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Attention Deficit Hyperactivity Disorder in Children and Adolescents: Neuropsychological Deficits and Functional Outcomes

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Attention Deficit Hyperactivity Disorder in Children and Adolescents: Neuropsychological Deficits and Functional Outcomes

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

This thesis investigated the role of neuropsychological functioning in ADHD and some of the major functional consequences of the disorder: academic achievement and peer problems.

Study I used both a logistic regression and Venn diagrams to illustrate the neuropsychological heterogeneity of Attention Deficit Hyperactivity Disorder (ADHD) in a school-aged sample. More specifically, independent effects were observed for executive functioning, reaction time variability as well as for both positive and negative aspects of emotional functioning. There were no effects of gender, and group differences generally remained significant when controlling for either IQ, comorbid conduct problems or internalizing problems.

Study II investigated neuropsychological heterogeneity in a preschool sample. Independent effects of executive functioning, delay aversion and emotional functioning were found. Like Study I, the results of Study II showed that the associations between neuropsychological deficits and ADHD generally remained after controlling for IQ and comorbid conduct problems.

In Study III, the aim was to investigate how the multiple neuropsychological deficits can explain secondary impairments. The results showed that working memory and reaction time variability partially mediated the relation between ADHD and academic achievement, whereas regulation of anger partially mediated the relation between ADHD and peer problems. Neither gender nor comorbid Oppositional Defiant Disorder/Conduct Disorder (ODD/CD) moderated these findings.

In Study IV, neuropsychological deficits were investigated in relation to both ADHD symptoms and functional impairments, but here with a longitudinal design covering a period from preschool to late adolescence. Results show that executive and attention-related functions were primarily related to symptoms of inattention, while emotional functioning was predictive of both symptom domains. Hence, early onset neuropsychological deficits are predictive of development of ADHD. With regard to the role of comorbid ODD/CD, relations to anger disappeared when controlling for symptoms of ODD/CD, but the effect of regulation of happiness/exuberance remained significant for hyperactivity/impulsivity and just missed significance for inattention. These results emphasize the need to also include positive emotions as a possible cause of ADHD symptoms.

In summary, neuropsychological deficits should be considered important aspects to target in relation to ADHD as well as to academic achievement and peer problems. Several aspects of neuropsychological functioning are deficient in both preschool and school-aged children, but the relative impact of each specific deficit varies with age. Adding to previous research, this thesis suggests that deficient emotional functioning is an important pathway both to ADHD and associated peer problems. Furthermore, this thesis suggests that reaction time variability is not just strongly related to ADHD, but also to academic achievement.

LIST OF SCIENTIFIC PAPERS

I. Sjöwall, D., Roth, L., Lindqvist, S., & Thorell, L. B. (2013). Multiple deficits in ADHD: Executive dysfunction, delay aversion, reaction time variability and emotional deficits. *Journal of Child Psychology and Psychiatry*, *54*, 619–627.

II. Sjöwall, D., Backman, A., & Thorell, L. B. (in press). Neuropsychological heterogeneity in preschool ADHD: Investigating the interplay between cognitive, affective and motivation-based forms of regulation. *Journal of Abnormal Child Psychology.*

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IV. Sjöwall, D., Bohlin, G., Rydell, A. & Thorell, L. B. *Neuropsychological deficits in preschool as predictors of ADHD symptoms and academic achievement in late adolescence.* Submitted.

CONTENTS

LIST OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
ADHD-C	ADHD, combined type
ADHD-HI	ADHD, predominantly hyperactive/impulsive subtype
ADHD-I	ADHD, predominantly inattentive
ANCOVA	Analysis of covariance
APA	American Psychiatric Association
CANTAB	Cambridge Neuropsychological Test Automated Battery
CD	Conduct Disorder
CI	Confidence Intervals
DAv	Delay aversion
DSM	Diagnostic and Statistic Manual of Mental Disorders
EF	Executive functioning
IQ	Intelligence
ODD	Oppositional Defiant Disorder
RTVAR	Reaction time variability
SDQ	Strength and Difficulties Questionnaire
WISC	Weschsler Intelligence Scale of Children

1 INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders and occurs in most cultures in about 5% of children (American Psychological Association [APA], 2013). The list of functional consequences of ADHD is long and underscores the importance of identifying early markers of the disorder (APA, 2013). Importantly, it is increasingly acknowledged that ADHD is a heterogeneous disorder with regard to both the neuropsychological deficits and the functional impairments that individuals with ADHD encounter (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005). This means that not all individuals with ADHD display the same deficits and that they also develop different difficulties. For example, one child may need help focusing in the classroom, whereas another may need help regulating emotions in order not to be rejected by peers. If we are to understand the neuropsychological underpinnings of the disorder and be able to design effective treatments, it is important to take this heterogeneity into account. Importantly, this should be done at an early age, as interventions are more likely to change the course of the disorder if implemented early (Sonuga-Barke & Halperin, 2010).

Candidate factors used to explain the heterogeneity in ADHD have been suggested to be various aspects of neuropsychological functioning such as executive deficits, delay aversion, and reaction time variability (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Nigg et al., 2005 for reviews). All these functions have been shown to be related to ADHD in previous research, but very few studies have taken their overlap into consideration. Thus, it is important that these functions be investigated within the same study in order to better understand the relation between them and their independent associations with ADHD. If we neglect to do so, we cannot not know to what extent that they measure the same thing. Another aspect of neuropsychological functioning that has been increasingly acknowledged is emotional functioning (e.g., Martel, 2009; Nigg, 2006). However, relatively little research has examined emotional functioning in relation to ADHD, especially studies taking the possible overlap between emotional functioning and other neuropsychological functions into consideration.

Children with ADHD often go on to develop problems in academic settings (e.g., Daley & Birchwood, 2009; Loe & Feldman, 2007) and problematic peer relations (e.g., Hoza, 2007; McQuade & Hoza, 2008 for reviews). However, it is not known to what extent neuropsychological heterogeneity can explain why some individuals with ADHD develop functional impairments, whereas others manage relatively well in daily life.

The major aim of this thesis was therefore to include several aspects of neuropsychological functioning and study their independent relation to ADHD symptoms as well as to two of the functional impairments that have been shown to be most strongly related to the disorder: academic achievements and peer relations.

Four studies are included that examine the role of neuropsychological deficits in relation to ADHD and functional impairments. The first three studies use samples including both children diagnosed with ADHD and age- and gender-matched controls. The fourth study uses a

population-based sample of normally developing children followed from preschool until late adolescence.

1.1 DEFINING ADHD

1.1.1 Diagnostic criteria

According to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; APA, 2013), ADHD is characterized by elevated and persistent levels of inattention and/or hyperactivity-impulsivity (six or more symptoms within at least one domain). If six or more symptom criteria are met within both domains, the diagnosis will be specified as combined type (ADHD-C). If the criteria are only met for one domain, the diagnosis will be specified as either predominantly inattentive subtype (ADHD-I) or predominantly hyperactive/impulsive subtype (ADHD-HI). With regard to the symptom domains, inattention is manifested by difficulties with maintaining focus. Individuals with inattention problems often lack persistence and find themselves wandering off task as well as being more disorganized (e.g., they often have difficulty sustaining attention in tasks or play activities, and do not seem to listen when spoken to directly). Hyperactivity is characterized by excessive activity such as moving around or talking when it is not appropriate (e.g., often talks excessively). These symptoms are also expressed as fidgeting or tapping (e.g., often fidgets with or taps hands or feet or squirms in seat). Symptoms often decrease with age, but can then be manifested as extreme restlessness or intensity in adulthood. Impulsivity is expressed by rushed decisions without any consideration, such as interrupting or running out into traffic without looking. Impulsivity is also reflected in a propensity for immediate rewards rather than considering the long-term consequences. However, as both inattentive and hyperactive/impulsive symptoms can be observed to some extent in almost any child, it is crucial that we ask to what degree these symptoms interfere with functioning or development and to what extent the child's behavior deviates from what is considered normal at any given age. Other requirements are that some of the symptoms should be present before age 12, that symptoms must be present in more than one setting (e.g., home and school), that symptoms have persisted for at least 6 month and cannot be better explained by any other disorder.

1.1.2 Etiology

Regarding the causes of ADHD, perhaps one of the most important aspects to mention is that there may be many reasons why a given individual develops elevated levels of these symptoms (Nigg et al., 2005). This makes the search for biological markers of the disorder more difficult and is perhaps also a reason why the diagnostic procedure is still based on a symptom count. Research areas that have proven or been suggested to be of importance in unraveling the question

of the etiology of ADHD are genetics, prenatal and perinatal development, environment/early deprivation/nutrition, as well as epigenetics. These areas are not always clearly separable, but examples from these areas will be given below to illustrate that several different aspects are linked to the causes of ADHD.

