

Learning to remember and to forget: electrophysiological studies on attention-working memory interactions in typical development and ADHD

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Learning to remember and to forget:

**Electrophysiological studies on
attention-working memory interactions
in typical development and ADHD**

Marjolein Spronk

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Learning to remember and to forget:

Electrophysiological studies on attention-working memory interactions in typical development and ADHD

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Ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
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Chapter 1

General Introduction

Our rapidly changing environment requires constant updating of information and selection of only the most relevant information for our current intentions and goals. With these goals in mind, it is important not to get distracted by irrelevant information that is also present in the environment. For this to succeed well-functioning cognitive control is essential. Countless situations in everyday life require this cognitive control, for example making a complex assignment in a noisy classroom, or driving on a busy road watching traffic signs but ignoring advertisements. Important for successful cognitive control are working memory and attentional control, and these functions have therefore been studied extensively in the field of cognitive neuroscience. Attentional control is the ability to successfully select the information that is most important to the current task-goals and suppress the influence of task-irrelevant information, while working memory (WM) refers to the ability to keep this information active in mind for short periods of time. Theoretical WM models have assigned an important role to attentional control in determining one's WM capacity. In Baddeley's influential multicomponent WM model (Baddeley & Hitch, 1974), attentional control is exerted by the central executive (CE) that coordinates the information stream to and from the two short-term memory stores, the visuospatial sketchpad and the phonological loop that respectively hold visuospatial and acoustic/verbal information for short-periods of time.

Although attentional control was already assigned an important role in Baddeley's WM model, the past decade more knowledge has been derived from experimental studies about the relation between WM and attentional control (Awh et al., 2006; Kane et al., 2001; Kane & Engle, 2003; Vogel et al., 2005). By using experimental tasks in which both functions were manipulated at the same time, this research has shown that WM and attention are closely related. In experimental developmental research WM and attention functions have however mainly been studied in isolation so that not much is known about the development of the mechanisms underlying WM-attention interactions, despite observations of the existence of such links between inattentive behavior and WM problems (Lui & Tannock, 2007, Tillman et al., 2011).

Several factors play a role in an individual's cognitive control abilities, one of which is development. Neuroimaging studies on the underlying biological nature of WM and the ability to suppress irrelevant information in adults have shown that areas in the frontoparietal network, and especially the dorsolateral prefrontal cortex (DLPFC), are involved in these cognitive functions (Curtis & D'Esposito, 2003; Grimault et al. 2009; Rypma, Berger, & D'Esposito, 2002). Developmental research has shown that WM and attentional control follow a protracted development course that continues into late adolescence, and this has been linked to the immature frontoparietal network in children and adolescents (Luna et al., 2004; Luna et al, 2010). Since developmental studies have shown that development of WM and attentional control is linked to academic achievement (Alloway & Alloway, 2010; Rogers, Hwang, Toplak & Tannock, 2011) and the development of inattention

problems such as in attention-deficit/hyperactivity disorder (ADHD) (Kofler et al., 2010; Sowerby et al., 2010), but also in typical development (Lui & Tannock, 2007; Tillman et al., 2011), more research on the development of these cognitive functions is necessary.

The main research aim of the present thesis is therefore to study the development of WM-attention interactions by using paradigms derived from the adult literature in which both functions are simultaneously manipulated. Special attention will be given to adolescence since, as will be more elaborately explained below, this is a period of considerable changes in cognitive functioning, and it has been found that both WM and attentional control are still immature between 12 and 16 years (Anderson et al., 2001; Davies et al., 1999; Gathercole, 1999; Luciana, Conklin, Hooper, & Yarger, 2005; Luna, Garver, Urban, Lazar, & Sweeney, 2004; Luna et al., 2010; Segalowitz et al., 2010). These cognitive changes have been linked to ongoing cortical development, particularly in the prefrontal cortex (Bunge & Wright, 2007; Klingberg et al., 2002; Durston et al., 2002; Rubia et al., 2006). Although cognitive development during adolescence has been topic of much research during the past years, the relation between WM and attentional control in adolescents has only been studied separately, and interactions between them have not yet been addressed.

The developmental course of the interactions between WM and attentional control in healthy adolescents will be studied in the present thesis by using existing paradigms from adult studies. Furthermore, abnormal development of these cognitive functions in patients with ADHD will be examined. The experiments described in this thesis thus address the developmental course from adolescence to adulthood of WM and attentional control interactions in typical development and in ADHD. In addition, it is examined whether abnormalities in attentional control functions are already present in young children with ADHD symptoms, since this is a period in which basic cognitive control functions such as response inhibition are known to come online/develop very fast.

Before introducing the main research questions of this thesis, first some background on different topics will be given. First, the research that has been done on interactions between attention and WM in adults will be reviewed and existing theories will be discussed. Second, the underlying neural mechanisms of attention and memory in the mature brain will be introduced. Third, a short review will be given about what is known about the typical development of selective attention (filtering) and WM and their neural correlates, followed by what is known about the development of these cognitive functions and underlying brain circuitry in children, adolescents and adults with ADHD that are known to have impairments in WM and selective attention. Fourth, the methods that were used to study the development of attention-WM relations are explained, and motivated. Last, an overview will be given of the aims and research questions of the current thesis, and the contents of its chapters.

1.1 Theories and research on attentional control and working memory interactions in adults

In the last decade, different research groups have investigated interactions between WM and selective attention (interference control) in different ways. The group of Lavie (Lavie et al., 2004) has approached this issue by studying the effects of manipulation of WM load on interference control in a concurrently performed selective attention task in which the level of distraction was manipulated. These WM-attention tasks are so-called dual-tasks. In a dual-task, WM is loaded with different amounts of information (thereby varying the load) in order to reduce available WM capacity. If interference control is dependent on WM capacity, this should affect the ability to ignore distracting information in the concurrently performed attention task. Different types of attention tasks can be used. One task measuring interference control within one stimulus is the Stroop task (Stroop, 1935). Interference control is defined as the ability to select task-relevant information while simultaneously suppressing the influence of other available information that is not relevant to the current task-goals, and therefore conflicts with current task demands. In the original Stroop task, a color-word is presented that can be printed in the same or another color, and the subject is asked to name the ink color. The Stroop effect is taken as a measure of the efficiency of interference control and is computed as the reaction time cost that is observed when the ink color does not match the color word evoking response conflict that is not present when the ink and the word are the same color. Ever since, several other Stroop-like tasks, using different stimulus types, have successfully elicited interference effects. In a series of behavioral and neuroimaging studies Lavie and colleagues investigated the effect of manipulation of WM load on interference control in different types of attention tasks with distracter interference such as in Stroop, flanker or visual search tasks (De Fockert et al., 2001; Lavie et al., 2004; Lavie & De Fockert 2005). In all these studies higher occupancy of WM led to increased distracter interference in the concurrently performed selective attention tasks as measured by delayed reaction times and reduced accuracy when targets and distracters evoked conflicting responses, i.e. were incongruent (e.g. the word red printed in green in the Stroop task) as opposed to when both were congruent. This led to a Load theory suggesting that when WM is loaded, distracter interference in a Stroop task increases because concurrent WM processes consume resources necessary for goal maintenance. There is now accumulating evidence that the level of control one has on the effect of interfering information (such as inhibiting the response conflict induced by a non-matching color-word) is dependent on one's WM capacity.

Another way in which the interaction between WM and attention has been examined is by investigating whether individual differences in WM capacity influence performance on selective attention tasks that require suppression of irrelevant or distracting information. In a series of studies with different attention

tasks (e.g. dichotic listening, anti-saccade task, Stroop tasks and CPT-AX tasks) it was found that subjects with low WM capacity performed worse than those with high WM capacity. Based on these findings, it was suggested that WM could be defined as a system responsible for the active maintenance of goal-relevant information in the face of concurrent processing and/or interference (Conway et al, 2001, Kane et al., 2001, Kane and Engle, 2003). In this WM-attention theory, WM refers to the ability to maintain a task goal in memory in the face of salient interference and individuals who are more capable of doing so are less susceptible to interference or distraction. According to this theory, the ability to control or manage the effect of interference thus depends on the WM capacity.

The research described above examined the effects of WM load on top-down attentional control of distraction, but vice versa the effects of selective attention on WM capacity were investigated as well. This research originated from one of the central questions in WM research, namely which factors determine the limitations of information storage space in human memory. It is now widely recognized that most mature people can hold a maximum of around 3-4 items in visual memory for a short period of time (Cowan, 2001; Luck & Vogel, 1997; Todd & Marois, 2004). Maximum WM capacity is dependent on one's storage capacity, but it has also been shown that the ability to select relevant and to discard irrelevant information for memory storage is of major importance to an individual's memory capacity. Storage of distracting, irrelevant information takes up space in WM that will no longer be available for storage of task-relevant items, resulting in decreased performance on WM span tasks. Selective attention is thought to regulate memory access, or in other words, the efficiency with which an individual filters information for memory storage. This effect of selective attention on WM capacity has been confirmed by results from previous studies in which the relevance of information was manipulated by including distracting stimuli (Awh, Vogel, & Oh, 2006; Cowan et al., 2005; Kane, Conway, Bleckley & Engle, 2001; Fukuda & Vogel, 2009; McNab & Klingberg, 2008; Vogel, McCollough, & Machizawa, 2005; Zanto & Gazzaley, 2009). In general, less efficient filtering of information is seen in individuals with low-WM-span compared to individuals with high-WM-span.

In sum, there is much evidence that attentional control and WM are dependent on one another and rely on a common pool of resources. Different researchers have provided evidence for links between WM capacity and selective attention/interference control ability, investigating this in different causal ways using different paradigms and various types of stimulus information. The current thesis will focus on attentional control and WM interactions in verbal and visuospatial information processing, using paradigms based on the research by the groups of Lavie and Vogel.

1.2 Neural mechanisms underlying attentional control and working memory performance in the mature brain

The idea that WM and attentional control are mutually dependent is supported by neuroimaging studies that have shown activation of similar brain regions/networks including frontal, striatal and parietal cortex in WM and selective attention/interference control tasks (Bunge et al., 2001; Kane & Engle, 2002; LaBar et al., 1999; Postle et al., 2004). In recent years, studies including healthy adults have focused on activity in and connectivity between these brain areas to further disentangle the mechanisms behind WM and attentional control interactions. This research has indicated that especially frontoparietal networks are involved in the updating and maintenance of relevant information in WM and successful suppression of the influence of irrelevant information (Awh, Vogel, & Oh, 2006; Cowan et al., 2005; McNab & Klingberg, 2008; Vogel, McCollough, & Machizawa, 2005). Three areas have been identified as most important within these networks and are thought to have a different role in attention/WM tasks, these are: 1) the dorsolateral prefrontal cortex (DLPFC: associated with the resistance to interference by suppression of distracting information and top-down control over posterior regions that store representations in memory; Curtis & D'Esposito, 2003) 2) the anterior cingulate cortex (ACC: assigned an important role in performance monitoring/conflict control needed when competing or conflicting information is present and is also thought to detect the need for greater allocation of attentional resources; Botvinick et al., 2004; Cohen et al., 2000; MacDonald et al., 2000), and 3) the intraparietal sulcus (IPS: associated with processing of spatial object representations in WM when there is no visual stimulation; Linden et al, 2003; Todd & Marois, 2004; Xu & Chun, 2005; and thought to be important for mediating shifts of spatial attention to target locations, especially with higher WM loads (Coull & Frith, 1998; Silk et al., 2010). Since frontoparietal networks involved in cognitive control are still immature in adolescence, worse performance on cognitive control tasks is expected in this age group, which will be further explained below.

1.3 Typical development of attentional top-down control and working memory capacity

Both attentional control and WM follow a protracted developmental course from childhood throughout adolescence (Anderson et al., 2001; Davies et al., 1999; Gathercole, 1999; Luciana, Conklin, Hooper, & Yarger, 2005; Luna, Garver, Urban, Lazar, & Sweeney, 2004; Luna et al, 2010; Segalowitz et al., 2010). Children as well as adolescents have shown immature suppression of irrelevant information in selective attention/filtering tasks and in tasks demanding resolution of response conflict and

inadequate withholding of inappropriate responses (e.g. response inhibition). In these studies, several tasks have been used to measure such impairments in selective attention and inhibitory control. For example, Go-Nogo or cued Go-Nogo tasks measure the ability to respond to certain stimuli (Go-stimuli) but to refrain from responding when a so-called Nogo-stimulus is present. In a cued Go-Nogo task such as the CPT-AX the subject is furthermore asked only to respond to the Go-stimulus (letter X) when it is preceded by a cue-letter (letter A), and otherwise to refrain from responding. Previous studies have shown that children perform worse (made more errors and had longer reaction times) on these tasks than adults (Booth et al., 2003; Casey et al., 1997; Jonkman et al., 2003; Jonkman et al., 2006; Tamm et al., 2002). Other tasks measuring inhibitory control, or more precisely the suppression of irrelevant information, such as the flanker task, Simon task and Stroop task, have also shown impaired performance in children as well as adolescents (Durstun et al., 2002; Bunge et al., 2002; Davidson et al., 2006; Rubia et al., 2006). In these tasks children and adolescents have been found to make more errors and have slower and more variable reaction times than adults. Studies using WM tasks in children and adolescents have shown similar results, indicating that mature levels of WM performance are not reached before adolescence. Although some studies have shown mature WM performance in 10-12 year old children (Riggs, McTaggart, Simpson, & Freeman, 2006; Van Leijenhorst, Crone, & Van der Molen, 2007), this is probably due to the use of less cognitively demanding tasks in these studies. Other studies, in which tasks were used that required maintenance, updating and/or manipulation of information (and thus more attentional control/resources), have shown that mature levels of WM are not reached before the age of 16 (Gathercole, 1999; Luciana et al., 2005; Luna et al., 2004; Schleepen & Jonkman, 2010). These cognitive changes in WM and attentional control in childhood and adolescence are not isolated, but have been connected to the development of other important cognitive abilities like reasoning (Krawczyk et al., 2008), problem solving (Passolunghi et al., 1999), and academic skills such as reading and mathematics (Gathercole, Pickering, Ambridge, & Wearing, 2004; Gathercole, Alloway, Willis, & Adams, 2006) and fluid intelligence (Burgess & Braver, 2010; Conway, Cowan, Bunting, Therriault, & Minkoff, 2002; Fukuda, Vogel, Mayr & Awh, 2010). A better understanding of the developmental course of WM and attentional control, and especially the interactions between these cognitive functions, can therefore add to our knowledge of the development of these and other cognitive abilities that are important for a child's functioning in several areas of life.

1.4 Neural mechanisms underlying development of attentional control and working memory in childhood and adolescence

As the above short review showed, depending on required levels of attentional control, both WM and attentional control functions are still immature during childhood and adolescence and several studies have linked this with ongoing brain development and immature connectivity between brain regions. Structural developmental brain changes continuing throughout adolescence consist of grey matter loss and increases in white matter in frontal and striatal regions (Sowell et al., 1999), and increases in cognitive abilities are linked to myelination and synaptic pruning, which strengthen synaptic connections (Blakemore & Choudhury, 2006; Casey et al., 2000). Much research has shown that the ongoing development of frontal and parietal areas that are part of the frontostriatal and frontoparietal networks is indeed related to behavioral performance in WM and attention tasks (Bunge & Wright, 2007; Klingberg et al., 2002; Kwon, Reiss & Menon, 2002; Durston et al., 2002; Rubia et al., 2006). Improved WM and attention performance with age is often accompanied by increased activation in specific frontal and parietal brain areas (Bunge et al., 2002; Klingberg et al., 2002; Kwon, Reiss & Menon, 2002; Luna & Sweeney, 2004). DLPFC, that has been shown to be involved in adult WM performance especially during distraction, has been reported to develop relatively late, maturing throughout adolescence (Giedd, 2004; Lenroot & Giedd, 2006). Increased activation in DLPFC is especially observed when task demands are high, for example when high WM loads are imposed or when distracting information has to be ignored (Grimault et al., 2009; Rypma et al., 2002; Dolcos et al., 2007). These findings likely explain why adolescents (in contrast to younger children) do not experience problems in easy WM tasks, but do show impaired performance in more complex tasks that demand high levels of attentional control, such as when distracting information has to be ignored while holding information in WM. Furthermore, children and adolescents generally recruit larger and more diffuse regions of the prefrontal cortex compared to adults in cognitively demanding tasks (Luna & Sweeney, 2004; Luna et al., 2010; Casey et al., 2005; Durston & Casey, 2006).

Although a reasonable number of studies has investigated the neural mechanisms underlying attentional control and WM development during performance of tasks measuring these functions separately, not much is known about the neural mechanisms/networks underlying interactions between these functions in adolescents. No studies so far have examined how WM load affects interference control in adolescents, and to which extent attentional control plays a role in (impaired) WM performance in adolescents. From the point of view that brain regions that subserve cognitive control (the ability to suppress irrelevant information when performing a task) are still developing in adolescents, it would be expected that they have more trouble regulating task-goals and demands according to

instructions. Therefore both inhibitory and WM performance could suffer even more in difficult or complex tasks (that require higher cognitive control) in this age group than in adults. The development of these functions throughout adolescence and how they interact with each other is the subject of Chapter 3 and 4 of this thesis.

1.5 Selective attention and working memory problems in attention-deficit/hyperactivity disorder

ADHD is one of the most common developmental psychiatric disorders today, affecting 5-10% of all school-aged children (Polanczyk & Jensen, 2008; Polanczyk, de Lima, Horta, Biederman & Rohde, 2007), and symptoms often persist in adolescence (approximately in 5% of the population: Polanczyk et al., 2007) and adulthood (approximately 4.4% of the population: Kessler et al., 2006; Kessler et al., 2011). ADHD is characterized by symptoms of inattention, impulsivity and hyperactivity (DSM-IV-TR, APA, 2000) that can severely affect normal development, and can lead to academic underachievement (Rogers, Hwang, Toplak, Weiss & Tannock, 2011). The research in this thesis focuses on the deficits in attentional control and WM that are often observed in ADHD and the underlying brain processes that are thought to be involved in these processes.

According to Barkley's theory (1997) a problem with behavioural inhibition is one of the core deficits in ADHD patients. Behavioral inhibition refers to the ability to suppress a prepotent response that is incorrect, or to suppress irrelevant information that distracts a person from his or her current task goals. Inhibitory control or attentional control is impaired in school-aged children with ADHD as has been shown by studies reporting worse behavioural performance compared to healthy children. For example, in the previously discussed cued Go-Nogo task larger and more variable reaction times and more false alarms have been found in ADHD children compared to their healthy peers (Banaschewski et al., 2003; Durston et al., 2003; Fallgatter et al., 2004; Wiersema et al., 2006). Furthermore, insufficient resource allocation in response to cues was found in these children (Brandeis et al., 2002). However, not much research on response inhibition has been done in younger, pre-school children. Since executive functioning abilities such as inhibitory control are known to come online (show a quantitative development) during childhood in the ages from three to seven (Dowsett & Livesey, 2000; Carlson & Moses, 2001) this is an interesting period to examine children with and without ADHD symptoms to find out whether they already experience deficits of attentional control, and this question is addressed in Chapter 2.

Other types of attentional control, such as interference control (the ability to select task-relevant information while simultaneously suppressing the influence of distracting information that conflicts with task demands) and selective attention filtering (the ability to suppress irrelevant and distracting information through

selective attention) have also been found to be impaired in ADHD. For example, interference control deficits have been shown in children (Brodeur & Pond, 2001; Jonkman et al., 1999; Randall et al., 2008), adolescents (Biederman et al., 2008) and adults (Rapport et al., 2001) with ADHD. In selective attention filtering tasks, such as dichotic listening tasks and visual filtering tasks, children and young adolescents with ADHD have also shown impaired attentional control (Jonkman et al., 1997; 2004; Van der Stelt et al., 2001). The typical development of inhibitory/attentional control has been associated with the development of frontal-striatal brain networks (Casey et al., 2005; Vaidya et al., 1998). Much research has focused on the atypical brain development in ADHD patients during inhibition tasks to see whether frontal and/or striatal areas show altered activation patterns. Indeed dysfunction in frontostriatal networks as well as in linked posterior areas (frontoparietal networks) is thought to underlie problems with attentional control/filtering in children or adolescents with ADHD (Bush, 2011; Dickstein, Bannon, Castellanos & Milham, 2006; Durston, 2003).

In addition to problems with attentional control, deficits in WM functioning have also been observed in ADHD patients. Worse performance on WM tasks has been observed in ADHD children compared to typically developing children (Barkley, 1997; Mariani & Barkley, 1997; Westerberg, Hirvikoski, Forssberg, & Klingberg, 2004; Martinussen et al., 2005; Rommelse et al., 2008). These WM problems are not restricted to school-aged children but continue into adolescence (Martinussen, 2005; Toplak, Jain & Tannock, 2005), and are thought to be a risk factor for lower academic achievement in adolescents with ADHD (Rogers et al., 2011). Furthermore, WM deficits have been shown to persist in adults with ADHD (Barkley et al. 1996; Clark et al., 2007; Dige et al., 2010; Hervey, Epstein & Curry, 2004; McLean et al., 2004; Schoechlin & Engel, 2005; Schweitzer, 2000). Abnormal brain activation and connectivity in ADHD patients related to impaired performance on WM tasks has been found in previous studies (Cubillo et al., 2010; Schweitzer et al., 2004; Sheridan, Hinshaw & d'Esposito, 2010; Silk et al., 2005; Valera et al., 2005; Vance et al., 2007; Wolf et al., 2009).

In line with the interactions found between attentional control and WM functioning in healthy children and adults and the overlapping brain regions involved, neural dysfunction underlying impaired performance in WM and attention tasks is also observed in similar, particularly frontal regions in ADHD patients. Decreased activation in DLPFC, ACC, and also parts of the parietal cortex has been observed during tasks requiring high levels of attentional control and WM (see Dickstein et al., 2006 for a meta-analysis). However, little attention has been paid to the developmental course of information processing in such tasks and the interactions between WM and attentional control in ADHD patients. Since it is unknown how WM capacity is influenced by selective attention deficits in adolescents and adults with ADHD, the developmental course of WM capacity and filtering efficiency in ADHD adolescents and adults is compared to age-matched control subjects in Chapter 5.

1.6 Why study cognitive functioning with event-related potentials?

Event-related potentials (ERPs) are the electrophysiological responses of the brain to task-events, for example visual stimuli displayed on a screen, and are derived from averaging parts of the electroencephalographic (EEG) recording that are time-locked to certain types of stimulus events. Electrical brain activity is measured by electrodes that are placed on a person's scalp. The EEG signal is first amplified and filtered, and after several processing steps (such as baseline correction and artifact rejection or correction) the parts of the EEG-signal that are locked to a certain event are averaged together, to derive the event-related average signal. Depending on the experimental task, in the ERP several positive or negative components can be observed that are thought to reflect synchronized postsynaptic activity of neurons following each other in time and that have their own specific topography (Luck, 2005).

In the present thesis, ERPs were chosen as a measure of brain activity for several reasons. First of all, EEG is a non-invasive method of measuring brain activity during cognitive processing. Second, ERPs can be measured in all ages, from infants to children, adolescents and adults, and is therefore an appropriate method for use in developmental studies in which brain activity of different age groups is compared. Last, ERPs can provide information about brain activity associated with cognitive functioning at a very high temporal resolution, e.g. in milliseconds. Whereas functional magnetic resonance imaging has a high spatial resolution, this and other neuroimaging methods stay behind when it comes to temporal accuracy. ERPs however can provide a continuous measure of information processing that takes place from the moment a stimulus is presented to the time the subject responds, so one can determine which (sub)stage of processing is associated with an experimental manipulation (Luck, 2005). This is especially important in determining which subprocesses are immature in children or adolescents compared to adults in higher order cognitive functions such as cognitive control or complex WM. By using ERP information, deficient performance can be subscribed to one or more substages of processing, giving more precise information about the "weakest link" in the development of a cognitive function.

Since prior ERP studies including adults and sometimes also children have already provided knowledge about ERP activity or components associated with inhibitory control and WM processing, there is a strong base to start from. This includes activity associated with covert responses (that are not measurable in behavior) such as stimulus expectation, response preparation in reaction to a cue (Van Leeuwen et al., 1998; Banaschewski et al., 2003; Bekker et al., 2004), conflict monitoring (Nieuwenhuis et al., 2003; Donkers and Van Boxtel, 2004; Kenemans et al., 2005) but also maintenance of items in WM (Ikkai, McCollough, & Vogel, 2010; McCollough, Machizawa, & Vogel, 2007; Vogel & Machizawa, 2004). Especially when examining interactions between two cognitive processes (in this thesis attentional

control and WM) previous knowledge about components and which subprocesses they reflect, helps interpreting effects of WM on attentional control and vice versa. The ERP components measured to study memory and attention in this thesis are described in more detail in paragraph 1.7.

1.7 Aims and outline of the thesis

The present thesis has several aims with the common goal to broaden the existing knowledge on the neurocognitive development of WM and attentional control processing and especially their interactions in children, adolescents and adults without and with ADHD. The specific aims in the different chapters/studies are:

- 1) To investigate whether young children (5 to 7 year-olds) with ADHD symptoms already experience problems in the attention processing and/or response inhibition domain.
- 2) To examine the effects of manipulation of verbal WM load on interference control in a conflict task in typically developing adolescents (12-16 years) and healthy adults.
- 3) To investigate whether immature visuospatial WM performance observed in adolescents can be ascribed to lower WM storage capacity and/or less efficient filtering of irrelevant task stimuli.
- 4) To examine whether adolescents and adults with ADHD have lower visuospatial WM capacity storage space and/or difficulties in filtering irrelevant information for storage in WM compared to age-matched controls.

To address these questions ERPs were measured in addition to behavioral responses to disentangle the contribution of different subprocesses to behavioral outcome. In **Chapter 2** the nature of attention problems in young children is addressed. Although rapid changes occur in executive functioning between 5 and 7 years, not much is known about the development of inhibitory/attentional control and underlying neural mechanisms in preschool-aged children with ADHD symptoms. ERPs were recorded during a cued Go/Nogo task, to measure the level of attention that children paid to the cue and to measure the level of neural activation associated with the process of inhibiting an inappropriate, pre-cued response. Covert processes such as response preparation to the cue cannot be measured overtly. Reduced P3 in response to Go-trials was expected in children with attention problems, associated with a reduced ability to allocate attentional resources for optimal task performance, as previously observed in older children with ADHD (DeFrance et al., 1996; Strandburg et al., 1996; Overtom et al., 1998). Furthermore, attenuated P2 and P3 activity in response to the cues was expected since these are thought to reflect attentional control processes, namely early attentional selection and target expectation (Banaschewski et al., 2003; Van Leeuwen et al., 1998). Such early effects could indicate whether attentional control and/or response inhibition problems predict

later psychopathology, and could serve as a better alternative to hyperactivity/impulsivity symptoms that are part of the normal behavior in younger children and therefore less accurate predictors. **Chapter 3** addresses the question of how WM capacity influences interference control, the ability to suppress irrelevant information, in older children with more developed but still immature attentional control abilities. Whereas the ability to suppress irrelevant information comes online at a younger age (a quantitative development of interference control), adolescents still show improvement in tasks measuring interference control that continues into adulthood (a qualitative development of interference control; Luna et al., 2010). While adolescents perform much better on tasks requiring interference control than younger children, they still underperform compared to adults. Adolescents especially show impairments when a task demands high levels of mental resources for attentional control and WM processing. Possibly, available resources are not sufficient yet in adolescence to keep task-goals up to date and suppress irrelevant information, leading to impaired performance, as would be predicted by Load theory (Lavie et al., 2004): When WM is loaded, distracter interference in an attention task is suggested to increase because resources necessary for goal maintenance are consumed by concurrent WM processes. This was tested through manipulation of WM load in adolescents and adults while they performed a Stroop task with face-word stimuli that evoked conflicting responses of which one had to be suppressed (measuring interference control). ERPs were used to study the influence of reduced WM capacity on two specific neural processes known to be evoked in Stroop tasks during interference control; the process of detection of the Stroop conflict, reflected by a reduced negativity for incongruent trials at approximately 450 ms after stimulus presentation (N450), and processing of response-relevant information used to guide response selection resolution, associated with enhanced positivity for incongruent trials around 600 ms (sustained positivity, SP) (Jongen & Jonkman, 2011; Lansbergen et al., 2007; Liotti et al., 2000; West, 2003; West et al., 2004). It was expected that, due to immature frontoparietal networks in adolescents, they would show a reduced ability to suppress irrelevant information compared to adults especially when little WM capacity is available, which would be in line with Load theory by Lavie et al. (2004). **Chapter 4** also addresses the development of WM and attention but in contrast focuses on the necessity of attentional control during WM processing (the encoding and maintenance of information in memory), as previously found in adults by Vogel and colleagues (2004, 2005). In this study a change detection task designed by Dr. E.K. Vogel is used in which not only load is manipulated, but also the relevance of the presented items. Since attentional control is thought to be essential when selecting only relevant items for maintenance in memory and suppressing irrelevant items, and fronto-parietal brain networks associated with attentional control are still developing throughout adolescence, it was expected that WM performance would suffer more from distracting information in adolescents than adults because they would store more irrelevant items. Contralateral delay activity (CDA) was recorded over parietal-occipital cortex during the delay interval of a WM

task to evaluate encoding and maintenance of items in memory (Vogel et al., 2004; 2005). This component increased in amplitude with the amount of items (targets or distracters) held in memory and has been used in multiple studies as a neural correlate of WM maintenance or spatial updating of stimulus information. In **Chapter 5** the same task and ERP component is used to examine the developmental course of WM and filtering efficiency (the ability to suppress encoding of distracting items for maintenance in memory) in adolescents and adults with ADHD, and to compare this to typical development. Since both WM problems and problems with attentional control have been reported previously in ADHD patients, it was examined to what extent these deficits are related to one another in behavior and brain activity, and whether WM problems in ADHD originate mainly from encoding or maintenance deficits.

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Chapter 2

Response inhibition and attention processing in 5- to 7-year-old children with and without symptoms of ADHD: An ERP study

Based on:

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Abstract

Response inhibition and attention processing in 5- to 7-year-old children with or without symptoms of attention-deficit/hyperactivity disorder (ADHD) were examined. Twelve children with ADHD symptoms and 15 control children performed a CPT-AX task. Behavioral measures of inattention and impulsivity and ERP measures of conflict monitoring and inhibition (Nogo-N2 and Nogo-P3), cue-orientation and prestimulus target expectation (Cue-P2 and P3) and response preparation (CNV) were collected. ADHD children detected fewer targets and had higher Inattention scores accompanied by reduced centro-parietal Cue- and Go-P3 activity. Occipital CNV amplitude was larger in ADHD children. At fronto-central leads, strong and comparable fronto-parietal Nogo-N2 effects were found in both groups, whereas the Nogo-P3 was only marginally significant in both groups. The attenuated Cue- and Go-P3 effects in the ADHD-symptom group are interpreted as early signs of delayed attention development, resulting in less preparation and less alertness to detect significant events. Whereas the Nogo-N2 effects were interpreted as signs of comparable levels of conflict processing in both groups, the small Nogo-P3 suggests that inhibitory processing is still immature at this age. The present study shows that specific attention problems can already be detected in the behavior and brain activity of 5- to 7-year-old children with symptoms of ADHD performing a CPT-AX task, and might be better indicators for the risk of developing ADHD than impulsivity measures.

2.1 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common psychiatric disorder in children today, affecting 3-5% of all school-aged children (DSM-IV, American Psychiatric Association, 1994). Displaying symptoms such as hyperactivity, impulsiveness and inattention, ADHD interferes with many areas of normal functioning and can severely affect normal development. For these reasons the disorder has been given much attention in recent research.

While the behavioral impairments characteristic for ADHD are well known, there's still no consensus on the underlying nature and neural basis of this disorder. Barkley (1997) suggested that the impairments seen in ADHD are due to problems of executive functioning (EF) caused by impairments in behavioral inhibition. Behavioral inhibition refers to the ability to actively suppress or interrupt an activated response, and in recent years its development has been linked to the development of a network of frontal-striatal areas in the brain (Vaidya et al., 1998; Casey et al., 2005). Since frontal areas are not yet fully developed in childhood, children often perform worse on tasks measuring executive functions, and compared to adults they recruit larger, more diffuse prefrontal regions when performing cognitive control demanding tasks (Luna and Sweeney, 2004; Casey et al., 2005; Durston and Casey, 2006). After Barkley (1997) introduced his theory, much research has been devoted to investigating the development of executive control functions such as the ability to override conflict, response preparation and inhibition and its underlying neural circuitry in children with ADHD.

A task that is often used to assess different executive processes impaired in ADHD is the so called cued-Go/Nogo task or CPT-AX task, in which subjects have to respond to a Go stimulus (e.g. the letter X) provided that it is preceded by a predefined cue stimulus (e.g. letter A), and inhibit responses on Nogo trials (letters other than X that follow the cue). Several studies have shown that children, whose behavioral inhibition functioning and cognitive control is not yet fully developed, perform worse than adults in such Go/Nogo tasks. In a recent CPT-AX study, Jonkman (2006) found that young children (age 6-7) made less hits, had higher reaction time variability, higher Inattention and Impulsivity scores and made more errors of commission than older children (age 9-10) and adults (age 20-22). Furthermore, compared to adults they responded slower. Higher reaction times in children in a Go/Nogo task were found as well by Tamm et al. (2002) and Booth et al. (2003), and additionally, in the latter study more overall errors and especially more commission errors were made by children compared to adults.

Even though at school-age attention levels and inhibitory functioning are still immature in typically developing children, worse behavioral performance has already been reported at this stage in ADHD children. For example, larger and more variable reaction times (Banaschewski et al., 2003, 2004; Fallgatter et al., 2004; Wiersema et al., 2006a) were repeatedly found in cued Go/Nogo tasks in ADHD

children between the age of 8-14 years, indicating problems to sustain attention over extended periods of time, a process that has been related to frontal lobe functioning (Stuss et al., 2003; Bellgrove et al., 2004). Furthermore, ADHD children have been found to make more false alarm (Nogo) errors than healthy children (Yong-Liang et al., 2000; Durston et al., 2003; for an exception, see: Wiersema et al., 2006a) which suggests a deficit in inhibitory functioning.

By measuring event-related brain potentials (ERPs) additional to behavioral measures in the CPT-AX task, it is possible to further specify which subprocesses are involved in deficient performance in such tasks. For example, the measurement of ERPs in the CPTAX task provides the opportunity to study executive processes that do not require an overt response such as stimulus expectation and response preparation that appear in reaction to the cue (the letter A) and processes like conflict monitoring and response inhibition in reaction to the Nogo stimulus.

ERP components that have been associated with conflict monitoring and response inhibition are the Nogo-N2 and the Nogo-P3. The Nogo-N2 is reflected by an enhanced negativity at fronto-central scalp locations in response to Nogo stimuli (relative to Go stimuli) that is seen whenever there is a conflict between the prepotent response and the currently required response. In source localization studies, the source of the Nogo-N2 has been located in the Anterior Cingulate Cortex (ACC) in healthy adults (Nieuwenhuis et al., 2003; Bekker et al., 2004) and 6- to 10-year-old children (Jonkman et al., 2007). Whereas the debate on the exact functional significance of the Nogo-N2 is still proceeding (Smith et al., 2007), there is a fair amount of studies linking the Nogo-N2 to the process of conflict monitoring (Nieuwenhuis et al., 2003; Donkers and Van Boxtel, 2004; Kenemans et al., 2005). The Nogo-N2 is followed in time by a frontal-centrally distributed Nogo-P3 positivity (relative to the Go condition) that is demonstrated in adults (Bokura et al., 2001; Bruin et al., 2001; Bekker et al., 2004; Donkers and Van Boxtel, 2004; Smith et al., 2007) and healthy 7- to 12-year-old children (Dimoska et al., 2003; Johnstone et al., 2005, 2007; Jonkman, 2006).

Whereas there has been debate concerning the functional interpretation of the Nogo-P3, multiple older and more recent studies have related the Nogo-P3 to the process of response inhibition (Karlin et al., 1969; Roberts et al., 1994; Bruin et al., 2001; Bekker et al., 2004; Donkers and Van Boxtel, 2004; Jonkman, 2006). Bruin et al. (2001) for example showed that the Nogo-P3 amplitude was enhanced when responses were more strongly primed, thus requiring stronger inhibition. In Bekker et al. (2004), the level of response preparation (CNV amplitude) in the cue target interval appeared to be associated with Nogo-P3 amplitude. Interpretations of the Nogo-P3 relating to overlapping motor responses (instead of inhibition) have been refuted by research demonstrating that a Nogo-P3 still occurred in paradigms where no motor response was required (targets were counted mentally) as well as in paradigms in which Go and Nogo trials were not preceded by a cue (Pfefferbaum et al., 1985). Finally, Go-P3 activity is defined by enhanced positivity in the Go (vs. Nogo) condition at centro-parietal electrode sites and has on the basis of a long

history of experimental work, been associated with processes such as updating of task-relevant information (Donchin and Coles, 1988) and attention or resource allocation (Israel et al., 1980). In the CPT-AX task enhanced Go-P3 effects have been reported in children when compared to adults (a.o. Davis et al., 2003; Jonkman et al., 2003).

Besides Nogo-N2 and P3, the cued-CPT task also permits to study preparation processes of cue-orientation and response preparation in reaction to a cue-stimulus. Fronto-central Cue-P2 and centro-parietal Cue-P3 that occur first in range as a reaction to the cue stimulus are thought to reflect processes of cue-orientation, and prestimulus target expectation (Van Leeuwen et al., 1998; Banaschewski et al., 2003; Bekker et al., 2004). The more broadly distributed contingent negative variation (CNV) subsequently seen in reaction to cues is thought to be related to response preparation processes (Rohrbaugh and Gaillard, 1983; McCallum, 1988).

Whereas several developmental studies reported the presence of Nogo-N2 and Nogo-P3 in healthy 8- to 12-year-old children (Johnstone et al., 2007; Jonkman et al., 2003), recently strong trends in the development of Nogo-N2 and P3 were reported in children between age 6 and 10 by Jonkman (2006). In healthy 6- to 7-year olds, the Nogo-N2 was larger and had a more diffuse topography across frontal-parietal electrodes compared to 9- to 10-year-old children and adults and the fronto-central Nogo-P3 was absent at this young age. The lack of a Nogo-P3 at this age was interpreted as immature response inhibition processing in early childhood. With respect to cue processing, it was shown that the enhancement of the P2 in response to task-relevant cues (letter A) as compared to task-irrelevant cues was already present in early childhood (Jonkman, 2006). These results were interpreted as suggesting that cue-orientation or early selection processes might be fully matured in 6- to 7-year olds. In contrast, differences between adults and children were found for the Cue-P3 effect. Higher Cue-P3 effects (Cue > Nocue) were observed in children at occipital leads. Based on earlier suggested links between Cue-P3 and the process of Go-expectation in similar paradigms (Van Leeuwen et al., 1998; Banaschewski et al., 2003; Bekker et al., 2004), these results were interpreted as showing higher Go-expectation in children. Furthermore, reduced CNV amplitudes were observed in children and this was explained by immaturity of frontal-parietal networks which are involved in response preparation processing.

Several studies have investigated EF in ADHD children in a Go/Nogo task paradigm using ERP measures, but all these studies included children between 7- and 14-years old that were already diagnosed with ADHD. Concerning the Nogo-N2, most studies have found similar N2 activity in ADHD children as in their typically developing peers. For example, in children between 7- and 14-years old, Banaschewski et al. (2004), Fallgatter et al. (2004) and Wiersema et al. (2006a) found no differences in Nogo-N2 activity between an ADHD and a control group, indicating normal conflict monitoring in ADHD. Nogo-P3 activity in the CPT-AX task has also shown harmonious results, consisting of attenuated Nogo-P3 amplitudes and diminished anteriorization in ADHD (Brandeis et al., 2002; Fallgatter

et al., 2004, 2005; Wiersema et al., 2006a,b), suggesting problems of inhibition might be present in ADHD adults as well as in children between 7- and 14-years old. The parietal Go-P3 has been previously found to be reduced in ADHD children in middle and late childhood in the CPT-task, and this was interpreted as suggesting they have difficulties in updating task-relevant information (Overtoom et al., 1998). In two clinical studies including ADHD children between 7- and 14-years old, significantly reduced field power of Cue-P2/P3 has been reported. This reduced P2/P3 activity was interpreted as either impaired orienting (Van Leeuwen et al., 1998) or suboptimal energetical state regulation (Banaschewski et al., 2003, 2004) in the cue-target interval, causing these children to be less prepared/attentive for the upcoming task or stimulus event. The CNV, also seen in reaction to a cue, is in most studies reported to be smaller in ADHD children (Dumais-Huber and Rothenberger, 1992; Banaschewski et al., 2003), indicating less response preparation.

The above review shows that whereas performance and ERPs in the CPT-AX task have been studied multiple times in ADHD children in middle and late childhood, not much is known about the normal and deviant development of Go/Nogo performance and ERPs in younger children. The necessity of completing this knowledge is shown by several studies using Go/Nogo tasks indicating that precisely the period from 3 to 7 years is one of very rapid change in EF and motor control (Livesey and Morgan, 1991; Dowsett and Livesey, 2000; Carlson and Moses, 2001). Also, in a recent study, Livesey et al. (2006) reported a moderate significant correlation between accuracy on the day-night task (measuring cognitive inhibition) and externalizing behavior in 5- to 6-year-old children. Moreover, as mentioned earlier, Jonkman (2006) reported several developmental changes in ERP activity associated with executive control in the CPT-AX task in healthy 6- to 7 year olds. Surprisingly however, to our knowledge, no ERP studies examining cognitive control have been performed in ADHD children below the age of 7. To fill this gap, the present study compared the ERPs and behavior of a group of 5- to 7-year-old healthy children with that of a group of children with ADHD symptoms derived from the community sample.

Taken in consideration that symptoms of ADHD are already seen in children from age 3 to 7 (Kadesjö et al., 2001; Döpfner et al., 2004) it was expected that the ADHD children would perform worse on behavioral measures of attention and inhibition compared to typically developing children. Previously found Nogo-N2 effects in ADHD have for the greater part shown similar activity for ADHD and control children, so no differences in Nogo-N2 activity were expected in the present study. Significant Nogo-P3 activity was not present in 6- to 7-year olds in the study by Jonkman (2006), and was therefore not expected to be found in 5- to 7-year olds. In contrast, reduced Go-P3 effects (Go > Nogo) in children with ADHD aged above seven were reported by several other CPT studies (DeFrance et al., 1996; Strandburg et al., 1996; Overtoom et al., 1998) and was therefore also expected in the present study. Cue-P2 as well as Cue-P3 effects were hypothesized to be attenuated in children with ADHD symptoms based on previous studies showing attention deficits

in cue processing in older ADHD children. No clear hypotheses could be formulated for CNV activity because of inconsistencies in previous studies.

2.2 Methods

Subjects

Originally, 29 subjects participated in the study (16 controls and 13 ADHD), of which two were excluded during statistical analysis due to significant outliers in behavioral measures (1 in the Control group and 1 in the ADHD group). The 15 children in the Control group (4 boys and 11 girls) were recruited from two different elementary schools. The 12 children in the group with ADHD characteristics (10 boys and 2 girls) were recruited via advertisements in local newspapers and on the internet. Subjects were divided in two groups based primarily on scores derived from the Child Behavior Checklist (CBCL; Achenbach, 1991) that was filled out by the parents in both groups. The CBCL is an instrument used for detection of externalizing and internalizing behavioral and attention problems. The ADHD group consisted of children that scored in the clinical range (T-score > 63) on internalizing (I), externalizing (E), total problem (T) and attention problem (A) subscales of the CBCL. Kim et al. (2005) showed that a T-score of 60 or higher at the Attention Problems subscale of the CBCL resulted in a reasonable level of sensitivity (0.72) or positive predictive value (0.75) in the diagnosis of ADHD. The Control group consisted of children that scored in the non-clinical range on all four scales. For mean group T-scores on the different CBCL scales, see Table 1. To further confirm the presence of hyperactive/impulsive symptoms, the parents and teachers of the children in the ADHD-symptom group additionally were administered the 10-item Conners Abbreviated Parent-Teacher Questionnaire (Conners, 1973) via a telephone interview. The Conners ratings of four teachers are missing because of non-compliance, but all other ratings were well above the clinical cut-off score of 15 (max. score is 30) on both lists (parent-ratings: range = 24-30, M = 26.6, SD = 1.7; teacher-ratings: range = 16-26, M = 20.7, SD = 3.4). All children were free of other neurological or somatic health problems.

