A Novel Perspective on Interference Control and Distraction in ADHD

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ISBN: 9789086594276

Cover desing & Lay-out: Rosa van Mourik
Models: David en Stefan van der Linde
Printed by: Ipskamp drukkers

VRIJE UNIVERSITEIT

A Novel Perspective on Interference Control and Distraction in ADHD

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. L.M. Bouter,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de faculteit der Psychologie en Pedagogiek
op dinsdag 16 februari 2010 om 13.45 uur
in de aula van de universiteit
Boelelaan 1105

door

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geboren te Amsterdam

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prof.dr. J. Oosterlaan

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Chapter 1

General Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is characterized by inappropriate symptoms of inattentiveness (such as being easily distracted, forgetfulness, difficulty sustaining attention) and hyperactivity/impulsivity (such as talking excessively, fidgeting, blurting out answers before the question has been completed) or a combination of these two symptom groups (American Psychiatric Association, APA, 1994). The DSM-IV (APA, 1994) defines three different subtypes: children with primarily inattentive symptoms (ADHD-inattentive subtype), children with primarily hyperactive/impulsive symptoms (ADHD-hyperactive subtype) and children with a combination of inattentive and hyperactive/impulsive symptoms (ADHD-combined subtype). Children with ADHD often suffer from one or more comorbid disorders such as oppositional defiant disorder, conduct disorder, anxiety disorder, or depression. Comorbidity in ADHD seems to be the rule instead of the exception as it is estimated that about two third of the children with ADHD suffer from one or more comorbid disorders (Elia, Ambrosini and Berretini, 2008). Although estimations of syndromatic remission in ADHD (not fulfilling the full DSM-IV ADHD criteria) are around 60%, the majority of adolescents continues to struggle with ADHD symptoms and high levels of dysfunction in social, educational and occupational domains (Biederman, Mick, & Faraone, 2000). Furthermore, childhood ADHD is a risk for developing antisocial disorders and substance abuse in adulthood (Manuzza et al., 1993).

There is no single 'cause' for ADHD, but both biological (including genes); environmental (including prenatal risk factors) and psychosocial factors (including early deprivation) and their interactions contribute to the development of the disorder. Genes play the strongest role in the aetiology of ADHD, as they can explain around 76% of the variance of the disorder (Faraone et al., 2005). The genetic susceptibility of ADHD is complex, as many genes with a small effect are involved. Research has focused on genes involved in the catecholamine transmission, from which genes related to dopamine have received most attention (Faraone et al., 2005). Dopamine is a neurotransmitter that is released in response to salient or unexpected stimuli. Eight dopaminergic brain circuits have been identified, from which the nigrostriatal, the mesolimbic, and the mesocortical are involved in motivational and cognitive control of behaviour (Cools, 2008). Although the theory that ADHD is caused

by a dopaminergic deficit of genetic origin has been refuted as an oversimplification (Gonon, 2008), several studies point to the involvement of the fronto-subcortical systems in ADHD, brain structures that are rich in dopamine and noradrenaline (see for review Biederman, 2005).

Almost all theoretical accounts of ADHD address some form of cognitive control or executive dysfunction both of which thought to be mediated by fronto-subcortical pathways, underlying this disorder (Barkley, 1997; Casey, Nigg, & Durston, 2007; Pennington & Ozonoff, 1996; Sergeant, 2005; Sonuga-Barke, 2003). Cognitive control has been defined as the ability to generate, maintain and adjust sets of goal-directed processing strategies (Egner, 2008). Executive function has been defined as "those capacities that enable a person to engage successfully in independent, purposive, self-serving behaviour" (Lezak, 1995, p. 42). A crucial aspect in both definitions is the ability to selectively attend to what is relevant and ignore irrelevant or competing information (Casey et al., 2007; Pennington & Ozonoff, 1996). Each activity in daily life requires some ability to attend to certain features in the environment, while excluding other irrelevant or distracting features. For example, a child has to be able to concentrate on his or her schoolwork while other children are talking or pay attention to the traffic when cycling and ignore planes or birds in the sky. Children with ADHD experience difficulties in many daily life tasks that require this ability. Not surprisingly, their inattentive symptoms are predictive for academic underachievement (Massetti et al., 2008) and they are more accident-prone then their normal peers (Clancy, Rucklidge, & Owen, 2006).

Neurocognitive tasks can measure specific cognitive processes that are necessary for successfully attending relevant information and ignore irrelevant or competing features. ERPs (event-related potentials) can give detailed insight into the timing of these cognitive (sub) processes. The focus of this thesis is on the cognitive and neural processes of interference control and distractibility in children with ADHD. Interference control encompasses the ability to suppress selectively the processing of conflicting irrelevant information and the ability to inhibit automatic response tendencies in order to perform a more controlled action. Distraction occurs when distracting but not-conflicting information

disrupts performance on a task as attention is involuntarily captured by the distracting information. Both interference as distraction paradigms require the ability to selectively attend to relevant features and ignore irrelevant features. The difference between these concepts is that the irrelevant information is conflicting and integrated in the task in interference paradigms while it is not conflicting and unrelated to the task in distraction paradigms.

Interference control is typically measured with tasks that elicit conflict between an automatic response and a more controlled action, such as the Stroop Colour-Word task (Stroop 1935; see for review MacLeod, 1991). In the Stroop Colour-Word task, interference is operationalized in terms of the speed and accuracy of naming incongruent colour words (e.g. the word RED printed in blue ink; say blue) compared with naming the colour of a control item (e.g., a neutral word or a coloured bar) or a congruent colour word (e.g. the word BLUE printed in blue ink). There are various analogues of the Stroop Colour-Word task, such as an animal Stroop for children, in which the head of an animal is different from the body (Wright, Waterman, Prescot, & Murdoch-Eaton, 2003), an auditory Stroop in which the word meaning is incongruent with the pitch (McLain, 1983) or more 'spatial' Stroop-like tasks, such as the Simon task (Simon, 1990) or the Flanker task (Eriksen & Schulz, 1979) in which the direction of an arrow is incongruent with the side of the screen on which it appears (Simon task) or incongruent with flanking arrows (Eriksen Flanker task). The goal in these tasks is to ignore the conflicting and irrelevant information and respond to the relevant dimension or stimulus. Interference is reflected by increased error rates and/or reaction times in incongruent conditions compared with neutral or congruent conditions. Note that the Eriksen Flanker task differs from Stroop-like interference tasks with respect to the incongruent information, which is outside the primary stimulus in the Eriksen Flanker task, but integrated in the primary stimulus in Stroop-like taks.

Distraction differs from interference, as distraction is unrelated to the task and not conflicting with task demands. Distraction can be measured with different naturalistic and ecologically valid paradigms. Escera, Alho, Winkler and Näätänen (1998) developed a paradigm to measure distraction for ERP research. This paradigm has been adapted by Gumenyuk et al. (2001) to

measure distraction in children. In this distraction paradigm, the child performs a visual task while listening to standard tones and occasionally a novel environmental sound such as a mooing cow, an engine or a bell. All sounds should be ignored by the child. As novel and unexpected stimuli are hard to ignore, they cause distraction that is reflected by increased error rates and/or response latencies after the novel sounds compared with the standard tones.

This thesis aims to answer three main questions: 1) Is interference control disrupted in ADHD?, 2) are children with ADHD more easily distracted then their normal peers?, and 3) what are the neurophysiological correlates of interference and distraction in ADHD?

Aim 1: Is interference control disrupted in ADHD?

The first aim of this thesis is to answer the question whether interference control is disrupted in ADHD. Since the seventies of the last century, interference control has been intensively studied in ADHD, mostly with the Stroop Colour-Word task (Cohen, Weiss, & Minde, 1972). The conclusion of this first study employing the Stroop Colour-Word task in ADHD (adolescents previously diagnosed as hyperactives) was that there were no differences between the groups (adolescents previously diagnosed as hyperactives versus a normal control group) on any of the Stroop cards. In 1992, the neuropsychogical literature on ADHD was reviewed and it was concluded that children with ADHD were more impaired on the Stroop Colour-Word task, particularly on the interference part relative to normal children (Barkley, Grodzinsky, & DuPaul, 1992). These findings were interpreted as an indication that the Stroop Colour-Word task may be sensitive to the frontal lobe impairments hypothesized to exist in ADHD. However, it should be born in mind that not all studies controlled the interference score for word reading or colour naming. If the interference score is not corrected, it remains unclear whether differences in these score are attributable to larger interference or to slower naming speed in general. The search for a deficit in interference control, as measured with the Stroop Colour-Word task, continued and has yielded conflicting findings (Nigg, 2001). Therefore, in **Chapter 2** a meta-analysis on the Stroop Colour-Word task in ADHD is presented. In this analysis, we have

examined the strength of an interference deficit in ADHD and assessed the role of moderating variables (such as comorbidity, gender, age, ADHD subtypes) that could have influenced the results. Although the Stroop Colour-Word task is an elegant task to measure interference control, it has certain limitations in research on ADHD. Children with ADHD encounter difficulties with the baseline conditions (colour naming and word reading) possibly caused by a rapid naming deficiency (Tannock, Martinussen, & Frijters, 2000) or reading disorder, which co-occurs in approximately 20% of the individuals with ADHD (Del' Homme et al., 2007). An alternative explanation may be that children with ADHD may have more difficulties in keeping attention focused on one item at a time. For example, Brodeur and Pond (2001) showed that children with ADHD slow down more than their normal peers in the presence of distracters, irrespective of the nature of these distracters (meaningful or irrelevant). For these reasons, two alternative interference tasks were developed, a Simon task and an auditory Stroop task. These tasks are independent of reading ability, rapid naming or focused attention. In **Chapter 3**, a large group of clinically referred children with ADHD is compared with carefully selected typically developing children on these two tasks.

Aim 2: Are children with ADHD more easily distracted then their normal peers?

Three decades ago, Douglas and Peters (1979) reviewed the literature on distractibility in ADHD and concluded that a number of attempts to prove that children with ADHD are abnormally distractible have been unsuccessful despite the fact that apparent distractibility is such a major behavioural manifestation of children with ADHD (DSM-IV; APA, 1994). They even reported that in some studies the distraction conditions (such as music) *enhanced* the performance of children with ADHD (Scott, 1970; Zentall & Zentall, 1976). A deficit in attention has been thought to be secondary to a more central problem, such as inhibition (Barkley, 1997), the investment, organization and maintenance of attention and effort (Douglas, 1984) or to energetic factors (Sergeant, Oosterlaan, van der Meere, 1999). Especially inhibition has received much attention in the literature on ADHD. As a deficit in inhibition is a firmly established finding in the ADHD literature (see Willcutt, Sonuga-Barke, Nigg,

& Sergeant, 2008 for a meta-analytic review) one of the possible explanations of the apparent distractibility in children with ADHD may be that they have more difficulty in inhibiting their shift of attention towards distracting and irrelevant information that causes their apparent distractibility. Alternatively, it could be the result of a more fundamental problem, such as a lowered threshold for the breakthrough of unattended information. In **Chapter 5** an adaptation of a new and promising distraction paradigm was used in a group of children with ADHD and a normal control group. With this paradigm, it was previously demonstrated in a small sample that children with ADHD were more distractible than their normal peers (Gumenyuk et al., 2005).

Aim 3: What are the neurophysiological correlates of interference and distraction in ADHD?

The Stroop effect is probably one of the most widely studied phenomena in cognitive neuroscience. Various imaging studies employing fMRI and ERPs have elucidated which brain areas are involved (fMRI) and how interfering information is processed in time (ERPs). Studies using fMRI have identified a fronto-parietal network engaged in conflict processing[1] (see for review Roberts & Hall, 2008). Carter and van Veen (2007) proposed that the dorsal anterior cingulated cortex (ACC) plays a key role in the detection of conflict and subsequently activates the dorsolateral prefrontal cortex (DLPFC) to resolve such conflict. Neurophysiologically, detection of conflict is reflected by a larger negativity on incongruent trials compared to congruent and neutral trials between 400 and 500 milliseconds after stimulus onset, labelled the N450 (Rebai, Bernard, & Lannou, 1997). Selection of the appropriate response (conflict resolution) is reflected by a larger parietal positivity and a larger lateral-frontal negativity on incongruent trials compared to congruent or neutral trials between 600 and 800 milliseconds after stimulus onset, labelled the conflict sustained potential (West & Alain, 1999).

Functional and structural deficits have been found in brain areas involved in

[1] As interference always involves two conflicting streams of information, the terms interference control and conflict processing will be used interchangeably.

interference control in ADHD (Bush, Valera, & Seidman, 2005; Seidman et al. 2006). Abnormalities in the temporal processing of interfering information in ADHD have been found with Flanker tasks (Albrecht et al., 2008). However, there is a gap in our knowledge of the temporal processing of interfering information in ADHD with Stroop(-like) tasks, as ERPs have not yet been collected in ADHD during a Stroop(-like) task. There are two exceptions; one of them is a case study (Horrobin, McNair, Kirk, & Waldie, 2007) and the other an oddball version of the Stroop (Miller, Kavcic, & Leslie, 1996) in which children had to decide whether the colour of a word was congruent or incongruent with word meaning. As task demands differed in this oddball version and a case study may not be representative, the neural correlates of the temporal processing of interfering information in ADHD remain unknown. Knowledge about when deficits occur in the temporal processing of information is important, as it can help to characterize the underlying deficit in ADHD, which may lead to better future treatment options for ADHD. Therefore, in **Chapter 4**, the temporal processing of interfering information in children with ADHD is elucidated with an auditory Stroop task.

Distraction is typically measured with stimuli that are unrelated to the primary task, thus not conflicting. These unattended and task-irrelevant novel stimuli elicit a fronto-central P3a component (Cycowicz & Friedman, 1997; Escera et al., 1998). The P3a component is thought to reflect an evaluative, conscious aspect of the orienting respons and an attentional switch to the novel information (Friedman, Cycowicz, & Gaeta, 2001). The P3a has two subcomponents, an early P3a (around 200 milliseconds after stimulus onset) and a late P3a which peaks at around 300 milliseconds after stimulus onset. The P3a is followed by a frontally distributed negativity between 400 and 700 milliseconds. This negativity is interpreted as reflecting the reorienting of attention back to the main task after distraction (Schröger & Wolff, 1998), and it is labelled the reorienting negativity (RON). There is only one study that has investigated auditory distraction during a visual task in children with ADHD (Gumenyuk et al., 2005). This study showed that children with ADHD had an enhanced neural distractibility as indicated by a smaller early P3a, a larger late P3a and a smaller and earlier late frontal negativity. **Chapter 5** was aimed at

replicating and extending this important finding, as sample size and age range were small in this previous study.

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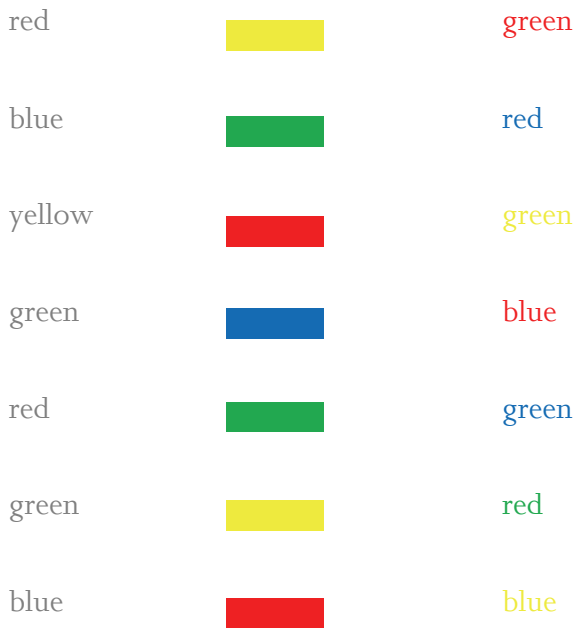
Chapter 2

The Stroop revisited: a meta-analysis of interference control in AD/HD



Published as: Van Mourik, R., Van Mourik, R., Oosterlaan, J., & Sergeant, J. A. (2005). The stroop revisited: A meta-analysis of interference control in AD/HD. *Journal of Child Psychology & Psychiatry, 46,* 150-165
link to original publication

Abstract

An inhibition deficit, including poor interference control, has been implicated as one of the core deficits in ADHD. Interference control is clinically measured by the Stroop Colour-Word Task. The aim of this meta-analysis was to investigate the strength of an interference deficit in ADHD as measured by the Stroop Colour-Word Task and to assess the role of moderating variables that could explain the results. These moderating variables included: methods of calculating the interference score, comorbid reading and psychiatric disorders, ADHD-subtypes, gender, age, intellectual functioning, medication, and sample size. Seventeen independent studies were located including 1395 children, adolescents, and young adults, in the age range of 6–27 years. A meta-analysis was conducted to assess the effect sizes for the scores on the word and the colour card as well as the interference score. Children with ADHD performed more poorly on all three dependent variables. The effect sizes for word reading (d = .49) and colour naming (d = .58) were larger and more homogeneous than the effect size for the interference score (d = .35). The method used to calculate the interference score strongly influenced the findings for this measure. When interference control was calculated as the difference between the score on the colour card minus the score on the colour-word card, no differences were found between ADHD groups and normal control groups. The Stroop Colour-Word Task, in standard form, does not provide strong evidence for a deficit in interference control in ADHD. However, the Stroop Colour-Word Task may not be a valid measure of interference control in ADHD and alternative methodologies may be needed to test this aspect of the inhibitory deficit model in ADHD.

Introduction

Numerous authors have highlighted the role of executive dysfunction in Attention Deficit/Hyperactivity Disorder (ADHD) (Pennington & Ozonoff, 1996; Sergeant, Geurts, & Oosterlaan, 2002). A key process in executive functioning is response inhibition (Barkley, 1997). Barkley (1997) distinguished three interrelated processes believed to constitute response inhibition: (1) inhibiting a prepotent response, (2) stopping an ongoing response, and (3) interference control. The Stroop Colour-Word Task (Stroop, 1935, see for review MacLeod, 1991) is widely used as a measure of interference control in studies with ADHD groups and is recommended as part of a psychological test battery in clinical settings (Doyle, Biederman, Seidman, Weber, & Faraone, 2000). Given both the clinical and research interest in the Stroop Colour-Word Task with respect to ADHD, we report here a quantitative meta-analysis of studies that compare children with ADHD and normal controls on the Stroop Colour-Word Task, as opposed to a head-count (Sergeant et al., 2002).

The standard Stroop Colour-Word Task (Golden, 1978) consists of three conditions, represented by three different cards. There are different versions, but in the ADHD literature, the 'Golden' version is the most widely used. On the first card, the 'word' card, the speed of word reading is measured: the subject is required to read rows containing four different colour words (red, green, yellow and blue) printed in black ink and presented in random order. On the second card, the colour card, the subject has to name the colours of either rows of four Xs or blocks that are printed in the colours red, green, yellow, and blue. This condition measures colour-naming speed. On the third card, the colour-word card, the subject is required to name colours of the colour-content mismatching colour-words; for example, the colour-word red may be presented in blue ink. On the third card, the distracter is the colour meaning of the word. Interference occurs when the to-be-named colour differs from the to-be-ignored word (incongruent). This causes response conflict (Posner & DiGirolamo, 1998). On all three cards, the subject is timed for 45 seconds and the number of correct responses is counted. All stimuli are presented in a random order and the subject is required to name them as

quickly as possible. A lower score on the colour-word card, in the presence of normal scores on the word and colour card reflects the interference effect (Golden, 1978).

Generally, there are two different theoretical models to explain the interference effect in the Stroop Colour-Word Task: sequential models and parallel models. In sequential explanations, processing in one stage must be completed (or almost completed), before the next stage can begin. Interference is supposed to occur only at the response stage. Sequential theories have not been very successful in explaining all the effects found with different task manipulations (MacLeod, 1991). Parallel theories emphasize the speed of processing and the automaticity of word reading and colour naming. Cohen, Dunbar, and McClelland (1990) have developed a parallel model that states that the two features of the stimuli on the colour-word card: word (meaning) and colour, are processed simultaneously. The relative automaticity of the two dimensions (word processing and colour processing) determines the direction and the degree of interdimensional interference (MacLeod & MacDonald, 2000). In this account, the two processes run in parallel through activation moving along pathways of different strength in the system. The degree of automaticity is a function of the strength of each pathway. The difference between this parallel model and previous parallel models is that interference can also occur during the processing of the stimuli and not simply at the end of a 'horse race'.

Neuro-imaging studies show that the brain areas that are active, while subjects perform Stroop-like tasks, include the anterior cingulate cortex (Adleman et al., 2002; Bush, Luu & Posner, 2000; Carter, Mintun, & Cohen, 1995; Pardo, Pardo, Janer, & Raichle, 1990; Peterson et al., 1999; Peterson et al., 2002), a region of the frontal cortex associated with the frontal executive networks (Posner & DiGirolamo, 1998). Other regions that consistently show differential increases in activation for the incongruent condition compared to a neutral control condition are: the frontal polar cortex (Bench et al., 1993; Carter et al., 1995), the lateral prefrontal cortex (Peterson et al., 1999; Zysset, Müller, Lohmann, & von Cramon, 2001), the inferior frontal regions (Adleman et al., 2002; Chung-Leung, Skudlarski, Gatenby, Peterson, & Gore, 2000; Peterson et al., 1999), and the inferior parietal lobule (Adleman et al., 2002; Carter et al.,

1995; Peterson et al., 1999). Note that neuro-imaging studies differ with respect to the neutral control condition (for example coloured Xs, coloured neutral words or congruent colour-
words) and that the tasks used were paced rather than self-paced, as conducted in the clinical Stroop card procedure. The neural networks, which are activated when subjects perform Stroop-like tasks, are also considered to be implicated in ADHD. Especially the frontal cortex has been hypothesised to play a major role in ADHD pathology (see for review Barkley, Grodzinsky, & DuPaul, 1992). Therefore, it might seem surprising that the search for a deficit in interference control in ADHD, as measured by Stroop-type tasks, has yielded conflicting findings (Nigg, 2001).

These conflicting findings can be explained in at least three possible ways. First, rapid naming deficiencies have also been observed in children with ADHD (Tannock, Martinussen, & Frijters, 2000). Thus, a lower score on the CW-card may also be due to slower rapid naming instead of poorer interference control. Not all studies that reported deficits in interference control in ADHD controlled for reading ability (the word condition) or naming speed (the colour condition). Second, estimates of children with ADHD who also have a comorbid reading disorder range from 25 – 40% (Dykman & Ackerman, 1991; Semrud-Clikeman et al., 1992). If a child cannot read well, it is probably easier to ignore the word meaning on the colour-word card. This could lead to relatively faster responses on the colour-word card in children with ADHD who are comorbid for reading disorder as compared to children with ADHD without a reading disorder. However, this is not always the case. Children with a reading disability actually show more interference than normal controls in some studies (Everatt, Warne, Miles, & Thomson, 1997; Helland & Asbjornsen, 2000). This suggests that a deficit in interference control might not be specific to ADHD. Third, an alternative explanation for the conflicting results might be that children with ADHD have often other comorbid disorders like a disruptive disorder or an anxiety disorder (Angold, Costello, & Erkanli, 1999). Results may be confounded by the high comorbidity of ADHD with other psychiatric disorders. Inhibition deficits have also been found in comorbid disruptive disorders (Oosterlaan, Logan, & Sergeant, 1998), whereas anxiety disorders have been associated with an increased ability to inhibit (Oosterlaan, 2001).

Thus, the presence of rapid naming difficulties, comorbid reading, or psychiatric disorders might have affected the interference scores found in the various studies.

Since the interference score is also determined by reading and rapid naming ability, the first goal of this meta-analysis is to test if children with ADHD have lower word or colour scores, indicating rapid naming, and/or reading problems. A second goal is to determine the strength of an interference deficit in ADHD. Third, we will examine the influence of eight possible moderating factors. These moderating variables include: methods of calculating the interference score, comorbid reading and psychiatric disorders, ADHD-subtypes, gender, age, intellectual functioning, the use of medication, and sample size. To assess if a deficit in interference control is specific to ADHD, we will compare ADHD groups with reading disorder and psychiatric disorder groups. Furthermore, the ADHD inattentive subtype is compared with the ADHD combined subtype. This issue is theoretically important because of the discussion on the validity of the distinction between these subtypes. ADHD inattentive subtype and ADHD hyperactive/impulsive subtype have been characterized as distinct, unrelated disorders (Milich, Balentine, & Lynam, 2001). Barkley (1997) explicitly states that his behavioural inhibition model of ADHD refers only to the ADHD combined and hyperactive/impulsive subtypes but not to the ADHD inattentive subtype. On average, children with ADHD have a lower IQ than their normal peers (Barkley, 1997). We wish to test if differences on the Stroop Colour-Word Task might be partly attributable to differences in IQ. The possible moderating effect of sample size is assessed to ascertain if the meta-analytic results are influenced by a publication bias.

Method

Description of the Studies

This meta-analysis covers seventeen studies published between 1990 and 2002. Table 2.1 summarizes the main features of these studies. In column 1, the authors are listed. Column 2 shows the subject groups and the number of subjects in each of these groups. Column 3 provides the mean age and the age

range for each of the groups. Information on the IQ of the children is summarized in column 4. We describe in column 5 how the different studies deal with various possible moderators including reading and psychiatric disorders, ADHD-subtypes, gender, age, IQ, and medication. Column 6 summarizes the main results. In column 7 appear some remarks on the study. The studies were located in Pubmed, PsycInfo, Science Direct, Web of Science, and Picarta. We combined search terms related to the Stroop Colour-Word Task (such as Stroop, interference, executive) with search terms related to ADHD (such as ADHD, hyperactive, attention). The reference lists of published articles were used to locate other relevant studies. To be included in the meta-analysis, studies had to meet the following criteria: (1) the studies contained at least one ADHD group and a comparison group of normal control children, (2) studies had to use the standard Stroop Colour-Word Task, and (3) for the interference score: studies were required to use one of the two (in the following section described) methods to calculate the interference score. Where studies did not report the interference score (Schmitz et al., 2002; Perugini, Harvey, Lovejoy, Sandstrom, & Webb, 2000) or another interference score was used than the two proposed in this meta-analysis (Willcutt et al., 2001), attempts were made to locate the primary author to provide the group means and the standard deviations of the group means in order to allow computation of the C-CW interference score. This meta-analysis reports on the results of 15 studies for the colour and word score, furthermore, meta-analytic results for the interference score pertain to 14 studies. With a single exception (Reeve & Schandler, 2001) all studies in this meta-analysis used DSM criteria (DSM-III-R; American Psychiatric Association, 1987; DSM-V; APA, 1994) to establish a diagnosis of ADHD. More specifically, for the studies included in the meta-analysis, 291 children were diagnosed as ADHD using DSM-III-R criteria and 306 children using DSM-IV criteria.

Studies were excluded if the same subject data were also (partly) published in an other study. Therefore, we excluded the following studies: Barkley, Grodzinsky, and DuPaul (1992); Seidman et al. (1995); Seidman, Biederman, Faraone, Weber, and Oullette (1997); and the study by Grodzinsky and Barkley (1999). We excluded studies that were published before 1990 (Cohen, Weiss, & Minde, 1972; Boucugnani & Jones, 1989; Gorenstein, Mammato, & Sandy,

1989) for one or both of the following reasons. First, these studies did not use DSM-IIIR or DSM-IV criteria. Second, some studies did not report the findings for the interference score and we were unable to locate the primary author of older studies in order to obtain the data that allows computation of the interference score. Computerized versions of the Stroop Colour-Word Task are not comparable with the standard version in terms of control condition, response mode, and Stroop stimuli. The studies by Carter, Krener, Chaderjian, Northcutt, and Wolfe (1995); Miller, Kavcic, and Leslie (1995) as well as the study by Gaultney, Kipp, Weinstein, and McNeill (1999) used a computerized Stroop. These studies were excluded from the present meta-analysis.