ADHD has been shown to be highly heritable (Wray, Lee, Mehta, Vinkhuyzen, Dudbridge, & Middeldorp, 2014; Thapar & Harold, 2014), not only concerning how symptoms are expressed at an early age, but also in adulthood. Simplified, the major causes of ADHD are traits that are inherited from one generation to the next. The association to genes is partially stable over time, but there are also new genes that come into play, which are associated with ADHD (Chang, Lichtenstein, Asherson, & Larsson, 2013). Moreover, ADHD is linked to several comorbid diagnoses and multiple deficits, which makes it more difficult to identify genes that are specific to ADHD. Even tough genetic factors are believed to account for the major part of the ADHD variance, the identified effect of genes that are related to ADHD is, of now, very limited (Volkow & Swansson, 2013), and the candidate gene approach has been questioned with regard to its usefulness in relation to ADHD.

ADHD may also be caused by complications during pregnancy or environmental factors during early development. These factors are dependent on internal causes such as inheritance as well as external factors. One such example is the increased risk for ADHD in children born pre-term (Tarver, Daley, & Sayal, 2014). Yet another example of an external influence is how diets can reduce ADHD symptoms. A recent review found some support for positive effects of fatty acids, but pointed out the methodological challenges that must be dealt with before any conclusions can be drawn with regard to elimination treatments and food supplements (Stevensson et al., 2014).

Of course, not all individuals are affected the same way by the environmental factors mentioned above. In order to enhance our understanding of ADHD and its etiology, many researchers have emphasized the need to look at how genes and environment interact (e.g., Nigg, 2012). This would explain why some children show susceptibility to environmental influences while others are not as easily affected. Perhaps one of the most interesting examples of how genes and environment interact concerns how early environmental exposures can effect development of ADHD through epigenetic mechanisms. For example, factors such as stress, toxins and diet can effect whether a gene is turned “on” or “off.” Such effects can make a great difference, as they may change phenotypes, i.e., lead to symptoms of ADHD. Epigenetic mechanisms may thus be an important key to demonstrating the development of ADHD. Moreover, the phenotype can be passed on to forthcoming generations, but, importantly, it may be that such epigenetic effects can be reversed. This emphasizes the need to study prenatal and perinatal factors for the purpose of discovering how a phenotype that leads to ADHD symptoms is created and how it can be reversed or prevented (Nigg, 2012).

The difficulty in answering the question of what causes ADHD is consequently reflected at the level of neuropsychological functioning as well. Genetic and environmental effects are believed to give rise to structural and/or functional alterations in the brain. These alterations then affect neuropsychological functioning, which in turn manifests as ADHD symptoms. ADHD is currently thought of as a heterogeneous disorder, where different neuropsychological deficits

give rise to ADHD symptoms (Castellanos et al., 2006). This could mean that the ADHD symptoms of one child are caused by executive deficits, whereas the ADHD symptoms of another child are based on another underlying deficit. Perhaps it is for this reason that the search for possible neuropsychological causes of ADHD always renders limited effect sizes, with no single factor explaining everything. The present thesis therefore includes several candidate neuropsychological functions and explores their joint ability to explain ADHD and the functional consequences of the disorder.

1.1.3 Comorbidity and the issue of specificity

ADHD is known to co-occur with several other disorders. In fact, it is more common than not that individuals with ADHD also display another disorder (Singh, 2008). As a consequence of this high comorbidity, the issue of specificity arises, i.e., how can we know that what we are observing is actually ADHD-specific behavior? At any level of research where the aim is to describe ADHD, there is a risk that the findings will be at least partially explained by the influence of another disorder. In the present thesis, this will be particularly important to consider when identifying predictors at the neuropsychological level (i.e., are the neuropsychological deficits associated with ADHD better explained by the co-occurrence of another disorder?). There are methodological and statistical ways of addressing this complex matter, for example by excluding participants with comorbid disorders or by using comorbid symptom levels as a covariate in the analyses. These matters will be described in more detail in the empirical studies, and when discussing the role of neuropsychological functioning in ADHD in the general discussion. In short, removing comorbid symptoms could mean taking away part of what one actually wants to study, and thus, we therefore report results both with and without such controls as a general rule. In this way, the reader can make up his/her own mind about how great an impact comorbid symptoms have on the results.

Oppositional defiant disorder (ODD) and conduct disorder (CD) are the most common co-occurring disorders in ADHD, with about 50% of children with ADHD also meeting the criteria for ODD or CD. In general, these disorders include defiant behavior and often take the form of disregarding the rights of others. Such behavior often leads to peer rejection and difficulties getting along with parents and teachers (Waschbush, 2002). Both ODD and CD include conduct problems, but CD is considered to be more severe due to the more aggressive behavior it encompasses (e.g., has been physically cruel to people). Furthermore, ODD includes problems of an emotional character, whereas “being angry” or “in a irritable mood” is not part of the description of CD. In addition to ODD and CD, emotionally related disorders also co-occur with ADHD to a large extent, with as much as 30% of children with ADHD displaying internalizing problems like anxiety disorders (Wilens et al., 2002).

Regarding the predictors included in the thesis, some previous studies (e.g., Martel, 2009, for a review) have suggested that features of emotion dysregulation may be predominantly marked in children with ADHD and comorbid ODD or CD. In addition, emotion dysregulation, especially

poor regulation of fear, has been shown to be associated with internalizing problems (e.g., Rydell, Berlin, & Bohlin, 2003). Thus, it is important for research examining the link between emotional functioning and ADHD to investigate to what extent this relation is an effect of comorbid ODD/CD or internalizing problems.

1.1.4 ADHD, a category or a dimension?

Even though ADHD is considered a category in current versions of the DSM (i.e., either you have the disorder or you do not), there is evidence to suggest that ADHD, as is the case with most psychiatric disorders, is better characterized as a continuum (Sonuga-Barke & Halperin, 2010). Twin studies have found that heritability estimates are about the same across severity levels (e.g., Gjone, Stevenson, & Sundet, 1996), meaning that ADHD is not only to be considered a highly heritable trait above the cut-off used by DSM. Moreover, one study investigating the latent structure of ADHD found no support for the notion that ADHD should be organized according to categories (Frazier, Youngstrom, & Naugle, 2007). Another aspect worth considering is that the number of ADHD symptoms within an individual is not stable over time (von Stauffenberg & Campbell, 2007). This means that individuals who are close to the cut-off of the DSM criteria may fulfill the criteria for ADHD at one time point, but not at another. This change from six to five symptoms does not mean that secondary problems like academic achievement suddenly disappear. The existence of a cut-off has the advantage of facilitating clinical decision-making, but it is important to remember that exactly where the cut-off is drawn is not based on an objective measure, but rather on societal norms about behavior and development (Sonuga-Barke & Halperin, 2010). Altogether, the multiple factors that cause ADHD symptoms are believed to be the same in normal and abnormal development with qualitative rather than quantitative differences between children with ADHD normal controls. Hence, this means that it is possible to conduct research on ADHD not just among children scoring above the DSM criteria for ADHD, but also in non-clinical samples.

1.2 NEUROPSYCHOLOGICAL FUNCTIONS IN ADHD

As mentioned above, ADHD is currently considered a heterogeneous disorder with multiple deficits contributing to it. Such factors implicate various aspects of neuropsychological functioning. Neuropsychological functioning is a general term that encompasses specific psychological processes and behaviors. Here, neuropsychological functioning is used as an umbrella term for the different aspects of functioning that are described below.

1.2.1 Executive functions

Executive functioning can be defined as processes responsible for purposeful, goal-directed behaviors (Anderson, 2002). Executive functions are closely related to our ability to concentrate and carry out analyses. Of the neuropsychological deficits that have been targeted as possible underlying explanations for the causes of ADHD symptoms, executive functions are the most studied. Executive functioning is related to ADHD even when confounding factors such as intelligence (IQ) and comorbidity are taken into account (for a review, see Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Influential work concerning the unity and diversity of executive functioning was presented by Miyake and colleagues (2000). By conducting a confirmatory factor analysis, they identified three major aspects that were modestly correlated but clearly separable: working memory, inhibition, and shifting (e.g., Miyake, Friedman, Emerson, Witzki, & Howerter, 2000). Working memory can be defined as the ability to actively manipulate relevant information, rather than passively store information. For example, working memory is used when you calculate math or try to remember in what order you should put things together from a recipe. Inhibition is the ability to purposefully inhibit dominant, automatic, or prepotent responses. There are several ways in which inhibition is used in daily life. One example of poor inhibition is when one bursts out an answer to a question without considering that one was supposed to raise one's hand first. Another example is when one fails to disregard what is happening outside the classroom window when one is supposed to be focusing on the task at hand. Shifting concerns how well one is able to shift back and forth between multiple tasks, operations, or mental sets, e.g., disregarding an irrelevant rule and then subsequently actively engaging in a relevant rule.

