METHYLPHENIDATE EFFECTS ON FOCUSED AND SELECTIVE ATTENTION PROCESSING IN CHILDREN WITH ADHD

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is the most prevalent psychiatric disorder of childhood. Despite extensive research on ADHD, two critical issues remain unresolved. First, the precise nature of the attentional processing deficit remains largely unknown. Second, although methylphenidate continues to be the most common intervention for ADHD, the mechanisms through which this medication exerts its effectiveness are not completely understood. The present study was designed to examine both the attentional processing deficit in children with ADHD and the effects of methylphenidate on attentional processing.

Performance on focused and selective attention tasks were compared in 20 children with a DSM-III-R diagnosis of ADHD and 20 children without ADHD. Medication effects were studied using a double blind, placebo-controlled design involving a lower (0.26mg/kg) and a higher (0.56 mg/kg) dose of methylphenidate. Event-related potentials were recorded and analyzed in the focused attention task only. On the focused attention task, the results revealed that the ADHD group off medication had lower levels of attention, higher impulsivity, and shorter reaction times to targets than children without ADHD. For these behavioural measure of focused attention, lower doses of methylphenidate normalized performance of the ADHD group and higher doses of methylphenidate did not improve performance further. The ERP data showed that off medication, the N2 latencies were shorter in the ADHD group than in the children without ADHD. The latency of this
component became longer in the ADHD group on higher doses of methylphenidate only. In contrast, the P3 latency was longer in children with ADHD off medication but was reduced (normalized) on both lower and higher doses of methylphenidate.

For the selective attention task, specific attentional processing deficits were not found and methylphenidate was not found to affect performance.

The combined performance and ERP data for the CPT were used to develop an attentional processing model. This model suggests that children with ADHD are faster in earlier aspects of attentional processing (stimulus evaluation and response decision), which was reflected in their greater impulsivity and in their faster reaction times and slower in post-decisional attentional processes, which creates greater inattentiveness. Methylphenidate acts to normalize these specific attentional processes, but there are different effects for different dose levels. Higher doses normalize both early stimulus evaluation and response decision processes as well as later post-decisional attentional processes, whereas lower doses normalize only the later post-decisional attention processes.
ACKNOWLEDGMENTS

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Completing a thesis is much like running a marathon. A long and hard struggle, but very satisfying in the end. Thank you!
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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is the most common psychiatric disorder of childhood (Swanson, Cantwell, Lerner, et al., 1991a), with estimates of prevalence in the general population at 9% in boys and 3% in girls (Szatmari, Offord, & Boyle, 1989). The disorder is characterized by problems in the areas of attention, overactivity, and impulse control. These problems are frequently associated with academic difficulties (Barkley, 1990) and pervasive difficulties with social interaction. ADHD is often comorbid with other conditions such as conduct disorder, oppositional defiant disorder, and learning disabilities. Stimulant medication, primarily methylphenidate, is the most common treatment for ADHD (Swanson, McBurnett, Christian, & Wigal, 1995) being used to treat an estimated 60 to 90% of diagnosed cases in the United States (Whalen & Henker, 1991).

In the past three decades, ADHD has been the focus of over two thousand studies. Despite this extensive research, two critical issues in ADHD remain unresolved. First, there remains a lack of understanding of the precise nature of the attentional deficit in ADHD. Second, the mechanism through which methylphenidate manifests its effects on attentional processing remains unknown. These are two issues that are central in the present study.

ADHD has been widely examined across a number of perspectives that involve neurocognitive, neuroimaging, neurochemical and neurophysiological disciplines. A major goal of each approach has been to identify the underlying pathophysiology of this disorder and although each has been successful in providing partial evidence, to date the complete specification regarding the etiology of the disorder remains unknown. For example, although the neuroimaging and neurocognitive studies have been useful in identifying potential neuroanatomical regions that may be involved in ADHD, their results are inconclusive and suggest further study. In addition, while studies using an electrophysiological approach to examine the specific temporal components of attentional...
processing in children with ADHD have identified potential components that may be
dysfunctional, they need to be investigated further to identify specific and consistent
attentional processing deficits. Thus, the precise nature of the attentional deficit in ADHD
remains to this date largely unknown and is still a critical issue for further research.

Stimulant medications are the most common treatment for ADHD. Several
neurochemical theories have been advanced on the basis of the generally accepted
effectiveness of stimulant medications in treating the disorder; however, the exact
neurochemical basis of ADHD has still not been adequately delineated and the current
neurochemical theories need to be tested empirically. As a result, the precise mechanism
through which methylphenidate exerts its effectiveness in treating the disorder is not
adequately understood. This is a second critical issue that remains unresolved in ADHD
research.

This study tried to address these two outstanding issues in children with ADHD by
directly studying their attentional processing and by examining how methylphenidate exerts
its effects on specific components of attentional processing. The following section will
review the current understanding of the attentional processing in ADHD. This review will
also highlight that despite the widespread use of stimulant medications and clinical
concerns of adverse medication effects, it is still unclear on precisely how methylphenidate
exerts its effects on attentional processing. Event-related potentials (ERPs) will be
introduced as a sensitive and noninvasive method for examining the temporal aspects of
attentional processing, and the effects of methylphenidate on these processes. Through this
review, a model of attentional processing, based on the processes involved in the
Continuous Performance Test (CPT) and a selective attention task will be introduced that
may provide insight into both the nature of the attentional deficit in ADHD and the effects
of methylphenidate on attentional processing.
Attentional Processing in ADHD - What is the Nature of the Attentional Processing Deficit?

Diagnostic Issues in ADHD - Lack of Consensus on the Nature of the Attentional Deficit

Attention deficit/hyperactivity disorder (ADHD) is a syndrome characterized by a constellation of behaviours that include inattention, impulsivity, and hyperactivity. Historically, there have been a number of changes in the conceptualization of ADHD, which reflect different classification systems that have been used for diagnosis. Prior to 1970, the core feature of ADHD was considered to be hyperactivity, as reflected in the term used to describe the disorder: Hyperkinetic Reaction of Childhood (Diagnostic and Statistical Manual of Mental Disorders (DSM), 2nd edition, 1968). In the decade that followed, this conceptualization changed to acknowledge the growing awareness that a deficit in attention was central to the disorder (Douglas, 1972). The DSM-III (1980) version incorporated this conceptualization with the introduction of the diagnosis Attention Deficit Disorder (ADD) as an independent disorder, along with the identification of three symptom domains (inattention, impulsivity and hyperactivity) and two subtypes of the disorder (ADD with and without hyperactivity). Next, in DSM-III-R (1987), the diagnostic classification changed dramatically with the merger of the three separate symptom domains in the previous classification system under a common rubric, Attention Deficit Hyperactivity Disorder (ADHD).

The most recent classification system DSM-IV (1994) has re-introduced multiple domains of symptoms and multiple subtypes of the disorder. In contrast to DSM-III (1980), the current version acknowledges two rather than three domains of symptoms by merging impulsivity and hyperactivity symptom domains while keeping the inattention domain separate. In addition, three subgroups of children with the disorder are identified: a predominantly inattentive type, a predominantly hyperactive/impulsive type, and a combined type. The diagnostic symptoms of ADHD specified by DSM-IV are listed in Table 1. The presence of at least 6 of 9 symptoms from both symptom domains are
required for a diagnosis of ADHD combined type, while the presence of at least 6 of 9 symptoms in only one of the two domains is sufficient for a diagnosis of one of the ADHD subtypes. The complete diagnostic criteria for ADHD are presented in Appendix 1.

Table 1.

**DSM-IV symptoms of ADHD**

<table>
<thead>
<tr>
<th>Inattention</th>
<th>Impulsivity/Hyperactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>fails to give close attention to detail</td>
<td>fidgets with hands or feet or squirms</td>
</tr>
<tr>
<td>has difficulty sustaining attention</td>
<td>leaves seat in classroom</td>
</tr>
<tr>
<td>does not seem to listen</td>
<td>runs seat in classroom</td>
</tr>
<tr>
<td>does not follow through (fails to finish)</td>
<td>runs about or climbs when inappropriate</td>
</tr>
<tr>
<td>has difficulty organizing tasks</td>
<td>difficulty playing quietly</td>
</tr>
<tr>
<td>avoids tasks requiring sustained effort</td>
<td>always “on the go” or “driven by a motor”</td>
</tr>
<tr>
<td>loses things</td>
<td>talks excessively</td>
</tr>
<tr>
<td>is distracted by extraneous stimuli</td>
<td>blurs out answers to questions</td>
</tr>
<tr>
<td>is forgetful</td>
<td>difficulty waiting turn</td>
</tr>
<tr>
<td></td>
<td>interrupts or intrudes on others</td>
</tr>
</tbody>
</table>

The changes in ADHD diagnostic criteria that have occurred with the different classification systems have led to different groups of children being considered with the disorder. This has presumably led to the wide variation in estimated prevalence across studies, from as low as 1% to as high as 20% (August & Garfinkel, 1989). In addition, the diagnosis of ADHD is further complicated by disentangling the disorder from other potentially overlapping disorders. Shaywitz and Shaywitz (1988) reported that 50% of children with ADHD have a learning disability and at least 50% meet criteria for oppositional defiant disorder. Other comorbid disorders include conduct disorder, anxiety
disorder, Tourette's Disorder, depression and bipolar disorder. It is also possible that some non-ADHD disorders may present as ADHD (Pennington et al., 1993), due to partially overlapping or correlated symptoms. Therefore, a classification system that clearly defines and diagnoses comorbid conditions with ADHD is important in the delineation of homogeneous subgroups, to allow for more precise and reliable research strategies (Fletcher, Morris, & Francis, 1991).

A problem with the broad behavioural descriptions of ADHD is the difficulty in mapping the behavioural symptoms to relevant neurological mechanisms and the processes subserving these behaviours. Thus, while inattention in ADHD has been widely examined, the individual components that comprise attention more broadly have not been carefully considered. This type of analysis is necessary to develop an understanding of the nature of the attentional processing deficit in ADHD (Voeller, 1991). However, this approach has not been undertaken and the precise nature of the attention processing deficit is still not well understood. In fact, it has been disputed whether a true attentional deficit even exists in ADHD (van der Meere & Sergeant, 1987). Given that DSM-IV recognizes attentional dysfunction as being central to the disorder, it is critical that the nature of this dysfunction is examined.

**Attentional Processing**

Attention is a global construct that in general refers to a variety of functional relationships between the environment and behaviour (Barkley, 1996). Although the composite components of attention have been widely debated, it is now considered that attention is not a single, unitary construct, but rather multidimensional in nature (e.g. Mirsky, Anthony, Duncan, et al., 1991; Posner & Cohen, 1987; Stuss, Shallice, Alexander & Picton, 1995). There has been a lack of consistency in the measurement of attention largely due to the widespread definitions of attention and wide range of instruments used. Attentional processing has been examined from diverse research approaches, which include
neuropsychological, neuroimaging, neurophysiological and neurochemical perspectives. In recent years, theoretical models of attention have emerged suggesting the involvement of specific components (Posner & Cohen, 1987), neuroanatomical regions (Mirsky et al., 1991) and neurochemical systems (Tucker & Williamson, 1984).

The currently held view is that attention is a complex multicomponent system, that is widely distributed throughout the brain (Colby, 1991), and that attentional dysfunction can result from a deficit in attentional processing at any point in the system. Recent models of attention have begun to integrate the complex network of attentional components, thus allowing for a potential systematic evaluation of attentional dysfunction. Several theories have been advanced, which attempt to account for the specific neural mechanisms and neuroanatomical regions involved (e.g. Mirsky et al., 1991, Stuss et al., 1995; Posner et al., 1988). However, a unified system of attention that includes both spatial and temporal aspects of attentional processing is still lacking.

Mirsky et al. (1991) have developed a model of attention that is based largely on the performance of subjects on neuropsychological tests. His model identifies a number of distinct elements of attention and postulates there are specific brain regions corresponding to each of these elements. The first element, focus/execute, reflects the ability to concentrate resources of attention on a task while screening out distracting stimuli. It is hypothesized to involve the superior temporal, inferior parietal, and striatal regions of the brain, based on both animal studies (e.g. Bakay-Pragy, Mirsky & Nakamura, 1987) and clinical studies using cancellation tasks. The second element is the ability to shift attentional focus. Shift involves executive processes, that have been proposed to involve the prefrontal cortex (Mirsky et al., 1991); shift has been measured with tasks such as the Wisconsin Card Sorting Test. The third element reflects the ability to sustain attention over time and is thought to involve the medial thalamus and reticular formation. Finally, the fourth attentional element is encode, which reflects stimulus representation and is proposed to involve the hippocampus. While each of the components has been supported by
empirical evidence, they are not integrated in a unified system of attention. Mirsky’s model has additionally been criticized for being based on only a limited number of studies with animals and with patients with brain damage who were given clinical tests (Halperin, 1996) and the neuroanatomical evidence has not been directly supported with neuroimaging data. Furthermore, the neuropsychological battery on which Mirsky’s model is based, is confounded by the fact that several distinct subcomponents are involved in each of the tasks proposed to examine specific attentional elements.

Even more recently, a model specifically examining anterior-based components of attentional processing has been provided by Stuss and his colleagues. Their model proposes seven distinct attentional processes that are involved in specific frontally-based attention tasks and suggests the corresponding anatomical basis for each of the processes: sustaining, involving right frontal regions; concentrating, involving the cingulate; sharing, involving the cingulate and orthofrontal region; suppressing, involving the dorsolateral area; switching, involving dorsolateral and medial frontal areas; preparing, involving the dorsolateral area and setting, involving the left dorsolateral and frontal areas. While this model represents an advance over Mirsky’s because it incorporates neurophysiological components that might be related to neuroanatomical components, since each process is viewed individually it too can be criticized for lacking integration. An integrated approach combining attentional processes and linking brain regions involved in attentional processing is more realistic given the multiple components involved in most attentional tasks. Furthermore, Stuss’s model lacks a recognition of the time-course of cognitive events involved in attentional processes during each of the tasks.

Posner and his colleagues (e.g. Posner & Cohen, 1987; Posner & Raichle, 1994) have provided an “evolving” model of attention, which in its most recent version may address the temporal nature of attentional processing, which is lacking in the models by Mirsky and Stuss. Originally, Posner proposed a model of visual-spatial selective attentional processing that was based largely on studies of alert monkeys and normal and
brain injured patients. Three operations of selective attention were identified: (1) disengaging from the current focus of attention; (2) moving attention from its current focus to a new location and (3) engaging a new focus of attention. A computer-administered task was developed to examine each of these operations and following a series of experiments involving normal subjects and brain injured patients with neuroanatomical lesions. Posner and colleagues (e.g. Posner & Cohen, 1987; Posner, 1988) advanced a complex neuroanatomical model of the human visual orienting system. Based on this series of experiments, specific anatomical areas for the disengage (parietal lobe), move (midbrain) and engage (thalamus) operations (Posner et al., 1984; Rafal and Posner, 1987) were proposed. Posner also identified two additional components involved in visual attentional processing: (1) an anterior system often referred to as an executive attention network, that is associated with enhancing attention towards cognitive tasks and (2) an attentional network that is involved in maintaining vigilance. In 1994, Posner & Raichle subsequently recognized that a difficulty in the logic of the lesion method of localizing brain activity is the uncertainty whether a missing function represents activity in the lesioned area or an adaptation of the remaining system. On this basis, and in corroboration with neuroimaging data, the model was further updated to incorporate the time-course of selective attentional processing with ERPs.