Table 2.1 Summary of articles on ADHD and the Stroop Colour-Word Task

Study	Participants	Age	IQ	Confounding Variables	Results	Remarks
1. Golden & Golden, 2002	43 LD (= RD) 43 NC 43 PD* 43 ADHD (ADHD-subtypes: 24 ADHD-C 14 ADHD-H; 5 ADHD-I)	10.0 9.9 9.4 9.9 Range: 6-15		Not Confounding: - Excluded: comorbidity: groups mutually exclusive - Matched on: All groups are matched with the LD group on: age, gender education, ethnicity - Statistically not different: age, education Not Reported: - Medication, IQ, ADHD-subtype	Interference: ADHD = PD = NC > LD Colour naming: ADHD = PD = NC > LD Word reading: ADHD = PD = NC > LD Colour-Word: NC > ADHD = PD = LD	PD = 6 CD, 11 ODD; 1 Mood Disorder NOS; 5 Anxiety Disorder; 18 Adjustment Disorder; 2 PTSD
2. Nigg et al.,2002	69 AD HD-C* 35 AD HD-I* 51 NC*	9.6 9.9 9.7 Range: 7-12	101.5 104.9 109.4	Not Confounding: - Excluded: Autism, Tourette, Depression, and Bipolar Disorder - Matched on: age, gender, recruitment source - Tested as a covariate: IQ, RD, ODD, CD, medication - Statistically not different: ADHD-subtype, gender	Interference: ADHD = NC Colour naming: NC > ADHD Word reading: NC > ADHD Colour-Word: NC > ADHD ADHD-I = ADHD-C	More data than presented in the article are used. In calculating the overall effect size, only ADHD-C and NC are included
3. Rucklidge & Tannock, 2002	35 ADHD 12 RD 24 ADHD + RD 37 NC	15.2 15.1 14.9 15.0 Range: 13-16	102.2 99.9 101.1 111.0	Not Confounding: - Excluded: medication - Matched on: age - Statistically not different: gender - Tested as a covariate: ODD, CD, PD,IQ, SES - Statistically different: comorbid RD Not Reported: ADHD-subtypes	Interference: ADHD = RD = ADHD + RD Colour naming: NC > ADHD, ADHD + RD Word-reading: NC > RD,ADHD + RD and ADHD > ADHD + RD Colour-Word: NC, ADHD, RD > ADHD +RD and NC > ADHD	

Table 2.1 (continued) Summary of articles on ADHD and the Stroop Colour-Word Task

Study	Participants	Age	IQ	Confounding Variables	Results	Remarks
4. Scheres et al., 2004	18 ADHD 20 NC (ADHD-subtypes: 8 ADHD-I 10 ADHD-C)	9.3 9.9 Range: 8-12	99.6 104.8	Not Confounding: - Excluded: girls, medication, PD - Statistically not different: ADHD- subtype - Possible Confounding: ODD, CD: symptoms correlated high with ADHD symptoms Confounding: Tested as a covariate: age, IQ Not Reported: RD	Interference: ADHD > NC ADHD-I = ADHD-C	A selection of subjects from the original study were analysed because not all children performed the Stroop.
5. Schmitz et al., 2002	10 ADHD-H 10ADHD-I 10 ADHD-C 60 NC	14.4 14.1 14.1 13.8 Range: 12-16	91.3 87.8 85.8 92.9	Not Confounding - Excluded: medication - Statistically not different: gender, IQ Confounding: -Tested as a covariate: education, age, SES -Statistically different: ADHD-subtype Not Reported: ODD , CD, PD, RD	Word reading: ADHD = NC Colour-Word: NC, ADHD-H, ADHD-C > ADHD-I	In calculating the effect size for word reading, only the ADHD-C and NC are included.
6. Reeve & Schandler, 2001	10 ADHD 10 NC	15.3 15.2 Range: 12-17	98.9 100.6	Not Confounding -Excluded: Medication, LD, ODD, CD - Matched on: age, gender Not Reported: - PD, ADHD-subtype	Interference: ADHD > NC Colour naming: NC > ADHD Word-reading: NC = ADHD Colour-Word: NC > ADHD	

Table 2.1 (continued) Summary of articles on ADHD and the Stroop Colour-Word Task

Study	Participants	Age	IQ	Confounding Variables	Results	Remarks
7. Seidman, et al., 2001	21 ADHD + 2 LD* 32 ADHD + AD 16 ADHD + RD 79 ADHD 127 NC	14.3 13.8 15.2 15.1 15.1 Range: 6-17	96.1 105.4 102.2 113.3 118.0	Not Confounding: - Excluded: girls - Tested as a covariate: IQ, age, PD, ODD CD, SES - Statistically not different: medication Confounding: - Statistically different: RD and AD Not Reported: - ADHD-subtype,	Interference: ADHD + RD > NC Colour naming: NC > ADHD + LD; ADHD > ADHD + LD > ADHD + 2LD Word reading: NC >ADHD > ADHD + LD; ADHD + AD >ADHD + 2 LD Colour-Word: NC >ADHD> ADHD + LD, ADHD + 2 LD	2 LD = combined reading and arithmetic disorder
8. Spalletta et al., 2001	8 ADHD 8 NC (7 ADHD-C, 1 ADHD-I)	9.4 9.0 Range: 6-14		Not Confounding - Excluded: PD, CD, medication -Matched on: age, gender, education. Not Reported: - IQ, ODD, RD, ADHD-subtype	Colour naming: NC > ADHD Colour-Word: NC > ADHD	PET-study
9. Willcutt et al., 2001	121 NC 93 RD 52 ADHD 48 RD+ADHD	10.7 10.4 10.8 10.6 Range: 8-16	113.3 100.1 101.1 99.2	Not Confounding - Excluded: Medication -Tested as a covariate: IQ, Reading ability, gender, ODD, CD Confounding: - Statistically different: age (older ADHD more impaired), RD Not Reported: - ADHD-subtype	Interference: NC = ADHD = RD = ADHD + RD Colour naming: NC = ADHD > ADHD + RD Word reading: NC = ADHD > RD, ADHD + RD Colour-Word: NC = ADHD = RD > ADHD + RD	

Table 2.1 (continued) Summary of articles on ADHD and the Stroop Colour-Word Task

Study	Participants	Age	IQ	Confounding Variables	Results	Remarks
10. Perugini, et al., 2000	21 ADHD 22 NC	9.6 9.2 Range: 6-12	110.1 114.2	Not Confounding: - Excluded: girls, medication - Statistically not different: age, IQ, ODD CD Not Reported: - PD, RD, ADHD- subtype	Colour-Word: ADHD = NC	
11. Seidman, et al., 2000	40 ADHD 116 NC (sibling of child with ADHD) 118 NC (no sibling of child with ADHD)	15.5 15.5 15.0 Range: 6-27	108.4 111.5 113.2	Not Confounding: -Tested as a covariate: gender, PD, ODD CD, LD, IQ, SES - Statistically not different: medication Confounding: - {LD, PD, SES} only on word reading Not Reported: - Age, ADHD-subtype.	Interference: ADHD = NC Colour naming: NC > ADHD Word reading: NC > ADHD* Colour-Word: NC > ADHD (No differences between the NC - groups)	* If controlled for {PD, LD, SES}: ADHD = NC on Word reading
12. Semrud-Clikeman et al., 2000	10 ADHD 11 NC	12.9 15.1 Range: 8–18	120.5 125.4	Not Confounding: - Excluded: Girls, PD, LD - Matched on: age and IQ Possible Confounding: - Medication Not Reported: - ODD, CD, ADHD-subtype	Colour naming: NC > ADHD Word reading: NC > ADHD Colour-Word: NC > ADHD	MRI study

Table 2.1 (continued) Summary of articles on ADHD and the Stroop Colour-Word Task

Study	Participants	Age	IQ	Confounding Variables	Results	Remarks
13. Houghton et al., 1999	32 ADHD-I 62 ADHD-C 28 NC	10.5 9.9 10.2 Range: 6-12	V: 107 P: 119 V:100 P:111 V:107 P:116	Not Confounding: - Excluded: PD, LD, medication - Tested as a covariate: gender, age Confounding: - Statistically different: ADHD-subtype	Interference: NC = ADHD-I = ADHD-C Colour naming: NC > ADHD-C Word reading: NC > ADHD-C, ADHD-I Colour-Word: NC > ADHD-C	In calculating the overall Effect size, only ADHD-C and NC are included.
14. Seidman et al., 1997	43 ADHD 36 NC	11.4 11.9 Range: 6-17	106.0 112.1	Not Confounding: - Excluded: boys - Matched on: age, SES, grade - Tested as a covariate: family history, PD, LD Possible Confounding: - Medication Not Reported: - ADHD-subtype, IQ	Interference: NC = ADHD Colour naming: NC = ADHD Word reading: NC = ADHD Colour-Word: NC = ADHD	
15. MacLeod & Prior,1996	12 NC 12 ADHD 10 CD 12 PD*	15.5 14.5 15.8 15.6 Range: 12-18	112.5 107.2 103.6 106.4	Not Confounding: - Excluded: PD and CD: groups mutually exclusive, medication. - Tested as a covariate: IQ and age Not Reported: - gender, RD, ADHD-subtype	Interference: ADHD, CD, PD > NC	*PD = 3 anorexia, 4 schizophrenia, 3 depression, 2 school refusals

Table 2.1 (continued) Summary of articles on ADHD and the Stroop Colour-Word Task

Study	Participants	Age	IQ	Confounding Variables	Results	Remarks
16. Grodzinsky & Diamond, 1992	66 ADHD 34 young 32 old 64 NC 30 young 34 old	 7.6 10.2 7.5 10.4 Range: 6-11	 112.9 110.1 112.9 115.5	Not Confounding: - Excluded: girls, LD, PD medication, ADHD-I - Statistically not different: age, IQ, motor performance Possible Confounding: - Tested as a covariate: SES Not Reported: - ODD / CD	Colour naming: NC > ADHD Word reading: NC > ADHD Colour-Word: NC > ADHD	
17. Lufi et al., 1990	29 AD HD 21 PD* 20 NC	12.7 13.2 12.7 Range: 9-16		Not Confounding: - Excluded: girls, medication Not Reported: - RD, PD, ODD / CD, ADHD-subtype, IQ	Interference: ADHD > PD Colour naming: NC = ADHD = PD Word reading: ADHD > PD Colour-Word: NC = ADHD = PD	* PD = various conduct and anxiety disorders

Note. Interference > = more interference. Other measures > = a better score, thus a faster response time

Index of abbreviations:

AD = Arithmetic Disorder
ADHD = Attention Deficit/ Hyperactivity Disorder
ADHD-I = predominantly inattentive subtype
ADHD-H = predominantly hyperactive subtype
ADHD-C = combined subtype
CD = Conduct Disorder
IQ = Intelligence Quotient
LD = Learning disorders (reading disorder or artithmetic disorder)
NC = Normal Controls
ODD = Oppositional Defiant Disorder
PD = Psychiatric Disorders (other than ADHD, ODD and CD)
RD = Reading Disorder
SES = Social Economic Status

Dependent Variables

This meta-analysis focused on the following three dependent variables derived from the Stroop Colour-Word Task:

(1) The number of words named correctly in 45 seconds on the word card: a rough indication of reading ability and rapid naming.

(2) The number of colours named correctly in 45 seconds on the colour card: an indication of speed of colour processing and rapid naming.

(3) The interference score: the measure of interference control in the Stroop Colour-Word Task. This measure quantifies how much slower colour naming becomes, when word reading interferes with colour naming. Two widely used methods of calculating the interference score are available. The first method controls only for colour naming, the second for both colour naming and word reading.

In the first method (the classical method), the score derived from the colour-word card was subtracted from the score on the colour card (Hammes, 1971). In the second method (Golden, 1978), correction for colour naming and word reading was achieved as follows: First, a colour-word (CW) score was predicted. This predicted score was subtracted from the uncorrected raw CW score. The predicted CW score can be calculated either by using a regression formula or by a theoretical formula (Golden, 1978). The regression formula is based on a mean score corrected for the subjects' age and education. The theoretical model suggests that the time to read one colour-word is actually the time to read one word followed by the time to name one colour. The following formula (Golden, 1978) can be deduced from the theoretical model:

$$\text{Interference score} = \text{CW score} - [(\text{W score} \cdot \text{C score}) \div (\text{W score} + \text{C score})]$$

In which the W score is the score on the word card, the C score represents the score on the colour card, and the CW score is the score on the colour-word card. The interference score is positive, when a subject is able to inhibit word reading and negative, when word reading actively interferes with the colour naming process. The two methods used to predict a CW score yield highly comparable results ($r = 0.96$) suggesting that these two methods are

interchangeable. Both methods will be referred to as the 'Golden' method, since Golden (1978) proposed both methods.

We compared the 'Golden' method (irrespective of how the CW score was predicted) with the classical method (C score – CW score, Hammes, 1971) as far as was possible with the available data. If no interference score was reported, the classical interference score was calculated using the raw mean data. We estimated the group standard deviation (*SD*) with the following formula:

$$SD\,(\text{C score - CW score}) = \sqrt{\{SD(\text{C score})^2 + SD\,(\text{CW score})^2 - 2[SD(\text{C score}) \cdot SD\,(\text{CW score}) \cdot r(\text{C score - CW score})]\}}$$

In this formula, r(C score – CW score) represents the average correlation between the number of correct responses on the colour card and the number of correct responses on the colour-word card. The r(C score – CW score) was set at 0.7 (C. J. Golden, personal communication, February 25, 2003).

Statistical Analyses

Analyses were conducted using a computer program developed by Borenstein and Rothstein (1999). The effect sizes (in terms of Cohen's *d*) were calculated for each study separately. An overall effect size was computed by weighting all the effect sizes with the sample size of the study. Following Cohen's guidelines, effect sizes of .20, .50, and .80 were used as thresholds to define small, medium, and large effects, respectively (Cohen, 1988). To test if the variability in effect sizes exceed that expected from sampling error alone, a test of heterogeneity was conducted (Borenstein & Rothstein, 1999).

Since it is unreasonable to assume that all of the heterogeneity in the effect sizes of the studies can be explained, the possibility of 'residual heterogeneity' must be acknowledged in the statistical analysis. The appropriate analysis is, therefore, a 'random effects' rather than a 'fixed effects' meta-regression model (Thompson & Higgins, 2002). In the 'fixed effects' model, it is assumed that all studies are derived from a common population, and the only source of

variation between the studies is random error. With a sufficiently large sample, this error will approach zero and the estimates of the effect sizes reflect together the true combined effect size. In the 'random effects' model, it is assumed that the effect sizes may differ because the subject characteristics vary from one study to another. When an attempt is made to combine data, two sources of variance need to be dealt with: random error and variance that reflects real differences between the populations from which subjects are sampled. A fixed effects analysis estimates the assumed common effect, whereas a random effects analysis estimates the mean of a distribution of effects across studies. If residual heterogeneity exists, a random effects analysis appropriately yields wider confidence intervals for the combined effect size than a fixed effects analysis (Thompson & Higgins, 2002).

The random combined effect sizes were calculated for the word, colour, and interference score of studies (1) comparing ADHD groups without comorbid reading disorder and ADHD groups with comorbid reading disorder, (2) comparing ADHD groups and reading disorder groups, (3) comparing ADHD groups and psychiatric control groups and, (4) comparing ADHD primarily inattentive subtype groups and ADHD combined subtype groups. Note that for the third comparison, it was not possible to calculate the effect sizes for the word and colour score because there were too few studies to conduct this comparison. Age, IQ, and sample size were correlated with the effect sizes for the word, colour, and interference score. The correlations for age and IQ were weighted for the relative number of subjects in the study (Stevens, 1996). The two methods for calculating the interference score were compared using a Wilcoxon rank order test. Alpha was set at .05 for all analyses.

Results

The results of the three dependent measures of interest: the word score, the colour score, and the interference score are summarized in Tables 2.2 to 2.4

Table 2.2 Comparison of the effect sizes for the word score in ADHD studies.

Study	Effect Size	*p*	Sample size		Schematic representation of effect sizes with 95% confidence interval
			ADHD	Controls	-4.0 -2.0 0.0 2.0 4.00
Golden & Golden, 2002	-.06	.80	43	43	
Grodzinsky & Diamond, 1992	.85	.00	32	34	
Grodzinsky & Diamond, 1992	.93	.00	34	30	
Hougton et al., 1999	.57	.01	62	28	
Lufi et al., 1990	.71	.02	29	20	
Nigg et al., 2002	.53	.00	69	51	
Perugini et al., 2000	.48	.13	22	21	
Reeve & Schandler, 2001	.44	.34	10	10	
Rucklidge & Tannock, 2002	.58	.02	35	37	
Scheres et al.,2004	.87	.01	18	20	
Schmitz et al., 2002	.10	.76	10	60	
Seidman et al., 1997	.35	.12	43	36	
Seidman et al., 2000	.38	.04	40	118	
Seidman et al., 2001	.22	.13	79	127	
Semrud-Clikeman et al., 2000	1.53	.00	10	11	
Willcut et al., 2001	.28	.09	52	121	
Combined (16)	**.49**	**.00**	**588**	**767**	

Note: Positive effect sizes indicate better performance for normal controls as compared to children with ADHD. Two different age groups are included for the Grodzinsky & Diamond study (1992). The random combined effect size is reported in the last row.

Table 2.3 Comparison of the effect sizes for the colour score in ADHD studies

Study	Effect Size	*p*	Sample size ADHD	Sample size Controls	Schematic representation of effect sizes with 95% confidence interval
Golden & Golden, 2002	.35	.11	43	43	
Grodzinsky & Diamond, 1992	.93	.00	32	34	
Grodzinsky & Diamond, 1992	.58	.03	34	30	
Hougton et al., 1999	.69	.00	62	28	
Lufi et al., 1990	.70	.02	29	20	
Nigg et al., 2002	.41	.03	69	51	
Perugini et al., 2000	.29	.35	21	22	
Reeve & Schandler, 2001	1.21	.01	10	10	
Rucklidge & Tannock, 2002	.93	.00	35	37	
Scheres et al., 2004	.82	.02	18	20	
Seidman et al., 1997	.32	.17	43	36	
Seidman et al., 2000	.40	.03	40	118	
Seidman et al., 2001	.17	.24	79	127	
Semrud-Clikeman et al., 2000	1.95	.00	10	11	
Spalletta et al., 2001	1.09	.05	8	8	
Willcut et al., 2001	.20	.23	52	121	
Combined (16)	**.58**	**.00**	**585**	**716**	

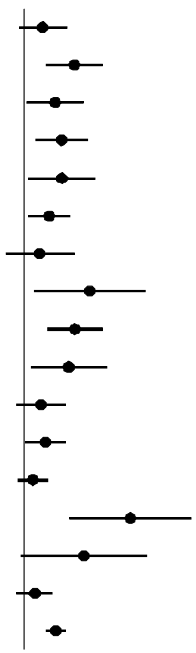
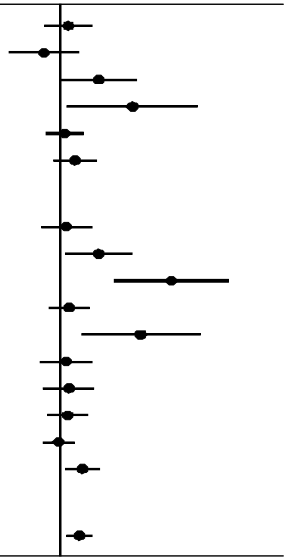


Table 2.4 Comparison of the effect sizes for the interference score in ADHD studies

Study	Interference score	Effect Size	*p*	Sample size ADHD	Sample size Controls	Schematic representation of effect sizes with 95% confidence interval
Golden & Golden, 2002	C-CW	.15	.50	43	43	
Perugini et al., 2000	C-CW	-.29	.35	21	22	
Scheres et al., 2004	C-CW	.70	.04	18	20	
Spalletta et al., 2001	C-CW	1.30	.02	8	8	
Willcut et al., 2001	C-CW	.07	.65	52	121	
Combined C-CW (5)		**.26**	**.18**	**142**	**214**	
Hougton et al., 1999	Golden	.11	.64	62	28	
Lufi et al., 1990	Golden	.69	.02	29	20	
MacLeod & Prior, 1996	Golden	2.00	.00	12	12	
Nigg et al., 2002	Golden	.16	.40	69	51	
Reeve & Schandler, 2001	Golden	1.45	.00	10	10	
Rucklidge & Tannock, 2002	Golden	.10	.66	35	37	
Seidman et al., 1997	Golden	.15	.50	43	36	
Seidman et al., 2000	Golden	.13	.48	40	118	
Seidman et al., 2001	Golden	-.03	.81	79	127	
Combined Golden (9)		**.40**	**.01**	**379**	**439**	
Combined (14)		**.35**	**.00**	**521**	**653**	



Note: Positive scores indicate better performance for normal controls as compared to children with AD / HD. Seperate combined effect sizes are shown in the 6th row for the C-CW score, in the 16th row for the 'Golden'score and in the last row for both methods combined.

The combined random effect size for the word condition (Table 2.2) was .49 and significant ($p < .001$). This effect is close to Cohen's standard for a medium effect size. The effect sizes for the word condition were heterogeneous ($p = .003$), indicating that there were large variations in the magnitude of the difference between children with AD/HD and normal controls. Two effect sizes were close to zero (Golden & Golden, 2002; Schmitz et al., 2002) and 14 effect sizes were positive.

The combined random effect size for the colour condition, .58 (see Table 2.3), is significant ($p < .001$) and corresponds to a medium effect size. Again, effect sizes were heterogeneous ($p = .003$). All the effect sizes for the colour condition were positive, which means that only the magnitude of the effect varied between studies. This indicates that in all studies, normal controls performed better than children with AD/HD in the colour naming condition.

The combined random effect size of the variable of primary interest, the interference score, was .35 (see Table 2.4) and significant ($p = .004$). This is considered a small effect size. The effect sizes for the interference scores were heterogeneous ($p < .001$). One effect size for the interference score was negative (Perugini et al., 2000). In eight studies, the effect sizes were around zero (Golden & Golden, 2002, Houghton et al., 1999, Nigg et al., 2002, Rucklidge & Tannock, 2002; Seidman et al., 1997, Seidman et al., 2000, Seidman et al., 2001, Willcutt et al., 2001;) and in five studies the effect sizes were positive (Lufi et al., 1990, MacLeod & Prior, 1996, Reeve & Schandler, 2001, Scheres et al., in press; Spalletta et al., 2001). This indicates that studies report inconsistent results for the difference between children with AD/HD and their normal peers with regard to the interference score.

Moderating Variables

Methods for Calculating the Interference Score

The overall effect size for the interference score (.35) was calculated with the interference score as reported by the authors. The effect size for the C-CW interference score was .26, not significant and heterogeneous ($p = .04$) while

the effect size for the Golden interference score was .40 and significant (p = .01) but heterogeneous ($p < .001$).

If both the raw mean data and the Golden score were available, a C-CW score was computed and compared with the Golden score. This was done for seven studies (Houghton et al., 1999; Lufi et al., 1990; Nigg et al., 2002; Reeve et al., 2001; Scheres et al., in press; Seidman et al., 2000, 2001). The random combined effect size for the C-CW interference score was -.003, not significant and homogeneous. The effect size for the Golden interference score, was .29, significant (p = .03) but heterogeneous (p = 0.02). No significant difference was found between these two methods (Z = - 1.69, p = .09), but this result suggests that there is a trend for the Golden score being larger than the C-CW score.

In Table 2.1 there is indicated how the studies deal with the moderating variables described in the following section.

Reading Disorder and Psychiatric Disorders

The meta-analytic results of the group comparisons between: (1) ADHD - ADHD and comorbid reading disorder, (2) ADHD - reading disorder, and (3) ADHD and psychiatric disorders are presented in Table 2.5.

Table 2.5 Random Combined Effect Sizes for the Word, Colour and Interference Score in Studies with ADHD groups, Reading Disorder groups and Psychiatric Disorder groups

Group Comparisons	**Sample size**	**Studies**	**Word**		**Colour**		**Interference**	
			d	*p*	*d*	*p*	*d*	*p*
ADHD - ADHD +RD	254	3	.96[a]	.00	.54[a]	.00	-.26[b]	.42
ADHD - RD	278	3	.64[a]	.00	.29[a]	.06	-.32[a]	.02
ADHD - PD	160	3	-	-	-	-	-.36[b]	.28

Note. Dashes indicate that the effect size was not calculated. Positive effect sizes indicate better performance for the ADHD group as compared to the other groups. d = random combined effect size, RD = reading disorder, PD = various psychiatric disorders. [a]Homogeneous effect. [b]Heterogeneous effect.

ADHD-Subtypes

Three studies (Houghton et al., 1999; Nigg et al. 2002; Scheres et al., in press) compared children with ADHD inattentive subtype (ADHD-I) and ADHD combined subtype (ADHD-C) and found no differences. Meta-analytic results, however, reveal a small, but significant and homogeneous combined random effect size of -.35 (p = 0.02) for the interference score. This effect size indicates that children with ADHD-I have less resistance to interference than children with ADHD-C. The effect sizes for the time-to-read words and the time-to-name colours were not significantly different between the subtypes (combined random effect size: -.14, *ns*, and .21, *ns*, respectively) and homogeneous.

Gender

Research has failed to find a substantial difference in the Stroop Colour-Word Task dependent measures between men and women at any age (MacLeod, 1991), although women may be somewhat faster especially in naming colours. In this meta-analysis, the proportion of boys and girls was approximately equal across ADHD groups and the normal control groups. Hence, there is no reason to suspect an influence of gender on the dependent variables.

Age

The interference effect begins early in the school years, rising to its highest level around grades 2 to 3 as reading skills develop (Schiller, 1966). Cognitive control is still developing after grades 2 and 3 with an accompanying improvement in interference control. No developmental changes have been reported until approximately 60 years, at which age interference control begins to decrease (Comalli, Wapner, & Werner, 1962).

No significant correlations were found between the effect sizes for each of the dependent variables and mean age. Thus, it seems that the differences on the Stroop Colour-Word Task between children with ADHD and their normal peers remain the same across the age range studied here.

Intellectual Functioning

No significant correlations were found between the difference between ADHD groups and normal control groups in IQ scores and the effect sizes for the word: $r(14) = -.31$, *ns,* colour: $r(13) = -.20$, *ns,* and interference score: $r(12) = .11$, *ns.*

Medication

Methylphenidate (MPH) is the most common pharmacological treatment for children with ADHD (Greenhill, Halperin, & Abikoff, 1999; MTA Cooperative Group, 1999). Recently, it has been shown that MPH improves colour naming and word reading, but that it has no effect on response interference (Bedard, Ickowicz, & Tannock, 2002). There were too few studies using the Stroop Colour-Word Task to analyse the effects of medication in this meta-analysis.

Sample Size

There was a strong negative correlation between sample size and the effect sizes for the dependent variables in this meta-analysis for the colour: $r(16) = -.68$, $p < .01$, word: $r(16) = -.42$, *ns* and interference score: $r(14) = -.60$, $p = .02$. This means that studies with larger samples report small effect sizes, while studies with small samples report large effect sizes. These correlations may reflect the difficulty of publishing studies including small samples and reporting no group differences.

Discussion

Impairments in interference control have been implicated as one of the core deficits in ADHD (Barkley, 1997). The Stroop Colour-Word Task has been frequently used to demonstrate this deficit and as an aid in clinical diagnosis. Seventeen independent studies, encompassing large groups of children, were analysed to determine the degree of this deficit in interference control in

children with ADHD compared with normal controls. The role of the following moderator variables was assessed: comorbid reading and psychiatric disorders, ADHD-subtypes, gender, age, IQ and sample size. The results reported here indicate that a deficit in interference control, as measured with the Stroop Colour-Word Task, is either absent or very small in children with ADHD and depends heavily on the method of calculation. Children with ADHD had lower word reading and colour naming scores than normal controls. Comorbid reading disorder was found to have a negative impact on colour naming and word reading, but there was no consistent effect on the interference score. Compared with children with a reading disorder, children with ADHD had a better word and colour score, but a lower interference score. There was no significant difference between children with ADHD and children with various psychiatric disorders on the interference score. A small difference was found in interference control between the ADHD-subtypes: Children with predominantly inattentive subtype had poorer control over interference than the children with ADHD-combined subtype. No effects of gender, age, and IQ were noted, but the correlations between the effect sizes and sample size suggest a publication bias.

Study Limitations

The negative correlation between sample size and the effect sizes for the colour and interference scores may be an indication of a publication bias. Small studies with significant results will probably be published more often than small studies with no significant results (see for a review Rosenthal, 1979).

Some children in the ADHD-inattentive subtype group may be just one hyperactivity symptom below the threshold for the ADHD-combined subtype or may be formerly children with ADHD-combined subtype, who have outgrown one or two symptoms of hyperactivity/impulsivity over time. The distinction between ADHD-inattentive subtype and ADHD-combined subtype may be confounded by problems of contamination of the inattentive subtype with subthreshold combined subtype cases.

The comparisons between children with ADHD and children with various psychiatric disorders, between children with ADHD with and without a comorbid reading disorder, and between children with ADHD and children with a reading disorder are based on a limited number of studies (three studies). Thus, the results pertaining to these group comparisons should be interpreted with caution.

No significant correlations were found between, on the one hand, age and IQ, and, on the other hand, the effect sizes for the word, colour, and interference scores. However, these correlations probably underestimate the associations that would be found if this analysis was conducted using data on a subject level. Furthermore, one study (Scheres et al., in press) found that covarying for age (and IQ) reduced the differences between children with ADHD and their normal peers.

What is the Best Method to Calculate Interference Control?

This meta-analysis shows that the method of calculating interference is crucial to the interpretation of the results. When interference is calculated by subtracting the CW score from the C score, there is no difference in interference control between children with ADHD and normal controls. Thus, because children with ADHD are slower on both cards (C card and CW card) compared with normal controls, there is no difference in the interference score. The Golden method is better in differentiating children with ADHD from normal controls than the classical C-CW score. It should be borne in mind that the interference score proposed by Golden (1978) is based on a comparison of an estimation of a CW score and the real CW score. This estimation is based on the assumption that the time to read one colour-word is actually the time to read one word followed by the time to name one colour. This assumption corresponds with older, sequential explanations of the Stroop effect: that processing in one stage must be completed (or almost completed) before processing in the next stage may begin. Neural imaging research on the Stroop Colour-Word Task supports the notion that Stroop stimuli are processed in parallel in a network of brain areas (Atkinson, Drysdale, & Fulham, 2003; Ukai et al., 2002; West & Alain, 1999). Therefore, the theoretical model on which

the formula is founded, does not stand on strong ground. For this reason, we suggest that the traditional method of calculating the interference score may be a more 'pure measure' of interference.

Do Children with ADHD Have a Reduced Resistance to Interference?

This meta-analysis suggests that there is little support for a deficit in interference control in ADHD, as measured by the Stroop Colour-Word Task. The fact that no deficit in interference control was observed using the traditional method to calculate interference, and that children with ADHD-inattentive subtype may have less resistance to interference than children with ADHD-combined subtype, does not support the inhibition deficit hypothesis (Barkley, 1997; Pennington and Ozonoff, 1996), which pertains to the ADHD combined subtype in particular.

Results of other studies, using a different design to measure interference control, are mixed. Scheres et al. (in press) and Jonkman et al. (1999) measured interference control with a Flanker Task and found an interference effect on errors. Cornoldi et al. (2001) found that children with ADHD had difficulties in controlling interference related to working memory. When a computerized version of the Stroop was used, Carter et al. (1995) found a difference in reaction time between children with ADHD and normal controls, while Gaultney et al. (1999) did not found such an effect.
An interesting finding emerges from interference studies with fMRI in which ADHD groups and normal control groups are compared on brain activation during a 'counting Stroop' (Bush et al., 1999) and a 'go-nogo' task (Durston et al., 2003). Activation patterns indicated that the normal adults activated the anterior cingulate cortex; specifically the cognitive division (Bush et al., 1999) and normal children activated fronto-striatal regions (Durston et al., 2003). In contrast, adults with ADHD failed to activate the anterior cingulate cortex, and children with ADHD failed to activate fronto-striatal regions. In both studies, the ADHD groups relied on a more diffuse network of regions, although in the study by Bush et al. (1999), no performance differences were observed between the control group and the ADHD group. Bush and colleagues interpreted these finding as demonstrating that adults with ADHD may

compensate for impairments by recruiting a different and less responsive pathway. Based on only the card version of the Stroop Colour-Word Task, one cannot conclude that children with ADHD have no deficit in interference control. This is because results from other interference tasks and imaging research indicate that ADHD is related to problems in interference control. The fact that this is not shown by the card version of the Stroop Colour-Word Task, may indicate that this is not a *generalized* deficit but may be context dependent.

Rapid Naming

Interference scores need to be controlled for at least colour naming. If this is not done, differences on the CW card may also reflect differences in rapid naming. Deficiencies on the W, C, and CW- card have been related to abnormalities in brain structure (Semrud-Clikeman et al., 2000). Semrud-Clikeman et al. (2000) demonstrated that poorer performance on all three cards of the Stroop Colour-Word Task was significantly related to reversed asymmetry of the caudate. Thus, a slower retrieval of colour-names and a slower reading speed may be an indication of abnormalities in brain structure in ADHD. Therefore it is important to assess these deficits in ADHD. Slow processing speed is frequently reported in children with ADHD compared to normal controls (e.g., Mason, Humphreys, & Kent, 2003; Sergeant, Oosterlaan, & van der Meere, 1999). This general slowing has been interpreted as reflecting a 'non-optimal activation state' (see for review, Sergeant & Van der Meere, 1990, 1991; Sergeant, Oosterlaan, & Van der Meere, 1999; Van de Meere, 1996). Other evidence that children with ADHD may be less able than their normal peers to maintain the state required for optimal task performance can be derived from the work of Leth-Steensen, King Elbaz, and Douglas (2000). Their results confirmed that the mean slower reaction times of boys with ADHD were not due to a generalized slowing of all responses but was due to a greater proportion of abnormally slower responses, as shown earlier by Sergeant (1988). Children with ADHD may be less able than their normal peers to maintain a stable reaction time over trials. This result can explain the slower naming and reading speeds and is consistent with the hypothesis that ADHD involves a non-optimal activation state. Unfortunately, the present data does

not allow this theoretical explanation to be tested. Future studies should address this issue.

Clinical Practice and Future Research

Based on this meta-analysis, we cannot recommend the Stroop Colour-Word Task in its standard form for use in clinical practice in ADHD. Another reason to advise against the use of the Stroop Colour-Word Task in clinical practice is its low negative predictive power: a normal score can be obtained despite the fact that the child has ADHD (Doyle et al., 2000; Grodzinsky & Barkley, 1999). The predictive validity can be improved, when used in combination with other executive tests (Perugini et al., 2000). Therefore, if the Stroop Colour-Word Task is used in clinical practice, it should always be used in combination with other executive function tests.

The interference score cannot differentiate between children with ADHD and children with various other psychiatric disorders. The interference score can differentiate between children with ADHD and children with a reading disorder. This difference probably reflects the fact that reading is less automatic in children with a reading disability. Word reading will thus interfere less with colour naming on the CW-card in children with a reading disorder.

A better alternative for research and clinical use may be a 'trial-by-trial' computerized version of the Stroop Colour-Word Task. Perlstein, Carter, Barch, and Baird (1999) showed that a trial-by-trial version of the Stroop Colour-Word Task showed greater sensitivity to attentional pathology. A second advantage is that a computer allows response times and the response variability to be measured with high accuracy. A computerized Stroop Colour-Word Task, and variations on this task, have already been used in various studies (Bush et al., 1999, Gaultney et al., 1999, Carter et al., 1995, Miller, Kavic, & Leslie, 1996).

Conclusion

The results, obtained with the Stroop Colour-Word Task, do not provide strong evidence for a core deficit in interference control in ADHD. This result argues against current theoretical models, which emphasise inhibitory control deficits in ADHD (Barkley, 1997; Pennington & Ozonoff, 1996). Studies, using other measures of interference control, however do provide evidence in favour of the interference control deficit hypothesis, which suggests that there might be a subtler and contextually dependent interference deficit in ADHD. Interestingly, in this meta-analysis, rapid naming deficiencies are more pronounced in ADHD than a deficit in interference control. Should we reject the Stroop Colour-Word Task in its standard form if we want to investigate interference control in children with ADHD? Our conclusion is affirmative to this question. The Stroop Colour-Word Task is not a golden standard to demonstrate an interference deficit in ADHD.