The division of executive functioning into three components (i.e., working memory, inhibition and shifting) suggested by Miyake and colleagues (2000) is based on adults. An important question is therefore whether the unity and diversity of executive functioning can be found also in preschool children. Garon and colleagues (2008) applied this division of executive functions to preschoolers and found that working memory develops first, followed by inhibition and, then, the ability to shift attention between tasks (Garon, Bryson, & Smith, 2008). These executive functions were recently included in a meta-analysis in order to investigate their respective associations with ADHD in preschool (Schoemaker, Mulder, Dekovic, & Matthys, 2012). The results demonstrated a medium effect size for inhibition and small effect sizes for working memory and cognitive flexibility. The fact that the effect size differed for these measures could be taken as an indication that executive functioning is a diverse rather than unitary construct among preschool children as well. It is important to consider the results of the moderation analyses performed in the meta-analysis, which indicated that the relative impact of these functions increases with age. In this context, it may also be important to consider that ADHD has been described as a developmental disorder, implying that children with ADHD are developmentally delayed (Barkley, 1997). In line with this reasoning, a task can only successfully discriminate between children with ADHD and normally developing children if it is easy enough for normally developing children to master, but difficult enough so that children with ADHD, who are developmentally delayed, will not perform well (Barkley, 1997).

Therefore, when evaluating the impact of possible deficits, it is important to have knowledge of when they develop and thus at what age they may show the strongest association with ADHD.

With regard to theoretical formulations describing the link between ADHD and executive functioning, Barkley's (1997) Hybrid Model of ADHD has received considerable attention. Barkley (1997) proposed a model in which inhibition is the primary deficit and this is believed to lead to secondary deficits with regard to the following executive functions: 1) non-verbal working memory, 2) internalization of speech (verbal working memory), 3) self-regulation of affect, motivation, and arousal, and 4) planning.

1.2.2 Delay aversion

Theoretical appraisals of the underlying causes of ADHD have also been postulated in relation to reinforcement and motivation, involving, for instance, the concept of delay aversion (for a review, see Luman, Oosterlaan, & Sergeant, 2005). Delay aversion is defined as the tendency to choose a smaller immediate reward rather than wait for a larger delayed reward (Sonuga-Barke, Taylor, Sembi, & Smith, 1992). According to this aspect of motivation, behavior is driven by a generalized aversion to delay, rather than by an impulsive drive for immediate reward. The behavior is hypothesized to derive from the fact that children with ADHD have an especially strong negative affect toward delay, leading to disengagement, in various ways, from long and boring tasks (Marco et al., 2009). According to this hypothesis, when a choice is given, the immediate reward will be chosen before a delayed reward. When no choice is given, it is possible that the child will direct his/her attention to something that will make time pass more easily (Sonuga-Barke, 2002). Empirical support for the delay aversion hypothesis has been demonstrated (see review by Pauli-Pott & Becker, 2011), although some studies have failed to find significant group differences (e.g., Karalunas & Huang-Pollock, 2011; Scheres et al., 2006; Solanto et al., 2007). Unlike the impact of executive functions that increases with age, the relative importance of delay aversion for ADHD seems to be greatest in early preschool samples (Pauli-Pott & Becker, 2011).

The role of motivation has also been included in a dual pathway model of ADHD, which places poor executive functions, like deficient inhibitory control, in one pathway and delay aversion in the other (Sonuga-Barke, 2002, 2003). In support for this model, several studies (e.g., Dalen, Sonuga-Barke, Hall, & Remington, 2004; Solanto et al., 2001; Sonuga-Barke, Dalen, & Remington, 2003) have found that ADHD is significantly related to delay aversion independent of deficits in inhibitory control. Hence, even though a partial overlap may exist between these two pathways, there are children with ADHD who are delay avers without displaying poor inhibitory capacities and children who show the opposite pattern (Nigg et al., 2005).

1.2.3 Reaction time variability

Another aspect that has been shown to be strongly associated with ADHD is reaction time variability (e.g., Castellanos et al., 2005; Karalunas, Geurts, Konrad, Bender, & Nigg, 2014; Tamm et al., 2012, for reviews). Reaction time variability (or sometimes called intra-individual variability in reaction times) in ADHD research is most often operationalized as the standard deviation of the time it takes to respond in tasks that require rapid response (see, however, Tamm et al., 2012 for a discussion of different ways of measuring this construct). Typically, reaction time variability is extracted from trials in which the participant responded correctly. Increased reaction time variability has been included in numerous studies on ADHD using many different tasks, and group differences between children with ADHD and normally developing controls often have a larger effect size compared to group differences for other neuropsychological functions (Tamm et al., 2012).

The exact nature of increased reaction time variability among children with ADHD has been debated (Tamm et al., 2012). Increased reaction time variability may suggest difficulty in sustaining effort due to non-optimal activation or arousal state (Sergeant, 2005), or impairment in time perception, which refers to the inability to anticipate when an impending stimulus will appear (Paule et al., 2000). It may also be the case that several processes can explain this pattern of responding. Most theories agree that reaction time variability is reflected by occasional lapses in attention or the inability to sustain attention. It seems that children with ADHD perform better when the pace of the task is fast, as this keeps them on their toes. In contrast, when tasks are slow, their reaction time variability increases. For example, fast-paced computer games that require high levels of attention could be suited to the level of intensity that children with ADHD prefer, whereas more slow-paced tasks could prove to be a greater challenge. However, we cannot rule out that such effects may be explained by the delay aversion hypothesis if the task is perceived as boring. In addition, there is some evidence to suggest that reaction time variability decreases when rewards are provided (Tamm et al., 2012). Hence, there could arguably be some degree of overlap between delay aversion and reaction time variability. This possible overlap has been acknowledged (see Sonuga-Barke, Wiersema, van der Meere & Roeyers, 2010), but very few empirical studies have investigated whether reaction time variability is related to ADHD independent of both delay aversion and executive functioning. In the few studies that have investigated the overlap, independent effects of reaction time variability were observed when controlling for executive functions and delay aversion (Kuntsi, Oosterlaan, & Stevenson, 2001; Wåhlstedt, Thorell, & Bohlin, 2009).

1.2.4 Emotional functioning

In addition to deficits in executive functioning, delay aversion and reaction time variability, it has been suggested that emotional functioning should be considered as a potential pathway to ADHD (see Martel, 2009; Shaw, Stringaris, Nigg, & Leibenluft, 2014 for reviews). Studies of school-aged children have shown that emotion dysregulation is related to ADHD (e.g., Anastopoulos et

al., 2011; Maedgen & Carlson, 2000; Walcott & Landau, 2004), and deficiencies have been found also with regard to other aspects of emotional functioning, such as emotion recognition (Kats-Gold, Besser, & Priel, 2007; Sinzig, Morsch, & Lehmkuhl, 2008; Yuill & Lyon, 2007).

Previous research investigating emotional functioning in ADHD has largely focused on broad aspects of negative emotions. However, studies that have taken different emotions into account have found that fear shows an especially strong link to internalizing problems, whereas anger is primarily related to externalizing problems (Kim, Walden, Harris, Karrass, & Catron, 2007; Rothbart & Bates, 1998; Rydell, Thorell, & Bohlin, 2007). Positive emotions have generally been associated with adaptive outcomes such as peer competence, prosocial behavior, and low levels of behavior problems (e.g., Denham, McKinley, Couchoud, & Holt, 1990; Eisenberg et al., 1996; Lengua, West, & Sandler, 1998). However, a previous non-clinical study found that dysregulation of happiness/exuberance was related to externalizing behavior (Rydell, et al., 2003). Thus, it may be the case that some specific aspects of happiness/exuberance are related to disruptive behavior. Some of the previous studies investigating emotion regulation deficits in ADHD have used measures that capture both how often and how intensely the child displays different emotions (i.e., emotional reactivity) and how well he/she can regulate different emotions (i.e., emotion regulation). However, temperament research has described reactivity and regulation as two different aspects of temperament (see Cole, Martin, & Dennis, 2004 for a review). Supporting this distinction, regulation and reactivity have been shown to be differentially associated with behavioral and functional outcomes (e.g., Eisenberg et al., 1995; Melnick & Hinshaw, 2000). Naturally, the exact aspect of emotional functioning that is studied in relation to ADHD will influence what conclusions are drawn. Hence, there is a need for a clearer conceptualization of the different aspects of emotional functioning within the field of ADHD research. This might be especially important in relation to positive emotions, as previous studies are inconsistent with regard to how positive emotions relate to behavioral outcomes.

In addition to more clearly defining the concepts under study, it is also of importance to study the relation between emotion dysregulation and other neuropsychological deficits shown to be related to ADHD. Few previous studies have addressed this issue, but some evidence is available suggesting that emotion functioning deficits are related to ADHD independent of deficits in other neuropsychological functions, such as inhibition and working memory (e.g., Berlin, Bohlin, Nyberg, & Janols, 2004; Blaskey, Harris, & Nigg, 2007). However, due to the lack of a clear definition of emotion regulation in many previous studies, as well as the scarcity of previous research on the topic, further studies addressing this issue are clearly needed.