**Attentional Processing in ADHD - Lack of a Temporal Approach.**

As reviewed above, the currently held view is that attention is a complex multicomponent system, which is widely distributed throughout the brain (Colby, 1991), and that attentional dysfunction results from a deficit in attentional processing at some point in the system. Recent research on attention has begun to integrate the complex network of attentional components, thus allowing for a potentially more systematic evaluation of attentional dysfunction. A dysfunction in attention has been reported in several childhood neuropsychiatric disorders involving diverse etiologies. Mirsky (1996) summarized these
disorders as being related to, 1) disorders related to familial/genetic factors (e.g. ADHD, seizure disorders and metabolic disorders); 2) disorders related to injury or infection (e.g. head injuries, asphyxia, and infectious diseases affecting the brain); 3) disorders associated with poverty (e.g. sequelae of exposure to lead, fetal alcohol or other toxins, malnutrition, and cultural or educational deprivation) and 4) disorders of unknown etiology (e.g. autism and Tourette’s disorder). From an attentional perspective, each of these disorders may be examined to determine the specific nature of the attentional processing deficit.

In cognitive processing, attention appears to be necessary from the time information is input and subsequently processed until a response is elicited. Several theories which have been advanced encompassing attention more broadly have attempted to account for the specific neural mechanisms and neuroanatomical regions involved in attention (e.g. Mirsky et al., 1991, Stuss et. al., 1995 and Posner, Early, Reiman, Pardo, et al., 1988). However, these theories have most often dealt with single attentional processes and have not examined multiple processes sequentially over time. If the attentional dysfunction in children with ADHD represents a dissociation at one or more points in the attentional system, then in order to characterize their attentional dysfunction one must determine where in the system the dysfunction occurs. This implies a temporally integrated approach to the study of ADHD.

**Attentional Processing in ADHD.**

ADHD has been examined from a variety of different research disciplines in order to determine the nature of the attentional processing deficit. Despite extensive research, a consensus on the nature of the attentional processing deficit in children with ADHD has not been reached. This is largely a result of the lack of consistency in the measurement of attention due in part to the varying definitions of attention and the wide range of instruments used to measure attention, as previously mentioned. Although children with ADHD differ from normal control children on clinical measures of attention (i.e. behavioural rating
scales), attempts to relate the behavioural attentional deficits to specific theoretical constructs of attention have not always been successful (Swanson et al., 1995). As a result, it has been suggested that the disorder is not characterized by a specific deficit in attention, but rather a deficiency in response inhibition and the capacity to delay responding (Barkley, 1996). In order to determine if children with ADHD have a specific attentional processing deficit well defined components of attention need to be examined. This is an aim of the present study.

Studies from several research perspectives have tried to identify specific deficits in children with ADHD. Several research groups using a neuropsychological approach have compared children with and without ADHD on neuropsychological tasks, in order to identify potential dysfunctions. Using this approach, evidence has been provided that children with ADHD have difficulties with tasks of executive function, which are thought to primarily involve the frontal lobes. Executive functions are often defined as the ability to maintain an intention to inhibit a response or defer it to a later more appropriate time and maintain a strategic plan of action sequences (Pennington & Ozonoff, 1996). Executive functions are involved in a number of neuropsychological tasks, including the continuous performance task, the Wisconsin Card Sorting Task, and the go/no-go task. In a review of 18 neuropsychological studies of executive functioning in ADHD, Pennington & Ozonoff (1996) reported that 15 showed a significant difference between ADHD and controls on an executive function measure. While this approach has identified potential neuroanatomical areas that may be dysfunctional in ADHD, there is a need for direct neuroanatomical corroboration.

Recent studies that have employed more direct neuroanatomical techniques in children with ADHD include, regional cerebral blood flow/computed tomography (rCBF/CT), magnetic resonance imaging (MRI), and positron emission tomography (PET). Hynd, Semrud-Clikeman, Lorys, Novey, Eliopoulos, et al. (1990) used MRI to compare brain morphology of children with ADHD, children with dyslexia, and a control group. Their
most striking finding was a difference in the width of the anterior region of the brain among
the groups: normal control children had a larger width in the right anterior than the left
anterior region, whereas the groups with ADHD or dyslexia had anterior regions that were
more symmetrical due to a smaller right anterior width. This smaller right anterior width
may contribute to a less well developed or a more poorly organized neural basis for the
complex processes regulated by the frontal lobes, consistent with the neuropsychological
studies of an executive function deficit in children with ADHD. In a second MRI study
(Hynd et al., 1991), a smaller corpus callosum (in the area of the genu and splenium) was
also found in the ADHD group compared to children without ADHD. These results were
partially corroborated by Semrud-Clikeman, Filipek, Biederman, et al. (1994) in a
subsequent study that also reported a smaller splenial area of the corpus callosum in
children with ADHD compared to children without ADHD. More recently, Giedd,
Castellanos, Casey, et al (1995) reported smaller areas in anterior regions of the corpus
callosum in children with ADHD. These MRI studies indicate specific neuroanatomical
differences between ADHD and control children and they suggest that neurodevelopmental
processes may indeed be abnormal in children with ADHD.

Lou, Henriksen, Bruhn, et al. (1984,1989) used rCBC/CT to compare brain
metabolic activity in children with ADHD and children without ADHD. This research
showed that children with ADHD had lower levels of metabolism in the region of the
caudate (a subcortical structure involved in the motor-regulatory system). This lower
metabolism was observed to be confined to the right striatal region in a subsequent study
(Lou et al., 1989), although methylphenidate acted to increase left striatal metabolism. The
findings of their research are intriguing given that they implicate lower levels of metabolic
activity in regions directly involved in the regulation of motor activity which project largely
to the frontal lobes. Castellanos, Giedd, Eckburg et al. (1991) using MRI found the volume
of the right caudate to be smaller in children with ADHD. This provides further evidence of
abnormalities in the frontal-striatal circuits in children with ADHD.
Using PET, Zanetkin et al. (1990) reported significant reductions in glucose metabolism in adults with attentional difficulties as children compared to normal adults. These reductions were observed in the superior frontal cortex and pre-motor cortex, which are thought to be integral components for motor inhibition and motor regulation. Although a more recent PET study by this same group on adolescent subjects reported no differences in glucose metabolism between subjects with ADHD and controls (Zanetkin, Liebenauer, Fitzgerald, et al., 1993; Ernst, Liebenauer, King, et al., 1994), lower levels of glucose metabolism were found in girls with ADHD versus without ADHD when adolescent girls were analyzed separately. This is interesting particularly as ADHD is more common in males than females, but the basis of this sex difference is unclear. More sophisticated PET studies examining specific components of attentional processing have not been conducted in children with ADHD.

While neuroimaging studies have shown neuroanatomical differences between ADHD and controls implicating a frontal lobe dysfunction, some inconsistencies still exist. One problem with these neuroimaging techniques is their poor temporal resolution. As event-related potentials (ERPs) are a technique for examining the time-course of cognitive events during attentional processing, they serve as a research tool for examining attentional processing in children with ADHD.

Event-Related Potentials - An Approach to Examine the Temporal Aspects of Attentional Processing

ERPs have emerged in recent years as a valuable methodology for studying the time-course of cognitive processing. ERPs are electrical potentials produced by the time-locked discharges of large populations of neurons that are recorded from the scalp. ERPs have a time resolution in the order of milliseconds and provide information on the timing of cognitive processing that is not currently available through other measures such as MRI or
PET (Hillyard & Picton, 1987). Functional MRI (fMRI), a powerful neuroimaging technique that provides both spatial and temporal information, in fact, only has a temporal resolution of seconds and is extremely expensive. Thus, ERPs are currently an optimal method to study the temporal aspects of attentional processing because they are both non-invasive and cost-effective.

**ERPs in Attention.**

ERPs have been used extensively to investigate the neurophysiology of attention (for a review see Woods, 1990). The ERP waveforms are designated by the polarity of the wave (N = negative and P = positive) and by the order in which they occur (e.g. P1, N1, P2, N2, P3 etc.) or by the latency in milliseconds following the presentation of a stimulus at which they occur (e.g. P100, N100, P260, P550 etc.). The waves are usually quantified in terms of their peak latency (ms) and maximum amplitude (μV) from a prestimulus baseline.

Research using ERPs to study visual attention has identified associated endogenous waves, which include N1, P2, N2 and P3. The cognitive processes associated with each of these waves and their underlying, cortical regions have not been definitively identified; however, increased specificity for ERP components are being advanced (e.g. Nobre, Allison & McCarthy, 1994) showing that components may be specific for cognitive processes at specific neuroanatomical locations. The following explanations of the cognitive processes associated with specific ERP components have been offered: (1) N1 is a posterior/parietal component that can reflect the shifting of attention to a location (Magnun, Hillyard, & Luck, 1993); (2) P2 is a frontal/central component, sensitive to spatial location (Luck & Hillyard, 1994); (3) N2 is anteriorly distributed and reflects target discrimination (Breton, Ritter, Simson, et al., 1988) and (4) P3 is a posterior component that reflects post-decisional processing and/or updating of working memory (Picton, 1992). A slow positive wave may also occur following the P3 that reflects the need for processing of difficult to detect stimuli (Picton & Hillyard, 1988). Through the analysis of ERP components, the temporal
processing of attention from stimulus detection to response execution and finally to post-decisional processing can be examined.

**ERPs in ADHD.**

A number of research groups have investigated ERPs in children with ADHD to establish an objective diagnostic measure of the disorder and to identify possible underlying neurophysiological correlates (e.g. Klorman, Salzman, Pass, et al., 1983; Klorman, Salzman & Borgstedt, 1988; Robaey, Breton, Dugas, et al., 1992; Satterfield, Schell, Backs, et al., 1984, Satterfield et al., 1994; Taylor et al., 1993). Most studies, have focused primarily on the P3 component as this component was associated with attentional levels in early research. It has been shown that compared to children without ADHD, children with ADHD have generally smaller P3 amplitudes (e.g. Klorman et al., 1983; Verbaten, Overtoom, Koelga, et al., 1994) which may reflect increased task difficulty (Picton, 1992). When stimulant medication is given, an increase in P3 amplitude has been observed, while reports of stimulant medication effects on P3 latency have been rare. However, several of the studies reporting P3 amplitude effects of methylphenidate, averaged ERP trials based on stimulus categories and not on responses (Verbaten et al., 1994). The inclusion of missed target trials in the averages can have the effect of reducing the amplitude. Recent studies that have averaged trials based on both stimulus category and response have found latency changes with methylphenidate, suggesting that methylphenidate may affect stimulus processing. Taylor et al. (1993), using a reading-related task, found that children who were positive responders to methylphenidate showed decreases in P3 latency with appropriate medication, which resulted in a “normalization” of P3 latency relative to children without ADHD. In contrast, nonresponders to methylphenidate treatment were not found to show a normalization of P3 latency (Sunohara, Voros, Malone & Taylor, in press) suggesting that ERPs are sensitive in distinguishing cognitive processing differences in subgroups of children with ADHD.
In terms of cognitive processing, the P3 is thought to reflect the aspect of processing that follows the decision whether or not to respond to a stimulus. This differs from the stimulus and response decision processing of the earlier ERP components. Verbaten et al. (1994) examined the effects of methylphenidate on the N1, P2, N2 and P3 components in children with ADHD as they performed a continuous performance test. Although the N2 and P3 amplitudes were increased with methylphenidate, there were no effects of medication on latency. This study was limited by the lack of a control group and as a result, specific attentional processing deficits in children with ADHD were not evaluated. There are few studies that have examined the earlier ERP components in attention tasks in children with ADHD and control children. Since these components are relevant for attentional processing, they would allow researchers to identify the specific stages of attentional processing from input to response that is dysfunctional in children with ADHD.

Methylphenidate Effects on Attentional Processing

Neurochemistry of ADHD

It is well recognized that neurochemical systems play an integral role in attentional processing, in general, by facilitating communication throughout the neural network of the attentional system. The two most widely described neurotransmitters are norepinephrine and dopamine. Norepinephrine is involved in the general maintenance of attention and arousal (Jutai, 1984), while dopamine plays an important role in the modification of behavioural outputs and in the shutting off of sensory input (Oades, 1985). In the noradrenergic system, neurons projecting from the locus coeruleus have been found to show decreased firing during a drowsy state and increased firing during a state of alertness (Foote et al., 1980). Given that adequate regulation of neurochemical functioning is critical in attention, it is not surprising that the possibility of a neurochemical dysfunction has been widely examined in ADHD.
Over the past several decades, a number of neurochemical theories of ADHD have been proposed. These theories are based largely on the fact that the disorder is widely treated with stimulant medications, which promote catecholamine neurotransmission. The majority of neurochemical theories have highlighted dopamine (Levy, 1991), norepinephrine (Hunt, Mindera & Cohen, 1985) or their interaction (Malone et al., 1994; McCracken, 1994) as underlying the etiology in the disorder. Attempts to validate these theories have included the measurement of neurotransmitters and their metabolites, the use of pharmacological probes, and the examination of candidate genes. However, none of these approaches has provided definitive evidence on the underlying neurochemical deficit in ADHD. Studies examining neurotransmitters and their metabolites from body fluids have not reported consistent differences in blood, urine or cerebrospinal fluid between groups with ADHD and controls (Zametkin & Rapoport, 1987). A particular problem with these studies is the difficulty in determining to what extent these data are reflective of peripheral or central nervous system processing. In addition, the data are confounded by the knowledge that exchange takes place between the cerebrospinal fluid and plasma for many metabolites (Rogeness, Javors & Pliszka, 1992).

To examine potential neurochemical dysfunction in ADHD, a frequently used approach has been the measurement of the clinical response to specific psychopharmacological agents that act selectively on neurochemical systems. Pharmacological studies have focused primarily on three neurotransmitter systems: dopamine, norepinephrine, and serotonin, since more than a single neurotransmitter system is likely to be involved in ADHD (Zametkin & Rapoport, 1987). McCracken (1991), who reviewed several pharmacological studies of medications used to treat ADHD, proposed that two primary properties are required for a medication to be effective: first there must be increased dopamine release; second, there must be increased adrenergic-mediated inhibition of the noradrenergic-locus coeruleus. If this is true, it implies a neurochemical imbalance in
ADHD characterized by decreased dopamine and increased norepinephrine. This is consistent with a neurochemical theory of ADHD (Malone et al., 1994).

Recently, molecular genetic approaches have begun to examine the association of candidate genes within the dopamine system with ADHD (Sunohara, Swanson, Lahoste, et al., 1996; Cook, Stein, Krasowski, et al., 1995; Lahoste, Swanson, Wigal, et al., 1996). This approach provides a direct means of testing neurochemical theories. Current neurochemical theories of ADHD (Pliszka, McCracken, & Maas, 1996) have begun to differentiate specific receptor subtypes within the dopamine system in their involvement with the disorder. However, the molecular genetic approach is still in its infancy and further research is necessary.