Acknowledgements

We would like to thank Dr. Joel T. Nigg and Dr. Russell A. Barkley for their helpful comments on an earlier version of this manuscript and for providing us with data. We are also most grateful to Dr. Larry J. Seidman, Dr. Gail M. Grodzinsky, Dr. Elisabeth Harvey, and Dr. Stephan Houghton for providing us with all the necessary information for conducting the meta-analysis. We also would like to thank Dr. Charles Golden for providing us with information about the Stroop Colour –Word Task

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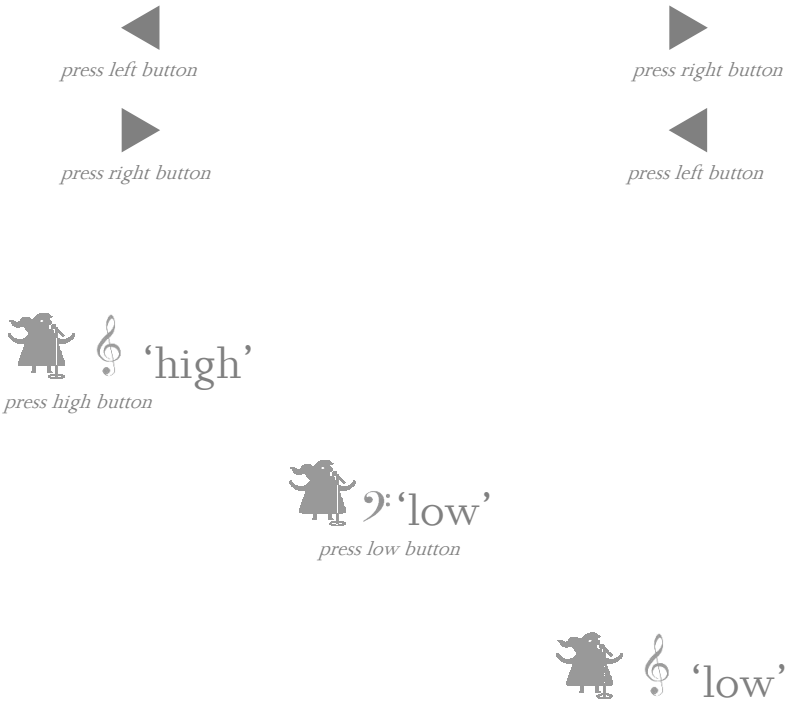
Chapter 3

Interference control in children with attention deficit/hyperactivity disorder



Published as: Van Mourik, R., Papanikolau, A., van Gellicum-Bijlhout, J., van Oostenbruggen, J., Veugelers, D., et al. (2009). Interference control in children with attention deficit/hyperactivity disorder. *Journal of Abnormal Child Psychology, 37,* 293-308.link to original publication

Abstract

The view that Attention Deficit/Hyperactivity Disorder (ADHD) is associated with a diminished ability to control interference is controversial and based exclusively on results of (verbal)-visual interference tasks, primarily the Stroop Color Word task. The present study compares medication-naïve children with ADHD (n = 35 and n = 51 in Experiments 1 and 2, respectively) with normal controls (n = 26 and n = 32, respectively) on two interference tasks to assess interference control in both the auditory and the visual modality: an Auditory Stroop task and a Simon task. Both groups showed reliable *but* equal degrees of interference on both tasks, suggesting that children with ADHD do not differ from normal controls in their ability to control interference in either modality.

Introduction

Interference control encompasses both the ability to inhibit selectively the processing irrelevant information and the ability to inhibit automatic response tendencies in order to perform a more controlled action. Although there is a relation between inhibition and interference control functions (Friedman & Miyake, 2004), not all inhibition-related functions are equally impaired in individuals with ADHD. While the preponderance of the evidence indicates that individuals with ADHD are impaired on response inhibition tasks, (Alderson, Rapport, & Koffler, 2007; Lijffijt, Kenemans, Verbaten, & Van Engeland, 2005; Oosterlaan, Logan, & Sergeant, 1998), the evidence for a deficit in interference control in ADHD is less clear. Interference control is an important aspect of 'executive functioning', which is incorporated in influential theoretical models of ADHD (Barkley 1997; Pennington and Ozonoff, 1996; Sergeant, 2005; Sonuga-Barke, 2003).

Interference control is typically measured with tasks that elicit conflict between an automatic response and a more controlled action, such as the Stroop Color-Word task (Stroop 1935; see for review MacLeod 1991). Interference control in ADHD is recently addressed in as much as six meta-analyses (Fraizer, Demaree, & Youngstrom, 2004; Hervey, Epstein, & Curry, 2004; Homack & Riccio, 2004; Lansbergen, Kenemans, & Van Engeland, 2007; Schwartz & Verhaeghen, 2008; van Mourik, Oosterlaan, & Sergeant, 2005) with mixed results: Mean weighted effect sizes (Cohen's d) ranged from .15 (Hervey et al.) to .54 (Frazier et al.). These inconsistent results might be attributable to different and even incorrect quantification methods of the interference score (Lansbergen et al.). All meta-analyses were almost exclusively based on studies that employed the Stroop Color-Word task to measure interference control.

Regions of the brain that are involved in interference control include the anterior cingulate cortex and the dorsolateral prefrontal cortex (MacLeod & MacDonald, 2000; Peterson et al., 2002). Volumetric abnormalities in these regions have been shown in individuals with ADHD (Seidman et al., 2006) and patterns of brain activation during interference tasks differ between ADHD groups and normal control groups (Bush et al., 1999; Schulz et al., 2005;

Vaidya et al., 2005; Zang et al., 2005). Surprisingly, at the performance level, no weakness in interference control was found in ADHD groups in these studies. This might be due to the very small sample size (eight to ten participants per group) employed in these studies. Another possibility is that the presumed deficit in interference control in ADHD is minor or only present in a small subsample.

The Stroop Color-Word task is an elegant task to investigate interference control but has limitations in research on ADHD. Children with ADHD encounter difficulties with the baseline conditions (color naming and word reading) of the Stroop Color-Word task, probably caused by a rapid naming deficiency (Tannock, Martinussen, & Frijters, 2000). Blue-yellow color perception problems may contribute to slower color naming (Banaschewski et al., 2006). Another limitation is that automatic reading skill is a prerequisite for the Stroop Color-Word task but reading disability tends to co-occur in approximately 20% of the individuals with ADHD (Del'Homme et al., 2007). Therefore, alternative methodologies are needed to answer the question whether children with ADHD have a deficit in interference control.

One alternative may be a Flanker task (Eriksen & Schultz, 1979), in which the individual is required to respond to a central arrow that is flanked by arrows that point in the same direction (congruent condition) or in the opposite direction (incongruent condition). Various studies (see for example Crone, Jennings, & van der Molen, 2003; Jonkman et al., 1999; Scheres et al., 2004; van Meel, Heslenfeld, Oosterlaan, & Sergeant, 2007) indicate that children with ADHD are more sensitive to interference in Flanker tasks: Children with ADHD make more errors or disproportionally slow down in the incongruent condition compared with the congruent condition. Negative findings for group differences have also been reported (for example Booth, Carlson, & Tucker, 2007). A possible confounding influence in the Flanker task is that children with ADHD have more problems restricting their visual attention to a limited spatial area resulting in more interference from the incongruent flankers. In support of this, Crone et al. showed that, in contrast to normal control children, children with ADHD slowed down more, when congruent flankers were introduced compared with a condition without flankers. Selective

attention deficits in ADHD have not only been shown in the visual domain, but also in the auditory domain (Brodeur & Pond, 2001; Jonkman et al., 1997), which suggests that the ability to focus attention and ignore irrelevant information is a more general problem in ADHD.

To determine the nature of the presumed deficit in interference control in ADHD, it is important to know whether this deficit is still present when the ability to restrict one's attention to a limited area is controlled. This can be achieved with interference tasks in which the conflicting information is incorporated in the stimulus itself, such as for example in a Simon task (Simon, 1990) or in a Counting Stroop task (Bush et al., 1998). In these tasks, the degree to which the conflicting information is processed is not partly dependent on the ability to focus attention, but relies solely on the ability to suppress the processing of conflicting information. Such interference tasks have been used in various behavioural and functional imaging studies of ADHD with mixed results. Most studies (Albrecht et al., 2008; Bush et al., 1999; Drechsler et al., 2005; Rubia et al., 2007; Schulz et al., 2005; Smith et al., 2006; Zang et al., 2005) reported no specific behavioural deficit in interference control in ADHD, while only one study reported specific difficulties in interference control in an ADHD group (Kaufman & Nuerk 2006).

The failure to find group differences in interference control at the performance level in functional imaging studies (Bush et al., 1999; Schulz et al., 2005; Smith et al., 2006; Zang et al., 2005) might be due to small sample sizes. The power in fMRI studies is enough to find large effects, typical for functional imaging results, but not for medium or small effects, that are typically found in performance studies. Drechsler et al. (2005) used a very fast stimulus presentation rate (100 ms) and an auditory warning preceded all stimuli. This triggered impulsive responding, resulting in more errors in the ADHD group, hence possibly obscuring the interference effect. Children with ADHD also showed increased error rates to both congruent and incongruent trials in the study of Rubia et al. (2006). These issues make the negative findings for group differences in interference control less reliable.

Another limitation of these studies is that interference control was assessed only in the visual domain. At this point, nothing is known about the effects of stimulus modality on interference control in children with ADHD. However, two recent meta-analyses, one on response inhibition (Alderson et al., 2007) and the other on working memory (Martinussen et al. 2005) in ADHD show that stimulus modality is an important moderator of impaired task performance. Performance deficits were more pronounced in visual tasks than in auditory tasks. Because interference control is related to both response inhibition (Friedman & Miyake 2004) and working memory (Kane & Engle 2003), it is plausible that interference control in ADHD is more affected in the visual domain than the auditory domain. Therefore, this study assessed interference control in both the auditory and visual modality in children with ADHD. Two different tasks are employed: a newly developed Auditory Stroop task (adapted from McClain, 1983) to assess interference control in the auditory domain and a Simon task (Simon, 1990) to measure interference in the visual spatial domain. An advantage of both tasks is that they are independent of reading ability and that they provide a relative 'pure measure of interference control' in which the interfering information is integrated in the stimulus itself, controlling for selective attention deficits.

Experiment 1

Methods

Participants and selection procedure

Thirty-five children with ADHD were recruited through a university affiliated outpatient clinic specialized in the assessment and treatment of ADHD. Twenty-six control children were recruited through local primary schools. All children were between the ages of 8 and 12 years. Parents completed a written informed consent prior to the study, which was approved by the local ethical committee. The children with ADHD were all identified as meeting the DSM-IV criteria (APA, 1994) for ADHD by a multidisciplinary team of professionals. They had never used psychostimulant medication previously.

Assessment included the Dutch version of the Disruptive Behavior Disorder rating scale (DBD; Oosterlaan et al., 2000; Pelham et al., 1992), completed by parents and teachers of all children. Parents of the children with ADHD were also administered the ADHD, ODD (Oppositional Defiant Disorder) and CD (Conduct Disorder) sections of the Diagnostic Interview Schedule for Children (DISC-IV; Shaffer et al., 2000), which generates DSM-IV diagnoses. IQ was estimated with two performance and two verbal subtests of the Dutch version of the Wechsler Intelligence Scale for Children, third edition (Kort et al., 2002; Wechsler 1991): Picture Arrangement, Block Design, Arithmetic, and Vocabulary. Reading ability in the ADHD group was assessed with a standard Dutch reading test, the Three-Minutes-Test (DMT; Brus & Voeten, 1973). Comorbid reading problems were defined as a standardized score below the 10th percentile. These stringent criteria were applied because there might be a negative relation between reading skill and interference (Protopapas, Archonti, & Skaloumbakas, 2006).

The children with ADHD entered the study, if they met the DSM-IV criteria for ADHD using the DISC-IV and, in addition, obtained parent and teacher ratings above the 90th percentile on the Inattention and/or the Hyperactivity/Impulsivity scales of the DBD. Normal controls were required to have scores below the subclinical threshold (90th percentile) on all DBD scales. The mean percentile score for the normal control group was around the 30th percentile, which clearly indicates that the normal controls were free of ADHD related symptoms. An estimated IQ score above 70 was required for all children and they had to be free of any neurological, sensory, or motor impairment or any developmental psychiatric disorder other than ADHD, ODD, CD or dyslexia. All children had normal or corrected to normal vision and children with hearing problems were excluded from the experiments. Subject characteristics are summarized in Table 3.1. Groups did not differ in age, male/female ratio or IQ.

Table 3.1 Participant Characteristics Experiment 1

	Group				
	ADHD (n = 35)		NC (n = 26)		Group Comparison
Measure	**M**	**SD**	**M**	**SD**	**F(1, 59)**
Boys/Girls	26/9	-	19/7	-	0.5[a]
Age (in months)	120	16	121	14	0.2
IQ	99	11	103	16	1.7
DBD Parents					
Inattention	17.0	5.2	1.9	2.2	192.8**
Hyperactivity/Impulsivity	14.0	5.0	1.3	1.4	157.1**
ODD	6.7	4.6	0.7	1.2	41.7**
CD	1.0	2.0	0.04	0.2	6.1*
DBD Teacher					
Inattention	17.7	4.3	1.1	1.7	321.7**
Hyperactivity/Impulsivity	15.4	7.3	0.7	1.1	95.7**
ODD	7.0	6.7	0.5	1.3	22.5**
CD	2.3	3.8	0.1	0.3	7.7*
DISC-IV Subtypes (ADHD-group)	15 ADHD-Combined subtype 15 ADHD-Inattentive subtype 5 ADHD-Hyperactive subtype				
Comorbidity (ADHD-group)	9 Oppositional Defiant Disorder 1 Conduct Disorder 8 Reading Problems				

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder, DBD = Disruptive Behavior Disorder rating scale, DISC = Diagnostic Interview Schedule for Children, CD = Conduct Disorder, M = Mean, NC = Normal Control, ODD = Oppositional Defiant Disorder, SD = Standard Deviation.

*p<.05.**p<.001;[a]χ^2

Auditory Stroop task

The Auditory Stroop task (McClain, 1983) was adapted for Dutch children. The task consisted of two experimental trial types (congruent and incongruent) and neutral control trials. All stimuli were binaurally presented through headphones at a high (734 Hz) and a low (167 Hz) pitch at approximately 60 dB. The child was instructed to respond to the pitch by pressing one of two response buttons. Half of the participants responded with their left hand to the high stimuli and with their right hand to the low stimuli, and the other half vice verse. The congruent trial types were the Dutch words for 'high' and 'low', presented at a respectively high and low pitch. In the incongruent trials, the word 'high' was presented at a low pitch and the word 'low' at a high pitch. In order to control for possible facilitation effects, two control conditions

were included: tones presented at a low and high pitch as well as the Dutch words for 'old' and 'young', presented at a low and high pitch. The neutral words 'old' and 'young' were chosen as a neutral control trials because the words 'high', 'low', 'old' and 'young' are all adjectives and their frequency in spoken Dutch is comparable (CGN, Corpus Spoken Dutch, 2004). A picture of an ear was shown at the centre of a computer screen and was present throughout the task. It then blinked once in a blue color for 300 ms to prime the child to pay attention. The stimuli were presented 500 ms after the prime with a duration of 720 ms. The interstimulus interval (ISI) was 4000 ms. This interval is relatively long to prevent an impulsive response strategy, such as responding at the first syllable of the word. Because the word meaning interferes with pitch, the participant was required to listen to the word; otherwise, the word could not interfere with the pitch. The task consisted of 256 trials (64 per condition) presented in random order and divided into 4 blocks. Although interference effects are stronger if there are more congruent trials compared to incongruent trials, this experiment consisted of an equal proportion of congruent and incongruent trials. The reason for this was that, if the majority of the trials had been congruent, a failure to maintain the goal of the task (respond to the pitch) might occur, leading to more errors on incongruent trials. It has been shown that individuals with low working memory capacity are especially sensitive to this manipulation compared to individuals with high working memory capacity (Kane and Engle 2003). Children with ADHD typically have lower working memory capacity compared to normal controls (Martinussen et al. 2005). Therefore, this manipulation would pose an extra challenge for the ADHD group. Because the goal was to measure interference control as purely as possible, an equal number of trials in each condition was chosen. Pilot results showed that the task was too difficult for children younger than 8 years, hence only children older than 8 years were assessed.

Task instructions were displayed on the computer screen and were read aloud by the child or, if this was too difficult, the experimenter read out aloud the instructions. The children participated in one or two practice blocks, including twenty-four trials with feedback on each response, until the child fully understood the task requirements. After the practice session, the child was instructed to respond as accurately and as fast as possible to the pitch and to ignore the word meaning. The child was informed about his or her performance: mean reaction time, number correct and number of errors appeared on the screen after each block. The dependent variables were mean reaction time (MRT) and percentage of errors.

Statistical analyses

Children responded slower to the tones than to the incongruent condition, which makes the tones unsuitable as a control condition. MRTs to the words 'old' and 'young' did not differ significantly from MRTs in the congruent condition, suggesting that there was no facilitation effect in this task. Therefore, only the congruent condition was compared with the incongruent condition. MRT was analyzed with a repeated measures ANOVA with one within subjects factor (condition: congruent - incongruent) and one between subjects factor (group: ADHD – normal controls). It was not possible to transform the percentage of errors to approach the normal distribution. Therefore, percentage of errors in the congruent and the incongruent condition were compared with a non-parametric Wilcoxon Rank test. Groups were compared with a Mann-Whitney U test on: (1) percentage of errors in the congruent condition, (2) percentage of errors in the incongruent condition, and (3) the difference in percentage of errors between the congruent and the incongruent condition (interference effect). All analyses were repeated removing those children with comorbid reading problems and the children with the inattentive subtype. The 10^{th} percentile of the interference score (incongruent minus congruent for mean reaction time) was calculated for the normal control group. In order to test whether interference control might be deficient in a subsample of children with ADHD, the participants that had an interference score lower than this 10^{th} percentile were counted in both groups. The relation between, on the one hand, hyperactivity/impulsivity and attention

problems and, on the other hand, interference control was examined by computing correlations (Spearman) between the interference scores (incongruent minus congruent for MRT and percentage of errors) and the Inattention and Hyperactivity/Impulsivity subscales of the DBD for both parent and teacher ratings. Two participants in the ADHD group who had a very low accuracy rate (below 60%) were excluded from the study. The two excluded participants were not entered into the analyses nor represented in any of the data in this paper.

Results

Task and Group performance

MRT and percentage of errors are displayed in Figure 3.1. A highly significant condition effect [$F(1, 59) = 15.63$, $p < .001$, $\eta^2 = .208$] and a marginal significant group effect [$F(1, 59) = 3.95$, $p = .051$, $\eta^2 = .062$] were found for MRT: Children were on average 42 ms slower in the incongruent condition compared with the congruent condition and children with ADHD were on average 123 ms slower than their normal peers. No significant group by condition interaction occurred for MRT [$F(1, 59) = 0.43$, $p = .512$, $\eta^2 = .006$]. Significantly more errors were made in the incongruent condition than in the congruent condition [$Z = -3.43$, $p = .001$, $\eta^2 = .183$]. Between group comparisons failed to reach significance for percentage of errors in the congruent condition, in the incongruent condition and for the difference in percentage of errors between the conditions [$U = 325$ $p = .056$, $\eta^2 = .066$; $U = 364$, $p = .183$, $\eta^2 = .017$; $U = 451$, $p = .953$, $\eta^2 = .003$ respectively]. Two children (out of 35) scored below the 10th percentile on the interference score in the ADHD group and two children (out of 26) in the normal control group.

Comorbid reading problems and ADHD subtype

To control for the potentially confounding effect of comorbid reading problems, we reanalyzed the data removing those children with comorbid reading problems ($n = 8$). The marginal significant group difference for MRT became non-significant [$F(1, 51) = 2.87$, $p = .096$, $\eta^2 = .039$]. None of the

other results differed from the previous analyses in terms of significant and non-significant effects. In order to test if deficient interference control was only present in ADHD combined or hyperactive/impulsive subtype, we removed those children that were diagnosed as ADHD-inattentive subtype (n = 15) from the analysis. Again, the marginally significant group difference for MRT became non-significant [$F(1, 44) = 1.92$, $p = .173$, $\eta^2 = .042$].

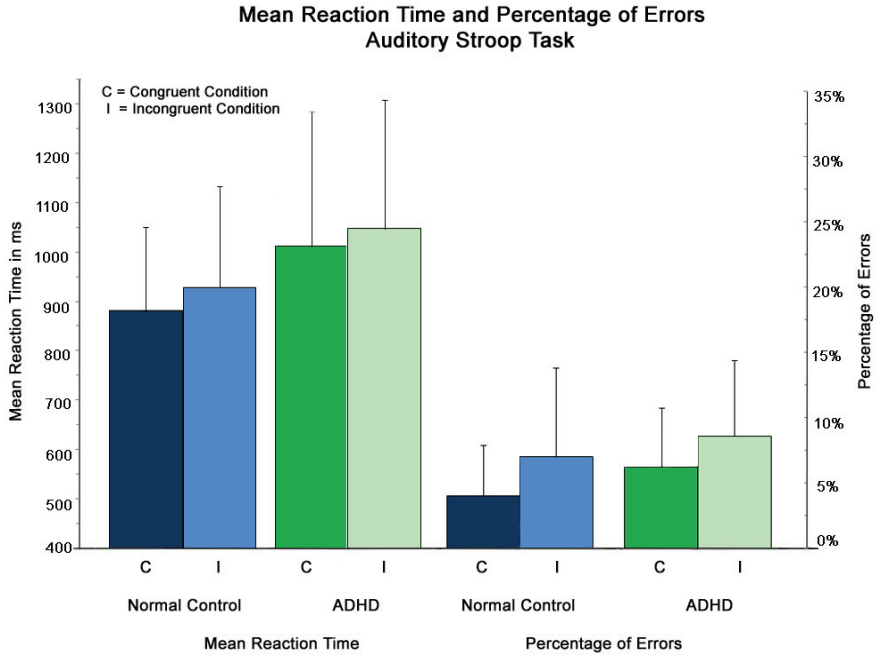


Figure 3.1 Mean reaction time and percentage of errors (with standard deviations) in the Auditory Stroop task for the normal control and ADHD group.

Correlations

In both groups, no significant correlations (n = 35 in the ADHD group and n = 26 in the normal control group) were found between parent and teacher ratings on the DBD (Inattention and Hyperactivity/Impulsivity subscales) and the interference scores (MRT and percentage of errors): rs ranged between -.24 and .31, all ps > .085.

Experiment 2

To confirm and extend the findings of Experiment 1, a second experiment was performed to investigate interference control in the visual-spatial domain. In the second experiment, the Simon task (Simon 1990) was used and adapted for children from the age of 6 to measure interference control.

Methods

Participants and selection procedure

A subsample (28 children from the ADHD group and 20 children from the normal control group) that participated in Experiment 1 also participated in Experiment 2. An additional 23 children with ADHD and 12 normal controls were recruited according to the selection procedure employed in Experiment 1. All children were between the ages of 6 and 12 years old. Subject characteristics are summarized in Table 3.2. Groups did not differ in age, male/female ratio or IQ.

Simon Task

The Simon task consisted of two experimental trial types: congruent trials and incongruent trials. A fixation cross was present throughout the task. An arrow appeared 3 cm left or right of the fixation cross for 500 ms. In the congruent condition, the arrow pointed to the same side as the side on which the arrow appeared and in the incongruent condition, the arrow pointed to the opposite side. The child was required to indicate the direction of the arrow with two response boxes and ignore the side on which the arrow appeared. The ISI was 2000 ms and 224 trials (112 congruent and 112 incongruent) were randomly presented over 4 blocks. The ISI was based on pilot work in which it was tried to evoke strong interference effects and to make the task suitable for even the youngest children in the groups. An equal proportion of congruent and incongruent trials was chosen for the same reason as in experiment 1. The task was designed as a navigation game in which the children had to navigate a spaceship by indicating the direction of the arrow.

Table 3.2 Participant Characteristics Experiment 2

	Group				
	ADHD (n = 51)		NC (n = 32)		Group Comparison
Measure	**M**	**SD**	**M**	**SD**	**F(1, 81)**
Boys/Girls	41/10	-	23/9	-	0.8[a]
Age (in months)	107	20	106	20	0.1
IQ	100	12	104	14	2.4
DBD Parents					
Inattention	15.9	4.8	1.9	2.3	240.1**
Hyperactivity/Impulsivity	15.4	6.3	1.8	2.1	140.0**
ODD	5.8	4.3	1.6	2.5	23.7**
CD	1.1	1.8	0.1	0.3	9.6*
DBD Teacher					
Inattention	16.5	5.1	1.7	2.0	238.0**
Hyperactivity/Impulsivity	15.9	7.8	1.0	1.4	115.0**
ODD	6.9	6.4	0.6	1.2	30.5**
CD	2.2	3.9	0.1	0.3	10.0*
DISC-IV Subtypes (ADHD-group)	26 ADHD-Combined subtype 19 ADHD-Inattentive subtype 6 ADHD-Hyperactive subtype				
Comorbidity (ADHD-group)	14 Oppositional Defiant Disorder 1 Conduct Disorder 8 Reading Problems				

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder, DBD = Disruptive Behavior Disorder rating scale, DISC = Diagnostic Interview Schedule for Children, CD = Conduct Disorder, M = Mean, NC = Normal Control, ODD = Oppositional Defiant Disorder, SD = Standard Deviation.

*p<.05.**p<.001;[a]χ^2

The testing procedure was the same as in Experiment 1, only the practice session differed in order to encourage children to respond fast. The children first practiced the task in three blocks of 12 trials with feedback ('correct', 'wrong', or 'too slow') on each response. In the first practice block, the children were required to respond to the stimulus within 2000 ms, in the second practice block the response limit was 1750 ms, and in the third practice block the response limit was 1500 ms, which was also the response limit in the experimental task. The dependent variables were mean reaction time (MRT) and percentage of errors.

Statistical analyses

The statistical analyses were identical to those of Experiment 1 with the addition that correlations were computed between interference measures of the both experiments. One participant from the ADHD group who had a very low accuracy rate (below 60%) was excluded from the analyses. None of the data of this participant is included in any section of this paper.

Results

Task and Group performance

MRT and percentage of errors are summarized in Figure 3.2. A highly significant condition effect was found for MRT [$F(1, 81) = 124.77$, $p < .001$, $\eta^2 = .61$]: Children were on average 54 ms slower in the incongruent condition than in the congruent condition. There was no significant group effect [$F(1, 81 = 0.34$, $p = .559$, $\eta^2 = .004$] or group by condition interaction [$F(1, 81) = 0.04$, $p = .842$, $\eta^2 < .001$]. Significantly more errors were made in the incongruent condition than in the congruent condition [$Z = -7.86$, $p < .001$, $\eta^2 = .682$]. Between group comparisons failed to reach significance for percentage of errors in the congruent condition, in the incongruent condition and for the difference in percentage of errors between the conditions [$U = 662$, $p = .146$, $\eta^2 = .024$; $U = 813$, $p = .974$, $\eta^2 = .001$; $U = 772$, $p = .677$, $\eta^2 = .017$ respectively]. In the ADHD group, two children (out of 51) had an interference score below the 10th percentile, whereas three children (out of 32) in the normal control group scored below the 10th percentile.

Comorbid reading problems and ADHD subtype

All analyses were repeated removing 8 children from the ADHD group with comorbid reading problems and removing 19 children with ADHD-inattentive subtype. None of these results differed in terms of significant and non-significant effects from the results obtained in the entire group.

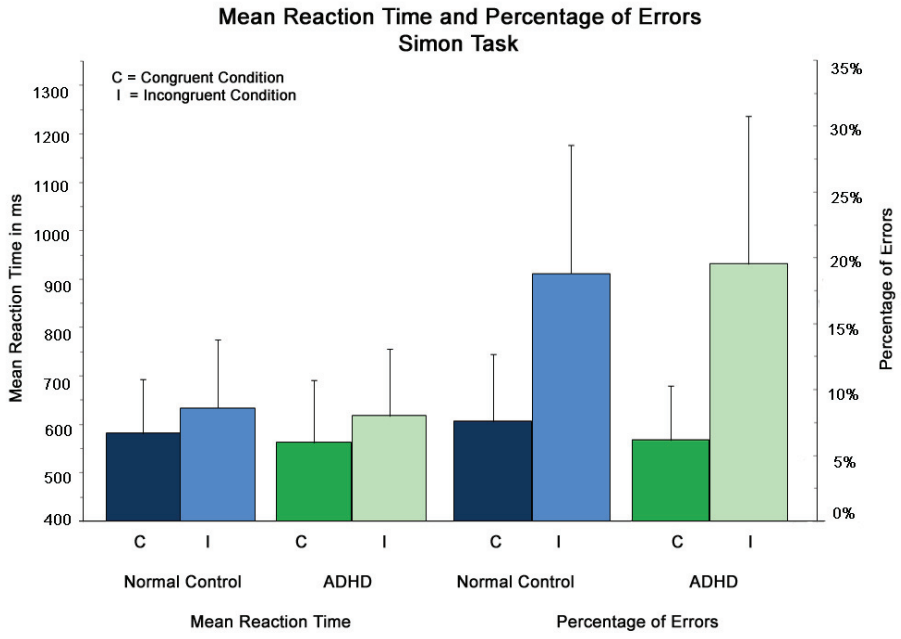


Figure 3.2 Mean reaction time and percentage of errors (with standard deviations) in the Simon task for the normal control and ADHD group.

Correlations

In the ADHD group, no meaningful relationships were revealed between the interference measures and the subscales of the DBD: *r*s ranged between -.29 and .11, all *p*s > .121. In the normal control group, a significant correlation was found only between the interference score (percentage of errors) of the Simon task and the Inattention subscale of the teacher DBD: $r = .52$, $p = .002$. However, no such relation was found in the entire group. No meaningful relation was found between the interference scores of the Simon task and the Auditory Stroop task: *r*s ranged between -.17 and .11, all *p*s > .486.

Discussion

This study was conducted to address the question whether children with ADHD have a diminished ability to control interference in both the auditory and the visual modality. The incongruent stimuli from the Auditory Stroop task and the Simon task evidently caused response conflict in both groups of children, thereby validating the tasks. This robust interference effect was reflected by increased response latency and an increased error rate in the incongruent condition compared with the congruent condition. The clear absence in both tasks of a significant group by condition interaction (F-values were below 1 and *p*-values above .50) convincingly demonstrates that both groups showed equal degrees of interference both in terms of reaction time and errors. These results seem to suggest that children with ADHD do not differ from normal controls in their ability to control interference and converge with recent empirical work that also reports the absence of a specific performance deficit in interference control in ADHD (Albrecht et al. 2008; Bush et al. 2008; Drechsler et al. 2005; Marchetta et al. 2008; Pritchard et al. 2007; Rubia et al. 2007). The finding that this effect was the same across two different interference tasks that differed in modality speaks to the reliability and generalizibility of the findings.

Surprisingly, the degree of interference in the Auditory Stroop task did not correlate with the interference effect in the Simon task. However, it has previously been found that even interference scores between different visual interference tasks do not correlate with each other (Stins et al. 2005). Possible explanations for the lack of correlations between different interference tasks may be due to modest reliability of interference scores in children (see Stins et al. 2005), because brain regions involved in interference control are not identical (Fan et al. 2002), or simply because different task characteristics such as modality (auditory versus visual) or task pace.