1.3 FUNCTIONAL IMPAIRMENTS IN ADHD AND THEIR RELATION TO NEUROPSYCHOLOGICAL DEFICITS

In addition to the symptoms of the disorder used as criteria for receiving a diagnosis, it is necessary to relate to overall functioning and development (APA, 2013). It has often been found

that children diagnosed with ADHD encounter interfering problems in the academic domain (e.g., Daley & Birchwood, 2009; Loe & Feldman, 2007) and in their relations to peers (e.g., Hoza, 2007; McQuade & Hoza, 2008). However, not all children with ADHD encounter these problems. As ADHD is thought of as a neuropsychologically heterogeneous disorder, it is possible that these deficits could help explain why some individuals with ADHD go on to develop problems in their daily life whereas others do not. Below, I will provide a summary of what is known from previous research regarding the role of neuropsychological deficits in explaining the link between ADHD and both academic achievement and peer relations.

1.3.1 Academic achievement

ADHD is associated with low grades, a need for specialist support, lower scores on standardized tests, and grade retention. However, as mentioned above, not all children with ADHD encounter problems in the academic domain. The relation between ADHD and academic achievement has been found to be stronger for symptoms of inattention compared to symptoms of hyperactivity/impulsivity (e.g., Traver, et al., 2014). Thus, academic difficulties are perhaps not primarily caused by the inability to remain seated in the classroom, but by the failure to concentrate. With regard to the neuropsychological deficits that might explain the link between ADHD and poor academic achievement, previous studies have seldom taken the neuropsychological heterogeneity of ADHD into account, but have instead focused on deficits in executive functioning. For example, an influential study by Biederman and colleagues (2004) compared ADHD children with and without executive dysfunctions and found that those with executive dysfunctions performed worse (Biederman et al., 2004). However, this was not found in a study with a similar design (Lambek et al., 2010). In studies using dimensional measures of executive functioning, effects on academic performance have been found also when controlling for ADHD symptoms (Barry, Lyman, & Klinger, 2002; Diamantopoulou, Rydell, Thorell, & Bohlin, 2007; Miller & Hinshaw, 2010; Miller, Nevado-Montenegro, & Hinshaw, 2012; Rogers, Hwang, Toplak, Weiss, & Tannock, 2011). Other possible predictors explaining why some children with ADHD perform poorly in school have not been thoroughly examined, although non-clinical studies indicate that motivationally based functions, such as delay aversion, do not contribute to the prediction of academic achievement over and above executive deficits (e.g., Brock, Rimm-Kaufman, Nathanson, & Grimm, 2009; Thorell, 2007).

Another way to study the role of neuropsychological functions in the relation between ADHD and functional impairments is to conduct mediation analyses. The strength of this analytical approach is that it clarifies to what extent deficits can explain the relation between ADHD and functional impairments such as poor academic achievement. This is arguably important when designing interventions for children with ADHD who underachieve in the academic setting. If, for example, executive functioning can account for the entire relation between ADHD and academic achievement, this would of course suggest that interventions should target such deficits. However, if executive functioning only partially explains this relation, there is a need for interventions to target additional deficits. When conducting mediation analyses, previous

research has found that executive functioning partially mediated the relation between inattention and both language skills and mathematics in a non-clinical preschool sample (Thorell, 2007). This needs to be studied in a clinical sample and moreover with a larger number of possible mediators, as executive functioning could only partially explain the relation between ADHD and academic achievement.

1.3.2 Peer relations

Peer relations is another domain in which many children with ADHD experience problems. More specifically, previous research has shown that children with ADHD are more often rejected both by children they know well and by children they have just met (e.g., review by McQuade & Hoza, 2008). Children with ADHD are often unaware that they behave differently compared to others, and that they are thought of as more aggressive, interfering and non-compliant. Of the studies that have investigated the role of neuropsychological functioning in relation to peer relations and ADHD, the majority have found that executive deficits are not related to more general measures of social functioning when the effect of ADHD symptoms is taken into account (Biederman et al., 2004; Diamantopoulou et al., 2007; Huang- Pollock, Mikami, Pfiffner, & McBurnett, 2009; Scholtens, Diamantopoulou, Tillman, & Rydell, 2012). Very few studies have investigated whether delay aversion and reaction time variability are related to peer problems when controlling for ADHD. One exception is the study by Scholtens and colleagues (2012), which found that reaction time variability was related to social acceptance, but not when symptoms of ADHD were controlled for. Clearly, then, there is a need to search for factors besides executive deficits and reaction time variability that can explain the link between ADHD and peer problems. In non-clinical studies, both emotion regulation and emotion recognition have been shown to be related to social abilities (e.g., Eisenberg, Hofer, & Vaughan, 2007; Mostow, Izard, Fine, & Trentacosta, 2002). Few studies of clinical ADHD samples have addressed this issue. However, Anastopoulos and colleagues (2011) demonstrated that emotional lability partially mediated the relation between ADHD and social skills, and Kats-Gold and colleagues (2007) found that emotion recognition difficulties were associated with social skills in children with ADHD.

1.4 CRITICAL ISSUES

1.4.1 ADHD and neuropsychological functioning

1.4.1.1 ADHD as a neuropsychologically heterogeneous disorder

There is need to evaluate the role of neuropsychological functioning in ADHD. As mentioned above, ADHD has been described as a heterogeneous disorder involving multiple neuropsychological deficits. However, there are very few studies available that have investigated

several different neuropsychological deficits within the same study. Such analyses are necessary if we are to draw conclusions about how much of the variance in ADHD symptoms these variables can explain together and about which deficits are related to ADHD independent of other neuropsychological deficits. Instead of investigating the overlap between different functions, most studies in the area of the ADHD research have investigated group differences between children diagnosed with ADHD and controls, focusing only on one variable at a time. Such group differences have generally generated moderate effect sizes, indicating that each deficit is present only among a subset of children with ADHD (Nigg et al., 2005).

In order to further clarify the impact of neuropsychological functioning in relation to ADHD, it has been suggested that it may be useful to classify children as impaired or unimpaired with regard to different neuropsychological functions. Nigg and colleagues (2005) conducted this type of analyses by defining a deficit as performing more poorly than 10% of the children in the control group. Thus, 10% of the controls were defined as having a deficit on each neuropsychological test, and this percentage was thereafter compared with the corresponding percentage in the ADHD group. Exactly where such a cut-off should be drawn is not the major issue (although this should be considered an important question to address in future studies). The purpose is to complement group differences with person-oriented analyses and thereby illustrate roughly how common neuropsychological deficits are among children with ADHD and to what extent the different deficits overlap with one another. Nigg and colleagues (2005) found that, when examining individual measures of either executive functioning or delay aversion, only between 30-50% of children with ADHD were classified as having a deficit. Nor did the combination of executive functioning deficits and delay aversion succeed in accounting for all cases of ADHD. Still, about 40% of individuals with ADHD showed no deficits with regard to either one of these two functions. However, it is important to emphasize that, in line with the dual pathway model (Sonuga-Barke, 2002, 2003), these two pathways are able to classify cases independently, meaning that some children were only impaired with regard to either executive functioning or delay aversion (Nigg et al., 2005).

Regarding the overlap between different deficits and using the same approach as used by Nigg and colleagues (2005), one non-clinical study included executive functioning, delay aversion and reaction time variability and found that about 70% were impaired with regard to at least one of these deficits (Wåhlstedt et al., 2009). These results need to be corroborated in a clinical study. Another interesting finding from the study by Wåhlstedt and colleagues (2009) is that about 30% of the cases showed no deficits, which indicates that more neuropsychological functions need to be included in order to more fully account for the neuropsychological deficits in ADHD. As suggested above (Shaw et al., 2014), emotional functioning could be yet another pathway to ADHD. Thus, it will be important for future research to investigate to what extent emotional deficits can explain the ADHD cases that are unaccounted for by executive functioning, delay aversion or reaction time variability. This is therefore one of the aims of the present thesis.

1.4.1.2 Early appearing neuropsychological deficits and their relation to future ADHD

Another critical issue in previous studies examining the link between neuropsychological functioning and ADHD is that the majority of studies have investigated concurrent relations in school-aged children. Thus, there is a need for preschool studies, especially longitudinal studies in which early onset ADHD symptoms can be investigated alongside neuropsychological deficits in relation to later ADHD symptoms. With regard to the longitudinal studies that do exist, few have investigated multiple aspects of neuropsychological functioning. Furthermore, follow-ups were conducted within relatively short time spans and, as a consequence, we do not know the long-term relevance of early neuropsychological deficits. Importantly, only a few of the longitudinal studies have taken the role of early ADHD symptom levels into account. It has been argued that preschool neuropsychological deficits may simply be a proxy of early ADHD symptom levels if they cannot explain some of the variance in the outcome variable, over and above ADHD severity at baseline (van Lieshout, Luman, Buitelaar, Rommelse, & Oosterlaan, 2013). However, if effects of neuropsychological functioning still remain when controlling for early ADHD symptoms, this would indicate that these deficits are of importance for the development of ADHD.

