to update memory and prepare for the next stimulus.

Methylphenidate was observed to normalize these effects but there were different dose-level effects. On low dose, only the P3 was reduced, to a level almost identical to controls. This suggests that at this dose level, children with ADHD were faster at post decisional processes; they may also have been less distracted during this interval. However, their N2 latencies still remained significantly faster than controls and were unchanged from baseline while the P2 latency was starting to increase but the effect was not significant. This suggests that at the lower dose, children with ADHD are still detecting and representing information too quickly and potentially less accurately.

At the higher methylphenidate dose, P2 and N2 latencies became significantly longer and did not differ from controls suggesting slower and more accurate stimulus encoding. The P3 latency, however, was even faster than controls by about 50 msec. These findings suggest that this higher dose level is effective in normalizing both early and later ERP components and presumably reflects improved processing of information. For the P3, however, the lower dose was sufficient for achieving the improvement.

This study, which provides very suggestive evidence on the mechanisms of methylphenidate action, has limitations which need to be considered. First, as the ADHD children were diagnosed by DSM-III-R criteria and were ostensibly, but not definitively, of the combined subtype, we cannot generalize our findings to all children with ADHD. It is important to repeat these studies with a sample representing different subtypes of ADHD diagnosed by the current DSM-IV standards. Second, the use of a maximum of 20 mg did not allow us to examine a further increase in methylphenidate dose level. While benefits of the two different dose levels were evident, it is not obvious whether performance would have continued to improve or would have deteriorated (as measured behaviourally and neurophysiologically) with increased doses.

In conclusion, this study has addressed the effects of methylphenidate on attentional processing, and has suggested that children with ADHD have deficits at separate stages of attention. Although methylphenidate was found to be effective in normalizing these deficits by slowing down the early processes and speeding up the later processes to normal levels, there were different effects of the two dose levels. Higher doses of medication were required to slow down the early response decision processes, while both lower and higher doses hastened the later post-decisional processes. This suggests a model for attentional dysfunction involving distinct components of attention that are disrupted in ADHD and respond differentially to methylphenidate.

ACKNOWLEDGMENTS

This study was conducted in partial fulfillment of Glen Sunohara's Ph.D. dissertation. It was supported by a RESTRACOM graduate studentship from the Research Institute at The Hospital for Sick Children. Special appreciation is extended to the staff at the Child Development Centre at The Hospital for Sick Children for facilitating this work.

REFERENCES

Barkley RA (1994): Impaired delayed responding. In Routh DK (ed), Disruptive Behaviour Disorders in Childhood. New York, Plenum Press

Barkley RA (1997): Behavioural inhibition, sustained attention, and executive functions; Constructing a unifying theory of ADHD. Psychol Bull 121(1):65–94

Breton F, Ritter W, Simson R, Vaughan HGJ (1988): The N2 component elicited by stimulus matches and multiple targets. Biol Psychol 27:23–44

Colby CL (1991): The neuroanatomy and neurophysiology of attention. J Child Neurol 6(suppl):S90–S118.

Conners CK (1973): Rating scales for use in drug studies with children. (Special Issue: Pharmacotherapy with Children.) Psychopharmacol Bull 9:24–84

de Sonneville LM, Nijiokiktjien C, Bos H (1994): Methylphenidate and information processing. Part 1: Differentiation between responders and non responders; Part 2: Efficacy in responders. J Clin Exp Neuropsychol 16:877–897

Douglas VI, Barr RG, Desilets J, Sherman E (1995): Do high doses of stimulants impair flexible thinking in ADHD? J Am Acad Child Adolesc Psychiatry 34:877–885

Dyme IZ, Sahakian BJ, Golinko BE, Rabe EF (1982): Perservation induced by methylphenidate in children: Preliminary findings. Prog Neuropsychopharmacol Biol Psychiatry 6:259–273

Friedman D, Boltri J, Vaughan H, Erlenmeyer-Kimling L (1985): Effects of age and sex on the endogenous brain potential components during two continuous performance tasks. Psychophysiology 22:440