In summary, despite considerable research in this area, the exact neurochemical deficit underlying ADHD remains largely unknown. In addition, although stimulant medication acts on the catecholamines, primarily the dopaminergic and noradrenergic systems (Patrick, Mueller, Gualtieri, et al., 1987; Zametkin & Rapoport, 1987), and increases striatal activity (Lou et al., 1989), the precise mechanism of action of stimulant medications is still not well understood in ADHD children.

Dose-Related Effects of Methylphenidate- Adverse Effects at Higher Doses

Stimulant medications, primarily methylphenidate, are the most common intervention for children with ADHD (Zametkin and Rapoport, 1987). A review of the literature by Swanson et al. (1995) reported that the administration of stimulant medication results in decreased ADHD symptomatology (hyperactivity, inattention, impulsivity) as well as a decrease in associated features such as defiance, aggression and negative social interactions. These stimulant medication effects make children with ADHD more “manageable” at school and is one of the primary reasons for the widespread popularity of this treatment.
Malone et al. (1994) proposed a neuroanatomical/neurochemical theory of ADHD based largely on a theory of asymmetric neural control systems (Tucker and Williamson, 1984) and extensive clinical observations of the effects of methylphenidate on children with ADHD. This theory suggests a neurochemical imbalance in ADHD children characterized by decreased dopaminergic functioning in the left hemisphere and increased noradrenergic functioning in the right hemisphere. Restoration of this neurochemical imbalance is thought to be mediated by stimulant medication. Malone et al. (1994) characterized the child with ADHD on multiple behavioural dimensions. Off medication, the child with ADHD is seen as highly aroused yet under-activated, and behaviourally as seeking novelty and change and expressing emotion outwardly. In contrast, on medication, the child with ADHD may be better in processing redundant information, maintaining goal-directed responding but also may appear emotionally less expressive and more introverted. The effects of stimulant medication specified by this theory suggest that although appropriate doses of methylphenidate may act to correct the neurochemical imbalance, higher doses may actually reverse the imbalance resulting in an adverse medication effect.

Clinical observations of adverse effects have documented that stimulant medications may make some children with ADHD overfocused (Swanson et al., 1991); cognitively constricted (Thurston, Sobel, Swanson et al., 1979); "zombie-like" (Swanson & Kinsbourne, 1978); and more "somber", "quiet", and "still" (Tannock, Schachar, Logan, et al., 1989). While most of the experimental research on ADHD has dealt with the beneficial effects of stimulant medications, only a few studies have actually addressed these potential adverse effects (Malone et al., 1994; Campbell, Malone & Kershner, 1996). Furthermore, the studies that have attempted to provide empirical support for these clinical observations have not always been successful.

Although adverse effects of moderate (0.3 mg/kg) and high (1.0 mg/kg) doses of methylphenidate on cognitive functioning and learning were documented in one early study by Sprague & Sleator (1977), most of the later studies have failed to document similar
adverse medication effects. For example, Solanto and Wender (1989) questioned whether the generalized constriction and overfocusing commonly seen when children take methylphenidate adversely affects performance on tasks that require cognitive flexibility or divergent thinking. The performance of children with ADHD on a test battery that required divergent thinking was studied under three methylphenidate dose conditions: 0.3, 0.6 and 1.0 mg/kg. Although dose-related adverse effects of methylphenidate were not found, the investigators did note a subgroup showed evidence of perseveration. However, the specific characteristics that distinguished this subgroup from the remaining sample was not determined.

Dyme, Sahakian, Golinko, et al. (1982), in a pilot study, examined the performance of children with ADHD on the Wisconsin Card Sorting Test on both placebo and 1.0 mg/kg of methylphenidate. It was reported that the high dose of methylphenidate produced an overfocusing of attention, as determined by an increase in perseverative errors over placebo. However, a subsequent study by Tannock and Schachar (1992), involving a larger sample size and repeated testing using the same task, there was less evidence of overfocusing effects. Children with ADHD performed the Wisconsin Card Sorting Test on both low (0.3 mg/kg) and high (1.0 mg/kg) doses of methylphenidate, and placebo, on two separate assessments. On the first assessment, both doses of methylphenidate produced an increased trend in perseverative errors relative to placebo (the higher dose produced more perseverative errors); however, on the second assessment there was a significant decrease in perseverative errors with increasing medication dose relative to placebo. Thus, these results are less supportive of an overfocusing on methylphenidate.

Additional studies that have searched for adverse medication effects have not been consistent. To determine whether a clinically optimal dose of methylphenidate increases attentional focusing, Malone, Kershner and Siegal (1988) examined the speed of word processing on a semantic matching task. Although their data failed to show a decrease in speed of processing, they did show that the high dose condition generally impaired
performance. Tannock, Schachar, and Logan (1993) compared a low (0.3 mg/kg) and a high (1.0 mg/kg) dose level of methylphenidate on focused attention in children with ADHD. Although these investigators predicted that the high dose may cause an overfocusing of attention, a significant effect did not emerge. However, children with ADHD did show increased clinical symptoms of overfocusing (e.g. intense concentration, reduced responsivity and motor stereotypy). This suggests that their task was not sensitive to the overfocusing effects or that there may be a differential effect of methylphenidate on behaviour and task performance. Recently, Douglas, Barr, Desilets, et al. (1995) assessed the effects of three doses of methylphenidate (0.3, 0.6 and 0.9 mg/kg) in children with ADHD on tasks designed to assess divergent thinking, perseveration, and the ability to shift mental set. Their results revealed no adverse medication effects of any dosage, on the measures used. However, in a recent study by Campbell et al. (1996) some evidence was found to suggest that a moderate dose of methylphenidate may induce slower cognitive processing without an improvement in task accuracy.

Thus, the majority of studies that have attempted to provide empirical evidence for the clinical observations of adverse medication effects have not produced supportive data. It is suggested that the tasks that were used may not have been sensitive to these medication effects. A research approach that uses a more sensitive technique for directly examining dose-related stimulant medication effects on specific attentional processes may be more successful in demonstrating both beneficial and adverse medication effects.

In summary, the effectiveness of methylphenidate in reducing ADHD symptomatology has been well documented, although concerns still exist regarding potential adverse effects associated with higher doses of medication. Despite extensive research, it remains unclear how methylphenidate affects attentional processing and whether adverse medication effects occur. ERPs offer a means for examining dose-related effects of methylphenidate on specific stages of attentional processing.
OVERVIEW OF THE PRESENT STUDY

This review of the literature has revealed several issues that remain unresolved despite the considerable research efforts that have been conducted. First, ADHD is a complex behavioural disorder with a core feature of inattention; however, the precise nature of the attentional deficit remains unknown. Second, the most common treatments for ADHD are stimulant medications, primarily methylphenidate; however, the mechanisms through which these medications exert their effects on attentional processing remain undetermined. Furthermore, there is little knowledge on the dose-related effects of stimulants on attentional processing.

The present study aims to address these limitations by examining the dose-related effects of stimulant medication on multiple components of attentional processing in children with ADHD, using an approach that incorporates: (i) the use of two neuropsychological paradigms that have been shown to involve different attentional processes and attentional systems, and (ii) the recording of ERPs to examine the time-course of attentional processing in ADHD and effects of stimulant medication on attention. The working hypothesis is that children with ADHD will show deficits in attentional processing, which are differentially affected by dose of stimulant medication and can be characterized with ERPs.

The two experimental paradigms used in this study were the Continuous Performance Test (Rosvold, Mirsky, Sarason, et al., 1956) and the Posner visual spatial selective attention task (e.g., Posner, 1988). These tasks served to examine the dose-related stimulant medication effects on attentional processing outlined below.

**Continuous Performance Test**

The Continuous Performance Test (CPT) generally requires the subject to monitor the presentation of a long series of stimuli and to make a response whenever an
infrequently-presented target stimulus appears, while inhibiting their responses to non-target stimuli. Errors of omission are thought to reflect inattention, while errors of commission are generally thought to represent impulsivity. The CPT as used in this study was a measure of focused attention, defined as concentrating resources of attention on a task while screening out distracting stimuli.

Several versions of the CPT are available and have been used to assess focused attention deficits in a variety of clinical populations. The target may be a single letter (e.g. "X", in the CPT-X version), a combination of letters (e.g. "X" only when it is immediately preceded by an "A", in the CPT-AX version), or a letter only when it is immediately preceded by the same letter (CPT-double). Other versions of the CPT have been used to measure focused attention with more complex targets or increased memory load to raise the level of task difficulty (e.g. Bergman, Winters & Cornblatt, 1991).

The CPT-double was used in the present study because the cognitive load is increased relative to the easier CPT-X and CPT-AX versions where only a single letter is target. On this task a series of letters are rapidly presented and the subject is required to maintain a letter in working memory and compare it to the next presented letter. If this letter is the same as the previous letter, a response is required but if the letter is different, the subject must withhold a response. Due to the requirements of this task, it is often considered a measure of executive function (Pennington, Benetto, McAleer, & Roberts, 1996).

**CPT performance in children with ADHD.**

The CPT has been used widely as a diagnostic instrument for ADHD and has also been used extensively in research. While several studies have found that children with ADHD make more errors of omission and commission on the CPT (e.g. Pelham et al., 1990; Coons, Korman & Borgstedt, 1987; Verbaten et al., 1994), evidence for a sustained
attention deficit as defined as a differential decline in performance over time relative to controls has not been consistently reported. Van der Meere and Sergeant (1989) found that although children with ADHD generally performed worse on the CPT than controls, a greater decrement in their performance over time relative to controls was not found, suggesting that children with ADHD do not have a sustained attention deficit. Corkum and Siegel (1993) in an extensive review of research using the CPT in children with ADHD, supported this conclusion. The lack of consistent findings using the CPT may be related to the several versions of the task that have been employed. Easier versions of the task, which have low error rates, may not be sensitive to performance decrements over time.

Halperin and colleagues (e.g. Halperin, Wolfe, Pascualvaca et al., 1988; Halperin, Newcorn & Sharma, 1991; Halperin, Matier, Bedi, et al., 1992) have conducted important research in children with ADHD using the CPT-AX task to assess attention and differentially assess impulsivity by examining different types of commission errors. In their 1988 study, they found that omission errors, were correlated with inattention whereas commission errors, which occurred when the subject responded to a letter following an A other than X, correlated with impulsive and hyperactive behaviour. Halperin and colleagues have also examined errors on the CPT-AX in a “pure” group of ADHD children, a pure group of children with conduct disorder, a mixed group of children with ADHD and conduct disorder and a control group. The pure ADHD group was the most inattentive, while the combined ADHD and conduct disorder group was more impulsive than the pure conduct disorder and control groups.

The CPT has also been used to study methylphenidate effects in children with ADHD. Sykes, Douglas, Weiss, et al. (1971) examined the effects of stimulant medication
on the performance of hyperactive children on the CPT and found that the group receiving stimulant medication made fewer errors of omission and commission than the placebo group. Similar effects of methylphenidate in children with ADHD on the CPT have also been reported (Bergman et al., 1990; Michael, Klorman, Salzman, et al., 1981). A consistent finding has been the normalized CPT performance measures on medication. However, the specific attentional processes that are benefited by methylphenidate are unclear.

In summary, research suggests that children with ADHD perform worse on specific measures of the CPT, although evidence for a sustained attention deficit is not clear. The CPT also seems to be a useful instrument for characterizing different co-morbid groups of ADHD. In general, methylphenidate improves performance on the CPT. However, the precise underlying attentional processing deficits in children with ADHD contributing to deficits in performance are not understood and the specific effects of methylphenidate on attentional processing leading to improved performance on the CPT, are not known.

An Attentional Processing Model for the CPT

Behaviourally, it may be postulated that several processes are involved while a subject performs the CPT. The subject must focus on the incoming stimulus, determine whether it is a target or not, respond if the stimulus is a target or alternatively inhibit a response if it is a non-target, and then prepare for the next stimulus. ERPs, because of their high temporal resolution provide a means of examining these millisecond by millisecond processes involved while a subject performs the CPT and in fact, may reflect the attentional processes involved during the CPT. The P2 ERP wave is thought to be sensitive to the allocation of attention and feature detection (Luck et al., 1993), while the N2 is thought to reflect focused attention to the features of the stimulus (Luck and Hillyard, 1994) and
stimulus classification (Breton et al., 1988). Thus, these two waves may reflect attentional processing involved in evaluating whether a stimulus is or is not a target and deciding whether to respond or inhibit a response. Faster processing at these early stages may reflect greater impulsivity. In contrast, the later P3 component is thought to reflect post-decisional processing such as finalizing a decision, revision of strategies for future trials memory updating (Picton, 1992). On the CPT, the P3 may reflect attentional processes following the decision to respond to a stimulus and subsequently to prepare for the next stimulus. Slower processing at this later component may reflect a lack of preparation for the next stimulus and thus inattention. Therefore examination of separate aspects of attentional processing, while the subject performs the CPT is possible. This will allow for the identification of specific attentional processing differences between children with ADHD and normal control children and may allow for characterization of an attentional processing deficit during the CPT.

It is hypothesized that children with ADHD will show deficits in attentional processing characterized by poorer performance and specific differences from controls on the ERP measures. In particular, it is predicted that children with ADHD will have longer P3 latencies than controls, which may be reflective of greater inattention. Specific predictions for the earlier components weren’t made because the basis for attentional processing differences has not been demonstrated.

The effects of methylphenidate on attentional processing during the CPT may also be examined with ERPs. Therefore, the specific aspects of attentional processing that are affected by methylphenidate may be explored, to determine where in the time-course of processing, that methylphenidate exerts its effects. It is hypothesized that methylphenidate will improve performance on the CPT and that this improvement will be related to specific ERP measures.
The Posner selective attention task

Posner and colleagues (e.g. Posner & Cohen, 1987; Posner, 1988) have proposed a model of visual-spatial selective attentional processing based largely on studies of alert monkeys and normal and brain injured patients. This model identifies three operations of selective attention: (1) disengaging from the current focus of attention; (2) moving attention from its current focus to a new location and (3) engaging a new focus of attention. A computer-administered task was developed to examine each of these operations and based on a series of experiments, specific anatomical areas for the disengage (parietal lobe), move (midbrain) and engage (thalamus) operations (Posner et al., 1984; Rafal and Posner, 1987) were proposed.

Several studies have recently served to examine Posner's model of visual selective attention with greater specificity. The hypothesized involvement of the thalamus in the engage operation of visual selective attention was validated by a PET study demonstrating the involvement of the thalamus in filtering out information from irrelevant locations and engaging attention (Laberge, 1990). The neuroanatomical localization of the move and disengage operations of visual selective attention have yet to be examined with PET imaging.

Posner (1988) has described his visual selective attention task in detail and a simple model is presented in Figure 1.
Figure 1. A model of the shifting task showing an example of a valid trial. Note that in an invalid trial, the target is presented opposite to the cued location. The subject is therefore required to disengage attention from the current focus, move and then engage attention at the new location.