1.4.1.3 Emotional functioning in ADHD

As mentioned above, there is a need to investigate whether emotional functioning constitutes a pathway to ADHD that is independent of other neuropsychological deficits. In such an investigation, one critical issue will be to more clearly define what specific aspects of emotional functioning are of most importance for the disorder. Relatively general measures, including both emotion regulation and how often and how intensely the child reacts emotionally (i.e., emotional reactivity), have often been used. Separating these two constructs is difficult. However, a child with few emotional reactions may display poor regulation and a child with intense emotions may be a relatively good regulator. Therefore, distinguishing between these two constructs could lead to a more precise understanding of which aspects of emotional functioning are related to behavior problems in children (e.g., Cole et al., 2004 for a review). Moreover, it will also be important to investigate emotional functioning with regard to different emotions, as basic emotions such as anger, fear, happiness/exuberance, and sadness may be differently related to ADHD and other outcomes.

A final issue of importance when evaluating the role of emotion regulation in ADHD will be to take ODD and CD into consideration (e.g., Martel, 2009), as these diagnoses often co-occur with ADHD (e.g., Waschbusch, 2002). This might be of particularly great importance when investigating emotion regulation deficits, as some of the rating scales used in previous studies include items that overlap with symptoms of ODD and/ or CD (e.g., temper outbursts). Thus, there is a risk of conflating emotion regulation with ODD/CD. Therefore, there is a need to 1) measure emotion regulation using scales that are separable from ODD/CD and 2) evaluate whether possible associations between emotion regulation and ADHD are explained by comorbid symptoms of ODD/CD.

1.4.2 ADHD, neuropsychological deficits and functional impairments

At a neuropsychological level, ADHD has been described as a heterogeneous disorder. However, it is not known to what extent the neuropsychological heterogeneity of ADHD can explain why some manage relatively well in daily life, whereas others go on to develop functional impairments. An important step in evaluating the usefulness of identifying neuropsychological deficits in individuals with ADHD is to investigate how such deficits relate to secondary outcomes of the disorder.

As mentioned above, most previous studies examining the link between ADHD and academic achievement have not taken the neuropsychological heterogeneity of ADHD into account, but have instead focused largely on executive functioning. Moreover, such studies have predominantly analyzed executive functioning as a global measure, limiting possible insights into how deficits in, for example, working memory and inhibition may be differentially related to functional impairments. Finally, few previous studies have investigated the link between ADHD, neuropsychological deficits and functional impairments using a longitudinal design.

Regarding the relation between ADHD, neuropsychological deficits, and peer problems, almost all previous studies have used broad measures of social functioning and/or composite executive functioning measures. As for academic achievement, there is a need to investigate independent effects of different executive functions in relation to specific aspects of social functioning, such as peer problems. When lumping variables together, one runs the risk of not acknowledging potentially important differences between different neuropsychological deficits regarding their link to outcomes. In addition, the limited ability of executive functioning to explain the link between ADHD and peer problems indicates that additional neuropsychological deficits have to be taken into account. In particular, there is a need to include various aspects of emotional functioning (Anastopoulos et al., 2011; Kats-Gold et al., 2007). Importantly, no previous study has investigated the effect of multiple mediators simultaneously. Thus, it is not known to what extent different neuropsychological mediators overlap in explaining the link between ADHD and peer problems. In addition, the mediating effects of different types of emotions (i.e., anger, fear, sadness, and happiness) on peer problems have not been investigated.

1.5 AIMS OF THE THESIS

The overall aim of this thesis is to investigate the role of neuropsychological deficits in ADHD and the extent to which neuropsychological deficits can explain the functional impairments associated with ADHD. More specifically, the questions addressed in the thesis were as follows:

- Do different neuropsychological deficits (executive functioning, delay aversion and reaction time variability) show independent effects in relation to ADHD, and do deficits in emotional functioning constitute yet another dissociable neuropsychological deficit in ADHD?
- Is ADHD a neuropsychologically heterogeneous disorder in preschool?
- To what extent are deficits in executive functioning, delay aversion, reaction time variability, and emotional functioning associated with two of the most important aspects of daily functioning in middle childhood: academic achievement and peer problems?
- Do neuropsychological deficits in preschool predict ADHD and academic achievement in late adolescence (age 18)?

2 SUMMARY OF EMPIRICAL STUDIES

2.1 STUDY I

Multiple deficits in ADHD: executive dysfunction, delay aversion, reaction time variability, and emotional deficits

2.1.1 Aims and background

Recent studies of ADHD have emphasized the neuropsychological heterogeneity of the disorder (Castellanos et al., 2006; Nigg et al., 2005). Despite this, there is a shortage of studies that have investigated independent effects of neuropsychological functions in an attempt to understand the extent to which different neuropsychological deficits overlap among children with ADHD. The aim of this study was therefore to investigate the possible independent effects of a range of different neuropsychological deficits (executive functions, delay aversion, reaction time variability) in ADHD. Importantly, we also investigated whether deficits in emotional functioning could explain independent effects in ADHD beyond the more established neuropsychological functions mentioned above. Finally, we explored possible gender differences, as most previous studies have failed to investigate this issue. Multiple analytic approaches were used. In addition to studying independent effects in a logistic regression, children were categorized as ‘‘impaired’’ versus ‘‘unimpaired’’ with regard to neuropsychological and emotional functioning to illustrate the overlap between these deficits using Venn diagrams (see Statistical Analyses in the full length article for a more detailed description).

2.1.2 Method

2.1.2.1 Participants

This study included 102 children (56 girls) aged 7– 13 years and diagnosed with ADHD, and a control group of 102 children individually matched to the clinical group with regard to gender and age (± 6 months). All children had been formally diagnosed with ADHD by a psychiatrist, and the children’s diagnostic status was also confirmed at the time of the study using the ADHD Rating Scale IV (DuPaul, Power, Anastopoulos, & Reid, 1998), which includes the 18 symptoms of ADHD as presented in DSM-IV (American Psychological Association [APA], 1994). In line with DSM-IV criteria, we also used the impact supplement from the Strength and Difficulties Questionnaire (SDQ; Goodman, 1997) to confirm that the symptoms had been present before age 7, for at least 6 months, and that impairment was found in multiple settings.

The control group was recruited by contacting schools in the Stockholm-Uppsala area in Sweden. Schools were chosen so that families of different socio-economic status would be

represented. The exclusion criteria for the control group were: (a) severe psychiatric or somatic problems as reported by parents and (b) scores above the 75th percentile on either the inattention or the hyperactivity subscale of the ADHD Rating Scale IV (DuPaul et al., 1998) as measured by teachers or parents. Controls and children with ADHD did not differ significantly with regard to parental education, both $\chi 2 \leq .61$, ns, parental age, both ts ≤ 1.64, ns, number of siblings, $t = .47$, ns, nonverbal intelligence, $t = 1.37$, ns, and birth country of the parents or the child, all $\chi 2 \leq 2.49$, ns.

2.1.2.2 Procedure and measures

The tests were chosen based on previous research identifying three major aspects of executive functioning: working memory, inhibition, and shifting (e.g., Miyake et al., 2000; Willcutt et al., 2001). All measures were standardized and some measures were reversed so that high values always indicated poor performance.

Working memory was measured using three tasks: one spatial and two verbal. Spatial working memory was measured using the 'Find the phone task,' which is similar in design to the spatial working memory task included in the Cambridge Neuropsychological Test Automated Battery (CANTAB; Owens, Downes, Sahakian, Polkey, & Robbins, 1990). In our version, telephones were shown on the computer screen and the task was to remember which telephone had already rung and to avoid selecting that phone several times. The number of times the children returned to a phone that had already rung was used as a measure of working memory deficits. The Children's Size-Ordering Task (McInerney, Hrabok, & Kerns, 2005) measured verbal working memory. The test administrator read a list of well-known nouns (e.g., pencil, mountain, train) to the participant, and the task was to remember the words and then organize them in order of size of the named object (from small to large). The number of word pairs that the child produced in the correct order was used to measure working memory. Verbal working memory was also measured using the total score for the backward condition of the digit span subtest (Wechsler, 1991). Individual scores were standardized and aggregated into one composite score (rs = .34– .50, $p < .001$).

Inhibition was measured using two tasks. The first task was the go/no-go task developed by Berlin and Bohlin (2002). Inhibition was measured as commission errors (i.e., pushing the button when a no-go target was displayed). The second task was a Navon-like task used by, for example, Miyake and colleagues (2000). A circle consisting of small squares, or the opposite, a square consisting of small circles, was displayed on the computer screen. In one session, the participants were asked to respond to the local stimuli (e.g., the small squares making up the circle) and in the other session they were asked to respond to the global stimuli (e.g., the circle made up by the squares). These two sessions were randomized and the child responded to the stimuli by pressing a key to the left (circle) or right (square) on the computer keyboard. In each session, 20 objects (10 squares and 10 circles) were shown. The objects were displayed for 500 ms and the participant had 3,500 ms to give an answer. The score used was number of errors during each session. Individual scores were standardized and aggregated into one composite score (rs = .26– .33, $p < .001$).

Shifting was measured using the Navon-like task (see description above). A third trial was performed in which participants had to shift between responding to the local or the global stimuli. A square and a circle in the lower corners of the computer screen indicated what stimulus to respond to (local trials = small circle/square, global trials = large circle/square). In line with recommendations by Davidson, Amso, Anderson, and Diamond (2006), number of errors was used to measure shifting. Two children in the ADHD group had missing data due to failure to understand the instructions.