Gittelman R, Mannuzza S (1985): Diagnosing ADD-H in adolescents. Psychopharmacol Bull 21:237–242

Halperin JM, Wolfe LE, Pascualvaca DM, Newcorn JH, Healey JM, O'Brien JD, Morganstein A, Young JG (1988): Differential assessment of attention and impulsivity in children. J Am Acad Child Adolesc Psychiatry 27:326–329

Herjanic B (1983): The Washington University Diagnostic Interview for Children and Adolescents. St. Louis, MO, Washington University Medical Center

Karis D, Fabiani M, Donchin E (1984): P300 and Memory: Individual differences in the von Restorff Effect. Cogn Psychol 16:177–216

Klee SH, Garfinkel BD (1983): The computerized continuous performance task: A new measure of inattention. J Abnorm Child Psychol 11:87–496

Klorman R, Salzman LF, Borgstedt AD (1988): Brain event-related potentials in evaluation of cognitive deficits in attention deficit disorder and outcome of stimulant therapy. In Bloomingdale LM (ed), Attention Deficit Disorder, Vol 5. Oxford/New York, Pergamon Press

Klorman R, Salzman LF, Pass HL, Borgstedt AD, Dainer KB (1983): Effects of two doses of methylphenidate on cross-situational and borderline hyperactive children's evoked potentials. Electroencephalogr Clin Neurophysiol 56:169–185

Luck SJ, Hillyard SA (1994): Electrophysiological evidence for parallel and serial processing during visual search. Percept Psychophys 48:603–617

Malone MA, Kershner JR, Siegel L (1988): The effects of methylphenidate on levels of processing and laterality in children with attention deficit disorder. J Abnorm Child Psychol 16:379–395

Malone MA, Kershner JR, Swanson JM (1994): Hemispheric processing and methylphenidate effects in attention deficit hyperactivity disorder. J Child Neurol 9:181–189

Mangun GR, Hillyard SA, Luck SJ (1993): Electrocortical substrates of visual selective attention. In Meyer D, Kornblum S (eds), Attention and Performance XIV. Hillsdale, New Jersey, Erlbaum

McCracken JT (1991): A two-part model of stimulant action on attention deficit hyperactivity disorder in children. J Neuropsychiatry 3:201–209

Mefford IN, Potter WZ (1989): A neuroanatomical and biochemical basis for attention deficit disorder with hyperactivity in children: A defect in tonic adrenaline mediated inhibition of locus ceruleus stimulation. Med Hypotheses 29:33–42

Mirsky AF, Anthony BJ, Duncan CC, Ahearn MB, Kellam SG (1991): Analysis of the elements of attention: A neuropsychological approach. Neuropsychol Rev 2:109–145

Nobre AC, Allison T, McCarthy G (1994): Word recognition in the human inferior-temporal lobe. Nature 372:260–263

Novak GP, Solanto M, Abikoff H (1995): Spatial orienting and focused attention in attention deficit hyperactivity disorder. Psychophysiology 32:546–559

Pelham WE, Milich R, Murphy D, Murphy HA (1989): Normative data on the IOWA Conners teaching rating scale. J Clin Child Psychol 18:259–262

Pennington BF, Ozonoff S (1996): Executive functions and developmental psychopathology. J Child Psychol Psychiatry 37:51–87

Picton TW (1992): The P300 wave of the human event-related potential. J Clin Neurophysiol 9:456–479

Pliszka SR (1989): Effects of anxiety on cognition, behaviour, and stimulant response in ADHD. J Am Acad Child Adolesc Psychiatry 28:882–887

Pliszka SR, McCracken JT, Maas JW (1996): Catecholamines in attention-deficit hyperactivity disorder: Current perspectives. J Am Acad Child Adolesc Psychiatry 35(3): 264–272

Posner MI, Cohen A (1987): Isolating attentional systems: A cognitive-anatomical analysis. Psychobiology 15:107–121

Schachar R, Tannock R, Logan G (1993): Inhibitory control, impulsiveness, and attention deficit hyperactivity disorder. Clin Psychol Rev 13:721–739