Mean age was 7.2 (SD 0.5) in the Control group and 6.8 (SD 0.9) in the ADHD group. The groups did not differ significantly in age ($p = .14$). To check for IQ, subjects were administered the Raven IQ test (Raven et al., 1983). In the Control group, IQ scores of five children are missing due to an administration error, but there were no indications of academic problems in these children as indicated by the CBCL. Of the remaining eleven 6- to 7-year old all but one in the Control group scored at or above the 50th percentile of the norm population, except for one scoring in the 25th percentile (M = 75th percentile, SD = 20.9, range 25-95th percentile). In the ADHD group 11 of the 12 children scored at or above the 50th percentile (M = 75th

percentile, $SD = 22.9$, range 25-95th percentile). IQ did not significantly differ between the two groups ($p = .74$). Furthermore, parents' educational level was determined and did not differ between the groups. On a 1-4 (low-high education) scale, the Control group scored 2.7 (.94) and the ADHD group 3.0 (.75) (Group effect $F(1,25) = .43$, $p = .82$). The present study was approved by the Local Ethical Committee, and prior to the study a written informed consent was obtained from the caretakers of all children according to the Declaration of Helsinki.

Table 1. Group means of t-scores on CBCL internalizing (I), externalizing (E), attention (A) and total problem (T) subscales (SD between brackets) in children.

	CBCL-I	CBCL-E	CBCL-A	CBCL-T
Control	49.7 (6.5) range: 39-61	48.0 (8.8) range: 33-61	52.7 (3.7) range: 50-61	47.1 (9.2) range: 26-59
ADHD	63.3 (5.5) range: 52-71	72.7 (6.2) range: 64-88	73.5 (4.8) range: 68-85	70.7 (3.6) range: 67-81

Procedure

The entire experimental session lasted 2-2.5 h. The session started with the attachment of the electrodes. During electrode attachment children watched cartoons. During the experimental session all children sat in front of a 17-in. VGA monitor with their eyes aligned to the centre of the screen at a distance of approximately 50 cm. The participants were instructed to minimize eye blinks and refrain from making movements during task performance. The experimental session started when all tasks were practiced until a predetermined performance criterion (80% correct detections and less than 10% false alarms) was reached. On demand, some parents sat behind their children during the experiment. After completion of the experimental session, the children were rewarded with a present (a toy).

CPT-AX task

The CPT-AX task consisted of a sequence of 11 different letters (A, B, C, D, E, F, G, H, J, L and X). The letters were white and were presented one by one between two vertical bars at the centre of the screen on a black background. The vertical bars and the letters had a height of 2 cm and letters had a width of 1.5 cm. Subjects were instructed to press a button with their right hand when the letter X appeared, but only when it was preceded by the letter A (A-X sequence, Go condition). When an A was followed by another letter, the prepared response had to be inhibited (A-not-X, Nogo condition). The task was administered in four separate blocks of 124 trials each, including 24 X and 24 A stimuli (of which 12 As and 12 Xs were part of the A-X (Go) sequence, 12 As were part of A not- X (Nogo) sequence and 12 Xs were presented alone, without a preceding A). Thus, the occurrence of Go and Nogo trials was

equiprobable (10% of all presentations). Total probability of As and Xs was comparable (20%), since As were presented in both Go and Nogo sequences and Xs were presented in Go sequences and alone. The remaining 76 trials consisted of 6 trials of the remaining letters (48 trials), with the exception of the letter H, which was presented 28 times to keep the probability (23%) comparable to that of the letters A and X. A total trial lasted 1650 ms, with a stimulus duration of 150 ms and a fixed interstimulus-interval (ISI) of 1500 ms. Before the start of the experimental session, the task was practiced (each subject received 25 practice trials) and all subjects scored at or above 80% correct responses and had less than 10% false alarms during the practice session.

Electrophysiological recording

For measurement of the EEG, an electro-cap consisting of 30 tin electrodes [Fp1, Fp2, F7, F3, Fz, F4, F8, FT7, FC3, FCz, FC4, FT8, T7, C3, Cz, C4, T8, Tp7, Cp3, CPz, CP4, TP8, T5, P3, Pz, P4, T6, O1, Oz, O2; nomenclature according to American Electroencephalographic Society (1991)] was used. All electrodes were referenced to the left mastoid and one of the electrodes in the electro-cap (FPz) was used as ground. The vertical EOG was recorded from infraorbital and supraorbital tin electrodes placed in line with the pupil of the left eye. For measurement of the horizontal EOG, two tin electrodes were attached to the outer canthi of both eyes. All electrode impedances were kept below 5 k Ω , with exception of EOG electrodes that were held below 18 k Ω . Signal acquisition was accomplished using Neuroscan synamps amplifiers and Neuroscan software (version 4.1). EEG and EOG signals were continuously sampled at 250 Hz and digitally filtered online with a high-pass filter of 0.05 Hz and a low-pass filter of 50 Hz.

Data analysis

Behavioral measures

Performance measures in the CPT-AX task included percentage of correct Go responses, mean reaction times to correctly detected Go stimuli, Go-reaction time variability, and percentage of false alarms. Furthermore, Impulsivity scores and Inattention scores were computed according to Halperin et al. (1988) and Overtom et al. (1998). The Impulsivity score was calculated as the sum of fast A-not-X errors (defined as a response to the letter following the A with an RT faster than the mean hit RT of a subject in the task) and slow A-only errors (premature responses to the A with RTs longer than 1250 ms) divided by the total number of A-X (Go) and A-not-X (Nogo) trials (144 trials). The Inattention score was computed as the sum of the total number of misses (no response to Go trial) and number of slow X-only errors (response to X not preceded by A with an RT higher than the mean hit RT of the subject in the task) divided by the total number of Go and X-only trials (96 trials).

Finally, a signal detection analysis was performed on the behavioral data to be able to dissociate sensory sensitivity from response bias. Since the distribution of false alarms was skewed, we performed a non-parametric signal detection analysis (see Boice and Gardner, 1988) on the sensitivity (A') and response bias (B') parameters.

EEG and ERP data

The continuous EEG was divided into 496 epochs of 1850 ms, from 200 ms prestimulus to 1650 poststimulus, all aligned to a baseline from -200 to 0 ms preceding the stimulus. First, vertical EOG artifacts (blinks) were removed from the data by applying an eye-movement correction algorithm (Semlitsch et al., 1986) provided in the Neuroscan analysis software package. Instead of using automatic procedure, for the computation of regression coefficient between VEOG and the EEG-signals at the different electrodes, adequate eye blinks were manually selected and checked. After having removed eye blinks from the EEG via the above described procedure, epochs containing artifacts or horizontal eye movements exceeding ± 100 μV were rejected from the database. Because of the presence of relatively enhanced high-amplitude, low frequency signals in five control and all ADHD subjects, in these groups a higher criterion of 120-125 μV was used. After running this artifact rejection procedure, accepted trials were manually checked for the presence of horizontal EOG or movement artifacts. The number of trials included in the averages of both groups is given below and was comparable. Next, average ERPs were computed separately for each subject in four different stimulus conditions: (1) Go trials (ERP to Xs preceded by A), (2) Nogo trials (ERPs to not-X letters following A), (3) Cue trials (ERPs to letters A summed over A-X and A-not-X categories) and (4) Nocue trials in which single letters were presented (B, C, D, E, F, G, J, L) that did not precede or follow an A or X. In the averaging procedure, only trials with correct responses (Go) or correctly rejected trials (Nogo, Cue and Nocue) were included. There was a maximum amount of 48 trials in the Go and Nogo conditions. In the Control group, the amount of artifact-free EEG epochs contained in the single-subject averages ranged from 19 to 45 trials in the Go condition (group mean = 30.13 trials, SD 8.6) and 23-46 trials in the Nogo condition (group mean = 36.5 trials, SD 7.5). In the ADHD group, included trials ranged from 20 to 42 trials (group mean = 30.2 trials, SD 6.6) in the Go condition and 26-47 trials in the Nogo condition (group mean = 35.5 trials, SD 5.6). In the Cue and Nocue conditions, all single-subject averages contained more than 53 trials; the maximum number of A and other letter trials was, respectively, 96 trials and 208 trials.

For the Nogo-N2 and P3 ERP analyses, mean area amplitudes at Fz and FCz (Nogo-N2 and Nogo-P3), and Cz and Pz (Go-P3) were computed in 20 ms time segments running from 120 to 580 ms. Cue-P2 and Cue-P3 analyses were performed by computing mean amplitudes at Fz and Cz, Pz and Oz in Cue and Nocue ERPs in, respectively, 20 ms and 50 ms segments within a time window running from 120 to 340 ms for P2 and from 250 to 850 ms for P3. For the CNV, mean area amplitude was

determined at Fz, Cz, Pz and Oz electrodes in one broader window from 1300 to 1650 ms in all subjects. Because of latency differences between the groups, it was first determined on the basis of group means at the relevant leads in which time segments the different ERP components were maximal. These time windows can be found in the results section. Next, mean amplitudes in the relevant windows and at relevant leads were entered in the statistical analyses.

Statistical Analysis

Behavioral Measures

For all behavioral measures in the CPT task (% hits, mean Go-RT, Go-RT variability, % false alarms, Inattention and Impulsivity scores, A' and B'), group effects were tested by performing independent sample t-tests. Equality of variances was tested with Levene's test and, if necessary, corrections for inequality were performed and accompanying t and p values reported. Two-tailed significance levels of 5% were adopted.

ERP Measures

To test whether there are developmental differences in cue-orientation, Go-expectation, response preparation (Cue/Nocue comparison) and conflict monitoring and response inhibition (Go/Nogo comparison), repeated measures analyses of variance were performed for Cue-P2, Cue-P3, CNV, Nogo-N2, Nogo-P3 and Go-P3, respectively, at the leads where the different waves are known to be most prominent (based on the literature).

For both the Nogo-N2 and Nogo-P3 analysis, a 2 x 2 x 2 repeated measures analysis of variance was performed, including the within factors Leads (Fz, FCz) and Stimulustype (Go, Nogo) and the between factor Group (Control, ADHD). Furthermore, a 2 x 2 x 2 repeated measures ANOVA was performed for the Go-P3 analysis, including the within factors Leads (Cz, Pz) and Stimulustype (Go, Nogo) and the between factor Group (Control, ADHD). For the Cue-P2 analysis a 2 x 2 repeated measures ANOVA with the within factor Cuetype (Cue, Nocue) and between factor Group (Control, ADHD) was performed at the Fz electrode. Cue-P3 was analyzed by a 2 x 2 x 2 repeated measures ANOVA including the within factor Leads (Cz, Pz, Oz) and Cuetype (Cue, Nocue) and between factor Group (Control, ADHD). CNV was analyzed in the same way as Cue-P3, but for the Leads Fz, Cz, Pz and Oz. On all repeated measures analyses of variance $p < 0.05$ (two-sided) was applied. A portion of the control data has been presented elsewhere in a paper examining the typical development of ERP signatures of attention and inhibition in the CPT-AX task (Jonkman, 2006).

Correlations

Correlations between the electrophysiological measures for which Group differences were found and behavioral data were calculated by means of Pearson correlation coefficients (r). Furthermore, to gather information about links between symptoms of internalizing, externalizing and attention problems as measured by the CBCL and attention or impulsivity related behavior in the CPT-AX task, Pearson correlations were calculated also between these measures (whole group data).

2.3 Results

Behavioral results

Mean percentages and SDs of hits (correct Go responses), mean RT to Go stimuli (Go-RT), Go-RT variability (differences in standard deviations of RT), Inattention scores, Impulsivity scores, total amount of false alarms (%) and non-parametric signal detection parameters A' and B' in the ADHD and control children are presented in Table 2. Significant group effects appeared for % hits ($F(1,25) = 4.6, p = .04$) and Inattention score ($F(1,25) = 5.6, p = .03$). No behavioral differences between the ADHD group and the Control group were found for the other behavioral measures (Group effects: Go-RT: $p = .60$; Variability Go-RT: $p = .44$; Impulsivity score: $p = .81$; A-not-X FA: $p = .45$). Non-parametric analyses did not change results.

Table 2. Group means (standard deviations between brackets) of the behavioral parameters in the CPT-AX task, arranged in order of attention and impulsivity measures.

	Attention measures			Impulsivity measures			Signal detection	
	Hits (%)	Go-RT (ms)	Variability Go-RT (ms)	Inattention score (%)	Impulsivity score (%)	A-not-X FA (%)	A'	B'
Control	90 (8)	536 (83)	152 (35)	5.1 (4.0)	0.7 (0.9)	2.0 (2.6)	0.97 (0.02)	1.2 (0.25)
ADHD	81 (14)	553 (82)	142 (30)	10.1 (6.7)	0.6 (0.7)	2.8 (3.0)	0.94 (0.35)	1.7 (0.20)

RT = reaction time; A-not-X FA = total amount of false alarms to Nogo stimuli.

NB: Grey fields indicate significant Group effects; compared to controls ADHD children had fewer hits, higher Inattention scores and a lower sensitivity for detection of the target stimulus.

Furthermore, to be able to distinguish between sensitivity and response bias, non-parametric signal detection analysis was performed and revealed that ADHD children had a lower sensitivity for detection of the target stimulus ($t(25) = -2.13, p <$

.05); A' was .94 (SD 0.35) and .97 (SD 0.02) in ADHD and Control groups, respectively. The groups did not differ significantly in response bias ($t(25) = -.039$, $p < .96$, that was .87 (SD 0.20 and 0.25)) in both ADHD and Control groups.

ERP results

Go-Nogo analyses

Grand average ERP waves in the ADHD and Control group in Go and Nogo conditions at Fz, FCz, Cz and Pz are depicted in Figure 1. Mean Go/Nogo-N2 and P3 area amplitudes and SDs at Fz and FCz and Mean Go/Nogo-P3 area amplitudes and SDs at Cz and Pz in predetermined time windows for the separate groups are shown in Table 3. Topographic maps of N2 and P3 in Go and Nogo conditions are presented in Figure 2.

Nogo-N2 effects

Nogo-N2 activity was maximal between 320 and 360 ms in the control group and between 340 and 380 ms in the ADHD group (Go/Nogo effects were significant in these windows with $p < .001$ at both Fz and FCz). Mean amplitudes in the above mentioned time windows were entered in a repeated measures analysis of variance to test for Leads (Fz, FCz) \times Stimulustype (Go, Nogo) \times Group (Control, ADHD). A 2-way interaction was found for Leads \times Stimulustype ($F(1,25) = 5.2$, $p < .05$), but no differences between the groups were found. The topographic maps show enhanced negativity in the Nogo condition (compared to Go) across fronto-central and parietal electrodes in both groups (see Figure 2). The more widely distributed Nogo activity across parietal electrodes in both groups is in agreement with topographies reported in an earlier developmental paper in typically developing children aged 6-7 years (Jonkman, 2006).

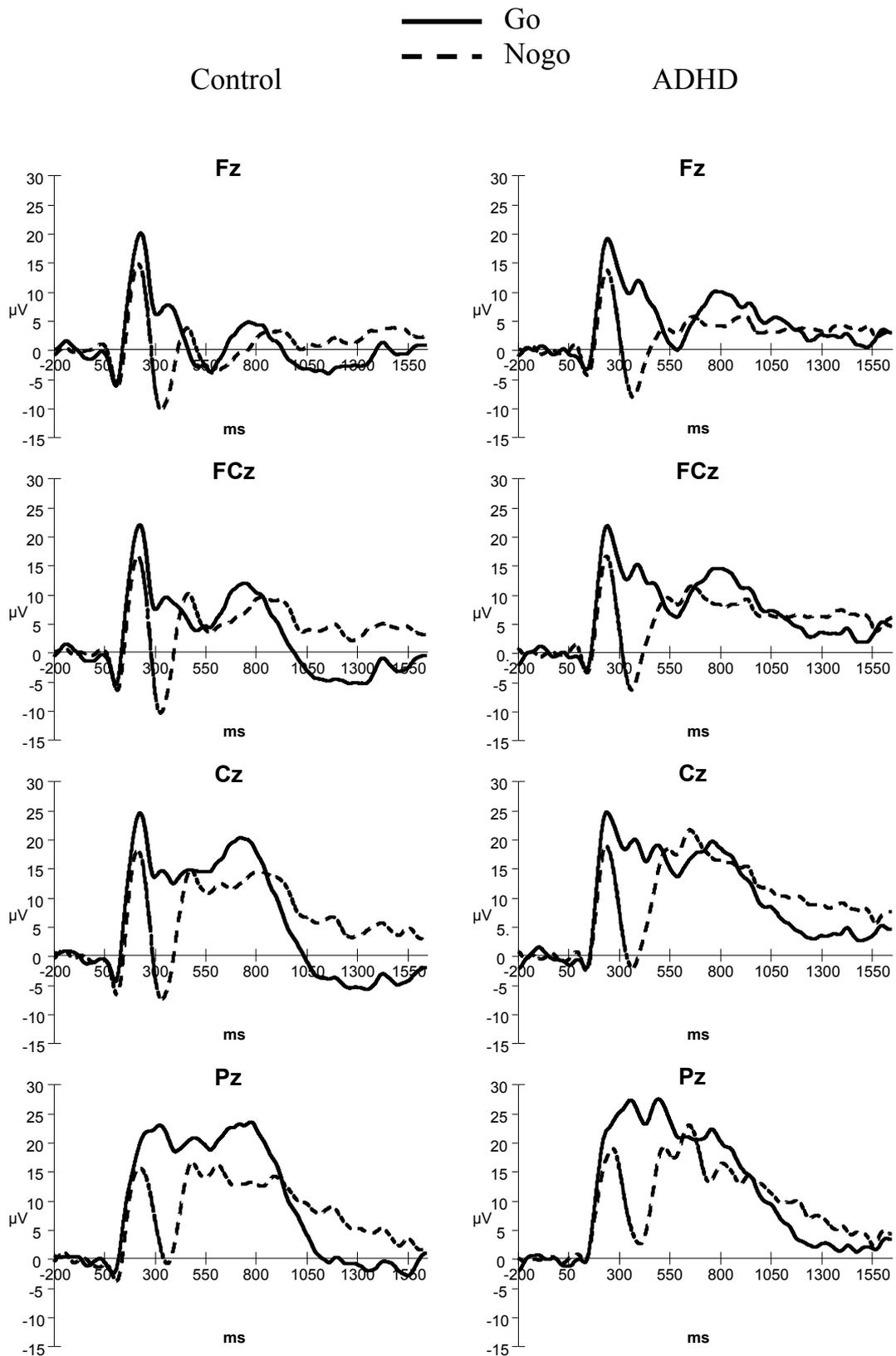


Figure 1. Grand average ERPs of control and ADHD children in Go and Nogo conditions at four midline leads (Fz, FCz, Cz and Pz).

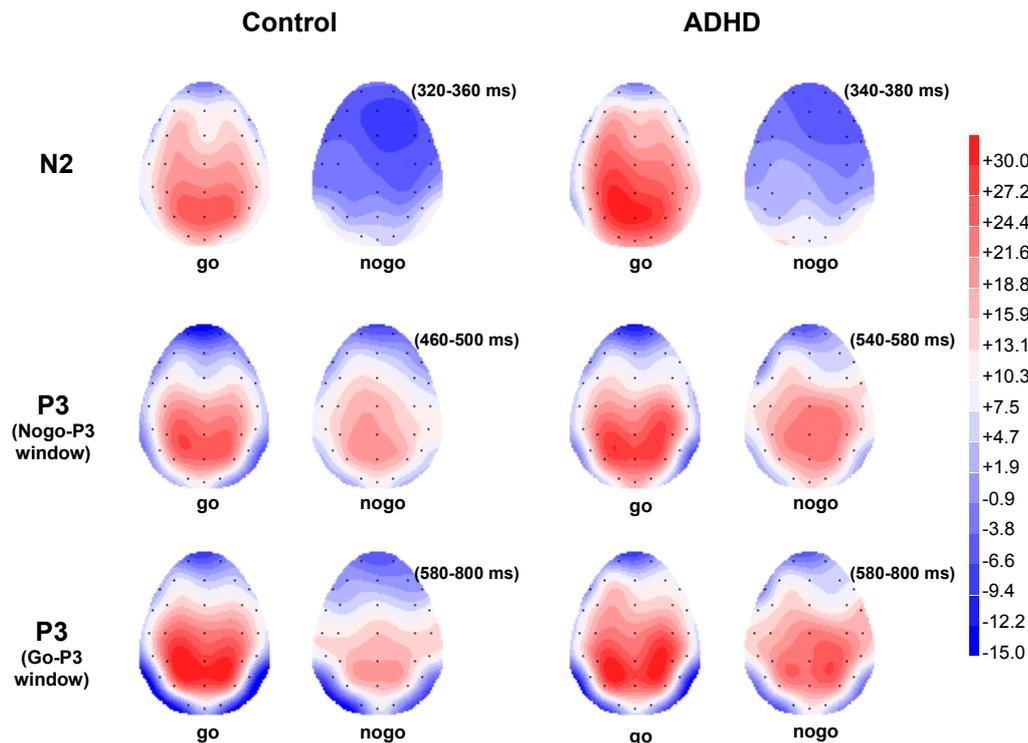


Figure 2. Topographic maps of control and ADHD children in Go/Nogo conditions across 30 electrodes. The maps are based on mean amplitudes in the time segments in which amplitudes were maximal in the different groups (see Table 3).

Nogo-P3 effects

The Grand average plots were indicative of the presence of small Nogo-P3 activity between 460 and 500 ms in the healthy group and between 540 and 580 ms in the ADHD group (see Figure 1). The analyses did however only reveal a marginally significant Stimulustype effect ($F(1,25) = 4.0, p = .06$), but no group effects, indicating very little Nogo-P3 activity was present at Fz and FCz in both groups. The absence of fronto-central Nogo-P3 activity (defined as larger positivity in Nogo vs. Go condition at these locations) can also be seen in the topographic maps of both Control and ADHD children, only showing parietal P3b activity (enhanced positivity in Go vs. Nogo condition) (see Figure 2).

Go-P3 effects

Go-P3 activity at Cz and Pz was present between 580 and 800 ms in both groups as can be seen in the Grand average plots (Figure 1). A repeated measures analysis revealed a significant Leads (Cz, Pz) \times Stimulustype (Go, Nogo) interaction ($F(1,25) = 9.7, p < .01$). Further testing revealed a Stimulustype \times Group interaction at Cz ($F(1,25) = 4.3, p < .05$), due to a significant Stimulustype effect for the Control group ($F(1,14) = 8.4, p < .05$) which was absent in the ADHD group ($p = .65$). At Pz, a main

Stimulustype effect showed an enhanced Go-P3 ($p < .01$) in both groups, but no difference between the groups was found. The topographic maps in Figure 2 show a normal and comparable Go-P3 distribution (enhanced positivity in Go vs. Nogo condition) across centro-parietal electrodes in both groups. Control children had larger central Go than Nogo-P3 activity, which was not the case in the ADHD group (Figure 2).

Table 3. Mean area amplitudes in μV (standard deviations between brackets) in the time windows in which Nogo-N2 and Nogo-P3 at Fz and FCz and Go-P3 at Cz and Pz were maximal (analyses windows indicated per group in first column) in Go and Nogo conditions.

	Fz		FCz	
	Go	Nogo	Go	Nogo
<i>Nogo-N2</i>				
Control (320-360ms)	7.3 (8.6)	-9.5 (10.2)	9.4 (11.1)	-9.2 (11.8)
ADHD (340-380ms)	10.5 (7.7)	-7.6 (8.6)	14.0 (6.9)	-5.8 (9.5)
<i>Nogo-P3</i>				
Control (460-500ms)	-1.5 (10.3)	2.5 (8.9)	4.6 (11.6)	9.4 (10.2)
ADHD (540-580ms)	0.7 (10.0)	3.2 (7.4)	6.6 (11.1)	9.1 (8.5)
	Cz		Pz	
	Go	Nogo	Go	Nogo
<i>Go-P3</i>				
Control (580-800ms)	18.7 (9.0)	12.7 (6.7)	22.3 (8.7)	14.0 (7.1)
ADHD (580-800ms)	17.5 (10.2)	19.0 (9.8)	21.2 (11.7)	18.2 (8.3)

Grey fields indicate significant Group x Go/Nogo interactions; compared to controls ADHD children showed no significant Go-P3 effect at Cz.

Cue-Nocue analyses

The grand average ERP waves of the ADHD and Control group in Cue and Nocue conditions at Fz, Cz, Pz and Oz are presented in Figure 3. The mean amplitude and SD of the P2, P3 and CNV in Cue and Nocue conditions in the different time windows and groups are presented in Table 4. Topographic maps of P2, P3 and CNV in Cue and Nocue conditions are presented in Figure 4.

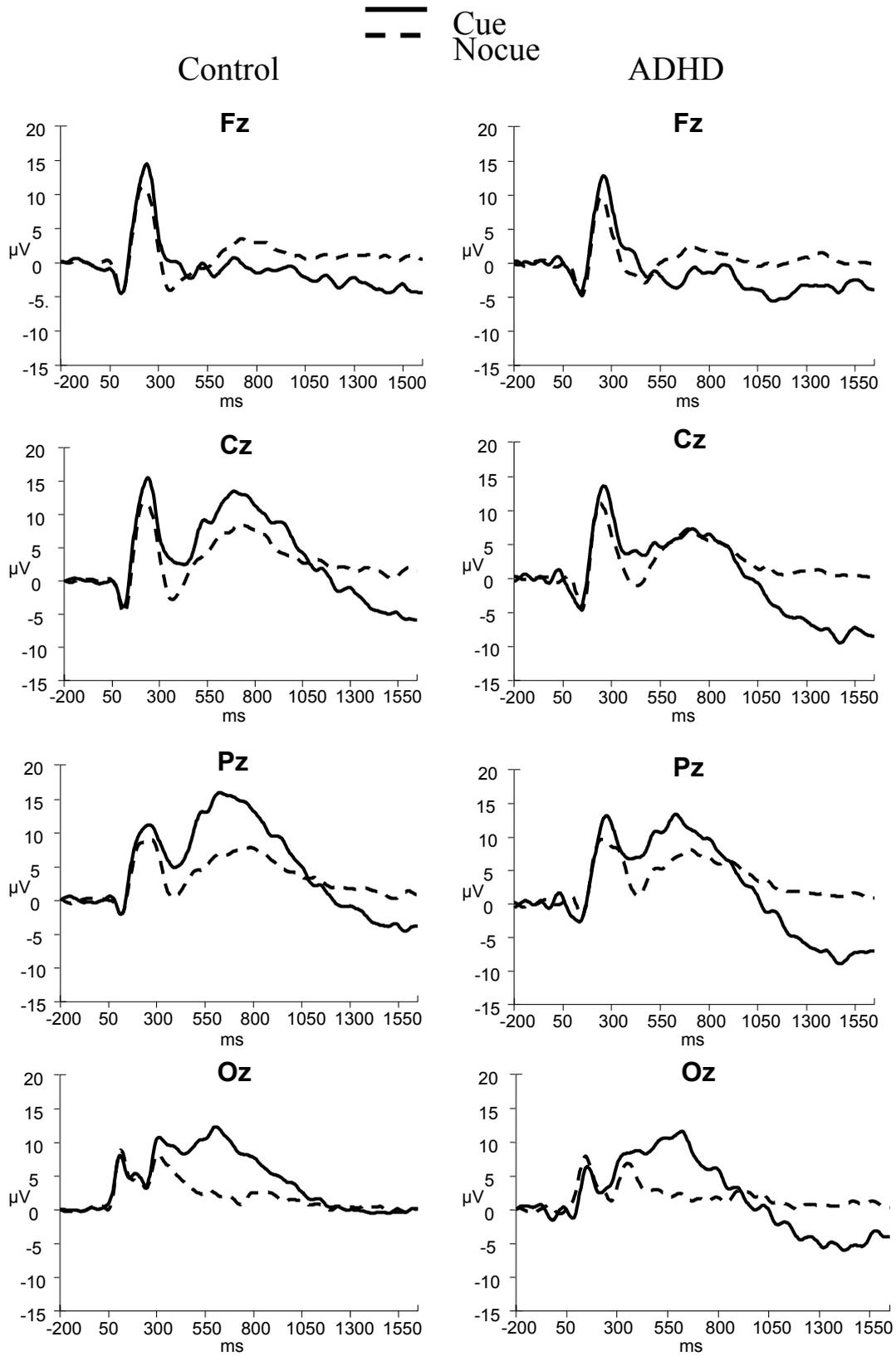


Figure 3. Grand average ERPs of control and ADHD children in Cue and Nocue conditions at Fz, Cz, Pz and Oz leads.

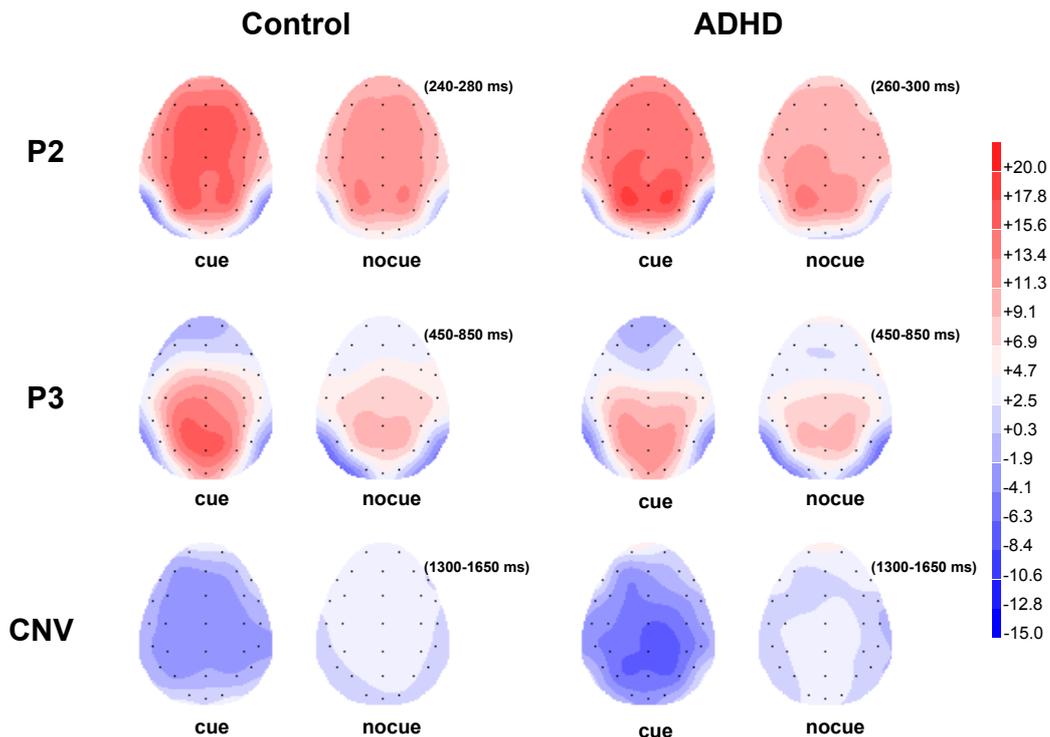


Figure 4. Topographic maps of control and ADHD children in Cue/Nocue conditions across 30 electrodes. The maps are based on mean amplitudes in the time segments in which amplitudes were maximal in the different groups (see Table 4).

Cue-P2 effects

The topographic maps show a similar frontal distribution of the Cue-P2 (enhanced positivity in response to cues vs. no-cues) in both groups (see Figure 4). Cue-P2 enhancement was present in both groups and was statistically largest between 240 and 280 ms in the Control group, and between 260 and 300 ms in the ADHD group ($p < 0.0001$ in Control group and $p < .001$ in ADHD group; see Figure 3). The analysis on activity in these windows showed a main effect of Cuetype ($F(1,25) = 42.9, p < .00001$), but no interaction with Group.

Cue-P3 effects

Parietal P3 effects (Cue > Nocue) were largest between 450-850 ms in both groups (Control group $p < .001$; ADHD group $p < .05$; see Figure 3) and Figure 4 shows comparable centro-parietal distributions of the Cue-P3 in both groups. Repeated measures analyses including mean amplitude in these windows showed there was a Leads \times Cuetype interaction ($F(1,25) = 23.6, p < .00001$). Further testing at the separate leads revealed a significant Cuetype \times Group interaction at Cz ($F(1,25) = 5.0, p < .05$) and Pz ($F(1,25) = 4.6, p < .05$). At Oz, only a significant Cuetype effect was found ($p < .00001$). The interaction effect at Cz was caused by a significant Cuetype effect in the

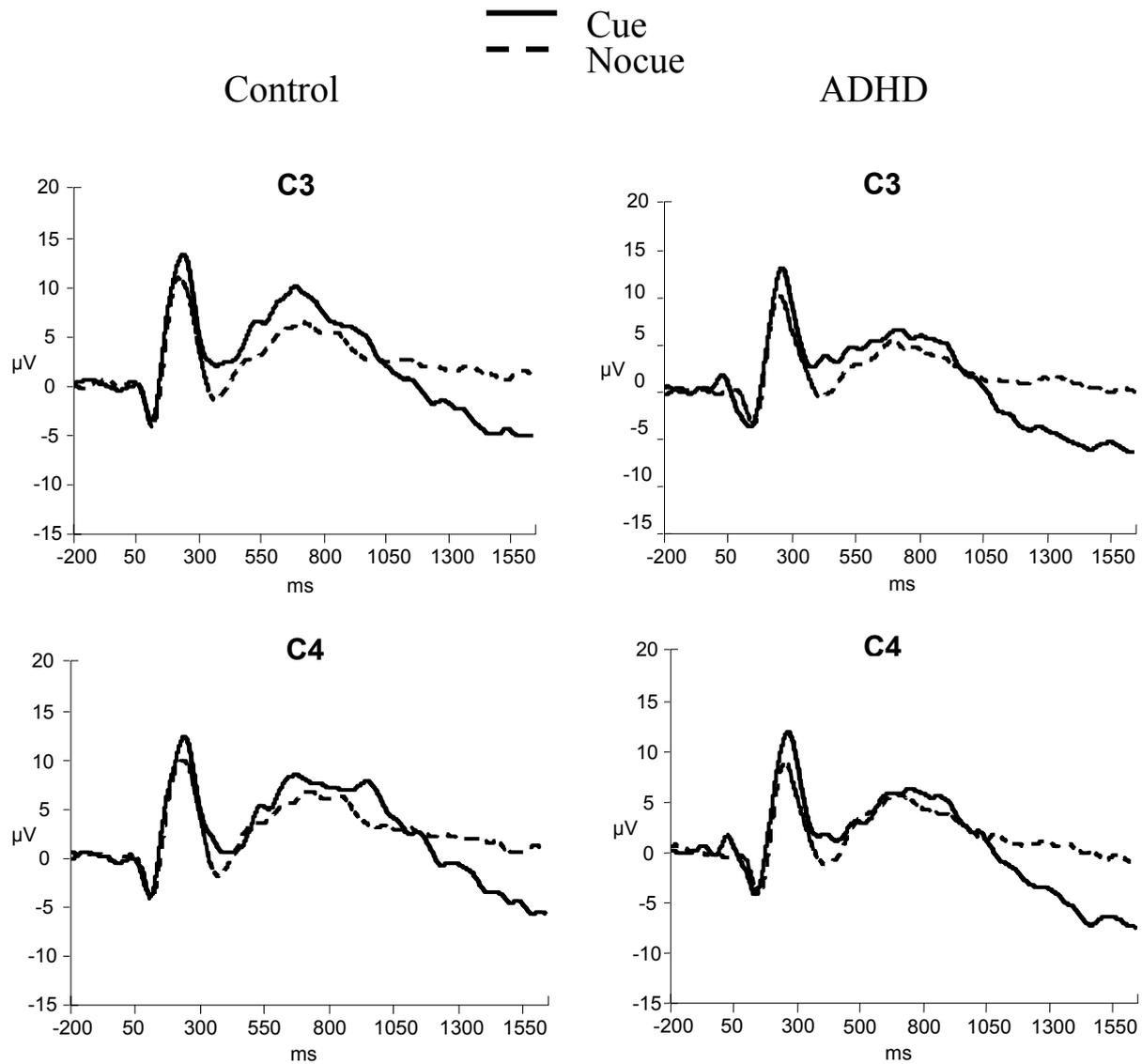


Figure 5. Grand average ERPs of control and ADHD children in Cue and Nocue conditions at C3 and C4 electrodes.

control group ($p < .001$), which was absent in the ADHD group ($p = .71$). At Pz the Cuetype effect was significant in both groups (Controls: $p < .00001$ and ADHD: $p < .01$), but much smaller in the ADHD group. To control for possible effects of hemispheric asymmetries, additionally, P3 activity at C3- and C4-electrodes was analyzed. This analysis did not yield any asymmetry in Cue-P3 (Electrode effects (C3-C4 difference): $p = .12$ and $p = .35$ in Control and ADHD groups, respectively) or NoCue-P3 (Electrode effects of $p = .48$ and $p = .56$ in Control and ADHD groups, respectively; see Figure 5). The CNV analysis also did not reveal any hemisphere effects in the analysis including C3-C4 electrodes (C3-C4 difference Cue-P3: $p = .48$ and $p = .66$; C3-C4 difference Nocue-P3: $p = .95$ and $p = .15$, in Control and ADHD groups, respectively).

Table 4. Mean area amplitudes in μV (standard deviations between brackets) in response to Cues and Nocues in control and ADHD children for the P2 (Fz), P3 (Cz, Pz, Oz) and CNV (Fz, Cz, Pz, Oz). The windows in which P2, P3 and CNV were scored are indicated in the first column.

	Fz		Cz		Pz		Oz	
	Cue	Nocue	Cue	Nocue	Cue	Nocue	Cue	Nocue
<i>P2</i>								
Control (240-280ms)	12.5 (6.1)	9.0 (5.1)	/	/	/	/	/	/
ADHD (260-300ms)	12.0 (5.4)	7.9 (4.0)	/	/	/	/	/	/
<i>P3</i>								
Control (450-850ms)	/	/	10.6 (4.0)	6.5 (3.0)	13.9 (4.8)	6.6 (3.8)	10.0 (4.5)	2.6 (3.9)
ADHD (450-850ms)	/	/	5.3 (5.3)	4.8 (2.3)	9.9 (4.2)	6.0 (2.6)	9.2 (4.5)	2.8 (3.1)
<i>CNV</i>								
Control (1300-1650ms)	-3.4 (3.5)	0.8 (1.9)	-4.0 (3.0)	1.4 (2.1)	-2.8 (3.8)	1.1 (1.9)	0.1 (2.8)	0.1 (1.5)
ADHD (1300-1650ms)	-3.5 (3.9)	0.5 (3.2)	-8.3 (3.6)	0.6 (3.5)	-7.6 (2.9)	1.2 (3.5)	-4.3 (2.5)	0.7 (2.9)

Columns in grey are indicative of significant Group \times Cue/NoCue interactions. Further testing showed that ADHD children had a reduced Cue-P3 at Cz and Pz and an enhanced cue-CNV at Oz.

Cue-CNV effect

The CNV analysis revealed a significant Leads \times Cuetype \times Group interaction ($F(1,25) = 4.4, p < .05$). Testing at the separate leads revealed a Cuetype \times Group interaction at Cz ($F(1,25) = 5.5, p < .05$), Pz ($F(1,25) = 7.0, p < .05$) and Oz ($F(1,25) = 11.6, p < .01$). At Fz, there was a significant Cuetype effect ($p < .00001$), but no Group difference. To further qualify the interaction, post-hoc testing was performed at the separate leads to find out whether this group difference was caused by amplitude differences in the Cue or the Nocue condition. As expected, group differences were only present in the Cue condition at Cz ($p < .01$), Pz ($p < .01$) and Oz ($p < .001$), indicating larger CNV amplitudes in the ADHD-symptom group. To account for the possible influence of preceding P3 activity (for which group differences were found at centro-parietal leads) on CNV activity, a baseline correction was performed on the individual averages using the 450-850 ms interval, subtracting Cue-P3 activity. Consequently, the larger Cue-CNV activity in the ADHD group was no longer present at Cz (Group: $p = .70$) or Pz (Group: $p = .70$), but still marginally significant at Oz (Group: $p = .08$). Figure 4 shows similar CNV distributions in control and ADHD-symptom groups.

Correlations

Correlations CBCL and behavioral data

Correlation plots for significant results are displayed in Figure 6. Significant correlations were found between all three CBCL subscales (E, I and A) and % hits (coefficients between $-.38$ and $-.45$, p between $.02$ and $.05$) on the one hand and Inattention score (coefficients between $.41$ and $.48$, p between $.01$ and $.04$) on the other hand on the CPT-AX. The CBCL-scales did not correlate with CPT-AX Impulsivity score (coefficients between $-.12$ and $.03$, p between $.55$ and $.90$) or % false alarms (coefficients between $-.04$ and $.09$, p between $.66$ and $.85$).

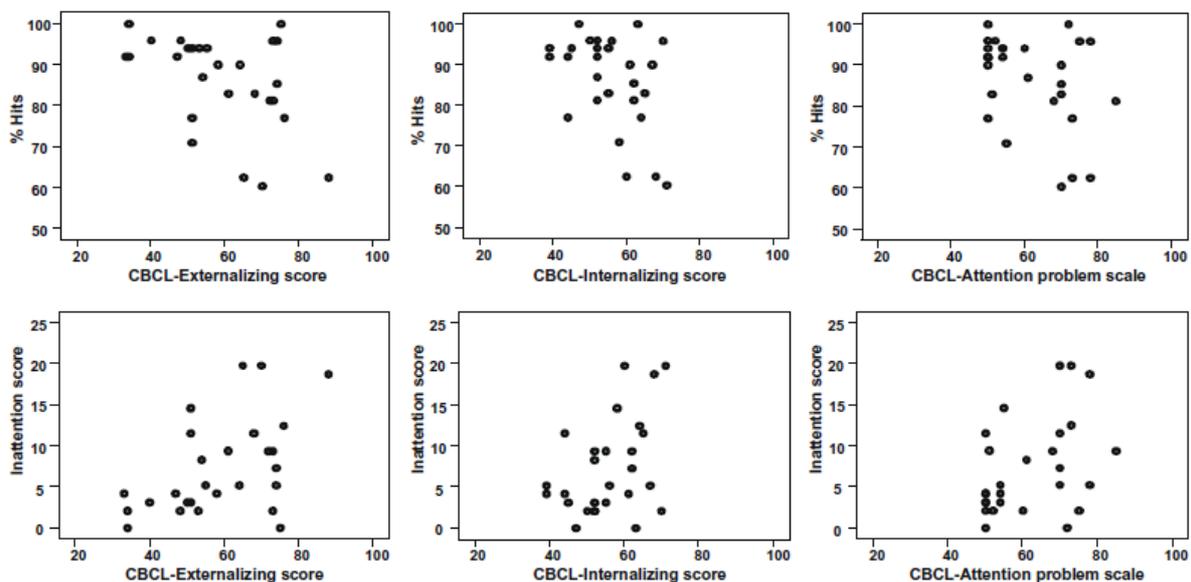


Figure 6. Correlation plots of CBCL scores (on E, I and A subscales) and behavioral data (% hits and Inattention score) that showed significant correlations.