Delay aversion was measured using the Choice Delay Task (Sonuga-Barke et al., 1992). Participants chose between an immediate small reward (2 s for one point) and a delayed large reward (30 s for 2 points). Delay aversion was measured as the number of times participants chose the small, immediate reward during the final 10 trials.

Reaction time variability was measured as the standard deviation of participants' reaction time for correct answers on the two nonshifting trials in the Navon-like task and correct answers on the go/no-go task (see descriptions above). Individual scores were standardized and aggregated into one composite score (r = .36– .65, p < .001).

Emotion regulation was measured through parental ratings using the Emotion Questionnaire developed by Rydell and colleagues (2003). It includes statements related to regulation of anger, fear, sadness, and happiness/exuberance. For each emotion, one general statement is presented (e.g., If sad, my child has trouble calming down by him-/herself) and two statements regarding regulation in specific situations (e.g., If my child has fallen and hurt him-/herself, my child has trouble calming down by him-/herself). Ratings are made on a scale ranging from 1 (do not agree at all) to 5 (fully agree), with higher values indicating greater problems with emotion regulation.

Emotion recognition was measured using facial images selected from the NimStim Set of Facial Expressions (672 images; http://www.macbrain.org/ resources.htm), which consists of naturally posed photographs (e.g., with hair, make-up) of 43 professional actors (25 male; 21 to 30-years-old). In this study, the children were shown 36 faces displaying six different emotions: anger, fear, sadness, happiness, surprise, and disgust. The score used was number of correct responses (maximum score = 6).

Control variables. Conduct problems and internalizing problem behaviors were measured using the mean of parent and teacher ratings on the SDQ (Goodman, 1997). IQ was measured using the block design subtest from the WISC-III (Wechsler, 1991), which has been shown to correlate highly with full-scale IQ (r = .93; Groth-Marnat, 1997). The results are first reported without controlling for these variables, and the analyses were thereafter rerun to examine whether the pattern of results would hold after control for comorbid problems and intelligence.

2.1.3 Results

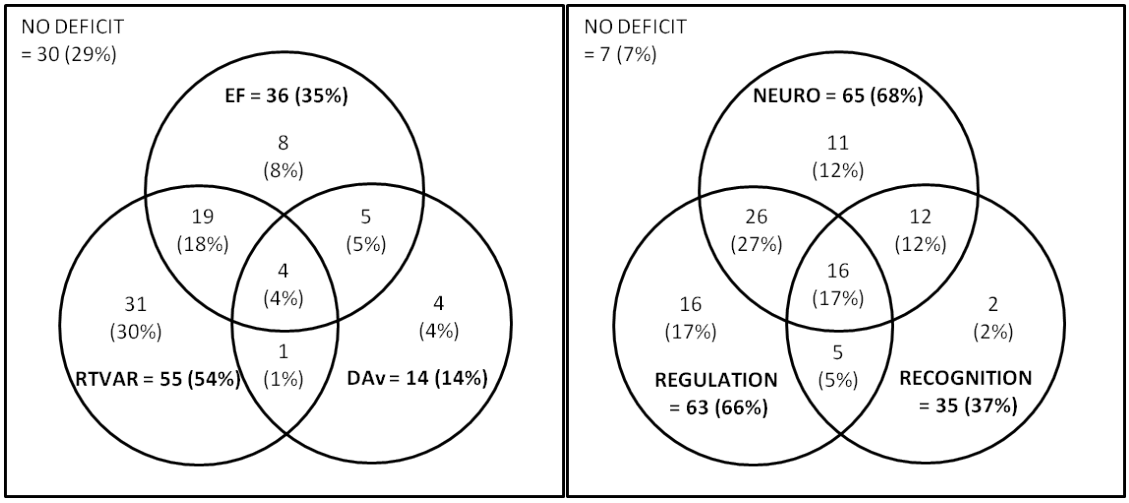
First, group differences were studied to determine what measures discriminated between children with ADHD and controls. The children with ADHD performed more poorly than controls did with regard to all neuropsychological functions, all *f*s ≥ 10.85, all *p*s < .001, except delay aversion and recognition of disgust, both *f*s ≤ 1.61. No main effects of gender and no significant interactions of group and gender were found, all *f*s ≤ 3.42. All group differences remained significant when controlling for multiple comparisons (i.e., Bonferroni). In addition, all group differences remained significant when controlling for either IQ, conduct problems, or internalizing problems, except for recognition of sadness, which did not remain significant when controlling for internalizing problems.

Next, a logistic regression analysis was performed to determine what deficits showed independent effects in relation to ADHD. Only variables for which a significant group difference had been found were included in this analysis. In the first step, there was a significant effect of reaction time variability, Wald = 27.09, $p < .001$, and a near significant effect of inhibition. In the second step, there were significant effects of anger recognition, Wald = 6.08, $p < .05$, regulation of anger, Wald = 19.60, $p < .001$, and regulation of happiness, Wald = 4.49, $p < .05$. The model successfully predicted 64.9% of the ADHD cases (i.e., sensitivity) and 84.3% of the controls (i.e., specificity) after the first step and 91.5% of the ADHD cases and 87.3% of the controls after the second step.

Thereafter, categorical analyses were conducted by defining impairment as performing more poorly than the 90th percentile of the children in the control group. Reaction time variability and anger regulation were the most common impairments. Chi-square analyses showed that the results were roughly the same as in the ANCOVAs (except for recognition of fear), with 'impairment' being significantly more common among children with ADHD than among controls for all variables except delay aversion and recognition of disgust; all significant $\chi 2 > 18.97$, $p < .001$, and with no significant gender differences being found (all $\chi 2 < 2.93$).

Figure 1(A) presents a Venn diagram showing the overlap between different types of neuropsychological impairment. To simplify the presentation of this categorical data, a mean value was computed for executive functioning. The results showed that 71% of children with ADHD were shown to have at least one type of neuropsychological impairment: executive functioning (35%), reaction time variability (54%), and delay aversion (14%). Only four children were shown to have impairments in delay aversion that did not overlap with impairment in the other two domains. Among the remaining 68 children with impairment in either reaction time variability or executive functioning, there was a substantial overlap (23 children having deficits in both these functions), but also subgroups with impairment in either executive functioning (13 children) or reaction time variability (32 children). Among the controls, 26% had at least one neuropsychological deficit.

A B



EF = Executive functioning (i.e., working memory, inhibition, shifting), RTVAR = Reaction time variability, DAv = Delay aversion, NEURO = Neuropsychological functioning, REGULATION = Emotion regulation, RECOGNITION = Emotion recognition

Figure 1 Proportion of ADHD cases with neuropsychological impairments (A) or impairments in neuropsychological and emotional functioning (B)

Next, we investigated the overlap between impairments in neuropsychological and emotional functioning (see Figure 1B). To be classified as impaired in neuropsychological functioning, the children had to be impaired with regard to at least one neuropsychological function (i.e., executive functioning, delay aversion or reaction time variability). For emotion recognition and emotion regulation, we computed two mean values. As with the other measures, impairment was thereafter defined as performing more poorly than the 90th percentile of the children in the control group. The results showed that only 7% of the children with ADHD, but 61% of the controls, were not impaired in any domain. Among the children with ADHD, 12% were impaired only in neuropsychological functioning, 24% were impaired only in emotional functioning, and 57% had impairments in both domains. Only two children had impairment in emotion recognition that did not overlap with impairment in either neuropsychological functioning or emotion regulation. Among the children in the control group, 21% were impaired only in neuropsychological functioning, 13% were impaired only in emotional functioning, and only 6% had impairments in both domains.

2.1.4 Conclusions

In line with current studies suggesting that ADHD is a heterogeneous disorder (e.g., Castellanos et al., 2006; Nigg et al., 2005), this study aimed to explore independent effects of a large number of candidate neuropsychological deficits in ADHD and to investigate whether deficits in emotional functioning might constitute yet another dissociable component of ADHD. Except for delay aversion and recognition of disgust, the results showed that children with ADHD performed more poorly than controls did on all variables. For the more

established neuropsychological variables, independent effects were only seen for reaction time variability and inhibition. Interestingly, both emotion regulation and emotion recognition showed independent effects over and above the influence of neuropsychological deficits and improved our ability to successfully distinguish between ADHD cases and controls. No significant gender differences were found.

In conclusion, this study has taken one important further step in trying to provide a more refined conceptual integration of the different neuropsychological and emotional impairments associated with ADHD. Of relevance to both theoretical development and clinical practice, our results emphasized the need to include not only executive functioning but also reaction time variability and emotional functioning.