The task requires the subject to press a response button as quickly as possible whenever a target stimulus is presented on a computer screen. The response measure is the response time (RT) following target onset. At the start of each trial (Time 1) the subject fixates on the center of the screen (as indicated by the “+” in Figure 1) and a cue is presented indicating the location where the target is most likely to occur (Time 2). The cue may either be a centrally presented arrow (endogenous cue) or a peripherally presented brightening of a box (exogenous cue). Exogenous cues have been proposed to reflect automatic effects while endogenous cues are thought to reflect controlled attentional processes (Muller & Rabbit, 1989). The cue draws the subject's attention to the cued location. A target is then presented (Time 3) at varying intervals following the cue and may appear at either the cued location or at the side opposite the cue. A cue that correctly predicts the side of the target represents a “valid” cue and one which incorrectly predicts the target is an “invalid” cue. Neutral cues are also presented, where a plus sign indicates that the target may occur either
left or right of the point of fixation. The time delay between cue and target presentation, called stimulus onset asynchrony (SOA) can be manipulated. A 100 ms SOA is thought to elicit covert shifts of attention controlled by a posterior attentional system, while an 800 ms SOA is thought to elicit overt shifts of attention controlled by an anterior attentional system. Performance patterns of normal subjects on this task have found: (1) RT is faster to targets after valid cues than after invalid cues (validity effect); (2) RT decreases as a function of increasing cue-target interval; and (3) RT does not differ for responses to targets in the left visual field (LVF) and the right visual field (RVF).

**The Posner task in clinical populations and effects of pharmacological probes on performance.**

The Posner task has been given to a number of clinical populations (e.g. schizophrenia, Parkinson’s Disease) to study their specific attentional dysfunction. It has also been used to examine the effects of the pharmacological manipulation of catecholamine levels on selective attention processing. Posner et al. (1988) studied a schizophrenic population and found an asymmetry in the hemispheric control of attention, which was demonstrated by an increased cost to a right visual field target following an invalid cue in the 100ms SOA condition. This led these investigators to speculate that schizophrenia involves a left hemispheric dysfunction located in the parietal lobe, due to abnormal disengage process. The neurochemical abnormality in schizophrenia is thought to involve excess dopamine, primarily based on clinical evidence that medications used to treat the disorder effectively, such as chlorpromazine and haloperidol, derive their mechanism of action through a dopamine antagonist effect. Therefore, their abnormal disengage process may be related to a neurochemical imbalance.

The Posner task has also been used to examine selective attention in several other clinical populations with probable neurochemical dysfunction. Parkinson’s disease is thought to involve hypodopaminergic functioning as a result of degenerative dopamine
pathways, based largely on the clinical improvement following therapy with dopamine agonists (e.g. L-Dopa, deprenyl). Wright et al. (1990) reported an impairment in the maintenance of attention in subjects with Parkinson's disease, as demonstrated by a reduced cost of invalid cueing relative to controls despite a normal RT benefit in the valid cue condition. Thus, although the covert movement and engagement of attention were unaffected for valid cues, a facilitation of the disengagement of attention was observed. This was described as a rapid shifting of attention resulting in an impairment in the maintenance of attention and may be due to decreased levels of dopamine.

The Posner task has further been used to examine the effects of neurochemical manipulation on selective attention through the administration of pharmacological probes to normal adults. Clark et al. (1989) administered a dopamine antagonist and an alpha agonist (suppressing central norepinephrine activity) to normal adults. The effect of decreasing dopamine through the administration of a dopamine antagonist was a reduced cost associated with an invalid cue, due to faster disengagement and switching of attention.

These lines of evidence suggest that the Posner task is a sensitive instrument that can discriminate between the manipulation of catecholamines and effects of neurochemical imbalances on the ability to orient and shift attention. The effect of decreased dopamine through the administration of a pharmacological probe or Parkinson's disease resulted in an increased shifting of attention. The effect of increased dopamine in schizophrenia resulted in a decreased ability to shift attention when targets were presented to the right visual field in the invalid condition.

**The Performance of Children with ADHD on the Posner Selective Attention Task.**

The Posner task has been used to examine selective attentional processing in children with ADHD. Swanson et al. (1991b; 1990) hypothesized that an ADHD group would show an asymmetry in the hemispheric control of attention as demonstrated by an
increased RT to targets presented to the left visual field in the 100 ms SOA invalid cue condition. The hypothesis was based on the study by Posner et al., (1988) who found a lateral difference in reaction time for the 100 ms invalid cue condition in the opposite direction of that predicted for the ADHD group (increased reaction time for targets presented to the right visual field). Since schizophrenics are treated with dopamine antagonists while children with ADHD are treated primarily with dopamine agonists, the investigators predicted similar attentional deficits in the two populations, but with opposite asymmetries.

The hypothesis was not supported. Rather, in the 800 ms SOA, the ADHD group showed a lateral difference in reaction time (right visual field > left visual field) in the neutral and invalid conditions but no lateral difference in reaction time in the valid condition. Therefore, the attentional deficit in ADHD was proposed to be associated with the orienting of attention (Posner, 1988) and a dysfunction in the left hemisphere (receiving the cue). As the ADHD group also demonstrated faster disengagement and shifting of attention in the 800 ms SOA condition, this suggests an inability to maintain orientation to the right visual field for a target over the 800 ms. This finding is consistent with a neurochemical and neuroanatomical theory of ADHD proposed by Malone et al. (1994) which is based primarily on a neurochemical imbalance between dopamine and norepinephrine and an asymmetric neural control system of attention.

Two recent studies have failed to completely replicate Swanson et al.’s (1991) findings. Carter, Krener, Chaderjian et al. (1995) using both exogenous (peripherally presented brightening of a box) and endogenous cues (centrally presented arrows), found that the ADHD group demonstrated an asymmetrical performance deficit only in the
endogenous cue condition, which was characterized by a loss of costs to invalidly cued targets in the left visual field in the 800 ms SOA condition. Novak, Solanto and Abikoff (1995) compared the performance of children with ADHD to children without ADHD on the Posner task and in addition, examined the effects of methylphenidate on the performance of the ADHD group. No RT differences were observed between the ADHD group and the control group or within the ADHD group on and off medication.

**An Attentional Processing Model for the Posner Task**

The Posner task provides a model for examining three component processes in selective attention: disengage, move and engage. The task has been shown to be sensitive to the manipulation of catecholamines and neurochemical imbalances in disease, on specific processes in selective attention. Therefore, the Posner task may be a sensitive instrument to discriminate children with ADHD from normal control children on specific selective attention processes (e.g. Swanson et al., 1991b). This would allow for the examination of specific selective processing deficits in ADHD. The Posner task also appears to be sensitive to pharmacological intervention and thus the dose-related effects of methylphenidate on components of selective attention processing may be examined.

Based on this review, it was hypothesized that children with ADHD would show characteristic differences on the Posner task and that performance would be affected by methylphenidate. Specifically, it was predicted that in children with ADHD, the disengage process would be more rapid as reflected in decreased RT in invalid conditions, consistent with the findings of Swanson et al. (1991). The predicted stimulant response was that decreasing norepinephrine and increasing dopamine may suppress responsivity of cortical
neurons to new input and result in a dose related increase in RT for invalid trials. It was further predicted that hypernoradrenergic functioning in ADHD may result in an increased responsivity to novel stimuli which would be reflected in quicker engaging and thus faster RTs on valid trials as well. The predicted stimulant response is a dose-related normalization or reversal of this processing.
METHODS

Subjects

Twenty children (16 males, 4 females, mean age = 10.5 ± 1.9 years) with a primary diagnosis of ADHD according to DSM-III-R criteria and twenty children without ADHD (16 males, 4 females, mean age = 10.8 ± 1.8 years) participated in the study. Children with ADHD were recruited from referrals to the Child Development Centre (CDC) at the Hospital for Sick Children for problems related to inattention, hyperactivity and impulsivity. Developmental pediatricians at the CDC identified these children as meeting DSM-III-R criteria for ADHD, based on the information outlined below. First, the developmental pediatrician met with the patient and patient’s family to obtain a detailed history and account of the patient’s ADHD symptomatology as well as any family issues that may impact on the child’s attention or behaviour. Second, both parents and teachers completed behavioural rating scales: 1) the 15 item CLAM (Conners, Loney & Millich, Swanson et al., 1995), and 2) the 23 item SNAP (Swanson, Nolan & Pelham, 1982) to assess ADHD symptomatology at home and at school. The CLAM incorporates items from the IOWA Conners Rating Scale (Pelham et al., 1989) and the Abbreviated Conners Rating Scale (Conners, 1973), which have both been used frequently to assess ADHD behaviour. Finally, parents completed a computerized version of the Diagnostic Interview for Children and Adolescents (DICA, Herjanic, 1983), which provided a variety of information about the patient regarding medical history, psycho-social stressors and presenting symptomatology of a number of childhood and adolescent disorders (e.g. ADHD, Oppositional Disorder, Conduct Disorder, Mania, Overanxious Disorder, Avoidant Disorder, Compulsions, Post-Traumatic Stress Disorder). This combination of information from meetings with patient and family, teacher and parent reports of ADHD symptomatology and computerized interview permitted the developmental pediatrician to make a well-informed diagnosis.

The following exclusionary criteria were applied to the selection of subjects for the study: (a) children with Conduct Disorder; (b) children with internalizing disorders (such as
anxiety), and (c) children with WISC-III IQ scores less than 80 (on the Vocabulary and Block Design subtests). Four of the subjects presented with comorbid Oppositional Defiant Disorder and eight of the subjects presented with comorbid learning disabilities and were not excluded from the study.

The control children were recruited through announcements posted in local community centres, libraries and local schools. Control children with a history of neurological, psychiatric or scholastic problems were excluded from the study. To ensure that control children did not have ADHD, the same behavioural rating scales were used for controls as for the ADHD subjects and to ensure that control children did not have any cognitive difficulties, the abbreviated WISC-III was administered. Exclusionary criteria for the control children was evidence of ADHD based on the behavioural rating scales or WISC-III IQ scores less than 80 (on the Vocabulary and Block Design subtests). None of the control children tested were excluded from the study.

The children with ADHD presented with greater ADHD symptomatology on both the SNAP, abbreviated Conners and IOWA Conners parent rating scales than control children (Table 2).
Table 2.

Mean scores for ADHD and control children on the SNAP and IOWA Conners

<table>
<thead>
<tr>
<th>Measure</th>
<th>ADHD Score (s.d.)</th>
<th>Controls Score (s.d)</th>
</tr>
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<tbody>
<tr>
<td><strong>SNAP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL SCORE</td>
<td>30.86* (8.74)</td>
<td>3.52 (3.02)</td>
</tr>
<tr>
<td>Hyperactivity Scale</td>
<td>6.83* (4.33)</td>
<td>1.05 (1.10)</td>
</tr>
<tr>
<td>Inattention Scale</td>
<td>10.81* (2.84)</td>
<td>1.26 (1.33)</td>
</tr>
<tr>
<td>Impulsivity Scale</td>
<td>12.45* (3.76)</td>
<td>1.16 (1.30)</td>
</tr>
<tr>
<td>Peer Interaction Scale</td>
<td>9.36* (5.39)</td>
<td>1.89 (2.32)</td>
</tr>
<tr>
<td><strong>CLAM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iowa Conners Scales</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inattention/overactivity</td>
<td>10.70* (2.51)</td>
<td>1.10 (1.05)</td>
</tr>
<tr>
<td>Oppositional/defiant</td>
<td>9.21* (4.22)</td>
<td>1.68 (2.11)</td>
</tr>
<tr>
<td><strong>Abbreviated Conners</strong></td>
<td>20.08* (5.61)</td>
<td>2.26 (1.82)</td>
</tr>
</tbody>
</table>

* <0.001

**Drug Trial Procedure**

Each ADHD child was tested first on baseline and then on placebo, lower, and higher dose of methylphenidate in a double-blind, placebo-controlled, crossover design. Testing was conducted in the morning and afternoon over two days. The aim at the outset of the study was to assess a lower dose of 0.3 mg/kg and a higher dose of 0.7 mg/kg.
However, the mean lower dose was 0.28 mg/kg (range 0.14 to 0.34 mg/kg) and the mean higher dose was 0.56 mg/kg range (0.28 to 0.70 mg/kg). Clinical restrictions at the CDC prevented the intended doses from being administered to all subjects since a maximum higher dose was set at 20 mg (doses higher than this are not typically administered at the CDC). Therefore, a child with a mass greater than 28.5 kg could not receive a higher dose of 0.7 mg/kg. In addition, the mg/kg doses were rounded off to the nearest 2.5 mg to facilitate the preparation of medication at the pharmacy.

Medication histories were taken for each child, with the majority having received stimulant medication. Children who were currently taking stimulant medications were asked to stop taking them for 24 hours before commencing the study. During the study, each child was first tested on baseline and subsequently on placebo, lower and higher dose methylphenidate in a randomized order. Medication and placebo were packaged in gelatin capsules and dispensed by the Pharmacy at The Hospital for Sick Children. The medication was administered by the primary investigator at the clinic, on the day of testing under the supervision of a developmental pediatrician. Testing was conducted 90 minutes after administration of medication or placebo to ensure maximum medication effect (Swanson et al., 1978). Written feedback in the form of a research-based report under the supervision of a registered psychologist, was given to the parents of all participants. This research report was placed in the medical files of each participant with ADHD.

**Recording of ERP and performance data**

ERPs were recorded while the children performed both the CPT and Posner selective attention tasks. The order of the presentation of the two tasks was randomized between subjects. ERPs were recorded using an electrode cap (Electro-Cap Inc., Ohio), based on the international 10-20 system, from 27 active electrodes (Fpz, Fp1, Fp2, Fz, F3, F4, F7, F8, Fc1, 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 (EOG) was
monitored from the outer canthus and supraorbital ridge of the eye to enable the rejection of
trials with eye movement artifact. Electrode impedance was always below 5 Kohms.
ERPs were recorded with a bandpass of 0.1-30 Hz. The sweep for the CPT was 800 ms and
started 50 ms prior to the presentation of each stimulus (letter). ERPs were recorded for the
presentation of each letter. For example, a letter was presented for 800 ms and ERPs were
recorded and following this another letter was presented for 800 ms and ERPs were once
again recorded. If the second letter was a repeat of the first letter, a response was required.
Trials that did not require a response (letter not repeated) were coded as non-target trials,
whereas trials that did require a response (letter repeated) were coded as target trials. Only
target trials in which a correct response was given were analyzed.

Attention tasks

CPT

A visual CPT adapted from Klee and Garfinkel (1983) was presented using an IBM
computer and Neurosoft (Virginia) software from Neuroscan. This task was programmed
using the Gentask software package for the Neuroscan system. The task required the press a
response button whenever two identical stimuli (letters) were presented consecutively.
Stimuli were presented on the computer monitor for 50 ms with a 1000 ms interval between
trials. A total of 360 trials were presented in a single block during each test session. Target
trials that required a response occurred on 20% of the total trials. Correct responses were
scored as correct detections or hits, while errors of omission were scored for missed targets
and errors of commission or false alarms were scored when a response was made to a
nontarget stimulus. ERPs were recorded while the children performed the task. Response
times were measured from the onset of the target stimuli to the onset of the response button
press.
**Posner Selective Attention Task.**

The Posner selective attention task was presented with an IBM computer using Neuroscan (Virginia) software. A fixation point was presented at the center of a computer monitor and a peripheral cue (brightening of a box) was then presented to predict the location of a target stimulus (star). The task required the child to press a response button when the target stimulus was presented. Response times (RT) were measured from the onset of the target to the onset of the response button press. Response times less than 100 ms (anticipation errors or false alarms) or greater than 3000 ms (omission errors) were recorded as errors. The interval between trials was 1000 ms.