Correlations behavioral data and Go and Cue-P3

Correlation plots for significant results are displayed in Figure 7. The Go-P3 effect (Go-Nogo difference score) at Pz correlated significantly (marginally significant at Cz) with the behavioral attention measures % hits ($r = .49$, $p < .01$ and $r = .38$, $p < .06$ at, respectively, Pz and Cz) and Inattention score ($r = -.51$, $p < .01$ at Pz and $r = -.37$, $p < .06$ at Cz). Go-P3 did not correlate with Impulsivity measures. The Cue-P3 effect (difference score Cue-Nocue) at Cz and Pz correlated significantly with both Attention (% hits and Inattention score) and Impulsivity (% false alarms and Impulsivity score) related behavioral measures. For attention measures: Cue-P3-% hits; $r = .52$, $p < .01$ at both leads; Cue-P3-Inattention score; $r = -.55/-51$ ($p < .01$) at, respectively, Cz and Pz. Impulsivity scores correlated significantly with Cue-P3 at all

electrodes (Cz: $r = -.45$, $p < .05$; Pz: $r = -.60$, $p < .01$; Oz: $r = -.46$, $p < .05$). The percentage of false alarms only significantly correlated with central and parietal Cue-P3 (Cz: $r = -.48$, $p < .05$; Pz: $r = -.46$, $p < .05$). No correlations between the behavioral data and the CNV effect were found.

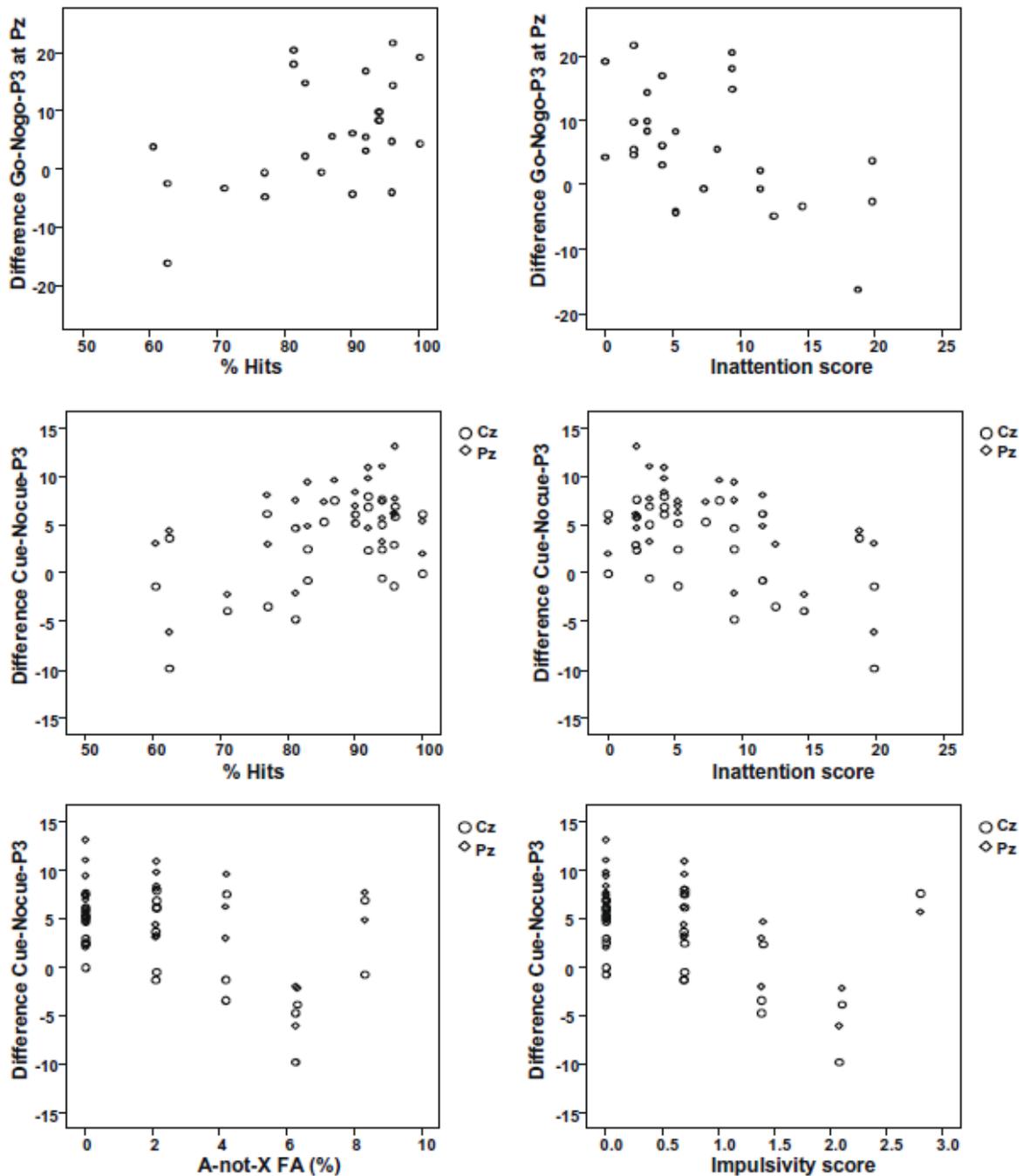


Figure 7. Correlation plots of behavioral data (% hits, Inattention score, % false alarms, Impulsivity score) and ERP activity (Go-P3 at Pz, Cue-P3 at Cz and Pz) that showed significant correlations.

2.4 Discussion

Much research has focused on cognitive control and attention in children with ADHD recently. Nevertheless, no event-related brain potential (ERP) studies examining cognitive control have been performed in ADHD children below the age of 7, a period in which the diagnosis of ADHD is problematic. It is important to identify the symptoms, behavioral parameters and related brain abnormalities in early childhood that might be most predictive of the development of ADHD at a later age. Therefore, in the present study, performance and brain activity of young children (aged 5-7) that did or did not display symptoms of ADHD were compared. More specifically, cue-orientation, target expectation and response preparation processes evoked by a warning stimulus and subsequent conflict detection and response inhibition were examined in a Go/Nogo (CPT-AX) task by means of event-related brain potentials.

Behavioral measures revealed specific attention problems in the children with ADHD symptoms, as they had fewer correct Go responses and higher Inattention scores than control children. A signal detection analysis showed that such attention differences were not due to response biases since only the perceptual sensitivity index A' was significantly lower in the ADHD-symptom group. Go-reaction time and variability did not differ between the groups, and neither did Impulsivity score and Nogo errors. These behavioral data suggest that already at an early age, in which it is difficult to reliably diagnose ADHD, children with ADHD symptoms have attention-related problems in the CPT-AX task. Comparable attention problems in ADHD patients were previously reported in middle and late childhood in Go/Nogo-task studies. For example, Fallgatter et al. (2004) and Yong-Liang et al. (2000) found that children with ADHD (6- to 12-years old) made more Go-errors than control children in a similar CPT-AX task. Also, higher Inattention scores were found in ADHD children aged 6-14 by Overtom et al. (1998). Furthermore, several studies have found higher and more variable reaction times in children (Overtom et al., 1998; Banaschewski et al., 2003, 2004; Fallgatter et al., 2004; Wiersema et al., 2006a) and in adults with ADHD (Wiersema et al., 2006b), compared to age-matched controls. The fact that such differences in response variability were not found in the present study might be due to a general immaturity of the frontal lobes in 5- to 7-year-old children, causing high response variability in both groups. The frontal cortex has been shown to play an important role in deploying attention over extended periods of time and controlling performance variability (Stuss et al., 2003; Bellgrove et al., 2004). The present results indicate that reaction time variability might not distinguish children with ADHD symptoms from healthy control children in early childhood.

As mentioned earlier, behavioral measures of inhibitory control such as the percentage of Nogo-errors (false alarms) and Impulsivity score did not significantly differ between the two groups. This finding seems to be in contrast with studies

reporting that ADHD patients in middle and late childhood do show inhibition related problems (enhanced number of Nogo-errors) in comparable tasks (Yong-Liang et al., 2000; Durston et al., 2003; Wiersema et al., 2006a). There was only one study that did not find a group difference in Impulsivity scores either in the CPT-AX between ADHD and control children aged 6-14 (Overtoom et al., 1998). It was hypothesized that differences in impulsivity measures besides differences in attentional measures would be found already in children below age 7, as ADHD symptoms of both inattention and impulsivity appear from the age of 3 (Kadesjö et al., 2001; Berlin et al., 2003). However, a recent study by Smidts and Oosterlaan (2007) indicated that in preschoolers, symptoms of inattention might be better predictors of later psychopathology than symptoms of hyperactivity/impulsivity since the latter are reported by about 50% of the parents of 4- to 5-year-old healthy children and appear to be part of the normal behavioral repertoire at this age. This might also explain why impulsive responding was comparable between the groups in the present study.

Correlations between CPT-AX (behavioral) data and behavior as measured by the CBCL showed that attention problems in the CPTAX task were correlated with inattention symptoms. Moreover, internalizing and externalizing behavior symptoms showed an equally strong relation to attention deficits in CPT-task performance. This finding suggests that in early childhood attention deficits in the CPT-AX are not specific to children with pure attention deficits. Furthermore, it was shown that impulsivity measures in the task were not related to the children's behavior symptoms, suggesting that impulsivity measures in 5- to 7-year-old children may not be indicative for a risk of developing ADHD in a later stage.

In order to examine neural activity underlying executive control or attention deficits, several ERP components indicative of (response) preparation (Cue-P2, P3 and CNV), inhibition (Nogo-P3) and conflict monitoring (Nogo-N2) were measured. Large and equally strong Nogo-N2 effects (Nogo > Go) were present in both groups. On the basis of prior work (Nieuwenhuis et al., 2003; Donkers and Van Boxtel, 2004; Kenemans et al., 2005; see introduction), this finding led to the conclusion that the perceived conflict that arises between the prepared and required response in the Nogo condition is similar in both groups. This is in concordance with several earlier studies reporting similar Nogo-N2 effects in older, diagnosed ADHD children and age-matched peers (Overtoom et al., 1998; Banaschewski et al., 2004; Fallgatter et al., 2004; Wiersema et al., 2006a). The present data are also in line with studies by Ridderinkhof et al. (1997) and Rueda et al. (2004) using the flanker task, in typically developing controls, that reported the largest effects of response conflict on performance below or around the age of 7. Johnstone et al. (2007) suggested that after 7 years of age levels of conflict reduce. This developmental pattern of response conflict corroborates with the strong Nogo-N2 activity found in the present study in both the ADHD-symptom group and control children. Finally, the broad topography of this Nogo-N2 effect (being present at both fronto-central and more posterior (parietal) electrodes) is also comparable between the groups, tentatively suggesting

the involvement of similar networks. This more posterior distribution was earlier reported to be specifically present in young children (compared to older children and adults) by Jonkman (2006). To explain this posterior Nogo-N2 topography during early childhood, source analysis showed that besides a commonly reported source in PFC (ACC) additional posterior sources were needed (Jonkman et al., 2007). The present study confirms that the frontal-parietal Nogo-N2 distributions during early childhood can probably be seen as a general developmental phenomenon.

The Nogo-P3 that follows the Nogo-N2 in time has been associated with the process of response inhibition in healthy adults (Bruin et al., 2001; Bekker et al., 2004; Donkers and Van Boxtel, 2004; Smith et al., 2007) and healthy 8- to 12-year-old children (Johnstone et al., 2005, 2007; Jonkman et al., 2003; Jonkman, 2006).

In contrast to the clearly present Nogo-N2 effect, only a marginally significant Nogo-P3 effect (Nogo > Go) could be derived from the ERP data in this study. Accordingly, a similar scalp distribution at fronto-central leads in control and children with ADHD symptoms is displayed. This was expected as Jonkman (2006) found no significant Nogo-P3 effects either in healthy 6- to 7-year olds and the present study included even younger children. The absence of a clear Nogo-P3 effect in both groups in the present study is interpreted as resulting from still immature response inhibition processes. The subjects were however capable of inhibiting their responses in the majority of the trials. Also, other studies showed that the Nogo-P3 develops relatively late, around age 10 (Okazaki et al., 2004). Reduced fronto-central Nogo-P3 activity has, however, been consistently reported in ADHD children compared to control children between 7- and 14-years old (Brandeis et al., 2002; Fallgatter et al., 2004; Wiersema et al., 2006a). Thus, due to developmental immaturity, reduced Nogo-P3 effects cannot be used as early predictors for the development of inhibitory control deficits in children with ADHD symptoms. In contrast to the absence of processing differences in Nogo-trials, the processing of target stimuli on Go-trials did differ between the groups. The results showed the absence of a Go-P3 effect at central electrodes in the ADHD-symptom group, whereas a significant enhanced Go- (vs. Nogo) P3 was found in the Control group. Furthermore, Go-P3 effects were specifically correlated with attentional performance measures in the sense that subjects with higher inattentive performance had lower or absent Go-P3 effects. Accordingly, the absence of a P3 effect at central leads in young (5- to 7-year old) children with symptoms of ADHD is interpreted as a reduced ability to allocate attentional resources to the task in a sustained manner, leading to occasional failures to detect target stimuli. Many studies have reported a similar reduced or absent centro-parietal P3 response (often referred to as P3b) in clinically diagnosed children with ADHD in the 7-12 age range, even when having responded correctly to target stimuli (for reviews see Barry et al., 2003; Jonkman, 2005). The relation between P3b and the ability to sustain attention across tasks is supported by animal studies showing that behavioral and brain (P3b) changes during attention tasks are mediated by Locus Coeruleus (LC)-norepinephrine (NE) innervations (for a review see Nieuwenhuis et al., 2005) that have earlier been shown to play an

important role in the control of vigilance and attention processes (Aston-Jones and Bloom, 1981; Aston-Jones et al., 1991, 2000; Foote et al., 1980). The present results show that such P3b deficits are already present in 5- to 7-year-old children that have clinical scores on ADHD-related symptom questionnaires filled out by the parents and teachers.

Besides the executive functions in response to a target, processes of cue-orientation, go-expectation and response preparation were also measured in the present study by analyzing ERPs in response to Cues preceding the Go/Nogo stimuli. Children displaying ADHD symptoms and control children did not differ with respect to early cue-orientation processes, as P2 effects (Cue-P2 > NoCue-P2) were comparable between groups. Also, both groups had a similar frontal Cue-P2 distribution. This P2 positivity is generally observed in adults, and is thought to reflect early automatic sensory activation/ orientation processes or early attentional selection because of its sensitivity to experimental manipulations targeting such processes (Van Leeuwen et al., 1998; Banaschewski et al., 2003; Bekker et al., 2004). The relative early development of sensory areas is thought to explain the presence of early mature cue-orientation and selection processes which are thought to be reflected by the Cue-P2 amplitude.

However, children with ADHD symptoms did display reduced centro-parietal P3 response to the Cue stimulus (the letter A in the CPT-AX task) compared to controls. Earlier studies have also found a reduced Cue-P3 in ADHD children with a clinical diagnosis between 8- and 14-years old (Van Leeuwen et al., 1998; Banaschewski et al., 2003, 2004). This reduced P3 activity was interpreted as either impaired orienting (Van Leeuwen et al., 1998) or suboptimal energetical state regulation (Banaschewski et al., 2003) in the cue-target interval. By varying stimulus frequency, in another study the Cue-P3 response in the CPT-AX task has been associated with the level of Go-expectancy; the higher the Cue-P3 response (vs. NoCue) the higher the expectancy of a subsequent Go trial (Bekker et al., 2004). These findings and earlier reports of the involvement of LC-NE-vigilance networks involved in the generation of P3 (Nieuwenhuis et al., 2005), might indicate that the reduced Cue-P3 response in the current ADHD-symptom group might signify a reduced ability to evoke attentional responses to a task-relevant warning event. This might cause subjects to be less prepared to detect a subsequent target stimulus. Such a hypothesis is supported by the finding that a greater percentage of hits was accompanied by higher Cue-P3 amplitudes. Furthermore, when Cue-P3 amplitudes were smaller, higher Inattention scores were found. These correlations thus confirm the hypothesis of attention deficits in 5- to 7-year-old children with ADHD symptoms. However, both Cue-P3 and Cue-P2 also correlate with behavioral measures of impulsivity, although to a somewhat lesser extent than percentage hits and Inattention score.

Finally, as expected, CNV amplitudes showed higher degrees of response preparation (Rohrbaugh and Gaillard, 1983; McCallum, 1988) in reaction to Go-stimuli compared to Nogo-stimuli at centro-parietal and parietal electrodes in the

present study. In typically developing children mature levels of the centro-parietal CNV were found in 9- to 10-year olds (Jonkman et al., 2003), but reduced centro-parietal CNV activity was present in 6- to 7-year olds (Jonkman, 2006), which was interpreted as a sign of reduced response priming in young children caused by yet immature frontal-parietal networks involved in motor regulation. Although in the present study prestimulus target expectation was suggested to be higher in control children (as reflected by enhanced Cue-P3), this did not result in enhanced centro-parietal CNV activity that would be a sign of enhanced motor preparation (Rohrbaugh and Gaillard, 1983; McCallum, 1988). Instead, the groups showed similar levels of central and parietal CNV activity. Whereas similar levels of response preparation have also been found by Van Leeuwen et al. (1998), most studies reported smaller CNV activity near or above the motor cortex in ADHD than in control children (Banaschewski et al., 2003; Perchet et al., 2001), although at an older age. Nevertheless, greater occipital CNV activity appeared in the children with ADHD symptoms. Similar results were reported by Hennighausen et al. (2000), who also observed a trend towards increased occipital CNV activity in ADHD children between 1000 and 1500 ms after presentation of the cue. Such enhanced occipital late CNV activity in the ADHD-symptom group might be related to differences in sensory (preparatory) processes. In so-called S1-S2 paradigms, a warning stimulus (S1) precedes the target stimulus (S2), in a way comparable to the A(S1)-X(S2) sequence in the present task. Grunewald-Zuberbier et al. (1978) reported that the alpha rhythm at occipital electrodes in the late S1-S2 interval was attenuated in children that were best able to visually discriminate target stimuli and was hence associated with a “predominantly sensory set”. In multiple other studies stronger visual attention or stronger sensory preparation for an upcoming stimulus or ocular fixation has been associated with reduced occipital alpha activity (Mulholland, 1969, 1972; Mulholland and Peper, 1972; Pollen and Trachtenberg, 1972). The present larger occipital late CNV activity in the inattentive subjects, who were shown to be deficient in target detection, might be the result of less suppression of occipital alpha activity caused by a less strong sensory set or less visual attention for the upcoming stimulus.

There are some limitations of the current study that have to be taken into account. First, a possible confound might be that the majority of the children in the ADHD-symptom group were boys, while the Control group consisted of mostly girls. However, several studies have shown that there are no effects of gender on performance or ERPs in CPT and Stop Signal tasks (Biederman et al., 2002; Seidman et al., 2005; Liotti et al., 2007), so it is not likely that this explains the attentional deficit in the ADHD-symptom group. Another issue is that whereas mean ages were not significantly different between the groups, children were not perfectly matched on age in the present study. Future research should investigate whether the present results can be replicated with even more closely age-matched groups. A final limitation of the present study is the rather small sample size, which might have led to a reduction in power. Nevertheless, consistent and correlated attention deficits were revealed in both behavior and ERPs of the 5- to 7-year-old children with ADHD

symptoms, indicating that these (as opposed to impulsivity measures) might be good predictors for the risk of developing ADHD.

Concluding, findings of attenuated parietal Go-P3 and reduced Cue-P3 activity as well as enhanced occipital CNV activity and behavioral measures of attention (correct responses and Inattention scores), and correlations between these measures, are all indicative of deficiencies in attention processing in 5- to 7-year-old children with symptoms predictive of a future ADHD diagnosis. Although inattention might not be a specific symptom of ADHD (as inattentive responding can be observed in several other disorders, see Overtom et al. (1998)), inattention symptoms are known to be present early in the developmental tract in ADHD children, and do not decline as much as hyperactivity and impulsivity symptoms with increasing age (Hart et al., 1995). Also, inattention symptoms appear to be better predictors of later psychopathology than symptoms of hyperactivity/impulsivity that are more common in younger children (Smidts and Oosterlaan, 2007). Response inhibition does not seem to be especially affected in children with ADHD symptoms in early childhood, although indications for response inhibition deficits in ADHD have been found in older children (Nigg, 2001). Correspondingly, inhibitory control as measured by the CPTAX or similar tasks has been shown to develop relatively late in childhood (Jonkman, 2006; Johnstone et al., 2007).

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Chapter 3

Electrophysiological evidence for different effects of working memory load on interference control in adolescents than adults

Based on:

Spronk, M., Jonkman, L.M. (2012). Electrophysiological evidence for different effects of working memory load on interference control in adolescents than adults. *International Journal of Psychophysiology*, 83(1), 24-35.

Abstract

The present study investigated how the development of interference control is influenced by the development of working memory (WM) capacity during adolescence. In a dual-task, 17 adolescents (12-16 years) and 19 adults (18-48 years) performed a gender word-face Stroop task, while WM capacity was manipulated by a concurrently performed N-back task. Behavior (reaction times, % errors and % misses) and event-related potentials associated with the detection (N450) of the Stroop conflict and response selection (sustained positivity; SP) were measured without or with a concurrent WM load. Adolescents had lower accuracy on N-back and Stroop trials than adults. N450 results showed Stroop conflict above temporal-occipital cortex which was suggested to be caused by processing of distracter faces. This N450 conflict response was smaller in adults and only present when holding a simultaneous WM load, whereas adolescents' N450 conflict responses were already present without a concurrent WM load and did not further increase with load. These N450 results indicate poorer distracter suppression in adolescence which is suggested to be due to insufficient attentional resources for top-down control. Irrespective of WM load, adolescents also had larger parietal SP conflict responses than adults, suggesting inefficient response selection in case of activation of two conflicting responses. The main conclusion is that adolescents have worse distracter suppression than adults, caused by lower availability of resources for top-down control.

3.1 Introduction

Inhibition-related functions are known to play an important role in the development of cognitive abilities such as fluid intelligence (Burgess and Braver, 2010), reasoning (Krawczyk et al., 2008), and problem solving (Passolunghi et al., 1999). One type of inhibition, interference control, is the ability to select task-relevant information while simultaneously suppressing the influence of distracting information that conflicts with task demands, such as for example in Stroop tasks (Stroop, 1935). In the past decade a considerable number of studies have provided evidence that the ability to control interference is related to the capacity of one's working memory (WM), i.e. the space to store and process information for short periods of time. One line of evidence comes from behavioral studies showing that adults with low WM-span experience more interference from distracters than adults with high WM-span in conflict-tasks such as Stroop and flanker tasks (Kane and Engle, 2003). On the basis of these studies Engle and Kane (2004) proposed their executive-attention theory of WM capacity, which explained the better performance of adults with high-WM capacity by a better ability to maintain goal-related information in memory and resolve response conflict. In a series of studies Lavie and colleagues have used a within subjects design to study WM capacity-selective attention/interference control relations more directly by manipulating WM capacity and interference control experimentally within one paradigm (De Fockert et al., 2001; Lavie and De Fockert, 2005; Lavie et al., 2004). These studies led to the conclusion that WM capacity is of crucial importance for the ability to suppress the influence of distracting or conflicting information, because reductions in WM resources led to enhanced interference in Stroop or flanker tasks. The aim of the present study was to investigate how the development of interference control is influenced by manipulations of WM resources (thought to reduce frontal-top-down control) during adolescence by using a WM-selective attention task similar to that used in de Fockert et al. (2001). Below more information about this task will be provided.

The present study focuses on adolescence since both WM capacity and inhibitory control have been consistently reported to follow a protracted qualitative development into this period, especially in situations that are highly cognitively demanding (Anderson et al., 2001; Davies and Rose, 1999; Demetriou et al., 2002; Gathercole, 1999; Klingberg et al., 2002; Kwon et al., 2002; Leon-Carrion et al., 2004; Luciana et al., 2005; Luna et al., 2004, 2010; Schleepen and Jonkman, 2010; Segalowitz et al., 2010). For example in a review article, Gathercole (1999) showed that especially complex WM (compared to phonological and visuospatial short-term memory) undergoes late development until 16 years of age. Also other studies have shown that mature WM capacity is not reached before late adolescence when executive control demands are high. Luciana et al. (2005), who used nonverbal WM tasks with varying degrees of executive demands, reported that WM capacity in a spatial WM task in which sequences of visually presented information (block tapping) had to be

recalled in backward order (requiring maintenance and manipulation) did not reach mature levels in adolescents until 13 or 15 years of age. Schleepen and Jonkman (2010) showed particularly late development of non-spatial WM capacity into adolescence in task conditions that required simultaneous maintenance, updating and suppression of irrelevant information in a verbal N-back task. Luna et al. (2004) also showed ongoing development of WM throughout adolescence using an oculomotor delayed response task (requiring eye movements guided by a target location in memory), as well as late development in adolescence of inhibitory control in an anti-saccade task. Immature suppression of irrelevant information has furthermore been reported in adolescents by Leon-Carrion et al. (2004) who examined interference control in a Stroop task and found a decrease in interference from irrelevant information in adolescence until 17 years of age. This late development of WM capacity and inhibitory control has been attributed to the protracted development of brain networks including frontal and parietal brain regions that are known to be involved in both WM and interference control (Bunge and Wright, 2007; Durston et al., 2002; Hopfinger et al., 2000; Klingberg et al., 2002; McNab and Klingberg, 2008; Rubia et al., 2006). Especially, the maturation of dorsolateral prefrontal cortex (DLPFC), a structure known to be involved in the resistance to interference when holding information in WM, has been shown to be immature in adolescence (Giedd, 2004; Lenroot and Giedd, 2006). DLPFC activation has been found during maintenance of items in memory and particularly when WM load is high (Grimault et al., 2009; Rypma et al., 2002), or when WM content is threatened by distraction (Dolcos et al., 2007). Such findings indicate that frontal areas are essential in keeping cognitive performance levels high through top-down attentional control.

One way to investigate the dependency of interference control on WM capacity is through the use of so-called dual-task paradigms. As was already shortly mentioned above, in a series of studies including healthy adults Lavie and colleagues manipulated WM load by letting subjects hold smaller or larger amounts of information in WM while concurrently performing tasks requiring selection/enhancement of task-relevant information and simultaneous suppression of task-irrelevant information, such as in Stroop, flanker or visual search tasks (De Fockert et al., 2001; Lavie and De Fockert, 2005; Lavie et al., 2004). In all these studies higher occupancy of WM led to increased distracter interference in the concurrently performed selective attention tasks as measured by delayed reaction times and reduced accuracy when targets and distracters evoked conflicting responses, i.e. were incongruent (e.g. the word red printed in green in the Stroop task) as opposed to when both were congruent. In the fMRI study by De Fockert et al. (2001), interference in the Stroop task was manipulated by presenting subjects with names of famous people that had to be categorized as being from a politician or pop star. Names were superimposed on distracter faces that had to be ignored and could either be congruent (name and face of Bill Clinton) or incongruent with the to-be-categorized names (e.g. name of Bill Clinton and face of Mick Jagger). This fMRI study showed

that healthy adults experienced more interference from distracter faces when WM was heavily loaded (leading to lower availability of frontal resources for top-down control), as shown by slower responding in the Stroop task and higher activation in fusiform face-processing areas with high WM load, the latter being indicative of higher processing of task-irrelevant distracter faces.

A task similar to that used in De Fockert et al. (2001) was used in the present study to examine whether the dependency of interference control on WM capacity shows developmental changes from adolescence to adulthood. To prevent influences of differences in familiarity of famous faces between adolescents and adults, Stroop interference was manipulated by presenting the words male/female (in Dutch in the present study) superimposed on male or female faces that were unfamiliar to the subjects (Egner et al., 2010; Padmala et al., 2011). Subjects had to categorize the words male/female by giving left/right responses, WM load was manipulated by a concurrently performed letter N-back task. In addition to behavior, event-related brain potentials (ERPs) were measured to get a precise view on when in time reductions in available WM capacity influence interference control the most in the different age groups. More specifically, the effect of loading WM was measured on two Stroop-related ERP components; the so called “N450” and the “sustained positivity” (SP), that have been reported to occur in regular color-word Stroop tasks (Lansbergen et al., 2007; Liotti et al., 2000; Markela-Lerenc et al., 2004; Qiu et al., 2006; West, 2003, 2004), but have recently also been reported in a face-name Stroop task (Jongen and Jonkman, 2011). The N450 represents a reduced positive component (negativity) in the incongruent condition relative to the congruent condition between 350 and 500 ms and has been associated with the process of conflict detection on the basis of its sensitivity to different experimental manipulations of conflict strength (Lansbergen et al., 2007; Liotti et al., 2000; Tillman and Wiens, 2011; West and Alain, 2000). The conflict SP (sometimes also called the P600 in the Stroop-ERP literature) that follows the N450 in time represents an enhanced positive component in the incongruent condition relative to the congruent condition starting around 600 ms. On the basis of the Stroop-ERP literature parietal-SP effects are suggested to reflect enhanced processing of response relevant information used to guide response selection in incongruent trials (Chen et al., 2011; Jongen and Jonkman, 2008; Lansbergen et al., 2007; Liotti et al., 2000; Markela-Lerenc et al., 2004; Qiu et al., 2006; West, 2003). Parietal-SP effects have been localized to parietal cortex in adults (Chen et al., 2011) and fMRI studies have reported evidence for a role of parietal cortex in supporting stimulus-response mappings that facilitate response selection in the Stroop task (Bunge et al., 2002; Casey et al., 2000; Rushworth et al., 2001).

Whereas these N450 and SP conflict components have been studied frequently in adults, studies in children or adolescents are scarce. In a developmental study using an object-Stroop task stimulus-response mappings were manipulated to study the differential contributions of stimulus and response interference to behavioral and electrophysiological Stroop effects across age (Jongen and Jonkman, 2008). Stimulus interference was not present in children (6-12 years of age) or adults. Response

interference effects were present on reaction time and accuracy in all 6-12 year-old children and adults, but children made relatively more errors than adults in the response-incongruent than the stimulus-incongruent condition. The fact that 12-year-olds still made more errors in the response-incongruent condition than adults points to continued maturation of response conflict processing during adolescence. An N450 conflict response with a parietal, lateral occipital distribution was larger to response-incongruent than stimulus-incongruent stimuli in 10-12 year-old children and adults, but was not present below 10 years of age. An SP effect with a broad scalp distribution across frontal, central and parietal electrodes was present in all children and adults. The facts that this SP-conflict response was larger on response- than stimulus-incongruent trials and that its magnitude was correlated with the RT response interference effect confirmed its relation to the process of conflict resolution also in children.

To our knowledge, no ERP studies have so far been done to directly examine the relationship between WM and interference control in adolescents in a dual-task. In a prior ERP study by Jongen and Jonkman (2011) the time-course of WM load effects on Stroop interference in a name-face task similar to that used in the fMRI study by de Fockert et al. (2001) was investigated in university students. They found that only the SP interference effect associated with conflict resolution was modulated by WM load; SP interference effects at parietal electrodes increased linearly with higher concurrent WM loads, and only when holding the highest WM load of four letters in memory additional frontal SP activation was found. This suggests that in healthy young adults additional frontal top-down control on posterior areas to prevent distracter processing is only needed when holding concurrent loads that are close to maximum WM capacity. Because of the relative immaturity of fronto-parietal networks in adolescence we expect that they will show an inability to suppress distracter processing in the Stroop task already with lower concurrent WM loads and/or that processing bottlenecks will become visible earlier in the information processing chain, e.g. at the level of conflict detection. In the present Stroop task, conflict is expected to occur when the genders of the name and distracter face do not match and can only occur after the gender of the face has been processed. Since neuroimaging studies have shown that the processing of stable aspects of faces such as gender takes place in inferior occipitotemporal regions and fusiform gyrus (Haxby et al., 2000, 2002) we expect the first (N450) interference effects associated with conflict detection (and effects of WM load manipulation on this) to take place in occipito-temporal cortex. Support for this also comes from studies by Fruhholz et al. (2009a,b), who previously investigated the effects of congruent and incongruent contextual information on the processing of facial expressions (valence recognition of faces). Their fMRI study revealed increased activity for incongruent compared to congruent trials in V4, the mid-lateral fusiform gyrus (BA 37) and the inferior occipital gyrus (BA 18). The activity in fusiform gyrus was thought to be related to categorical face processing (Fruhholz et al., 2009b). In another study, ERP data collected with the same task showed interference effects similar to the N450 (reduced

positivity for incongruent compared to congruent trials) at parietal and occipital electrodes; source activity for these effects as shown by principal component analysis were located in parietal cortex (Fruhholz et al., 2009a).

3.2 Methods

Subjects

Originally, 40 healthy subjects (native Dutch speakers) participated in the study (20 adolescents and 20 adults), of which four were excluded during statistical analyses due to outliers in behavioral measures (three adolescents and one adult). The 17 subjects (8 boys and 9 girls) in the adolescent group were recruited from preparatory secondary vocational education schools, which is the lowest secondary level of regular education, attended by 60% of the Dutch adolescents, and therefore thought to be most representative of typically developing adolescents. The 19 adults (11 male and 8 female) were recruited from the normal population via advertisements in local newspapers and had educational levels similar to the adolescents (i.e. all adults completed non-compulsory post-secondary education). Mean age was 14.5 years in the adolescent group (range 12.9-16.4 years; SD=1.1) and 32.6 years in the adult group (range 18.7-48 years; SD=11.4).

To check for absence of attention- and/or ADHD behavioral problems, the adolescents themselves filled out the Youth Self Report form (YSR; Achenbach, 1991b) and one of their parents filled out the Child Behavior Checklist (CBCL; Achenbach, 1991a). In adolescents, mean score on the ADHD subscale was 54.5 on the CBCL (SD3.8, range 50-62) and 53.5 on the YSR (SD 3.7, range 50-63), and on the Attention subscale mean score was 54.1 on the CBCL (SD3.8, range 50-61) and 52.2 on the YSR (SD 2.6, range 50-57). Participating adults filled out the Adult Self Report (ASR; Achenbach and Rescorla, 2003). Mean score was 53.4 on the ADHD subscale (SD 4.2, range 50-65) and 54.1 on the Attention subscale (SD 4.5, range 50-63). None of the subjects scored within the clinical range on the ADHD or attention subscales. Furthermore, all subjects were free of other neurological or somatic health problems.

To check for IQ, subjects in the adolescent group were administered the Vocabulary and Block design subtests of the Wechsler Intelligence Scale for Children (WISC-III; Wechsler, 1991). Subjects in the adult group were administered the same subtests of the Wechsler Adult Intelligence Scale (WAIS-III; Wechsler, 1997). Mean reliability and validity of this estimated IQ-score compared to the complete IQ-test has been reported to be .9 for both scales (Jeyakumar et al., 2004; Spreen and Strauss, 1998). The mean IQ-score was 95.0 (SD 11.0) in the adolescent group and 102.2 (SD 12.4) in the adult group. IQ-scores did not significantly differ between groups. The present study was approved by the Local Ethical Committee of the Faculty of Psychology and Neuroscience at Maastricht University, and prior to the study a

written informed consent was obtained from the children and their caretakers and the adults according to the Declaration of Helsinki. All subjects were paid for their participation in the experiment.

Procedure

The entire experimental session lasted 2.5-3 h. The session started with the Block Design test, Vocabulary test and the Digit Span test, followed by the attachment of the electrodes. During the experimental session all participants sat in front of a 17-inch VGA monitor with their eyes aligned to the center of the screen at a distance of approximately 70 cm. They were instructed to minimize eye blinks and refrain from making movements during task performance. The experimental session started when all tasks were practiced until a predetermined performance criterion (75% correct responses) was reached.

Experimental Task

The experimental task, programmed in Presentation (version 11.0) consisted of a Stroop task combined with an N-back task, in such a way that each N-back trial was followed by a Stroop trial (see Figure 1). A gray background (131, 131, 131) was displayed throughout the task. Stroop stimuli consisted of the Dutch equivalents of the words MALE/FEMALE ("MAN" or "VROUW" printed in white color, font size 60) superimposed on faces of men and women (width 450 pixels, height 600 pixels) that were either congruent (e.g. the face of a man and the word "MAN") or incongruent (e.g. the face of a woman and the word "MAN") with each other, and were presented at the center of the screen. The face stimuli consisted of a selection of 16 neutral faces from the Karolinska Emotional Faces Set (Lundqvist et al., 1998) from which 8 men and 8 women were matched as much as possible on hair color and hair length. Pictures were displayed in grayscale. In the Stroop task subjects were instructed to attend to the word and ignore distracter faces and press a left button with the left index finger when the word stimulus shown was "MAN" (50% of all trials; 25% congruent with distracter face of a man, 25% incongruent with distracter face of a woman) or press a right button with the right index finger when the word stimulus was "VROUW" (other 50% of trials; 25% congruent with distracter face of a woman, 25% incongruent with distracter face of a man). The level of interference is determined by comparing reaction time and accuracy between congruent and incongruent Stroop stimuli.

To vary the level of WM load, different N-back trials were presented. N-back stimuli were the letters A, S, X, B, T, F, H, G, K, L, W and Z (white color, font size 50). In the 0-load condition, subjects performed a simple detection task by pressing the left button whenever a letter X was presented and pressing the right button to all other letters (A, S, B, T, F, H, G, K, L, W and Z). The 1-load condition was a 1-back

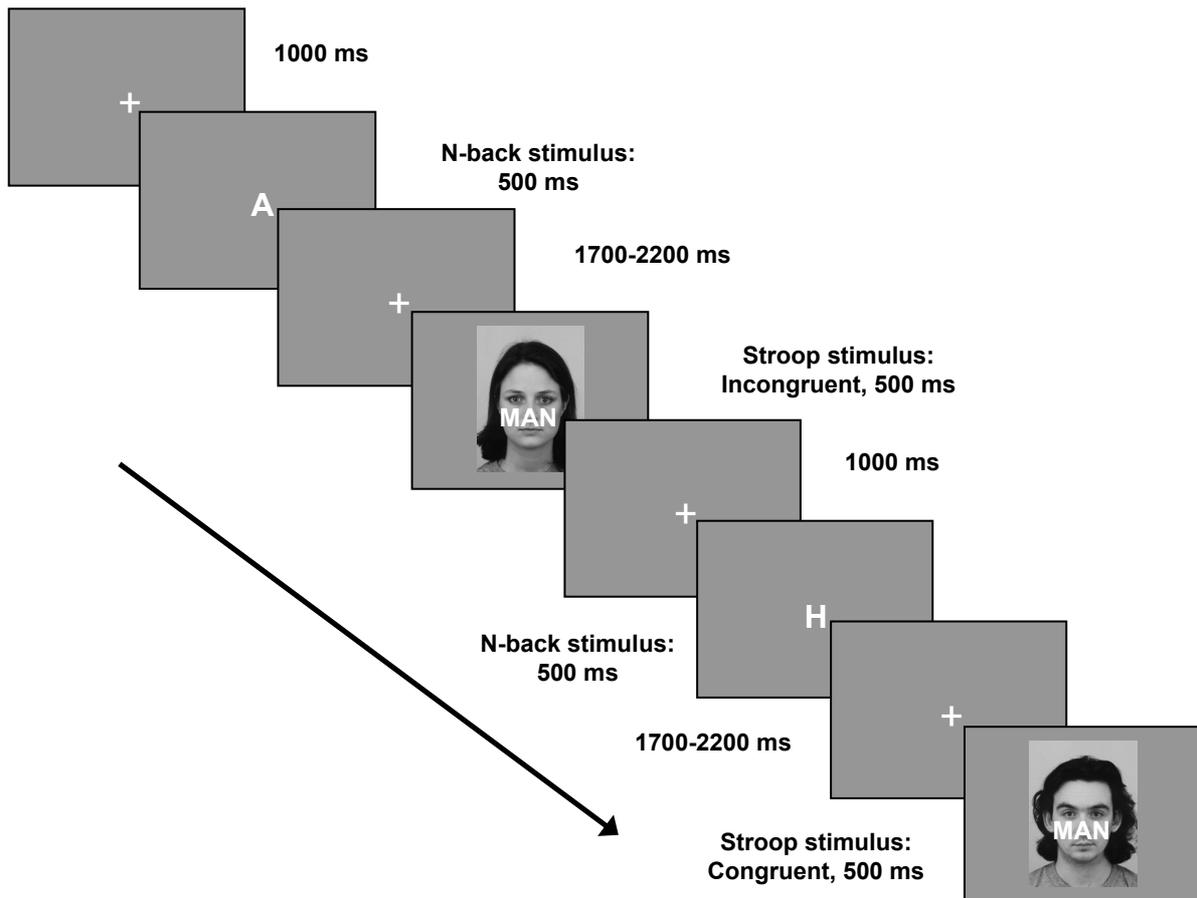


Figure 1. Illustration of two trials from the combined N-back and face-word Stroop task. In this task a presentation of a letter was followed by a Stroop trial in which the subject had to discriminate between the word “MAN” (male) and “VROUW” (female). In the WM load-0 condition the subject had to indicate for each letter whether it was an X or not. In the WM load-1 condition the subject had to indicate for each letter whether it was the same letter as the previous one, or different.

task and subjects reported whether the presented letter was similar to (left button press) or different from (right button press) the preceding letter. Comparable WM-face/name Stroop dual-tasks have been used in other studies that investigated WM load-interference/attention control interactions in healthy adults (De Fockert et al., 2001; Jongen and Jonkman, 2011; Pecchinenda and Heil, 2007). Note that 0-back and 1-back dual-tasks consisted of exactly the same stimuli and required similar goal maintenance and dual-task responses. The task goals and response requirements in the Stroop task were exactly the same between 0- and 1-back conditions, so the only difference was that in the 1-back condition one had to maintain the letter in memory during Stroop performance whereas no maintenance was required in the 0-back task.

The WM-Stroop task was administered in two blocks, differing in WM load (one 0-back block and one 1-back block), and the order of the blocks was counterbalanced between participants within groups. Each block consisted of 112 N-back and Stroop trials, with 50% congruent and 50% incongruent trials in the Stroop task (56 trials per condition). Similarly, N-back trials required an equal amount of left button presses (preceding 25% of congruent and 25% of incongruent Stroop trials)

and right button responses (preceding 25% of congruent and 25% of incongruent Stroop trials).

A total trial (one N-back + one Stroop stimulus) lasted 3700-4200 ms, a trial started with a fixation cross presented for 1000 ms, followed by an N-back letter stimulus presented for 500 ms, followed by a fixation cross with a duration varying between 1700 and 2200 ms, followed by a Stroop stimulus of 500 ms duration (see Figure 1).

Electrophysiological Recording and Analysis

For measurement of the EEG, an Easycap consisting of 60 Ag/AgCl electrodes was used (Fpz, Fz, FCz, Cz, CPz, Pz, Oz, Fp1, Fp2, AF7, AF8, AF3, AF4, F7, F5, F3, F1, F2, F4, F6, F8, FT7, FC5, FC3, FC1, FC2, FC4, FC6, FT8, T7, C5, C3, C1, C2, C4, C6, T8, TP7, CP5, CP3, CP1, CP2, CP4, CP6, TP8, P7, P5, P3, P1, P2, P4, P6, P8, PO7, PO3, PO4, PO8, O1, O2, and the right mastoid A2). During measurement all electrodes were referenced to the left mastoid (A1) and one of the electrodes in the cap (AFz) was used as ground. Offline, EEG data were re-referenced to the average of the right and left mastoids. The vertical EOG was recorded from infraorbital and supraorbital electrodes placed in line with the pupil of the left eye. The horizontal EOG was recorded from two electrodes that were attached to the outer canthi of both eyes. All electrode impedances were kept below 10 k Ω , with the exception of reference and ground electrodes that were held below 5 k Ω . Signal acquisition was accomplished using Neuroscan synamps amplifiers and Brain Vision Recorder software (version 1.10). EEG and EOG signals were continuously sampled at 250 Hz with a high-pass filter of 0.05 Hz and a low-pass filter of 30 Hz.

The continuous EEG of the Stroop trials was divided into 112 epochs of 1850 ms, from 200 ms prestimulus to 1650 ms poststimulus, all aligned to a baseline from -200 to 0 ms preceding the Stroop stimulus. First, vertical EOG artifacts (blinks) were removed from the data by applying an eye-movement correction algorithm (Semlitsch et al., 1986) provided in the Neuroscan analysis software package. Instead of using the automatic procedure, for the computation of regression coefficients between VEOG and the EEG-signals at the different electrodes, adequate eye blinks were manually selected and checked. After having removed eye blinks from the EEG via the above described procedure, epochs containing artifacts or horizontal eye movements exceeding ± 100 μ V were rejected from the database.