2.2 STUDY II

Neuropsychological heterogeneity in preschool ADHD: Investigating the interplay between cognitive, affective and motivation-based forms of regulation

2.2.1 Aims and background

ADHD is often diagnosed in middle childhood, but it is becoming increasingly common to diagnose children prior to school entry (see Egger, Kondo, & Angold, 2006 for a review). One reason for earlier diagnosis may be research findings showing that preschool ADHD is a serious condition that is linked to severe negative outcomes both concurrently and longitudinally (e.g., Sonuga-Barke, Thompson, Abikoff, Klein, & Brotman, 2006). Besides taking early ADHD symptoms into account, it is important that we gain more knowledge about the possible neuropsychological underpinnings of the disorder. By doing so, we could become better able to identify children at risk and, moreover, such deficits could also be informative when it comes to predicting what functional impairments will follow. Despite this, there is a lack of studies investigating ADHD in the preschool years, at least studies including a large range of different neuropsychological functions. Cognitive, affective, and motivation-based forms of regulation have been shown to be linked to ADHD in previous research on school-aged children (Nigg et al., 2005; Shaw et al., 2014). However, independent and interactive effects between these three forms of self-regulation in relation to preschool ADHD have not been investigated, and this was therefore the aim of the present study.

2.2.2 Method

The present study included 104 preschool children (36 girls) between 4-6 years of age. In order to obtain a sample of children scoring across the full range of ADHD symptom severity, about 1/3 of the sample was clinically referred. These children had been formally diagnosed with ADHD by a psychiatrist, and the children's diagnostic status was confirmed at the time of the study using both parent and teacher ratings on the ADHD Rating Scale IV (DuPaul et al., 1998). The remaining 2/3 of the sample were typically developing children recruited through local preschools. No exclusion criterion with regard to ADHD symptoms was used for these children, and some children were rated by teachers as having a relatively large number of ADHD symptoms. The total sample is therefore best characterized as spanning the full range of ADHD symptom severity rather than as two discrete groups (i.e., skewness = 0.53 and kurtosis = - 0.76 for inattention; skewness = 0.75 and kurtosis = - 0.56 for hyperactivity/impulsivity, which indicates normality (Kline, 1998).

The present study included cognitive (inhibition, working memory, shifting, reaction time variability, sustained attention), affective (regulation with regard to anger, fear, sadness, happiness/exuberance), and motivation-based (delay aversion) forms of regulation. For a

more detailed description of each respective measure, see the method section for Study I above (page 18-19). In addition to including the same measures as used in Study I, the present study also included a measure of sustained attention as an additional cognitive measure. To measure sustained attention, we used number of omissions (i.e., failure to respond to a go stimulus) on the go/no-go task (the same task as for inhibition).

In line with the reasoning that ADHD is better captured as a continuous trait rather than as two discrete categories (e.g., Marcus & Barry, 2011; Sonuga-Barke & Halperin, 2010), and because our sample was normally distributed with regard to ADHD symptoms, the data were analyzed using a dimensional approach. ADHD symptoms were rated on a 4-point scale: never or rarely (0), sometimes (1), often (2), or very often (3) with regard to the 18 symptoms of ADHD as presented in DSM-IV (APA, 1994). The mean scores for symptoms of inattention and hyperactivity/impulsivity were used in the analyses. Teacher ratings were used to assess ADHD symptoms, as parents assessed emotion regulation and we wanted to avoid source bias. Reliability, measured by consistency, was found to be very high for both symptoms of inattention ($\alpha = 0.93$) and symptoms of hyperactivity/impulsivity ($\alpha = 0.96$).

Regarding covariates, age and sex were included in all analyses, as they were significantly related to several of the predictors, as well as the outcome variables. We also analyzed the data while controlling for conduct problems (see cursive number in Table 1). Conduct problems were measured using teacher ratings on the SDQ (Goodman, 1997). Furthermore, as with conduct problems, we re-ran analyses while controlling for intelligence. Intelligence was measured using the block design subtest from the WISC-III (Wechsler, 1991). This was done to allow the reader to make his/her own interpretation of the results (e.g., Barkley, 1997).

2.2.3 Results

First, we investigated interrelations between the different forms of regulation that were included in the study. Correlations between the different forms of regulation were overall very weak, all rs $\leq .25$, indicating that they did not overlap to such a large extent.

2.2.3.1 Correlations Between Regulation and ADHD Symptoms

Second, we wanted to investigate how the different forms of regulation were related to ADHD symptoms (see Table 1). All measures of cognitive regulation except for shifting, as well as delay aversion, were significantly related to symptoms of inattention. However, only inhibition and working memory were significantly related to hyperactivity/impulsivity. In addition, all measures of emotion regulation except for regulation of sadness were associated with both inattention and hyperactivity/impulsivity. All significant effects remained when controlling for IQ.

Table 1 *Cognitive, affective and motivation-based regulation in relation to symptoms of inattention or hyperactivity/impulsivity (one-tailed)*

	Inattention	Hyperactivity/impulsivity
Cognitive regulation deficits		
Inhibition	.258**	*.241**
Working memory	.428***	.363***
Shifting	.055	.136
Sustained attention	.268**	.083
Reaction time variability	.292**	.152
Motivation-based regulation deficits		
Delay version	.261**	.092
Affective regulation deficits		
Anger	.417***	*.389****
Sadness	.166	.191
Fear	.334***	*.325****
Happiness/exuberance	.417***	.424***

* $p < .05$, ** $p < .01$, *** $p < .01$. Numbers in italics indicate relations that changed to non-significance when controlling for symptoms of ODD

Moreover, we wanted to investigate whether any of the measures of regulation were related to ADHD symptoms mainly due to the large overlap between ADHD symptoms and conduct problems. The results showed that most of the relations remained the same as those presented in Table 1. The exceptions were that there were no effects of inhibition, regulation of fear, or regulation of anger on symptoms of hyperactivity (see numbers in italics in Table 1).

2.2.3.2 Independent Effects

Third, we examined to what extent measures of affective regulation could contribute significantly to the explained variance in ADHD symptoms over and above the influence of the other forms of regulation. Using hierarchical regression analyses, we entered the two covariates (i.e., age and sex) in Step 1, and all variables that were significantly correlated with the two ADHD dimensions (except emotion regulation) in Step 2. In Step 3, all significant emotion regulation variables were included. As shown in Table 2, the variables entered in Step 2 were significantly associated with inattention. Altogether, they explained 26% of the variance, with both working memory and delay aversion contributing independently. Adding the emotional regulation variables in Step 3 increased the explained variance to 37%, and only regulation of happiness/exuberance contributed independently. For symptoms of hyperactivity/impulsivity, 14% of the variance was explained by the variables entered in Step 2, with an independent contribution only for working memory. Emotion regulation increased the explained variance to 25%, with none of the variables contributing independently except for a trend toward a significant effect for regulation of happiness/ exuberance.

Table 2 *Regression analyses examining predictors of ADHD symptoms*

	ß	R^2 change
Inattentive symptoms		
Step 1		.061*
Sex	- .143	
Age	- .192^{+}	
Step 2		.258***
Inhibition	.149	
Working memory	.346**	
Sustained attention	.042	
Reaction time variability	.164	
Delay version	.187*	
Step 3		.111***
Anger	.139	
Fear	.045	
Happiness/exuberance	.248*	
Hyperactive/impulsive symptoms		
Step 1		.107**
Sex	- .176^{+}	
Age	- .263**	
Step 2		.144***
Inhibition	.179^{+}	
Working memory	.365***	
Step 3		.111**
Anger	.140	
Fear	.043	
Happiness/exuberance	.232^{+}	

$^{+}$ < 0.10, * p < .05; **p < .01; *** p < .001

2.2.3.3 Interaction Effects

Fourth, we investigated whether there were any significant interactions between cognitive, affective and motivation-based regulation. A significant interaction effect would indicate that the different neuropsychological deficits combine synergistically (i.e., that the combination of two deficits has an effect on ADHD symptoms that is larger than the sum of its two parts). Of all possible interactions, only the effect of reaction time variability and regulation of happiness/exuberance in relation to inattention reached significance (β = - 0.21, p < 0.05). However, it should be noted that this could have been a chance finding due to the very large number of interactions investigated (i.e., 58 interactions altogether).

2.2.4 Conclusions

The present study investigated neuropsychological heterogeneity in preschool ADHD by studying cognitive, affective, as well as motivation-based forms of regulation. Results showed that these regulatory processes were all independently associated with ADHD

symptoms. Both executive functioning and delay aversion were shown to have independent effects in relation to symptoms of inattention, and we found no significant interaction effects of executive functioning and delay aversion in relation to ADHD symptoms. This can be taken as further support for the dual-pathway model of ADHD, in which it is stated that these two processes should be regarded as constituting two separate pathways to ADHD (cf. Sonuga-Barke, 2002). Importantly, most previous preschool studies have only included cognitive regulation, and to some extent motivation-based regulation. By also including affective regulation, we were able to explain a larger proportion of the variance in ADHD symptoms. However, it should be noted that the amount of variance explained was still small in comparison with what has been found in studies of school-aged children.