A total of 360 trials were presented in 3 blocks of 120 trials in each test session. Within these trials, 20% were uncued and 80% were cued. On the cued trials, 80% of the targets were presented at the cued location (valid trials) while 20% of the targets were presented at the uncued location (invalid trials). Half of the targets were presented in the right visual field (RVF) and half in the left visual field (LVF). On half of the cued trials, the stimulus onset asynchrony (SOA) was 100 ms and on the other half, the SOA was 800 ms. On the uncued trials, the target was presented 1100 ms or 1800 ms after the previous response.

**Data Analysis**

**Performance Data.**

For the CPT, the ADHD group was compared to the control group on each of the dependent measures (%hits, %false alarms and RT) in separate ANOVAs for each of the four medication conditions (baseline, placebo, lower dose and higher dose). The ADHD group was then compared across medication conditions with separate ANOVAs. *Post hoc* t-tests were conducted to locate differences. For the Posner selective attention task, the dependent variable was RT. Data analysis consisted of ANOVAs using three within subject factors (cue, visual field and delay) and group as the between subject factor for comparisons of the ADHD group in each of the four medication conditions with the control
group. A separate analysis using medication condition as a within subjects factor was used to compare the ADHD group across medication conditions. Post-hoc analyses were performed using Bonferroni corrections for multiple testing using SPSS. Results were considered to be significant if the p value was less than 0.01.

**ERP data.**

ERP data were not analyzed for the Posner selective attention task. Since the sweep began with the presentation of the cue, the waveforms for the cue and for the target overlapped and were difficult to distinguish, particularly in the 100ms cue condition. Therefore, ERP data were analyzed only for the CPT, as follows: Grand averages were compiled for target trials only for each group and medication condition. These averages served as templates for detection of peaks for each child's individual data. The N1, N2 and P2 peaks were measured within 50 ms of the peak's latency and the P3 peak was measured within 150 ms 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

CPT

Performance Data

ADHD baseline vs. controls. The performance of the ADHD group on baseline and the controls is summarized in Table 3. The control group showed a trend towards greater accuracy than the ADHD group on baseline, responding correctly to more targets as indicated by %hits (F(1,38)=6.7, p=0.04). The control group was less impulsive than the ADHD group on baseline, responding incorrectly to fewer nontargets as indicated by %false alarms (F(1, 38)=7.9, p=0.008). The RTs to targets were faster and standard deviation of RTs were larger in the ADHD group on baseline than the control group (F(1,38)=7.8, p=0.008; F(1,38)=13.86, p=0.001).

ADHD placebo vs. controls. Similar results on performance data as reported above were found for the comparison of the ADHD group on placebo and the control group. These data are summarized in Table 3. The control group was more accurate (F(1,38)=10.8, p=0.002) and showed a trend (F(1, 38)=5.7, p=0.020) towards being less impulsive than the ADHD group on placebo. A trend towards faster RTs to correctly identified targets and larger standard deviation of RTs were found in the ADHD group on placebo compared to the control group (F(1,38)=3.84, p=0.03; F(1,38)=5.28, p=0.027).

ADHD on methylphenidate vs. controls. There were no differences in performance between the ADHD group on lower and higher doses of methylphenidate compared to the control group.

ADHD across medication conditions. A trend towards a medication condition effect was found for % hits (F(3,57)=3.37, p=0.025) and a significant effect was found for false alarms (F(3,57)=4.82, p=0.005). Post-hoc analyses revealed the following effects:
ADHD group on the lower and higher dose of medication had fewer false alarms than at baseline (lower dose $t(38)=2.41$, $p=0.021$; higher dose $t(38)=2.45$, $p=0.019$): ADHD group on the higher dose scored a higher percentage of hits than on placebo ($t(38)=2.35$, $p=0.024$) (Table 3). No differences were found across medication conditions for RT or standard deviation of RT.

Table 3.

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).

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>ADHD Baseline</th>
<th>ADHD Placebo</th>
<th>ADHD Lower Dose</th>
<th>ADHD Higher Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Hits</td>
<td>71.4 (15.4)</td>
<td>57.9+ (18.1)</td>
<td>53.6* (18.8)</td>
<td>61.4 (19.9)</td>
<td>66.7 (17.1)</td>
</tr>
<tr>
<td>% False Alarms</td>
<td>3.3 (2.9)</td>
<td>11.7* (12.2)</td>
<td>8.3+ (8.9)</td>
<td>4.8 (4.8)</td>
<td>4.7 (4.5)</td>
</tr>
<tr>
<td>Mean RT to targets (ms)</td>
<td>577.15 (46.0)</td>
<td>510.20*(99.21)</td>
<td>525.76+ (86.37)</td>
<td>552.85 (63.24)</td>
<td>546.74 (77.28)</td>
</tr>
<tr>
<td>Mean SD in RT to targets (ms)</td>
<td>131.74 (26.1)</td>
<td>167.69*(44.31)</td>
<td>161.39+(52.43)</td>
<td>135.22 (38.21)</td>
<td>133.61(25.53)</td>
</tr>
</tbody>
</table>

* $p<0.01$ for comparison of ADHD group and control group
+ $p<0.05$ for comparison of ADHD group and control group
**ERP Data**

Grand average ERPs elicited by targets comparing the ADHD group on baseline and the control group at all electrode sites are shown in Figure 2. The grand average at the Pz electrode site comparing the ADHD group on baseline and the control group are presented in the top panel of Figure 3 while the grand average at the Pz electrode site comparing the ADHD group on higher dose and the control group is shown in the bottom panel of Figure 3. These figures illustrate differences in ERP latencies for the N2 and P3 components between the ADHD group off medication and the control group, that are normalized on medication. These differences are also illustrated graphically in Figure 3.

**ADHD baseline vs. controls.**

**N1.** No differences were found for N1 latency or N1 amplitude.

**P2.** A trend towards significant group effect for P2 latency was found (F(1,32)=5.06, p=0.031), due to shorter P2 latencies in the ADHD group. P2 amplitude differences were not found between the two groups.

**N2.** A significant group effect was found for N2 latency (F(1,31)=21.51, p=0.001), due to shorter latencies in the ADHD group on baseline than the control group. Inspection of individual data revealed that 100% of the children with ADHD had shorter mean N2 latencies than the mean N2 latency of the control group. No differences in N2 amplitude were found.

**P3.** A significant group effect for P3 latency was found (F(1,32)=10.16, p=0.003), due to longer P3 latencies in the ADHD group on baseline (Table 4). Inspection of individual data revealed that 94.1% of the children with ADHD had longer mean P3 latencies than the mean P3 latency of the control group. These data are also illustrated in Figure 4. P3 amplitude differences were not found between the two groups.
Figure 2. ERP waveforms at all electrodes for the ADHD group on baseline (red) and control group (blue)
Figure 3. Grand average ERPs to targets on the CPT showing (A) the ADHD group on baseline in red and the control group in blue and (B) the ADHD group on higher dose in red and the control group in blue.
ADHD Placebo vs. controls.

N1. No differences were found for N1 latency or N1 amplitude between ADHD placebo and controls.

P2. No P2 latency or amplitude differences were found between the ADHD group on placebo and controls.

N2. As with the ADHD baseline vs. controls, a significant group effect was found for N2 latency ($F(1,31)=11.66$, $p=0.002$), due to shorter latencies in the ADHD group on placebo than the control group. Inspection of individual data revealed that 100% of the children in the ADHD group had shorter mean N2 latencies than the mean N2 latency of the control group. N2 amplitude differences were not found.

P3. Similar results as reported for the ADHD on baseline vs. controls were found for the ADHD group on placebo vs. controls, whereby there was a strong trend towards a significant group effect for P3 latency ($F(1,30)=7.07$, $p=0.012$). Once again, this effect was due to longer P3 latencies in the ADHD group on placebo (Table 4). Inspection of individual data revealed that 93.3% of the children in the ADHD group had longer mean P3 latencies than the mean P3 latency of the control group. P3 amplitude differences were not found between the two groups.

ADHD on methylphenidate vs. controls.

N1. A trend towards a significant group effect was found for N1 latency ($F(1,33)=5.77$, $p=0.022$), as a result of shorter N1 latency in the ADHD group on lower dose methylphenidate. This effect was not found when comparing the ADHD group on higher dose and the controls. No N1 amplitude differences were found.

P2. On lower dose of methylphenidate, no significant differences were found between the ADHD group and controls for P2 latency or P2 amplitude. On the higher dose of methylphenidate a trend towards a significant group effect was found for P2 latency.
(F(1,32)=4.51, p=0.041), due to longer P2 latencies in the ADHD group than controls. No P2 amplitude group differences were found.

**N2.** A significant group effect was found for N2 latency (F(1,32)=37.90, p=0.001), as a result of shorter N2 latencies in the ADHD group on lower dose methylphenidate compared to the control group. Inspection of individual data revealed that 100% of the children with ADHD had shorter mean N2 latencies than the mean N2 latency of the control group. No N2 latency differences were found between the ADHD group on higher dose methylphenidate and the control group. No N2 amplitude group differences were found.

**P3.** On both the lower and higher doses of methylphenidate, no significant differences were found between the ADHD group and the controls for P3 latency. On the higher dose of methylphenidate, the ADHD group in fact had slightly shorter P3 latency than the controls; however, this did not reach significance. No P3 amplitude group differences were found. These data are presented in Table 4 and illustrated in Figure 4.

**ADHD across medication conditions.**

**N1.** No N1 amplitude differences were found when the ADHD group was compared across the four medication conditions. A trend towards a significant condition effect was found for placebo vs. lower dose (F(1,32)=6.66, p=0.015), which was due to longer N1 latencies on placebo.

**P2.** No differences in P2 amplitude or P2 latency were found between baseline vs. placebo. Across electrodes, a trend towards a condition effect was found for P2 latency baseline vs. lower dose (F(1,32)=3.49, p=0.039) and was significant for the ADHD on baseline vs. higher dose (F(1,32)=4.26, p=0.008). This was due to shorter latencies on baseline than on lower or higher dose of methylphenidate. No differences in P2 amplitude were found in these comparisons. No differences in P2 latency or P2 amplitude were found between lower vs. higher dose of methylphenidate.
N2. No N2 amplitude differences were found across all four medication conditions. In pairwise comparisons a significant condition effect was found for baseline vs. higher dose (F(1,30)=36.32, p=0.001) and placebo vs. higher dose (F(1,30)=32.34, p=0.001), which were both due to longer N2 latencies on the higher dose. Inspection of individual data revealed that 92.3% of the children with ADHD had longer N2 latencies on higher dose than on both baseline and placebo.

P3. No differences in P3 amplitude or P3 latency were found for baseline vs. placebo. A trend towards a condition effect was found for P3 latency for placebo vs. lower dose (F(1,32)=5.10, p=0.032) and a significant condition effect for placebo vs. higher dose (F(1,32)=8.41, p=0.001) was found. This was due to longer latencies on placebo than on lower or higher dose methylphenidate and inspection of individual data revealed that this was true for all of the children with ADHD. Similar results were found when baseline was compared to the medication conditions. No differences in P3 latency were found between lower dose vs. higher dose of methylphenidate. A trend towards a condition effect was found for P3 amplitude between placebo vs. lower dose (F(1,32)=4.47, p=0.044), which was due to smaller amplitudes on placebo. This trend was also found for placebo vs. higher dose (F(1,32)=4.27, p=0.048).
Figure 4. The mean latencies (ms) of N2, P2 and P3 for the control group and the ADHD group across medication conditions are shown.

Table 4.

Mean N1, N2, P2 and P3 latencies (ms) and P3 amplitude (μv) for the control group and ADHD groups (±SD)

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>ADHD Baseline</th>
<th>ADHD Placebo</th>
<th>ADHD Lower Dose</th>
<th>ADHD Higher Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1 Latency</td>
<td>199.97 (8.02)</td>
<td>194.88 (5.57)</td>
<td>207.19 (8.86)</td>
<td>174.12* (8.23)</td>
<td>194.18 (6.21)</td>
</tr>
<tr>
<td>P2 Latency</td>
<td>292.51 (8.07)</td>
<td>275.85* (10.21)</td>
<td>295.12 (2.98)</td>
<td>302.96* (6.21)</td>
<td>310.65 (5.10)</td>
</tr>
<tr>
<td>N2 Latency</td>
<td>377.03 (16.16)</td>
<td>312.97* (11.14)</td>
<td>336.54* (8.10)</td>
<td>330.44* (13.08)</td>
<td>391.67 (6.41)</td>
</tr>
<tr>
<td>P3 Latency</td>
<td>542.47 (37.52)</td>
<td>616.15* (32.69)</td>
<td>605.95* (34.92)</td>
<td>541.91 (32.21)</td>
<td>496.8 (26.56)</td>
</tr>
<tr>
<td>P3 Amplitude</td>
<td>17.84 (3.14)</td>
<td>18.94 (3.84)</td>
<td>14.56 (2.84)</td>
<td>20.24 (3.40)</td>
<td>19.15 (4.24)</td>
</tr>
</tbody>
</table>

* p<0.01 for comparison of ADHD and controls
+ p<0.05 for comparison of ADHD and controls
Correlation between N2 and P3 Latency

For the control group, a correlation between N2 and P3 latency was not found. For the ADHD group, a significant correlation was found between N2 and P3 latency at baseline ($r=0.855$, $p<0.001$) and placebo ($r=0.621$, $p=0.001$) and a trend was found on the lower dose ($r=0.448$, $p=0.019$). On the higher dose a correlation between N2 and P3 latency was not found.

Distribution

There were no significant hemispheric effects or interactions in any of the analyses of the ADHD group and the control group. Similarly, no significant hemispheric effects or interactions were found when the ADHD group was compared across medication conditions. When anterior and posterior electrode sites were analyzed, no significant group effects or interactions were found. The topographical distribution of the N2 and P3 for the control group and ADHD group on baseline, lower dose and higher dose is shown in Figure 5. Although the latencies of these components were different, and amplitudes varied somewhat between groups and across medication conditions, this figure illustrates that the topographical distribution of these components was not significantly altered by ADHD or medication.

Consistent significant electrode main effects that were found across all comparisons, as follows: 1) A significant N1 latency effect was found due to longer latencies at posterior electrode sites; 2) a significant P2 amplitude and P2 latency effect was found due to larger amplitudes at posterior electrode sites and longer latencies at anterior electrode sites; 3) a significant N2 amplitude effect was found due to larger amplitudes at posterior electrode sites; 4) a significant P3 amplitude main effect was found due to larger amplitudes at the posterior electrode sites. These significant anterior posterior effects are illustrated in Figure 5.
Figure 5. Grand average ERP waveforms for A) controls; B) ADHD group on baseline; C) ADHD group on lower dose; and D) ADHD group on higher dose. Topographical maps for N2 and P3 for each condition show distribution of these components.
Posner selective attention task.