Next, average ERPs were computed separately for each subject in four different task conditions: (1) 0-load congruent stimuli, (2) 0-load incongruent stimuli, (3) 1-load congruent stimuli, and (4) 1-load incongruent stimuli. In the averaging procedure, only trials with correct responses on the Stroop trials as well as on the following N-back trial were included. There were a maximum number of 224 trials in the task (112 trials in the 0-back-Stroop block and 112 trials in 1-back-Stroop block). The minimum number of included trials per block (WM load 0 or 1) was 60. The

mean number of artifact-free EEG epochs contained in the single-subject averages was 184 trials (SD 27) in the adult group and 143 trials (SD 29) in the adolescent group.

Based on findings in previous studies (see introduction) two effects of Stroop interference were expected in the present ERP data. For incongruent relative to congruent trials an increased negativity has been observed around 450 ms (in the Stroop literature also referred to as the "N450"; Lansbergen et al., 2007; Liotti et al., 2000; Tillman and Wiens, 2011; West and Alain, 2000) and an increased positivity was expected around 600 ms (in the literature referred to as the "P600" or the "SP"; Chen et al., 2011; Jongen and Jonkman, 2008, 2011; Lansbergen et al., 2007; Liotti et al., 2000; Markela-Lerenc et al., 2004; Qiu et al., 2006; West, 2003). Consistent with this, inspection of global field power (GFP) plots of grand average ERP activity in both groups (averaged across all leads and all subjects in the separate groups) confirmed the presence of these interference effects (with similar timing) in our face-name Stroop task in both adults and adolescents (see Figs. 4 and 5; plots derived from BESA 5.0 software). In both groups the N450-interference effect was most pronounced between 420 and 460 ms and was distributed over parietal (P1, P2) and parietal-occipital (PO7, PO8) sites. The SP interference effect was most pronounced between 620 and 780 ms in adolescents and between 760 and 840 ms in adults at centro-parietal (CP1, CP2) and parietal (P1, P2) sites.

Statistical Analysis

Behavioral measures

To be able to check for potential group differences in verbal short term memory (STM) and verbal WM span forward and backward digit span measures were obtained from all adolescents and adults (derived from WISC-III for adolescents and WAIS-III for adults). Forward-span scores are considered to be measures of verbal STM, whereas backward-span scores are considered measures of verbal WM capacity, at least in children (St. Clair-Thompson, 2010). Raw scores on forward and backward digit span tests were entered in univariate ANOVA to check for age differences. Apart from raw scores, standardized digit span scores were also computed (according to the WISC-III and WAIS-III manuals) in each group.

For 0-back and 1-back WM trials, reaction time (RT) for correctly detected targets (0-back) or WM-probes (1-back), percentage of incorrect responses (% errors) and percentage of missed responses (% omissions) were computed. A repeated measures ANOVA with within-subjects factor Load (0-back, 1-back) and between-subjects factor Age (adolescents, adults) was conducted.

Furthermore, reaction time for correct responses (RT), % errors and % omissions for Stroop trials were computed. Tests were performed for all behavioral Stroop measures to examine effects of WM load (low or high) on Stroop interference (congruent vs. incongruent trials) by conducting a repeated measures ANOVA with

within-subjects factors Load (Stroop trials preceded by a 0-back or a 1-back trial) and Congruence (congruent, incongruent), and between-subjects factor Age (adolescents, adults). Significant Load \times Congruence interactions were further explored by testing the congruence effects of the separate levels of WM load. Two-tailed significance levels of 5% were adopted.

ERP measures

For both expected components of Stroop interference, conflict detection (N450) and conflict resolution (SP), mean voltage values in the specified time windows and at the specified locations were entered into a 2 (Load; 0-load, 1-load) \times 2 (Congruence; congruent, incongruent) \times 2 (Location; see specified locations per component) \times 2 (Hemisphere; Left, Right) \times 2 (Age; adolescents, adults) repeated measures ANOVA. Significant 5- or 4-way interactions were followed up by performing 4- or 3-way ANOVA's respectively at the different levels of the Location factor. In case such interactions (involving levels of Load, Congruence and Age) were found, further testing was done by first splitting up on the Load factor to explore Age \times Congruence effects in both Load (0-back vs. 1-back) conditions. Age \times Congruency interactions were explored further by testing Congruency effects in the separate Age groups. For all repeated measures ANOVAs two-tailed significance levels of 5% were adopted. Partial-eta squared effect sizes are reported with the ANOVA effects.

3.3 Results

Behavioral results

STM and WM capacity (digit span)

No significant Age differences were found for raw forward and backward digit span scores: forward digit span was 8.8 (SD 2.1) in adolescents, and 9.6 (SD 2.4) in adults (Age effect $F(1,34) = 1.0, p = .32$), and backward digit span was 6.1 (SD = 1.8) in adolescents, and 6.7 (SD = 2.8) in adults (Age effect $F(1,34) = 0.6, p = .44$). Mean standardized digit span scores (including both forward and backward scores; for computation see WISC-III/WAIS-III manual) were 10.1 (SD = 3.3) and 10.4 (SD = 3.5) in adolescent and adult groups respectively and were not significantly different (Age effect: $F(1,34) = 0.1, p = .83$).

N-back task performance

Means of RT, percentage of incorrect responses (errors) and percentage of missed responses in the 0-back and 1-back tasks are displayed in Table 1. Reaction times for

correctly responded trials ($F(1,34) = 19.4, p < .0005, \eta_p^2 = 0.36$), % errors ($F(1,34) = 98.3, p < .00001, \eta_p^2 = 0.74$) and % omissions ($F(1,34) = 7.30, p < .05, \eta_p^2 = 0.18$) increased in the 1-back condition compared to the 0-back condition in which no information had to be retrieved from memory, but similar left/right categorization responses had to be given (see Figure 2A and B for reaction times and % errors). A main effect of Age ($F(1,34) = 4.7, p < .05, \eta_p^2 = 0.12$) for % errors confirmed worse performance in adolescents (compared to adults) in the 1-back as well as the 0-back task. No Age \times Load interaction and no Age effects for RT and % omissions were found in the N-back task.

Stroop task performance

Means of RTs, percentage of incorrect responses and percentage of missed responses in the Stroop task are displayed in Table 1. For reaction time (RT), a main effect of Load ($F(1,34) = 10.3, p < .005, \eta_p^2 = 0.23$) showed slower Stroop responses in the 1-back condition compared to the 0-back condition (see Figure 3A). A main effect of Congruence ($F(1,34) = 17.1, p < .0005, \eta_p^2 = 0.34$) showed slower responding to incongruent than to congruent Stroop stimuli. Similar to RT, the percentage of errors also increased with Load ($F(1,34) = 55.0, p < .0001, \eta_p^2 = 0.62$; more errors in 1-back than 0-back) and Congruence ($F(1,34) = 7.7, p < .01, \eta_p^2 = 0.18$; more errors in response to incongruent vs. congruent Stroop stimuli) (see Figure 3B). Main Age effects were present for % errors ($F(1,34) = 15.2, p < .001, \eta_p^2 = 0.31$) and % omissions ($F(1,34) = 9.8, p < .005, \eta_p^2 = 0.22$), indicating less accurate Stroop performance in adolescents than adults, reaction times were not different between the age groups. No Load \times Congruence or Age \times Load \times Congruence interaction effects were found.

Table 1. Group means (standard deviations between brackets) of the behavioral parameters for the N-back trials and Stroop trials in the combined N-back and face-word Stroop task.

		N-back trials			Stroop trials			
		RT (ms)	Errors (%)	Omissions (%)		RT (ms)	Errors (%)	Omissions (%)
Adolescents (N=17)	WMload0	708 (133)	7 (8)	4 (3)	C	740 (176)	18 (13)	0.7 (1.6)
					IC	755 (184)	20 (17)	1.4 (2.5)
	WMload1	790 (171)	18 (12)	11 (15)	C	781 (178)	36 (18)	1.2 (1.4)
					IC	816 (197)	39 (14)	1.4 (1.9)
Adults (N=19)	WMload0	752 (120)	3 (3)	3 (2)	C	778 (129)	6 (6)	0.1 (0.4)
					IC	803 (132)	9 (8)	0.4 (1.3)
	WMload1	852 (129)	12 (6)	6 (7)	C	835 (100)	20 (12)	0.0 (0.0)
					IC	865 (105)	20 (15)	0.5 (0.8)

RT = reaction time, C = Congruent, IC = Incongruent

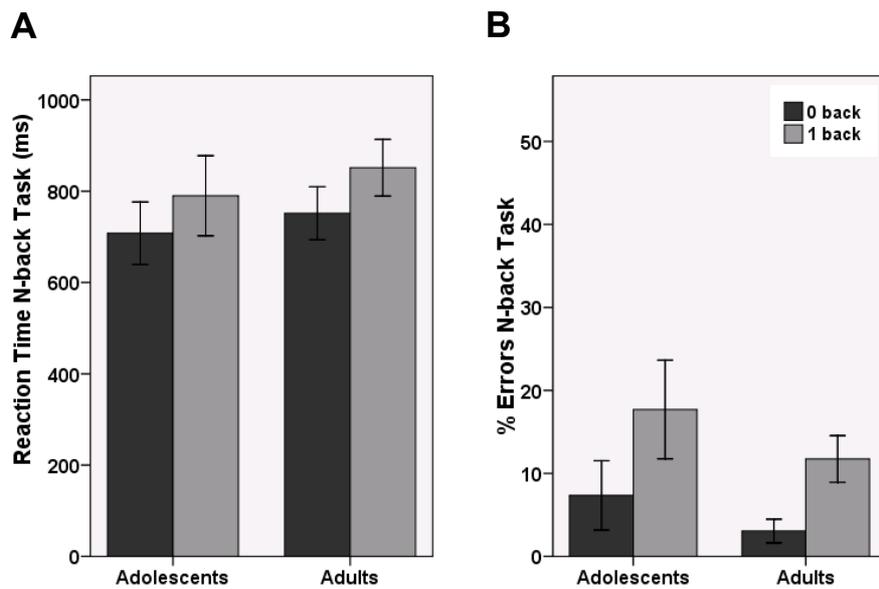


Figure 2. Behavioral N-back measures. Bar graphs of (A) average reaction times (in ms) and (B) percentage of errors for adolescents and adults in the WM load-0 and WM load-1 conditions of the N-back task. Error bars indicate 95% confidence intervals.

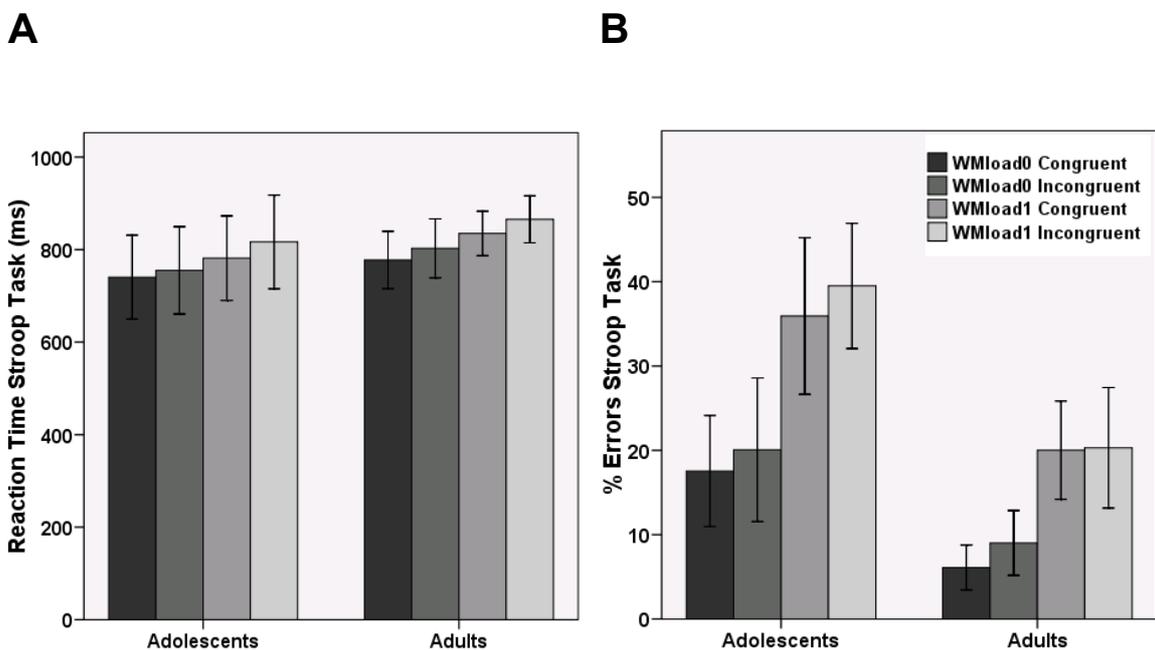


Figure 3. Behavioral Stroop measures. Bar graphs of (A) average reaction times (in ms) and (B) percentage of errors for adolescents and adults in the WM load-0 Congruent, WM load-0 Incongruent, WM load-1 Congruent and WM load-1 Incongruent conditions of the Stroop task. Error bars indicate 95% confidence intervals.

ERP results

N450

The N450 interference effect was analyzed in a window from 420 to 460 ms at left and right occipito-temporal (PO7, PO8) and at parietal (P1, P2) electrodes. Selection of this time window and electrodes for analyses is based on: 1) global field power information, 2) topographic maps of N450 interference effects at maximum amplitude (for points 1 and 2; see Figure 4), 3) the average ERPs (see Figure 5) and 4) prior neuroimaging studies reporting on the location of gender face processing in occipito-temporal cortex (Haxby et al., 2000, 2002).

The ANOVA analyses yielded a significant Load \times Congruence \times Age \times Location \times Hemisphere interaction $F(1,34) = 6.0, p < .05, \eta_p^2 = 0.15$. This 5-way interaction was further explored by performing Load \times Congruence \times Age \times Hemisphere analyses separately at parietal and occipito-temporal electrodes (per level of the Location factor). For the *occipital-temporal* (PO7, PO8) electrodes the 4-way Load \times Congruence \times Hemisphere \times Age interaction ($F(1,34) = 4.11, p = .051, \eta_p^2 = 0.11$) was significant. This 4-way interaction was further explored by testing for 2 (Age) \times 2 (Congruence) \times 2 (Hemisphere) interactions per level of the Load factor. In the Load-0 (0-back) condition, the analyses yielded significant Congruence ($F(1,34) = 4.7, p < .05, \eta_p^2 = 0.12$) and significant Age \times Congruence effects ($F(1,34) = 10.6, p < .005, \eta_p^2 = .24$). There were no effects of Hemisphere. Further testing per Age group showed that adults had no significant N450 interference effect in the 0-back condition (Load 0: Congruence: $F(1,18) = 1.1, p = .307, \eta_p^2 = 0.06$) whereas adolescents did show a N450 interference effect ($F(1,16) = 8.3, p < .05, \eta_p^2 = 0.34$), marked by larger negativity to incongruent trials (see Figure 5). In the Load-1 (1-back) condition, the analysis yielded significant effects of Congruence ($F(1,34) = 11.6, p < .005, \eta_p^2 = 0.28$), Congruence \times Hemisphere ($F(1,34) = 9.8, p < .005, \eta_p^2 = 0.22$) and a trend-significant Age \times Congruence \times Hemisphere interaction ($F(1,34) = 3.9, p = .06, \eta_p^2 = 0.10$). Follow-up testing of this 3-way interaction did not reveal significant Age \times Congruence interactions at PO7 ($p = .08$) or PO8 ($p = .58$), but main Congruence effects were significant at PO7 ($F(1,34) = 16.5, p < .0001, \eta_p^2 = 0.33$) and PO8 ($F(1,34) = 5.1, p < .05, \eta_p^2 = 0.13$), although the latter effect would not survive Bonferroni correction. This signifies similar N450 interference effects in adolescents and adults above left occipital cortex in the 1-back condition.

Further 2 (Load) \times 2 (Congruence) \times 2 (Hemisphere) \times 2 (Age) analyses at *parietal* (P1, P2) electrodes only showed significant Congruence ($F(1,34) = 15.4, p < .001, \eta_p^2 = 0.31$) and Age \times Congruence effects ($F(1,34) = 7.4, p < .05, \eta_p^2 = 0.15$) and a marginally significant Hemisphere effect ($p = .07$), no further effects of Hemisphere or Load effects were found. The Congruence \times Age interaction was followed up by testing for Congruence effects in separate groups. Adolescents showed a significant main Congruence effect at parietal electrodes (Congruence: $F(1,16) = 12.8, p < .005, \eta_p^2 = 0.45$), indicating higher parietal negativity to incongruent than congruent Stroop

stimuli, irrespective of n-back condition. Adults did not show a significant main Congruence effect ($F(1,18) = 1.7, p = .20, \eta_p^2 = 0.09$) at parietal leads. A post-hoc analyses however showed that this was caused by the presence of a Load \times Congruence interaction at parietal leads in adults ($F(1,18) = 5.6, p < .05, \eta_p^2 = 0.24$), further testing per Load level revealed no significant N450 interference effect in the 0-back condition ($F(1,18) = 0.37, p = .55, \eta_p^2 = 0.02$), but there was a significant N450 interference effect in the 1-back condition when a concurrent load had to be maintained in WM ($F(1,18) = 9.4, p < .01, \eta_p^2 = 0.34$).

Summarizing these N450 results; in the 0-back condition when there was no concurrent WM load adolescents showed significant N450-interference effects at all parieto-occipital (PO7, PO8) and parietal (P1, P2) electrodes whereas adults did not. In the 1-back condition, when a letter had to be maintained in WM while performing the Stroop task, adolescents and adults now both showed significant N450-interference effects at PO7, P1 and P2 electrodes, but not at PO8.

Table 2. Mean area values and standard deviations (between brackets) of the N450 (420-460ms for adolescents and adults) and SP and frontal effect (adolescents: 620-780 ms; adults: 760-840 ms) windows in the Stroop task, for congruent and incongruent stimuli in load-0 and load-1 conditions.

		Stroop trials					
			N450 (P1/2)	N450 (PO7/8)	SP (P1/2)	SP (CP1/2)	Frontal effect (F5/7)
Adolescents (N=17)	WMload0	C	14.5 (9.1)	8.2 (6.0)	5.9 (6.0)	5.1 (5.1)	0.3 (6.5)
		IC	12.3 (8.8)	6.1 (5.7)	8.5 (7.6)	7.2 (6.8)	1.6 (6.0)
	WMload1	C	13.4 (10.7)	7.2 (6.9)	7.4 (6.5)	6.1 (5.7)	2.6 (6.7)
		IC	10.7 (9.1)	5.3 (5.2)	10.5 (7.3)	9.4 (6.3)	3.4 (5.7)
Adults (N=19)	WMload0	C	6.7 (6.8)	2.7 (4.2)	2.0 (3.2)	2.1 (3.7)	-0.7 (4.1)
		IC	7.0 (6.9)	3.1 (4.6)	3.1 (3.5)	3.2 (3.8)	-0.1 (3.9)
	WMload1	C	7.0 (5.5)	3.0 (3.7)	3.8 (2.8)	3.6 (2.8)	1.9 (2.1)
		IC	5.8 (5.5)	2.1 (3.6)	4.2 (3.1)	4.2 (3.5)	1.8 (3.8)

C = Congruent, IC = Incongruent

SP/P600

The SP interference effect was analyzed in a window from 760 to 840 ms in adults and from 620 to 780 ms in adolescents at centro-parietal (CP1, CP2) and parietal (P1, P2) electrodes at which the SP reached maximal amplitude (see topographic maps and GFP plots in Figure 4). Mean area amplitude measures in the above mentioned time windows were entered in Repeated Measures Age \times Load \times Congruence \times

Location (CP, P) × Hemisphere (left, right) ANOVAs. This analysis did yield no five-, four- or three-way interactions, but revealed only three two-way interactions:

1) A significant Congruence × Age interaction ($F(1,34) = 7.8, p < .01, \eta_p^2 = 0.17$), of which further testing showed significant centro-parietal SP Congruence effects in both groups (e.g. higher SP amplitude in incongruent Stroop trials), but effects had larger effect sizes in adolescents (Congruence: $F(1,16) = 16.8, p < .001, \eta_p^2 = 0.51$) than in adults ($F(1,18) = 7.3, p < .05, \eta_p^2 = 0.29$).

2) A Location × Age interaction ($F(1,34) = 5.0, p < .05, \eta_p^2 = 0.13$) showed maximum centroparietal SP amplitude in adolescents (Location: $F(1,16) = 5.7, p < .05, \eta_p^2 = 0.26$), whereas SP amplitude did not differ between centroparietal and parietal locations in adults (Location: $F(1,18) = .002, p = .967, \eta_p^2 = 0.00$).

3) A Load × Hemisphere interaction ($F(1,34) = 11.5, p < .005, \eta_p^2 = 0.25$) showed that SP amplitude increased on both congruent and incongruent trials when a concurrent WM load was imposed (1-back) as compared to when no load was imposed (0-back) (see Table 2), this increase was larger above the left ($F(1,34) = 8.3, p < .01, \eta_p^2 = 0.20$) than right ($F(1,34) = 5.8, p < .05, \eta_p^2 = 0.15$) centroparietal cortex.

Frontal activity in the SP window

An additional analysis at frontal leads in the SP time window was conducted since clear amplitude differences between conditions were observed in the average ERPs and topographic maps over left frontal leads (see SP/P600 maps in Figure 4). A 2 (Age) × 2 (Load) × 2 (Congruence) × 2 (Electrode; F5, F7) repeated measures ANOVA did not yield a four-way interaction or any effects of the Congruence factor. There however was a three-way Load × Electrode × Age interaction ($F(1,34) = 4.7, p < .05, \eta_p^2 = 0.12$). This interaction was further explored by testing for Electrode × Load effects in separate groups. In adults there was a main Load effect ($F(1,18) = 19.0, p < .001, \eta_p^2 = 0.51$), indicating larger left frontal SP activity with increased load during processing of both congruent and incongruent stimuli at both F5 and F7. In adolescents, a Load × Electrode interaction was found ($F(1,16) = 5.1, p < .05, \eta_p^2 = 0.24$); the Load effect was only significant at F5 ($F(1,16) = 6.0, p < .05, \eta_p^2 = 0.27$), but not at F7 ($F(1,16) = 2.8, p = .11, \eta_p^2 = 0.15$).

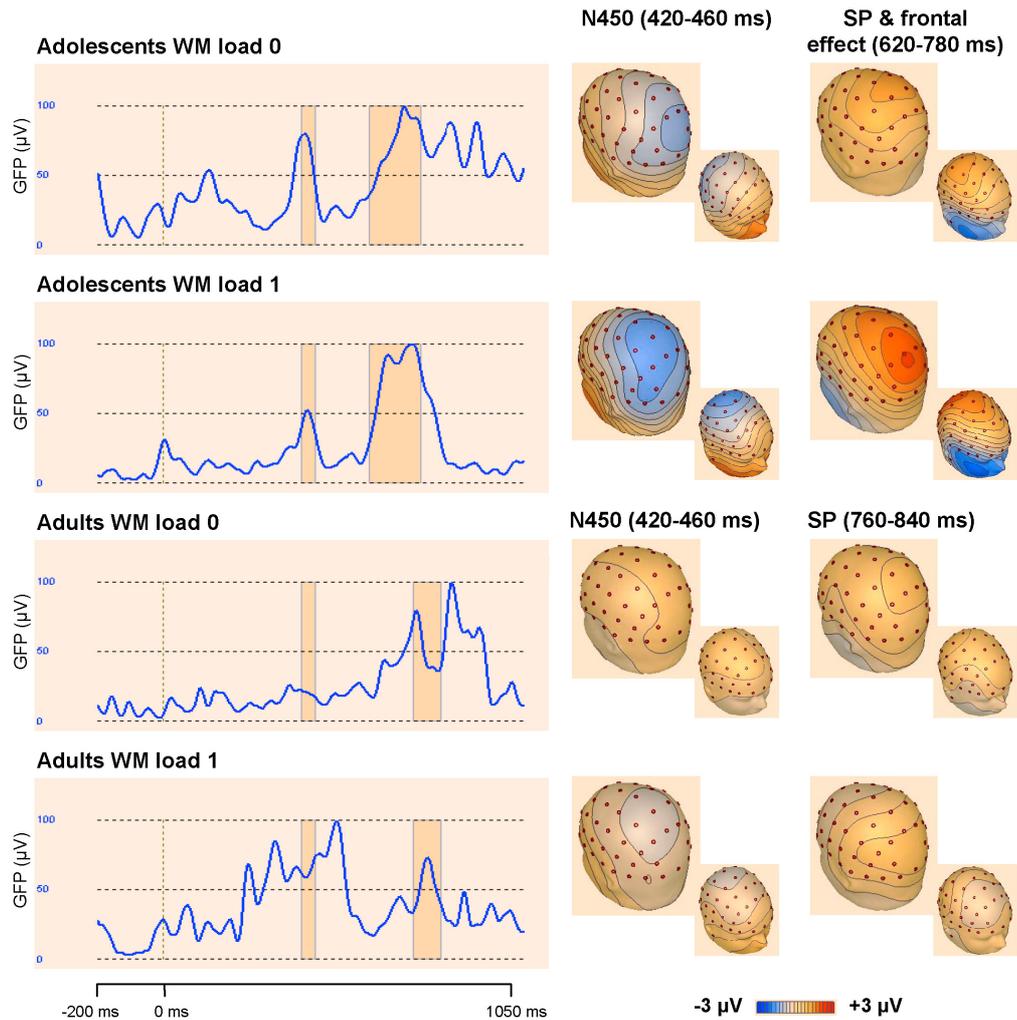


Figure 4. Global Field Power of Stroop trials and Topographic maps of Stroop N450 effects (420-460 ms in adults and adolescents) and SP and frontal effects (620-780 ms in adolescents and 760-840 ms in adults) across 60 electrodes in WM load-0 and WM load-1 conditions. The plots and maps are based on the amplitudes of Incongruent minus Congruent conditions; maps depict time points at which the effects were maximal.

3.4 Discussion

In this study a dual-task paradigm was used to measure the effects of WM load manipulation on the control of interference by distracting stimuli (faces) in a word-face Stroop task in adolescents and adults. In adults, decreases in interference control or the ability to suppress the influence of distracters have previously been reported when WM is occupied by holding high loads of information (de Fockert et al., 2001; Lavie and De Fockert, 2005; Lavie et al., 2004). Since fronto-parietal networks that are involved in the regulation of such WM-maintenance-interference control interactions are still immature in adolescents, we expected adolescents to have more problems than adults with suppressing the processing of distracter faces, especially when

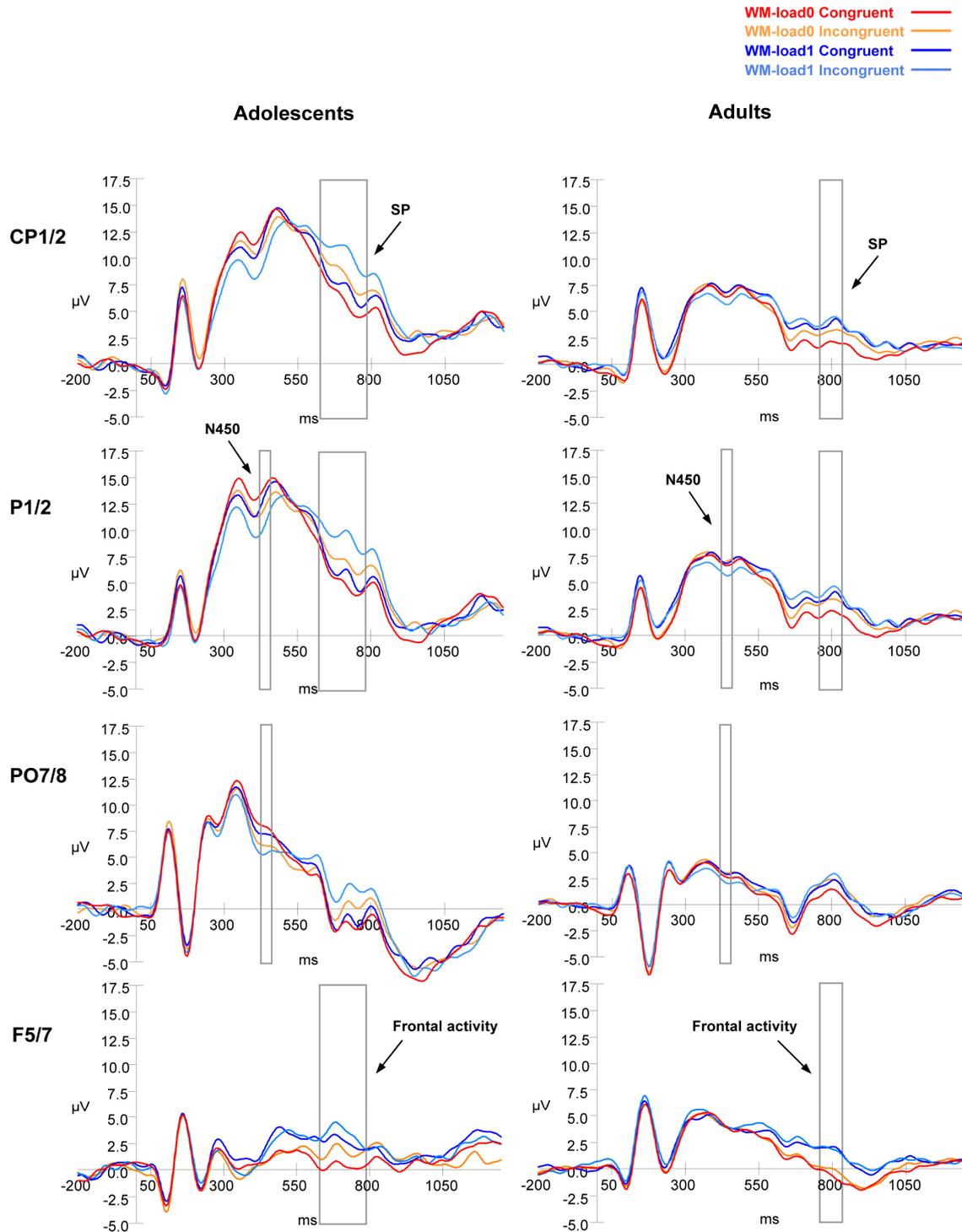


Figure 5. Grand-averaged ERPs of adults and adolescents at combined (averaged) electrodes CP1&CP2, P1&P2, PO7&8 and F5&F7 in WM load-0, WM load-1, Congruent and Incongruent conditions elicited by face-word Stroop stimuli. Analyzed windows for N450 and SP and frontal activity are indicated by gray rectangles.

demands on prefrontal cortex (PFC) increase by manipulating distraction and WM load at the same time.

Behavioral Stroop interference and effects of WM load

Manipulation of WM load was successful as shown by significantly lower accuracy and slower responding in the 1-back than 0-back task. Manipulations of Stroop congruence (interference) were also successful. Both with and without a concurrent WM load, responding slowed and errors and omissions increased in the presence of incongruent distracter faces, compared to when faces were congruent with the to be categorized word (e.g. face of a female and word female). Besides these effects for all participants, it was found that adolescents made more errors than adults in 0-back, 1-back and Stroop tasks and also missed more trials in the latter. This suggests that attention/cognitive control functions still continue to develop throughout adolescence, as was suggested in previous studies (Casey et al., 2005; Luna et al., 2001, 2010).

The expected extra increase in interference with a concurrent WM load was however not revealed by the behavioral data, not in adults nor in adolescents. According to Load theory, an active top-down mechanism of attentional control mediated by prefrontal cortical areas depends on WM and plays an important role in the maintenance of goal directed behavior in the presence of interference (Lavie et al., 2004). When WM is loaded, distracter interference in a Stroop task is suggested to increase because resources necessary for goal maintenance are consumed by concurrent WM processes. Evidence for this theory has been shown, mainly by Lavie and co-workers, in a number of studies (for a review, see Lavie and De Fockert, 2005). However, there are also behavioral studies that did not replicate WM load effects on interference control in adults when using similar face-word or other paradigms (Jongen and Jonkman, 2011; Kim et al., 2005; Park et al., 2007; Woodman et al., 2001). One explanation might be that subjects do experience higher distracter interference with load but have enough capacity to resolve conflict online so that it is no longer visible in the response. In this case load \times congruence effects should be visible in ERPs, for which there is some evidence that will be discussed below.

Effects of WM load on conflict detection (N450)

Stroop interference effects (N450 and SP) were observed in adults and adolescents. In line with previous studies (Chen et al., 2011; Jongen and Jonkman, 2011; Lansbergen et al., 2007; Liotti et al., 2000; Markela-Lerenc et al., 2004; Qiu et al., 2006; West, 2003, 2004) the N450 effect was the first interference effect in the brain and was marked by enhanced negativity around 450 ms in response to incongruent compared to congruent stimuli. On the basis of its sensitivity to different experimental manipulations of conflict strength the N450 has been linked to the process of conflict detection (Lansbergen et al., 2007; Liotti et al., 2000; Tillman and Wiens, 2011; West

and Alain, 2000; West et al., 2005). In our study the N450 response had a posterior distribution above parietal and occipital-temporal cortex in contrast to the central-frontal distribution reported in color-word Stroop tasks. This posterior distribution is similar to “N450” distributions reported in the only other ERP study that we know of that used a highly similar word-face Stroop task (Jongen and Jonkman, 2011) and in a developmental study in which a color-object Stroop task was used (Jongen and Jonkman, 2008). The present occipital-temporal N450 effect would be in line with higher attentional processing of the (gender of) the distracter face in the incongruent condition. Whereas we did no source localization in the present study, prior fMRI (Haxby et al., 2000, 2002) and ERP studies (Sun et al., 2010) have provided evidence for gender-face processing in/above fusiform cortex and face processing studies have localized activity above temporal-occipital cortex to fusiform cortex (Rossion et al., 2003; Schweinberger et al., 2002). Furthermore two studies by Fruhholz et al. (2009a,b) provided evidence that interference effects similar to N450 can be observed at parietal and occipital electrodes when processing face stimuli (in the presence of irrelevant contextual information), and that increased activity for incongruent trials in the fusiform cortex is related to this face categorization. On the basis of this literature we suggest that the posterior N450 response in our word-face Stroop task reflects enhanced processing of the distracter faces when to-be categorized gender names are incongruent with the distracter.

Based on Load theory and the protracted development of frontal-parietal networks used for interference control in adolescents (Luna et al., 2004, 2010) we expected ERP conflict responses (N450 and/or SP) to be increased in adolescents due to reduced availability of resources for top-down control, especially in situations when high demands are put on top-down executive control such as when one has to hold a load in WM while simultaneously suppressing Stroop-induced conflict (as in the current 1-back-Stroop task). This hypothesis was partly confirmed by a 5-way Load \times Congruence \times Age \times Location \times Hemisphere interaction effect for the N450. Further testing of this interaction showed that in adults the posterior N450-interference response was modulated by WM load (Load \times Congruence interaction) as predicted by Load theory. More specifically, adults did not show an N450 interference effect when no concurrent WM load had to be maintained (in the 0-back condition). However, when simultaneous refreshing of letter information in the 1-back task was required during performance of the Stroop task, there was a significant N450 Stroop interference effect above left occipital cortex (PO7) and parietal cortex. In contrast, adolescents already showed a significant N450 Stroop interference effect when no information had to be maintained concurrently in WM (e.g. in the 0-back condition). When a concurrent WM task was performed, the N450-interference effect was still present above left temporal-occipital cortex and parietal cortex, but did not further increase. We suggest that the higher parietal-occipital N450 conflict response found in adults when holding a concurrent WM load is caused by reduced (frontal) top-down control on distracter, in this case face, processing. Such an interpretation would be consistent with findings from a prior fMRI study that used a similar WM-

face-name Stroop task and reported increased activation in fusiform face areas associated with distracter face processing when higher WM loads were imposed in their adult subjects (de Fockert et al., 2001). It is not clear why adolescents did not show a further increase in the N450 interference effect with increasing WM load. One explanation might be that adolescents already reached a maximum level of resource depletion in the 0-back condition (due to dual-task demands) allowing no further rise in interference effects (or distracter processing), but such a conclusion would need further experimentation. Nevertheless, the overall reduced accuracy in the Stroop and 0- and 1-back tasks and the larger N450-interference effect in the 0-back condition in adolescents suggest that they have still immature attentional or interference control functions. Although this cannot be confirmed in the present study this is suggested to be caused by the protracted development of the networks including frontal, striatal and parietal brain regions (Sowell et al., 1999) known to be involved in WM and distracter suppression (Bunge and Wright, 2007; Hopfinger et al., 2000; Klingberg et al., 2002; Luna et al., 2010; McNab and Klingberg, 2008).

Effects of WM load on the SP/P600 interference effects

A conflict SP effect (sometimes also called a P600 effect in the Stroop literature) followed the N450 and was marked by enlarged positivity above centro-parietal cortex when the gender of the distracter face was in conflict with the to-be-categorized gender-word compared to when it was not. A significant Age \times Congruence interaction showed that this centro-parietal SP Stroop interference effect was significantly larger in adolescents than adults in both load conditions. On the basis of the Stroop-ERP literature parietal-SP effects are suggested to reflect enhanced processing of response-relevant information used to guide response selection in incongruent trials (Chen et al., 2011; Jongen and Jonkman, 2008, 2011; Lansbergen et al., 2007; Liotti et al., 2000; Markela-Lerenc et al., 2004; Qiu et al., 2006; West, 2003). Parietal-SP effects have been localized to parietal cortex in adults (Chen et al., 2011) and fMRI studies have reported evidence for a role of parietal cortex in supporting stimulus-response mappings that facilitate response selection in the Stroop task (Bunge et al., 2002; Casey et al., 2000; Rushworth et al., 2001). When adopting this response selection SP relation, the higher SP interference effects in adolescents might reflect the recruitment of more resources to guide response selection in situations with high response-conflict. Such increased resource demands for response selection on incongruent trials in adolescents is not surprising in light of the above discussed N450 findings of their higher conflict detection responses above occipital cortex. Higher detection of conflict (e.g. higher processing of distracter-faces) might have led to higher activation of the incorrect response requiring more resources for subsequent selection of the correct response. The centro-parietal SP increased in amplitude in both age groups when a WM load was imposed, but this increase occurred for both the congruent and incongruent Stroop trials (main Load effect) and was hence thought to be associated with general depletion of resources. In

an earlier ERP study using a similar WM-Stroop task (Jongen and Jonkman, 2011), adults only showed a WM load effect on the later SP/P600 and only on incongruent trials. In our adults processing bottlenecks occurred earlier in time, already on the N450, and during the response selection (SP/P600) stage affected both congruent and incongruent processing. This might be due to the fact that our subjects were collected from a community sample to match them with our adolescents on education level and thus had lower verbal STM/WM capacity and considerably lower IQ scores than the adults in the Jongen and Jonkman (2011) study, perhaps causing earlier depletion of resources.

Adults additionally showed a higher load-related amplitude increase above left frontal cortex in the time window in which the centro-parietal SP occurred. This load-related increase in left frontal activity was also seen in adolescents but only at electrode F5 and with a much smaller effect size. Since these load-related increases were not specific for situations in which there was conflict between names and faces they are thought to reflect enhanced attention control needed for dual-task performance. There are two possible explanations for this higher left frontal activity when subjects had to hold a letter from the 1-back task in WM during Stroop processing. The first explanation is that it reflects higher top-down control on posterior conflict processing areas when holding a concurrent load. Such a conclusion is supported by an fMRI study from Egner and Hirsch (2005) in which a similar face-name Stroop task was used (without WM load manipulation) and PFC activation was accompanied by a decrease in behavioral Stroop interference. But since ERP results do not allow for strong conclusions about sources based solely on scalp topography such conclusions remain speculative at this stage. The weaker load effect on frontal activity in the Stroop task in adolescents is supported by earlier Stroop and inhibition studies also reporting reduced PFC activity in adolescents (Adleman et al., 2002; Rubia et al., 2000). A second possibility is that the load-related left PFC activity increase is a reflection of the rehearsal or refreshment of letters from the n-back task during Stroop processing. Left PFC activation has been linked to processes of rehearsal in prior studies (Braver et al., 1997; Curtis and D'Esposito, 2003). Adopting such a rehearsal account, the weaker left frontal load effects of adolescents might mean that they engaged in less rehearsal and this would be congruent with the larger number of memory errors made by adolescents in the 1-back task and with findings that individuals with higher WM capacity show more PFC recruitment in WM tasks that are demanding (Osaka et al., 2003). Moreover, in a previous study adults were also found to have larger increases in frontal activation with increases in WM load than children (Thomason et al., 2009). But such conclusions need further investigation.

Conclusion

The present combination of a WM-Stroop dual-task and the application of ERPs has provided new information about the time-point at which WM capacity influenced selective attention processes needed during interference control in adolescents and adults. ERP results suggest that interference control is differentially affected by changes in WM capacity in adolescents than adults. Adolescents performed worse than adults on Stroop trials and WM trials. In adults, enhanced N450 interference effects were found above face processing areas when a concurrent WM load had to be held in memory and based on the literature this was interpreted as evidence for enhanced interference from distracter faces in the face-name Stroop task. N450 results in adolescents showed that they experienced stronger interference from distracter faces than adults and this interference was already present when WM was not loaded. SP results showed higher conflict responses at parietal sites in adolescents than adults, irrespective of WM load. Based on the literature these parietal SP interference effects were suggested to reflect higher recruitment of resources for selection/enhancement of the correct response and/or suppression of the incorrect response in incongruent trials. This higher SP response in adolescents is consistent with their larger N450 conflict detection response that might have evoked larger incorrect response activation the suppression of which needed more resources during the later SP-response-processing stage. In addition, load-related increases above left frontal cortex in the SP interval were present in both groups, but were weaker in adolescents and might reflect immature rehearsal processes or reduced top-down attentional control over posterior areas involved in conflict processing. The main conclusion is that adolescents have worse distracter suppression than adults, caused by lower availability of resources for top-down control.

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Chapter 4

Are visuospatial working memory deficits in adolescents related to reduced storage capacity and/or impaired filtering efficiency?

Based on:

Spronk, M., Vogel, E.K., Jonkman, L.M. (submitted). Are visuospatial working memory deficits in adolescents related to reduced storage capacity and/or impaired filtering efficiency?

Abstract

The present study investigated whether adolescents' worse performance in working memory (WM) tasks is caused by smaller storage space or inefficient use of storage space caused by an inability to block irrelevant information from memory, or both. In a visuospatial WM task with manipulations of WM load and distraction, behavior was measured, as well as electrophysiological contralateral delay activity (CDA); a neural correlate of the number of targets and distracters encoded and maintained in WM. Significantly lower visuospatial WM capacity (Cowan's K) was found in adolescents than adults, and adolescents' performance suffered more from the presence of distracters. Distracter-related CDA responses were higher in adolescents and positively correlated with performance measures of distracter interference, indicating that higher interference in adolescents was caused by an inability to block distracters from WM. Adolescents' lower K was accompanied by more variable load-related occipital-parietal CDA responses. These findings point to immaturity of frontal-parietal WM-attention networks.

4.1 Introduction

Working memory (WM), our system for storage and maintenance of information for short periods of time, plays a crucial role in the development of cognitive abilities. Especially WM capacity is an important factor for the development of academic skills such as reading and mathematics (Gathercole & Alloway, 2006; Gathercole et al., 2004) and fluid intelligence (Conway et al., 2002; Fukuda et al., 2010).

The limits of WM capacity have been extensively researched, leading to the assumption that adults can only maintain a maximum of three to four items simultaneously in WM (Cowan, 2001; Luck & Vogel, 1997; Todd & Marois, 2004). However, recent work has shown that the capacity of WM does not only depend on how many items can be stored in short-term memory, but also on the efficiency with which items are stored. The latter means that only items that are relevant to current task goals should be selected for access to and maintenance in WM. Selective attention, mediated by fronto-striatal-parietal networks, is thought to play an important role in this regulation of access to WM (Awh et al., 2006; Cowan et al., 2005; McNab & Klingberg, 2008; Vogel et al., 2005). Recent studies have shown that low WM capacity can indeed be caused by inefficient filtering of information that enters WM for maintenance (Awh et al., 2006; Fukuda & Vogel, 2009; Kane et al., 2001; McNab & Klingberg, 2008; Vogel et al., 2005; Zanto & Gazzaley, 2009).