Inattention, as rated by the teacher, correlated with the interference score of the Simon task, but only in the normal control group. However, this result should be interpreted with caution, because one third of the children in the normal control group received a score of 'zero'on this subscale, and this relation was not found

in the entire group. The relationship between neurocognitive deficits and behavioural problems is a complicated one and probably dependent on multiple factors such as for example motivation and cognitive strategies to compensate for problems to regulate behavior. Recent models (Sergeant 2005; Sonuga-Barke 2003; Willcutt et al. 2008) emphasize that there is not a single core deficit in ADHD, but rather multiple pathways that may lead to the diverse attentional and behavioural problems that characterize this heterogeneous disorder. In this study, there was no evidence that a subgroup of children with ADHD showed poorer interference control. This finding indicates that interference control per se is presumably not one of the pathways that leads to attentional and behavioural problems in ADHD. Furthermore, the results did not change if children with the inattentive subtype were excluded from the analyses. Thus, a deficit in interference control does not seem present in the ADHD group as a whole, nor in the combined or hyperactive-impulsive subtype. These results are in line with previous work that failed to find group differences on neuropsychological profiles between children with the inattentive subtype and the combined subtype (Chhabildas et al. 2001).

A remarkable finding was that children with ADHD responded slower than normal controls in the Auditory Stroop task, but not in the Simon task. This finding is in contrast with previous research (Alderson et al. 2007; Martinussen et al. 2005) where children with ADHD were less impaired on auditory tasks compared to visual tasks. It is possible that the faster event rate in the Simon task (ISI was 2000 ms) was more arousing for children with ADHD than the slow pace of the Auditory Stroop task (ISI was 4000 ms). It has been repeatedly found that performance of children with ADHD is more impaired if a long ISI is used (Scheres et al. 2001; Wiersema et al. 2006; see Sergeant et al. 1999 for an explanation of event rate effects in terms of the cognitive energetic model). Another possibility could be that an auditory task poses a greater challenge to the attentional resources of children with ADHD: It might be more difficult to keep attention focused on what they hear as opposed to keeping attention focused on a computer screen. However, if the inattentive subtype or children with ADHD and comorbid reading problems were removed from the analyses, there were no significant differences in response speed on the Auditory Stroop task.

The present study further clarifies the controversy on interference effects in ADHD and sheds some light on the question under what conditions children with ADHD demonstrate deficits in interference control. Although there might be a small deficit in interference control, as measured by the Stroop Color-Word task (Carter et al. 1995; Lansbergen et al. 2007; van Mourik et al. 2005), this finding does not seem to generalize to other interference tasks such as the Simon task and the Auditory Stroop task. It should be noted that in our tasks as well as in the Stroop Color-Word task, the interfering information was incorporated in the stimulus, thus both conflicting and non-conflicting aspects of the stimulus need to be processed, when the stimulus is perceived, just as in the classic Stroop Color-Word task. The current interference tasks measured the ability to suppress the processing of the irrelevant information and automatic response tendencies. The important ability to focus on what is relevant and ignore irrelevant surrounding information (crucial in Flanker tasks) was not addressed here. Deficits in this important and related aspect of information processing might be present in ADHD, as is shown by impaired performance on Flanker tasks (Crone et al. 2003; Jonkman et al. 1999, Scheres et al. 2003; van Meel et al. 2007). It has been shown that children with ADHD are less sensitive to the nature of distracters (incongruent or neutral) than normal controls, but slow down more than normal controls when distracters were introduced (Brodeur and Pond 2001; Crone et al. 2003). However, distraction that is not conflicting and unrelated to the task may even have beneficial effects on task performance of children with ADHD, possibly by increasing their arousal to an optimal level (van Mourik et al. 2007). These results indicate that the extent to which irrelevant information disrupts or improves performance is task or situation dependent and that dealing with response conflict that is elicited by incongruent stimuli per se is unlikely to be disrupted in ADHD.

As noted in the introduction, the neural networks involved in the suppression of interference on various tasks have been shown to differ not only in childhood ADHD (Konrad et al. 2006; Vaidya et al. 2005; Zang et al. 2005), but also in adolescence (Schulz et al. 2005), and adulthood (Bush et al. 1999; Bush et al. 2008), despite participants with ADHD showing similar task

performance compared to normal controls. Increased activation in the fronto-striatal network during interference suppression has been interpreted as reflecting possible compensatory processes, or a greater effort to control interference. These compensatory processes may not be specific for interference control per se, but may be recruited by individuals with ADHD, when they perform difficult cognitive tasks that measure executive functioning (Fassbender and Schweitzer 2006). Thus, although our results do not support the theory that children with ADHD suffer from a core deficit in interference control, we cannot exclude the possibility that interference control is more effortful in children with ADHD and that performance measures alone may not be sufficiently sensitive to detect difficulties in interference control.

Limitations

A limitation of this study is that the interference effects in our tasks are not as strong as in the classical Color-Word Stroop. Because the tasks consisted of equal numbers of incongruent and congruent trials, interference effects may have been less pronounced compared to other designs. However, the effect sizes of the interference effects were large in both tasks, thus the Auditory Stroop task and the Simon task are sensitive measures of interference control. Another limitation is that, as opposed to the classical Color-Word Stroop, no facilitation effects were found in the Auditory Stroop task. All children responded slower on one of the initial control conditions in the Auditory Stroop task (tones) compared to the other conditions. Spoken language is probably processed faster than tones because children are so familiar with speech. This could make judging tones more difficult, and therefore unsuitable as a neutral control condition. In the Simon task, no neutral control condition was included, thus there was no control for possible facilitation effects. The Auditory Stroop task was only assessed in children above the age of 8 years, because pilot results showed that this task was too difficult for younger children. This is a limitation of the task and it suggests that it may be difficult for younger children to form an association between a word and the pitch or use their former semantic knowledge on the words. The concepts 'high' and 'low' may still pose a challenge for some of the children included in the study,

resulting in overall slower reaction times or increased error rates in these children.

Clinical implications and future directions

Apart from a small deficit on the Stroop Color-Word task, children with ADHD do not demonstrate deficits on interference tasks in which the interfering information is integrated in the stimulus. These measures of interference control are unrelated to ratings of inattentive and hyperactive/impulsive behaviour in ADHD. Therefore, we advise against the use of these sorts of interference tasks in clinical practice as an aid in characterizing the deficits of children with ADHD. However, several issues warrant future research. Most importantly, the relation between aberrant brain activity, on the one hand, and normal performance on interference tasks on the other hand, needs to be elucidated. It is important to determine the factors contributing to this paradoxal result. It might be possible
that children with ADHD demonstrate a deficit in interference control only when task demands are high. For example, a very low proportion of incongruent trials or a switch manipulation could be a fruitful approach. Thus, although interference control per se seems to be intact in ADHD, it is possible that individuals with ADHD show a diminished ability to control interference in more complex situations or tasks.

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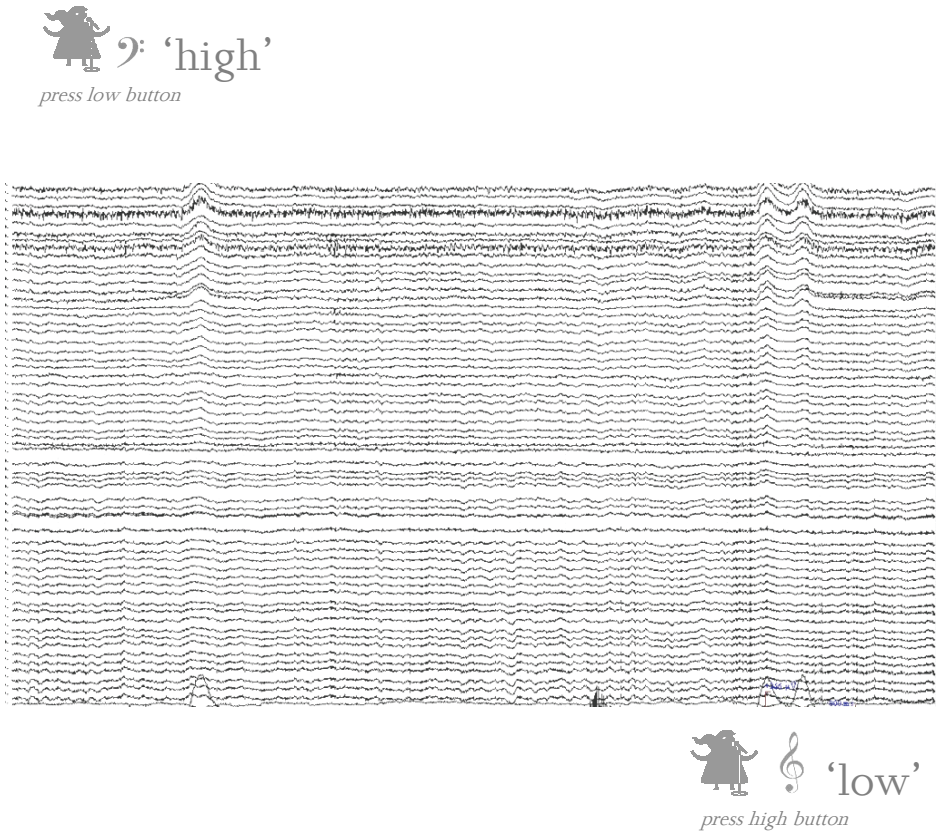
Chapter 4

Conflict processing in ADHD: Deviating ERPs in the absence of a behavioural deficit



Revised manuscript submitted.

Abstract

Impaired cognitive control has been implicated as an important developmental pathway to ADHD. Cognitive control is crucial to suppress interference resulting from conflicting information and can be measured with Stroop-like tasks. This study was conducted to gain insight into conflict processing in children with ADHD. ERPs were recorded in an auditory Stroop task. Twenty-four children with ADHD were compared with twenty-four control children (aged 8 - 12 years). No performance deficit was found on the auditory Stroop task in ADHD. Furthermore, no differences between the groups occurred in the early conflict related ERPs. However, the difference between the congruent and the incongruent condition in the 450-550 ms time window was absent in the ADHD group compared to normal controls. In addition, the conflict sustained potential was found frontally in the ADHD group and parietally in the normal control group. These findings suggest that children with ADHD evaluate conflict to a lesser extent and use a different neurophysiological strategy to suppress interference and select appropriate responses.

Attention Deficit/Hyperactivity Disorder (ADHD) is one of the most common childhood psychiatric disorders characterized by inattentiveness, hyperactivity and impulsivity (DSM-IV; American Psychiatric Association, 1994). Theoretical accounts on the neurocognitive basis of ADHD emphasize poor cognitive control as an important developmental pathway to this disorder (Casey, Nigg, & Durston, 2007). 'Cognitive control' describes the ability to generate, maintain and adjust sets of goal-directed processing strategies (Egner, 2008). Conflict between competing information is thought to serve as a signal for the recruitment of cognitive control, which reduces interference by biasing information processing in line with current task demands (Egner, 2008). A classic measure of interference, which has frequently been used in neuropsychological studies on ADHD, is the Stroop task (Stroop, 1935, see for review MacLeod, 1991). In this task, interference is operationalized in terms of the speed and accuracy of naming incompatible colour words (e.g., the word GREEN printed in blue ink; say 'blue') compared with naming the colour of a control item (e.g., a neutral word, a coloured bar) or a compatible colour word (e.g., the word BLUE printed in blue ink).

At the performance level, interference effects in this task are equal in groups with ADHD and control groups (Schwartz & Verhaeghen, 2008). However, patterns of brain activation during Stroop (-like) tasks differ between ADHD groups and control groups (Bush et al., 1999; Zang et al., 2005). Recently van 't Ent et al. (2009) reported that children with attention problems also show decreased activation to response interference in the DLPFC, parietal and temporal brain regions, but increased activation in other regions compared with children without attention problems. This distinct brain activation in the absence of a performance deficit in individuals with ADHD has been interpreted as reflecting compensatory mechanisms to maintain task performance (Bush et al., 1999, Van 't Ent et al., 2009; Zang et al., 2005).

fMRI studies have elucidated the brain areas involved in interference control in ADHD, but they cannot indicate the temporal processing of interference. The temporal processing of interfering information in the Stroop has been described in healthy adults by various ERP studies. Detection of conflict in Stroop tasks occurs between 400 and 500 milliseconds after stimulus onset and

is reflected by a larger negativity on incongruent trials as compared to congruent and neutral trials, labelled the N450 (Rebai, Bernard, & Lannou, 1997; West & Alain, 2000). The source of the N450 has been localized in the anterior cingulate cortex (ACC) (Liotti, Woldorff, Perez, & Mayberg, 2000). Selection of the appropriate response (conflict resolution) is reflected by a larger parietal positivity and a larger lateral-frontal negativity on incongruent trials compared to congruent or neutral trials between 600 and 800 milliseconds after stimulus onset, labelled the conflict sustained potential (SP) (West & Alain, 1999). The source of the conflict SP has been located in the lateral region of the prefrontal cortex (West, 2003) and near the ACC (Lansbergen, Van Hell, & Kenemans, 2007).

ERPs have not yet been collected in ADHD during a Stroop task, with the exception of a case study (Horrobin, McNair, Kirk, & Waldie, 2007) and an oddball version of the Stroop (Miller, Kavcic, & Leslie, 1996) in which children had to decide whether the colour of a word was congruent or incongruent with word meaning. As task demands differed in this oddball version and a case study may not be representative, the neural correlates of the temporal processing of interfering information in ADHD remain unknown. Knowledge about when deficits occur in the temporal processing of conflicting information is important, as it can help to characterize the underlying deficit in cognitive control in ADHD, which may lead to better future treatment options. One of the problems of the Colour Word Stroop task is that it involves reading, and reading problems are very common in ADHD (Del' Homme, Kim, Loo, Yang, & Smalley, 2007). An alternative Stroop task, not involving reading demands and suitable for ERP research in children with ADHD, is thus needed.

The auditory Stroop task (McClain, 1983) is such an alternative. Goal of this task is to respond to the pitch of a spoken word (which is either 'high' or 'low') and ignore the word meaning ('high', 'low' or neutral words). The auditory Stroop task reliably evokes response conflict (van Mourik et al., 2009). Furthermore, the fronto-parietal network that is recruited by visual Stroop tasks, is also engaged in conflict processing in the auditory Stroop task (Roberts & Hall, 2008). For these reasons, the auditory Stroop task is very suitable to unravel the temporal processes that underlie interference control in ADHD. The

aim of the present study is to gain insight into the processes that are crucial for effective interference control in ADHD: conflict detection and evaluation, and resolution of conflict (response selection).

Methods

Participants

Twenty-four children with a clinical DSM-IV diagnosis of ADHD and twenty-four healthy control children participated in the study (see Table 1). Age ranged between eight and twelve years. Children were free of any neurological, sensory, or motor impairment and only children without comorbid developmental psychiatric disorders (except oppositional defiant disorder, conduct disorder and dyslexia) were allowed to participate in the study. The children's parents gave their written informed consent. The local Ethical Committee of the VU Medical Center approved the study. The children with ADHD taking methylphenidate discontinued their medication at least 36 hours before testing allowing a complete washout (Pelham et al., 1999). No other medication was used in the ADHD group. All children were rewarded for their participation with a gift voucher of € 7,50.

Both parent and teacher ratings for the ADHD group fell within the clinical range (95^{th} – 100^{th} percentile) for the Inattention and/or the Hyperactivity/Impulsivity scale on the Disruptive Behavior Disorder rating scale (DBD; Pelham et al., 1992; Oosterlaan et al., 2000). Control children scored below the subclinical range (90^{th} percentile) on all scales of the parent and teacher DBD. Based on the Diagnostic Interview Schedule for Children Version IV (DISC-IV; Shaffer et al., 2000) twenty children met the criteria for ADHD combined subtype, three for ADHD inattentive subtype and one for hyperactive subtype. Fourteen children with ADHD were also diagnosed with ODD; one child met the criteria for both ODD and CD. ODD symptoms were not entered in the analysis as a covariate because there was a correlation between ODD symptoms and hyperactivity/impulsivity and attention problems, suggesting that ODD was related to symptom severity in our sample. Groups were too small to run separate analyses for ADHD only and

ADHD+ODD. Hearing was screened at 20 dB. All children had normal hearing. Reading ability was assessed with a standard Dutch reading test, the One-Minute-Test (EMT; Brus, & Voeten, 1973). Four children in the ADHD group and two children in the normal control group obtained scores that fell one or more standard deviation below average. IQ was estimated with two performance and two verbal subtests of the Dutch version of the Wechsler Intelligence Scale for Children, third edition (Wechsler, 1991; Kort et al., 2002): Picture Arrangement, Block Design, Arithmetic and Vocabulary. All children had an estimated IQ greater than 70.

Table 4.1 Participant Characteristics

	Group				
	ADHD (n = 24)		NC (n = 24)		
Characteristic	**M**	**SD**	**M**	**SD**	**F(1, 46)**
Boys/Girls	20/4	-	21/3	-	0.2[a]
Age	10.3	1.3	10.5	1.0	0.4
IQ	98	10	116	16	20.8**
Reading ability[b]	5.0	1.8	5.8	1.6	2.6
DBD Parents					
Inattention	18.1	5.4	2.9	1.8	166.8**
Hyperactivity	18.6	3.8	2.3	2.5	298.8**
ODD	11.2	4.8	2.1	2.4	66.8**
CD	2.6	2.1	0.3	0.7	26.4**
DBD Teacher					
Inattention	14.9	6.0	1.4	2.4	97.4**
Hyperactivity	13.5	5.5	0.7	1.6	116.2**
ODD	8.7	8.6	0.8	1.9	18.3**
CD	1.8	3.0	0.0	0.2	7.8**

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder, DBD = disruptive Behavior Disorder rating scale, CD = Conduct Disorder, M = Mean, NC = Normal Control, ODD = Opositional Defiant Disorder, SD = Standard Deviation.
*p<.05.**p<.001;[a]χ^2; [b] Age-appropriate norms (standardized scale, mean = 5, SD = 2).

Auditory Stroop Task

Participants performed an auditory Stroop task originally developed by McClain (1983) and adapted for Dutch children by van Mourik et al. (2009). The task comprised three conditions encompassing congruent, incongruent and neutral trials. On congruent trials, the Dutch words for 'high' and 'low', presented at a respectively high and low pitch. On incongruent trials, the word 'high' was presented at a low pitch and the word 'low' at a high pitch. Neutral trials

comprised the Dutch words 'old' and 'young' at a low and high pitch. The words 'old' and 'young' were chosen for the neutral control trials because the words 'high', 'low', 'old' and 'young' are all adjectives and their frequency in spoken Dutch is comparable [CGN; Corpus Spoken Dutch]. A female native Dutch speaker recorded all words and these words were presented through a speaker at a high (734 Hz) and a low (167 Hz) pitch at approximately 60 dB. The words occurred equally often within each condition. The child had to ignore the word meaning and respond to the pitch by pressing one of two response buttons. A picture of an ear was shown at the centre of a computer screen and was present throughout the task. On each trial, it blinked once in blue for 300 ms and acted as a warning signal and to prevent horizontal eye movements during the task. The stimuli were presented 500 ms after the prime with duration of 720 ms. The interstimulus interval (ISI) ranged from 3800 to 4200 ms. The task consisted of 360 trials (120 per condition) presented in random order and divided into 6 blocks each including 20 trials of each condition. Total task duration was 24 minutes. Mean reaction time (MRT) and number of errors were the dependent variables.

Electrophysiological Recording

The electroencephalogram (EEG; 0.05–200 Hz, sampling rate 1000 Hz) was recorded with 60 tin electrodes on-line referenced to one earlobe. EEG signals were offline re-referenced to the average of both earlobes. Blinks and vertical eye movements were monitored with electrodes placed at the outer canthi of each eye and below and above the left eye. The ground electrode was placed on the cheek. Impedances were kept below 10 kΩ. After additional filtering (0.1 – 30 Hz), blinks were corrected using a subtraction algorithm (Semlitsch et al., 1986). Epochs of -100 to 900 ms relative to trial onset were created from the continuous EEG data. Only trials with correct responses between 200 and 2000 ms after trial onset were analyzed. Epochs were baseline corrected to a 100-ms prestimulus interval (-100 to stimulus onset) and trials containing artefacts exceeding ± 100 μV at any electrode were rejected. No baseline differences were found between the groups. Supportive material is provided in the appendix. Stimulus-locked averages were derived separately for each condition. The mean number of epochs in the average was 95 in the congruent condition

and 94 in the incongruent condition in the ADHD group, while this was 94 and 95 respectively in the normal control group. It was decided to include the same electrodes as in the study at conflict processing of West et al. (2005): Fz, Fz, F4, FC1, Cz, FC2, P3, Pz, P4. Because we were primarily interested in the differences between congruent and incongruent, a difference wave (incongruent minus congruent) was computed in order to visualize the difference between the conditions. After visual inspection of the difference wave and the topographical maps of the difference wave, it was decided to analyze the mean amplitude for the congruent and incongruent condition as within subject factor in the following time windows around each peak: 150-250 (electrodes F3, Fz, F4, FC1, Cz, FC2), 250-300 (electrodes F3, Fz, F4, FC1, Cz, FC2), 300-375 (electrodes Fz, Cz, P3, Pz, P4), 375-450 (electrodes F3, F4, FC1, FC2), 450-550 (electrodes FC1, Cz, FC2, P3, Pz, P4) and 650-800 (negative: electrodes F3, Fz, F4, FC1, FC2; positive: electrodes P3, Pz, P4).

Statistical analyses

For the analyses of both performance and neurophysiological data, only responses between 200 and 2000 ms after the stimulus were analyzed. In the ADHD group, the mean percentage of excluded responses was 5% while this was 1% in the normal control group. No difference was found in the proportion of excluded trials between the conditions. The neutral condition was excluded from the analysis because no facilitation effects were present on MRT and stimulus characteristics were different thereby complicating the interpretation of ERP differences. One child in the ADHD group (a child with ADHD-hyperactive subtype) was excluded because he had a very high proportion of errors (44%). One child from the normal control group was excluded because of too few artefact-free epochs. For this child, only the behavioural results were analyzed. MRT was analyzed with a repeated measures ANOVA with group (ADHD group, control group) as between subjects factor and condition (congruent, incongruent) as within subject factor. Group differences in the ratio interference score (congruent divided by incongruent for MRT and incongruent divided by congruent for percentage of errors) were analyzed with a univariate ANOVA. It was not possible to transform the percentage of errors to approach the normal distribution. Therefore, we used a

non-parametric Wilcoxon Rank test to compare percentages of errors in the congruent versus the incongruent condition, and a Mann-Whitney U test to analyze possible group differences in the congruent and incongruent condition and the ratio interference score for errors.
ERPs were analyzed in the same way as MRT. The average ERP amplitudes from the congruent and incongruent condition were entered in a repeated measures ANOVA with two within subjects factors (Condition, Electrode) and one between subject factor (Group) for each of the 6 windows separately. If sphericity occurred in the ERP or MRT data, the Greenhouse-Geisser correction was applied. In the text the original degrees of freedom and the adjusted *p*-values are reported.

Results

Behavioural Data

As can be seen in Table 4.1, the mean estimated IQ in the control group was higher than in the ADHD group. Reading ability was not significantly different between the groups. No significant correlations between IQ or reading ability with any of the performance measures were found (all *r*s < .2; all *p*s > .11) thus IQ and reading ability were not entered into the analysis as covariates. Group performance means can be found in Table 2. As expected, children were slower in the incongruent condition compared with the congruent condition [$F(1, 45) = 15.5$, $p < .01$, $\eta p^2 = .26$]. Overall, the ADHD group responded, on average, 93 ms slower than the normal control group, but this effect escaped conventional levels of significance [$F(1, 45) = 3.3$, $p = .07$, $\eta p^2 = .07$]. No significant group by condition interactions occurred and no difference between the ratio score for MRT was found.

Table 4.2 Behavioural Performance

	Group	
	Normal Control	**ADHD**
MRT (SD)		
Congruent	766 (142)	858 (197)
Incongruent	793 (145)	887 (212)
Ratio (congruent/incongruent)	0.97 (.06)	0.97 (.06)
Mean Percentage of Errors (SD)		
Congruent	3.6 (3.1)	5.8 (6.6)
Incongruent	6.0 (3.5)	7.3 (3.5)
Ratio (congruent/incongruent)	0.71 (.56)	0.89 (.84)

Note. MRT = Mean Reaction Time (ms), SD = Standard Deviation.

A condition effect was observed: more errors were made in the incongruent condition as compared with the congruent condition [$Z = -3.6$, $p < .01$], indicating that an interference effect was present on percentage of errors. No significant group differences were found for either percentage of errors or ratio score.

Electrophysiological Data

No correlations were found between IQ and the average amplitudes for the congruent and incongruent condition in the selected time windows except for the 250-300 time window in the congruent condition (rs ranged between -.36 and -43, $p < .05$). For this window only, the analysis was repeated with IQ as a covariate. Covarying for IQ did not alter the pattern of results, thus only the findings without IQ as a covariate are reported. Figure 4.1 illustrates the grand-averaged ERPs and the mean amplitudes for the neutral, congruent and incongruent stimuli at Fz, Cz and Pz for both groups as these electrodes are representative for the effects. ERPs for all selected electrodes can be found in appendix 2 and appendix 3.

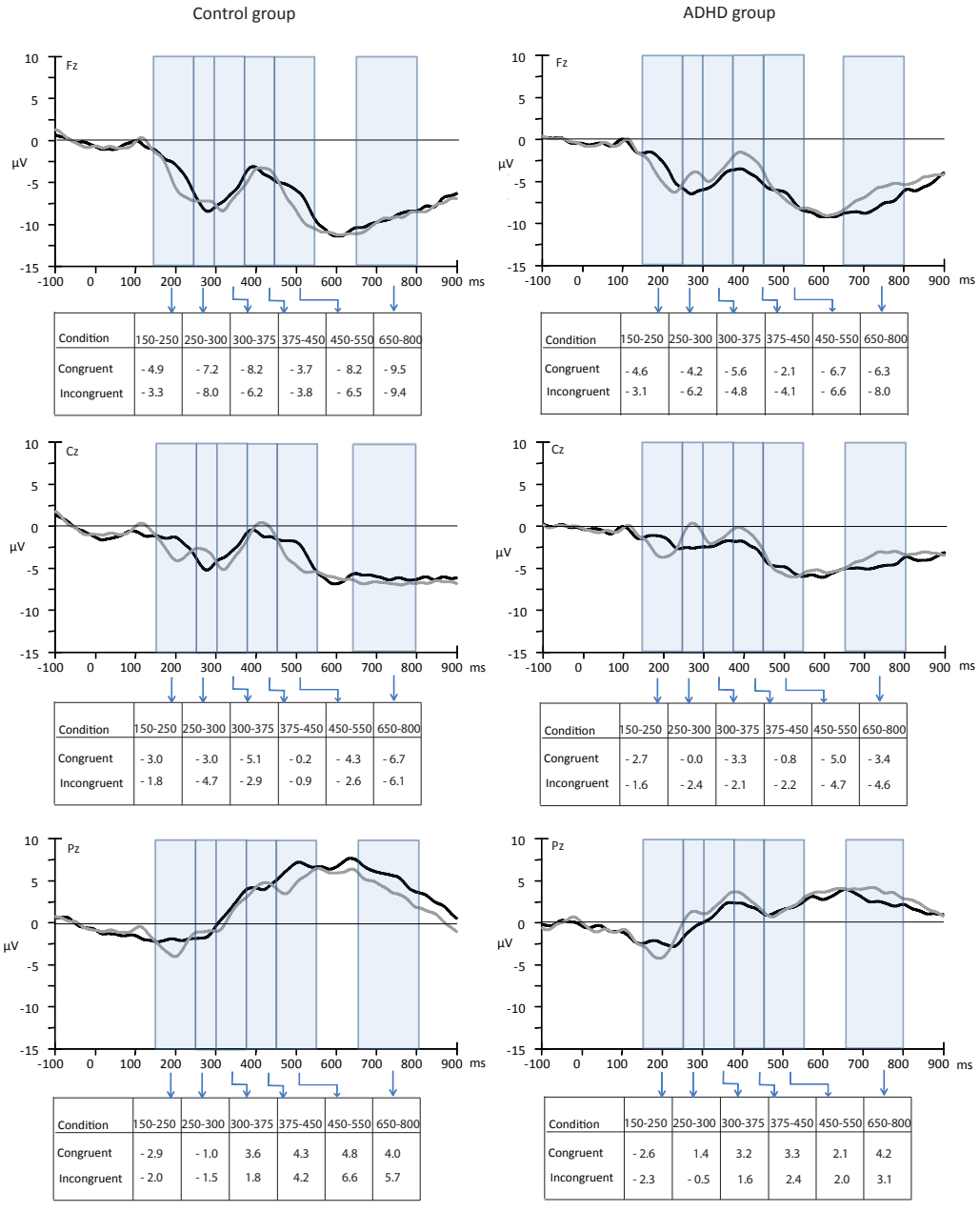
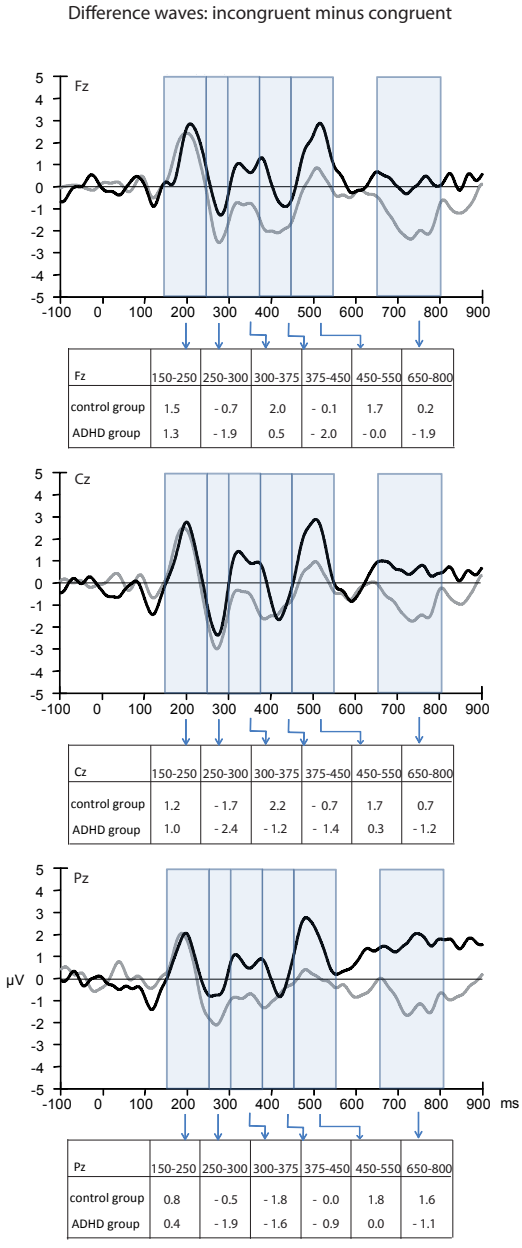


Figure 4.1 Grand average ERPs and mean amplitudes for the selected windows. The congruent condition is represented by a grey line and the incongruent by a black line.



Fz	150-250	250-300	300-375	375-450	450-550	650-800
control group	1.5	- 0.7	2.0	- 0.1	1.7	0.2
ADHD group	1.3	- 1.9	0.5	- 2.0	- 0.0	- 1.9

Cz	150-250	250-300	300-375	375-450	450-550	650-800
control group	1.2	- 1.7	2.2	- 0.7	1.7	0.7
ADHD group	1.0	- 2.4	- 1.2	- 1.4	0.3	- 1.2

Pz	150-250	250-300	300-375	375-450	450-550	650-800
control group	0.8	- 0.5	- 1.8	- 0.0	1.8	1.6
ADHD group	0.4	- 1.9	- 1.6	- 0.9	0.0	- 1.1

Figure 4.2 Difference waves and mean amplitudes for the selected windows. The grey line represents the ADHD group and the black line the normal control group.

The difference waves (Figure 4.2) show that differences between the conditions occur as early as 150 ms and are sustained for the entire interval.

For each time window, main effects for condition, group and interactions between group and condition are reported. If condition interacted with group, the analysis was repeated per group separately. In Table 4.3, the main results are summarized.