Performance Data

A repeated measures ANOVA using three within subject factors (cue, visual field and delay) and group as the between subject factor was performed on the comparisons presented below. The overall RTs for the valid and invalid conditions in both the 100 ms and 800 ms conditions are presented in Table 5. The complete data for all trial types are presented in Appendix 2. In general, no significant differences between the ADHD group and the control group across medication conditions were found. In addition, no significant medication effects were found. Significant results were consistently found for cue and delay and are reported below.

**ADHD baseline vs. controls.** The effects that were significant in this analysis were cue (F(2,76)=66.46, p=0.001) and delay (F(1,38)=81.10, p=0.001). These effects were due to faster RTs in the valid condition than the invalid condition and faster RTs in the 800 ms delay than the 100 ms delay (Table 5). No group effects or group interactions were found.

**ADHD placebo vs. controls.** No group effects or group interactions were found. Once again the effects that were significant were cue (F(2,118)=70.65, p=0.001) and delay (F(1,59)=86.91, p=0.001). Once again, these effects were due to faster RTs in the valid condition than the invalid condition and faster RTs in the 800 ms delay than the 100 ms delay (Table 5).

**ADHD methylphenidate vs. controls.** No group effects or group interactions were found. On lower dose, significant effects were found for cue (F(2, 158)=107.29, p=0.001) and delay (F(1,79)=141.88, p=0.001). Similar effects were found on higher dose
for cue (F(2,198)=144.45, \( p=0.001 \)) and delay (F(1,99)=167.87, \( p=0.001 \)). These effects were due to RT differences reported above.

**ADHD across medication conditions.** For this analysis, medication condition was added as a within subject variable. Effects were found for cue (F(2,42)=67.47, \( p=0.001 \)) and delay (F(1,21)=46.43, \( p=0.001 \)). This was due to faster RTs in the valid condition than the invalid condition and faster RTs in the 800 ms delay than the 100 ms delay. A effect for medication condition was not found.

Table 5.

Performance data on the Posner selective attention task showing mean overall RTs of the valid and invalid trials for the controls and ADHD groups

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>ADHD Baseline</th>
<th>ADHD Placebo</th>
<th>ADHD Lower Dose</th>
<th>ADHD Higher Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>100 ms SOA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall valid</td>
<td>441.50 (85.74)</td>
<td>435.65 (64.16)</td>
<td>474.59 (115.46)</td>
<td>468.38 (77.76)</td>
<td>467.57 (102.96)</td>
</tr>
<tr>
<td>Overall invalid</td>
<td>502.35 (94.84)</td>
<td>507.50 (106.74)</td>
<td>540.32 (117.30)</td>
<td>523.76 (88.29)</td>
<td>513.38 (107.48)</td>
</tr>
<tr>
<td><strong>800 ms SOA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall valid</td>
<td>357.20 (64.46)</td>
<td>377.30 (54.07)</td>
<td>364.68 (103.69)</td>
<td>358.95 (106.59)</td>
<td>359.67 (81.83)</td>
</tr>
<tr>
<td>Overall invalid</td>
<td>410.05 (92.08)</td>
<td>436.40 (70.54)</td>
<td>418.64 (120.20)</td>
<td>401.95 (109.35)</td>
<td>417.52 (84.53)</td>
</tr>
</tbody>
</table>
DISCUSSION

Summary of the CPT

On the performance measures of the CPT, the ADHD group relative to the control group scored a lower percentage of hits to targets and made more false alarms to non-targets, which improved with methylphenidate. In addition, the ADHD group was found to have shorter RTs to targets while off medication (baseline) than the control group, which were normalized with methylphenidate. The RT changes were consistent with observed changes in behaviour and performance style during the task.

The ERP data for the CPT revealed that the N2 latency was shorter in the ADHD group off medication and on placebo than the normal control group. In contrast, the P3 latency was longer in the ADHD group off medication than the control group. The N2 and P3 latencies were correlated in the ADHD group off medication. A correlation between these two latencies in the control group was not found. The present study also found a differential medication effect between the latencies of the N2 component and the later P3 component. While only the higher dose of methylphenidate increased N2 latency, a different effect was found for P3 latency, where both lower and higher doses decreased P3 latency. A correlation between N2 and P3 latency was not found on the higher dose of medication. When individual difference profiles were examined, the above findings were found for the majority of children with ADHD. To our knowledge, this is the first report of a dissociation of effects that are each normalized with medication.
The combined performance and ERP data will be discussed in terms of an attentional processing model for the CPT. This will allow for the characterization of the attentional deficit in children with ADHD on this task and the examination of the effects of methylphenidate on attentional processing.

**An Attentional Processing Model for the CPT - Characterizing the Attentional Deficit.**

An attentional processing model for the CPT was introduced at the outset of this study, which identified several processes that are involved while a subject performs this task. First, the subject must focus on the incoming stimulus and determine whether it is a target or non-target. Second, the subject must make a response if the stimulus is a target or inhibit a response if it is a non-target and finally, the subject must prepare for the next stimulus. An attentional processing model for the CPT was introduced suggesting that the ERPs may reflect the different attentional processes involved during the task and allow for the characterization of a specific attentional processing deficit in ADHD.

The N2 ERP component, is believed to reflect focused attention to the features of the stimulus (Luck & Hillyard, 1994) and the classification of presented stimuli (Breton et al., 1988). Ritter, Simson, Vaughan, et al. (1979) examined single trial waveforms of ERPs during a vigilance task and found that N2 covaried in latency with RT. Similar results were reported by Breton et al. (1988), suggesting that N2 reflects decisional processes controlling behavioural responses. Similarly, the P2 is also thought to be involved in the detection of features in a stimulus and thus on the CPT, both the N2 and P2 may reflect attentional processing involved in evaluating whether a stimulus is a target or non-target and deciding whether to respond or inhibit a response.

In contrast, the later P3 component is thought to reflect post-decisional processing, such as closure of the decision process, revision of strategies for future trials, preparing for the upcoming stimulus and the updating of memory (Picton, 1992). Several investigators
have examined the relationship between RT and the P3 (for a review see Picton, 1992). Ritter et al. (1972) recorded RT simultaneously with the P3 in a simple oddball task and found that the RT occurred about 50 ms before the peak of the P3. Since time is required for impulses to travel from the brain to the muscles, it is impossible for the P3 to represent the decision process that invokes the response (Picton, 1992). As a result, the P3 is believed to reflect post-decisional processes as described above. Thus, on the CPT, the P3 may reflect post-decisional attentional processes involved while the subject prepares for the next stimulus or reviews strategies for the next stimulus.

In this study, the N2 latency was found to be shorter in children with ADHD off medication than in the control group, with a trend in the same direction for P2 latency. This suggests that off medication and on lower doses of medication, children with ADHD are quicker in their evaluation of stimuli and in their decision to respond. This faster processing was reflected in greater impulsivity (i.e. increased false alarms) and faster RTs off medication.

In contrast, the P3 latency was found to be longer in children with ADHD off medication than in the control group. This suggests that off medication, children with ADHD are slower in post-decisional processes, including preparing for the next stimulus. They may be more distracted during this period and as a result less prepared for the next stimulus. This may be reflected in inattention and, indeed, children with ADHD were more inattentive off medication (i.e. lower %hits).

The combined performance and ERP data provides a model for the attentional processing deficits displayed by children with ADHD on this version of the CPT: 1) children with ADHD are faster in response decision processing, taking less time to evaluate each stimulus, which is reflected by shorter N2 latencies, greater impulsivity and faster RTs than controls; 2) children with ADHD are slower in post-decision processing, reflected by longer P3 latencies and greater inattention than the control group. Thus, this model of the
attentional processing deficit is specific to the cognitive processes involved in the temporal processing of stimuli and demonstrates attentional deficits at different points.

Although this interpretation of the data through the identification of specific attentional deficits at different temporal stages is intriguing, an alternative view has been suggested (Zelazo, personal communication) which attributes both the faster N2 processing and slower P3 processing to the ADHD child's being captured by environmental stimuli. This interpretation of the data suggests that the child with ADHD is captured by the target stimulus and processes the stimulus quickly, as reflected by faster N2 processing and faster RTs off medication but then continues to process the stimulus longer than in children without ADHD, resulting in longer P3 latencies. This interpretation of the data is interesting since children with ADHD have been described as being more likely to be captured by novel situations and environmental stimuli than children without attention deficits (Malone et al., 1994). However, when children with ADHD are observed in naturalistic settings, they tend to switch from one activity to another and as a result, do not appear to stick to any one activity for a long period of time. Thus while this interpretation of the data as being captured by environmental stimuli may account for the faster N2 processing and faster RTs in the ADHD group off medication, it is unclear if the longer P3 latencies are attributable to the same process.

**Effects of Methylphenidate on Attentional Processing on the CPT.**

It was introduced at the outset of this study that the effects of methylphenidate on attentional processing during the CPT may be examined with ERPs, allowing for the identification of specific aspects of attentional processing that are affected by medication. The present study found that the latency of the N2 component was shorter in the ADHD group off medication and on lower dose than the control group. However, when the ADHD group on higher dose was compared to the control group, no difference in latency was found, signifying a normalization of the N2 latency component on the higher dose. In
addition when the ADHD group was compared across medication conditions, longer N2 latencies were found on higher dose than off medication suggesting the ADHD group was taking longer to evaluate the stimuli and slower in response decision processing. This was reflected by a normalization on impulsivity and RT measures and suggests that methylphenidate exerts its effectiveness on these response decision processes, allowing the child with ADHD to slow down and choose responses more carefully.

The P3 component, which was found to be longer off medication in the ADHD group compared to controls, was also normalized on medication. This normalization occurred at both the lower dose and higher doses of medication, unlike the N2, where normalization only occurred at the higher dose. These results suggest that on medication the ADHD group is faster on post-decisional processes and is better prepared to evaluate the upcoming stimulus and once the decision was made that the stimulus was a target. Methylphenidate may exert its effectiveness by quickening the processes involved in bringing closure to the present trial and preparing for the upcoming stimuli. This is reflected by a lack of difference in %hits between the ADHD group on medication and controls.

Thus, the effects of methylphenidate on attentional processing on the CPT may be summarized as follows: 1) normalization of response decision processing on higher dose, characterized by a normalization of N2 latency, %false alarms and RT and 2) normalization of post-decision processing on both lower and higher doses, characterized by normalization of P3 latency and %hits.

**General Discussion of the Attentional Processing Model for the CPT and Effects of Methylphenidate**

**Overview.**

The attentional processing model for the CPT and the model of effects of methylphenidate on attentional processing are limited to the version of the CPT that was
used in the present study. The CPT-double is characterized by a fast stimulus presentation (50 ms), a short ISI (1 second) and the requirement to respond to an infrequent target (repeated letter). This is different from the Conners (1994) version of the CPT which requires the subject to respond to all stimuli except for an X and varies the interstimulus interval between 1 and 4 seconds and the van der Meere (1995) version of the CPT, which involves a rare target presentation rate (less than three per minute). These versions of the CPT may involve different attentional processes and different results would be expected. It would be interesting to record ERPs while children with ADHD performed both of these versions of the CPT to specifically examine the effects of ISI on attentional processing on the Conners CPT, and the effects of slow target presentation rate on the van der Meere version of the CPT. It is hypothesized that children with ADHD would demonstrate a similar attentional deficit on the short ISI condition of the Conners CPT; however, on the long ISI condition on the Conners and on the van der Meere CPT, it is hypothesized that children with ADHD would not demonstrate shorter N2 latencies, but would still demonstrate longer P3 latencies. The effects of long ISI or lower target frequency would act to slow down the fast response decision processes observed with more rapid presentation and increased target frequency.

The attentional processing model developed in the present study is not only limited to the specific version of the CPT that was used, but also limited to the classification of ADHD according to DSM-III-R criteria that was presently used for diagnosis. The most recent classification system DSM-IV, has identified two symptom domains (inattention and hyperactivity/impulsivity) and has specified three subtypes of the disorder: a predominantly inattentive type, a predominantly hyperactive/impulsive type and a combined type. In
contrast, DSM-III-R used a single symptom list and identified only a single form of the disorder, ADHD. A review of the histories of the subjects in the present study, revealed that the majority would meet criteria for the DSM-IV diagnosis of ADHD-combined type.

In future studies, it would be interesting to examine the performance of children with different subtypes of ADHD on the CPT. It is hypothesized that the predominantly inattentive subtype would show similar problems with inattention and longer P3 latencies, but would not demonstrate faster N2 latencies and faster RTs. Furthermore, it is hypothesized that the predominantly impulsive/hyperactive subtype would display faster N2 latencies and faster RTs but would not display longer P3 latencies and higher levels of inattention and that the combined type would display a similar pattern found in the present study. This line of investigation would follow the approach of Halperin and colleagues (e.g. Halperin, Newcorn, Sharma et al., 1990; Halperin, O’Brien, Newcorn et al., 1990; Newcorn, Halperin, Healey et al., 1988; Halperin, Wolf, Pascualvaca et al., 1988) looking at CPT error patterns in different subtypes of children with ADHD and different co-morbidities that occur with ADHD. Their research has shown that the CPT is an instrument that can discriminate between different subtypes of the disorder. The accurate diagnosis of ADHD is critical to ensure homogeneous groups for research. In addition, an accurate understanding of the nature of the attentional processing deficit may aid in the prediction of stimulant medication response and thus, help with treatment decisions. Further development of the attentional processing model for the CPT in different subtypes of ADHD will aid in both the diagnosis and treatment of the disorder.
**Performance Data.**

The present study is consistent with several previous reports of deficits in CPT performance in groups with ADHD (Coons et al. 1987; Michael et al.: 1981; Rapport, Dupaul, Stoner, et al., 1986). Michael et al. (1981) using the CPT-X and CPT-BX found that children with ADHD made more errors of omission and commission than a control group. Rapport et al. (1986) found similar results with the CPT-AX. However, a limitation of these studies is their inability to characterize the nature of the attentional deficit, contributing to these performance deficits. Through the combined analysis of early and late ERP components and performance data, the present study suggests that the specific attentional processing deficits on the CPT for children with ADHD are at the stimulus evaluation stage and post-decisional processing stage. Corkum & Siegel (1993) reported that children with ADHD do not show evidence of a sustained attention deficit on the CPT as defined by a differential decline in performance over time compared to normal controls. However, the CPT measures additional parameters than solely sustained attention and this study suggests that children with ADHD do indeed have specific attentional processing deficits on this task.

In the present study, the finding of shorter RTs to targets in the ADHD group off medication compared to controls was not expected. While most other studies have examined omission and commission errors, few studies employing comparable versions of the CPT have examined RT. Although Verbaten et al. (1994) measured RT to hits, a control group was not included in the study so that comparison in performance with the ADHD group was not possible. Conners (1994) examined RT to hits, but a much different version of the CPT was employed. Although control children were tested in this study, their
performance was not compared to a ADHD group. Recently, van der Meere et al. (1995) used a version of the CPT with a very slow target presentation and found a ADHD group had significantly longer RTs to targets than controls. The ADHD group also demonstrated progressively slower RTs to targets over time. However, this version of the CPT is markedly different than the version used in the present study, making it difficult to compare results.