Developmental studies have consistently shown that mature WM capacity is only reached during late childhood or adolescence. Whereas some studies report mature visuospatial working memory (VSWM) capacity around 10-12 years-of age (Riggs et al., 2006; Van Leijenhorst et al., 2007), other studies report that mature WM capacity is not reached before the age of 16 (Gathercole, 1999; Luciana et al., 2005; Luna et al., 2004). Such developmental differences seem to depend on the level of executive control processes that are needed to perform a specific WM task. As mentioned above, one such important executive process is filtering efficiency, that is, the efficiency with which the individual is capable of excluding irrelevant information to get access to, or interfere with the current contents of WM. Schleepen and Jonkman (2010) showed particularly late development of non-spatial WM capacity into adolescence in task conditions requiring simultaneous maintenance, updating and suppression of irrelevant information.

This late development of WM capacity in tasks demanding high attentional control has been attributed to the protracted development of fronto-striatal-parietal networks that are known to be involved in regulating access to WM (Bunge & Wright, 2007; Hopfinger et al., 2000; Klingberg et al., 2002; McNab & Klingberg, 2008). In healthy adults, activations of parietal structures like the intraparietal sulcus (IPS) during VSWM tasks have been found to increase with WM load, leveling off at maximum capacity and are hence thought to be associated with storage capacity (Linden et al., 2003; Todd & Marois, 2004; Xu & Chun, 2006). The dorsolateral prefrontal cortex (DLPFC) on the other hand is thought to play an important role in

attentional control over which information should be maintained and rehearsed in WM in the retention interval of a task (Curtis & D'Esposito, 2003). Increased activity in DLPFC during WM tasks has been observed especially under high WM load conditions (Grimault et al., 2009; Rypma et al., 2002), suggesting frontal areas are essential in keeping performance levels high through cognitive control. Moreover, Edin et al. (2009) have found that DLPFC might also be able to boost parietal areas (IPS) to achieve higher WM capacity during a visuospatial WM task. Bunge and Wright (2007) reviewed the developmental functional imaging literature in the field of spatial attention and WM: They reported that better performance on WM tasks across age, especially when these tasks require more cognitive control, coincides with increased recruitment of frontal and parietal areas, like DLPFC and IPS.

Overall, previous behavioral and functional neuroimaging studies indicate that the development of spatial memory capacity continues until late childhood or adolescence, which becomes evident in situations where high attentional control is required. Nevertheless, in most of these studies conclusions about developmental differences in storage capacity were derived from performance measures such as differences in recognition or change detection accuracy in tasks in which test displays have to be compared to what has been earlier stored in WM. Before arriving to a response in such tasks subjects pass through several processing stages, namely encoding, maintenance and a comparison/decision process. Thus, there are several possible stages of processing from where developmental differences in behavior between adults and adolescents can arise. Behavioral and functional imaging studies miss the temporal resolution to distinguish between these stages. Therefore, it cannot be concluded from previous studies whether the deficient WM performance in adolescents is due to smaller storage space, and/or a lack of attentional control abilities to prevent irrelevant information from being encoded in WM, which will also lead to lower WM capacity. Results from a recent study by Cowan et al. (2010) suggest that attentional control is indeed reduced in children, especially when VSWM load is high, but the authors also stress that there are other possible causes for age differences in WM capacity. In the current study event-related brain potentials (ERPs), that have a millisecond time resolution, are collected in an attempt to investigate the origin of such developmental differences in WM capacity.

In 2004, Vogel and Machizawa reported ERP activity above the parietal cortex that increased in amplitude with the number of items maintained in WM and that was correlated with a behavioral measure of VSWM capacity (Cowan, 2001). Vogel and Machizawa named this activity the contralateral delay activity (CDA), since it occurs during the delay interval of a WM task in which items have to be encoded and maintained and was present above the parietal hemisphere contralateral to the visual hemifield in which the to-be-memorized items were presented. Based on these findings, the CDA was adopted as a neural correlate of the number of items encoded and/or maintained in WM during the delay interval of their change-detection task in the present study (Ikkai et al., 2010; McCollough et al., 2007; Vogel & Machizawa, 2004).

Another study by Vogel et al. (2005) showed that the CDA could also be used as a measure of filtering efficiency since it also increased in amplitude when irrelevant items were stored in WM, despite instructions. This was shown in one experiment where subjects had to memorize the orientation of either two or four red items (the targets) for a later memory test. In a third condition two target items were accompanied by two distracter (e.g. blue-colored) items (T2D2; 2 targets, 2 distracters) that should not be stored in WM. The idea was that subjects with inefficient filtering abilities would also store the two distracter items in WM, having a total storage load of 4. Taken that the CDA amplitude varies with the number of stored items, this should be reflected by overlapping CDA's in the T4D0 and T2D2 conditions. This was indeed what was found, but only in subjects with low-WM capacity. In subjects with high WM capacity the T2D2-CDA overlapped with the T2D0-CDA and was smaller than the T4D0-CDA, showing that they had successfully prevented storage of the two distracter items. Thus, in this paradigm, the CDA can be used as a neural correlate of the number of relevant and irrelevant items that are encoded or maintained in memory in the retention interval of the task.

In the present study the change-detection task and the ERP-CDA measure were used to investigate whether the often reported worse performance of adolescents in WM tasks is caused by a lower storage capacity and/or by still immature selective attention/filtering capacity. For this purpose, we compared performance and CDA amplitudes of adolescents and adults performing a VSWM change detection task. To our knowledge, this is the first time that the CDA has been used to investigate the online storage of irrelevant and relevant information in VSWM in adolescence. In the present task three conditions are relevant; a one target, no distracter condition (T1D0), a three target, no distracter condition (T3D0) and a one target, 2 distracters condition (T1D2). Cowan's K was computed as a behavioral VSWM capacity measure that estimates each individual's mean number of objects memorized, corrected for guessing (Cowan, 2001). First, we expected lower WM capacity in adolescents to be reflected by lower K scores compared to adults. Also, in addition to Cowan's K , we obtained another measure of WM capacity -independent from the change detection task- from a Digit Span task (Wechsler, 1997). Performance on the Standardized Digit Span task has been shown to correlate with performance in other WM tasks that require executive control (Hill et al., 2010) and was also expected to be lower in adolescents. If the lower performance on the VSWM task is due to lower storage capacity, we expect to find a relation between CDA-amplitude increases with increases in load from 1 to 3 items and WM performance decreases. In case of immature WM filtering in adolescents we expected larger unnecessary storage of distracter items in WM, which would present itself as 1) larger distracter interference effects on behavior (RT, accuracy, K) in adolescents than adults and 2) overlapping CDA's in T3D0 and T1D2, or at least larger T1D2 than T1D0 CDA amplitudes in adolescents, whereas behavioral distracter interference effects (on RT, accuracy and K) and T1D0-T1D2 CDA differences should be smaller in adults.

4.2 Methods

Subjects

Forty-three subjects participated in the study (23 adolescents and 20 adults), of which five were excluded due to significant outliers in behavioral measures (two in the adolescent group and three in the adult group). The 21 adolescents (ten boys and eleven girls) were recruited from a school providing vocational education for 12- to 16-year-olds. The 17 adults (eight males and nine females) were recruited via advertisements in local newspapers, and were required to have educational levels comparable to that of the adolescents.

Mean age was 14.8 years (SD 1.4, range 12-16 years) in the Adolescent group and 31.6 years (SD 8.9, range 20-45 years) in the Adult group.

To check for the absence of attention- and/or ADHD behavioral problems, the adolescents themselves filled out the Youth Self Report form (YSR; Achenbach, 1991b) and one of their parents filled out the Child Behavior Checklist (CBCL; Achenbach, 1991a). Mean scores on the attention subscales were 52.5 on the YSR (SD 3.6; range 50-60) and 53.8 on the CBCL (SD 4.2; range 50-62), and on the ADHD subscales 53.0 on the YSR (SD 4.1, range 50-67) and 53.4 on the CBCL (SD 4.0, range 50-63). Participating adults filled out the Adult Self Report form (ASR; Achenbach & Rescorla, 2003). Mean score on the attention scale was 52.6 (SD 3.5, range 50-59) and on the ADHD scale 52.8 (SD 4.2, range 50-63). None of the subjects scored within the clinical range on the ADHD or attention subscales. Furthermore, self-reports indicated that all subjects were free of other neurological or somatic health problems.

To index IQ, subjects in the Adolescent group were administered the Vocabulary and Block Design subtests of the Wechsler Intelligence Scale for Children (WISC; Wechsler, 1991). Subjects in the Adult group were administered the same subtests of the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1997). Mean reliability and validity of this estimated IQ-score compared to the complete IQ-test has been reported to be .9 for both scales (Jeyakumar et al., 2004; Spreen & Strauss, 1998). The mean IQ-score was 95.0 (SD 8.5) in the Adolescent group and 99.7 (SD 11.6) in the Adult group. IQ-scores did not significantly differ between groups ($F(1,38) = 2.1, p = .154$).

The present study was approved by the Local Ethical Committee of the Faculty of Psychology and Neuroscience at Maastricht University, and prior to the study a written informed consent was obtained from the children and their caretakers and the adults according to the Declaration of Helsinki (1964). All subjects were paid for their participation in the experiment.

Procedure

The experimental session lasted 2.5-3 hours. The session started with three tests from the WISC-III (Wechsler, 1991) and WAIS-III (Wechsler, 1997); the block design test, vocabulary test and the digit span test. The latter (digit span forward and backward) was performed by the participants to obtain an independent measure of WM capacity. Subsequently, the electrodes were attached. During the experimental session all participants sat in front of a 17-inch VGA monitor with their eyes aligned to the centre of the screen at a distance of approximately 75 cm. The participants were instructed to minimize eye blinks and to refrain from making head or eye movements during task performance. The experimental session started when all tasks were practiced until a predetermined performance criterion (75% correct responses) was reached.

Experimental Task

To measure developmental differences in WM capacity and the efficiency of excluding irrelevant items from access to memory, a Visual Short-Term Memory task comparable to that used by Vogel and Machizawa (2004) and Vogel et al. (2005) was presented to the subjects.

The task consisted of bilateral stimulus displays in which colored squares ($0.76^\circ \times 0.76^\circ$) or rectangles ($1.15^\circ \times 0.57^\circ$) were presented within two $4^\circ \times 7.3^\circ$ rectangular regions presented 3° to the left and right from of a central fixation cross; see Figure 1). On each trial, the positions of the items were randomly distributed within upper and lower quadrants of the screen with the constraint that the distance between objects within a hemifield was at least 2° (centre to centre). The colour of squares and rectangles was randomly selected on each trial with limited replacement from a set of seven easily distinguished colours (red, blue, green, violet, yellow, black and white). The number of targets and distracters was always the same in both hemifields, only location and color of the stimuli could differ between hemifields. All stimuli were presented on a grey background.

A trial started with the presentation of an arrow cue that indicated the hemifield that subjects should attend to on the following memory display. The subject's task was to remember the location and colors of the squares (T: targets) in this cued hemifield for a later test. A total of 480 trials were presented. On half of the trials the squares were accompanied by distracters (D: colored rectangles) that had to be ignored. In total, there were four different types of memory displays differing in the number of targets and distracters. Either one or three targets (squares) were presented alone (T1D0 or T3D0; memory load of 1 or 3 items) or were accompanied by two distracters (T1D2 or T3D2). The T3D2 condition was included to be able to determine whether capacity limits were reached. All memory displays were followed by a test display 900 ms later in which one colored square was presented at one of the locations in the memory display within the upper or lower quadrant (to both

hemifields). The subjects had to press a left button with the left index finger when the test stimulus shown at this location had the same color as that in the previous memory display (50% of all trials) or press right with the right index finger when it was different. A new memory display followed 500-700 ms after a response was given. See Figure 1 for an example of a complete trial of the T1D2 condition with exact timing parameters.

The behavioral measures derived from the VSWM change detection task in T1D0, T1D2 and T3D0 were: 1) reaction times for correct detections (RT), percentage correct responses (% Hits), and K scores. Also an Unnecessary Storage measure was computed by subtracting K -T1D2 from K -T1D0.

Only reaction times to correct responses that fell within a response window from 250-4000 ms after the memory probe were included in the analysis. Cowan's memory capacity measure K in T1D0 and T3D0 conditions was computed with a standard formula (Cowan, 2001): $K = (H + CR - 1) N$, in which H is the hit rate, CR are the correct rejections in an array with N items. To derive a behavioral measure of filtering efficiency, following a study by Lee et al. (2010) we also computed K in the distracter condition (T1D2) by filling in 1 for N since there was 1 target item; if distracters are perfectly filtered out K will be 1, in case of imperfect filtering K will be lower than 1. This T1D2- K measure was subtracted from the T1D0- K to obtain an "Unnecessary Storage" measure.

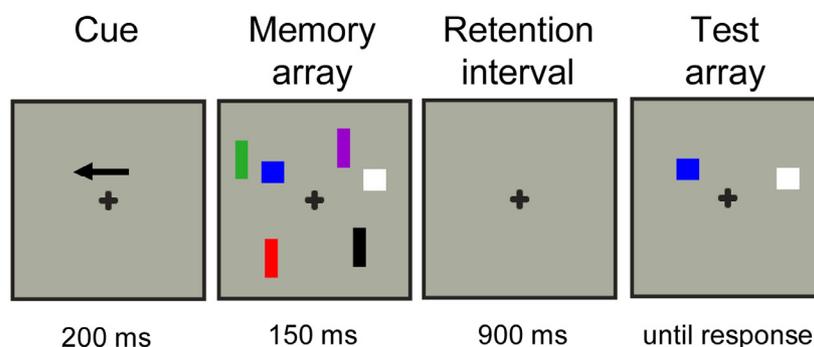


Figure 1. Example of distracters-present trial (T1D2) for the left hemifield.

Electrophysiological Recording and Analysis

For measurement of the EEG, an elastic cap (Easycap) containing 60 Ag/AgCl electrodes was used. The montage included 7 midline sites (Fpz, Fz, FCz, Cz, CPz, Pz, Oz), and 52 lateralized sites (Fp1, Fp2, AF7, AF3, AF4, AF8, F7, F5, F3, F1, F2, F4, F6, F8, FT7, FC5, FC3, FC1, FC2, FC4, FC6, FT8, T7, C5, C3, C1, C2, C4, C6, T8, TP7, CP5, CP3, CP1, CP2, CP4, CP6, TP8, P7, P5, P3, P1, P2, P4, P6, P8, PO7, PO3, PO4, PO8, O1, O2), and the right mastoid A2. During measurement all electrodes were

referenced to the left mastoid (A1) and one of the electrodes in the cap (AFz) was used as ground. Offline, EEG data were re-referenced to the average of the right and left mastoids. Blinks, vertical and horizontal eye-movements were measured by bipolar electrodes placed above and below the left eye and at the outer canthi of both eyes. All electrode impedances were kept below 10 k Ω , with the exception of the reference and ground electrodes which were held below 5 k Ω . Signal acquisition was accomplished using Brainamp amplifiers and Brain Vision Recorder software (version 1.10). EEG and EOG signals were continuously sampled at 250 Hz with a high-pass filter of 0.05 Hz and a low-pass filter of 30 Hz.

ERP analysis was done in Neuroscan 4.3.1. The continuous EEG was divided into 480 epochs of 1250 ms, from 200 ms prestimulus to 1050 ms poststimulus, all aligned to a baseline from -200 to 0 ms preceding the memory array. First, vertical (blinks) and horizontal electro-oculogram (VEOG and HEOG) artifacts were removed from the data by applying an eye-movement correction algorithm (Semlitsch et al., 1986). For the computation of regression coefficients between VEOG and the EEG-signals at the different electrodes, adequate eye blinks were manually selected and transmission coefficients were computed on the basis of these selected trials. In a similar way, by manually selecting horizontal eye movements separately for right and left cued displays for each individual, regression coefficients between HEOG and the EEG-signals at the different electrodes were computed. All transmission coefficients were carefully checked to have strengths, signs and topographies congruent with expected patterns for vertical and horizontal movements before they were applied to remove eye blinks and horizontal eye movements from the EEG through the Semlitsch et al. procedure. After EOG-artifact removal, epochs still containing artifacts exceeding $\pm 75 \mu\text{V}$ were rejected from the database. Whereas the above procedure should have removed all HEOG activity from the EEG signal, to be sure that our CDA load and distracter effects were not due to any residual HEOG activity we performed an extra check by examining load and distracter effects on the HEOG signal in the three conditions. If our CDA load and distracter effects would have been caused by residual HEOG activity at parietal electrodes, we should find comparable effects on the HEOG signal itself. ANOVAs conducted on the HEOG activity from 300-1050 ms in T1D0, T1D2 and T3D0 conditions did not reveal any significant load or distracter effects confirming that our CDA results are not explained by ocular artifacts (for average HEOG signal in the three conditions see Figure 3). Next, average ERPs were computed separately for each subject in three different task conditions: (1) one target square only (T1D0; where T = number of targets and D = number of distracters), (2) one target square plus two distracter rectangles (T1D2), (3) three target squares only (T3D0). The fourth condition (T3D2) was not included in the analyses since its number of shapes (five) exceeds the maximum WM capacity of four items. In the averaging procedure, only trials with correct responses were included. There was a maximum number of 120 trials in each task condition. The minimum number of included trials in each condition was 20. Across conditions, the mean number of artifact-free EEG epochs

contained in the single-subject averages was 101 trials (SD 16) in the adult group and 74 trials (SD 24) in the adolescent group.

We computed contralateral waveforms by averaging the activity recorded at right hemisphere electrode sites when subjects were cued to remember the left side of the memory array with the activity recorded from the left hemisphere electrode sites when they were cued to remember the right side. CDA was measured at posterior parietal and lateral occipital electrode sites (P1/2, P3/4, P5/6, P7/8, PO3/4, PO7/8, O1/2) as the difference in mean amplitude between the ipsilateral and contralateral waveforms. Since the differences between conditions generally seem to decrease over time in the delay period (Delvenne et al., 2010), which may indicate different processing stages, two measurement windows were selected for analyses, an early window of 300-550 ms and later window of 550-1050 ms after the onset of the memory array.

Statistical Analysis

Behavioral measures

Potential differences in verbal and VSWM capacity between the two Age groups were tested with Bonferroni-corrected independent samples t-tests for backward, forward and standardized digit span tests (verbal WM) and *K* in T1D0, T1D2 and T3D0 conditions (VSWM). To test for group differences in WM-access filtering efficiency two planned mixed ANOVA analyses with Trial-type (either T1D0 vs. T1D2 or T1D2 vs. T3D0) and Age as factors were performed on change detection reaction time (RT) and accuracy (% correct). With worse filtering efficiency T1D0-T1D2 RT differences will increase and T1D2-T3D0 RT differences will decrease due to longer search times in T1D2 (due to unnecessary storage of distracters). In the same way T1D0-T1D2 accuracy differences will increase and T1D2-T3D0 accuracy differences will decrease. An independent t-test was performed to test whether adolescents and adults had different Unnecessary Storage scores (difference score between *K*-T1D0 and *K*-T1D2).

ERP measures

For the parietal/occipital CDA windows, mean amplitudes were compared across conditions by repeated measures ANOVAs. Three planned mixed ANOVA's were performed in both time windows, with a within-subject factor Trial-type with two levels (T1D0 & T1D3 or T1D0 & T1D2 or T1D2 & T3D0) and a between-subjects factor Age (adolescents, adults). In case of significant Age x Trial-type interactions, post-hoc tests were performed for the separate groups.

Correlations

Correlations between WM capacity measures, behavioral differences in T1D0 and T1D2 and CDA amplitude differences in T1D0 and T1D2 for the early and late CDA window were calculated using Pearson correlation coefficients.

4.3 Results

Behavioral Results

Developmental differences in verbal (Digit Span) and visuospatial span (Cowan's K)

Forward, backward and standardized spans were collected for both groups to obtain verbal WM span measures and visuospatial span was measured by computing K in T1D0 and T3D0 conditions of the present delayed-WM task. For means and standard deviations of scores in the digit span task see Table 1. For K scores (and SD's) in T1D0, T3D0 and T1D2 conditions see Table 1 and Figure 2A. Bonferroni-corrected independent t -tests showed significantly lower forward, backward and standardized digit span scores in adolescents than adults (forward digit span: $t(36) = -2.99$, $p < .05$; backward digit span: $t(36) = -3.94$, $p < .005$; standardized digit span: $t(36) = -3.52$, $p < .005$). Bonferroni-corrected independent t -tests for K showed a trend towards lower K scores in adolescents than adults in T1D0 ($t(36) = -2.1$, $p = .08$), and significantly lower K scores in adolescents than adults in T3D0 ($t(36) = -2.5$, $p < .05$) and T1D2 ($t(36) = -3.2$, $p < .01$) conditions.

Table 1. Group means (standard deviations between brackets) of forward, backward and standardized digit span scores (WAIS III), and WM capacity K in T1D0, T1D2 and T3D0 conditions of the VSWM change detection task in adolescents and adults.

	Digit span			WM capacity K (visuospatial)		
	Forward	Backward	Standardized	T1D0	T1D2	T3D0
Adolescents	8.2 (1.6) * Range: 5-13	5.4 (2.0) *** Range: 2-11	8.8 (2.8) *** Range: 3-17	.80 (.14) Range: .42 - .98	.65 (.18) ** Range: .33 - .93	1.75 (.51) * Range: .78 - 2.50
Adults	10.1 (2.3) Range: 6-14	8.4 (2.6) Range: 5-14	12.5 (3.6) Range: 7-19	.90 (.14) Range: .43 - .99	.83 (.16) Range: .39 - .98	2.16 (.48) Range: 1.20 - 2.83

NB: stars indicate significant group differences (P values after Bonferroni correction).

* $P < .05$; ** $P < .01$; *** $P < .005$

Effect of distracters on the speed (RT) of change detection performance

For means of reaction times (and 95% confidence intervals) for adolescents and adults, see Figure 2, panel B. The ANOVA for the T1D0 vs. T1D2 comparison showed an Age \times Trial-type trend interaction ($F(1,36) = 2.8, p = .10$). Subsequent ANOVA's for the separate groups indicated a stronger effect of Trial-type in the adolescents ($F(1,21) = 24.9, p < .00001$) than in the adult group ($F(1,16) = 6.9, p < .05$); change detection times increased when distracters had been presented in the memory display (T1D2). For the T1D2 vs. T3D0 comparison an Age \times Trial-type interaction ($F(1,36) = 5.5, p < .05$) was found, due to a significantly larger effect of Trial-type in the adult group ($F(1,16) = 43.5, p < .00001$) than in the adolescent group ($F(1,20) = 6.2, p < .05$). Adults showed slower decision times in T3D0 than in T1D2, pointing to some filtering of distracters, whereas this RT difference between T1D2 and T3D0 was much smaller in adolescents (see Figure 2).

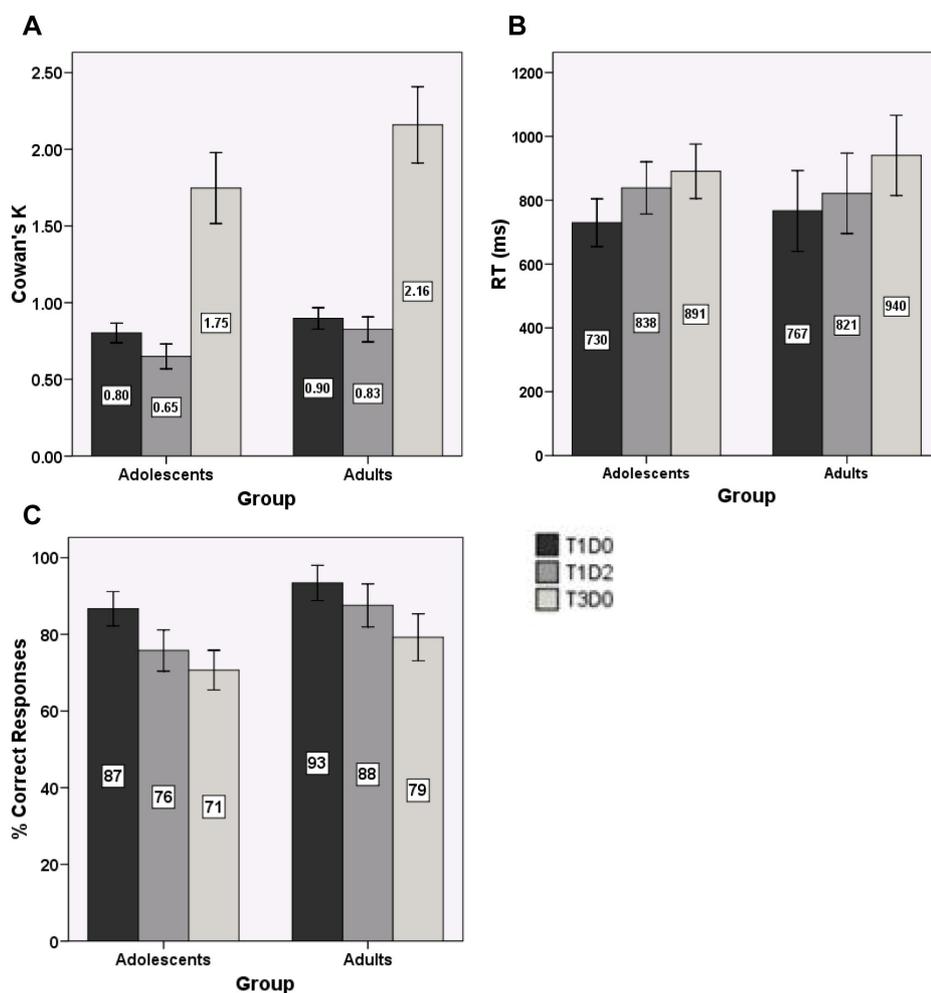


Figure 2. Bar graphs of (A) Cowan's K , (B) average reaction times (in ms), and (C) percentage of correct responses for adolescents and adults in T1D0 (one target), T1D2 (one target, two distracters) and T3D0 (three targets) conditions of the VSWM change detection task. Error bars indicate 95 % confidence intervals.

Effects of distracters on the accuracy of change detection performance

Memory accuracy (proportion of correct responses) for both groups is shown in Figure 2, panel C. An Age \times Trial-type interaction was found for the T1D0 vs. T1D2 comparison ($F(1,36) = 4.17, p < .05$), due to adolescents showing a steeper decline in memory accuracy for a WM load of 1 item when it was accompanied by distracters than adults. The T1D2 vs. T3D0 comparison resulted in a main effect of Trial-type ($F(1,36) = 32.6, p < .00001$) caused by reduced accuracy of holding 3 items in memory compared to holding 1 item in the presence of distracters. Furthermore, a main group effect ($F(1,36) = 8.1, p < .01$) showed overall higher accuracy in adults than adolescents across the T1D2 and T3D0 conditions. The Unnecessary Storage measure derived from K scores in T1D2 and T1D0 conditions (see Methods page 11) was significantly higher in adolescents (.15) than in adults (.07) ($t(36) = 2.3, p < .05$), confirming higher storage of distracters in the former group.

CDA Results

Grand ERP averages of CDA at occipital and parietal sites (P1/2, P3/4, P5/6, P7/8, PO3/4, PO7/8, O1/2) in the Adolescent and Adult group for the three task conditions are depicted in Figure 3. Mean amplitudes and SDs of the CDA amplitude in the predefined 300-550 and 550-1050 ms time windows per task condition and age group are shown in Table 2.

Effects of load and distracters on CDA in encoding interval (300-550 ms)

Mean amplitudes of parietal-occipital CDA in the first time window (300-550 ms) for T1D0 and T3D0 were entered into a repeated measures analysis of variance to test for Age (adolescents, adults) \times Trial-type interactions. A significant Age \times Trial-type interaction was found for the T1D0 and T3D0 comparison ($F(1,36) = 4.6, p < .05$); whereas the means are indicative of larger T3D0 amplitudes in adolescents than adults this was only marginally significant ($p < .10$). Adults did have statistically stronger T1D0-T3D0 CDA effects ($F(1,16) = 24.6, p < .00001$) than adolescents ($F(1,20) = 14.9, p < .005$), due to larger variance in load-related CDA responses in the adolescent group. The comparison between T1D0 and T1D2 also showed a significant interaction between Age and Trial-type ($F(1,36) = 6.0, p < .05$), reflecting the expected larger CDA amplitude increase from T1D0 to T1D2 in adolescents ($F(1,20) = 17.7, p < .00001$) than in adults ($F(1,16) = 10.5, p < .01$). Follow-up tests showed that the interaction was caused by significantly higher T1D2 CDA amplitudes in adolescents than adults ($p < .05$), whereas T1D0 CDA amplitudes were not different between the groups ($p = .98$). This presence of a group difference in CDA amplitude only in the distracter-present condition is evidence for increased distracter processing in adolescents. The absence of Trial-type or Trial-Type by Age effects for the T1D2-

T3D0 comparison in this early window indicates CDA overlap between these conditions in both groups.

In the initial CDA-WM-filtering study in Nature by Vogel et al. (2005), adults with high WM capacity showed a pattern of smaller T1D0-T1D2 CDA differences but higher T3D0-T1D2 CDA differences during encoding than adults with low-capacity because of perfect filtering of distracters. Our adults did show smaller T1D2-T1D0 amplitude differences than adolescents, but did not show smaller T1D2 than T3D0 CDA amplitudes. Considering the CDA literature that only adults with high WM capacity (high K scores) show T3D0-T1D2 differences (Vogel et al., 2005), the T1D2 and T3D0 CDA overlap in our adults can be explained by the fact that the majority of our adults tended towards low capacity as becomes evident from their low mean K score of about 2 items. Since CDA amplitude reaches its maximum amplitude at maximum capacity, the overlap between T3D0-T1D2 CDA is likely caused by a “ceiling” effect in T3D0 because CDA reached its maximum with storage of two items. To support such an explanation by data, we created high (K T3D0 score ≥ 2.5) and low (K T3D0 score ≤ 2.5) WM capacity groups and performed an ANOVA to see if we could replicate the patterns reported in Vogel’s study for subjects with high and low WM capacity. Our high/low split resulted in a group of 6 adults with high WM capacity (mean K scores of 2.7, SD .14) and a group of 11 low WM capacity adults (mean K score of 1.9, SD .41); this difference was highly significant ($t(15) = 5.58, p < .00001$). Congruent with CDA patterns reported in Vogel et al. the ANOVA analyses yielded a significant WM capacity \times Trial-type interaction ($F(1,15) = 8.12, p < .05$; two-tailed), caused by a significant Trial-type effect of higher T3D0 than T1D2 amplitudes in high-span subjects ($t(5) = 2.19, p < .05$, one-tailed) and the absence of a Trial-type effect in low-span subjects ($t(10) = -0.99, p = .17$, one tailed). Replicating Vogel et al., T1D0-T1D2 CDA differences were only significant in the low-capacity group ($t(10) = -4.34, p = .005$, one-tailed); see Figure 4 for mean amplitudes in T1D0, T1D2 and T3D0 in both groups.

Effects of load and distracters on CDA amplitude during maintenance (550-1050 ms)

The T1D0-T3D0 comparison yielded a significant Age \times Trial-type interaction ($F(1,36) = 8.8, p = .005$), showing that only adolescents had a significantly higher CDA with a load of 3 than 1 items ($F(1,20) = 11.8, p < .005$), whereas in adults the T3D0 dropped in amplitude and now overlapped with T1D0 ($F(1,16) = .002, p = .97$). The T3D0 amplitude was significantly higher in adolescents than adults ($p < .005$). For the T1D0-T1D2 comparison, again, an interaction of Age \times Trial-type was found ($F(1,36) = 7.6, p < .01$). Post-hoc tests revealed enhanced parietal-occipital CDA amplitude in T1D2 compared to T1D0 only in adolescents ($F(1,20) = 10.0, p = .005$), indicating distracter maintenance (e.g. suboptimal filtering). In adults T1D2 amplitudes dropped in amplitude and now overlapped with T1D0 amplitude ($p = .77$), suggesting adults filtered out some distracters during this later stage. The T1D2 amplitudes were significantly higher in adolescents than adults ($p < .005$), whereas

T1D0 amplitudes did not differ between groups ($p = .82$). The absence of Trial-type or Age \times Trial-type effects for the T1D2-T3D0 CDA comparison showed that T1D2 and T3D0 CDA's overlapped in both age groups, but due to different patterns as in the earlier window; in adolescents this was due to maintenance of distracters (exactly similar pattern as in the earlier window), whereas in adults this was due to a drop in T3D0 CDA amplitude to the level of T1D0 after 550 ms (see Figure 3).

Table 2. CDA data from the VSWM change detection task. Mean CDA amplitude (standard deviations between brackets) averaged over lateral parietal and occipital electrode sites (μV) in encoding (300-550 ms) and maintenance (550-1050 ms) time windows, in T1D0, T1D2 and T3D0 for adolescents and adults.

		T1D0	T1D2	T3D0
CDA (300-550 ms)	Adolescents	-0.14 (1.62)	-1.27 (1.40)	-1.18 (1.55)
	Adults	-0.15 (0.45)	-0.50 (0.49)	-0.53 (0.40)
CDA (550-1050 ms)	Adolescents	-0.37 (1.39)	-1.12 (1.06)	-1.25 (1.22)
	Adults	-0.30 (0.46)	-0.26 (0.39)	-0.29 (0.39)

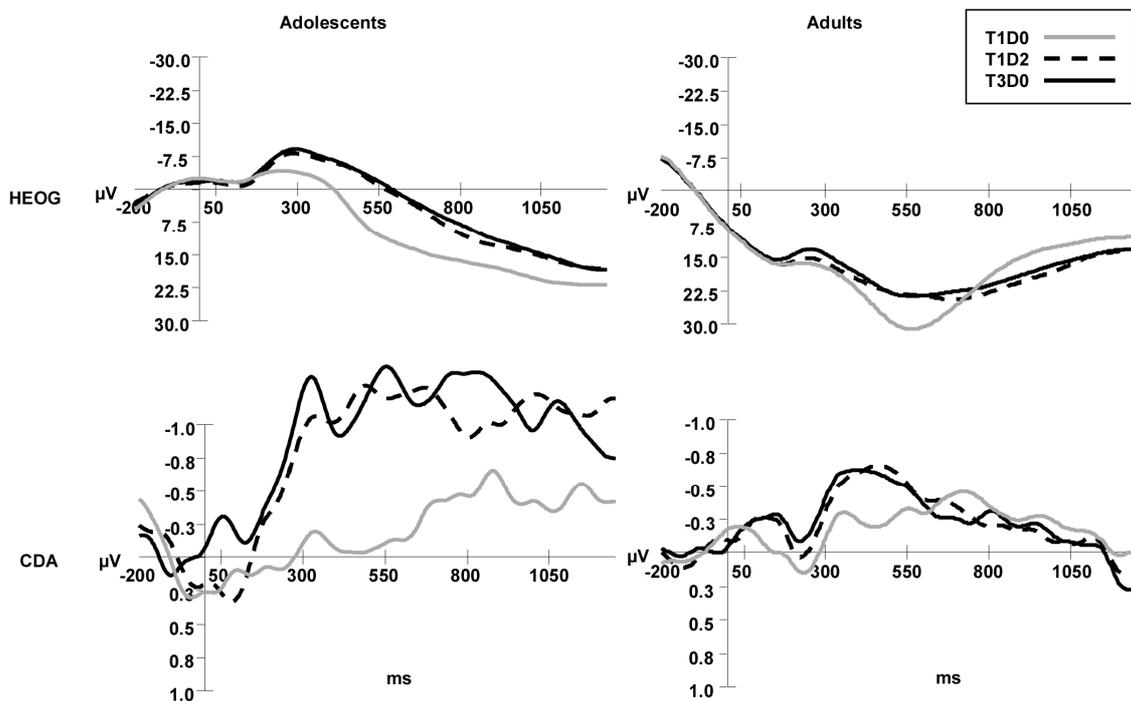


Figure 3. Average HEOG activity ($(\text{HEOG left visual field trials} \times -1 + \text{HEOG right visual field trials})/2$) and CDA activity (computed by subtracting ipsilateral from contralateral activity) after smoothing with a 6 Hz low-pass filter, time-locked to the memory array and averaged across occipital and posterior parietal electrode sites for adolescents and adults, in conditions T1D0, T1D2 and T3D0.

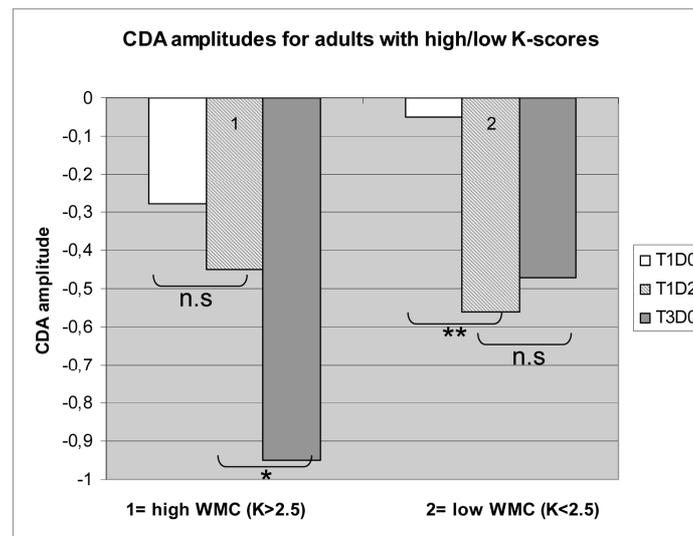


Figure 4. Mean CDA amplitudes (μV) in T1D0, T1D2 and T3D0 conditions in adults with high ($N=6$) and low ($N=11$) working memory capacity (WMC) determined by a K -T3D0 score larger or smaller than 2.5. * = $p < .05$, one-tailed, ** = $p < .01$, one-tailed, n.s. = non-significant.

Correlations between performance and electrophysiological CDA measures

Correlations were computed between performance and CDA measures of WM capacity and filtering efficiency. Figure 5 depicts the significant correlations.

K (T3D0) was significantly correlated ($r(38) = -.46$, $p = .003$) with the Unnecessary Storage measure (K -T1D0 minus K -T1D2); subjects with higher WM capacity had lower Unnecessary Storage scores (see Figure 5A). K and load related (T3D0 - T1D0) CDA effects were only marginally correlated in adults and only in the 550-1050 ms window ($r(17) = .45$, $p = .07$); adults with higher WM capacity scores had smaller T3D0-T1D0 CDA load effects during the later part of the delay interval. In adolescents K (T3D0) was not correlated with CDA load (T3D0-T1D0) effects.

The Unnecessary Storage measure correlated negatively with distracter-related CDA effects (T1D2 amplitude - T1D0 amplitude) in the encoding window from 300-550 ms ($r(38) = -.43$, $p = .006$) and in the maintenance window from 550-1050 ms ($r(38) = -.38$, $p = .014$) (see Figure 5B). Similar negative correlations were found between distracter-related RT increases (RT-T1D2 minus RT-T1D0) and distracter-related CDA increases in the two windows ($r(38) = -.48$, $p = .002$ and $r(38) = -.55$, $p < .00001$ respectively; see Figure 5C). These correlations indicate that individuals with larger distracter interference effects on accuracy (reflected by Unnecessary Storage measure) and speed of memory performance also had larger distracter-related CDA amplitude increases and individuals with low distracter interference effects on performance showed small distracter-related CDA amplitude increases. This is evidence for a functional relation between performance and CDA measures of distracter interference.

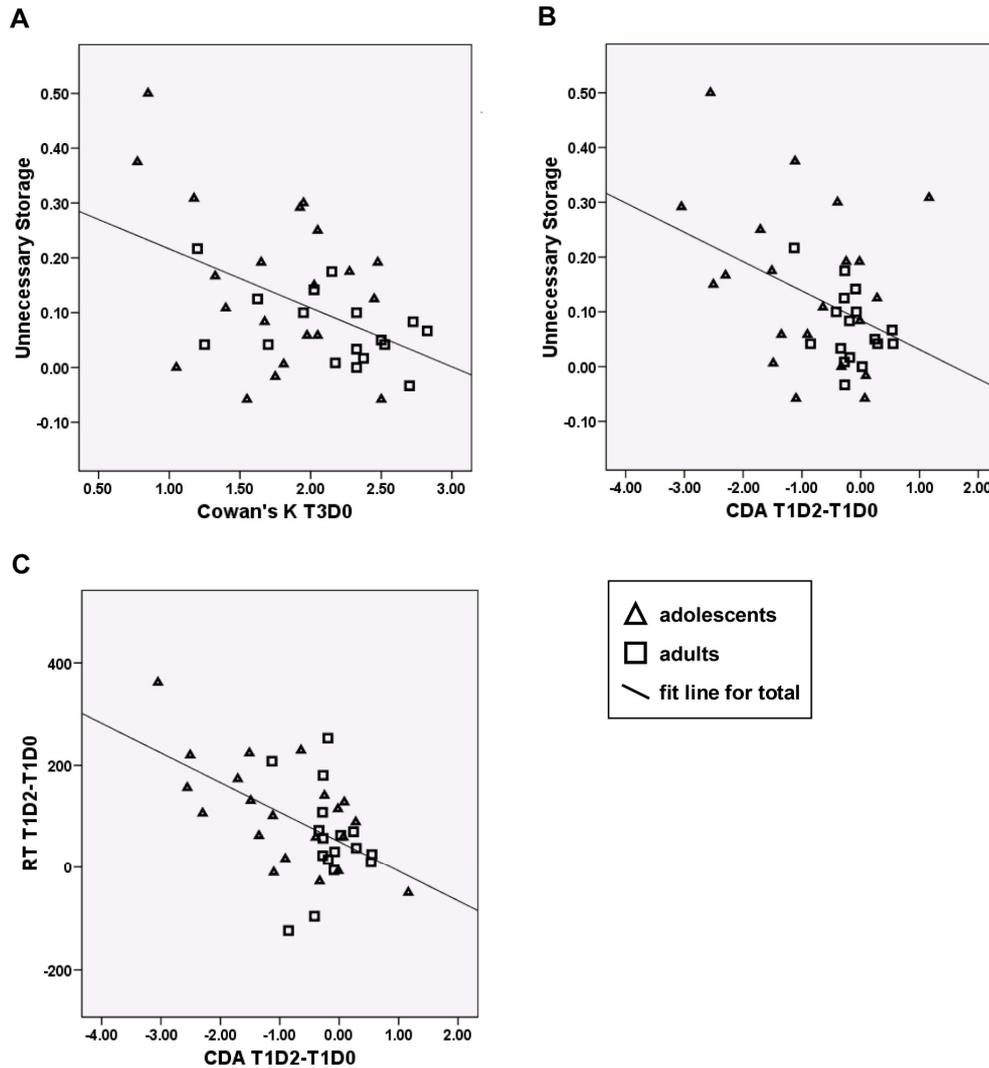


Figure 5. Scatterplots of significant correlations between behavioral and CDA measures. (A) Correlation between K -T3D0 and Unnecessary Storage (K -T1D0 minus K -T1D2) for adolescents (triangles) and adults (squares). (B&C). Correlations between distracter related parietal-occipital CDA effects (CDA-T1D2 minus CDA-T1D0) averaged over entire interval from 300-1050 ms (x-axis) and Unnecessary Storage (K -T1D0 minus K -T1D2; panel B) or RT distracter effects (RT-T1D2 minus RT-T1D0; panel C).

4.4 Discussion

Several previous studies have shown that adolescents have still immature WM capacity (Luciana et al., 2005; Luna et al., 2004; Schleepen & Jonkman, 2010). This raises the question of whether this reduced capacity is caused by smaller storage space or inefficient use of storage space caused by less efficient attentional selection of which information enters WM, or both. To answer this question, a delayed visuospatial WM (VSWM) change detection task with manipulations of WM load and distraction (Fukuda & Vogel, 2009) was administered to adolescents and adults in the current study. In addition to change detection performance, contralateral delay

activity (CDA) was measured, as a time-sensitive neural correlate of the number of targets and distracters that subjects encoded and maintained in WM during the delay interval of the task.