Early conflict processing

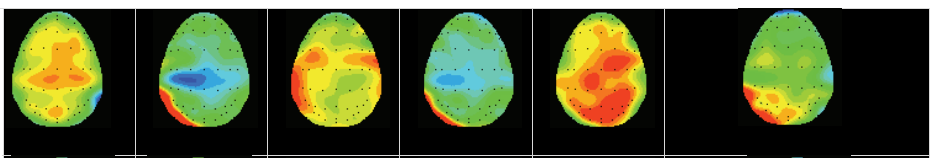
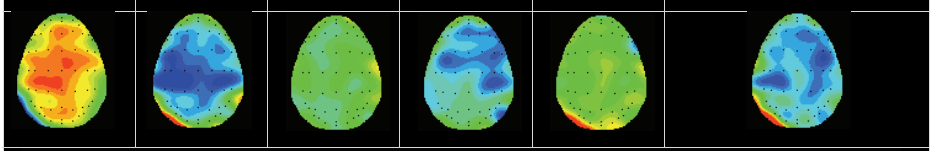
A robust condition effect was found in the 150-250 ms time window, in the 250-300 ms time window and in the 375-450 ms time window. The congruent condition was more negative than the incongruent condition in the 150-250 ms time window while the incongruent condition was more negative than the congruent condition in the 250-300 ms time window and in the 375-450 ms time window. No condition effects were found for the 300-375 ms time window. No significant interactions or group effects occurred in these windows, indicating that the effects were equal in the groups.

Stimulus evaluation and response selection

In the 450-550 ms time window, a condition effect was found and a group by condition interaction occurred. Overall, the amplitude in the incongruent condition was more positive than in the congruent condition in this window. Analyses per group revealed that this condition effect was significant only in the normal control group [$F\ (1, 22) = 13.0$, $p = .002$, $\eta p^2 = .37$] and not in the ADHD group [$F\ (1, 22) = .01$, $p = .94$, $\eta p^2 = .00$]. In the last time window (650-800 ms, analyzed separately for the positive amplitude at parietal electrodes and the negative amplitude at frontal electrodes), a condition by group interaction was found in the absence of an overall condition effect. Children with ADHD had a larger frontal negativity in the incongruent condition as compared with the congruent condition [$F\ (1, 22) = 14.7$, $p = .001$, $\eta p^2 = .40$] but this effect was absent in the normal control group [$F\ (1, 22) = 0.16$, $p = .69$, $\eta p^2 = .01$]. Children in the control group showed a larger parietal positivity in the incongruent condition compared to the congruent

condition [F (1, 22) = 8.4, p = .008, ηp^2 = .28] while children with ADHD had a larger parietal positivity in the congruent condition compared to the incongruent condition [F (1, 22) = 5.7, p = .026, ηp^2 = .21].

Table 4.3 Analysis of the mean amplitudes in the selected windows

	Time window in milliseconds						
Effect	150-250	250-300	300-375	375-450	450-550	650-800 (N)	650-800 (P)
Group							
F(1, 44)	0.04	3.72	0.00	0.00	1.52	1.00	1.74
p-value	.85	.06	.95	.98	.22	.32	.19
ηp^2	.00	.08	.00	.00	.03	.02	.04
Condition							
F (1, 44)	**13.63**	**10.46**	1.92	**6.85**	**6.17**	3.61	0.15
p-value	**.00**	**.00**	.17	**.01**	**.02**	.06	.70
ηp^2	**.24**	**.19**	.04	**.14**	**.12**	.08	.00
Group x Condition							
F(1, 44)	0.15	1.59	0.02	2.48	**6.69**	**6.51**	**14.00**
p-value	.70	.21	.96	.12	**.01**	**.01**	**.00**
ηp^2	.00	.04	.00	.05	**.13**	**.13**	**.24**
	Scalp Distribution difference wave						
	185-215	260-290	322-352	412-442	485-515	710-740	
Control group							
ADHD group							
Scale in µV	- 3			0			+3

Note. Bold numbers indicate significant differences. For the last time window (650-800), the negative conflict SP (N: F3, Fz, F4, FC1, FC2) and the positive conflict SP (P: P3, Pz, P4) were analyzed separately. For each time window, the scalp distribution of the difference wave represents the mean activity in a smaller time window as this gave a better representation of the differences.

Discussion

We conducted this study to gain insight into the temporal processing of interfering information in children with ADHD. Behaviourally, the interference effect was reflected by a robust increase in response latency and error rate in the incongruent condition compared with the congruent condition. Children with ADHD did not show performance deficits on this task. Neurophysiological differences between children with ADHD and normal controls occurred in the last two time windows (450-550 ms and 650-800 ms). As this is the first ERP study into auditory interference control in children, the analyses are exploratory. This should be born in mind when interpreting the results.

Early conflict processing

In the auditory Stroop, interference effects started at 150 milliseconds, which suggest faster processing of conflict in this task compared with the classical Stroop. An explanation may be that the first syllable of the words high and low ('hoog'and 'laag') informs the child on the presence of conflict resulting in early detection and processing of conflict. The larger negativity in the 375-450 ms time window in the incongruent condition compared with the congruent condition is suggestive of a N450 component reflecting detection of conflict.

No differential effect of incongruent information compared to congruent information was found in these windows (150-250; 250-300 and 375-450) in children with ADHD, which indicates that early processing and detection of conflict is intact in children with ADHD in this task. This result is in contrast with a recent study into interference from flankers, in which children with ADHD did show early processing abnormalities (Johnstone, Barry, Markovska, Dimoska & Clarke, 2009). This difference might be due to the different modality or to different task demands in Flanker and Stroop tasks. Flanker tasks require selective attention to one stimulus (the stimulus in the centre) while Stroop tasks require selective attention to one dimension (for example colour or pitch). In Flanker tasks, the fronto-central negativity that is related to the congruence of the stimuli occurs earlier than in Stroop tasks: between 200-400 ms, which corresponds to an N2 component (van 't Ent, 2002). The N2 is

enhanced for incongruent stimuli compared with congruent stimuli and, like the N450, the source of this N2 has also been localized in the ACC (Nieuwenhuis, Yeung, van den Wildenberg, Ridderinkhof, 2003). Thus, although the latency of the N450 and the N2 differ and they are elicited by different conflict tasks, these components do share similarities in functional significance and source. ERPs in ADHD have been recorded in Flanker tasks (Albrecht et al., 2008; Jonkman et al., 1999, Johnstone et al., 2009; van Meel, Oosterlaan, Heslenfeld, & Sergeant, 2007). Albrecht et al. and Johnstone et al. showed that the typical N2 amplitude enhancement for incongruent stimuli was reduced in ADHD, but Jonkman et al., 1999 did not found group differences in the N2 enhancement for incongruent stimuli. Our results show that early processing and early detection of auditory conflict is intact in ADHD.

Stimulus evaluation and response selection

The 450-550 ms time window falls within the range of the P3b and the scalp distribution (largest amplitude at parietal sites) is consistent with a P3b. The amplitude of the P3b has been interpreted as reflecting attention and memory processing which originates from termporal-parietal mechanisms (Polich & Criado, 2006). One of the most robust and replicated ERP findings in ADHD is a diminished parietal P3b (see for review Barry, Johnstone, & Clarke, 2003). In the normal control group, a larger positivity was found for the incongruent condition as compared with the congruent condition , but this effect was absent in the ADHD group. Thus, children with ADHD seem to fail to recruit extra resources in the presence of conflicting information. A different type of conflict may arise when children commit an error, resulting in conflict between the given response and the correct response. Abnormalities in error processing such as a reduced ERN (Van Meel et al., 2007 and reduced post error positivity (Jonkman et al., 2007) have been reported in ADHD. Together with these studies, our results add to the growing literature that children with ADHD may have more difficulties with the adjustment of cognitive control (Casey et al., 2007). At the neurophysiological level children with ADHD fail to recruit extra resources during the evaluation of conflicting information which is also evident during error processing.

A second important result of our study was the finding that children with ADHD showed a predominantly frontal conflict SP: a larger negativity in the incongruent condition as compared to the congruent condition in the 650-800 ms time window, while control children showed a parietal conflict SP: a larger positivity in the incongruent condition in this time window. In healthy adults, the source of the conflict SP has been localized in the lateral region of the prefrontal cortex and near the ACC (Lansbergen et al., 2007; West, 2003) which gives rise to a parietal positivity *and* a frontal negativity for incongruent trials compared to congruent trials. The conflict SP has, to our knowledge, not yet been described in children, which complicates the interpretation here. The literature on the neurophysiological correlates of Stroop like conflict tasks is inconsistent on the conflict SP: some studies report it as a parietal positivity (Larson, Kaufman, & Perlstein, 2009; West et al., 2005), some as a frontal negativity (Curtin & Fairchild, 2003; West & Alain, 1999), and others report both (Lansbergen et al., 2007; West, 2003).

Our results show that the scalp site of the conflict SP differs across the groups. It seems plausible that children with ADHD use a different neurophsyological strategy to resolve conflict, in line with fMRI studies that show that ADHD groups perform similar as normal control groups but activate different brain areas (Bush et al., 1999; Konrad et al., 2006). In this task, children with ADHD seem to be able to recruit successfully cognitive control mechanisms to reduce interference, although in a different manner than normal controls. Frontal-parietal between group differences in ERPs have also been reported for a simple two tone discrimination paradigm (Johnstone & Barry, 1996), which indicates that the recruitment of a different frontal strategy in ADHD is not task-dependent. It is possible that this different strategy is more effortful. However, the fact that a frontal conflict SP has also been reported in normal adults (Lansbergen et al., 2007; West & Alain, 1999) contradicts this interpretation. Perhaps the conflict SP has not yet been fully developed in children and children with ADHD may show a different developmental trajectory compared to their normal peers. This may be due to differences in brain network organization: children with ADHD show less global efficiencies but more local efficiencies compared to their normal peers (Wang et al., 2009). Furthermore, a recent diffusion tensor imaging study revealed white matter abnormalities in

ADHD in various regions within the right parietal occipital regions and the left fronto-temporal regions (Silk et al., 2009). This reduced integrity of white matter underlying fronto-parietal regions may underpin the diminished neurophysiological activity related to conflict resolution at parietal sites in ADHD.

In sum, our results show that abnormalities in the neurophysiological correlates of interference control occur relatively late (after 550 milliseconds) and are related to poorer evaluation of conflict and to a different neurophysiological strategy to resolve conflict and select the appropriate response. The pronounced effect of ADHD on these components, coupled with the absence of a behavioural impairment in interference control, is in line with the cited fMRI studies and underlines the flexibility of the brain in ADHD: children with ADHD *are* able to perform equally to normal controls but may need more or different neural resources to achieve this. However, more research is needed to answer the question if the ability to use a different neural strategy is beneficial for performance and behaviour in ADHD.

Limitations

A limitation is that the N450 component that reflects detection of conflict was diminished in our task compared to other studies on Stroop interference. Possible explanations could be that conflict in our task may have been lower than in other conflict tasks, resulting in a diminished N450 component or that conflict detection occurred at a different time in the auditory Stroop. A second limitation is that the approach to analyze differences between the conditions is exploratory, as ERPs in an auditory Stroop task have not yet been reported and differ from visual Stroop tasks.

Clinical Implications

For a clinician, it is first of all important to acknowledge that auditory interference control at the performance level is intact in ADHD. However, neurophysiological abnormalities in conflict processing are present in these children despite normal performance on interference tasks. Cognitive control in

children with ADHD may be more effortful, which could explain failures in daily life to use these cognitive control abilities.

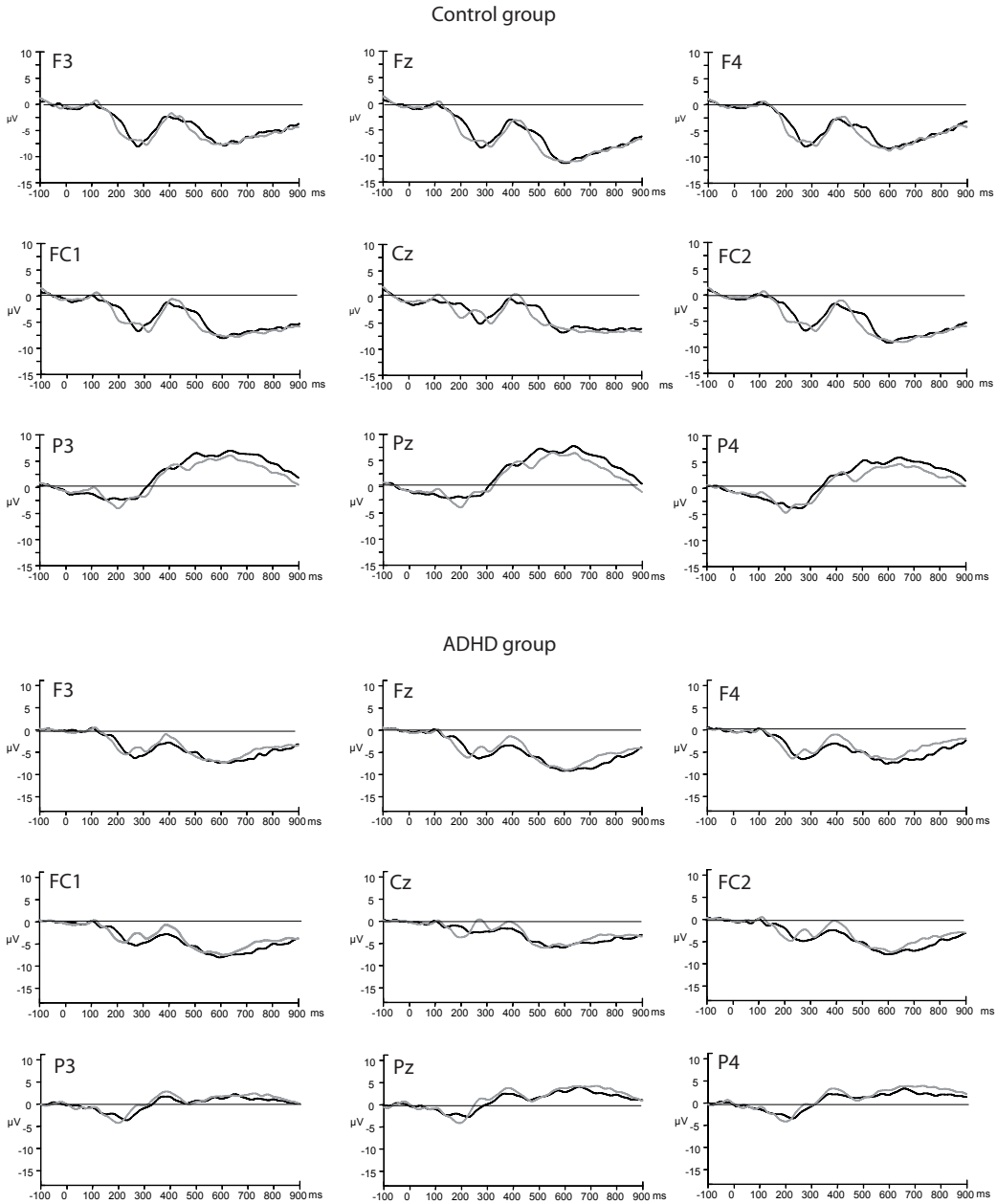
Appendix 1

Analysis of the baseline

Baseline differences were assessed because of the possibility that the groups might differ on stimulus preceding negativity (SPN). For the analyses of the baseline, epochs of -300-0 before stimulus onset were baseline corrected to a pre-prime interval of -100 to prime onset. The slope was calculated by subtracting the mean amplitude in the time window just before the stimulus (-50 to 0) from the mean amplitude at the begin of the epoch (- 300 to - 250). The slope of the baseline differed significantly from zero at Fz [$t(45) = 4.3$, $p < .0005$] Cz [$t(45) = 4.5$, $p < .0001$] and Pz [$t(45) = 3.5$, $p = .001$], thereby validating the SPN. Furthermore, there was no significant difference between the groups on SPN at either electrode ($p > .10$ for Fz, Cz and Pz).

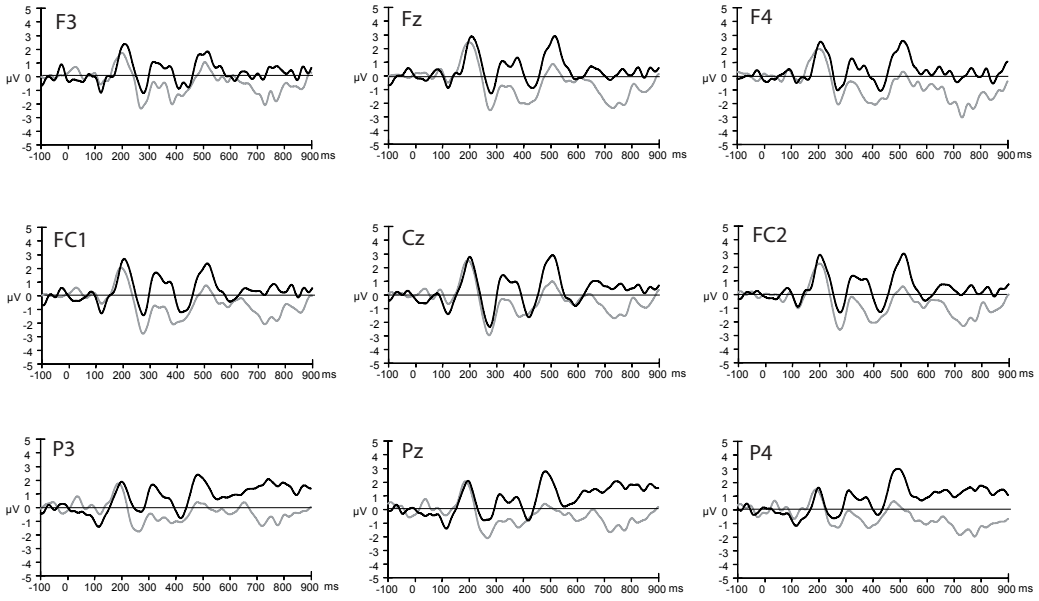
Appendix 2

Grand average ERPs for both groups. The congruent condition is represented by a grey line and the incongruent by a black line.



Appendix 3

Difference waves for both groups. The ADHD group is represented by a grey line and the control group by a black line.



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Chapter 5

When distraction is not distracting: A behavioural and ERP study on distraction in ADHD

Published as: Van Mourik, R., Oosterlaan, J., Heslenfeld, D. J., Konig, C., & Sergeant, J. A. (2007). When distraction is not distracting: A behavioural and ERP study on distraction in ADHD. *Journal of Clinical Neurophysiology, 118,* 1855-1865. link to original publication

Abstract

Although an increased distractibility is one of the behavioural criteria of Attention Deficit Hyperactivity Disorder (ADHD), there is little empirical evidence that children with ADHD are in fact more distractible than their normal peers. We recorded event-related potentials (ERPs) to distracting novel sounds (novels) and standard sounds, (standards) while children performed a visual two-choice reaction time task. Twenty five children with ADHD were compared with eighteen normal controls (aged 8 to 12 years). Children with ADHD showed a larger early P3a (150 – 250 ms), both in response to the standard and in response to the novel. The late phase of the P3a had a larger amplitude in the ADHD group in the 250 – 300 ms window compared to the control group, which was only present in response to the novel. Interestingly, the novel reduced the errors of omission in the ADHD group to a greater extent than in the normal control group. Although children with ADHD show an increased orienting respons to novels, this distracting information can enhance their performance temporarily, possibly by increasing their arousal to an optimal level, as indicated by the reduced omission rate. These data indicate that distraction is not always distracting in children with ADHD and that distraction can also have beneficial effects.

Introduction

One of the behavioural manifestations of children with Attention Deficit Hyperactivity Disorder (ADHD) is their abnormal apparent distractibility (DSM-IV; American Psychiatric Association 1994). Especially in the classroom, children with ADHD often pay more attention to events happening in and outside the classroom and less attention to their schoolwork than their normal peers. Surprisingly, a number of attempts to prove that children with ADHD are abnormally distractible have been unsuccessful (see for review Douglas and Peters, 1979). Selective or focused attention tasks, such as visual search paradigms with distracters, often do not differentiate children with ADHD from normal controls (Van der Meere and Sergeant, 1988; Mason et al., 2003; Huang-Pollock et al., 2005). However, it has been frequently reported that children with ADHD have greater difficulty in inhibiting conflicting stimuli that are incorporated in a task, i.e. they show poorer performance on Stroop- and Flanker-tasks (Scheres et al., 2004), although the difference in interference control between normal control groups and ADHD groups on the Stroop task is small (see for meta-analysis Van Mourik et al., 2005). Apparent distractibility in the classroom may have multiple causes, for example, children with ADHD could have less intrinsic motivation (Carlson et al., 2002), suffer from a failure to inhibit stimuli extraneous to the task (Barkley, 1997), or distractibility could be a functional attempt to modulate underarousal by seeking stimulation (Zentall and Zentall, 1983). Alternatively, children with ADHD could have an abnormally low threshold for the breakthrough of unattended (and usually irrelevant) information, which is found even in children with subclinical attentional problems (Kilpeläinen et al., 1999).

Most distraction or selective attention tasks are not ecologically valid measures of distraction in daily life situations, because in daily life, the distraction that has to be inhibited is outside the task and not conflicting with task demands, for example, a child is doing schoolwork while other children are talking. Escera et al., (1998) developed a paradigm to measure this kind of distraction with event-related potentials (ERPs). This paradigm has been adapted by Gumenyuk et al. (2001) to measure distraction in children. In this paradigm, the child performs a visual task while listening to standard tones and

occasionally a novel environmental sound, such as a mooing cow, an engine, or a bell. These sounds should be ignored by the child. Novel and unexpected stimuli are hard to ignore and cause distraction. Behaviourally, this distraction is observed as deterioration in performance in the task as shown by increased reaction times and/or decreased performance accuracy (Escera et al., 1998; Gumenyuk et al., 2004).

At the electrophysiological level, unattended and task irrelevant novel stimuli elicit a P3a component in adults (Squires et al., 1975; Escera et al., 1998) and children (Cycowicz and Friedman, 1997; Čeponienė et al., 2004; Gumenyuk et al., 2004). The P3a component is thought to reflect an evaluative, conscious aspect of the orienting response and an attentional switch to the novel information (Friedman et al., 2001). The dorsolateral prefrontal cortex has an important role in response to auditory distraction (Campbell, 2005). Both the noradrenergic (Missonnier et al., 1999) and the dopaminergic (Kähkönen et al., 2002) system have been found to modulate the P3a. Previous studies indicated that the P3a has two subcomponents in adults (see for review Escera et al., 2000) and in children (Čeponienė et al., 2004; Gumenyuk et al., 2004): an early P3a (eP3a) component with its peak latency around 200 ms and a late P3a (lP3a), which peaks at around 300 ms. Čeponienė et al. (2004) suggested that the eP3a might be a receiver of the sensory information and governs the direction of the attentional focus as reflected by the lP3a. The lP3a is thus more closely related to the actual orienting of attention (Escera et al., 2000). Since the latency of the eP3a component is similar to that of the auditory P2 peak, it could be argued that the eP3a is actually an enhanced P2 in response to the physical features of the novel sounds. Although the scalp topography of these two positivities differs (fronto-central for the eP3a and centro-parietal for the P2, see Čeponienė et al., 2002) further studies are needed to clarify whether the generators of the auditory P2 differ from those of the eP3a.

An enhanced lP3a may indicate that too much attention is attributed to the novel stimuli, which may result in increased distractibility at the behavioural level. An enhanced lP3a has been found in children with major depression (Lepistö et al., 2004) and in adults with closed head injury (Kaipo et al., 1999). Inconsistent findings have been reported with regard to children with

ADHD. Two studies found no differences in P3a response to novel sounds (Holcomb et al., 1986; Kemner et al., 1996). One study found a reduced P3a in the ADHD group in response to novel visual stimuli (Keage et al., 2006) and another study found an enhanced lP3a and a reduced eP3a in the ADHD group in response to novel sounds (Gumenyuk et al., 2005). A possible explanation for these inconsistent results is that one study (Gumenyuk et al., 2005) used a variety of novels, whereas in other studies the same novel was repeated, reducing the novelty effect with trials.

The P3a to distracting sounds is sometimes followed by a frontally distributed negativity with a latency of 400 - 700 ms. This negativity was interpreted by Schröger and Wolff (1998) as reflecting the reorienting of attention back to the main task after distraction, and it was labelled as the reorienting negativity (RON). A recent fMRI study indicated that a prefrontal-temporal network including the left superior and right middle temporal cortex, right frontal eye fields, the left inferior frontal gyrus and the right precuneus underlies reorienting (Mayer et al., 2006). In children, a similar frontal late negativity (hereafter LN) was found in response to distracting novel sounds, which is sometimes referred to as LN (Gumenyuk et al., 2004), Negative Component (Čeponienė et al., 2004; Määtä et al., 2005), or RON (Wetzel et al., 2004). The LN in children with ADHD has been found to be reduced in comparison to control children (Gumenyuk et al., 2005). Interestingly, Konrad et al. (2006) demonstrated that children with ADHD tend to recruit more fronto-striatal-insular activation than normal controls during reorienting in the absence of behavioural differences, which is explained in the context of neural compensation. Using a different paradigm, it has also been found that children with ADHD have behavioural difficulties in reorienting of attention (Pearson et al., 1991) and in disengaging attention when voluntary control is required (Wood et al., 1999).

Although behavioural distractibility is a major clinical feature of ADHD, little research has been conducted to elucidate the neural mechanisms that underlie this behavioural distractibility in the disorder. The only ERP study that investigated auditory distraction during a visual task in children with ADHD is by Gumenyuk et al. (2005). Their results indicated that children with ADHD

showed an enhanced distractibility, both at the behavioural as well as at the electrophysiological level. This very important finding needs to be replicated and extended, since these authors had only small sample size (10 children in each group) and a small age range (only 8 – 10 years old children were included). Therefore, the present study aimed at examining both distraction and reorienting in a larger group of children with a broader age range (8 – 12 years old) with and without ADHD, by recording ERPs from task-irrelevant standard tones and novel sounds, while children performed a visual demanding task. The visual task was different from the task used in the study of Gumenyuk et al. (2005) in order to make it more suitable for older children. Behaviourally, the hypothesis was tested that novel sounds compared to standard tones would result in a larger deterioration in performance (i.e. increased reaction times and/or decreased performance accuracy) in the ADHD group than in the normal control group. At the psychophysiological level, ERPs were measured to elucidate the neural mechanisms of the presumed distractibility in the ADHD group. Differences in the early P3a after the novel compared with the standard (as found in the study of Gumenyuk et al., 2005) could be interpreted as abnormalities in directing attention, a relatively larger late P3a in the ADHD group would be evidence that children with ADHD attribute too much attention to irrelevant and distracting information, while a relatively reduced LN would suggest that children with ADHD are less capable of reorienting attention back to the main task after temporary distraction.

Method

Participants

Twenty-five children aged between 8 and 12 years with ADHD were compared with eighteen normal control children. Subject characteristics are summarized in Table 5.1.

Table 5.1 Subject Characteristics for the ADHD and Normal Control Groups

		Whole groups		IQ-matched subgroups	
		NC(n= 18)	ADHD(n=25)	NC(n=14)	ADHD(n=14)
Boys/girls		17/1	22/3	13/1	11/3
Age	Mean (SD)	10.5(1.1)	10.2 (1.2)	10.6 (1.1)	10.0 (1.2)
	Median (Range)	10.4 (3.4)	9.9 (4.6)	10.4 (3.4)	9.8 (4.4)
IQ	Mean (SD)	117 (16)	97 (10)**	112 (13)	104 (7)
	Median (Range)	120 (59)	97 (42)	114 (43)	101 (26)

Asterixes indicate significant differences between Normal Control and the ADHD group, for the whole groups (third and fourth column) and the selected groups matched on IQ (fifth and last column).
** $p < .01$

The ADHD group was recruited via an advertisement on a website and via a university affiliated outpatient department for ADHD. They all had a formal clinical diagnosis of ADHD by their health care professional. The control children were recruited from primary schools. None of the children had any neurological, sensory or motor impairment or any other developmental psychiatric disorder. Written informed consent was obtained from the children's parents prior to the study, and children also had to agree by writing down their name on a permission form. The Ethical Committee of the Vrije Universiteit Medical Centre approved the study.

Parents and teachers completed the Dutch version of the Disruptive Behavior Disorder rating scale (DBD; Pelham et al., 1992; Oosterlaan et al., 2000), which allowed the assessment of symptoms of ADHD and comorbid Oppositional Defiant Disorder of Conduct Disorder. Parent and teacher ratings for the ADHD group had to fall within the clinical range (95^{th} – 100^{th} percentile) for the Inattention and/or the Hyperactivity/Impulsivity subscale. Control children were included if they received scores below the 90^{th} percentile on all subscales. In order to confirm the DSM-IV diagnosis of ADHD, the Diagnostic Interview Schedule for Children Version IV (DISC-IV, Schaffer et al., 2000) was administered to the parents of the children with ADHD. Only those children with a DSM-IV diagnosis of ADHD participated in the study. Within the clinical group twenty-two children met the DISC-IV criteria for the ADHD combined subtype and three for the ADHD inattentive subtype. Fourteen

children with ADHD were also diagnosed with ODD, and two other children with ADHD also received a diagnosis of ODD and CD.

Hearing was screened at 20 dB. All children had normal hearing. IQ was estimated with two performance and two verbal subtests of the Dutch version of the Wechsler Intelligence Scale for Children, third edition (Wechsler, 1991; Kort et al., 2002): Picture Arrangement, Block Design, Arithmetic and Vocabulary. All children had an estimated IQ greater than 70. The mean estimated IQ in the control group (M = 117, SD = 16.20) was higher than in the ADHD group (M = 97, SD = 10.28) [t(41) = 5.02, $p < .001$]. The children with ADHD taking methylphenidate stopped their medication at least 36 hours before testing allowing a complete washout (Pelham et al., 1999). The children were rewarded for their participation with a gift voucher of € 7,50.

Distraction Paradigm

The present study employed a modification of the distraction paradigm of Gumenyuk et al. (2001) that is schematically depicted in Figure 5.1.

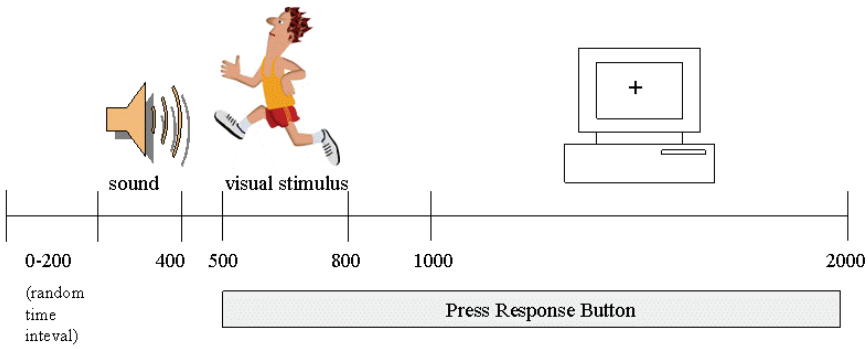


Figure 5.1 Schematic diagram of the distraction paradigm. The sounds consisted of standards and novel sounds and children performed a forced choice visual (left/right) task.

The experiment consisted of a visual two-choice task in which an irrelevant sound preceded the visual stimulus. The visual stimulus was a coloured picture

of a runner, which was either turned to the left or to the right. Children were asked to indicate the direction of the runner with a button press. The runner was displayed in the middle of a white screen. The irrelevant sound was presented prior to the visual stimulus through a speaker. The sound was either a 600 Hz tone (p = .80) or a novel sound (p = .20). All sounds had an intensity of approximately 60 dB. Trials were completely randomized, with the exception that at least three standard tones had to occur between any two successive novel sounds. The novel sounds were 99 different environmental sounds, such as a dog barking or a bell ringing. Each novel sound was presented once.