The finding of a “normalization” of omission and commission errors on medication is consistent with previous research (Bergman et al., 1990; Michael et al., 1981; Rapport et al., 1986). In addition, in the present study RT differences between the ADHD group on medication and the control group were not found. Although the RTs for the ADHD on medication were slower than the RTs off medication, the differences were not significant. Thus, a slowing of RT across medication conditions was not found. However, the ADHD group displayed a different response style on medication, characterized in general by an improved, consistent focused attention throughout the task, which was reflected in a smaller standard deviation to hits on medication.

The analyses of the ADHD group on the performance measures of the CPT across medication conditions did not reveal any significant dose-related (lower dose vs. higher dose) increase or decrease (although there was a trend towards an increase in %hits on the higher dose of methylphenidate compared to the lower dose). Dose-related improvements on the CPT may be predicted by a neurochemical theory proposed by Malone et al. (1994), whereby methylphenidate is thought to restore balance between an underactivated left lateralized dopaminergic system and an overaroused right lateralized noradrenergic system in a child with ADHD. Clinical observations suggest that the child with ADHD on
medication is better able to maintain goal-directed responding and process redundant information. Therefore, increasing the dose level should improve behaviours related to improved performance on the CPT. The trend towards an increase in %hits on higher dose suggests that if we had used an increased higher dose, we may have found a dose related improvement. However, it is also possible that the lower dose is sufficient for increased performance on the CPT and increasing dose may not result in improved performance. In the present study, a higher fixed dose of 20 mg was set as the upper limit that would be administered due to concerns at the Child Development Centre of medication side effects commonly associated with doses exceeding this amount. Thus, although our aim was to assess a higher dose of 0.7 mg/kg, the restriction of the higher dose limit resulted in a mean higher dose of 0.56 mg/kg. Assessment over a wider dose range than used in the present study may be needed to determine the dose response profile of performance on a CPT task.

**ERP Data.**

Consistent N1 amplitude or N1 latency differences between the ADHD and controls and the ADHD group across medication conditions were not found. Verbalen et al. (1994) is one of the few studies that has examined the N1 on the CPT. Using the CPT-X, this group did not find any effects of methylphenidate on the N1. The N1 has been most widely studied in the auditory modality using a selective attention paradigm (e.g. Hillyard et al., 1973; Woods, 1990), consisting of rapid and random dichotic presentations of brief tone pips. It has been demonstrated in adults that a higher amplitude N1 is elicited by attended vs. non-attended tones (for a review see Hillyard & Hansen, 1986). In studies with hyperactive and “formerly hyperactive” adolescent boys, the N1 to attended tones was
found to be reduced in comparison to controls (Loiselle et al., 1980; Zambelli et al., 1977). The effects of methylphenidate were not examined in these studies. This paradigm however, reflects channel selectivity which was not manipulated in the present study.

More recently, the N1 has been examined in visually cued selective attention tasks and increased N1 amplitudes to cued targets have been reported (Luck et al. 1993). These larger N1 amplitudes may reflect increased arousal to the cued targets. N1 amplitude differences were not found in the present study. However, they may be expected given that ADHD has been described to be associated with increased arousal (Malone et al., 1994).

The failure to find N1 amplitude differences may reflect the nature of the present CPT, whereby sustained attention over a long period is required and hence may fail to invoke arousal. Analysis of the ERP data in the Posner selective attention task may reveal increased N1 amplitudes in the ADHD group off medication compared to controls, which would be reflective of arousal differences.

The P2 component is thought to be sensitive to the allocation of attention and feature detection (Luck et al., 1993). In the present study only a trend towards faster processing at P2 was found for children with ADHD on baseline compared to controls, which was normalized on the higher dose of medication. This suggests that children with ADHD may be faster in early processes, believed to reflect extraction of information about the stimulus and that methylphenidate serves to slow down these processes.

The N2 latency in the present study was found to discriminate the ADHD group and the control group. On baseline, placebo, and a lower dose of methylphenidate, the ADHD group had significantly shorter N2 latencies than the control group; however on higher dose, there were no differences between the ADHD group and control group. Across medication
conditions, significant differences in N2 latency were found between the ADHD group on baseline vs. higher dose and the ADHD group on placebo vs. higher dose, which were both due to longer N2 latencies on the higher dose.

Although slower processing at the latency of the N2 component may be necessary to evaluate stimuli more completely and inhibit impulsive responding, a trade-off between slower processing and improved performance should be considered. Although in the present study, a higher dose of methylphenidate was needed to normalize the latency of the N2, the higher dose did not further improve performance over the lower dose. Trade-off between slower processing and improved performance may be studied in future research by examining methylphenidate effects over a wider range of doses.

Few studies have examined the N2 in children with ADHD. One exception is a study by Verbaten et al. (1994), in which they examined the effects of methylphenidate on the N2 during a CPT-X task. In this study, N2 amplitude to targets were observed to increase with methylphenidate, whereas there were no effects of methylphenidate on N2 latency. Verbaten et al. (1995) interpreted the lack of methylphenidate effects on N2 latency to the fact that only a single low dose of 10 mg was administered. In the present study involving two dose levels, medication effects were only with the higher dose level (19.5 mg).

The P3 has been the most widely measured ERP component in ADHD research. The P3 in the present study was found to differentiate the ADHD group off medication and the control group, whereby P3 latency in the ADHD group on baseline and placebo was significantly longer than the control group. Thus, the ERPs reflected slower processing in the ADHD group off medication compared to controls. This is consistent with a study by
Taylor et al. (1993) in which longer P3 latencies were reported in children with ADHD at baseline than controls, using an oddball talk. Further evidence was found by Sunohara et al. (in press) in a study that reported significantly longer P3 latencies in ADHD responders and nonresponders to methylphenidate treatment on baseline than controls. However, P3 latencies were only found to be reduced (normalized) in children who were responders to methylphenidate treatment. Thus, there is increasing evidence from Dr. Taylor’s laboratory that children with ADHD off medication have longer P3 latencies than control children in CPT and reading type tasks.

In the present study, both lower and higher doses of methylphenidate resulted in a significant decrease in P3 latency. These results suggest faster processing in the ADHD group on medication. On lower dose methylphenidate, a “normalization” of P3 latency in the ADHD group was found, as latencies between the ADHD group on lower dose and controls were almost identical. A further decrease in P3 latency beyond the lower dose was found on the higher dose of methylphenidate; however, this decrease was not significant. The effects of lower dose methylphenidate in the present study are similar to a report of a normalization of P3 latency in ADHD responders to methylphenidate on their optimal dose of medication (0.3 mg/kg, Taylor et al. 1993). The optimal dose of methylphenidate where the normalization of P3 latency occurred was similar to the lower dose used in the present study. Taylor et al. (1993) only examined the optimal dose of responders to methylphenidate, therefore, dose-response effects were not reported. The present study found a trend towards a decrease in P3 latency on higher dose beyond the control group or a "supernormalization" of P3 latency. Recall that due to the higher fixed dose limit of 20
mg, the mean higher dose was 0.56 mg/kg which was well below that target of 0.7 mg/kg. This may have limited our ability to see dose-related response effects.

In contrast to the findings of this study and previous studies in our laboratory demonstrating that methylphenidate reduces P3 latency, the majority of the studies in the literature have reported amplitude rather than latency changes. A number of studies have demonstrated smaller P3 amplitudes in children with ADHD that are increased with methylphenidate (Klorman et al. 1979; Klorman et al. 1983; Michael et al. 1981; Satterfield et al. 1990). However, in contrast, Klorman et al. (1987) and Klorman et al. (1988), did not find P3 amplitude increases with methylphenidate. A possible explanation for inconsistent methylphenidate effects on P3 amplitude may be related to differences across studies in the methods used for averaging ERPs. While our laboratory, along with others, have averaged ERPs on the basis of response categories (hits and correct rejections), other research groups have averaged ERPs on the basis of stimulus categories (targets and nontargets). Verbaten et al. (1994) suggested that averaging across stimulus categories, thereby including all signal trials regardless of response accuracy, will result in much different ERPs across medication conditions. If no detection is made between a signal and a nonsignal (miss), there is no difference in P3 amplitude between these two stimulus classes. However, if a signal is detected, a larger P3 amplitude is produced. Since methylphenidate generally improves response accuracy, there will be a higher number of hits to targets on medication and thus an increased P3 amplitude. A review conducted by Verbaten et al. (1994) reported that in studies averaging on the basis of stimulus classes (Klorman et al., 1979; Klorman et al., 1983), methylphenidate increased P3 amplitude. In contrast, in studies where averaging
on the basis of response class (hits), methylphenidate did not increase P3 amplitude (Klorman et al., 1987; Klorman et al., 1988).

Another plausible explanation for our finding of methylphenidate effects on P3 latency but not P3 amplitude may be related to task difficulty. The CPT-double version, which we gave, is more difficult than many of the other oddball tasks used in the literature (where there is only one target). In the CPT-double any letter can be a potential target and the subject must hold a letter in working memory and compare it to the next letter presented. Future studies employing both simple oddball tasks and more difficult tasks such as the CPT-double with the same sample, may help determine if medication changes in amplitude and latency are a function of task.

**Summary of the Posner selective attention task**

The Posner selective attention task failed to show any differences between the ADHD groups on and off medication and the control group. In the 100 ms cue condition, the RT pattern of the ADHD group was similar to the control group whereby RTs were faster in the valid than in the invalid or no cue conditions and no significant lateral differences in RTs were found. In the 800 ms cue condition, the RT pattern of the ADHD group was also similar to the pattern of the control group, which was reflected in a decrease in RT relative to the 100 ms condition. Thus, the performance of the ADHD group was similar to the control group and a selective attention processing deficit was not found.

Although it was hypothesized that methylphenidate would affect performance on this task, medication was not found to affect differentially the specific processing
components examined. Thus a medication effect on the ability to shift attention was not demonstrated.

**An Attentional Processing Model for the Posner Task.**

It was argued at the outset of this study, that the Posner task would provide a model for examining three component processes in selective attention: disengage, move and engage. Through a review of the literature, it was demonstrated that the task is sensitive to the manipulation of catecholamines and neurochemical imbalances on specific processes in selective attention. Therefore, the Posner task was believed to be a sensitive instrument to discriminate children with ADHD from normal control children on specific selective attention processes and allow for the specific examination of selective processing deficits in ADHD.

The present study did not find a selective processing deficit in children with ADHD. The results for the 100 ms SOA are consistent with RT patterns found in normal adults (e.g. Posner et al. 1987) and in children with ADHD off medication (Carter et al., 1995 and Swanson et al., 1991, 1990). The results of the present study provide further evidence that children with ADHD are able to perform covert shifts of attention in a comparable fashion to a control group. Furthermore, these data suggest that the posterior visual-selective attentional system in children with ADHD is functioning normally and specific deficits in the disengage, move or engage operations of the posterior visual-selective attentional system are not found.

In the present study, the results for the 800 ms condition are consistent with performance in normal adults (e.g. Posner et al., 1987). However, the results are in contrast to previous studies of children with ADHD, reporting laterality differences in RT in the 800
As a result, support for the hypothesis that off medication, children with ADHD would disengage attention more rapidly than controls as demonstrated by a decreased cost of invalid cues, was not found. Swanson et al. (1991, 1990) reported an asymmetrical pattern of performance in children with ADHD characterized by reduced costs to invalidly cued targets in the left visual field. This finding was interpreted to reflect a dysfunction in the hemisphere receiving the invalid cue (left hemisphere) and since the asymmetrical pattern was found only in the 800 ms SOA condition, a disruption of the anterior attentional mechanism was proposed. Swanson et al. (1990, 1991) theorized that the children with ADHD demonstrated an inability to sustain attention at the invalidly cued location over the 800 ms.

Carter et al. (1995) designed a study to confirm the presence of a lateralizing deficit in children with ADHD using two different cue types (exogenous and endogenous), citing that exogenous cues as employed by Swanson et al. (1990, 1991), produce a biphasic response. Carter et al. described in the exogenous cue condition, SOAs less than 350 ms, produce RTs to valid targets that are shorter than invalid targets, but at SOAs longer than 350 ms, RTs to valid trials are longer than invalid trials. This increase in RTs for the SOAs longer than 350 ms was attributed to an inhibition of return. Carter et al. reported similar findings as Swanson et al. (1990, 1991) of an asymmetrical performance deficit characterized by reduced costs to invalidly cued left visual field targets, but only in the endogenous cue condition. However, they interpreted their results differently suggesting that this performance pattern was due to a right hemisphere deficit in ADHD. The authors rationalized that in the endogenous cue condition, a deficit must reflect a problem orienting
to the location of the target and not disengaging from the invalid cue as proposed by Swanson et al. (1991, 1990).

Although Carter et al. (1995) did not find the lateralizing deficit using the exogenous cues, there appear to be some concerns with the methodology employed in this study. In the endogenous cue condition, the arrow cues correctly predicted the location of the target on 80% of the cued trials and incorrectly predicted the location of the target on 20% of the cued trials. However, in the exogenous cue condition, the cue had no predictive value as targets were presented at the cued location on only 50% of the trials. Since different conditions were employed with the endogenous and exogenous cues, it is difficult to compare the two tasks and interpret the differential findings. In addition, as reviewed previously, Carter et al. (1995) identified that in the exogenous cue condition RTs to validly cued targets are longer than for invalidly cued targets when SOAs are longer than 350 ms. However, this effect is generally found only when using a “double cueing” paradigm, whereby subjects are (1) cued to a peripheral location, (2) cued back to a central fixation and (3) presented a target at the location that was first cued. Under these conditions, RTs to validly cued locations are longer than invalidly cued locations due to an inhibitory effect called inhibition of return (Rafal et al., 1989) that is suggested to favour novelty in visual scanning. Carter et al. (1995) did not use this double cueing procedure and found longer RTs to valid targets than invalid targets in the longer SOA condition in the single exogenous cue paradigm. This finding was reported to be as expected and attributed to an inhibition of return. However, inhibition of return was not experimentally manipulated in their study and thus there finding of the absence of a validity effect at the longer SOA must
be viewed as unexpected and inconsistent with performance in normal adults (Posner et al., 1987), and normal children and children with ADHD (Swanson et al., 1991, 1990).

Given the methodological concerns of the Carter et al. (1995) study, their results must be viewed cautiously. As a result, there is limited evidence to suggest asymmetrical performance of children with ADHD on the Posner task and in fact, Swanson’s own research group was unsuccessful in replicating these findings in a subsequent study (Nigg et al., 1993). Thus, the failure of the present study to replicate the findings of Swanson et al. (1991, 1990) is not surprising. Swanson (personal communication) has suggested that the asymmetrical performance may be limited to a “pure” group of children with ADHD without comorbid conditions. However, analysis of a subgroup of pure children with ADHD in the present study did not reveal an asymmetrical performance, although the power of this analysis was substantially reduced due to the lower number of subjects.

**Effects of Methylphenidate on the Posner Selective Attention Task**

It was suggested at the outset of this study that the Posner selective attention task is a sensitive instrument of catecholaminergic manipulation through pharmacological intervention, and thus the dose-related effects on components of this task may be examined. However, methylphenidate effects on the selective attention processing components examined were not found. Thus, support for the predicted dose-related increase in RT in invalid trials was not found.