Development of VSWM capacity throughout adolescence

The behavioral results showed that adolescents indeed had lower verbal WM capacity than adults as measured by the Digit Span task and lower visuospatial WM capacity as measured by Cowan's *K* in the VSWM change detection task. Adolescents made significantly more memory errors (29% vs. 21%) and had lower *K* scores than adults (1.75 vs. 2.16) when three target items had to be maintained in VSWM. Earlier studies also reported immature WM capacity in adolescents but mostly in tasks requiring high levels of attentional control (Luciana et al., 2005; Luna et al., 2004; Schleepen & Jonkman, 2010). The present study shows that adolescents also have immature capacity in a relatively simple VSWM change detection task in which they have to store a maximum of three items. Our findings seem to be in contrast with findings by other studies using VSWM change detection tasks that reported mature VSWM capacity already at age 10-12 (Cowan et al., 2005; Cowan et al., 2010; Riggs et al., 2006). This discrepancy can however be explained by differences in task parameters. In our study memory array presentation duration and maintenance delays were shorter than in the other developmental studies. Longer delays might have enabled the use of verbal coding strategies that help to improve visual memory in older children. It is known that older children are prone to use verbal strategies to enhance visual memory (Hitch et al., 1989). Vogel et al. (2001) showed that with the currently used presentation duration of 150 milliseconds and total maintenance delay of 1050 ms, the use of verbal coding strategies is highly unlikely. Furthermore, selective attention demands were larger in our task because of the bilateral stimulus displays that also required the subjects to ignore the irrelevant items presented in the unattended visual field.

If the lower VSWM capacity in adolescents is to be explained by lower storage capacity, this was expected to become visible as larger load-related CDA increases in adolescents than adults. Both adults and adolescents showed the normally reported CDA amplitude increase with load, e.g. a significantly higher CDA when holding three than one items in memory from 300-550 ms after presentation of the memory display, when encoding is taking place (Emrich et al., 2009; Ikkai et al., 2010; Lee et al., 2010; McCollough et al., 2007; Vogel & Machizawa, 2004). A significant Trial-type \times Age interaction for the early encoding part of the delay period however showed that whereas there was a trend for adolescents to have higher T3D0 amplitudes than adults ($p < .10$), T1D0-T3D0 CDA effects were statistically stronger in adults than in adolescents. This is due to larger variability in parietal-occipital CDA load effects in adolescents suggesting that parietal areas that are involved in WM-storage or their connections with other parts of the WM network are still developing. This higher variability of load-related CDA responses in adolescents is consistent with

developmental findings recently reported by Sander et al. (2011) who even reported an absence of load-related CDA responses in younger, 10-12 year-old children when presentation times were comparable to that in the present study (100ms). The fact that we did find overall significant (albeit more variable) CDA load effects in our older adolescent group even with short presentation times suggests that the neurocognitive mechanisms underlying WM capacity undergo important development between late childhood and late adolescence.

From 550-1050 ms, during the later maintenance interval, a significant Load x Age interaction showed that the load-related CDA increase sustained in adolescents but was no longer significant in adults due to a T3D0 CDA amplitude decrease. Within the interpretation that the CDA during later parts of the maintenance interval is a neural correlate of the number of items maintained in WM after encoding, these data would suggest that adults could maintain fewer items in memory throughout the retention interval than adolescents. Such a conclusion is however in contrast with performance data that showed *higher* memory capacity in adults than adolescents in the 3-item condition. Then how can the combination of higher load-related CDA increases after 550 ms during later maintenance with lower K in adolescents be explained?

One possible explanation is that the CDA amplitude during the later, maintenance part of the retention interval is not a direct measure of the amount of information stored, but reflects the allocation of spatial attention that is needed to keep the visual representations active during the delay until a response is needed. Because of their higher WM capacity adults might not need as much spatial attention as adolescents to keep location representations active when the memory array is no longer visible, at least not with the small number of two items they could maximally maintain (K was 2.16). The trend-significant correlation showing a relation of higher K scores with lower load-related CDA effects from 550-1050 ms in adults is supportive of such a conclusion. Note that similar drops in CDA amplitude with storage of two to three items after 600 ms have been reported before in adults (Drew et al., 2011; Vogel & Machizawa, 2004). Support for a relation between late CDA amplitude and spatial attention or monitoring of spatial positions comes from two studies measuring the CDA in a spatial tracking task in which different numbers of moving targets had to be continuously tracked, an assignment requiring continuous shifting of spatial attention and spatial updating of target locations (Drew et al., 2011; Drew & Vogel, 2008). In the former study by Drew et al., load-related CDA responses (one vs. three items) were compared between a VSWM task and a spatial tracking task. Just as in the present study, the adults' load-related CDA response did not sustain during later periods of the maintenance interval in the VSWM task whereas it was persistent in the tracking task. On the basis of the outcome of several experiments the authors concluded that the persistent load-related CDA response in the tracking task was due to the need for continuous shifting of spatial attention or monitoring of target positions. The lack of a similar sustained CDA response in the VSWM task (at least when holding two to three items) is then explained by lower

spatial attention needs for adults to keep memory displays active. Further support for a relation of posterior CDA activation with spatial attention/rehearsal during the maintenance part of the delay period also comes from other studies. An fMRI study showed that when more maintenance effort is required due to lengthening of the delay period, the parietal activation no longer levels off at the maximum memory capacity of three to four items, but even exceeds it (Magen et al., 2009). The authors concluded that this result would be congruent with a spatial attention or spatial rehearsal account of the parietal delay-related activity, since maintenance of multiple items for longer periods of time would require spatial attention or spatial rehearsal to keep the location representations active. There indeed is behavioral and brain evidence for a role for spatial selective attention in the *active* maintenance of information in spatial WM (Awh et al., 1998; Postle et al., 2004).

Summarizing the developmental load-related behavioural and CDA results, CDA data from the early encoding interval show significant load-related CDA responses in adolescents and adults, but statistics show that these CDA effects are stronger in adults than adolescents due to higher variability in load related CDA responses in the adolescent group. This finding points to immaturity of posterior areas (or their connections) involved in WM storage and is congruent with the late development of frontal-parietal networks underlying VSWM performance (Bunge & Wright, 2007; Kwon et al., 2002). Furthermore, in adolescents the load-related parietal CDA increase sustained throughout the entire delay period, whereas the T3D0-CDA showed a drop in amplitude after 550 ms in adults. The sustained load-related CDA response in adolescents might be related to enhanced allocation of spatial attention to keep item-locations active that was not needed by the higher-capacity adults. Such a conclusion however needs further experimentation.

Development of filtering efficiency in WM in adolescence

The hypothesis that adolescents' WM performance in a visuospatial change detection task would suffer more from the presence of distracters in the memory array than that of adults was confirmed by reaction time, accuracy and K data. The presence of distracters in the memory array (T1D2) led to a larger drop in memory accuracy for the target in adolescents than adults. This was shown by a significant Age \times Trial-type interaction for accuracy data (T1D0 vs. T1D2 comparison) and a significantly larger Unnecessary Storage score in adolescents than adults. This Unnecessary Storage score was derived by subtracting K in T1D2 (1 target, 2 distracters) from K in T1D0 (no distracters); in case of storage of distracters the Unnecessary Storage score is higher than 0 (Lee et al., 2010), which was the case in both groups, but more so in adolescents. Unnecessary Storage was significantly correlated with K , showing that subjects with higher WM capacity showed less interference from distracters on their WM performance. Besides these effects on accuracy, Age \times Trial-type interactions for reaction time (RT) showed larger T1D0-T1D2 and smaller T1D2-T3D0 reaction time differences in adolescents than adults. Both effects show that adolescents' change

detection response times were more slowed by the presence of distracters in the memory array than those of adults. Cowan and Morey (2006) suggested that especially low-WM capacity individuals might use the strategy to store and maintain the entire stimulus display and only decide afterwards whether any changes are visible in the test array. This strategy would result in relatively longer reaction times in distracter-conditions which were indeed observed for adolescents (versus adults) in the present study.

The CDA was measured in addition to the above discussed performance measures to study the online storage and maintenance of distracters during the delay interval of the task before a response was generated. We hypothesized on the basis of the change detection-CDA literature that larger WM-distracter interference in adolescents would be due to more problems with blocking distracter items from encoding or maintenance in WM. If so, this would show itself in the CDA data by larger T1D2 amplitude increases, relative to that in T1D0, in adolescents than in adults. Significant Age \times Trial-type (T1D0-T1D2) CDA interaction effects in both encoding and maintenance windows confirmed significantly higher T1D2-CDA amplitudes in adolescents than adults, whereas T1D0 amplitudes were comparable between both age groups. In line with the change detection-CDA literature these larger distracter-related CDA increases in adolescents signify higher encoding and maintenance of distracter items in WM (Jost et al., 2011; Lee et al., 2010; Vogel et al., 2005). This was further confirmed by the positive correlation that was found between distracter-related performance and CDA effects; subjects with higher parietal-occipital CDA T1D2-T1D0 amplitude increases also had higher Unnecessary Storage performance scores and showed stronger distracter interference effects on reaction time.

It has to be noted that in the encoding window from 300-550 ms, in both adolescents and adults T1D2 amplitude overlapped with T3D0 amplitude whereas in case of more efficient filtering in adults one might expect that, besides the smaller T1D0-T1D2 difference that we found, adults would also show higher T3D0 than T1D2 CDA amplitude, as has been reported in adults with high WM capacity (Vogel et al., 2005). However, our adult subjects on average had a low WM capacity of about only two items, as shown by their K score in the T3D0 condition. Since CDA amplitude is known to reach its maximum amplitude with an individual's maximum capacity (Vogel & Machizawa, 2004), it is assumable that the T3D0-T1D2 overlap in our adult group is caused by the fact that the mean CDA amplitude already reached its maximum with storage of two items and could not further increase (e.g. reached a "ceiling") in the T3D0 condition. To support this by data we performed an analysis in which we formed high and low-span adult groups based on their K scores and investigated whether adults with high WM capacity (mean K score of 2.7) would show significantly higher T3D0 than T1D2 CDA amplitudes as found in high-span subjects in the initial Vogel et al. study, whereas adults with relatively low K scores (mean 1.9) would not. This was exactly what was found and explains why in the

present study higher distracter encoding in adolescents than adults was only significant when comparing T1D0 and T1D2 CDA amplitudes.

The reason for the lower WM capacity and imperfect filtering performance in our adults compared to that in other studies is explained by the fact that we selected adults with moderate education levels from the normal population with the purpose of matching them on education levels (and thereby IQ) with adolescents. This resulted in an adult sample with relatively lower IQ scores (99) than that in other studies that mostly included university students. But importantly, this did lead to the absence of IQ differences between our adolescent and adult groups which is very important in cognitive developmental research since if groups are not matched on IQ it is impossible to exclude that WM differences are due to general IQ differences. This is especially important in WM research since WM capacity is known to be related to fluid intelligence. Also in our study IQ was positively correlated with WM capacity (the latter measured by WAIS Digit Span and *K* in the VSWM task), IQ explained 35% of the variance in *K*. Interestingly, Fukuda et al. (2010) recently reported data that led to the conclusion that this IQ-WM-span relationship is mediated by the number of representations that can be simultaneously maintained in WM, rather than by the precision of those representations.

Summarizing the developmental filtering efficiency results, our performance measures confirmed our hypothesis of worse WM filtering (higher distracter interference) in adolescents and CDA data showed that this was due to higher distracter processing during encoding and maintenance. Adolescents showed higher CDA responses to distracters than adults from 300-550 ms, and after 550 ms the T1D2 CDA response in adults further dropped to the level of T1D0, which indicates that they were able to filter out distracters from WM after encoding. Interestingly, Fukuda and Vogel (2011) recently showed that distracters initially capture attention in both low and high capacity individuals, but that individuals with lower capacity might be slower at disengaging their attention from distracters. Within such an interpretation, the sustained T1D2-CDA response in adolescents after 550 ms might be due to an inability to disengage attention from distracters due to immaturity of WM-attentional control networks. There is evidence that especially left dorsolateral prefrontal cortex (DLPFC) activation is functionally related to executive controlled distracter suppression during spatial WM encoding (Sandrini et al., 2008; Toepper et al., 2010). Absence of DLPFC activation has been reported in late childhood in non-spatial (Crone et al., 2006) and visuospatial WM tasks (Scherf et al., 2006).

Conclusion

In conclusion, the present study showed that adolescents performed worse than adults in a VSWM change detection task. The combination of performance and CDA results led to the conclusion that this worse performance is due to lower storage capacity overall and by an inability to block distracter items for maintenance in WM, causing inefficient use of storage space.

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Chapter 5

Electrophysiological correlates of storage capacity and filtering efficiency in working memory in adolescents and adults with attention-deficit/hyperactivity disorder.

In preparation:

Spronk, M., Vogel, E.K., Jonkman, L.M. Electrophysiological correlates of storage capacity and filtering efficiency in working memory in adolescents and adults with attention-deficit/hyperactivity disorder.

Abstract

Attention-deficit/hyperactivity disorder (ADHD) patients have both working memory (WM) and attention problems. Good attention skills are important for WM performance given that WM capacity is higher when one is able to prevent storage of irrelevant information through efficient filtering. Since it is unknown how filtering ability is associated with WM performance in ADHD, this was investigated in the present study. A visuospatial working memory (VSWM) change detection task with distracting stimuli was administered to adolescents (12-16 years old) and adults (20-46 years old) with and without ADHD matched on IQ. Besides performance, contralateral delay activity (CDA) was measured; a neural correlate of the number of targets and distracters encoded and maintained in WM during the retention interval. Performance data showed similar WM load, distracter and developmental effects in ADHD and non-ADHD groups. Adolescents' performance on the WM task deteriorated more than that of adults in the presence of distracters and with higher WM load, irrespective of Diagnosis. The CDA data suggested that initially all groups encoded distracting information, but only adults were able to filter out this information later in the retention interval, which was related to better WM performance as shown by correlation analyses. The only effect of Diagnosis was a smaller CDA in adolescents and adults with ADHD than in age-matched controls when a low load of one item had to be maintained, which was possibly related to an inability to keep attention focused at the cued hemifield. Overall, the development of filtering efficiency and VSWM storage capacity in adolescents with ADHD was not different from that in typically developing adolescents.

5.1 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder with a high prevalence of 6-9% in children (Polanczyk & Jensen, 2008), and is characterized by symptoms of inattention, impulsivity and hyperactivity (DSM-IV-TR, APA, 2000). In approximately 80% of children these symptoms persist into adolescence (Faraone et al., 2003). Whereas hyperactivity and impulsivity symptoms tend to decline most with age, the cognitive problems related to inattention show the least reduction in adolescence (Biederman et al., 1996; Hart et al., 1996; Wilens et al., 2002). An important cognitive deficit in ADHD is working memory (WM) impairment and several researchers have included WM as a significant cognitive factor in their theoretical models explaining the symptoms of ADHD (Barkley, 1997; Rapport et al., 2001). WM refers to the temporary storage and manipulation of information and one influential model of WM was introduced by Baddeley and Hitch (1974). Their multicomponent memory model consists of two short-term memory stores; a visuospatial sketchpad to hold visuospatial information and a phonological loop to hold acoustic or verbal information. The third component of the model is the central executive (CE), thought to be responsible for the attentional control of memory, coordinating the two subsidiary systems.

Impaired performance on neuropsychological memory tasks has been reported in children (Barkley, 1997; Mariani & Barkley, 1997), adolescents (MacLeod & Prior, 1996; Rommelse et al., 2008; Westerberg et al., 2004) and adults (Barkley et al., 1996; Schweitzer, 2000; McLean et al., 2004; Schoechlin & Engel, 2005; Clark et al., 2007; Dige et al., 2010) with ADHD and thus does not seem to resolve with age. Two meta-analysis studies reported deficits with large effect sizes in visuospatial short-term memory (VSSTM) or working memory (VSWM) in children, adolescents and adults with ADHD (Martinussen et al., 2005; Chamberlain et al., 2010). Impairments in verbal STM and WM are also reported in ADHD but with smaller effect sizes than visuospatial deficits (Martinussen et al., 2005). Whereas it is known that both verbal and visuospatial STM- and WM capacity undergo development into adolescence (Gathercole et al., 2004; Tillman, 2011), not many studies have investigated the development of WM performance in ADHD. This is however very important, since WM capacity is an important factor in the development of academic skills such as reading and mathematics (Gathercole et al., 2004; Gathercole et al., 2006) and fluid intelligence (Conway et al., 2002; Fukuda et al., 2010), and therefore reduced WM capacity in ADHD patients can have implications for academic achievement (e.g. in mathematics; Rogers et al., 2011).

Some studies indicate that there might be a developmental delay especially in visuospatial WM span in ADHD. In a cross-sectional study, it was found that visuospatial WM impairments were present in younger (6-7 year-old-) and older (8-12 year-old-) children with ADHD combined-type (compared to typically developing children), whereas impairments in verbal WM were only found in the younger group

(Sowerby et al., 2010). Furthermore, Westerberg et al. (2004) compared VSWM span between children with and without ADHD and reported VSWM deficits in ADHD children that were largest during adolescence. In these studies, ADHD and control groups were however not matched on IQ and since WM performance is highly correlated with IQ scores (Engle et al., 1999; Fry & Hale, 1996; Kyllonen & Christal, 1990), it is not clear to what extent these developmental effects were in fact caused by IQ differences.

An important question is to what extent a possible developmental delay in VSWM capacity in ADHD is related to their inattention problems. Some studies have reported links between memory impairments and inattentive behavior in typical development as well as in ADHD. Lui & Tannock (2007) showed that in 7-12 year-old children from a community sample, performance on WM tasks (verbal backward span, visuospatial backward span and a real-life task) was related to their inattentive behavior as reported by parents in a questionnaire. In a study with 6-16 year-old children from the general population (Tillman et al., 2011), it was shown that higher levels of inattention (according to ADHD symptoms in the DSM-IV, American Psychiatric Association, 1994) were associated with poorer visuospatial and verbal STM and WM (measured with simple span and size ordering manipulation tasks). In ADHD, relations between memory and inattention symptoms have also been found. Kofler et al. (2010) for example measured performance in phonological and visuospatial WM tasks in 8-12 year-old children with ADHD. Visual orienting to the monitor or keyboard during these tasks was used as a measure of attentive behaviour. They reported a larger decrease in attentive behaviour with increasing WM load in children with ADHD than in typically developing controls. By comparing performance on tasks that did or did not require CE processing (WM tasks vs. a drawing task), Kofler et al. showed that CE processes accounted for larger decreases in attentive behaviour in ADHD than in controls. Exceeding storage capacity also resulted in decreased attentive behaviour in children, but not more in children with ADHD than control children.

The above studies all examined the relation between WM (or STM) performance and inattention symptoms in overt behavior (questionnaires, observation), but no studies so far have directly examined WM-attention relations in ADHD by manipulating both in one experimental task. This is important since the mechanisms by which attention influences memory performance or vice versa in ADHD are still unknown. Recent studies including healthy adult subjects have indicated that restrictions in visuospatial WM capacity can be related to filtering efficiency/selective attention deficits. This conclusion was derived from studies using so-called change detection WM tasks in which VSWM capacity was measured by presenting subjects with displays of varying numbers of items that had to be kept in memory for short periods of time, after which they were tested for memory accuracy (McCullough et al. 2007; Vogel & Machizawa, 2004). These tasks have revealed a maximum visuospatial storage capacity of 3-4 items in adults (Cowan, 2001; Luck and Vogel 1997; Vogel & Machizawa, 2004). Besides manipulation of the number of

to-be-stored items (allowing for the measurement of WM capacity), in some studies the relevancy of presented items was also manipulated by including distracters in the memory set (measuring filtering efficiency) (Kane et al., 2001; Fukuda & Vogel, 2009; McNab & Klingberg, 2008; Vogel et al., 2005; Zanto & Gazzaley, 2009). These studies showed that an individual's maximum WM capacity was not only determined by the maximum number of items that can be kept in memory, but also by the ability to select relevant and ignore irrelevant items for maintenance in memory. If too much irrelevant information is stored in memory this will also result in lower WM capacity measures for tested items, since these items need space in WM. Hence, selective attention, e.g. the ability to enhance relevant information and suppress irrelevant information, plays a crucial role in determining which information enters WM and how much WM space is still available. Since impairments in selective attention or interference control are central to ADHD across all ages, (Brodeur & Pond, 2001; Jonkman et al., 1999; 2004; Randall, 2008; Biederman et al., 2008; Rapport et al., 2001; Murphy et al., 2001; Boonstra et al., 2005), they might be a significant factor in the lower VSWM capacity often observed in ADHD patients. This will be investigated in the present study.

Neuroimaging studies have shown that fronto-parietal brain networks play an important role in the filtering of irrelevant information for storage in WM in adults (Awh et al., 2006; Cowan et al., 2005; McNab & Klingberg, 2008; Vogel et al., 2005). In typical development increasing activity is seen in regions associated with these fronto-parietal networks when performing WM tasks that require high levels of cognitive control (Bunge and Wright 2007; Kwon et al. 2002). Sheridan et al (2007) have reported altered activation in brain regions that are part of this network (e.g. dorsolateral prefrontal cortex, DLPFC) during a verbal WM task in adolescents with ADHD. In general, studies report functional and structural abnormalities in children and adolescents with ADHD in fronto-striatal networks that are known to play an important role in the regulation of inattention symptoms (for reviews see: Durston, 2003; Bush, 2011). In adults with ADHD, similar impairments in fronto-striatal and fronto-parietal networks are associated with cognitive deficits (Dickstein et al., 2006; Schneider et al., 2010). Considering previously reported selective attention/interference control problems (Biederman et al., 2008; Boonstra et al., 2005; Brodeur & Pond, 2001; Jonkman et al., 1999, 2004; Lansbergen, Kenemans, & van Engeland, 2007; Murphy et al., 2001; Nigg, 2001; Randall, 2008; Rapport et al., 2001) and abnormal functioning of fronto-parietal networks in the ADHD literature, it could well be that WM capacity problems in ADHD in part originate from inefficient filtering of irrelevant information.

In the present study a visuospatial change detection WM task with targets and distracters (adapted from Vogel et al., 2005) was used to assess the development of visuospatial WM capacity and filtering efficiency in ADHD during adolescence. Besides performance measures, an electrophysiological measure called the contralateral delay activity (CDA) was obtained as an online neural marker of the number of items encoded and stored in WM (Ikkai et al., 2010; McCollough et al.,

2007; Vogel & Machizawa, 2004). The CDA occurs above the lateral parietal cortex and is thought to be a direct neural measure of the number of items stored in WM since its amplitude has been found to increase linearly with the number of presented items and to reach a plateau when the maximum number of items a person can store in memory is exceeded (Ikkai et al., 2010; McCollough et al., 2007; Vogel & Machizawa, 2004). CDA amplitude does not only increase with the number of relevant items stored; similar amplitude rises can be found when irrelevant items (distracters) are stored in WM despite task instructions to ignore them. This was shown by Vogel et al. (2005) who used a task in which subjects had to memorize the orientation of either two or four red items (the targets) for a later memory test. In a third condition two target items were accompanied by two distracter (e.g. blue-colored) items (T2D2; two targets, two distracters) that should not be stored in WM. The idea was that subjects with inefficient filtering abilities would also store the two distracter items in WM, having a total storage load of four items. Taken that the CDA amplitude varies with the number of stored items, this should be reflected by overlapping or more similar CDA's in the T4D0 and T2D2 conditions than in T2D2 and T2D0. This was indeed what was found, but only in subjects with low WM capacity. In subjects with high WM capacity the T2D2-CDA overlapped with the T2D0-CDA and was smaller than the T4D0-CDA, showing that they had successfully prevented storage of the two distracter items. Thus, in this paradigm, the CDA can be used as a neural correlate of the number of relevant and irrelevant items that are encoded or maintained in memory in the retention interval of the task.

To our knowledge, this is the first time that the change detection task and the CDA-ERP measure are used to investigate the online storage of irrelevant and relevant information in VSWM in ADHD patients. Importantly, in the present study adolescents as well as adults with and without ADHD were included to study the developmental course of potential WM filtering and capacity deficits in ADHD. According to developmental lag theories of ADHD, cognitive deficits may be due to a developmental delay and persons with ADHD might eventually catch up with typically developing persons. For example, a developmental lag was previously proposed for inhibition (Barkley, 1998; Doehner et al., 2010) and for verbal memory (Sowerby et al., 2010), with larger differences between children with and without ADHD than between adolescents with and without ADHD. If a developmental lag for WM filtering and storage capacity indeed exists, larger differences could be expected between control adolescents and adolescents with ADHD than between adults with and without ADHD. Another important aspect of the present study is that ADHD and control groups were matched on IQ and educational level to exclude the possibility that group differences in WM capacity or filtering efficiency are explained by IQ differences, which might have been the case in earlier studies. The visuospatial change detection task used in the present study closely resembles that used in previous change detection studies (Vogel & Machizawa, 2004; Vogel et al., 2005; Ikkai et al., 2010) and comprises three relevant stimulus conditions; a one target condition without distracters (T1D0) in which subjects have to store a low load of one

item in WM, a three target condition without distracters (T3D0; storage of a higher load of three items) and a one target condition with two distracters (T1D2; storage of 1 item in case of perfect filtering). Based on earlier reported visuospatial WM capacity and attentional filtering deficits in ADHD, we expected larger unnecessary storage of distracter items in WM in ADHD patients, at least during adolescence. This would be reflected by 1) larger distracter interference effects on behavioral change detection measures (RT, accuracy, Unnecessary Storage (difference in capacity score K between T1D0 and T1D2)) and 2) by larger T1D0-T1D2-CDA differences and/or smaller T1D2-T3D0 CDA differences in ADHD than control groups. The relation between Unnecessary Storage and WM capacity will also be examined.

5.2 Methods

Subjects

Seventy-seven subjects participated in the study (21 control adolescents, 18 adolescents with ADHD, 19 control adults, and 19 adults with ADHD), of which seven were excluded because of low ($IQ \leq 80$) or high ($IQ \geq 120$; excluded to match groups on IQ) estimated IQ scores (two control adolescents, two adolescents with ADHD, one control adult, and two adults with ADHD) and four were excluded due to significant outliers in behavioral measures (one control adolescent, one adolescent with ADHD, and two control adults). The remaining 19 control adolescents (9 boys and 10 girls) were recruited from a school providing secondary vocational education for 12- to 16-year-olds, and the 16 control adults (8 males and 8 females) were recruited via advertisements in local newspapers. The 15 adolescents with ADHD (11 males and 4 females) and 17 adults with ADHD (9 males and 8 females) were recruited via the RIAGG (Regional Institute for Ambulant Mental Health Care) in Maastricht (the Netherlands) and had a clinical diagnosis of ADHD (inattentive or combined type) according to the DSM-IV-TR diagnostic criteria (American Psychiatric Association, 2000). In addition to this diagnosis, to ensure the presence of childhood inattention problems in adults with ADHD, retrospective and current reports of ADHD symptoms were assessed by a self-report questionnaire for ADHD symptoms (Kooij & Buitelaar, 1997). Due to an administrative error scores of two adults were missing. Mean scores were 7 out of 9 for retrospective inattention symptoms, and 8 out of 9 for symptoms of inattention in the past six months. All subjects in the ADHD groups were free from other DSM-IV comorbidity, except for three adolescents with ADHD that had a comorbid diagnosis of Oppositional Defiant Disorder (ODD).

Mean age was 14.8 years (SD 1.4, range 12-16 years) in the control adolescent group, 14.8 years (SD 1.0, range 13-16 years) in the ADHD adolescent group, 31.0

years (SD 8.8, range 20-46 years) in the control adult group, and 28.2 years (SD 5.9, range 21-38 years) in the ADHD adult group.

To confirm the absence of attention- and ADHD behavioral problems in the control subjects, all adolescents filled out the Youth Self Report form (YSR; Achenbach, 1991) and all adults the Adult Self Report form (ASR; Achenbach, 2003). The adolescents and adults with ADHD also filled out these lists to be able to compare scores between the groups. Mean scores on the attention subscales of the YSR were 52.6 (SD 3.7; range 50-60) for control adolescents and 61.6 (SD 7.8; range 52-78) for adolescents with ADHD and differed significantly ($F(1,33) = 19.0, p < .001$). ASR attention scores were 52.8 (SD 3.5; range 50-59) for control adults and 72.2 (SD 6.5; range 59-87) for adults with ADHD and differed significantly ($F(1,32) = 110.1, p < .00001$). On the ADHD subscales of the YSR mean scores were 53.1 (SD 4.3, range 50-67) for control adolescents and 64.9 (SD 6.7, range 54-77) for adolescents with ADHD, this difference was significant ($F(1,33) = 37.2, p < .00001$). ASR mean scores on the ADHD subscale were 52.7 (SD 3.9, range 50-63) for control adults and 77.1 (SD 8.9, range 64-95) for adults with ADHD. ADHD scores differed significantly between adult groups ($F(1,32) = 100.1, p < .00001$).

To derive an estimated IQ score, all adolescents were administered two subtests of the Wechsler Intelligence Scale for Children (WISC-III; Wechsler, 1991); Vocabulary and the Block Design tests. Adults performed the same subtests from the WAIS (WAIS-III; Wechsler, 1997). The estimated IQ score based on these two subtests has a mean reliability and validity of .9 (Jeyakumar et al., 2004; Spreen & Strauss, 1998). The estimated mean IQ-score was 96.5 (SD 7.3) in the adolescent control group, 99.1 (SD 11.6) in the adolescent ADHD group, 97.9 (SD 9.3) in the adult control group, and 103.0 (SD 10.0) in the adult ADHD group. IQ-scores did not significantly differ between groups ($F(1,63) = 1.5, p = .230$).

The present study was approved by the Medical Ethics Committee of the azM and Maastricht University (MEC azM/UM), and prior to the study a written informed consent was obtained from the children and their caretakers and from the adults according to the Declaration of Helsinki (1964). All subjects were paid for their participation in the experiment.

Procedure

The experimental session lasted 2.5-3 hours. The session started with three tests from the WISC-III (Wechsler, 1991, for adolescents) and WAIS-III (Wechsler, 1997, for adults); the block design test, vocabulary test and the digit span test. The latter (digit span forward and backward) was performed by the participants to obtain an independent measure of verbal short-term and WM capacity. Subsequently, the electrodes were attached. During the experimental session all participants sat in front of a 17-inch VGA monitor with their eyes aligned to the centre of the screen at a distance of approximately 75 cm. The participants were instructed to minimize eye blinks and to refrain from making head or eye movements during task performance.

The experimental session started when all tasks were practiced until a predetermined performance criterion (75% correct responses) was reached.

Experimental Task

To measure differences in WM capacity and the efficiency of excluding irrelevant items from memory between Age and Diagnosis groups, a VSWM task comparable to that used in earlier change detection studies (Vogel & Machizawa, 2004, Vogel et al., 2005) was presented to the subjects.

This task consisted of bilateral stimulus displays in which colored squares ($0.76^\circ \times 0.76^\circ$) or rectangles ($1.15^\circ \times 0.57^\circ$) were presented within two $4^\circ \times 7.3^\circ$ rectangular regions presented 3° to the left and right from of a central fixation cross; see Figure 1). On each trial, the positions of the items were randomly distributed within upper and lower quadrants of the screen with the constraint that the distance between objects within a hemifield was at least 2° (centre to centre). The colour of squares and rectangles was randomly selected on each trial with limited replacement from a set of seven easily distinguished colours (red, blue, green, violet, yellow, black and white). The number of targets and distracters was always the same in both hemifields, only location and color of the stimuli could differ between hemifields. All stimuli were presented on a gray background.

A trial started with the presentation of an arrow cue that indicated the hemifield that subjects should attend to on the following memory display. The subject's task was to remember the locations and colors of the squares (targets: T) in this cued hemifield for a later test. A total number of 480 trials was presented. On half of the trials the squares were accompanied by distracters (D: colored rectangles) that had to be ignored. In total, there were four different types of memory displays differing in the number of targets and distracters. Either one or three targets (squares) were presented alone (T1D0 or T3D0; memory load of 1 or 3 items) or were accompanied by two distracters (T1D2 or T3D2). The T3D2 condition exceeded maximum capacity and was included to obtain equal numbers of trials with or without distracters. All memory displays were followed by a test display 900 ms later in which one colored square was presented at one of the locations in the preceding memory display within the upper or lower quadrant (to both hemifields). The subjects had to press a left button with the left index finger when the test stimulus shown at this location had the same color as that in the previous memory display (50% of all trials) or press right with the right index finger when it was different. A new memory display followed 500-700 ms after a response was given. See Figure 1 for an example of a complete trial of the T1D2 condition with exact timing parameters.

The behavioral measures derived from the VSWM change detection task in T1D0, T1D2 and T3D0 were: 1) reaction times for correct detections (RT), percentage correct responses (% Hits), and *K*-scores (see below). Also a measure of Unnecessary Storage was computed by subtracting *K*-T1D2 from *K*-T1D0.

Only reaction times to correct responses that fell within a response window from 250-4000 ms after the memory probe were included in the analysis. Cowan's memory capacity measure K in T1D0 and T3D0 conditions was computed with a standard formula (Cowan, 2001): $K = (H + CR - 1) N$, in which H is the hit rate, CR are the correct rejections in an array with N items. To derive a behavioral measure of filtering efficiency, following a study by Lee et al. (2010) we also computed K in the distracter condition (T1D2) by filling in 1 for N since there was 1 target item; if distracters are perfectly filtered out K will be 1, in case of imperfect filtering K will be lower than 1. This K -T1D2 measure was subtracted from K -T1D0 to obtain an "Unnecessary Storage" measure.

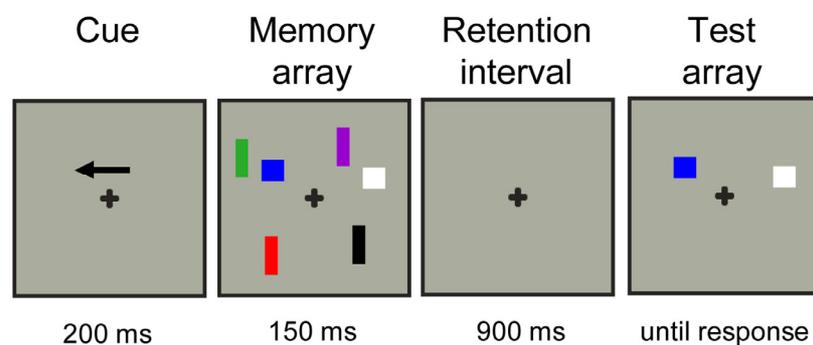


Figure 1. Example of distracters-present trial (T1D2) for the left hemifield.

Electrophysiological Recording and Analysis

For measurement of the EEG, an elastic cap (Easycap) containing 60 Ag/AgCl electrodes was used. The montage included 7 midline sites (Fpz, Fz, FCz, Cz, CPz, Pz, Oz), and 52 lateralized sites (Fp1, Fp2, AF7, AF3, AF4, AF8, F7, F5, F3, F1, F2, F4, F6, F8, FT7, FC5, FC3, FC1, FC2, FC4, FC6, FT8, T7, C5, C3, C1, C2, C4, C6, T8, TP7, CP5, CP3, CP1, CP2, CP4, CP6, TP8, P7, P5, P3, P1, P2, P4, P6, P8, PO7, PO3, PO4, PO8, O1, O2), and the right mastoid A2. During measurement all electrodes were referenced to the left mastoid (A1) and one of the electrodes in the cap (AFz) was used as ground. Offline, EEG data were re-referenced to the average of the right and left mastoids. Blinks, vertical and horizontal eye-movements were measured by bipolar electrodes placed above and below the left eye and at the outer canthi of both eyes. All electrode impedances were kept below 10 k Ω , with the exception of the reference and ground electrodes which were held below 5 k Ω . Signal acquisition was accomplished using Brainamp amplifiers and Brain Vision Recorder software (version 1.10). EEG and EOG signals were continuously sampled at 250 Hz with a high-pass filter of 0.05 Hz and a low-pass filter of 30 Hz.

ERP analysis was done in Neuroscan 4.3.1. The continuous EEG was divided into 480 epochs of 1250 ms, from 200 ms prestimulus to 1050 ms poststimulus, all

aligned to a baseline from -200 to 0 ms preceding the memory array. First, vertical (blinks) and horizontal electro-oculogram (VEOG and HEOG) artifacts were removed from the data by applying an eye-movement correction algorithm (Semlitsch et al., 1986). For the computation of regression coefficients between VEOG and the EEG-signals at the different electrodes, adequate eye blinks were manually selected and transmission coefficients were computed on the basis of these selected trials. In a similar way, by manually selecting horizontal eye movements separately for right- and left cued displays for each individual, regression coefficients between HEOG and the EEG-signals at the different electrodes were computed. All transmission coefficients were carefully checked to have strengths, signs and topographies congruent with expected patterns for vertical and horizontal movements before they were applied to remove eye blinks and horizontal eye movements from the EEG through the Semlitsch et al. (1986) procedure. After EOG-artifact removal, epochs still containing artifacts exceeding $\pm 75 \mu\text{V}$ were rejected from the database. Whereas the above procedure should have removed all HEOG activity from the EEG signal, to be sure that our CDA load and distracter effects were not due to any residual HEOG activity we performed an extra check by calculating the correlations between CDA and HEOG in each condition between 450 and 825 ms. No significant correlations between CDA and HEOG in T1D0, T1D2 or T3D0 were found in the four groups (for average HEOG signal in the three conditions see Figure 3). Next, average ERPs were computed separately for each subject in three different task conditions: (1) one target square only (T1D0; where T is the number of targets and D is the number of distracters), (2) one target square plus two distracter rectangles (T1D2), (3) three target squares only (T3D0). The fourth condition (T3D2) was not included in the analyses since its number of shapes (five) exceeds the maximum memory capacity of four items. In the averaging procedure, only trials with correct responses were included. There was a maximum number of 120 trials in each task condition. The minimum number of included trials in each condition was 20. Across conditions, the mean number of artifact-free EEG epochs contained in the single-subject averages was 74 trials (SD=24) in the control adolescent group, 101 (SD=12) in the ADHD adolescent group, 101 trials (SD=16) in the control adult group, and 115 (SD=5) trials in the ADHD adult group.

We computed contralateral waveforms by averaging the activity recorded at right hemisphere electrode sites when subjects were cued to remember the left side of the memory array with the activity recorded from the left hemisphere electrode sites when they were cued to remember the right side. CDA was measured at posterior parietal and lateral occipital electrode sites (P1/2, P3/4, P5/6, P7/8, PO3/4, PO7/8, O1/2) as the difference in mean amplitude between the ipsilateral and contralateral waveforms. Since the differences between conditions generally seem to decrease over time in the delay period (for example see Delvenne et al., 2010), which may indicate different processing stages, two measurement windows were selected for analyses, an early window of 450-550 ms and later window of 550-825 ms after the onset of the memory array.

Statistical Analysis

Behavioral measures

Effects of Age (adolescents vs. adults) and Diagnosis (control vs. ADHD) and possible interactions between both on verbal and VSWM capacity were tested by performing 2 x 2 univariate ANOVA analyses separately for forward, backward and standardized (including both forward and backward scores; for computation see WISC-III/WAIS-III manual) digit span tests (verbal WM), and *K* in T1D0, T1D2 and T3D0 conditions (VSWM).

To test for group differences in filtering efficiency in the change detection task planned ANOVA analyses with Trial-type (either T1D0 vs. T1D2 or T1D2 vs. T3D0), Age (adolescents, adults) and Diagnosis (control, ADHD) as factors were performed on reaction time (RT) and accuracy (% correct). With worse filtering efficiency T1D0-T1D2 RT differences will increase and T1D2-T3D0 RT differences will decrease due to longer search times in T1D2 (due to unnecessary storage of distracters). In the same way T1D0-T1D2 accuracy differences will increase and T1D2-T3D0 accuracy differences will decrease in case of inefficient filtering. Differences in Unnecessary Storage (difference score between *K*-T1D0 and *K*-T1D2) between Age and Diagnosis groups were tested with a 2 (adolescents vs. adults) x 2 (control vs. ADHD) univariate ANOVA.

ERP measures

For the parietal/occipital CDA windows, mean amplitudes were compared across conditions by repeated measures ANOVAs. Three planned mixed model ANOVA's were performed in both time windows, with a within-subject factor Trial-type with two levels (T1D0 & T1D3 or T1D0 & T1D2 or T1D2 & T3D0) and two between-subjects factors Age (adolescents, adults) and Diagnosis (control, ADHD). In case of significant Age x Diagnosis x Trial-type interactions or Age x Diagnosis interactions, post-hoc tests were performed for the separate Age groups. In case of Age x Trial-type or Diagnosis x Trial-type interactions, further testing was done to reveal possible effects of Trial-type.

Correlations

Correlations between behavioral measures of storage capacity, filtering efficiency (T1D0-T1D2 RT and accuracy differences or Unnecessary Storage) and CDA amplitude differences in T1D0 and T1D2 for the early and late CDA window were calculated using Pearson correlation coefficients.

5.3 Results

Behavioral Results

Developmental differences in verbal (digit span) and visuospatial span (Cowan's K) in ADHD and controls

Forward, backward and standardized digit spans were collected for all groups to obtain measures of verbal WM span, and visuospatial WM span was measured by computing K in T1D0, T1D2 and T3D0 conditions of the VSWM task. For means and standard deviations (SD's) of scores in the digit span task see Table 1. For mean K scores (and SD's) in the VSWM task see Table 1 and Figure 2A.

The adolescent groups had significantly lower verbal span than the adult groups as shown by forward, backward and standardized digit span (univariate ANOVA, factor Age: forward digit span: $F(1,63) = 10.4, p < .005$; backward digit span: $F(1,63) = 20.1, p < .0001$; standardized digit span: $F(1,63) = 12.7, p < .001$). The ADHD groups only showed lower forward span compared to the control groups (ANOVA, factor Diagnosis: $F(1, 63) = 4.5, p < .05$).

Adolescents had significantly lower VSWM capacity, reflected by lower K scores than adults in conditions T1D0 (ANOVA, factor Age: $F(1,63) = 7.4, p < .01$), T1D2 ($F(1,63) = 14.2, p < .001$) and T3D0 ($F(1,63) = 11.3, p < .005$). No differences between ADHD and control groups (no effects of Diagnosis) were found for VSWM capacity.

Effect of distracters on the speed (RT) and accuracy of change detection performance

For both RT and accuracy data two planned 2 (Age; adolescents, adults) \times 2 (Diagnosis; ADHD, control) \times 2 (Trial-type; T1D0-T1D2 OR T1D2-T3D0) ANOVA's were carried out to test for effects of distracters on VSWM performance (see Figure 2B and 2C for means of RT and accuracy 95% confidence intervals respectively).

Reaction time (RT). The first comparison (T1D0 vs. T1D2) yielded a significant Age \times Trial-type interaction effect ($F(1,63) = 7.9, p < .01$), indicating that adolescents showed stronger RT increases from T1D0 to T1D2 (due to the presence of distracters) than adults. The T1D2 vs. T3D0 comparison also yielded a significant Age \times Trial-type interaction ($F(1,63) = 11.5, p < .005$), showing that reaction time increased less from T1D2 to T3D0 in adolescents than in adults (see Figure 2, panel B). No effects of Diagnosis were found for reaction time.

Accuracy. The first comparison (T1D0 vs. T1D2) yielded a significant Age \times Trial-type interaction effect ($F(1,63) = 7.1, p < .01$), showing a steeper decline in memory accuracy from T1D0 to T1D2 (with distracters) in adolescents than adults

Table 1. Group means (standard deviations between brackets) of forward, backward and standardized digit span scores (WAIS III), and WM capacity *K* in T1D0, T1D2 and T3D0 conditions of the VSWM change detection task in adolescents and adults.