Every trial began with the presentation of a small fixation cross in the centre of the screen for a random time interval ranging from 0 to 200 ms. The sound was then presented for 200 ms followed by a 100 ms delay. The fixation cross was on during the sound and the delay. Thereafter, the runner was presented for 300 ms. immediately after presentation of the runner, the fixation cross reappeared for 1200 ms. Children could respond to the runner by pressing a response button with their left or right thumb. The interstimulus interval was on average 1900 ms (range: 1800 to 2000 ms).

The task consisted of three blocks each of 166 trials. After each block (5,3 min) a short break was given. Performance feedback (mean reaction time, percentage correct and percentage incorrect) was given after each block. After the first block, children were told that they did well, but were not in the top three, following the second block they were told that they were third and after the last block that they had won the first price.

Electrophysiological Recordings

The electroencephalogram (EEG; 0.05-200 Hz, sampling rate 1000 Hz) was recorded at 60 scalp sites using electrode caps with tin electrodes referenced to one ear lobe. The ground electrode was placed on the cheek. Horizontal and vertical eye movements (EOG) were recorded from the outer canthi of each eye and below and above the left eye. Impedances were maintained below 10 kOhm. Pre-processing of the EEG data was performed with scan 4.3 software

(Compumedics). After additional filtering (0.25-30 Hz), vertical ocular artifacts were corrected using a subtraction algorithm (Semlitsch et al., 1986). The EEG was re-referenced to the mean of both ear lobes. Epochs were extracted from the continuous data file over a 1000 ms period starting 100 ms before each sound onset. Epochs containing EEG or horizontal EOG artifacts that exceed ± 100 μV at any electrode were excluded. ERPs were obtained separately for the tones occurring before a novel (standards) and the novel sounds (novels). Averaged ERPs for standards and novels consisted of 85 epochs on average (at least 43 epochs because one child missed a block) per condition per child. In contrast to earlier studies (e.g. Gumenyuk et al., 2004; Schröger and Wolff, 1998), it was decided to analyze both the standards and the novels instead of the difference wave. The reason for this was that we were interested if there were any differences at baseline (standards) between the groups. Because the overlap of the visual stimuli after the sound was the same after the novel and the standard, this could not cause differences between the novel and the standard. After visual inspection of the grand average ERPs, it was decided to include the electrodes Fz and Cz, and to analyze the mean amplitude of the standards and the novels in 7 separate windows of 50 ms starting 150 ms until 500 ms after sound onset. These windows gave better insight into the temporal dynamics of the differences than only one window per component and covered the components of interest: the eP3a, the lP3a and the late negativity.

Procedure

Following the attachment of the electrode cap and EOG electrodes, the children sat comfortably in a chair in an acoustically and electrically shielded room, which was dimly lit. Stimuli were displayed on a 17-inch monitor at 2.4 meter distance from the child's eyes. Children were monitored by video during the entire experiment and could communicate with the experimenter in the adjacent room via an intercom. Before the experimental task, the children participated in one or two short practice blocks, including twenty trials with feedback on each response and without the novel sounds, until the child fully understood the task requirements. After the practice session, the child was

instructed to respond as accurately and as fast as possible to the runner and to ignore the sounds. The experimenter left the room and initiated the task.

Data analysis

Performance measures included mean response times (MRT), percentage of commission errors and percentage of omission errors. Strategy effects were tested by correlating the percentage of commission errors with MRT. In order to test the hypothesis that the performance of children with ADHD was more easily disrupted by the novels compared to the standards, a repeated measures analysis of variance (ANOVA) was performed with group (ADHD – normal controls) as between subjects factor and condition (standard – novel) as within subjects factor for MRT, percentage of commission errors and percentage of omission errors separately. IQ was not entered in the analysis as a covariate because a lower IQ is highly associated with ADHD (Kuntsi et al., 2004). ANCOVA is only appropriate when individuals have been randomly assigned to groups but when naturally occurring groups are compared, this method can yield spurious results (Miller and Chapman, 2001). The influence of IQ on group effects was investigated by computing correlation coefficients between performance measures (differences between the novel and the standard with regard to MRT, errors of commission and errors of omission) and IQ for groups separately. Furthermore, IQ-matched subgroups were selected from the whole sample and all analyses were also performed with these subgroups

In order to assess possible differences in electrophysiological responding to the novels compared to the standards, the average ERP amplitudes from the novels and standards at Fz and Cz were analyzed with a repeated measures ANOVA including the following factors: Group (ADHD - normal controls) as a between subjects factor and Sound (standard – novel) as within subjects factor for each of the 7 windows separately. The influence of IQ on group effects was investigated by computing correlation coefficients between the mean ERP amplitudes (differences between the novel and the standard for each of the 7 windows separately) and IQ for each group separately. Furthermore, partial correlation coefficients were calculated for groups separately to explore if there was a relation between the effect of the novel sound on MRT relative to the

standard (novel minus standard) and the mean amplitudes of the ERPs (novel minus standard, all 7 windows) while controlling for IQ. Because multiple correlations are performed, only correlations with a p-value < .01 are reported, with an exception of the correlations between MRT and commission errors were alpha was set at .05, because in that analysis, only two correlations were tested.

Results

Performance measures

In the ADHD group, there was no significant correlation between IQ and the difference scores (novel minus standard) on mean reaction time, percentage of commission and omission errors. Thus IQ did not influence performance differences between the conditions in the ADHD group. In the control group there was a significant correlation between the difference in the percentage of omission errors and IQ (r = .60, p < .01), but no significant correlations between the other performance measures and IQ. In order to control for possible effects of IQ on the performance measures, the groups were matched for IQ (n = 14 in each group), all analyses were performed with these subgroups and with the entire group. Although the results did not differ in terms of significant and nonsignificant effects from the results obtained in the entire group, for the sake of completeness, the results of the subgroups are summarized in Table 1. The results described in the text apply to the entire group. In both groups, there was evidence for a speed accuracy trade-off: the correlation between the mean reaction time and errors was -.42, p < .05 in the ADHD group and -.59, p < .01 in the control group respectively. Children who reacted faster made more errors. However, there was no significant difference between these correlations (correlation test; Preacher, 2002), thus possible performance differences between the groups could not be explained by a difference in response strategy between the groups.

Table 5.2. Performance Data for the ADHD and the Normal Control Groups

		Whole groups		IQ-matched subgroups	
		NC (n= 18)	**ADHD** (n=25)	**NC** (n=14)	**ADHD** (n=14)
Performance	**Stimuli**	**Mean (SD)**		**Mean (SD)**	
RT (ms)	Novel	610 (65)	648 (100)	625 (64)	642 (69)
	Standard	577 (68)	616 (99)	588 (73)	613 (62)
	Difference	33 (26)	31 (40)	37 (26)	29 (38)
Errors (%)	Novel	11 (7)	16 (10)	10 (6)	17 (9)
	Standard	15 (9)	19 (10)	15 (9)	19 (9)
	Difference	-4 (6)	-3 (7)	-5 (7)	-2 (7)
Misses (%)	Novel	0.6 (1)	4 (5)**	0.7 (1)	3 (3)*
	Standard	1 (2)	9 (12)**	1 (2)	9 (9)*
	Difference	-0.6(0.8)	-6 (8)**	-0.7 (0.9)	-5 (6)*

Note: Difference = novel minus standard, NC = Normal Controls
Asterixes indicate significant differences between Normal Control and the ADHD group, for the whole groups (third and fourth column) and the selected groups matched on IQ (fifth and last column).
* $p < .05$
** $p < .01$

Table 5.2 presents the mean reaction times, and percentages of commission and omission errors. Condition effects were found for mean reaction time [$F(1, 41) = 45.63$, $p < .0005$], commission errors [$F(1, 41) = 11.63$, $p < .001$] and omission errors [$F(1, 41) = 11.89$, $p < .001$]. The children responded slower on the trials, after the novels were presented compared to the trials after the standards but made fewer errors of commission and omission on these trials. The ADHD group committed more omission errors overall than the control group [$F(1, 41) = 7.34$, $p < .01$], while there was no difference in mean reaction time and commission errors. A group by condition effect was found for omission errors [$F(1, 41) = 7.87$, $p < .01$]. The novel sound was associated with a decrease in errors of omission with 6% in the ADHD group and only with 0.6% in the control group. Although the difference in omission errors between the groups was smaller after novels than after standards, children with ADHD still made more omission errors than controls [$t(41) = 2.89$, $p < .01$].

Event-related potentials

Figure 5.2 displays the ERPs at Fz and Cz for the standard, the novel and the difference wave (novel minus standard) for both groups. The auditory stimulus was presented at 0 ms and the visual stimulus at 300 ms. As can be seen in Figure 2, the P3a had a biphasic structure with an early phase, the eP3a (150 - 250 ms) and a late phase, the lP3a (250 - 400 ms). The eP3a had its maximum amplitude over the fronto-central scalp. The lP3a was more widely distributed than the eP3a and had a central maximum. The LN (400 – 800 ms) had a wide distribution with a frontal maximum.

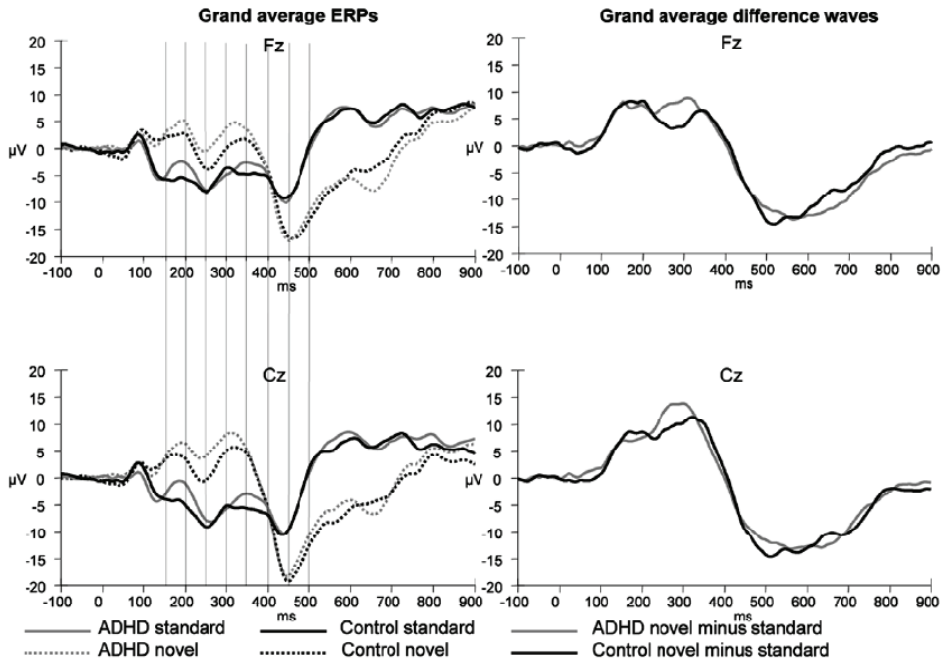
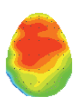
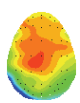
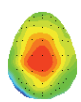
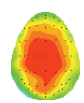
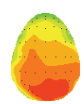
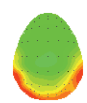
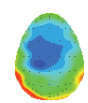
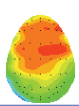
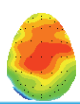
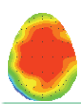
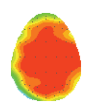
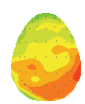
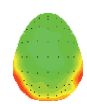
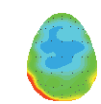


Figure 5.2 ERPs in response to the novel and the standard (left) and the difference wave (novel minus standard, right) for both groups. Vertical lines indicate the windows that were analysed.

Table 5.3 displays the significant effects of condition, group and their interaction for all selected windows at Fz and Cz and the scalp distribution for the difference.

Table 5.3 Summary of significant effects of the ANOVA's of the ERPs after a novel compared with the standard at Fz and Cz and the scalp distribution of the difference waves for both groups within seven 50-ms time window

				Time Window			
Electrode: Fz	150-200	200-250	250-300	300-350	350-400	400-450	450-500
Effect							
Group							
ηp^2							
$F(1, 41)$							
Condition							
ηp^2	.72	.56	.54	.66	.28	.27	.75
$F(1, 41)$	104.3**	57.7**	47.6**	79.8**	15.7**	14.8**	123.1**
Group x Condition							
ηp^2			.15				
$F(1, 41)$			7.2**				
Electrode: Cz							
Group							
ηp^2	.09	.16					
$F(1, 41)$	4.2*	7.8**					
Condition							
ηp^2	.67	.62	.69	.79	.36	.36	.76
$F(1, 41)$	84.8**	68.0**	61.8**	151.9**	22.9**	23.0**	129.1**
Group x Condition							
ηp^2							
$F(1, 41)$							
Scalp Distribution difference NC							
Scalp Distribution difference wave ADHD							
Scale (μV)							
	-15	-10	-5	0	+5	+ 7	+10

wave in both groups. Only significant *F*-values and effect sizes are reported. Condition effects were found for all selected windows: The novel elicited a larger positivity in the windows of the eP3a (150 - 250 ms) and the lP3a (250 - 400 ms) and a larger negativity in the windows of the LN (400 - 500 ms). A group effect was found for the windows of the eP3a (150 – 250 ms) at Cz: the ADHD group had a larger positivity, both in response to the standard and to the novel. An interaction between Group x Condition was found for the 250-300 ms window at Fz: The novel elicited a larger positivity in the ADHD group in this window than in the control group. This increased positivity reflects that the first part of lP3a is larger in the ADHD group at Fz. The scalp distribution for this window (250 – 300 ms) shows that this positivity is more widespread in the ADHD group than in the control group.

In order to test whether there was a relation between IQ and the mean ERP amplitudes, correlations were computed in each group between total IQ scores and the difference in amplitude in all selected windows. None of these correlations was significant. These difference windows were also correlated with the difference in reaction time (novel minus standard), while controlling for IQ in order to test if there was a relation between distraction effects at the behavioural level and at the electrophysiological level. Again, none of these correlations reached significance, indicating that there is no direct relationship between performance measures and ERPs.

Discussion

The main findings of the present study were that the novel sounds reduced the percentage of errors of omissions in the ADHD group more than in the normal control group and enhanced the mean amplitude of the second part of the P3a (lP3a) to a greater extent in the ADHD group than in the normal control group. First, the performance results are discussed and then the ERP results.

Performance

Our study showed that irrelevant novel sounds distract children's performance by increasing reaction time after the occurrence of a novel compared with a

standard. This is in line with previous studies on distraction (Escera et al., 1998; Gumenyuk et al., 2004). The increase in reaction time was similar in children with ADHD and normal control children; thus children with ADHD did not disproportionally slow down when distracted. Importantly, it was found that, after a novel sound, both groups committed fewer errors. This finding contrasts with earlier studies on distraction in children, which reported that more errors are committed after distracting sounds (Gumenyuk et al., 2004; Gumenyuk et al 2005). A possible explanation for these contrasting findings might be that, because the task here was designed as a runner's game, the children were especially focused on speed and, therefore, committed more errors. When a novel sound captured their attention, they automatically slowed down, resulting in less fast guesses. The speed accuracy trade-off effect in both groups supports the idea that children tend to make less errors, if they slow down on this task.

An intriguing finding was that children with ADHD committed fewer omission errors after the occurrence of a novel. Overall, children with ADHD made more omission errors, a finding that has been frequently reported in continuous performance tasks (see for meta-analysis Losier et al., 1996) and is related to various ADHD symptoms including difficulties sustaining attention and being easily distracted (Epstein et al., 2003). The novel sounds in this task could serve as stimulation for children with ADHD by making them more alert and focused on the task resulting in a decreased number of omission errors. That children with ADHD benefit from extra-task distraction has been established in several studies (Zentall and Meyer, 1987; Abikoff et al., 1996; Leung et al., 2000) and can be considered as support for the optimal stimulation theory of ADHD (Zentall and Zentall, 1983) and the cognitive energetic model of ADHD (Sergeant et al., 1999; Sergeant, 2005). The optimal stimulation theory postulates that the performance of children with ADHD benefits from extra-task distraction because this increases their arousal to an optimal level. The cognitive energetic model emphasizes that children with ADHD might suffer from an energetical dysfunction and are, therefore, unable to adjust their activation to meet task demands. The reduction of omission errors after a novel can be interpreted as the result of increased activation to a more adequate level. However, it should be noted that there might have been a ceiling effect in the

normal control group. The normal control group did not commit many omission errors and thus they had no room for improvement.

Event-related potentials

The ERPs consisted of biphasic P3a with an early and a late phase (eP3a and lP3a) followed by a LN component, which were visible, both in the raw ERPs as well as in the difference wave. The ADHD group showed a larger positivity at Cz in the 150 – 250 ms window in response to the standard and to the novel. As stated earlier, it is difficult to separate the eP3a from the P2 component. Enhanced P2 components in ADHD groups compared with normal controls in various tasks were reported by Robaey et al. (1992) and Oades et al. (1996) and might be related to altered automatic information processing in ADHD. Specifically, abnormalities in the P2 amplitude topography and latency in the ADHD group have been interpreted as atypical inhibition of sensory input from further processing (Johnstone et al., 2001). However, the eP3a has been described as a component that is related to govern the direction of the attentional move, which, in turn, would be reflected by the lP3a. Thus, although the latency of the P2 and the eP3a is the same, the functional interpretation is somewhat different. Following other studies of distraction (Escera et al., 2000; Gumenyuk et al., 2004, 2005), the positivity in the 150 – 250 ms window in this study is interpreted as reflecting the eP3a, and not the P2. A larger eP3a in the ADHD group could indicate that 'the call for attention' is stronger in the ADHD group, both in response to the standard as to the novel. Contrary to our findings, Gumenyuk et al. (2005) found a reduced eP3a in the difference wave (novel minus standard) in the ADHD group compared with the normal control group. Since in that study only the results of the difference wave were presented, it is difficult to compare that finding with our results.

The lP3a in response to the novel compared to the standard was enhanced in the ADHD group at Fz in the 250 - 300 ms window. This positivity was more widespread than in the control group. This larger positivity in the lP3a window points to a stronger involuntary switching of attention to the novel in the ADHD group. This finding is in line with the results of Gumenyuk et al.

(2005). The P3a is known to be modulated by the noradrenergic system (Missonnier et al., 1999) and the dopaminergic system (Kähkönen et al., 2002). A dysregulation in the noradrenergic and dopaminergic systems has been implicated in the psychopathology of ADHD (Biederman and Spencer, 1999; Solanto, 2002; Pliszka, 2005).

Berridge and Waterhouse (2003) suggested that the noradrenergic system might enhance cognitive functioning under 'noisy' conditions in which irrelevant stimuli could impair performance, by reducing 'noise' and/or facilitating processing of relevant sensory signals. Following this line of reasoning, the enhanced lP3a in response to the novels in the ADHD group could be the result of insufficient noradrenergic modulation of the fronto-subcortical pathways, which could lead to a greater sensitivity to irrelevant stimuli.

Polich and Criado (2006) developed a theoretical model of the P3a and the P3b. They stated that the P3a originates form stimulus-driven disruption of frontal attention engagement during task processing, while the P3b originates when temporal-parietal mechanisms process the relevant stimulus information for memory storage. A P3a can thus be elicited by novel and distracting stimuli across modalities, but also by non-novel stimuli in a difficult oddball paradigm (target/standard discrimination) in response to infrequent, irrelevant, but non-novel distracters (Comerchero and Polich, 1998; Polich and Comerchero, 2003). Both saliency of the distracter as task difficulty of the primary task rather than novelty per se contribute to eliciting of the P3a (Polich and Criado, 2006). A P3b is typically elicited by infrequent target stimuli. Interestingly, this task relevant P3b has been found to be reduced in ADHD (Satterfield et al., 1994) indicating that children with ADHD suffer from deficient preferential processing of to be attended stimuli. Methylphenidate, which increases noradrenergic and dopaminergic neurotransmission in the prefrontal cortex (Berridge et al., 2006), has been found to enhance the amplitude of the P3b and to improve performance in ADHD (Jonkman et al., 1997). It is possible that a dysfunction in the noradrenergic and dopaminergic systems in ADHD could lead to an altered balance between the attentional resources in which target stimuli receive less attention, while irrelevant novel stimuli elicit more

attention compared to normal controls. Future research is necessary to test this hypothesis and to examine the influence of methylphenidate on the P3a in response to distracting irrelevant stimuli.

No differences were found between the groups for the LN component, which suggests that children with ADHD did not have more difficulty than their normal peers in reorienting their attention back to the task after having been distracted. Konrad et al. (2006) reported that children with ADHD tend to recruit more fronto-striatal-insular activation than normal controls during reorienting in the absence of behavioural differences in reorienting, which is explained in the context of neural compensation. Gumenyuk et al. (2005) did found differences in the LN (a larger LN in an early time window and a smaller LN in a later time window) in an ADHD group compared to a control group. In their study, the differences in the LN in the ADHD group might be related to their increased omission rate after a novel. Perhaps children with ADHD do not have a functional deficit in reorienting of attention, but their reorienting capability may be more dependent on task demands.

Taken together, it may be concluded that children with ADHD show an increased orienting to novel auditory information as indicated by the larger positivity in the lP3a window, but they seem to have normal reorienting abilities. Thus, the distractibility observed in the classroom in children with ADHD could be caused by an enhanced orienting reaction to unattended and irrelevant information, which is probably modulated by the dopaminergic and noradrenergic systems. However, this increased orienting to novels does not necessarily lead to larger behavioural distraction effects in the ADHD group. Instead, the present results provide evidence that the performance of children with ADHD can be improved by temporary distraction, as indicated by the reduced omission rate. Possibly, novels can increase the arousal of children with ADHD to an optimal level (Zentall and Zentall, 1983), which results in improved performance. In this case, the distraction is not detrimental, but has a stimulating effect on the performance accuracy (specifically on omission errors) in the ADHD group.

Acknowledgements

We would like to thank all the children who participated in this study, Durk Talsma for his advice on the paradigm, Eric van Rossum for editing the novel sounds, Paul Groot for his assistance in programming the task and Joost Witlox for his assistance with the electrophysiological recording.

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Chapter 6

General Discussion and conclusions

This thesis aimed to answer three main questions: 1) Is interference control disrupted in ADHD?, 2) are children with ADHD more easily distracted than their normal peers?, and 3) what are the neurophysiological correlates of interference and distraction in ADHD?

Aim 1: Is interference control disrupted in ADHD?

The meta-analysis in Chapter 2 suggests that there is little empirical support for a deficit in interference control in ADHD, as measured by the Stroop Colour-Word task. The differences in interference control between ADHD groups and normal control groups are small. In comparison to their normal peers, children with ADHD have more difficulties with the baseline conditions of the Stroop Colour-Word task: word reading and colour naming. The conclusions of the meta-analysis are strengthened by our findings in Chapter 3 in which we used two sophisticated paradigms (a Simon task and an auditory Stroop task) to measure interference control in an ADHD group and a normal control group. We found no evidence for a difference in interference control between children with ADHD and their normal peers in both the auditory and the visual modalities. Thus, this thesis argues against the assumption that interference control is disrupted in ADHD at the performance level.

The Stroop Colour-Word task in ADHD: the debate continues

The Stroop Colour-Word task is a very appealing task for both the clinician and the researcher: it is short, easy to administer and the interference effect is huge. Although the meta-analysis (Chapter 2) showed that the Stroop Colour-Word task has certain limitations in ADHD, the task continues to appear in ADHD research. After the publication of the meta-analysis in 2005, six studies appeared that assessed interference control with the classical Stroop Colour-Word task (card version) in individuals with ADHD (Albrecht, et al., 2008; Kiliç, Sener, Koçkar, & Karakas, 2007, Marchetta, Hurks, Krabbendam, & Jolles, 2008; Pritchard, Neumann, & Rucklidge, 2007; Roessner, Becker, Banaschewski, & Rothenberger, 2007; Semrud-Clikeman, Pliszka, & Liotti, 2008). Two of them did not report an interference score (Kiliç et al., 2007; Semrud-Clikeman et al., 2008), but reported that children with ADHD

performed worse on the conditions that involved colour naming. Three studies (Marchetta et al., 2008; Pritchard et al., 2007; Roessner et al., 2007) did not find differences in the interference score. Only one study found that children with ADHD performed significantly worse than their normal peers on the interference score of the Stroop Colour-Word task (Albrecht et al., 2008). These recent studies strengthen the conclusion of our meta-analysis. Although there may be a small deficit in interference control in ADHD on the classical Stroop Colour word task, this finding is not consistent across studies and individuals with ADHD also encounter problems with colour naming.

In addition to the six experimental studies on the Stroop Colour-Word task in ADHD, two other meta-analyses on this topic have appeared recently (Lansbergen, Kenemans, & van Engeland, 2007; Schwartz & Verhaegen, 2008). Athough Lansbergen et al. (2007) did find a large effect size (d = 1.11) if Stroop interference was calculated as 'time per item', the mean effect size for the difference score ('time per item' and 'number of itmes named in 45 seconds' together) was small (d = 0.24). They concluded that interference control was consistently compromised in ADHD and that earlier results may have been biased by incorrect methods of quantification of the interference score. Therefore, they proposed a ratio score, which is more sensitive compared to the 'Golden' method or the difference score. The ratio score is calculated by dividing the colour-word score by the colour score. Ratio scores were also advocated in the meta-analysis of Schwartz and Verhaegen. However, Schwartz and Verhaegen showed that the ratio of the colour-word over the colour condition was identical in both ADHD and control groups. They drew the conclusion that the Stroop interference effect is not larger in ADHD than in normal controls and that there are no differential maturation effects for interference control. As the usefulness of the card version of the Stroop Colour-Word task in ADHD stands on very weak ground, the debate on interference control in ADHD as assessed with this task is no longer fruitful.

Alternative interference tasks

We failed to find group differences between children with ADHD and their normal peers in interference control in both the auditory Stroop and the Simon

task (Chapter 3). These results converge with recent empirical work that reports the absence of a specific performance deficit in interference control in ADHD (Rubia et al., 2007; Smith et al., 2006). Surprisingly, a recent review on interference control as assessed with Flanker and Simon tasks in children with ADHD did suggest weaker interference control in ADHD (Mullane, Corkum Klein, & McLauglin, 2009). In that review, the combined data of seven Flanker studies and four Simon studies were analyzed. With respect to the Simon task, only two of the included studies were published and these two studies did not find significant overall group differences on interference control as assessed with the Simon task (Drechsler et al., 2005; Tsal et al., 2005). Tsal et al. did find deficits in interference control in a subsample with a more severe form of ADHD. As the proportion of Flanker tasks was larger, it is possible that the conclusion of the meta-analysis is primarily based on Flanker effects. In Chapter 3 it was noted that an important difference between Flanker and Simon tasks is that the interfering information is outside the primary stimulus in Flanker tasks but integrated in the primary stimulus in Simon tasks (as in most other interference tasks). Nevertheless, the results of Mullane et al. are important, as they suggest that children with ADHD do show poorer interference control in the presence of conflicting information presented in close proximity to the primary stimulus.

Besides differences in interference control on Flanker tasks, individuals with ADHD also show more interference than their normal peers on a computerized Stroop Colour-Word task (Albrecht et al., 2008; Carter, Krener, Chaderjian, Northcutt, and Wolfe, 1994) but not on a Counting Stroop task (Albrecht et al., 2008, Bush et al., 1999). These findings indicate that deficits in interference control may be present in ADHD on Flanker and computerized Stroop Colour-Word tasks. Interference control does not seem to be a general deficit in ADHD, as it is not found on alternative interference tasks more suitable for individuals with ADHD. Suitable interference tasks for this group are independent of reading ability or focused attention, as children with ADHD often have reading problems (Del' Homme et al, 2007) and experience more difficulties when they have to focus on a relevant target in the presence of distracters (Brodeur & Pond, 2001). Note that the the ability to focus attention in children with ADHD may be disrupted in flanker paradigms (Brodeur &

Pond, 2001; Crone, Jennings, & van der Molen, 2003) but not in other paradigms (Huang-Pollock, Nigg, & Carr, 2005; van der Meere and Sergeant, 1988).Nevertheless, it is important to isolate the effects of interference that are independent of focused attention. These results underline the importance of assessing interference control in different paradigms and different modalities, as conducted in Chapter 3.

Aim 2: Are children with ADHD more easily distracted than their normal peers?

The distraction task in Chapter 4 revealed a very interesting pattern of behavioural results. After a novel sound, both children with ADHD and their normal peers slowed down, but their error rate *decreased*. This finding suggests that the novel sounds influenced their speed-accuracy trade-off, as both groups of children became slower but more precise. Additionally, children with ADHD had a larger rate of missed responses regardless of whether the trial was preceded by a novel sound or a standard tone. In the ADHD group, the novel sounds reduced the omission rate by 6% while this was only 0.6% in the control group. These findings argue against the view that children with ADHD are more easily distracted by novel and unexpected information because the effects on errors and mean reaction time were comparable to the effects of their normal peers. Furthermore, the results suggest that this type of distraction can even have beneficial effects in ADHD as indicated by the decrease of missed responses. As this type of distraction has a beneficial effect on the omission rate, future studies should explore what conditions produce benefits in children with ADHD.

Should we distract the distractibles?

In Chapter 5, we argued that novel sounds might help children with ADHD to increase their arousal to an optimal level for task performance. It has been noted that hyperactive boys tend to look away to distractors more frequently than nonhyperactive boys, while maintaining adequate levels of performance (Bremer & Stern, 1976). A more recent study showed that auditory alerting cues during a sustained attention task enhanced electrodermal arousal in both

children with ADHD and normal children but specifically reduced errors of commission in the ADHD group on the trials immediately following a cue (O' Connel, Bellgrove, & Dockree, & Robertson, 2006). Thus, although the neural (late P3a, Chapter 5) and behavioural response (looking away, Bremer and Stern, 1976) to distracting information may be greater, the effect on performance is absent (Bremer & Stern, 1976) or even beneficial (O' Connel et al., 2006; Chapter 5). The aforementioned studies all employed single task-irrelevant stimuli. In addition to these findings, studies that employed continuous task irrelevant stimuli, such as white noise (Söderlund, Sikström, & Smart, 2007) and music (Abikoff, Courtney, Szeibel, & Koplewicz, 1996; Scott, 1970) also found specific beneficial effects on performance in ADHD. Thus, both continuous (white noise, music) and non-continuous (novel sounds, auditory cues) can have a beneficial effect on the performance of children with ADHD.

Distraction in daily life does not consist of white noise or unexpected auditory stimuli alone. In order to test the impact of daily life distraction, Adams, Finn, Moes, Flannery, and Rizzo (2009) designed a virtual reality classroom in which children had to perform a continuous performance task. They showed that the distractions in this virtual reality classroom had a negative impact on the performance of children with ADHD, although the effect just approached significance. Perhaps, if the distracting information is too attractive (such as in the virtual reality classroom), the effects can be detrimental for performance. Maybe a child with ADHD can profit from listening to music during schoolwork, but not from looking at television and making homework at the same time.

Aim 3: What are the neurophysiological correlates of interference and distraction in ADHD?

The temporal processing of interfering and distracting information in ADHD was elucidated in Chapters 4 and 5. In both paradigms, strong task effects were found, but no performance deficit in the ADHD group occured. In normal control children, a large difference between the congruent and incongruent condition occurred in the 460-450 milliseconds time window after the

stimulus, while this difference was absent in the ADHD group. Furthermore, the conflict sustained potential (650-800 ms time window) was found frontally in the ADHD group but parietally in the normal control group. These findings suggest that children with ADHD evaluate conflict to a lesser extent and may use a different neurophysiological strategy to suppress interference and select appropriate responses. Thus, the manner in which the brain of children with ADHD resolves conflict and selects appropriate responses differs from normal controls. Perhaps, more frontal mechanisms are involved in ADHD, which may give rise to a frontal conflict sustained potential in ADHD as opposed to a parietal conflict SP in their normal peers.