Novak et al. (1995) is the only published study that has examined the effects of methylphenidate on the Posner selective attention task in children with ADHD. Similar to the present study, main effects of medication on RT were not found. However, only a
single dose of approximately 0.3 mg/kg was administered and, thus, dose-response effects of the medication on the Posner selective attention task were not examined. In addition, a single SOA of 300 ms was used, making comparisons with studies typically using both longer and shorter SOAs difficult.

The failure to find medication related changes in performance on the Posner selective attention task presently may signify that the task is not sensitive to medication-related effects. However, Clark et al. (1989) examined the effects of pharmacologically manipulating catecholamine levels in normal adults and found that administration of the dopamine antagonist, droperidol and the alpha agonist, clonidine produced reductions in the costs of invalid cues; suggesting that both dopamine and norepinephrine are involved in facilitating the disengagement of attention. Similarly, Wright et al. reported a reduction in the cost of invalid cues in subjects with Parkinson’s disease. Since dopamine agonists (e.g. L-dopa, deprenyl) are commonly used to treat Parkinson’s disease, the cognitive impairment of the disorder may be related to degenerative dopamine pathways. In contrast, subjects with schizophrenia (thought to be related to increased dopamine) were found to have a decreased ability to shift attention in certain conditions (Posner et al., 1988). Together, these data suggest that the Posner selective attention task discriminates the manipulation of catecholamine levels pharmacologically and also discriminates neurochemical imbalances in specific neurological disorders.

An alternative explanation for the lack of evidence in the present study to support our hypothesis of a methylphenidate-induced decrease in the ability to shift attention, is that the doses administered were not sufficient to produce such an effect. Although the initial aim of the study was to assess a higher dose of 0.7 mg/kg, the mean higher dose
administered was 0.56 mg/kg. Thus, although the aim of the study was to address potential adverse effects of methylphenidate, we were restricted in testing our hypothesis of a methylphenidate induced decrease in the ability to shift attention due to clinical concerns of administering higher doses for a research study.

In general studies that have administered higher doses of methylphenidate for research, have not always been successful in finding empirical evidence for the adverse effects of methylphenidate observed clinically. For example, Tannock et al. (1993) did not find an overfocusing effect of methylphenidate on a pre-cued RT test at high doses of 1.0 mg/kg. Although a “substantial proportion” of the subjects displayed clinical symptoms of motor stereotypy and reduced responsivity at 1.0 mg/kg, only the observation of intense concentration was significantly related to sustained focused attention at this high dose of methylphenidate. Douglas et al. (1995) administered a high dose of 0.9 mg/kg and found little evidence of adverse medication effects on divergent thinking, perseveration or the ability to shift mental set. Conversely, the most common pattern of performance indicated a linear improvement across doses of 0.3, 0.6 and 0.9 mg/kg and adverse side effects of methylphenidate were not reported to emerge as a serious problem. However, it has recently been shown that methylphenidate may induce slower cognitive processing without an improvement in task accuracy (Campbell et al., 1996).

Generally, the results of these studies seem to contradict clinical observations, suggesting that stimulants may reduce ADHD symptomatology, but also make some children with ADHD over-focused (Swanson et al., 1991), “zombie-like” (Swanson et al., 1978), overly passive/submissive (Granger et al., 1993) and “dampened” in their identification of social behaviours in other children (Whalen et al., 1990). Rie (1976)
reported that children on doses moderate to high doses of methylphenidate appeared "more bland or flat emotionally, lacking both the age-typical variety and frequency of emotional expression...they responded less, exhibited little or no initiative or spontaneity. offered little indication of either interest or aversion, showed virtually no curiosity, surprise or pleasure and seemed devoid of humour" (p.258). Recently, Malone et al. (1994) has described differences in the unmedicated and medicated child with ADHD. The unmedicated child with ADHD is described as "animated" or to having a certain "spark", which is in contrast to the medicated child with ADHD who is described as over-serious, over-focused, emotionally unexpressive and even depressed despite a decrease in ADHD symptomatology. These observations of flattened affect are viewed as unacceptable side effects of methylphenidate (Malone et al., 1994).

The majority of studies that have failed to provide empirical support for these clinical observations have focused primarily on cognitive tasks. It is possible that the medication-related improvement in general task behaviour (i.e. improved attention and reduced impulsivity) may overshadow adverse effects. However, even if these studies had shown adverse cognitive effects demonstrated by attentional over-focusing, an increase in perseveration or a decreased ability to shift attention, it would be difficult to determine how these effects may extrapolate to behaviour outside the laboratory. While there is concern surrounding the potential adverse effects of methylphenidate on affect and social interaction, few studies have addressed these issues specifically. Future studies that correlate the dose related effects of methylphenidate on sensitive cognitive measures with more qualitative measures on affect and social interaction are recommended. Although the
Posner selective attention task was believed to be sensitive to the dose-related effects of methylphenidate on specific aspects of attentional processing, this was not found to be true. As a result, the data obtained from this study did not support a neurochemical theory of ADHD proposed by Malone et al. (1994).

**Limitations of the Study**

The attentional processing model and the model of effects of stimulant medication on attentional processing are limited to the version of the CPT that was used in the present study. In addition, the model is limited to children with ADHD diagnosed according to DSM-III-R criteria as DSM-IV was not available at the time this study was conducted. While children with predominantly inattentive or predominantly hyperactive/impulsive ADHD subtypes may differ in their attentional processing deficits, the nature of the attentional processing deficits in these subtypes were not examined in the present study.

Dose-related effects of methylphenidate were not found on the performance measures of the CPT. Due to clinical restrictions at the Child Development Centre, the study was limited to a higher fixed dose of 20mg which prevented the target higher dose of 0.7mg/kg from being administered to the majority of subjects. This limitation on dose may have prevented adverse medication effects on the CPT from emerging. It is possible that higher doses may slow down processing of the N2 component beyond normal levels, reflecting over-evaluation of the stimulus. This dose restriction may have also prevented potential medication effects on shifting of attention on the Posner task from emerging. Although 20mg was set as the high dose limit, it should be noted that this dose is often considered as moderate and several practitioners commonly prescribe doses well in excess
of this amount. Despite the lack of adverse effects of the higher dose in the present study, a true high dose of medication was not actually examined.

The control group in the study was tested on only a single occasion, while the ADHD group was tested on four separate occasions. As a result, it is possible that both practice effects and boredom from repeated testing may have affected the performance of the ADHD group. Although medication conditions were randomized within the ADHD group to eliminate order effects, the only way to overcome the limitation of repeated testing would have been to test the control group on multiple occasions as well. Due to the difficulty in recruiting control subjects, it would have been difficult to obtain consent for controls to be tested on four separate occasions.

ERP data for the Posner task were not analyzed in the present study because of the complexity of these data. The onset of the ERP sweep was at the presentation of the cue and as a result, ERP components for the cue and for the target were difficult to disentangle. Analysis of early ERP components following the cue may be useful for the identification of arousal differences in children with ADHD and control group, and for the examination of medication effects.

ERP data for the CPT were only analyzed for correctly identified target trials, limiting the results to these specific trials. Although the examination of ERP waveforms for error trials, whereby the subject either responded incorrectly to a stimulus or failed to respond to the target would be interesting, this task did not produce enough errors to make this analysis possible. Future research that employs a task that elicits a greater number of errors may allow for this analysis.
A further limitation of the present study was the possibility of comorbidity in our sample of children with ADHD. Although children with conduct disorder and internalizing disorders (such as anxiety) were excluded, four of the subjects had comorbid Oppositional Defiant Disorder and eight of the subjects had comorbid learning disabilities. As there is suggestion that the significant findings reported by Swanson et al. (1991b), on the Posner task were limited to children without comorbid conditions (Swanson, personal communication), our lack of difference on this task may have been due to the inclusion of children with behavioural and learning comorbidities. A larger sample that would have enabled us to separate children with “pure” ADHD from children with comorbid conditions may have provided significant effects.

Implications

From a theoretical perspective, this study examined the nature of the attentional processing deficit in children with ADHD and the effects of methylphenidate on attentional processing. In terms of attentional processing, the ADHD group was found to have difficulties at two separate stages characterized by faster processing at an earlier stimulus evaluation stage, which may be related to greater impulsivity, and by slower processing at a later post-decisional processing stage, which may be related to greater inattention.

Methylphenidate was found to induce changes on attentional processing, resulting in similar processing at these two stages compared to the control group. From a “real life” perspective, the results may be placed in the context of the everyday life of the child with ADHD. The faster stimulus evaluation processing and impulsivity may be directly related to the characteristic difficulties that children with ADHD have with “thinking before acting”
or “putting on the brakes”. In a classroom setting, these difficulties may be viewed negatively and may result in school work that is incomplete or rushed. In a social setting, this impulsive behaviour may lead to inappropriate social interactions and eventual rejection by peers (Wiener, 1987).

The effects of methylphenidate to slow down this faster stimulus evaluation processing and speed up the later post-decisional processing may be directly related to the behavioural improvements or decrease in ADHD symptomatology that is commonly found with stimulant medications. These medication effects may have a beneficial impact in a classroom setting and on peer interactions. However, it is also possible that other non-medical treatments, such as metacognitive or behaviour therapy may help children with ADHD to slow down faster stimulus evaluation processing. The effects of different therapeutic approaches on attentional processing need to be evaluated systematically in future studies.

Although it is interesting to speculate about the implications of this study to real world situations, as with any research using laboratory measures, placing the results in such a context is often difficult, unless the ecological validity of the measure is clearly established. Since the ecological validity of the CPT is unclear (Barkley, 1996), implications of this study should be viewed cautiously.

**Conclusions**

The aims of this study were to address the nature of the attentional processing deficit in ADHD and the effects of methylphenidate on attentional processing. The results showed that children with ADHD have deficits at two separate stages of attentional processing.
First, at an early processing stage, when children are evaluating a stimulus to determine whether it is a target, children with ADHD are processing information faster than those without ADHD. Faster processing at this stage may be related to the impulsive behaviour that these children display. Second, at a later stage, after a decision has been made whether a stimulus is or is not a target and the child is preparing for the next stimulus, children with ADHD are slower than those without ADHD. Slower processing at this stage may be related to the inattentive behaviour they display. This suggests two deficits in children with ADHD: they respond to stimuli too quickly making them impulsive, and in the interval they are preparing for the next stimulus, they are slower than children without ADHD suggesting increased inattentiveness. 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 observed to be 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 two distinct components of attention that are disrupted in ADHD and which respond to methylphenidate at different dose levels.

In conclusion, clear differences in attentional processing between children with ADHD and normal controls was found. Methylphenidate was found to normalize different components of attentional processing in a dose dependent fashion.
REFERENCES


APPENDIX 1. DSM-IV criteria for Attention Deficit Hyperactivity Disorder

The essential diagnostic feature of ADHD outlined in DSM-IV, is the "persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals at a comparable level of development" (p.78). Although the majority of children present with symptoms of both inattention and hyperactivity-impulsivity, there are some children in which symptoms are more predominant in one of these two categories. Therefore, DSM-IV has established two subtypes of the disorder: ADHD-Predominantly Inattentive Type and ADHD-Predominantly Hyperactive-Impulsive Type. In addition, for a diagnosis of ADHD the following criteria must be met: 1) onset of symptoms before the age of seven; 2) impairment from the symptoms in two or more settings (e.g. at home and at school); 3) evidence of clinically significant impairment in social, academic or occupational functions and 4) evidence of the symptoms in the absence of Pervasive Developmental Disorder, Schizophrenia or other psychotic disorders. The current diagnostic criteria for ADHD are presented in detail below.

(A) Either (1) or (2):

(1) six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level.

\[\text{Inattention}\]

(a) often fails to give close attention to details or makes careless mistakes in schoolwork, work or other activities
(b) often has difficulty sustaining attention in tasks or play activities
(c) often does not seem to listen when spoken to directly
(d) often does not follow through on instructions and fails to finish behaviour or failure to understand instructions)
(e) often has difficulty organizing tasks and activities
(f) often avoids, dislikes or is reluctant to engage in tasks that require
(g) often loses things necessary for tasks or activities (e.g. toys, school assignments, pencils, books or tools)
(h) is often easily distracted by extraneous stimuli
(i) is often forgetful in daily activities

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(2) six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

*Hyperactivity*

(a) often fidgets with hands or feet or squirms in seat
(b) often leaves seat in classroom or in other situations in which remaining seated is expected
(c) often runs about or climbs excessively in situations in which it is inappropriate
(d) often has difficulty playing or engaging in leisure activities quietly
(e) if often “on the go” or often acts as if “driven by a motor”
(f) often talks excessively

*Impulsivity*

(g) often blurts out answers before questions have been completed
(h) often has difficulty awaiting turn
(i) often interrupts or intrudes on others (e.g. butts into conversations or

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.

C. Some impairment from the symptoms is present in two or more settings (e.g. at school and at home).

D. There must be clear evidence of clinically significant impairment in social, academic or occupational functioning.

E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g. Mood Disorder, Anxiety Disorder, Dissociative Disorder or a Personality Disorder).

A diagnosis of ADHD-Combined Type is given if both criteria A1 and A2 are met for the past 6 months. ADHD-Predominantly Inattentive Type requires that criteria A1 is met but criteria A2 is not met for the past 6 months. Finally, ADHD-Predominantly Hyperactive-Impulsive Type requires that criteria A2 is met but criteria A1 is not met for the past 6 months.
APPENDIX 2. Performance data on the Posner selective attention task showing mean RTs for the controls and ADHD group across medication conditions.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>ADHD Baseline</th>
<th>ADHD Placebo</th>
<th>ADHD Lower Dose</th>
<th>ADHD Higher Dose</th>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Overall valid</td>
<td>441.50 (85.74)</td>
<td>435.65 (64.16)</td>
<td>474.59 (115.46)</td>
<td>468.38 (77.76)</td>
<td>467.57 (102.96)</td>
</tr>
<tr>
<td>Overall invalid</td>
<td>502.35 (94.84)</td>
<td>507.50 (106.74)</td>
<td>540.32 (117.30)</td>
<td>523.76 (88.29)</td>
<td>513.38 (107.48)</td>
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<tr>
<td>Overall no cue</td>
<td>507.85 (80.32)</td>
<td>496.45 (74.68)</td>
<td>552.05 (129.73)</td>
<td>552.76 (93.57)</td>
<td>543.81 (112.55)</td>
</tr>
<tr>
<td>Left valid</td>
<td>449.00 (91.40)</td>
<td>441.15 (76.03)</td>
<td>473.91 (115.16)</td>
<td>477.67 (79.90)</td>
<td>471.95 (113.22)</td>
</tr>
<tr>
<td>Left invalid</td>
<td>502.45 (97.70)</td>
<td>481.55 (92.96)</td>
<td>541.41 (108.33)</td>
<td>532.14 (98.71)</td>
<td>518.05 (109.80)</td>
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<tr>
<td>Left no cue</td>
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<td>497.30 (82.65)</td>
<td>503.18 (154.24)</td>
<td>557.38 (100.99)</td>
<td>538.42 (122.05)</td>
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<td>463.77 (114.37)</td>
<td>470.67 (84.17)</td>
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<td>537.95 (117.75)</td>
<td>547.90 (119.16)</td>
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<td>401.95 (109.35)</td>
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<td>360.67 (98.34)</td>
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