Shaywitz BA, Shaywitz SE (1988): Increased medication use in attention-deficit hyperactivity disorder: Regressive or appropriate. JAMA 260:2270–2272

Shue KL, Douglas VI (1992): Attention deficit hyperactivity disorder and the frontal lobe syndrome. Brain Cognit 20(1):104–124

Solanto MV, Wender EH (1989): Does methylphenidate constrict cognitive functioning? J Am Acad Child Adolesc Psychiatry 36:897–902

Sprague RL, Sleator EK (1977): Methylphenidate in hyperkinetic children: Differences in dose effects on learning and social behaviour. Science 198:1274–1276

Stuss DT, Shallice T, Alexander MP, Picton TW (1995): A multi-disciplinary approach to anterior attentional functions. Ann N Y Acad Sci 769:191–211

Sunohara GA, Voros JG, Malone MA, Taylor MJ (1997): Effects of methylphenidate in children with attention deficit hyperactivity disorder: a comparison of event-related potentials between medication responders and non-responders. International J Psychophys 27:9–14

Swanson JM, Kinsbourne M, Roberts W, Zucker K (1978): Time-response analysis of the effect of stimulant medication on the learning ability of children referred for hyperactivity. Pediatrics 61:21–29

Swanson J, Nolan R, Pelham W (1988): Swanson, Nolan and Pelham rating scale (SNAP). Pittsburgh, PA, Department of Psychiatry, Western Psychiatric Institute and Clinic

Swanson JM, Cantwell D, Lerner M, McBurnett K, Hanna G (1991): Effects of stimulant medication on learning in children with ADHD. J Learn Disab 24:219–230

Swanson JM, McBurnett K, Christian DL, Wigal T (1995): Stimulant medications and the treatment of children with ADHD. In Ollendick TH, Prinz J (eds), Advances in Clinical Child Psychology, Vol 17. New York, Plenum Press

Szatmari P, Offord DR, Boyle MH (1989): Ontario child health study: Prevalence of attention deficit disorder with hyperactivity. J Child Psychol Psychiatry 30:219–230

Tannock R, Schachar R (1992): Methylphenidate and cogni-

tive perseveration in hyperactive children. J Child Psychol Psychiatry 33:1217–1228

Tannock R, Schachar RJ, Carr RP, Logan GD (1989): Dose-response effects of methylphenidate on academic and overt behaviour in hyperactive children. Pediatrics 84:648–657

Taylor MJ, Voros JG, Logan WJ, Malone MA (1993): Changes in event-related potentials with stimulant medication in children with attention deficit hyperactivity disorder. Bio Psychol 36:139–156

Thurston CM, Sobol MP, Swanson J, Kinsbourne M (1979): Effects of methylphenidate on selective attention in hyperactive children. J Abnorm Child Psychol 7:471–481

van der Meere JJ, Sergeant JA (1987): A divided attention experiment with pervasively hyperactive children. J Abnorm Psychol 15:279–392

van der Meere JJ, Sergeant JA (1988): Controlled processing and vigilance in hyperactivity: Time will tell. J Abnorm Child Psychol 15:279–292

van der Meere J, Wekking E, Sergeant J (1991): Sustained attention and pervasive hyperactivity. J Child Psychol Psychiatry 21:275–284

Verbaten MN, Overtoom CC, Koelga HS, Swaab-Barneveld H, van der Gaag RT, Buitelaar J, van Engeland H (1994): Methylphenidate influences on both early and late ERP waves of ADHD children in a continuous performance test. J Abn Child Psychol 22:561–578

Voeller KS (1991): Toward a neurobiologic nosology of attention deficit hyperacticity disorder. J Child Neurol 6(suppl): S2–S8

Wechsler D (1991): Wechsler Intelligence Scale for Children - Third Edition. Toronto, Harcourt Brace & Company

Wender PH (1987): The hyperactive child, adolescent, and adult. New York, Oxford University Press

Whalen CK, Henker B (1991): Social impact of stimulant medication treatment for hyperactive children. J Learn Disab 24:231–241