	Digit span (verbal)			WM capacity <i>K</i> (visuospatial)		
	Forward	Backward	Standardized	T1D0	T1D2	T3D0
Control Adolescents	8.3 (1.7) ** Range: 5-13	5.3 (2.0) ** Range: 2-11	8.7 (2.9) ** Range: 3-17	.81 (.15) * Range: .42 - .98	.67 (.17) ** Range: .33 - .93	1.82 (.48) ** Range: .78 - 2.50
ADHD Adolescents	7.5 (1.6) ** Range: 5-11	5.3 (1.9) ** Range: 4-10	8.3 (2.8) ** Range: 3-14	.78 (.17) * Range: .49 - .97	.64 (.20) ** Range: .31 - .93	1.61 (.49) ** Range: .73 - 2.30
Control Adults	10.0 (2.3) ** Range: 6-14	8.1 (2.4) ** Range: 5-14	12.1 (3.4) ** Range: 7-19	.89 (.14) * Range: .43 - .99	.82 (.16) ** Range: .39 - .98	2.15 (.50) ** Range: 1.20 - 2.83
ADHD Adults	8.8 (1.9) ** Range: 4-15	7.2 (2.0) ** Range: 4-13	10.2 (2.9) ** Range: 5-19	.89 (.13) * Range: .51 - 1.0	.82 (.18) ** Range: .22 - .98	2.09 (.50) ** Range: .95 - 2.80

NB: stars indicate significant Age differences (*p* values): * $p < .01$; ** $p < .001$

(see Figure 2C). For both conditions an Age effect was found (T1D0: $F(1,63) = 7.8$, $p < .01$; T1D2: $F(1,63) = 14.3$, $p < .001$). The second comparison (T1D2 vs. T3D0) yielded a main effect of Trial-type ($F(1,63) = 56.4$, $p < .00001$) indicating that all subjects were less accurate in the T3D0 condition than in the T1D2 condition. Whereas the size of this decline in accuracy was not different between adolescents and adults (no Trial-type \times Age interaction), a main effect of Age ($F(1,63) = 13.8$, $p < .001$) did show that adolescents generally made more errors than adults in both the distracter (T1D2) and the high WM load (T3D0) condition. There were no effects of Diagnosis.

As indicated earlier, worse filtering efficiency will become visible as larger T1D0-T1D2 performance (or CDA) differences and smaller T1D2-T3D0 performance (or CDA) differences; which is exactly the pattern that was found for the RT results (and partly also the accuracy results) in adolescents (when compared to adults).

Finally, a main Age effect ($F(1,63) = 6.9$, $p < .05$) for the Unnecessary Storage measure showed significantly higher storage of distracters in adolescents (.14) than in adults (.07). There were no differences in Unnecessary Storage between ADHD and control groups (no effect of Diagnosis or Diagnosis \times Age interaction was found).

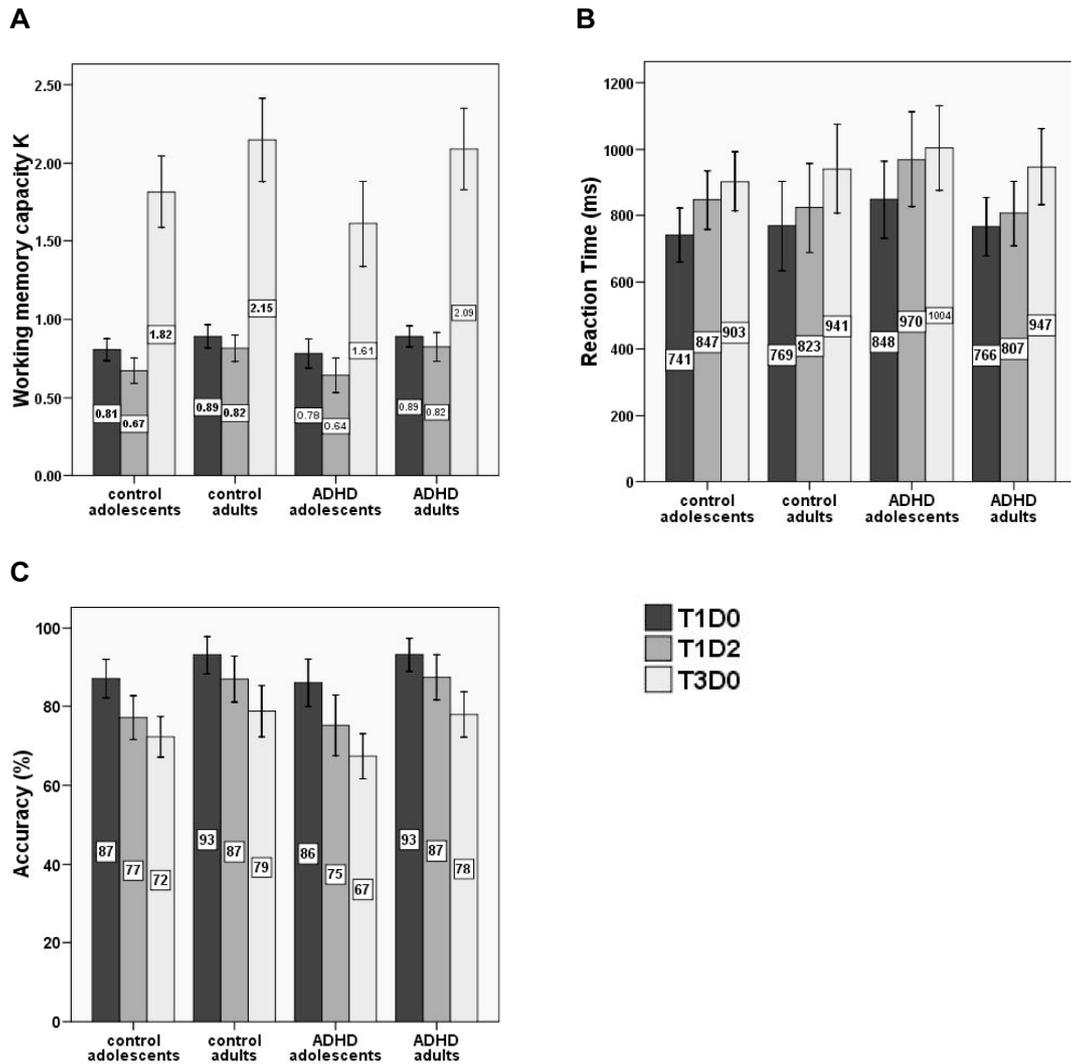


Figure 2. Bar graphs of (A) Cowan's K , (B) average reaction times (in ms), and (C) percentage of correct responses for control and ADHD adolescents and adults in T1D0 (one target), T1D2 (one target, two distracters) and T3D0 (three targets) conditions of the VSWM change detection task. Error bars indicate 95 % confidence intervals.

CDA Results

Grand ERP averages of CDA at occipital and parietal sites (P1/2, P3/4, P5/6, P7/8, PO3/4, PO7/8, O1/2) in the adolescent and adult groups for the three task conditions are depicted in Figure 3. Mean CDA amplitudes and SD's in the predefined 450-550 and 550-825 ms time windows per condition and Age groups are shown in Table 2.

Effects of load and distracters on CDA in the encoding interval (450-550 ms).

To test for *effects of increasing load* (maintenance of one vs. three items), mean amplitudes of parietal-occipital CDA in the first time window (450-550 ms) in T1D0 and T3D0 conditions were entered into a 2 (Age; adolescents vs. adults) x 2

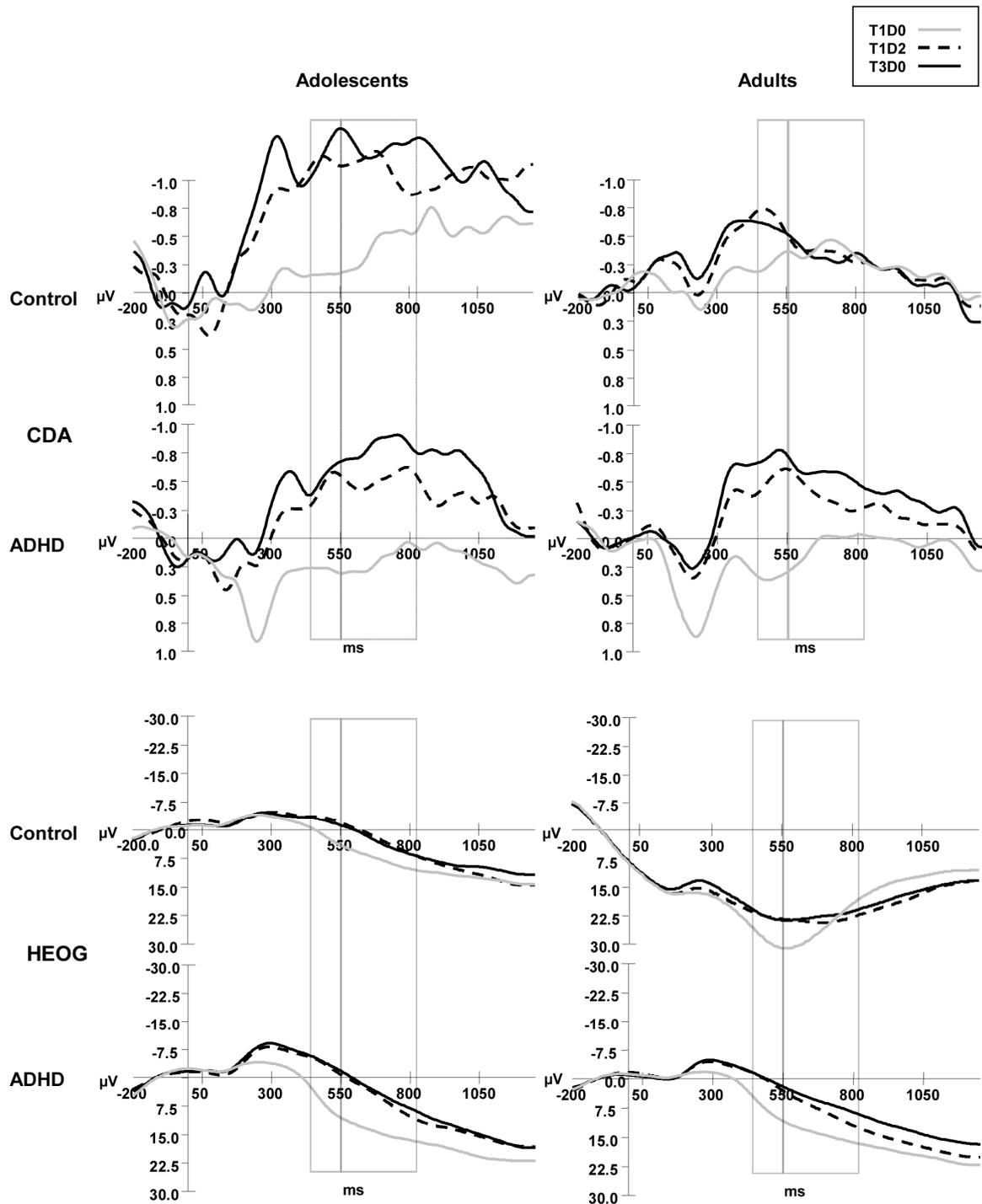


Figure 3. Average CDA activity (computed by subtracting ipsilateral from contralateral activity) and HEOG activity ($(\text{HEOG left visual field trials} \times -1 + \text{HEOG right visual field trials}) / 2$) after smoothing with a 6 Hz low-pass filter, time-locked to the memory array and averaged across occipital and posterior parietal electrode sites for control and ADHD adolescents and adults, in conditions T1D0, T1D2 and T3D0. Grey bars indicate time windows for analysis: 450-550ms and 550-825ms.

(Diagnosis; ADHD vs. control) \times 2 (Trial-type) repeated measures analysis. A significant interaction between Age, Diagnosis and Trial-type was found ($F(1,63) = 5.1, p < .05$); this interaction was followed up by testing for Trial-type \times Diagnosis effects in adolescent and adult groups separately. In the adolescent groups there was a main effect of Trial-type ($F(1,32) = 18.5, p < .001$) signifying a CDA amplitude increase with increasing load, but there was no interaction with Diagnosis among adolescents. In the adult groups however, there was a significant Trial-type \times Diagnosis interaction ($F(1,31) = 12.7, p < .01$), showing a larger load-related CDA increase in adults with ADHD (Trial-type effect: $F(1,16) = 38.4, p < .0001$) than in typically developed adults ($F(1,15) = 6.6, p < .05$). No other main or interaction effects were found. To test whether CDA increase with load was also larger in adolescents than control adults, two extra comparisons were done (control adolescents vs. control adults and ADHD adolescents vs. control adults). The effect of Trial-type on CDA was different for control adolescents and control adults (interaction Trial-type \times Age: $F(1,33) = 4.4, p < .05$). There was however no such difference between ADHD adolescents and control adults, but only an overall increase in CDA amplitude in these groups for increasing load (Trial-type-effect: $F(1,31) = 9.8, p < .005$).

To test for *effects of distracters* on CDA amplitude, similar $2 \times 2 \times 2$ repeated measures analyses of variance were conducted for T1D0 vs. T1D2 and for T1D2 vs. T3D0 conditions. The comparison between T1D0 and T1D2 showed significant increases in CDA amplitude with the presence of distracters in all four groups (main effect of Trial-type: $F(1,63) = 40.6, p < .0001$). Furthermore, a main effect of Diagnosis ($F(1,63) = 4.8, p < .05$) showed that CDA amplitudes (in T1D0 and T1D2) were larger in the control groups than in the ADHD groups. No other significant main or interaction effects were found, except for a trend significant interaction Age \times Diagnosis \times Trial-type ($F(1,63) = 3.3, p = .075$) which was not further tested. For the

Table 2. CDA data from the VSWM change detection task. Mean CDA amplitude (standard deviations between brackets) at posterior parietal and lateral occipital electrode sites (μV) over the indicated time windows, in the three conditions for adolescents and adults.

		T1D0	T1D2	T3D0
CDA (450-550ms)	Control Adolescents	-0.30 (1.41)	-1.21 (1.25)	-1.24 (1.44)
	ADHD Adolescents	0.23 (0.95)	-0.47 (1.31)	-0.54 (1.03)
	Control Adults	-0.28 (0.56)	-0.67 (0.62)	-0.60 (0.56)
	ADHD Adults	0.35 (0.35)	-0.54 (0.86)	-0.76 (0.81)
CDA (550-825 ms)	Control Adolescents	-0.39 (1.43)	-1.11 (1.10)	-1.31 (1.39)
	ADHD Adolescents	0.14 (1.07)	-0.51 (1.11)	-0.82 (0.99)
	Control Adults	-0.38 (0.53)	-0.35 (0.40)	-0.38 (0.51)
	ADHD Adults	0.06 (0.44)	-0.37 (0.68)	-0.59 (0.67)

T1D2-T3D0 comparison, no main or interaction effects for Trial-type, Age or Diagnosis were found. The pattern of T1D0 < T1D2 = T3D0 CDA amplitude that was found in all subjects in this early encoding window shows that there was distracter encoding (suboptimal filtering) in all subjects.

Effects of load and distracters on CDA amplitude during the maintenance interval (550-825 ms).

The test for *effects of increasing load* (T1D0 vs. T3D0) showed a main Trial-type effect ($F(1,63) = 24.1, p < .0001$). Furthermore, an Age \times Trial-type interaction was found ($F(1,63) = 5.8, p < .05$). Adolescents with and without ADHD had a larger increase in CDA amplitude when three items had to be remembered compared to one ($F(1,32) = 16.2, p < .001$) than adults with and without ADHD ($F(1,31) = 10.4, p < .01$). No other main or interaction effects were found.

Again, to test for *effects of distracters* on CDA amplitude in this later processing window, two trial-type (T1D0-T1D2 and T1D2-T3D0) comparisons were carried out. T1D0-T1D2 comparison yielded two significant effects. First, a main trend significant effect of Diagnosis ($F(1,63) = 3.9; p = .053$) indicated that adolescents and adults with ADHD had overall smaller T1D0 and T1D2 CDA amplitudes than typically developing adolescents and adults, just as in the earlier encoding window. Second, a significant Age \times Trial-type interaction ($F(1,63) = 4.5; p < .05$) indicated that in this processing window different effects of distracters were found on the CDA in younger and older participants. Follow-up tests showed a main Trial-type effect in adolescents ($F(1,32) = 11.4; p < .005$), signifying significantly higher parietal-occipital CDA amplitude in T1D2 than in T1D0), indicating distracter maintenance (e.g. suboptimal filtering). In adults with and without ADHD however, this CDA amplitude enhancement was not significant (Trial-type effect: $F(1,31) = 3.7; p = .064$). For the T1D2-T3D0 comparison main effects of Trial-type and Age were found. The Trial-type effect ($F(1,63) = 4.3, p < .05$) indicated that the T3D0-CDA was significantly higher than the T1D2-CDA, suggesting that, as opposed to in the earlier encoding window, in this later maintenance window some filtering has taken place in all four groups. Second, a main effect of Age ($F(1,63) = 6.0, p < .05$), indicated that CDA amplitudes (in both T1D2 and T3D0 conditions) were larger in adolescents than in adults, irrespective of Diagnosis. Thus, in this later maintenance interval, in adolescents a T1D0 < T1D2 < T3D0 CDA pattern was found, indicating that they maintained distracters in WM during the delay. Adults, however, showed a T1D0 = T1D2 < T3D0 pattern that has in earlier studies been associated with distracter filtering (see Vogel et al., 2005).

Correlations between performance and electrophysiological CDA measures

Correlations were computed between performance and CDA measures of WM capacity and filtering efficiency. Figure 4 depicts the most important significant correlations.

For all subjects it was found that participants with higher visuospatial memory span also had higher verbal memory span; *K* scores in all three conditions were correlated to forward, backward and standardized digit span scores (except for *K* in T3D0 and forward digit span). The strongest correlation was found between *K*-T3D0 and backward digit span ($r(67) = .409, p < .001$), and the weakest correlation between *K*-T1D2 and forward digit span ($r(67) = .244, p < .05$).

A relationship between storage capacity and filtering efficiency was also found. Subjects with higher VSWM capacity stored less irrelevant items in memory, reflected by a significant correlation between *K* (T3D0) and the Unnecessary Storage measure (*K*-T1D0 minus *K*-T1D2) ($r(67) = -.336, p < .01$, see Figure 4A).

Furthermore, correlations were found indicating that adolescents and adults with larger distracter interference effects on accuracy (reflected by the Unnecessary Storage measure) and speed of memory performance also had larger distracter-related CDA amplitude increases during the maintenance window. Firstly, the Unnecessary Storage measure showed a negative correlation with distracter-related CDA effects (T1D2 amplitude – T1D0 amplitude) for all subjects together in the maintenance window from 550-825 ms ($r(72) = -.250, p < .05$) (see Figure 4B). Secondly, a similar negative correlation was found between distracter-related RT increases (RT-T1D2 minus RT-T1D0) and distracter-related CDA increases in all subjects in the maintenance window (550-825ms) ($r(69) = -.395, p < .001$) (see Figure 4C).

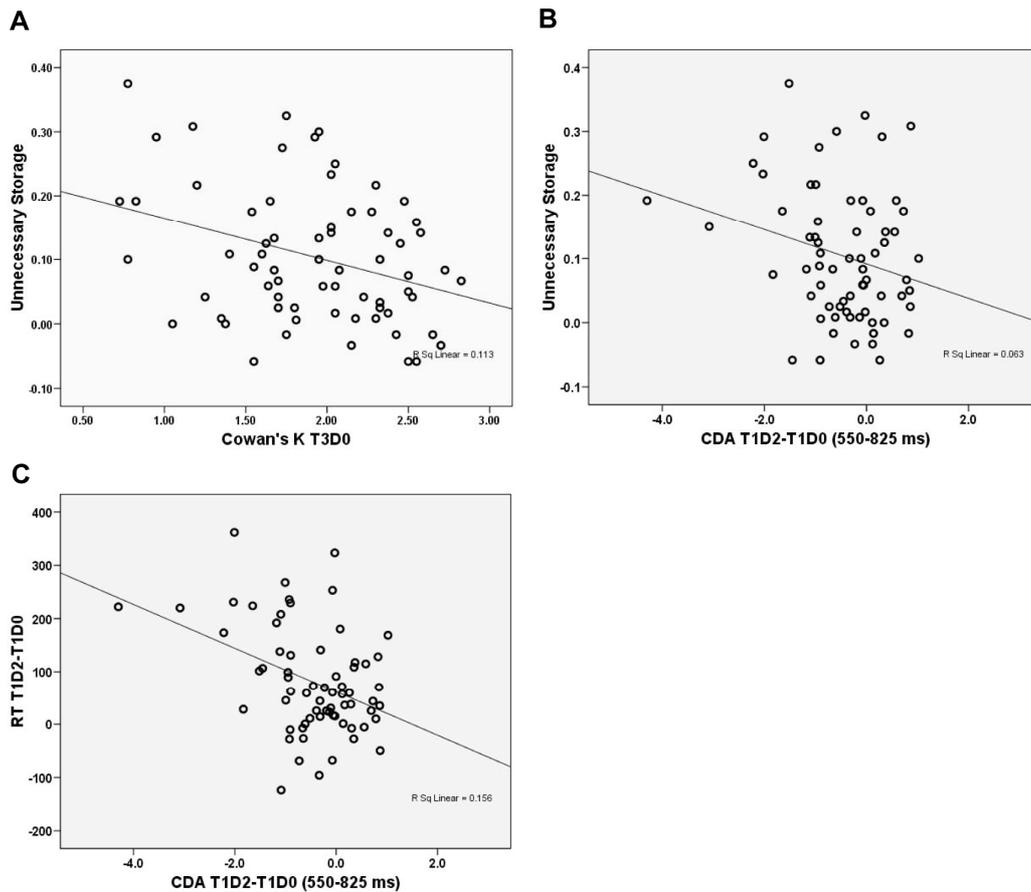


Figure 4. Scatterplots of significant correlations between behavioral and CDA measures. (A) Correlation between K-T3D0 and Unnecessary Storage (K-T1D0 minus K-T1D2) for all subjects. (B & C) Correlation between distracter-related parietal/occipital CDA effects (CDA-T1D2 minus CDA-T1D0) from 550-825 ms (x-axis) and Unnecessary Storage (K-T1D0 minus K-T1D2; panel B) in control and ADHD groups, or RT distracter effects (RT-T1D2 minus RT-T1D0; panel C) and Unnecessary Storage (K-T1D0 minus K-T1D2; panel E) in control and ADHD groups.

5.4 Discussion

The present study investigated the development of visuospatial WM capacity and its relations with filtering efficiency during adolescence in ADHD. Recent studies including healthy adult subjects have indicated that low WM capacity is related to problems with selective attention/filtering (Kane et al., 2001; Fukuda & Vogel, 2009; McNab & Klingberg, 2008; Vogel et al., 2005; Zanto & Gazzaley, 2009). That is, subjects with low WM capacity appear to store more irrelevant information (have worse filtering abilities), thereby limiting storage space. Memory impairments and filtering deficits have independently been reported in ADHD but their relation has never been directly investigated. This was done in the present study by measuring performance and CDA activity in a visuospatial WM task with targets and distracters in adolescents and adults with and without ADHD that were matched on IQ.

Filtering efficiency in a VSWM task in adolescents and adults with ADHD

Differences in WM-filtering efficiency, e.g. the ability to prevent storage of distracter information in WM, between the different age and diagnostic groups were investigated by looking at 1) the Unnecessary Storage measure, which was computed on the basis of behavioral accuracy measures (hits/false alarms) in no distracter (T1D0) and distracter (T1D2) conditions (see methods and study by Lee et al., 2010) 2) speed of memory decisions following displays with and without distracters and 3) differences in the CDA amplitude between non-distracter and distracter conditions. The CDA is a neurophysiological online marker of the number of irrelevant or relevant items stored in WM during different periods of the delay interval of the task.

WM performance (e.g. accuracy and speed of memory decisions) suffered from the presence of distracters in the memory set in all subjects as shown by the Unnecessary Storage and reaction time measures. However, this distracter interference was larger in adolescents than adults. These developmental effects did not differ between non-ADHD and ADHD groups. The CDA-ERPs were calculated separately for the distracter-present and distracter-absent trials in early and late intervals of the delay period to get insight into online filtering and storage of distracters in the brain. In an early phase of the retention interval during which stimuli were encoded in WM (450-550 ms after presentation of the memory display), CDA amplitude was increased when distracters were present (vs. absent) in all groups. The T1D2-CDA (one target, two distracters) was significantly higher than the T1D0-CDA (only one target) and overlapped with the T3D0-CDA (3 targets, no distracters), suggesting that all subjects initially encoded the distracters, irrespective of Diagnosis or Age. This pattern changed during a later, maintenance part of the delay interval (550-825 ms). An interaction between Age and Trial-type for this late CDA showed that adolescents maintained the distracters in memory during the entire delay interval (T1D0-T1D2 CDA differences sustained) whereas in adults the distracter-related T1D2-CDA dropped in amplitude to the level of T1D0. This finding provides evidence for some distracter filtering in adults (with and without ADHD) during the later part of the delay interval. The T3D0-CDA was larger than the distracter-related T1D2-CDA in all participants, indicating some filtering had taken place.

This combination of behavioral and CDA findings leads to the conclusion that adolescents' WM performance suffers more from the presence of distracting information than that of adults due to immature filtering mechanisms, as was shown by the CDA that reflects the online storage of targets/distracters in memory. Correlation analyses indeed showed that during the late part of the maintenance interval, in which the developmental effects in filtering of distracters were found, behavioral and CDA measures of filtering efficiency were related; subjects with the largest T1D0-T1D2 CDA differences had the highest Unnecessary Storage scores or largest increases in memory decision speed. We suggest that still immature functioning of dorsolateral prefrontal cortex (DLPFC) or its connections with

posterior cortex might underlie immature filtering in adolescents in WM tasks (Crone et al., 2006; Scherf et al., 2006; Luna et al., 2010) because of recent evidence that activation in this region is related to executive controlled distracter suppression during spatial memory encoding or maintenance (Sandrini et al., 2008; Toepper et al., 2010).

The developmental differences in filtering efficiency did not differ between non-ADHD and ADHD groups. These data thus do not provide evidence for a developmental lag in distracter filtering ability in ADHD when subjects are carefully matched on IQ and education level. The only significant effect of Diagnosis was the overall smaller CDA amplitude in T1D0 and T1D2 conditions in adolescents and adults with ADHD than in age-matched controls during the early and late part of the retention interval. Because the CDA is the result of the subtraction of ipsilateral from contralateral activity, these smaller CDA amplitudes could have been the result of lower contralateral or larger ipsilateral activity in response to the bilaterally presented stimulus set. Wandering of attention to the non-cued side of the display (e.g. that side one should not attend) would cause relatively enhanced ipsilateral activity, reducing lateralized CDA activity. Arend and Zimmer (2011) recently investigated the effect of irrelevant information in the non-cued hemifield on the ipsilateral CDA in healthy adults by varying the number of items on the non-cued side of the screen. They found that ipsilateral CDA activity was increased by the number of irrelevant items presented in the non-cued hemifield, but only when the to-be-stored WM load in the cued-display was low (1 item). The authors explained this by assuming that capacity that was not used for the processing of information in the contralateral hemifield “spilled over” to the non-cued side, despite instruction to keep focused on the cued hemifield. Post-hoc analyses confirmed that in the early encoding window, ipsilateral activity was significantly increased in the ADHD groups compared to in the control groups to the T1D0 display (effect Diagnosis $P = .052$), but not to the T1D2 display ($P = 0.23$), consistent with the view that ADHD patients had even more problems than controls with focusing attention on the cued-hemifield when WM encoding/processing demands are relatively low.

VSWM capacity in adolescents and adults with ADHD

Even though no WM filtering deficits were found in adolescents and adults with ADHD when matched on IQ with their peers, they still might show lower visuospatial WM (VSWM) span than typically developing controls. As reviewed in the introduction, prior studies have provided evidence for lower VSWM span in ADHD, with largest differences during late childhood/adolescence (Sowerby et al., 2010; Westerberg et al. (2004), but in these studies subjects were not matched on IQ. The present data provide no evidence for developmental differences in visuospatial span or storage space (Cowan’s K or CDA) between ADHD and non-ADHD groups when matched on IQ. A main effect of Age however indicated that independent of diagnosis, adolescents had lower K -scores than adults, pointing to similar

developmental delays in VSWM span in ADHD and non-ADHD groups. Some other studies using a change detection task have reported mature VSWM capacity around age 10-12 (Riggs et al. 2006; Cowan et al., 2010). The late development of VSWM span in the present study might be due to the relatively low IQ levels of our subjects (which were not reported for the primary school children in the studies by Riggs and Cowan and colleagues). Scores on the digit span test, an extra obtained measure of verbal WM-span, indicated that all our adolescents (with a mean age of 14.8 years) scored below their norm groups. That is, our typically developing adolescents had a mean digit span score of 13.7 which is normally at the level of 13-year-olds' span and our adolescents with ADHD had a mean score of 12.8, which is at the level of 11.5-year-old typically developing children. The present data show that matching on IQ is highly important when investigating developmental differences in memory performance between non-clinical and clinical groups.

CDA-ERP amplitudes in the early interval (450-550 ms) displayed increased activity when more memory items were present in the memory display (one vs. three) in all groups, suggesting more items were encoded in memory (Emrich et al., 2009; Ikkai et al., 2010; Lee et al. 2010; McCollough et al. 2007; Vogel & Machizawa, 2004). This load-related CDA increase was higher in adults with ADHD than in control adults during the early encoding window, as indicated by a three-way interaction between Trial-type, Diagnosis and Age. During the later maintenance window the load-related increase in CDA was larger in adolescents than adults, as shown by an interaction between Age and Trial-type. Possibly, this sustained CDA response with load in adolescents is related to enhanced allocation of spatial attention and shows that they needed more spatial attention (possibly for spatial rehearsal) than adults to refresh the location of the items in memory during the maintenance interval (support for such an interpretation of the CDA amplitude was given by Drew and Vogel, 2008). Interestingly, similar larger load-related CDA responses have recently been reported in children compared to adults in another developmental change detection study (Sander et al., 2011), although these differences were only found when stimulus presentation times were relatively long (e.g. 500 ms). With short presentation times of only 100 ms, comparable to those used in the present study, load-related CDA effects were no longer present in these younger children, because according to the authors, children were thought to "give up" in high load conditions due to time constraints. The fact that in the present study load effects on the CDA were present in adolescents even with 150 ms display presentation times shows that important development of resources/strategies takes place between childhood and adolescence.

Last, the measure of cost of distracters in accuracy in the VSWM task, Unnecessary Storage, was negatively correlated with K for three memory items in all subjects. This shows that participants with higher WM capacity experienced less interference from distracters than lower capacity subjects. This relation between WM capacity and filtering efficiency was previously also found by Lee et al. (2010) in adults, and emphasizes the interaction between storage capacity and efficient

filtering. Both typically developing adolescents and adolescents with ADHD show impaired performance on *both* measures compared to adults in the present data set.

A possible limitation of the current study is the age range that was used in the adolescent groups. This range, 12-16 years, is quite broad and might include adolescents who are in different stages of cognitive development (Luna, 2010). Since sample size in the present study was too low to split adolescents into young- and old-adolescent groups, future studies should find out whether behavior and CDA activity in a change-detection task differ between early and late adolescence.

Conclusion

The present results indicate that the development of filtering efficiency and VSWM storage capacity throughout adolescence in ADHD is not different from typical development, and no evidence for a developmental lag in filtering efficiency within WM was found in our ADHD participants. Filtering in WM was found to be still immature in adolescents with and without ADHD and was related to significantly lower VSWM capacity. Electrophysiological brain activity (CDA responses) during retention of items in memory showed that distracting information was encoded in all participants, but only adults were able to filter out this information later in time. Better filtering was furthermore related to better performance when irrelevant items were part of the memory display. Adolescents and adults with ADHD showed lower CDA amplitudes for low loads than control participants, possibly reflecting an inability to ignore irrelevant information in the non-cued hemifield. Larger CDA-increase with load in adolescents was thought to reflect greater allocation of spatial attention during maintenance of items.

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Chapter 6

General Discussion

In an environment that is constantly changing and with the numerous goals people have in mind, it is important to be able to keep these goals active, and only select information from the environment that is relevant to these goals, while ignoring other information. For children in a classroom, this could for example mean that they have to remember the outcome of a sum that is needed to solve a larger attention-demanding mathematical problem while in the meantime trying not to be distracted by the noise of other children playing outside. For this to happen successfully, one needs well-functioning working memory and attentional control. Working memory (WM) refers to our ability to temporarily maintain and manipulate a limited amount of information in mind. Attentional control is defined as the ability to select relevant information from the environment, while suppressing the influence of information that is not relevant to our current task-goals. Several studies have already indicated that in adults, WM and attention are mutually dependent on each other (Awh, 2006; Lavie et al., 2004; Vogel et al., 2005). These findings are supported by neuroimaging findings showing activation in similar brain networks including frontal, striatal and parietal cortex in WM and attention tasks (Bunge et al., 2001; Kane & Engle, 2002; LaBar et al., 1999; Postle et al., 2004). During development, connections between brain regions in these networks are still increasing in strength and incorporating more long range connections, even throughout late adolescence (Luna et al., 2010). This brain development has been linked to immature performance on WM and attention tasks in children (Klingberg et al., 2002; Durston et al., 2002) and adolescents (Bunge & Wright, 2007; Kwon, Reiss & Menon, 2002; Luna, 2010; Rubia et al., 2006).

To our knowledge no studies so far have investigated attention-WM dependency during development. Examining this relation is however important considering the crucial role that attention and especially WM capacity appear to play in the successful development of other important cognitive abilities such as reasoning (Krawczyk et al., 2008), problem solving (Passolunghi et al., 1999), reading and mathematics (Gathercole, Pickering, Ambridge, & Wearing, 2004; Gathercole, Alloway, Willis, & Adams, 2006) and fluid intelligence (Burgess & Braver, 2010; Conway, Cowan, Bunting, Therriault, & Minkoff, 2002; Fukuda, Vogel, Mayr & Awh, 2010). The main aim of this thesis was to come to understand more of the relations between WM and attention during development, by letting our subjects perform experimental tasks in which attention and/or WM capacity was manipulated while measuring their performance and specific Event-Related Brain activity coupled to interference control or WM processing. Event-related brain potentials (ERPs) were used since they provide information at a high temporal (millisecond) resolution, thereby giving a continuous measure of what effects attentional or WM load manipulations have on different information processing stages, from the first perception of a stimulus to the generation of a response to it. Furthermore, this is a non-invasive method with which brain activity can be measured relatively easy and at all ages in children. The main focus of this thesis (except in Chapter 2) was on development during adolescence since this is a period marked by considerable

changes in complex cognitive functioning, and it has been found that both WM and attentional control are still immature between 12 and 16 years (Anderson et al., 2001; Davies et al., 1999; Gathercole, 1999; Luciana, Conklin, Hooper, & Yarger, 2005; Luna, Garver, Urban, Lazar, & Sweeney, 2004; Luna et al., 2010; Segalowitz et al., 2010). Besides in typically developing populations, attentional control and WM capacity development was also studied (with the same task and dependent measures) in children and adolescents with attention-deficit/hyperactivity disorder (ADHD), who are known to have specific impairments in attentional control and WM abilities (Martinussen et al., 2005).

The **first aim** of this thesis was to examine whether young children (5-7 years of age) with symptoms of ADHD already experience specific problems with response inhibition and attentional control compared to their healthy peers (Chapter 2). The **second aim** was to investigate the typical development of interactions between WM and attentional control in adolescents. This was done by examining effects of a WM load manipulation (performing a concurrent N-back task) on behavior and ERPs (conflict-related N450 and SP) in a Stroop task in adolescents and adults (Chapter 3). The **third aim** was to investigate developmental differences in filtering efficiency and its effects on WM capacity between healthy adolescents and adults. This was done by letting them perform a visuospatial change detection task with WM load and distraction manipulations and measuring effects on performance and the electrophysiological CDA (Chapter 4). The **fourth aim** was to examine similar filtering efficiency-WM capacity relations in adolescents and adults with ADHD who have been reported to suffer from visuospatial WM deficits and problems with attentional filtering (Martinussen et al., 2005; Toplak, Jain & Tannock, 2005; Hervey, Epstein & Curry, 2004; McLean et al., 2004; Biederman et al., 2008; Rapport et al., 2001; Boonstra et al., 2005) (Chapter 5). The following paragraphs will discuss the results of these studies in the light of the existing theoretical background and give implications for future research.

6.1 Specific attention problems in young children with ADHD symptoms

Attention deficit hyperactivity disorder (ADHD) is characterized by a cognitive deficit in attentional control (Biederman et al., 2008; Brodeur & Pond, 2001; Jonkman et al., 1999; 2004; Murphy et al., 2001; Randall, 2008; Rapport et al., 2001). In Chapter 2, 5-7 year-old children with ADHD symptoms and control children performed a CPT-AX task. The children with ADHD symptoms were shown to have attention-related problems in behavior (fewer correct Go responses and higher inattention scores). ERPs associated with response preparation and evaluation were measured before and after target presentation to examine the processes underlying these early attentional problems. A centro-parietal P3 in response to the cue is thought to reflect

orienting or the ability to evoke attentional responses to a warning event (Bekker et al., 2004 and Van Leeuwen et al., 1998), and was found to be reduced in children with ADHD symptoms in Chapter 2. Furthermore, less visual attention for the upcoming stimulus (a greater occipital CNV just before target presentation) was also found in Chapter 2. In response to the target, a reduced ability to allocate sustained attentional resources to the task (measured by central Go-P3) was found. Previous studies have reported a similar reduced or absent centro-parietal P3 in 7-12 year-old children with ADHD (for reviews see Barry et al., 2003; Jonkman, 2005). Except for the CNV, the above-mentioned processes were correlated with the behavioral attention problems in the task. The study in Chapter 2 showed that attention-related problems can already be detected in 5-7 year-old children with symptoms that are predictive of future ADHD.

Considering the WM-attention relations that are known to exist in adults, it would be interesting to examine whether such attention deficits are related to potential WM deficits in young children at risk for ADHD. Because of practical limitations, the present thesis has focused on adolescence when studying the WM-attention interactions in ADHD and provides no insight about the development of WM-attention interactions in young childhood, but a literature review learns that besides attention deficits, WM deficits have often been found in both children and adults with ADHD (Barkley, 1997; Clark et al., 2007; Dige et al., 2010; Martinussen et al., 2005; McLean et al., 2004; Rommelse et al., 2008; Schweitzer, 2000; Westerberg, Hirvikoski, Forsberg, & Klingberg, 2004). Whereas studies investigating WM-attention relations in young children with ADHD are scarce there is one study by Sonuga-Barke et al. (2002) with 3 to 5.5 year-old children that reports no correlation between WM span (in an auditory sequencing task requiring maintenance of locations of picture-noise pairings, e.g. a dog - barking) and inhibitory control (in a modified Go-Nogo task), or WM and ADHD symptoms (according to a modified version of the Parental Account of Childhood Symptoms; PACS parent interview). However, in older children (8-12 years old) evidence *was* found for a relation between WM impairments (mostly in central executive processing, but also visuospatial and phonological storage) and attention problems in ADHD. Kofler et al. (2010) for example found a larger decrease in attentive behavior in children with ADHD (as observed by the experimenters and scored with Observer 5.0) than controls during a visuospatial WM task (in which sequences of dots had to be remembered) or phonological WM task (in which Letter-Number sequences had to be remembered), which was mainly due to central executive deficits. One reason for a potential discrepancy between younger and older children in the relation between WM and ADHD (inattention) symptoms could be the typical developmental course of WM. In a recent review (Pauli-Pott & Becker, 2011) it was suggested that the presence of early WM problems might not be a useful predictor of ADHD symptoms, since the majority of preschoolers have not yet reached full WM functioning making it difficult to distinguish between developmental immaturity or deficit.

The above studies measuring WM-attention relations used data from questionnaires or observation, but one study examined the relation between WM and attention with cognitive tasks. Espy & Bull (2005) found some evidence that an early relation between WM and attention might exist in typically developing preschoolers, as shown by Espy and Bull (2005). Whereas response suppression task performance did not differ between preschoolers with low and high (digit) span scores in their study, performance on tasks requiring attentional control (in the Shape School-C, measuring proactive interference, and NEPSY Visual Attention tasks, where targets had to be detected among distracters) was better in the high span than low span children. Although not measured within one task-paradigm, these findings indicate that WM-attention relations could already be present at an early age, depending on the cognitive tasks that were used to measure attentional control (interference control and target detection rather than response inhibition). Additional research using cognitive tasks needs to further examine the development of such WM-attention relations in young children and whether there are different relations between WM and attention depending on the type of tasks used (e.g. whether interference control and response inhibition shown different relations with WM).

6.2 Working memory capacity in typically developing adolescents

Before discussing what knowledge the studies in this thesis have provided on the relation between attentional control and WM capacity during adolescence, it will first be discussed what the different studies tell us about the development of WM capacity itself during this developmental period. Information about the typical development of WM capacity during adolescence was obtained from measures in the developmental Stroop study (Chapter 3) and in the change-detection (VSWM) study (Chapter 4). First of all, verbal digit span measures (a subtest of the WISC/WAIS) were collected from adolescents and adults in both studies. In the developmental literature the forward span test is often taken as a measure of short-term memory, whereas the backward span measure is considered to be a measure of WM capacity in children (St. Clair-Thompson, 2010), but is considered a measure of short-term memory in adults. Whereas adolescents had lower verbal span scores than adults on forward and backward digit span tasks in Chapter 4, in the sample in Chapter 3 adolescents and adults did not significantly differ in performance on these tasks. However, when the subjects of Chapter 3 and 4 were analyzed together, *t*-tests showed significantly lower forward ($F(1,72) = 7.6, p < .01$) and backward span scores ($F(1,72) = 10.2, p < .005$) in adolescents than adults, suggesting ongoing development of verbal short-term and WM during adolescence. Lack of such a developmental difference in Chapter 3 might thus be ascribed to a problem of statistical power. Similar to these verbal memory capacity results, Cowan's *K* and accuracy in the

change detection task in Chapter 4 also indicated ongoing development of visuospatial WM (VSWM) capacity in adolescents when a load of three items (which is close to maximum VSWM capacity) had to be maintained.

In the developmental literature, different tasks have yielded different results regarding the maturation of WM capacity. Some studies have found mature WM capacity around age 12 in visuospatial WM tasks resembling that used in Chapters 4 and 5 (Cowan et al., 2010; Riggs et al., 2006), whereas others have shown that WM develops into late adolescence (in verbal WM tasks: Anderson et al., 2001; Schleepen & Jonkman, 2010; in visuospatial WM tasks: Klingberg et al., 2002; Luna et al., 2004; Luciana et al., 2005). Contradictions between results in developmental WM studies might be due to several factors. Important are task conditions like (1) the domain that is tested (visuospatial WM and verbal WM follow independent developmental trajectories; Gathercole et al., 2004) and (2) to which extent central executive processing is needed (Gathercole, 2004). The studies in this thesis indicate that verbal and visuospatial WM capacity are still immature in adolescence. The results from Chapter 4 and 5 suggest that especially in the visuospatial domain the maturity of performance on WM tasks is for a significant part determined by the extent to which the task demands attentional control. If tasks involve only simple maintenance of visuospatial information for very short periods of time (e.g. 1 or 2 seconds) without distraction, mature performance levels seem to be reached at age 10-12 (Cowan et al., 2010; Riggs et al., 2006). In Chapter 4 and 5 the load manipulation also required only maintenance of items in VSWM for no longer than a second, yet adolescents did not show mature WM capacity. We explained this later maturation in our task to the fact that (due to the measurement of contralateral ERPs) our task consisted of bilateral stimulus displays. With bilateral displays one has to attend only one side of the screen while ignoring the other side. When visuospatial information has to be maintained in the face of concurrent distraction, as in the present change-detection tasks with bilateral stimulus displays (Chapter 4 & 5), performance is not yet mature at age 16. Other factors, such as (3) memory array presentation durations and (4) the length of maintenance delays might also affect task performance and change developmental patterns. For example, in a study by Sander et al. (2011) memory array presentation times were varied and WM capacity (K) for four items was found to be higher in children with longer presentation times (500 ms), than with shorter presentation times (100 ms). With longer presentation times, children were thought to be able to use more strategic control processes, which resulted in higher WM capacity scores. The length of maintenance delays can also influence memory performance since children might experience problems with maintaining items for longer periods of time, due to a diminished availability of attentional resources for (phonological) rehearsal or refreshment. The contribution of the use of higher-order verbal recoding strategies in visuospatial tasks cannot be excluded with longer delays. Since the use of such higher-order strategies also differs across age and is primarily seen during later childhood (Hitch et al., 1989), this complicates conclusions about whether developmental span differences are due to limited

storage capacity per se or to developmental differences in strategy use when longer presentation or maintenance delays are used in WM tasks. Further important to note is that the extensive set of WM tasks available might lead to varying results, since some tasks not only require more cognitive control or central executive processing than others (Riggs et al., 2006), but are also dependent on other abilities such as arithmetic skills, which are also subject to development during childhood (Towse et al., 2002). For instance, an often used and well accepted verbal WM task in the adult WM literature is the O-span task, which requires subjects to solve mathematical operations while they try to remember words. Because of this appeal on mathematical abilities, this task seems less suitable for developmental research. It is highly recommended that future developmental WM-attention studies include the same WM tasks to make it easier to compare between studies. One good alternative for this might be the Automated Working Memory Battery (AWMA) developed by Alloway (2007) and for which norm scores are available. However, most tasks that show late development of WM in adolescence are tasks that require relatively high levels of executive control (Luciana et al., 2005; Luna et al., 2004; Schleepen & Jonkman, 2010).