The electrophysiogical findings in Chapter 5 show a different picture of distraction in ADHD than the behavioural findings. First, both novel sounds and standard tones resulted in a larger early P3a in ADHD compared to their normal peers. This finding could indicate that the call for attention is stronger in the ADHD group, irrespective of novelty. Furthermore, the late P3a in response to the novel sounds compared to the standard tones was enhanced in the ADHD group, which suggests a stronger involuntary switching of attention to the novel stimuli. But, as no differences occurred in the late negativity, reorienting back to the main task after distraction may be unimpaired in the ADHD group.

Neural correlates versus performance and behaviour in ADHD

In Chapter 4, we found a pronounced effect of ADHD on the neurophysiological correlates of interference control (after 460 milliseconds) coupled with the absence of an impairment in interference control in performance. While there is a gap in our knowledge of the neurophysiological correlates of conflict processing in ADHD as measured by Stroop-like tasks, ERPs in ADHD have been recorded in Flanker tasks (Albrecht et al., 2008; Jonkman et al., 1999, van Meel et al., 2007). Flanker tasks are related to Stroop tasks, as they also measure interference control. However, they differ with respect to the locus of the incongruent information (integrated in the primary stimulus in Stroop-like tasks, but in near proximity of the primary stimulus in Flanker tasks). Albrecht et al. showed that the typical N2 amplitude

enhancement for incongruent stimuli was reduced in ADHD, but Jonkman et al. did not find group differences in the N2 enhancement for incongruent stimuli. Behaviourally, Albrecht et al. did not found evidence for a deficit in interference control as assessed with the Flanker task (the interference effect on errors was even more pronounced in the normal control group). In contrast, both Jonkman et al. and van Meel et al. did find that children with ADHD comitted disproportionally more errors when incongruent flankers were presented. As other imaging techniques provide additional information on the neural correlates of interference control in ADHD, we will first summarize recent imaging work other than ERP studies on this topic before we discuss our results and related findings.

Three imaging studies (near infrared spectroscopy and fMRI) with a modified Colour-Word Stroop in children with ADHD (Jourdan Moser, Cutini, Weber, & Schroeter, in press), adults with ADHD (Banich et al., in press) and children with attention problems (van ' t Ent et al, 2009) appeared recently. All studies found large differences in brain activation but no behavioural deficit in interference control in ADHD. Jourdan Moser et al. reported higher oxygen consumption and brain activation in the right dorsolateral prefrontal cortex of boys with ADHD compared to their age-matched peers in a colour-word matching Stroop task (Zysset et al., 2001). They concluded that children with ADHD require elevated oxygen consumption in the right dorsolateral prefrontal cortex to cope with interference. Banich et al. employed a sophisticated Stroop paradigm to assess both sustained and transient aspects of interference control in young adults with ADHD. While they found reduced activity in the dorsolateral prefrontal cortex in ADHD, they observed a greater degree of activation in regions related to linguistic processing, such as the left temporal gyrus, which suggests increased processing of task-irrelevant information. Surprisingly, they also found that adults with ADHD showed *less* interference than the control group. Van 't Ent et al. also reported that children with attention problems showed decreased activation to response interference in the dorsolateral prefrontal cortex, parietal and temporal brain regions, but increased activation in other regions compared with children without attention problems. Again, no performance deficit in children with attention problems for Stroop interference was reported.

While there are some differences in the neural correlates of interference control between the studies, probably because of different task paradigms and age groups, almost all studies report differences between the groups in the neural correlates of interference control in the absence of a performance deficit in interference control. How is it possible that children and adults with ADHD show consistently large differences in both brain activation and ERPs related to interference control in the absence of a specific performance deficit? Several answers are possible:

First, measures of neural activity may be more sensitive than performance measures to detect abnormalities in conflict processing. Performance is the output of several covert processes in the brain. Due to its excellent time resolution, ERPs can give detailed insight into all covert processes that are involved in conflict processing. FMRI studies can elucidate which brain areas are involved in conflict processing. Because many subprocesses such as sensory registration, detection and evaluation of conflict do not require overt responses, abnormalities in these processes may be undetectable in performance. If both neural activity measures and behavioural correlates would be different in ADHD, a chicken and egg problem would arise: Are children with ADHD performing worse *because* of abnormalities in neural activity or are the differences in neural activity simply a reflection of poorer performance? Fortunately, this problem does not apply to interference control, as task performance is normal in our study and in many if not most other studies. Thus, a strong case can be made that the neural correlates of interference control are disrupted in ADHD as the neural effects are not confounded by behavioural differences. A relation has been found between ADHD symptoms (attention problems) and differences in neural activation between congruent and incongruent conditions (interference) in the ventrolateral prefrontal cortex, anterior prefrontal cortex and the basal ganglia (correlations vary between .72 and .79) while no relation between performance and neural activation was found in ADHD (Schulz et al., 2005). This result suggests that differences in neural correlates during interference control may represent deficits in ADHD that underlie their behavioural symptomatology. Performance

measures alone may be insufficiently sensitive as they are the output of many normal and abnormal neural processes.

A second explanation, reviewed by Fassbinder and Schweitzer (2006) is that differential brain activation in the absence of performance deficits reflects neural compensation. Individuals with ADHD are able to resist interference, but they need more brain areas to achieve this. This neural strategy to compensate for difficulties in task performance may be more effortful. In Chapter 5, the frontal-parietal between group differences may be a reflection of this more effortful neural strategy, a different tactic used by the brain to resolve conflict and select appropriate responses. For exploratory purposes, we analysed if there was a relation between behavioural interference (mean reaction time in the incongruent condition minus mean reaction time in the congruent condition) and the difference in the frontal sustained potential (sustained potential in the incongruent condition minus sustained potential in the congruent condition). We found a significant relationship for the total sample (n = 46, r = -.33, p < .05), for the ADHD group separately (n = 23, r = -.48, p < .05), but not for the control group separately. This finding might indicate that a frontal conflict sustained potential in ADHD is related to larger behavioural interference. The fact that the relationship is negative (the more negative the frontal sustained potential, the larger the interference effect) suggests that a frontal conflict sustained potential may indicate a more effortful strategy. However, this correlation should be interpreted with caution, as sample size was small and it was not significant in the normal control group separately, which makes this finding very speculative. If the hypothesis of neural compensation is correct, one would expect that children with ADHD become more efficient in recruiting neural compensation mechanisms when they grow up. Neural compensation is the recruitment of alternative brain regions in a task to compensate for weaknsesses in the network of brain areas that are normally recruited in a specific task. Support for this theory is reviewed by Halperin and Schultz (2006), who argued that the prefrontal cortex and its interconnections may be primarily involved in the recovery from ADHD as indicated by the developmental remission of symptomatology. Besides behavioural remission of symptoms, some neuropsychological deficits, such as for example time reproduction, sustained attention and inhibitory control also decline with age

(Gunther, Jolles, Herpertz-Dahlman, & Konrad, 2009; Rommelse et al., 2007). Certain brain structures, such as the dorsolateral prefrontal cortex, do not reach adult level until the early 20s (Giedd, 2004) which makes possibe neural compensation mechanisms that become more efficient with age a tenable hypothesis.

A third possibility is that neural and neurophysiological differences in conflict processing reflect a delayed brain maturation in ADHD. Developmental differences in ERPs have been reported for interference control (Jongen & Jonkman, 2008; Rueda, Posner, Rothbart, & Davis-Stober, 2004) for selective attention (Mueller, Bremer, von Oertzen, Li, & Lindenberger, 2008) and for distraction (Gumenyuk, Korzyukof, Alho, Escera, & Nätäänen, 2004) which indicates that these abilities are developing during childhood. However, if differences between the groups would be attributable to a maturational lag, it would be expected that children with ADHD would be comparable to normal children of a younger age. Although both ERP studies and studies into behavioural symptoms have failed to support this notion (Callaway, Halliday, & Naylor, 1983; Gustafsson et al., 2008), it has been noted that some abnormalities in the baseline EEG may represent a maturational lag in ADHD (Clarke, Barry, McCarthy, & Selikowitz, 2001) and that there is neuroanatomical evidence for a delay in brain maturation in ADHD (Rubia, 2007). A developmental study into distraction showed that the late P3a was larger in younger children (8-9 years) as compared to older children (12-14 years; Gumenyuk et al., 2004). The larger late P3 in response to novels in ADHD compared to their normal peers (Chapter 5) might also be consistent with the view that ADHD is associated with a maturational delay in neural processing. Unfortunately, the groups were too small in our studies (Chapter 4 and Chapter 5) to analyze the data in separate age groups, thus the hypothesis of a maturational delay could not be confirmed or rejected.

To summarize this section, abnormalities in the neural and neurophysiological correlates of interference control in the absence of a behavioural deficit in ADHD may reflect disruptions in specific subprocesses underlying interference control, a more effortful neural strategy, a maturational delay or a combination of these explanations.

Study limitations

Like every study, this thesis has certain limitations that should be mentioned before conclusions are drawn regarding interference control and distraction in ADHD. A first limitation is the heterogeneity of our samples. Although all children in the ADHD groups had a primary diagnosis of ADHD, some of them had comorbid oppositional defiant disorder (ODD), conduct disorder (CD), or reading disorder (RD). (We did not assess reading disorder in our sample but screened for technical reading problems in the ADHD group in Chapter 3). It is noteworthy that there is a very large comorbidity between ADHD and other disorders. Recently, Elia, Ambrosini and Berretini (2008) estimated that two third of the children with ADHD have one or more comorbid disorders, ODD being the most frequent with estimated rates of 40%. It has been argued that children with ADHD and comorbid ODD/CD represent a separate pathological entity as they have a different neurocognitive profile (Luman et al., in press) and a different ERP profile (Banaschewski et al., 2003). Recently, de Jong et al. (2009) showed that deficits in visual-spatial working memory were only present in a pure ADHD group, and not in an ADHD with comorbid RD group. Thus, the inclusion of children with comorbid ODD, CD or RD may have biased our results. Furthermore, some children may also have suffered from subclinical symptoms of other disorders such as anxiety disorder or childhood depression, which may have influenced the results. For example, Jonsdottir, Bouma, Sergeant and Scherder (2006) found that a deficit in executive functioning was related to comorbidity, such as depressive or autistic symptoms, but not to ADHD symptoms. Although our sample is not a 'pure' ADHD group, all children had a clinical DSM-IV diagnosis of ADHD (APA, 1994) that was confirmed by a structured interview (Diagnostic Interview Schedule for Children, DISC-IV; Shaffer et al., 2000) and both parent and teacher rating scales (Disruptive Behaviour Disorder rating scale; Pelham et al, 1992; Oosterlaan et al., 2000). Furthermore, we included children with ADHD regardless of ADHD-subtype, which might also have contributed to the heterogeneity in our samples.

An advantage of this heterogeneity is that the results of this thesis can be more easily generalized to the clinical ADHD population, as this is a highly

heterogeneous one. A disadvantage is that there is more between-subject variability in our ADHD sample, which reduces the chance of finding significant differences between the ADHD groups and the normal control groups. However, even in a sample of children with ADHD only, there may be large differences between the children. For example, Swanson et al., (2000) found that children with ADHD that had a repeat allele of the dopamine receptor D4 gene (a genetic vulnerability for ADHD) performed *normally* on neuropsychological tasks, while children with ADHD without this genetic vulnerability were impaired in their performance as expressed by slow and variable responses, despite the same severity of symptoms.

A second limitation of this thesis is that the tasks to assess interference control and distractibility were newly developed and never used in large groups to test the validity and the reliability of the tasks. In the distraction task, both the standard tones and the novel sounds might have acted as warning cues, as they were presented just before the stimulus. However, the novel sounds did elicit distraction at the behavioural level (prolonged response times) and at the neurophysiological level (enhanced late P3a), which contradicts this limitation. Although there were strong interference effects in the Simon and the auditory Stroop task at the group level, some children did not show the expected interference effects in the auditory Stroop task (prolonged response times and/or enhanced error rates in the incongruent condition compared to the congruent and neutral condition). This might be due to a different behavioural strategy employed by these children. Instead of listening to the pitch of a word (high or low) they might have categorized the pitch into gender of the speaker (high = female; low = male), thereby reducing the interference effect. Actually, the speaker was a female and the pitch of the words was digitally adjusted in order to have exact two octaves difference between the high and the low pitch.

A third limitation is that our samples were too small to assess age effects and that we studied only a small age range (8-12 years in Chapter 4 and 5, 6-12 years in Chapter 3). Furthermore, boys were overrepresented in our samples as ADHD affects more boys than girls. We selected an approximately equal number of boys for our control groups as in our ADHD groups, but this

approach makes it difficult to generalize our findings to girls with ADHD, as they are a minority in our studies.

Conclusions

The main conclusions of this thesis are:

- Although there may be a small deficit in interference control in ADHD as assessed with the Stroop Colour-Word task, the majority of children with ADHD have a normal ability to resist interference in both the auditory and the visual modality if the interfering information is incorporated in the primary stimulus.

- Children with ADHD show a stronger orienting reaction to novel auditory stimuli, but this does not impair their performance on a simple choice reaction time task. On the contrary, novel and unexpected sounds may even enhance their performance temporarily as indicated by a reduced omission rate.

- Children with ADHD differ from their normal peers in the temporal processing of interfering information. These abnormalities probably reflect disruptions in the evaluation of conflict and the selection of the appropriate response.

Theoretical and clinical implications

A key process in almost all theoretical accounts on ADHD is executive functioning or cognitive control (Barkley, 1997; Casey, Nigg, & Durston, 2007; Pennington & Ozonoff, 1996; Sergeant, 2005; Sonuga-Barke, 2003). The ability to selectively attend to relevant information and ignore irrelevant information is a crucial aspect of cognitive control. In two carefully controlled experiments, we demonstrated that children with ADHD are able to ignore interfering information to the same extent as their normal peers in terms of performance. Furthermore, although children with ADHD showed an enhanced neurophysiological distractibility, as evidenced by a larger late P3a, this did not

lead to disruptions in task performance that were larger than those of normal developing children. This suggests that under experimental conditions, children with ADHD are able to exert the amount of cognitive control required for normal task performance.

Theoretically, our findings imply that we can ignore interference control as an important aspect of cognitive control and executive functioning in ADHD. The contribution of interference control in current models of ADHD has been overestimated, as there is little proof of disrupted interference control at the performance level in ADHD (Chapter 2, 3 and 4). The question may arise whether these models are still valid if we eliminate interference control from them? We suggest that models that include a form of cognitive control or executive function will be improved by eliminating functions that are not disrupted such as interference control. Deficits in ADHD have been shown in related aspects of executive functioning such as inhibition and working memory (see for review Willcutt et al., 2008). The presumed deficit in executive functioning may be more narrow than assumed and may not include interference control.

It seems curious that the inability to ignore irrelevant information is not impaired in general in ADHD as distractibility is a major defining characteristic of ADHD in the DSM-IV (APA, 1994). It may be naïve to assume that in a highly heterogeneous population attentional problems are caused by a deficit in interference control or an inability to ignore distracting sounds. Possibly the nature of their attention problems is as diverse as the ADHD population itself, with some children suffering from a motivational deficit, some suffering from a inhibition deficit and others from an energetic deficit or a developmental delay. Nonetheless, there may be a subgroup of children that has a deficit in ignoring irrelevant conflicting or non-conflicting background information but this may very much depend on the task or the situation. Should distractibility still be a defining characteristic of ADHD in DSM-V? Although the causes of their distractibility may differ, the behaviour of most children with ADHD is characterized by apparent distractible and chaotic behaviour in various situations. (Not in all situations, as they often are very 'undistractible' when they play an exciting video game). Although this distractibility may be

unrelated to an inability to ignore irrelevant information, it may still be useful to include distractibility as a defining characteristic in DSM-V as it describes behaviour irrespective of the causes.

There are many situations in which children with ADHD suffer from an increased apparent distractibility. In these situations they may fail to recruit the required cognitive control mechanisms. Casey et al. (2007) argued that the control systems in ADHD may function adequately when 'on line' but may not be brought on line when needed, due to failures in bottom-up signalling mechanisms. The neurotransmitter dopamine is of specific importance in their model, because dopamine is involved in forming predictions about future outcomes and optimizing behaviour by detecting discrepancies between actual and expected outcomes (Schultz, Dayan, & Montague, 1997). Deficits in learning to detect regularities or irregularities in the environment could lead to less signalling of control systems to help alter or adjust behaviour accordingly. The implicated brain regions involved in this bottom-up signalling (basal ganglia, cerebellum and parietal cortex) are thought to be part of unique circuits that project both to and from the prefrontal cortex, thus providing a means for signalling prefrontal regions when top-down control needs to be imposed. Our results suggest that cognitive control mechanisms work adequately under certain experimental conditions with explicit task demands such as in distraction or interference paradigms. Daily life circumstances are different, and as interference control or the ability to ignore distracting information may be more effortful, it is possible that children with ADHD fail to bring these mechanisms 'on line' effectively in various situations resulting in apparent distractibility.

For the clinician, it is difficult to measure distractibility in ADHD with neurocognitive tasks, as the ability to ignore irrelevant information is not disrupted in laboratory situations. Cognitive interference control is unrelated to ratings of inattention or hyperactive/impulsive behaviour in ADHD (Chapter 3). Thus, the Stroop Colour-Word task and other interference or distraction tasks are of limited use as an aid in characterizing the deficits of children with ADHD. Another clinical implication is that auditory background information can have a beneficial effect on performance in ADHD. It has been established

earlier that children with ADHD benefit from extra-task distraction (Zentall and Meyer, 1987, Abikoff et al., 1996, Leung et al., 2000; Scott, 1970). Perhaps children with ADHD may profit from listening to music during schoolwork. Alternatively, they may also listen to unexpected novel sounds, alerting cues or white noise. Possibly, this auditory background information may also help to reduce distraction from other sources, such as peers talking.

Future directions

Developmental studies

While our findings add a small piece to the puzzle of ADHD, they also raise new questions. An important issue that has been ignored in this thesis is development. Deficits in interference control may be present in early childhood, but may disappear during middle and late childhood, as children with ADHD possibly develop effective compensatory neural strategies or outgrow these deficits. Therefore, imaging studies in which children with ADHD are followed during their development are recommended. These future studies may shed light on the question if there is indeed evidence for a neural compensation mechanism that becomes more efficient with age or if children with ADHD suffer from a maturational delay. Both theories are consistent with the findings that there is a decline in neurocognitve deficits and symptoms with age (Biederman, Mick, & Faraone, 2000). On the one hand, if the theory of neural compensation would be correct, one would expect that neural differences increase with age, as children with ADHD become more efficient in recruiting these mechanisms. On the other hand, if the theory that children with ADHD have a maturational delay would hold, it would be expected that children with ADHD resemble normal children at a younger age during development until a subgroup of children in which ADHD goes into remission catches up with their normal peers in neural development.

Ecological valid tasks versus tasks grounded in neuroscience

An important question is, is the approach to isolate single deficits in ADHD fruitful? Although we tried to isolate interference control from selective

attention by incorporating the irrelevant information in the stimulus, the tasks still taps on different abilities such as the detection of conflict, decision speed, keeping in mind the goal of the task, etcetera. As neural differences were found in windows that were related to the evaluation or detection of conflict and the resolution of conflict (selecting the appropriate response), one approach might be to try to manipulate these aspects of information processing. For example, tasks can be used in which the goal is to detect various levels of conflict within a stimulus instead of responding to the relevant dimension. Recent research (Jourdan-Moser et al., in press) indeed shows that children with ADHD have slower overall reaction times when they have to categorize stimuli into the presence or absence of conflict. But it is an open question if it is possible to design tasks that tap only on one ability. Furthermore, it may even be more difficult to translate these findings to real world situations, in which many abilities work in concert.

A different approach is to make tasks more ecologically valid as was done in the virtual reality experiment by Adams et al. (2009). An advantage of this kind of tasks is that a researcher can elicit behaviour that also occurs in daily life. This approach can advance our understanding of the defining characteristics of behaviour and performance of children with ADHD. A disadvantage is that this approach does not allow the identification of one single causal mechanism that explains poorer performance.

As both approaches have their advantages and disadvantages, they should supplement each other in future research. For example, if we wish to study distraction in ADHD, we can manipulate the exact timing of distractors with respect to the task in order to see when they are distractive and/or beneficial. Distractors could consist, for example, of irrelevant sounds, static or moving visual stimuli on a computer screen. In the real world example, we could let the child do a computer task in a busy classroom (for example in a kindergarten), in a classroom were everybody works silent (for example during an exam), in a room alone, or in a room with an experimenter. In this example, it would also be interesting to manipulate task difficulty, as task difficulty has been shown to affect the neural orienting response (P3a; Berti & Schröger, 2003).

Heterogeneity

The advice to incorporate the heterogeneity of the ADHD sample in new research designs sounds very much as 'kicking in an open door'. Researchers have repeatedly pointed at the importance of heterogeneity (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005). At the moment large studies into the genetics of ADHD (IMAGE; see for example Lambrechts-Rommelse, 2008) are being conducted that include imaging research, neurocognitive research and phenotypic assessments. These studies provide us with a detailed understanding of the genetic underpinnings of ADHD and the diversity of genes that are involved. This makes it possible to define subtypes according to genotype. Another approach is to identify subtypes according to functional or neural deficits or according to pathological mechanisms (for example preterm birth). These methods can advance treatment options. For example, it has been shown that EEG phenotypes in ADHD can predict treatment response to stimulant medication (Arns, Gunkelman, Breteler, & Spronk, 2008). It is thus very likely that such subgroups are more homogeneous in behaviour, neurocognition and treatment response than the total ADHD population. In the future, when risk genes for ADHD and their relation to neurocognitive deficits and behaviour have been defined, it may be possible to first characterize the subtype according to the presence or absence of specific risk genes and subsequently assess the child on abilities that are strongly related to these risk genes. A child will thus be categorized by a specific genotype and a specific (endo)phenotype. The diagnostic process will be more complex, but also more valid and can lead to better and more personalized treatment options and better clinical outcomes. Hopefully there are not as many subtypes as there are children with ADHD.

Would an impaired resistance to interference and distraction be a possible subtype for ADHD? In Chapter 3 we did not found evidence that interference control was impaired in a subsample of our children with ADHD. As positive findings have been reported for Flanker tasks (Mullane et al., 2008), there may be a subgroup of children that has a decreased ability to selectively attend to one target which may lead to increased interference from surrounding stimuli. Furthermore, deficits have also been found on computerized Stroop Colour-Word tasks, despite their limitations in ADHD. Thus, although interference

control does not seem a general deficit in ADHD, a specific deficit in interference control may be present in a subsample. Regarding distractibility (Chapter 5) more research is needed to identify the mechanisms that may lead to the observed decreased resistance to distraction. Clinically, it may also be useful to test if there is a specific subgroup that profits from distracting background information, as this has direct implications for the particular child.

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Nederlandse samenvatting

Summary in Dutch

ADHD (aandachtstekort stoornis met hyperactiviteit) is een veel voorkomende kinderpsychiatrische stoornis: geschat wordt dat ongeveer 2-4% van alle kinderen onder de 16 jaar ADHD heeft. De belangrijkste symptomen zijn aandachts-en concentratie problemen, overbeweeglijkheid (hyperactiviteit) en impulsiviteit. De oorzaak voor deze stoornis is complex, zowel biologische factoren (zoals genetische afwijkingen) omgevingsfactoren (zoals prenatale risicofactoren) en psychosociale factoren (zoals verwaarlozing) en de interactie tussen deze factoren dragen bij aan de ontwikkeling van ADHD. Genen hebben veruit de grootste rol in het ontstaan van ADHD, geschat wordt dat ze 76% van de variantie in ADHD kunnen verklaren (Faraone et al., 2005). Recentelijk wijzen onderzoekers ook op het belang van de interactie tussen bepaalde genen en omgevingsfactoren voor de ontwikkeling van ADHD (Laught et al., 2008; Stevens et al., 2009).

Veel toonaangevende theorieën over ADHD veronderstellen afwijkingen in 'cognitieve controle' of in 'executief functioneren' als onderliggend mechanisme dat leidt tot de geobserveerde gedragsproblemen in ADHD (Barkley, 1997, Casey, Nigg, & Durston, 2007; Pennington & Ozonoff, 1996; Sergeant, 2005; Sonuga-Barke, 2003). Hoewel de precieze betekenis van de definities van cognitieve controle en executief functioneren verschillen, omvatten beide concepten de vaardigheid om doelgericht te kunnen handelen. Een belangrijk aspect hierbij is om selectief de aandacht te kunnen richten op wat belangrijk is en irrelevante of conflicterende informatie te kunnen negeren. Zo moet een kind op school zich bijvoorbeeld richten op zijn schoolwerk, en andere gebeurtenissen in de klas kunnen negeren. Bij kinderen met ADHD gaat dit vaak mis, zij zijn veel sneller afgeleid door wat er om hen heen gebeurt en reageren hier ook eerder op.

Om meer inzicht te krijgen in de aard van de onderliggende problematiek bij ADHD hebben we in dit proefschrift verschillende neurocognitieve taken afgenomen bij een groep kinderen met ADHD en bij een groep kinderen zonder ADHD van vergelijkbare leeftijd. Met deze neuorcognitieve taken kunnen we specifieke cognitieve processen meten die noodzakelijk zijn om je aandacht te kunnen richten op datgene wat relevant is en wat irrelevant is te negeren. Daarnaast hebben we ERPs (event-related potentials) gemeten

gedurende deze taken. ERPs kunnen een nauwkeurig inzicht geven in de timing van verschillende cognitieve (sub) processen die noodzakelijk zijn voor de verwerking van informatie. Dit proefschrift richt zich specifiek op interferentie controle en afleidbaarheid bij kinderen met ADHD. Deze concepten zal ik in de volgende twee delen van de samenvatting verder toelichten waarna een korte beschrijving van de onderzoeken in dit proefschrift over interferentie en afleidbaarheid volgen (hoofdstuk 2, 3 en 5). Daarna volgt een deel over de neurofysiologie van interferentie controle en afleidbaarheid gevolgd door een samenvatting van het onderzoek in dit proefschrift hiernaar bij kinderen met ADHD (hoofdstuk 4 en 5). Tot slot beschrijf ik de belangrijkste conclusies van dit proefschrift en welke implicaties de resultaten uit dit proefschrift hebben voor de theorievorming rond ADHD, toekomstig onderzoek en de klinische praktijk.

Interferentie controle

Interferentie controle wordt gemeten met taken die conflict oproepen tussen een automatische reactie en een meer gecontroleerde reactie, zoals de Stroop Kleur-Woord taak (Stroop, 1935, Nederlandstalige versie Hammes, 1971). De Nederlandse versie bestaat uit drie kaarten. Op de eerste kaart, de Woord-kaart, moeten 100 woorden (rood, groen, geel, blauw) zo snel mogelijk worden gelezen. Op de tweede kaart, de Kleur-kaart, moet de kleur van 100 kleurvlakjes () zo snel mogelijk benoemd worden. Op de laatste kaart, de Kleur-Woord-kaart, staan 100 gekleurde woorden waarvan de kleur verschilt van de betekenis van het woord (geel, blauw, rood, groen). De bedoeling van deze kaart is om de kleur te benoemen en de betekenis van het woord te negeren. Op deze kaart ontstaat er conflict tussen de betekenis van het geschreven woord en de kleur van het woord. Hierdoor zijn kinderen en volwassenen trager en onnauwkeuriger op de derde kaart in vergelijking met de tweede en eerste kaart. Er zijn verschillende manieren om een interferentie score te berekenen. Meestal wordt de prestatie op de Kleur-Woord-kaart vergeleken met de prestatie op de Kleur-kaart (door middel van een verschil score).

De Stroop Kleur-Woord taak is de meest gebruikte taak om interferentie controle te meten bij verschillende stoornissen waaronder ADHD, zowel in de klinische praktijk als in het wetenschappelijk onderzoek. De wetenschappelijke resultaten zijn echter inconsistent. Desondanks is interferentie controle een belangrijk aspect binnen de huidige theorieën over ADHD. De eerste centrale vraag van dit proefschrift is dan ook of interferentie controle in ADHD verstoord is.

In hoofdstuk 2 hebben we dit onderzocht door middel van een meta-analyse over alle onderzoeken naar ADHD tussen 1990 en 2002 waarbij de Stroop Kleur-Woord taak is gebruikt. Het interferentie effect in de Stroop Kleur-Woord taak is zeer groot, wat deze taak bij uitstek geschikt maakt om interferentie controle te meten. Uit de meta-analyse die beschreven is in hoofdstuk 2 bleek echter dat de verschillen in interferentie controle tussen groepen met ADHD vergeleken groepen zonder ADHD klein waren. We vonden wel aanzienlijke verschillen in het benoemen van kleuren en het lezen van de woorden, waarbij de groepen met ADHD langzamer waren dan de groepen zonder ADHD. Blijkbaar hebben kinderen met ADHD meer moeite met de basisvoorwaarden voor de Stroop Kleur-Woord taak (kleuren benoemen en lezen) dan dat ze moeite hebben met interfererende informatie. Deze bevinding maakt duidelijk hoe belangrijk het is om te controleren voor basisvaardigheden binnen het neurocognitieve onderzoek. In ouder onderzoek werd de interferentie score soms niet gecontroleerd voor de snelheid waarmee kinderen met ADHD kleuren benoemden. Het was dan niet duidelijk of kinderen met ADHD meer last hadden van interferentie of simpelweg langzamer waren in het benoemen van kleuren. Hierdoor werd de slechtere prestatie op de Stroop Kleur-Woord taak van kinderen met ADHD soms ten onrechte toegeschreven aan een interferentie probleem. Uit recent onderzoek (Lansbergen et al., 2007) blijkt dat de manier waarop de taak wordt afgenomen (totale tijd voor 100 items of aantal items goed in 45 seconden; de laatstgenoemde methode wordt vaak in Angelsaksische landen toegepast) en de manier waarop de interferentie score wordt berekend (verschil score, ratio score of volgens de methode van Golden; zie Golden, 1978) tot uiteenlopende resultaten leidt. Zij stelden voor om een ratio score te gebruiken waarbij ze de score op de Kleur-Woord-kaart delen door de score op de Kleur-kaart. Schwartz

en Verhaegen (2008) zijn ook voorstander van deze methode, maar toonden aan dat deze ratio niet verschilde tussen ADHD groepen en controle groepen op geen enkel moment in hun ontwikkeling van kind tot volwassene.

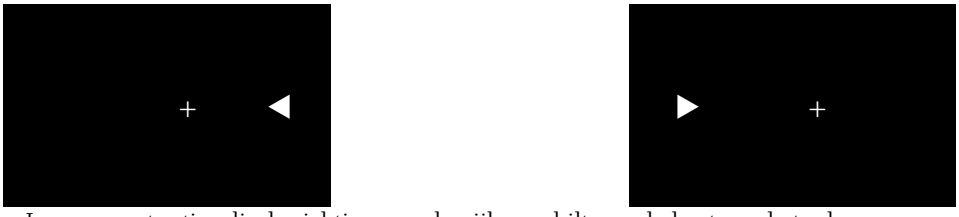
De evidentie voor een gebrekkige interferentie controle in ADHD gemeten met de Stroop Kleur-Woord taak is dus zwak. Bovendien kent deze taak enkele beperkingen als de taak gebruikt wordt voor onderzoek naar kinderen met ADHD. Het grote nadeel is dat kinderen met ADHD ook meer moeite hebben met de controle condities: het snel en foutloos lezen van woorden en benoemen van de kleuren. Mogelijk wordt dit veroorzaakt door een algemeen probleem met 'rapid naming' (snel benoemen) of door een leesstoornis. Leesstoornissen komen bij ongeveer 20% van de kinderen met ADHD voor (Del'Homme et al., 2007). Een alternatieve verklaring zou kunnen zijn dat kinderen met ADHD meer moeite hebben om hun aandacht gericht te houden op een item per keer waardoor ze meer afgeleid worden door de omringende woorden of kleuren. Uit eerder onderzoek blijkt inderdaad dat kinderen met ADHD meer beïnvloed worden door de aanwezigheid van flankerende stimuli (Brodeur & Pond, 2001). Vanwege deze beperkingen van de Stroop Kleur-Woord taak, hebben we twee interferentie taken ontwikkeld, een auditieve Stroop taak en een Simon taak, die onafhankelijk zijn van lezen, rapid naming en gerichte aandacht. Deze taken hebben we afgenomen bij een groep kinderen met ADHD en een controle groep. Dit onderzoek is beschreven in hoofdstuk 3.