6.3 Typical development of working memory and attention interactions in adolescents

The results from Chapter 3 and 4 showed development of interactions between WM and attention in two directions. First, in Chapter 3 Load theory of Selective attention by Lavie et al. (2004) was tested in adolescents and adults. According to this theory, when WM is loaded, resources are consumed (for maintenance of information) that would normally be available for goal maintenance in the Stroop task, leading to increased distracter interference. Second, in Chapter 4 the line of change detection studies by Vogel et al. (2004; 2005) was followed. These studies have shown a regulating effect of selective attention on memory access and hence memory capacity. In other words, the efficiency with which an individual filters information for memory storage (filling available memory capacity with only relevant, or also irrelevant information) determines, at least partly, one's WM capacity. This efficiency of filtering is determined by one's attentional control abilities (Awh, Vogel, & Oh, 2006; Cowan et al., 2005; Kane, Conway, Bleckley & Engle, 2001; Fukuda & Vogel, 2009; McNab & Klingberg, 2008; Vogel, McCollough, & Machizawa, 2005; Zanto & Gazzaley, 2009). In both studies, it was shown that WM-attention relations still undergo development in adolescence.

Effects of WM load manipulation on interference control in adolescence

Results from the dual-task in Chapter 3 showed no increased distracter interference effect in behavior (RT and accuracy) when WM load was imposed in the concurrently performed N-back task in adolescents and adults. ERPs however showed that refreshing of letter information while performing the Stroop task led to higher conflict detection (N450) caused by the presence of incongruent distracter faces in parietal and fusiform areas when the gender of the target-word conflicted with the face on which it was superimposed. It was suggested that this effect reflects increased processing of distracter faces due to less available WM resources (induced by the load manipulation) to ignore or suppress processing of these faces (de Fockert et al., 2001). In adolescents, the N450 interference effect did not further increase with load, but a significantly larger interference effect was already present without a concurrent load, suggesting they experienced larger distracter interference than adults in this early processing stage of conflict detection. A later ERP component, the SP, which is linked to conflict resolution, was also larger in adolescents than adults in both load conditions. In adults the N450 conflict response was only present when a concurrent WM task was performed, which is congruent with Load theory. On the basis of the present results it is difficult to conclude whether WM resources are also crucial for the resistance to interference in adolescents because performing a dual-task (also the 0-back-stroop is a dual-task) might already be so resource consuming that no further increases in interference were possible as was hypothesized in Chapter 3. This can only be estimated when one would also have information about performance in a stand-alone Stroop task. Also inclusion of higher loads or manipulations of the strength of interference in future studies might give more information about when resources are depleted or not and when maximum interference is reached. Another limitation of the present study was that, whereas manipulations of WM load had an effect on ERP activity associated with interference processing (conflict detection), this did not result in increased behavioral interference in adolescents or adults in the present study. It seems relevant to discuss some possible reasons for this discrepancy here. First it has to be noted that other studies including adult subjects failed to find WM load effects on RT-interference effects in Stroop or other conflict tasks (Jongen & Jonkman, 2011; Kim, Kim & Chun, 2005; Park, Chun & Kim, 2007; Pratt et al., 2011; Woodman, Vogel & Luck, 2001; Pratt et al., 2011). Positive findings were primarily reported by LaVie and colleagues (Lavie et al., 2004; Lavie & De Fockert 2005). Although it might in the study in Chapter 3 be possible that WM load manipulations were not demanding enough to affect interference because subjects only held 1 item in memory, accuracy rates for WM and Stroop trials do not suggest this was an easy task. Furthermore, although other studies used higher WM loads of about 4 or 5 items (Jongen & Jonkman, 2011; De Fockert et al., 2001), this also did not always lead to increases in behavioral interference so this does not seem to be the only determining factor. Another possibility is that the absence of WM load effects on behavioral measures of Stroop-

interference are due in part to relatively short trial durations resulting in speed-accuracy trade-offs in the most difficult task conditions. Pratt et al. (2011) (who measured WM-attention relations in a combined flanker interference control and Sternberg WM task) only found an effect of WM load on accuracy measures and not RT measures of interference control and explained this by speed-accuracy trade-offs in the most difficult dual-task conditions. Indeed, whereas we also did not find WM load effects on accuracy measures of interference control, in our study (Chapter 3), longer RTs were associated with a decrease in errors in several conditions in the face-word Stroop task. RT and error rate were negatively correlated in the congruent and incongruent conditions with load ($r = -.37, p < .05$ and $r = -.33, p < .05$ respectively) and the incongruent condition without load ($r = -.39, p < .05$) in adolescents and adults. It might thus be that in part no increase in behavioral interference was found in Chapter 3 due to a speed-accuracy trade-off. Another possibility that was mentioned in Chapter 3 is that the larger conflict experienced with higher WM load might have been resolved before the response and was therefore not detectable in behavioral measures of adolescents and adults. At least ERPs showed that even without holding a concurrent WM load (but performing a dual-task), activation during both conflict detection (N450) and conflict resolution (SP) stages was higher in adolescents and adults, and suggests processing was more effortful in the former group. This enhanced activation might have prevented load effects on interference control to become visible in behavior. Future studies should investigate whether such compensatory activity is also possible or sufficient to prevent behavioral interference with increasing WM load at younger ages. ERPs showed that although WM load had an effect on the processing of response-relevant information used to guide response selection (centro-parietal sustained positivity "SP") in adolescents and adults, this was an overall effect and proportionally the same for congruent and incongruent face-word stimuli. In the present study interference during response selection-related processes were not modulated by WM load.

As mentioned above, a larger effect of WM load on interference control in adolescents than adults *was* found for detection of the conflict (N450), indicating ongoing development of WM-attention interactions in this early process. From the results in Chapter 3 it thus seems that there is indeed an ongoing development of WM-attention interactions during adolescence. WM resources do not seem sufficient yet in a demanding dual-task in adolescents. However, dual-tasking also requires resources and no single N-back and/or single Stroop task was used in Chapter 3, making it difficult to conclude whether the interference effects found in adolescents in the low load condition gave a good representation of their interference control abilities. Future research should take this into account by using stand alone (Stroop) task conditions. Furthermore, higher load manipulations could be used to find out whether this affects interference control on performance levels also.

Effects of filtering efficiency on visuospatial WM capacity in adolescence

In the visuospatial change detection task with distracters in Chapter 4, the effect of the presence of irrelevant stimuli in the memory set on WM performance (RTs and accuracy) was larger in adolescents than adults. Unnecessary Storage scores furthermore indicated less efficient filtering in adolescents than in adults, and a correlation between Unnecessary Storage and WM capacity suggested that participants with higher capacity were better in selecting only relevant information in the task than those with lower capacity. In addition to behavior, ERP activity above the parietal-occipital cortex contralateral to the visual hemifield in which the to-be-maintained memory array was presented was measured during the delay interval. This contralateral delay activity (CDA), thought to reflect the number of items that are maintained in WM (McCollough et al., 2007; Vogel & Machizawa, 2004), showed higher amplitude increases in adolescents than adults in the encoding and maintenance stages of processing, when distracter items were presented alongside the target item compared to when the target item was presented alone. This result, and its correlation with Unnecessary Storage scores (previously also found in adults in Jost et al., 2011; Lee et al., 2010; Vogel et al., 2005), suggests that adolescents encoded and stored more distracters than adults, and this resulted in reduced memory capacity. Consistent with this, a behavioral study in which children had to report whether a probe item had been part of a previously presented 4-item WM set (Astle et al., 2011) found that 6-7 years olds who were better at filtering out distracters had higher VSWM capacity, suggesting a similar attention-WM relation in children. Astle et al. (2011) furthermore found that this relation was domain-specific since there was no relation between distracter filtering and verbal WM measures, similar to the result in Chapter 4 were no correlation between Unnecessary Storage in the visuospatial WM task and verbal short-term memory (digit span scores) was found in adolescents and adults.

By using ERPs in addition to behavioral measures, the underlying subprocesses of attentional control (interference control in the Stroop task) and WM (online storage of items in visuospatial WM in the change detection task) could be distinguished. The studies in Chapter 3 and 4 showed prolonged development of WM-attention interactions, since attention (detection of a stimulus conflict) in adolescents was more affected by reduced verbal WM capacity (there was higher attentional capture or less suppression of distracters in adolescents in Chapter 3) and they were less efficient in blocking irrelevant items from WM (in Chapter 4 and 5), resulting in lower VSWM capacity than adults. The common pool of resources that has been suggested to underlie WM and attention seems to be liable to brain maturation, supposedly that of frontal-parietal and other networks (Bunge & Wright, 2007; Luna et al., 2010), which is reflected in adolescents' behavior on WM and attention tasks. The specific networks involved in WM and attention tasks that thought to undergo development during adolescence will be discussed in section 6.4.

The visuospatial change detection task in Chapter 4 showed ongoing development of WM-attention relations in adolescents, both at the behavioral and electrophysiological level. This was the first study that measured neural activity related to filtering efficiency in adolescents with the change detection paradigm by Vogel et al. (2005). The presence of a CDA in adolescents indicates that this is a suitable task to examine attention control and its neural mechanisms in this age group. Larger numbers of participants are necessary than in adult studies however, since the CDA amplitude is more variable in adolescents than adults (as was previously also found in the only other study measuring WM load-related changes in CDA in children; Sander et al., 2011).

6.4 Brain networks underlying development of WM and attention in adolescence

A question that arises from the studies in this thesis is to what kind of brain maturation changes the findings concerning typical development in adolescence might be linked. The reorganization and specialization of two circuits, as well as increased connectivity between them, are thought to underlie the development of cognitive control during adolescence (Luna et al., 2010). The first circuit is the frontoparietal network, thought to regulate cognitive abilities such as inhibitory control and WM. This network regulates top-down control and could be involved in the suppression of distracter faces (e.g. Stroop N450 effect Chapter 3) or the selection of items for maintenance in memory (e.g. encoding phase in Chapter 4). For example, the intraparietal sulcus (IPS) that is part of this network is thought to play an important role in top-down control by interpreting cues, and the inferior parietal lobule (IPL) and dorsolateral prefrontal cortex (DLPFC) are thought to be involved in adjusting top-down control in response to feedback (Dosenbach et al., 2008). If still immature in adolescents, activity in this network might have led to higher interference from distracters and less efficient filtering in the studies in Chapter 3 and 4. The second circuit is the cingulo-opercular network, which is thought to retain a response state (which refers to the ability to organize task demands to be able to apply cognitive skills in a consistent and flexible manner during a task), and includes among other regions the anterior cingulate cortex (ACC) and the anterior prefrontal cortex (Luna et al., 2010; Segalowitz, 2010). This network could be highly appealed to in dual-tasks like that in Chapter 3 where a WM task and an interference control task were combined. Here, task demands switch continuously, but must all be maintained and arranged in order to perform successfully. An immature cingulo-opercular network could thus have led to general regulation difficulties and eventually worse performance (e.g. more errors and misses) in adolescents in the dual-task. Indeed, in Chapter 3 adolescents had general worse performance in the Stroop task (on both congruent and incongruent trials) and in WM task accuracy. A third network that is

thought to undergo development and might influence cognitive control performance is a default network. Connections within this network strengthen with age and are thought to be responsible for internal thoughts (introspection) that are assumed to be suppressed during a task when attention is needed (Fair et al., 2008). If activity of the default network is not suppressed, internal thoughts can interfere with task demands and lead to worse performance in children and adolescents. During development, the organization of these frontoparietal, cingulo-opercular and default networks changes from a local to a more distributed and segregated architecture (Fair et al., 2009; Luna et al., 2010), and these changes are thought to lead to improved attentional control and VSWM functioning with age (Bunge & Wright, 2007; Klingberg et al., 2006; Luna & Sweeney, 2004). Although not directly measured here, worse performance on Stroop and visuospatial change detection tasks in adolescents, as shown in this thesis, might thus be related to ongoing segregation of these networks and ongoing strengthening of connections between regions in these networks.

6.5 Effects of selective attention on visuospatial WM in adolescents and adults with ADHD

In Chapter 5 the relation between selective attention (filtering efficiency) and VSWM capacity was directly investigated in adolescents and adults with ADHD. Behavioral or CDA data showed no evidence for worse filtering of information for storage in VSWM in the ADHD groups compared to the control groups. Regarding WM capacity measures, forward digit span was found to be significantly decreased in adolescents and adults with ADHD compared to their age-matched controls. Most studies interpret forward span as a measure of storage or attention, while backward span is also associated with central executive processing (St. Clair-Thompson, 2010). Previous studies have shown mixed results for digit span tasks in ADHD populations. In contrast to results in Chapter 5, some studies have found only lower backward, or lower forward *and* backward span scores in children with ADHD (McInnes et al., 2003; Pasini et al., 2007) and adults with ADHD (Boonstra et al., 2005; Dige & Wik, 2005). Other studies have found no differences on digit span scores between adolescents (Rucklidge & Tannock, 2002) or adults with and without ADHD (Hale et al., 2007). The latter study did find greater activation in right frontal and parietal areas during the forward digit span task, which possibly reflects compensatory visuospatial processing or increased cognitive effort. Regarding these mixed results in previous research, it is difficult to conclude that storage (as measured by forward digit span) is impaired in ADHD, and further research should find out whether adolescents and/or adults with ADHD show a deficit in short-term storage or not.

Important in this study, and different from several other ADHD studies, is that controls were matched to ADHD the subjects on education levels and

(estimated) IQ scores. Results from Chapter 5 show that when studying WM-attention interactions in ADHD it is important to ensure that differences between clinical and control groups cannot be caused by a confounding factor such as IQ. Another developmental study (including only girls) that controlled for IQ, also found worse forward digit span in ADHD. This longitudinal study had two measurement time points; at 6-12 years of age, and 11-18 years of age, and showed that the memory impairment in ADHD persisted in adolescence (Hinshaw et al., 2007). Prior studies on selective attention-WM interactions have provided evidence for lower VSWM span in adolescents with ADHD (Sowerby et al., 2010; Westerberg et al., 2004), but in these studies subjects were not matched on IQ. The present data did not show differences in visuospatial span and the influence of distracters on span (Cowan's *K* and CDA measures) between ADHD and non-ADHD groups when matched on IQ. All adolescents in Chapter 5 had relatively low storage capacity and did not filter distracters optimally. When examining developmental differences in WM performance between clinical and control groups it is important to keep IQ similar between clinical and control groups, and future studies should also include adolescents with higher levels of IQ to see whether maturational differences between ADHD and control groups on filtering efficiency and WM capacity can be detected.

Deficits in verbal WM have been reported in ADHD as well, but were found less frequently (Willcutt et al. (2005). It would however also be interesting to examine the development of WM-attention interactions in a verbal WM task with distracters, in a study that matches groups on IQ as well.

Studying WM and attentional control across age in ADHD can provide more information on the development and persistence of deficits in these cognitive functions. According to developmental lag theory (Kinsbourne, 1973), deficits in ADHD may be due to a developmental delay and persons with ADHD might catch up with typically developing persons at some point. A developmental lag was previously proposed for inhibition (Barkley, 1998; Doehnert et al., 2010). Some evidence for such a delay in verbal WM (but not visuospatial WM) has also been found in a cross-sectional ADHD study, with differences between children with and without ADHD that were not present in adolescents (Sowerby et al., 2010; but subjects were not matched on IQ). The results from Chapter 5 however do not support the existence of a developmental lag for WM-attention interactions in adolescents in visuospatial memory, since no developmental effects in behavior or electrophysiological activity specific to the ADHD groups were found. The development of filtering efficiency effects on visuospatial WM capacity in ADHD seems to be similar in control and ADHD groups in this attentional control/change detection task.

Results in Chapter 5 *did* show developmental effects across ADHD and control groups. Differences between adults and adolescents were found for Digit Span, Cowan's *K* WM capacity, Unnecessary Storage, and accuracy and reaction times in the change detection task. According to CDA results, all participants initially encoded distracters. Unlike the results in Chapter 4, adolescents did not show larger

CDA increase with distracters than adults in Chapter 5 during this interval. However, in Chapter 4 *and* 5 only adults were able to filter these items out of memory in the maintenance part of the retention interval. Maintenance-CDA also correlated with behavioral performance that showed worse filtering in adolescents compared to adults. Also, WM capacity (K) was again related to higher storage of unnecessary items, similar to results in Chapter 4.

In Chapter 5 a difference between the CDA in the filter condition (with two distracters) and in the high load condition in the maintenance interval, similar to that found in Vogel et al. (2005), showed that some filtering of distracters had taken place in the adolescent and adult groups. The fact that such a distracter-related CDA difference was not found in Chapter 4 might have to do with the large variance in K in the participants. Only when splitting the data for low and high K scores (which was done for the adult group in Chapter 4 in an extra analysis) it was shown that adults with high WM capacity had lower distracter-related CDA amplitudes than high load CDA amplitudes, whereas in low WM capacity adults, CDA amplitudes were similar in both conditions. For the complete groups with large K variance however, more subjects were necessary (like in Chapter 5) to find such a CDA difference between T1D2 and T3D0.

6.6 Implications of the present findings

The ERP studies in this thesis have provided more insight into the underlying mechanisms of development of attention and WM, specifically on the time-course of WM- and attention-processing, and have added to the literature on neurocognitive development of WM and attentional control by showing that these functions highly depend on each other also throughout adolescence. Some suggestions for future research are given below.

Investigating development by combining cognitive neuroscience methods

An important next step for further research on these interactions would be to investigate which neurobiological changes underlie the development of the time-specific WM-attention relations investigated in the present thesis. Since EEG measurements have high temporal, but low spatial resolution, such developmental changes cannot be studied with EEG alone. A good solution would be to combine EEG with another method, functional magnetic resonance imaging (fMRI), in order to find the sources underlying the different subprocesses of interference control and WM that were now studied with ERPs. In such a way, we would not only be able to say when in time WM load manipulations (like those in Chapter 3) affect interference control in adolescents or adults most, but also which (functional) networks and activity in which regions underlie these specific processes. In adolescence,

connections within distributed circuitries have been found to strengthen and incorporate more long-range connections. Luna et al. (2010) for example suggested that whereas children are already able to use frontal regions to suppress an inappropriate response, development of inhibitory control in adolescence mainly entails enhancements in the recruitment of widespread regions. The integration of frontal regions with other areas is thought to improve during adolescence, resulting in better inhibitory performance. By combining data on these changing connections within circuitries (e.g. from functional connectivity MRI studies) with time-course information from EEG measurements during WM/attention tasks, an integrated view on the neurocognitive development of these functions during adolescence can be obtained. It should be noted however that the interpretation of BOLD response differences in the context of development is not well established, and it is often hard to ascribe a clear developmental meaning to fMRI findings (Luna et al., 2010). Developmental changes in neurovascular coupling for example may have confounding effects on the BOLD signal when studying age-related effects, since the dependence of blood-flow on neural activity changes during development. Also, O₂ use changes with development, making it difficult to interpret developmental effects (Harris et al., 2011).

Another method that could be helpful in future research on WM-attention interactions is transcranial magnetic stimulation (TMS). TMS studies could provide more insight into developmental differences in brain networks used to regulate top-down control of attention in adults and adolescents. By perturbing functions in certain brain regions with TMS, e.g. regions in the frontal cortex thought to be involved in top-down control of attention, the effects on activity in other cortical regions can be measured (Zanto et al., 2011). In this way, causal connections between brain regions that are part of frontoparietal networks can be studied in different stages of development. Combining different methods (EEG, fMRI, TMS) can in this way open up new possibilities for research on cognitive development.

A practical implication: WM training

First results of WM training studies suggest that computerized training of WM has positive effects on the amount of information that children can maximally maintain in memory (Holmes et al., 2009; Klingberg et al., 2005; Klingberg, 2010). The interaction found between WM and attentional control in the present thesis implies that WM training might also have effects on attention problems, for example in individuals with ADHD or low WM capacity. Indeed, positive effects of computerized WM training (called Cogmed) have been found on parent ratings of inattention symptoms in ADHD and on response inhibition in a Stroop task (Klingberg et al., 2005; Beck et al., 2010). This indicates that WM training can improve attention, which is consistent with our results in adults from Chapter 3 showing that less Stroop interference was experienced and subjects responded faster when enough WM resources were available. The first results of WM training studies have shown

that this could be a promising approach to decreasing WM impairments in ADHD and improve academic achievement. It has to be said however, that it is not yet clear whether WM training effects as described above are still present at long-term or show transfer to everyday life tasks. A study by Jaeggi et al. (2008) has shown transfer of WM training (using an N-back task) to fluid intelligence (visual analogy problems), possibly because of common reliance on interference control (Burgess et al., 2011). Also, the underlying cognitive or neural mechanisms trained by WM training programs are not yet defined (Conway & Getz, 2010), and require more research in the future.

In a recent review (Astle et al., 2010) it was suggested that improvements in WM capacity in children can be partly explained by maturation of attentional control abilities, which is in line with results from studies in the present thesis (Chapter 4 and 5) that also indicate this importance of suppression of irrelevant information for WM capacity, not only in adults, but also in adolescents. A WM training should thus not only focus on increasing maximum capacity itself, but should also tax attentional control processes (Perrig et al., 2009), in order to prevent distraction and make storage more efficient. In a study by Prehn-Kristensen (2011) it was shown that methylphenidate (MPH: the first-line treatment in ADHD) improved WM performance in a delayed matching task, but *not* when distracters were present during the delay interval. Together, these findings suggest that WM training might be a good treatment alternative *if* it also involves training of attentional aspects of WM.

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Summary

Summary

Imagine making a complex assignment in a noisy classroom, or driving on a busy road while paying attention to traffic signs but ignoring advertisements. These environments (and numerous other environments in everyday life) require us to keep our goals active in mind and only pay attention to relevant information, while preventing irrelevant information from distracting us. To do this successfully, we need well-functioning cognitive control. Two important factors for cognitive control are working memory and attentional control. *Working memory* (WM) refers to our ability to temporarily maintain and manipulate a limited amount of information. *Attentional control* is the ability to select relevant information from the environment, while suppressing information that is irrelevant to our current task-goals. Both WM and attentional control have been found to be still immature in adolescents, which has been linked to the immaturity of networks consisting of frontal and parietal brain regions that are involved in both cognitive functions. Furthermore, impaired performance on WM and attentional control tasks is often found in adolescents and adults with attention-deficit hyperactivity disorder (ADHD). Since cognitive control has been associated with the successful development of other cognitive abilities like reasoning, problem solving, reading, mathematics, and fluid intelligence, it is important to closer examine the typical and atypical development of WM and attentional control.

Studies in healthy adults have already indicated that WM and attentional control are closely related functions, and depend on similar frontoparietal networks. By means of selective attention we determine which information enters WM for maintenance and manipulation (by selecting relevant and suppressing irrelevant information). The other way around, when available WM capacity is intentionally reduced, performance on tasks that require attentional control decreases. Since no research has been done on the developmental patterns of these interactions in adolescents yet, and considering that the development of both cognitive functions is of vital importance to the other cognitive abilities mentioned above, the aim of the present work was to examine the developmental course of interactions between WM and attentional control. Besides typical development, cognitive development in children and adolescents with ADHD was studied, since they are known to have problems related to attentional control and WM (Martinussen et al., 2005).

Chapter 1 introduces the rationale of this thesis, explains its main theoretical and methodological aspects and ends with the aims of this work and an outline of its chapters. With the present research we aimed to investigate a) the nature of the attention problems in young (5-7 year-old) children, by studying the underlying neural mechanisms of attentional control development in healthy children and children with attention problems (Chapter 2), b) the development of interactions between WM and attentional control in healthy adolescents, by examining the influence that intentionally reduced WM capacity has on interference control

(Chapter 3), c) the developmental course of top-down modulation of selective attention on WM performance during adolescence, by manipulating the relevance of the to-be-remembered items in a WM task, thereby measuring attentional filtering efficiency (Chapter 4), and d) the development of WM and filtering efficiency in adolescents and adults with ADHD, who are known to have cognitive control deficits (Chapter 5). To address these issues, besides behavior, event-related potentials (ERPs: the electrophysiological responses of the brain to task-events) were measured, which have a very high temporal (millisecond) resolution, providing information on all stages of cognitive information processing in the brain.

Chapter 2 showed that young children (5-7 years old), who are not yet diagnosed with ADHD, but show early symptoms (as measured by questionnaires), performed worse than children without ADHD symptoms on an attention task which required them to respond to a target letter when a certain cue was given, but inhibit the response when this cue was absent. Behavioral data showed that children with ADHD symptoms especially experienced problems of attention, but not of inhibition. Moreover, ERPs also showed a deficit in the ability to allocate attentional resources to the task in a sustained manner in children with ADHD symptoms. In response to the cue, these children furthermore showed impaired orienting or a reduced ability to evoke attentional responses to the warning cue and, just before the target appeared, less visual attention for the upcoming stimulus. These findings suggest that attention problems are already present in young children with symptoms of ADHD, and might be better predictors than early hyperactivity/impulsivity symptoms (since the latter seem to be part of normal behavior at this age).

Together, the results of the studies in Chapter 3 and Chapter 4 indicate that in adolescents attentional control as well as WM are still immature, and develop into adulthood. In Chapter 3, adolescents and adults performed a dual-task that consisted of an attentional control (Stroop) task and a verbal WM (N-back) task. In the gender face-word Stroop task, poorer distracter suppression in the presence of a conflicting stimulus (e.g. the word “man” written on the face of a woman, see page 73) as measured by ERPs as well as worse behavioral performance was found in adolescents compared to adults, indicating still immature attentional control. Adolescents also performed worse on the verbal WM task, and (in Chapter 4) had lower digit span scores and worse behavioral performance in the change detection task. ERPs reflecting encoding and maintenance of items in memory (or the allocation of spatial attention) also showed prolonged development in this change detection study.

An important goal of the present thesis was to investigate the developmental course of the interactions between attentional control and WM during adolescence. In Chapter 3 this was examined by reducing WM capacity by manipulating load in the verbal WM task that was concurrently performed with the attentional control (Stroop) task. Although no effect of reduced WM capacity on behavior in the face-word Stroop task was found, refreshing of letter information during the Stroop task

led to an increase in conflict detection-related ERP activity in adults. No such effect of reduced WM capacity was found in adolescents, but this might be explained by the already higher ERP activity without WM load, suggesting they experienced more conflict even without WM load. Letter refreshing also had an effect on the ERP activity related to response selection, but not to a greater extent for conflicting stimuli (e.g. the word “man” on a female face) than for non-conflicting stimuli (e.g. the word “man” on a male face).

In Chapter 4 a different approach was taken to examine WM and attentional control interactions. A change detection task with relevant items that had to be remembered and irrelevant items that had to be suppressed was used to examine the effects of attentional filtering efficiency on WM capacity (see page 100). The behavioral and ERP results from Chapter 4 suggested that adolescents were not able to suppress irrelevant information and were therefore not as efficient as adults in selecting only the relevant information for maintenance in WM. Furthermore, measures of filtering efficiency and WM capacity were correlated, indicating that lower WM capacity in adolescents is related to a reduced ability to block distracting items from being processed in WM. Immature frontoparietal networks are thought to be responsible for this developmental effect. In Chapter 3 and 4 adolescents between 12 and 16 years old were included in the adolescent groups. Future studies should take into account possible attentional growth spurts within this age range, and the role of WM in this, by including separate groups of young and old adolescents. Furthermore, functional MRI (magnetic resonance imaging) studies could identify which brain regions are involved in the WM and attentional control interactions observed in adolescents in future research.

In Chapter 5 the same change detection task was conducted in adolescents and adults with ADHD and age-matched controls. Results from this study again showed large developmental differences between adolescents and adults (with and without ADHD), but no deficits in filtering efficiency or WM capacity in ADHD patients. Only smaller CDA amplitudes (ERPs) with low load (maintenance of one item) were found in adolescents and adults with ADHD due to increases in ipsilateral activity, suggesting wandering of attention to the non-cued hemifield in these groups. The development of filtering efficiency and VSWM storage capacity in adolescents with ADHD was not different from that in typically developing peers when matched on IQ.

Finally, the results from the studies in this thesis were discussed and general conclusions were drawn in Chapter 6. Taken together, the studies on typical development showed that the interdependency of attentional control and WM is subject to developmental changes from adolescence to adulthood. On the one hand, interference control was shown to be differentially affected by changes in WM capacity in adolescents than adults. Lower availability of resources for top-down control was thought to be responsible for worse distracter suppression in adolescents. On the other hand, an inability to block distracter items from memory and a lower storage capacity resulted in worse performance on a visuospatial WM

task in adolescents than adults. Possibly because of prolonged development of frontoparietal networks, responsible for both cognitive control functions, performance and ERP activity related to attentional control and WM was still immature in adolescents. Furthermore, the ADHD studies showed that young children with ADHD symptoms already have attentional problems, which might be good indicators for the risk of developing ADHD. Results from the last study showed similar patterns of WM and attentional control interactions in adolescents with and without ADHD when groups were matched on IQ, and provides no evidence for a developmental lag for WM-attention interactions in adolescents with ADHD.

Samenvatting

Samenvatting

Stel je voor dat je in een lawaaierige klas een moeilijke opdracht probeert te maken, of dat je op een drukke weg rijdt terwijl je probeert de verkeersborden in de gaten te houden, maar de reclameborden te negeren. Voor deze situaties (en voor ontelbare andere situaties uit het dagelijks leven) is het nodig om onze doelen actief in gedachten te houden en alleen op de relevante informatie uit de omgeving te letten, terwijl we proberen ons niet te laten afleiden door irrelevante informatie. Om dit succesvol te laten verlopen, hebben we goed functionerende cognitieve controle nodig. Twee belangrijke factoren voor cognitieve controle zijn werkgeheugen en aandachtscontrole. *Werkgeheugen* (WG) verwijst naar ons vermogen om tijdelijk een beperkte hoeveelheid informatie vast te houden en te manipuleren. *Aandachtscontrole* is ons vermogen om relevante informatie te selecteren, terwijl we informatie die irrelevant is met betrekking tot onze huidige doelen proberen te onderdrukken. Voor zowel WG als aandachtscontrole is gevonden dat deze nog niet volledig ontwikkeld zijn in de adolescentie, wat te maken heeft met de onvolwassenheid van netwerken bestaande uit frontale en pariëtale hersengebieden die betrokken zijn bij cognitieve controle functies. Ook in adolescenten en volwassenen met aandachtstekort hyperactiviteitstoornis (ADHD) wordt vaak een slechtere prestatie op WG- en aandachtscontrole taken gevonden. Aangezien cognitieve controle geassocieerd wordt met een goede ontwikkeling van andere cognitieve vermogens zoals redeneren, probleem oplossen, lezen, wiskunde, en fluïde intelligentie, is het belangrijk om de normale en atypische ontwikkeling van WG en aandachtscontrole beter te bestuderen.

Studies met gezonde volwassenen hebben al uitgewezen dat WG en aandachtscontrole sterk aan elkaar gerelateerd zijn, en afhankelijk zijn van dezelfde frontaal-pariëtale hersennetwerken. Door middel van selectieve aandacht kunnen we bepalen welke informatie in het WG wordt opgenomen om onthouden en gemanipuleerd te worden (door relevante informatie te selecteren en irrelevante informatie te onderdrukken). Andersom zien we dat, wanneer de hoeveelheid beschikbare WG capaciteit opzettelijk verminderd wordt, de prestatie op taken die aandachtscontrole vereisen afneemt. Omdat er nog geen onderzoek is gedaan naar de ontwikkelingspatronen van deze interacties bij adolescenten, en gezien het feit dat de ontwikkeling van beide cognitieve functies zo belangrijk is voor andere cognitieve vermogens zoals hierboven genoemd, was het doel van het huidige werk om het verloop van de ontwikkeling van interacties tussen WG en aandachtscontrole te onderzoeken. Naast de normale ontwikkeling is ook de cognitieve ontwikkeling van kinderen en adolescenten met ADHD onderzocht, omdat het bekend is dat zij problemen hebben die gerelateerd zijn aan aandachtscontrole en WG (Martinussen et al., 2005).

Hoofdstuk 1 begint met de beweegredenen achter deze thesis, verklaart de belangrijkste theoretische en methodologische aspecten en eindigt met de doelen van

dit werk en een overzicht van de verschillende hoofdstukken. Met het huidige onderzoek hebben we geprobeerd het volgende te bekijken: a) de aard van de aandachtsproblemen in jonge kinderen (5-7 jaar oud), door de onderliggende neurale mechanismen van aandachtscontrole-ontwikkeling te bestuderen in gezonde kinderen en kinderen met aandachtsproblemen (Hoofdstuk 2), b) de ontwikkeling van interacties tussen WG en aandachtscontrole in gezonde adolescenten, door de invloed van opzettelijk verminderde WG capaciteit op interferentiecontrole te bestuderen (Hoofdstuk 3), c) het ontwikkelingsverloop van top-down modulatie van selectieve aandacht op WG prestatie tijdens de adolescentie, door de relevantie van te onthouden items in een WG-taak te manipuleren, en zo de filter-efficiëntie van aandacht te meten (Hoofdstuk 4), en d) de ontwikkeling van WG en filter-efficiëntie in adolescenten en volwassenen met ADHD, waarvan bekend is dat ze een tekort aan cognitieve controle hebben (Hoofdstuk 5). Om het bovenstaande te onderzoeken, hebben we naast gedrag ook “event-related potentials” (ERPs; de psychofysiologische reacties van de hersenen op gebeurtenissen tijdens een taak) gemeten, welke een zeer hoge temporele resolutie hebben (van milliseconden), en zo informatie kunnen geven over alle fases van de cognitieve verwerking van informatie in de hersenen.

Hoofdstuk 2 liet zien dat jonge kinderen (van 5 tot 7 jaar oud) die nog geen diagnose ADHD hebben, maar vroege symptomen laten zien (gemeten door middel van vragenlijsten), een slechtere prestatie hadden dan kinderen zonder ADHD symptomen op een aandachtstaak waarbij ze op een bepaalde letter (stimulus) moesten reageren wanneer vooraf een speciaal teken werd gegeven, maar om deze respons te onderdrukken wanneer dit teken niet van tevoren aanwezig was geweest. De gedragsdata lieten zien dat kinderen met ADHD symptomen vooral problemen met de aandacht hadden, maar niet met het onderdrukken van de respons zelf. Verder lieten de ERPs van de kinderen met ADHD symptomen een tekort zien in het vermogen om de beschikbare aandacht doorlopend voor de taak te gebruiken. Als respons op het waarschuwingsteken lieten deze kinderen verder een verminderd oriënteren zien of een verminderd vermogen om een aandachtsrespons op te roepen wanneer dit waarschuwingsteken werd gegeven, en lieten ze vlak voor het verschijnen van de daaropvolgende stimulus minder visuele aandacht zien. Deze bevindingen wijzen erop dat aandachtsproblemen al op een jonge leeftijd aanwezig zijn in kinderen met symptomen van ADHD, en betere voorspellers zouden kunnen zijn dan vroege symptomen van hyperactiviteit/impulsiviteit (omdat deze laatste op deze leeftijd tot het normale gedragsrepertoire lijken te behoren).

Samen lieten de resultaten van de studies in Hoofdstuk 3 en 4 zien dat in adolescenten zowel aandachtscontrole als WG nog onvolwassen zijn, en zich nog verder ontwikkelen tot in de volwassenheid. In Hoofdstuk 3 namen adolescenten en volwassenen deel aan een duo-taak die bestond uit een aandachtscontrole-taak (Stroop taak) en een verbale WG-taak (N-back taak). In de gender gezicht-woord Stroop taak werd een slechtere distracter suppressie gevonden in adolescenten dan in volwassenen bij de aanwezigheid van een conflicterende stimulus (bijvoorbeeld

het woord “man” geschreven op het gezicht van een vrouw, zie pagina 73) gemeten door middel van ERPs, en een slechtere prestatie in gedrag, wat wijst op een nog onrijpe aandachtscontrole. Adolescenten presteerden ook slechter op een verbale WG-taak, en hadden (in Hoofdstuk 4) een lagere cijfer spanne en een slechtere gedragsprestatie in een zogenaamde “change detection” taak (waarin men moest aangeven of één of meer items van kleur veranderd waren ten opzichte van eerder getoonde items op dezelfde plaats). ERPs die het encoderen en vasthouden van items in het geheugen reflecteerden (of het toekennen van spatiële aandacht daaraan), lieten een vóórtdurende ontwikkeling zien in deze change detection studie.

Een belangrijk doel van dit proefschrift was het ontwikkelingsverloop van de interacties tussen aandachtscontrole en WG tijdens de adolescentie te onderzoeken. In Hoofdstuk 3 werd dit onderzocht door de beschikbare WG-capaciteit te verminderen door de hoeveelheid informatie te manipuleren in de verbale WG-taak die tegelijkertijd met de aandachtscontrole (Stroop) taak werd uitgevoerd. Hoewel er geen effect van verminderde WG-capaciteit werd gevonden op het gedrag in de gezicht-woord Stroop taak, leidde het steeds oprispen van letterinformatie tijdens de Stroop taak wel tot een toename in ERP activiteit gerelateerd aan conflict detectie (bv. bij het zien van het woord “man” op het gezicht van een vrouw) in volwassenen. Dit effect van verminderde WG-capaciteit werd niet gevonden in adolescenten, maar dit komt mogelijk doordat hun ERP activiteit al hoger was zonder de extra WG-lading, wat erop wijst dat ze al meer conflict beleefden zonder WG-lading. Het oprispen van letterinformatie had ook een effect op de ERP activiteit die geassocieerd wordt met de selectie van een respons, maar niet méér voor conflicterende stimuli (bv. het woord “man” op het gezicht van een vrouw) dan voor stimuli zonder inwendig conflict (bv. het woord “man” op het gezicht van een man).

In Hoofdstuk 4 is een andere benadering gebruikt om interacties tussen WG en aandachtscontrole te onderzoeken. De change detection taak met relevante items die onthouden moesten worden en irrelevante items die onderdrukt moesten worden, werd gebruikt om de effecten van de efficiëntie van aandachtfilteren op WG-capaciteit te onderzoeken (zie pagina 100). De gedrags- en ERP-resultaten uit Hoofdstuk 4 wezen erop dat adolescenten niet in staat waren om irrelevante informatie te onderdrukken en daarom niet zo efficiënt waren als volwassenen in het selecteren van alleen de relevante informatie voor opslag in het WG. Verder waren de maten van filter-efficiëntie en WG-capaciteit ook gecorreleerd, wat er op wijst dat een lagere WG-capaciteit bij adolescenten gerelateerd is aan een verminderd vermogen om afleidende items te blokkeren (met als gevolg dat deze items door adolescenten wel in het WG worden opgenomen). Mogelijk wordt dit ontwikkelingseffect veroorzaakt door nog onvolwassen frontaal-pariëtale netwerken. In Hoofdstuk 3 en 4 zijn adolescenten tussen de 12 en 16 jaar oud opgenomen in de adolescentengroepen. Toekomstige studies zouden rekening moeten houden met mogelijke groeisprunten van aandachtsfuncties in deze leeftijdsperiode, en de rol van WG hierbij, door verschillende groepen bestaande uit jonge en oude adolescenten op te nemen. Verder zouden functionele MRI (magnetic resonance imaging) studies in

toekomstig onderzoek kunnen identificeren welke breangebieden precies betrokken zijn bij WG- en aandachtsinteracties zoals gevonden in adolescenten.

In Hoofdstuk 5 werd dezelfde change detection taak afgenomen bij adolescenten en volwassenen met ADHD die in leeftijd gelijk waren aan de controlegroepen. De resultaten van deze studie laten wederom grote ontwikkelingseffecten zien tussen adolescenten en volwassenen (met en zonder ADHD), maar geen tekorten in filter-efficiëntie of WG-capaciteit in ADHD patiënten. Er werden alleen kleinere CDA amplitudes (ERPs) gevonden bij een lagere WG-lading (het onthouden van één item) in adolescenten en volwassenen met ADHD doordat deze een toename in ipsilaterale activiteit lieten zien, mogelijk als gevolg van het afdwalen van de aandacht naar het niet-gecuede visuele veld in deze groepen. De ontwikkeling van filter-efficiëntie en visuospatiële WG-opslagcapaciteit in adolescenten met ADHD was echter niet verschillend van die in leeftijdsgenoten met een typische ontwikkeling, wanneer gematched op IQ.

Tot slot werden de resultaten van de studies in deze thesis besproken en werden er algemene conclusies getrokken in Hoofdstuk 6. Samen lieten de studies over de normale ontwikkeling zien dat de onderlinge afhankelijkheid van aandachtscontrole en WG onderhevig is aan ontwikkeling in de periode van adolescentie tot volwassenheid. Aan de ene kant werd aangetoond dat interferentiecontrole op een andere manier beïnvloed werd door veranderingen in WG capaciteit in adolescenten dan in volwassenen. Een verminderde beschikbaarheid van bronnen voor top-down controle was verantwoordelijk voor de slechtere distracter suppressie die werd gevonden in adolescenten. Aan de andere kant werd een slechter vermogen om voor afleidende (irrelevante) items de toegang tot het geheugen te blokkeren en een lagere WG capaciteit in adolescenten verantwoordelijk gehouden voor de gevonden slechtere prestatie op een visuospatiële WG-taak in deze groep dan in volwassenen. Mogelijk waren gedrag en ERP activiteit die gerelateerd zijn aan aandachtscontrole en WG nog onvolwassen in adolescenten door een vóórtdurende ontwikkeling van frontaal-pariëtale netwerken, die verantwoordelijk zijn voor beide cognitieve functies. Verder lieten de ADHD-studies zien dat jonge kinderen met ADHD symptomen al aandachtsproblemen hebben, welke goede indicatoren zouden kunnen zijn voor het risico om ADHD te ontwikkelen. De resultaten van de laatste studie in dit proefschrift lieten vergelijkbare patronen van WG-aandachtscontrole interacties zien in adolescenten met en zonder ADHD wanneer de groepen overeenkwamen in IQ, en levert geen bewijs voor het bestaan van een vertraagde ontwikkeling van WG-aandacht interacties in adolescenten met ADHD.

Dankwoord

Dankwoord

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Marjolein

Curriculum Vitae

Marjolein Spronk was born on the 24th of May 1983 in Gorinchem, the Netherlands. In 2001 she completed her secondary school education at Gymnasium Camphusianum in Gorinchem. From 2001 until 2007 she studied Psychology at Utrecht University. After completing research internships under the supervision of Dr. F.S. van den Bergh at the Department of Psychopharmacology (Utrecht University), where she studied the effects of food and tone manipulations on premature responding in rats, and Dr. F.P. de Lange at the Intention and Action group (Donders Institute Nijmegen), where she conducted an fMRI project on understanding the action intentions of other agents, she received her master's degree in Biological and Neuropsychology. In the same year, she started her PhD project at the department of Cognitive Neuroscience, section Developmental Cognitive Neuroscience, at Maastricht University under the supervision of Dr. Lisa Jonkman and Prof. Dr. Chantal Kemner, resulting in this thesis.