De auditieve Stroop taak is gebaseerd op eerder onderzoek naar auditieve interferentie van McClain (1983) en door ons aangepast voor Nederlandstalige kinderen. Het kind krijgt in deze taak de woorden 'hoog' en 'laag' te horen die of op een hoge (734 Hz), of op een lage (167 Hz) toon zijn uitgesproken. De stimulus is incongruent als er een conflict is tussen de betekenis van het woord en de toonhoogte (het woord 'hoog' uitgesproken op een lage toon en het woord 'laag' uitgesproken op een hoge toon). De stimulus is congruent als de beide dimensies gelijk zijn (het woord 'hoog' op een hoge toon en het woord 'laag' op een lage toon). We hebben deze taak afgenomen bij 35 kinderen met ADHD en 26 kinderen zonder ADHD. De kinderen waren tussen de 8 en 12 jaar oud. Het bleek dat de kinderen trager en onnauwkeuriger reageerden op incongruente stimuli in vergelijking tot congruente stimuli. Deze bevinding

geeft aan dat er sprake was van interferentie bij het benoemen van de toonhoogte van incongruente woorden. Er was echter geen verschil in de sterkte van dit interferentie effect tussen de groepen. Kinderen met ADHD werden dus niet méér in verwarring gebracht door de incongruente informatie dan kinderen zonder ADHD.

Sommige kinderen die jonger waren dan 8 jaar bleken moeite te hebben met de concepten hoog en laag, waardoor ze op deze taak erg traag reageerden en veel fouten maakten. Om deze reden hebben we de auditieve Stroop alleen afgenomen bij kinderen vanaf 8 jaar. Omdat we ook interferentie controle wilden meten bij jongere kinderen én omdat de eerste taak alleen interferentie controle meet in het auditieve domein, hebben we ook een tweede, visueel-spatiële, interferentie taak afgenomen bij 51 kinderen met ADHD en een controle groep van 32 kinderen zonder ADHD. Alle kinderen waren tussen de 6 en 12 jaar. Deze Simon taak is gebaseerd op het onderzoek van Simon (1990) en aangepast voor kinderen door het in de vorm van een ruimtevaartspelletje te presenteren. Bij de Simon taak ziet het kind een pijl die links of rechts van het midden van het scherm verschijnt. Deze pijl wijst naar links of rechts. Het doel van de taak is om te reageren op de richting die de pijl aanwijst en de kant van het scherm waar de pijl verschijnt te negeren. Hieronder staat een schematische weergave van de taak.

Congruente stimuli: de richting van de pijl komt overeen met de kant van het scherm waar deze verschijnt.



Incongruente stimuli: de richting van de pijl verschilt van de kant van het scherm waar deze verschijnt.

De kinderen maakten meer fouten en reageerden trager op incongruente stimuli vergeleken de congruente stimuli. Dus interferentie trad ook duidelijk op in deze taak. Net als op de auditieve Stroop vonden we geen verschillen tussen kinderen met ADHD en kinderen zonder ADHD in interferentie controle.

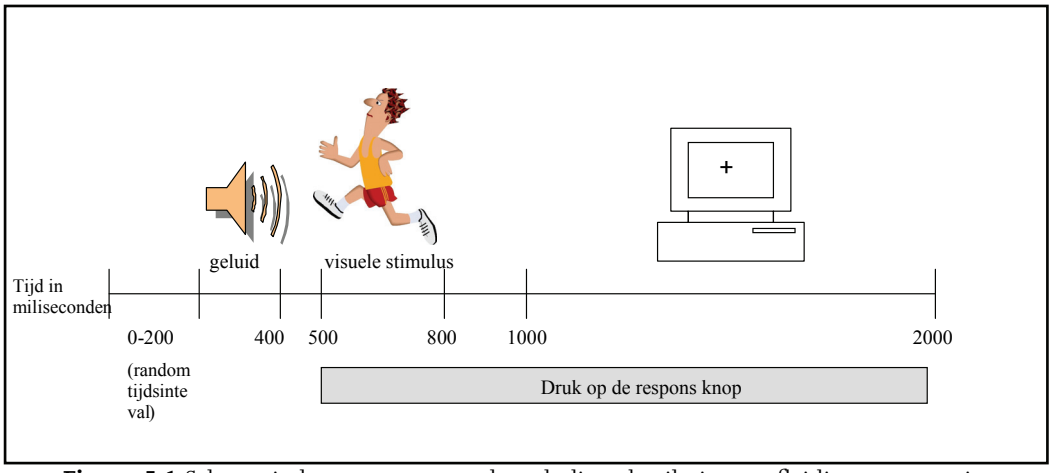
Met deze bevindingen tonen we aan dat kinderen met ADHD geen problemen hebben met interferentie controle, niet in de auditieve modaliteit en ook niet in de visuele modaliteit. Het gaat bij dit type interferentie om taken waarbij de interfererende informatie geïntegreerd is in de primaire stimulus. In taken waarbij de interfererende informatie in dichte nabijheid van de stimulus staat, zoals bij Flanker taken, wordt soms wel gevonden dat kinderen met ADHD een slechtere interferentie controle hebben (Jonkman et al., 1999; Scheres et al., 2004; van Meel, Heslenfeld, Oosterlaan, & Sergeant, 2007). Mogelijk zijn kinderen met ADHD minder goed in staat om hun aandacht te richten op de stimulus in het midden, waardoor de flankerende stimuli meer kans krijgen om te interfereren. In Flanker taken wordt dan ook gevonden dat kinderen met ADHD meer vertragen in het algemeen als naast de primaire stimulus ook flankerende stimuli gepresenteerd worden (Brodeur & Pond, 2001; Crone, Jennings, & van der Molen, 2003) ongeacht of deze stimuli incongruent, congruent of neutraal zijn.

Afleidbaarheid

Hoewel afleidbaarheid gerelateerd is aan interferentie controle, zijn er toch twee fundamentele verschillen tussen de oparationalisatie van deze twee concepten. Om afleidbaarheid te meten wordt namelijk altijd gebruik gemaakt van afleiding die niet gerelateerd is aan de taak (in ons onderzoek is het zelfs in een andere modaliteit) en de afleidende stimuli roepen ook geen conflict op, zoals bij interferentie taken wel altijd het geval is. Afleidbaarheid kan op verschillende manieren worden gemeten. In dit proefschrift wordt gebruik gemaakt van een paradigma dat speciaal ontworpen is om afleiding te meten voor ERP onderzoek (Escera, Alho, Winkler, & Naätänen, 1998) en aangepast is voor kinderen (Gumenyuk et al., 2001). Hierbij voert het kind een visuele taak uit terwijl hij of zij luistert naar standaard tonen en af en toe een nieuw geluid (zoals een loeiende koe, een motor of een bel). Het kind moet de geluiden

negeren en zich richten op de visuele taak. Omdat nieuwe en onverwachte geluiden moeilijker te negeren zijn dan standaard tonen, verslechtert de prestatie vaak direct na nieuwe geluiden. Dit uit zich in een tragere reactietijd en/of meer fouten. De tweede centrale vraag van dit proefschrift is of kinderen met ADHD meer afgeleid worden dan kinderen zonder ADHD. Dit onderzoek wordt beschreven in hoofdstuk 5. Hieronder volgt een korte samenvatting van de prestatie van de kinderen op deze taak. De ERP resultaten komen in het volgende deel van de samenvatting aan bod.

De kinderen die deelnamen aan dit experiment (25 kinderen met ADHD en 18 kinderen zonder ADHD, allen tussen de 8 en 12 jaar) voerden een eenvoudige visuele taak uit. De kinderen zagen een hardloper en zij moesten zo snel mogelijk de richting waarin de hardloper rende aangeven met een responsknop (links of rechts). Vlak voordat de hardloper verscheen hoorden ze meestal een standaard toon (600 Hz) en af en toe een onverwacht en nieuw geluid. Een schematische weergave van de taak is hieronder weergegeven.



Figuur 5.1 Schematische weergave van de taak die gebruikt is om afleiding te meten in hoofdstuk 5.

Het doel van deze taak was om de geluiden te negeren en zo snel en nauwkeurig mogelijk de richting van de hardloper aan te geven. Alle kinderen vertraagden na het nieuwe geluid. Er was geen verschil in de mate van vertraging tussen kinderen met ADHD en kinderen zonder ADHD. Een onverwacht resultaat was dat de kinderen niet meer fouten maakten na het nieuwe geluid, maar juist minder. Dit resultaat is in tegenspraak met eerdere onderzoeken naar afleidbaarheid, waar kinderen juist méér fouten maakten na een afleidend geluid (Gumenyuk et al., 2004; Gumenyuk et al 2005). Een mogelijke verklaring voor deze verschillende resultaten kan zijn dat onze taak was ontworpen als een hardloperstaak en in eerder onderzoek gebruik was gemaakt van een tweekeuze taak die minder gericht was op snelheid (aangeven of een stimulus een dier of geen dier is). Hierdoor is het mogelijk dat de kinderen vooral gericht waren op snelheid en daardoor meer fouten maakten. Als een nieuw geluid hun aandacht trok, dan vertraagden ze waardoor ze minder fouten maakten door te snel gokken.

Een verrassend resultaat was dat kinderen met ADHD specifiek minder omissie fouten maakten (niet reageren op de stimulus) na het nieuwe geluid. Bij kinderen zonder ADHD was dit effect veel minder sterk, waarschijnlijk omdat zij in het algemeen al weinig omissie fouten maakten. Bij kinderen met ADHD had het afleidende nieuwe geluid dus een gunstig effect. Een verklaring zou kunnen zijn dat het nieuwe geluid tijdelijk zorgt voor een hogere alertheid, wat leidt tot minder omissie fouten bij kinderen met ADHD. In eerder onderzoek is ook gevonden dat kinderen met ADHD kunnen profiteren van geluiden die buiten de taak aangeboden worden, zoals muziek (Abikoff, Courtney, Szeibel, & Koplewicz, 1996; Scott, 1970) of witte ruis (Söderlund, Sikström, & Smart, 2007).

Neurofysiologie van interferentie en afleidbaarheid

De laatste centrale vraag van dit proefschrift is of er verschillen zijn tussen kinderen met ADHD en kinderen zonder ADHD in de neurofysiologische verwerking van interfererende en afleidende informatie. In hoofdstuk 4 wordt een ERP onderzoek naar interferentie controle bij kinderen met ADHD beschreven. Aan dit onderzoek deden 24 kinderen met ADHD mee die werden

vergeleken met 24 kinderen zonder ADHD. Hierbij werd gebruik gemaakt van de eerder beschreven auditieve Stroop. Hoofdstuk 5 gaat over het onderzoek naar afleidbaarheid (zowel op het niveau van taakprestatie als op ERP niveau), waarvan we de resultaten op de taak hierboven al beschreven zijn. De ERP resultaten volgen in dit deel van de samenvatting.

Neurofysiologie van interferentie

Binnen de neurofysiologische verwerking van interferentie zijn twee processen cruciaal en goed beschreven in de literatuur: het onderscheiden van conflicterende informatie binnen een stimulus (conflict detection) en het selecteren van de juiste reactie ondanks de aanwezigheid deze conflicterende informatie (conflict solution/response selection). Er zijn aanwijzingen uit de literatuur dat de anterieure cingulate cortex (ACC, een hersengebied dat het voorste deel omvat van de cingulate cortex) een belangrijke rol speelt bij het herkennen van conflict en dat deze structuur vervolgens een signaal stuurt naar de dorsolaterale prefrontale cortex (DLPFC, een gebied in het voorste deel van de hersenen) waar dit conflict opgelost wordt door de goede reactie te selecteren (Carter & Van Veen, 2007). Neurofysiologisch is het herkennen van conflict zichtbaar als een grotere negativiteit na conflicterende stimuli vergeleken niet-conflicterende stimuli tussen de 400 en 500 milliseconden na aanbieding van de conflicterende informatie, deze negativiteit wordt de N450 genoemd (Rebai, Bernard, & Lannou, 1997). Het selecteren van de goede reactie is zichtbaar als een grotere parietale positiviteit en een grotere lateraal-frontale negativiteit bij conflicterende stimuli ten opzichte van niet conflicterende stimuli en wordt de conflict sustained potential of de sustained potential genoemd (zie bijvoorbeeld West et al., 2005).

Bij ADHD zijn functionele en structurele afwijkingen gevonden in de hersengebieden die betrokken zijn bij interferentie controle (Bush, Valera, & Seidman, 2005; Seidman et al. 2006). Daarnaast zijn er afwijkingen gevonden in de neurofysiologische verwerking van interfererende informatie met een Flanker taak (Albrecht et al., 2008). Er is echter nog weinig bekend over de neurofysiologische verwerking van interferentie zoals gemeten met de Stroop Kleur-Woord taak of vergelijkbare taken waarbij de conflicterende informatie

verwerkt is in de primaire stimulus. In hoofdstuk 4 hebben we de eerder beschreven auditieve Stroop gebruikt om de neurofysiologie van interfererende informatie bij kinderen met ADHD te ontrafelen omdat deze taak beter geschikt is voor kinderen met ADHD dan de standaard Kleur-Woord Stroop. Een nadeel van het gebruik van deze taak is dat de bevindingen minder goed vergelijkbaar zijn met eerder onderzoek naar interferentie met de Stroop Kleur-Woord taak of verwante taken, omdat in eerder ERP onderzoek naar interferentie alleen visuele taken zijn gebruikt.

In de auditieve Stroop vonden we al voor 400 milliseconden na de stimulus verschillen tussen de congruente en de incongruente conditie. Maar deze vroege verschillen tussen de condities waren vergelijkbaar tussen de groepen. We vonden geen duidelijke N450 in deze taak bij de kinderen. Dit kan te maken hebben met het type taak (auditief versus de visuele onderzoeken waarin de N450 is gevonden) of met het feit dat het opmerken van conflict er neurofysiologisch anders uit ziet bij kinderen in vergelijking met volwassenen doordat de hersenen zich nog ontwikkelen. Mogelijk vindt het opmerken van conflict eerder plaats, gezien de vroege verschillen die we vonden. Het is ook goed mogelijk dat dit juist pas later plaats vindt, omdat we wel een groot verschil vonden tussen de congruente en de incongruente conditie tussen 460 en 540 milliseconden na het aanbieden van de stimulus in de groep kinderen zonder ADHD. De incongruente conditie was in dit tijdswindow positiever dan de congruente conditie, dit in tegenstelling tot de N450, die negatiever is in de incongruente conditie. Dit verschil was afwezig in de ADHD groep. Mogelijk maken kinderen met ADHD minder goed onderscheid tussen woorden die conflict oproepen en woorden die dit niet doen, zij evalueren de woorden dus eigenlijk onvoldoende. Verder vonden we een verschil tussen de congruente en de incongruente conditie tussen de 650 en 800 milliseconden na het aanbieden van de stimulus. Dit verschil was bij kinderen met ADHD zichtbaar als een grotere frontale negativiteit in de incongruente conditie ten opzichte van de congruente conditie. Bij kinderen zonder ADHD was dit verschil echter parietaal te zien en was de incongruente conditie juist postitiever dan de congruente conditie. De resultaten van beide groepen komen overeen met de eerder beschreven conflict sustained potential, waarbij er sprake is van een frontale negativiteit én een parietale positiviteit. Het opvallende van dit resultaat

is dat de groepen verschillen in de neurofysiologische kenmerken van de conflict sustained potential. Mogelijk is er sprake van een iets ander neurofysiologisch mechanisme in de ADHD groep om de goede reactie te selecteren bij interfererende informatie.

Neurofysiologie van afleidbaarheid

Afleidbaarheid wordt gemeten met stimuli die niet gerelateerd zijn aan de primaire taak, dus ook geen conflict kunnen oproepen. Wij hebben in het eerder beschreven experiment (hoofdstuk 5, zie pagina 171 in de samenvatting) gebruik gemaakt van 99 verschillende nieuwe geluiden en 400 standaard tonen. Ieder nieuw geluid werd slechts één keer aangeboden. We hebben de nieuwe geluiden vergeleken met de standaard tonen. Op deze manier kunnen we onderscheid maken welke neurofysiologische activiteit hoort bij de verwerking van geluid, en welke activiteit gerelateerd is aan de afleiding zelf. Nieuwe geluiden roepen een grotere fronto-centrale P3a component op (Cycowicz & Friedman, 1997; Escera et al., 1998) dan standaard tonen. Deze nieuwe geluiden leiden dan ook meer af dan standaard tonen, wat in ons onderzoek zichtbaar was als een tragere reactietijd na de nieuwe geluiden vergeleken de standaard tonen. Verondersteld wordt dat de P3a een soort evaluatie is van de afleidende informatie en het bewuste aspect van de 'orienting respons' reflecteert. De 'orienting respons' is eigenlijk het richten van je aandacht op de nieuwe informatie. De P3a bestaat uit twee subcomponenten, de vroege P3a (rond 200 milliseconden na het aanbieden van de stimulus) en een late P3a rond 300 milliseconden na de stimulus. Waarschijnlijk is met name de late P3a gerelateerd aan de switch van je aandacht naar de nieuwe afleidende informatie (Escera et al., 2000). Als iemand afgeleid wordt is het belangrijk dat hij of zij de aandacht weer terug te kan brengen naar zijn of haar oorspronkelijke bezigheid. Dit proces is zichtbaar als een frontale negativiteit die optreedt na ongeveer 400 milliseconden na het horen van het nieuwe geluid. Deze negativiteit wordt de 'reorienting negativity' genoemd of kortweg RON (Schröger & Wolff, 1998).

De neurofysiologische resultaten in hoofdstuk 5 geven een ander beeld van afleidbaarheid in ADHD dan de resultaten op de taak zelf. De resultaten op de

taak wezen er op dat kinderen met ADHD niet meer afgeleid waren door de nieuwe geluiden dan andere kinderen en dat de afleiding zelfs een positief effect had op het aantal omissie fouten. Neurofysiologisch vonden we wel duidelijke aanwijzingen voor een verhoogde afleidbaarheid. Ten eerste bleken kinderen met ADHD een grotere vroege P3a te hebben, zowel na de standaard tonen als na het nieuwe geluid. Dit zou erop kunnen wijzen dat de 'call for attention' in het algemeen misschien sterker is in de ADHD groep. Ten tweede vonden we dat kinderen met ADHD een grotere late P3a hadden (250-300 milliseconden na het aanbieden van het geluid) in vergelijking met kinderen zonder ADHD als reactie op nieuwe geluiden in vergelijking met de standaard tonen. Deze tweede bevinding geeft aan dat kinderen met ADHD een sterkere aandachtsswitch naar de nieuwe en irrelevante informatie laten zien dan kinderen zonder ADHD. Tot slot vonden we geen verschillen in de late frontale negativiteit (400-500 milliseconden na het aanbieden van de stimulus) dus het weer terug brengen van de aandacht naar de primaire taak lijkt normaal bij kinderen met ADHD.

Conclusies en implicaties van de bevindingen

Voordat ik de implicaties beschrijf die deze bevindingen hebben voor de theorievorming rond ADHD, toekomstig onderzoek en de klinische praktijk, volgen hieronder eerst de belangrijkst conclusies van dit proefschrift:

- Op de Stroop Kleur-Woord taak zijn de verschillen in interferentie controle tussen kinderen met ADHD en kinderen zonder ADHD klein. Daarnaast kunnen kinderen met ADHD interfererende informatie even goed onderdrukken als kinderen zonder ADHD op visuele en auditieve interferentie taken waarbij de interfererende informatie in de stimulus geïntegreerd is.

- Neurofysiologisch besteden kinderen met ADHD meer aandacht aan nieuwe, irrelevante en onverwachte geluiden maar hun prestatie leidt hier niet onder. Het blijkt zelfs deze nieuwe geluiden hun prestatie op een positieve manier beïnvloeden: kinderen met ADHD maken namelijk minder omissie fouten na deze nieuwe geluiden.

- Kinderen met ADHD verschillen van kinderen zonder ADHD in de neurofysiologische verwerking van interfererende informatie. Deze afwijkingen wijzen waarschijnlijk op verstoringen in het evalueren van conflict en het selecteren van de goede reactie.

Theoretische en klinische implicaties

Een belangrijk proces in bijna alle theorieën rondom ADHD is executief functioneren of cognitieve controle (Barkley, 1997; Casey, Nigg, & Durston, 2007; Pennington & Ozonoff, 1996; Sergeant, 2005; Sonuga-Barke, 2003). De vaardigheid om selectief te letten op relevante informatie en irrelevante informatie te negeren is een cruciaal aspect van executief functioneren en cognitieve controle. Uit dit proefschrift blijkt echter dat kinderen met ADHD nauwelijks afwijkingen hebben wat betreft hun prestatie op taken die interferentie controle meten ook al zijn er wel neurofysiologische afwijkingen bij het verwerken van deze interfererende informatie. Onder experimentele condities zijn kinderen met ADHD blijkbaar goed in staat zijn om voldoende cognitieve controle processen te genereren om tot een normale prestatie te komen. De bijdrage van een verstoorde interferentie controle als onderliggend deelproces van cognitieve controle en executief functioneren in ADHD is in het verleden mogelijk overschat. De mogelijkheid blijft wel bestaan dat deze cognitieve controle weliswaar goed werkt als het geactiveerd wordt zoals in taken met een duidelijk doel, maar dat kinderen met ADHD het niet goed weten te activeren in onduidelijkere situaties zoals in het dagelijks leven (zie Casey, Nigg, & Durston, 2007 voor een uitgewerkt model van deze theorie). Dan zou het probleem bij ADHD dus niet zitten in de cognitieve controle processen zelf, maar in het activeren van deze processen als ze nodig zijn.

Taken die interferentie controle en afleidbaarheid meten zijn slechts van beperkt nut in de klinische praktijk om de onderliggende problemen bij ADHD in kaart te brengen. Bovendien bleek interferentie controle niet samen te hangen met scores op gedragsvragenlijsten voor aandacht en hyperactiviteit/ impulsiviteit (hoofdstuk 3), wat aangeeft dat een slechtere interferentie controle geen objectieve maat zou kunnen zijn voor bijvoorbeeld

aandachtsproblemen of impulsief gedrag. Een tweede klinische implicatie is dat irrelevante geluiden op de achtergrond een gunstig effect kunnen hebben op de prestatie van kinderen met ADHD. Mogelijk kunnen kinderen met ADHD profiteren van achtergrond geluid doordat dit hun alertheid verhoogd.

Implicaties voor toekomstig onderzoek

De bevindingen in dit proefschrift leveren een kleine bijdrage aan de huidige theorieën over ADHD. Daarnaast roepen deze bevindingen ook weer nieuwe vragen op. Problemen met interferentie controle zouden bijvoorbeeld aanwezig kunnen zijn in de vroege kindertijd, maar verdwijnen gedurende de lagere schoolperiode omdat kinderen met ADHD bepaalde strategieën leren om hiermee om te gaan. Ook zou het kunnen zijn dat bepaalde hersengebieden kunnen compenseren voor hersengebieden die normaal gesproken betrokken zijn bij interferentie controle (ACC en DLPFC) en bij ADHD mogelijk minder goed functioneren. Vanuit de fMRI literatuur is er wel enige evidentie voor dat kinderen en volwassenen met ADHD andere hersengebieden activeren gedurende het verwerken van interfererende informatie (zie bijvoorbeeld Bush et al., 1999; Zang et al, 2005). Ontwikkelingsstudies waarbij fMRI gebruikt wordt zouden duidelijkheid kunnen verschaffen over de vraag of er inderdaad sprake is van compensatie mechanismen die mogelijk efficiënter werken als kinderen ouder worden.

Een andere vraag is of het zinvol is om kinderen met ADHD taken te laten doen in de gebruikelijke zeer gestructureerde experimentele situaties waarbij één op één begeleiding is, of dat we meer toe moeten naar ecologisch valide experimenten. In experimentele situaties is het doel vaak een aspect van de informatie verwerking te isoleren, maar in het dagelijks leven zijn vaak veel verschillende vaardigheden gelijktijdig nodig. Omdat de experimentele en ecologisch valide manier van aanpak duidelijke voor-en nadelen hebben, zouden ze elkaar misschien goed kunnen aanvullen in toekomstig onderzoek. Als een onderzoeker bijvoorbeeld afleidbaarheid wil meten, kan hij in een experimentele situatie de precieze timing van de afleidende irrelevante stimuli bepalen, om na te gaan wanneer deze daadwerkelijk afleidend zijn en wanneer ze juist een gunstig effect hebben bij kinderen met ADHD. In het ecologisch

valide experiment zou de onderzoeker het kind een taak kunnen doen in een drukke klas, in een rustige klas, of in een kamer alleen. Op dit moment vinden de meeste studies naar ADHD vooral plaats onder gestructureerde experimentele omstandigheden.

Aangezien er zeer grote verschillen zijn tussen kinderen met ADHD, is het in de toekomst ook wenselijk om meer rekening te houden met deze heterogeniteit in het wetenschappelijk onderzoek. Naast de verschillende subtypes (voornamelijk aandachtsproblemen, voornamelijk hyperactief of gecombineerd) en de aan-of afwezigheid van bepaalde comorbide stoornissen (zoals oppositionele stoornis of dyslexie) zou je kinderen me ADHD in ook kunnen indelen op basis van het pathologisch mechanisme. Mogelijk zijn er grote verschillen tussen kinderen die voldoen aan de diagnose ADHD na een premature geboorte en kinderen met ADHD die verschillende risico genen bezitten. Ook is het misschien mogelijk om subgroepen te maken op basis van de aan- of afwezigheid van neurocognitieve of neurofysiologische afwijkingen. Uiteindelijk moet dit er toe leiden dat we beter weten wat de prognose is en welk kind het meeste baat heeft bij een bepaalde behandeling.

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Dankwoord

Acknowledgements

Na alle 'droge' en wetenschappelijke stukken volgt hier het meest persoonlijke deel uit mijn proefschrift, het dankwoord:

Ten eerste wil ik hier alle kinderen bedanken, omdat ze zich zo belangeloos hebben ingezet tijdens alle onderzoeken. Zonder jullie deelname waren deze onderzoeken niet mogelijk geweest. Een uur met een EEG –cap opzitten is best pittig, maar jullie vonden het vaak enorm interessant, vooral om de invloed van kauwbewegingen op het EEG te zien. Ook ben ik de ouders van alle deelnemers dankbaar en de scholen die ons onder schooltijd hun kinderen lieten testen (Amsterdam: Annie M.G. Schmidt school, Anne Frank School, 2e openluchtschool, 8e montessorischool, Amsterdamse montessorischool, Nieuw Vennep: op Dreef, Rehoboth, Heemskerk: De Regenboog).

Natuurlijk ben ik ook mijn beide promotoren, Jaap Oosterlaan en Joe Sergeant dankbaar voor de goede begeleiding. Jaap, bedankt voor je grote betrokkenheid, je vertrouwen in me, je heldere visie, en het grondig lezen van stukken. Joe, bedankt voor alle inspiratie en dat je me alle vrijheid liet om zelf de lijn in mijn proefschrift te bepalen. Bedankt voor je netwerk (ik heb de eunethydis meetingen altijd erg leuk gevonden) en je enorme kennis over ADHD. Ik heb heel erg veel van jullie geleerd.

Ook ben ik alle medewerkers en ex-medwerkers van de ADHD-poliklinieken (Claudia, Alky, Joyce, Annebeth, Janneke, Diana, Ceacilia, Lieke, Debbie, en de vele studenten) heel dankbaar voor hun bijdrage aan dit project. Ik vond het leuk om met jullie te hebben samengewerkt en verheug me op verdere samenwerking voor mijn neurofeedback en sport project. Sarah, jij ook ontzettend bedankt voor je inzet voor het pilot-neurofeedback onderzoek. Op het moment dat ik dit dankwoord schrijf, is het alweer bijna jouw laatste dag.

Laura, Mere, Sonja, Laurens en Joost, bedankt voor jullie waardevolle bijdrage aan het testen van kinderen voor dit proefschrift. Paul Groot, bedankt voor alle ondersteuning met e-prime en het EEG, Eric van Rossum dank voor het maken van de geluidjes in hoofdstuk 5. Dirk, bedankt voor jouw advies tijdens de ERP-analyses. Durk, dank voor het meedenken tijdens het opzetten van de ERP-experimenten.

Ik wil hier ook graag al mijn collega's (Erik, Jan Berend, Ans, Christien, Marjolein, Laura, Sophie, Bart, Roxane, Karin, Marloes, Hanneke, Karlijn, Astrid, Jorrit, Dirk, Vanessa, Annebeth, Frank, Nanda de K., Saskia en Hester) en ex-collega's (Crista, Katrien, Rob, Monique, Joukje, Nanda, Patrick, Rinske, Maartje, Michiel, Tako, Diana, Durk, Pascalle, Liselotte, Anneke, Koene, Marijn en Marije) van de afdeling klinische neuropsychologie bedanken voor de gezellige tijd, de sfeer, de borrels en etentjes en nog veel meer. Tot voor kort zei ik vaak dat ik na mijn promotie weg zou gaan bij de VU omdat ik er ook gestudeerd heb dus al erg lang bij de VU ben, maar ik vind jullie veel te leuk om te verlaten en kan gelukkig dankzij een ZonMw subsidie blijven. Joukje, Laura en Marjolein (Mario), het is alweer erg lang geleden dat we samen als AIO begonnen, ik vond het bij elkaar eten en voor elkaar koken altijd erg leuk en lekker (Laura's befaamde pompoensoep en Joukje's indische gerechten). Christien, ik vond het leuk om samen met jou ons proefschrift af te ronden en alle frustraties daaromheen te kunnen delen onder het genot van een kopje capuccino. Katrien, zowel persoonlijk als werk-gerelateerd kan ik altijd goed met je opschieten, en ik hoop dat dit zo blijft nu je in Rotterdam werkt.

De leden van de promotie-commissie: Prof. dr. Eco de Geus, Prof. dr. Jelle Jolles, Prof.dr. Jan Buitelaar, Dr. Lisa Jonkman en Dr. Sarah Durston wil ik bedanken voor de tijd een aandacht die ze aan dit proefschrift hebben besteed. Prof. dr. Tobias Banaschewski und Prof. dr. Dani Brandeis, vielen Dank für ihre Zeit um diese Dissertation zu lesen.

Ik wil hier ook even kort mijn vriendinnen bedanken, ondanks dat ik door de drukke combinatie van werk en gezin jullie af en toe wat verwaarloos, ben ik blij dat jullie zulke trouwe vrienden blijven.

Mijn ouders, Kees en Willy, dank voor heel veel, jullie steun, betrokkenheid, jullie vertrouwen in me, dat jullie zulke fantastische grootouders zijn voor David en Stefan (en als ouders zijn jullie natuurlijk ook fantastisch, dat ben ik nog meer gaan waarderen sinds de komst van David). Ik vind het heel erg lief en bijzonder dat jullie dit boekje wilden bekostigen, ik ken niemand die zulke ouders heeft.

Saar en Jan, ik had me geen betere broer en zus kunnen wensen en ben blij dat jullie mijn paranimfen willen zijn. Erg fijn dat jullie op een gegeven moment ook maar niet meer vroegen ‘wanneer is je proefschrift nou af ?’

Jasper, jij bent al sinds mijn afstuderen de man van mijn leven. Ik ben heel gelukkig met jou.

David & Stefan, jullie zijn zulke leuke en lieve jongens. Promoveren is leuk, maar jullie zijn veel belangrijker. Stefan, jij dacht een tijdje dat ik bij de schaatsbaan werkte omdat je me daar een keer hebt gezien met collega’s en David jij wil altijd graag muizen gaan vangen op mama’s werk.