2.3 STUDY III

Functional impairments in Attention Deficit Hyperactivity Disorder: the mediating role of neuropsychological functioning

2.3.1 Aims and background

In addition to the three major symptoms of the disorder, children diagnosed with ADHD often face problems in daily life, such as poor academic achievement (e.g., Daley & Birchwood, 2009; Loe & Feldman, 2007) and problematic peer relations (e.g., Hoza, 2007, and McQuade & Hoza, 2008 for reviews). At the neuropsychological level, ADHD has been described as a heterogeneous disorder (e.g., Nigg et al., 2005) that involves deficits in multiple functions such as executive functions (Barkley, 1997), delay aversion (e.g., Sonuga-Barke, 2002), reaction time variability (e.g., Castellanos et al., 2005), and emotional functioning (e.g., Martel, 2009; Sjöwall, Roth, Lindqvist, & Thorell, 2013). However, it is not known to what extent this neuropsychological heterogeneity can explain why some individuals with ADHD develop functional impairments, whereas others manage relatively well in daily life.

The aim of the present study was therefore to investigate a large range of neuropsychological deficits as possible mediators in the relation between ADHD and two of the most central aspects of daily functioning in childhood: academic achievement and peer problems. In order to address the limitations of previous research, we conducted full mediation analyses using a statistical method that allowed us to investigate the independent contributions of different neuropsychological deficits. As most previous studies have failed to investigate the moderating effects of gender and ODD/CD, we also explored this issue.

2.3.2 Method

The measures used in the present study were the same as in Study I: inhibition, working memory, shifting, reaction time variability, delay aversion, regulation with regard to anger, fear, sadness, happiness/exuberance, recognition of anger, fear, sadness, happiness, surprise, and disgust. For a more detailed description of each respective measure as well as sample characteristics, please see the method summary in Study I. Below a description is given of the measures and analytic procedures that were unique to this study.

The outcome variables in the present study were peer problems and academic achievement. Peer problems were assessed using the "peer relationship subscale" from the SDQ (Goodman, 1997). The peer problems scale in the SDQ includes items such as "generally liked by other children" and "has at least one good friend," and it has been shown to be highly correlated with the corresponding scale in the Child Behavior Checklist (Goodman & Scott, 1999). Ratings were made on a scale from 1 to 5, and the mean scores for parent and teacher ratings ($r = .69$, $p < .001$) were used. The measure of academic achievement consisted

of two separate questions: “How do you rate the child’s school performance in relation to children in the same age for (a) mathematics (b) language skills?” Ratings were made on a scale from 1 to 5 (1 = “much below average”; 2 = “below average”; 3 = “average”; 4 = “above average”; 5 = “much above average”). Concerning the validity of such ratings, Henricsson and Rydell (2006) showed that teacher ratings of language skills and mathematics are very highly correlated with results on national tests in these two subjects (rs = .82, p < .001). Thus, this measure should be considered a valid measure of children’s school performance.

In line with principles of mediation analyses, the following three relations were examined before mediation analyses were conducted: (1) the relations between the independent variable (i.e., ADHD status) and each one of the potential mediators (i.e., neuropsychological deficits), (2) the relation between the independent and the dependent variable (i.e., functional impairments), and (3) the relation between the mediator and the dependent variables when controlling for the independent variable. The first two relations were investigated using independent t-tests. The third relation was investigated using partial correlations, with group status, age and sex as covariates. Control for multiple comparisons was carried out using the Holm-Bonferroni method, which is a sequentially rejective version of the simple Bonferroni correction (Holm, 1979).

Next, we tested for simple and multiple mediation using Preacher and Hayes’ (2008) bootstrapping methodology for indirect effects based on 5000 bootstrap resamples. This method describes the confidence intervals (CIs) of indirect effects such that no assumptions are made about the indirect effect being normally distributed. Interpretation of the bootstrap data is accomplished by determining whether zero is contained within the 95% CIs. This method has been argued to be superior to the commonly used Sobel test, as it has higher statistical power while maintaining adequate control over the Type I error rate (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). Age and sex were included as covariates. In line with previous studies (e.g., Anastopoulos et al., 2011; Huang-Pollock et al., 2009), the percentage of the total effect explained by each mediator (i.e., the standardized estimate for the indirect effect divided by the standardized estimate for the total effect) was calculated as a measure of effect size in the mediation analyses. Finally, possible moderating effects of gender and comorbid ODD/CD were investigated.

2.3.3 Results

Significant group differences were seen for all proposed mediators, all ts ≥ 3.24, all ps > .001 (except delay aversion and recognition of disgust, ts ≤ 1.18, ns). Significant group differences were also seen for all three outcome variables ts ≥ 7.08, all ps > .001. Effect sizes were medium to large (d = .45–1.75) for the significant mediators and large (d = 1.02–1.60) for the outcome variables. All significant effects remained after controlling for multiple testing.

Next, we investigated the relation between the mediators and the outcomes when controlling for ADHD status, sex, and age. Delay aversion and recognition of disgust were not included in these analyses, as group differences had not been found for these two variables. The results from these analyses can be seen in Table 3.

Table 3 *Partial correlations between mediators and functional impairments, controlling for group, gender and age (one-tailed)*

	Language skills	Mathematics	Peer problems
Neuropsychological functions			
Inhibition	**-.21****	-.18**	-.01
Working memory	**-.33*****	**-.41*****	.04
Shifting	**-.19****	**-.20****	.05
Reaction time variability	**-.26*****	**-.33*****	.02
Emotion regulation			
Regulation of sadness	*.02*	-.04	.13*
Regulation of fear	.04	.05	*.14**
Regulation of anger	.04	-.11	**.20****
Regulation of happiness	.08	.11	.14*
Emotion recognition			
Recognition of anger	**.18****	.03	-.14*
Recognition of fear	.12	-.02	.01
Recognition of happiness	.03	-.10	-.09
Recognition of sadness	.10	*.03*	-.01
Recognition of surprise	.13*	.11	-.07

* $p < .05$, ** $p < .01$, *** $p < .001$

Bold-faced numbers indicate relations that remained significant when controlling for multiple comparisons. Numbers in italics indicate where a significant interaction effect with gender was found.

Mediation was thereafter examined using the bootstrapping procedure presented by Preacher and Hayes (2008). These analyses show to what extent the neuropsychological predictors act at mediators in the relation between ADHD and the outcomes, without taking their possible overlap into account. Only variables for which the relation between the proposed mediator and the outcome was significant when controlling for ADHD status, and which survived control for multiple testing, were included in these analyses. Regarding language skills, simple mediation effects were found for all three executive functions as well as for reaction time variability and recognition of anger (see Table 4).

Table 4 *Results of simple mediation, including estimates, standard errors (SE) and confidence intervals (CI). The percentage of the total effect is also reported*

	Estimate	SE	Lower CI	Upper CI	Indirect effect %
LANGUAGE SKILLS					
Inhibition	-.0743	.0282	-.1382	-.0277*[a]	16
Working memory	-.1098	.0342	-.1862	-.0507*[a]	24
Shifting	-.0578	.0254	-.1199	-.0161*	13
Reaction time variability	-.1581	.0485	-.2594	-.0685*[a]	35
Recognition of anger	-.0712	.0314	-.1404	-.0173*[a]	16
MATHEMATICS					
Working memory	-.1289	.0360	-.2062	-.0674*[a]	28
Shifting	-.0600	.0244	-.1178	-.0207*	13
Reaction time variability	-.1903	.0439	-.2837	-.1102*[a]	41
PEER PROBLEMS					
Regulation of anger	.1357	.0515	.0377	.2455*[a]	22

* Significant mediator (i.e., zero is not contained within the confidence intervals)

[a] Indicate where a mediation is significant when controlling for IQ

Working memory, shifting and reaction time variability were significant mediators of mathematics, and regulation of anger was a significant mediator of peer problems. As also shown in Table 4, the significant mediators varied with regard to how much of the total effect they were able to explain. Finally, all simple mediation analyses were re-run while controlling for IQ. As shown in a footnote to Table 4, most of the mediation effects remained significant for the two measures of academic achievement, whereas regulation of anger remained significant for peer problems.

2.3.3.1 Multiple Mediation

Multiple mediation analyses were conducted to obtain estimates of the total indirect effect, as well as the independent contribution of each mediator (i.e., the effect of each mediator when controlling for the effect of the other significant mediators in the model). Multiple mediation analysis was not performed for peer problems, as only one significant mediator (i.e., regulation of anger) had been identified for this variable. For the relation between ADHD status and language skills (see Figure 2A), the mediators together explained 53% of the total effect (i.e., multiple $\beta = .24$ divided by the total effect $\beta = .45$), but only the effect of working memory was significant. For mathematics (Figure 2B), the mediators together explained 54% of the total effect (i.e., multiple $\beta = .25$ divided by the total effect $\beta = .46$). Both working memory and reaction time variability had significant independent effects. As can be seen in Figures 2A and 2B, the direct effect of ADHD status on the dependent variables remained significant for both language skills and mathematics, which means that only partial mediation was demonstrated. Partial mediation was also demonstrated for peer problems ($\beta = .63$, $p < .001$ for the direct path between ADHD and peer problems when the mediator was not included, and $\beta = .49$, $p < .001$ when the effect of regulation of anger was taken into account).

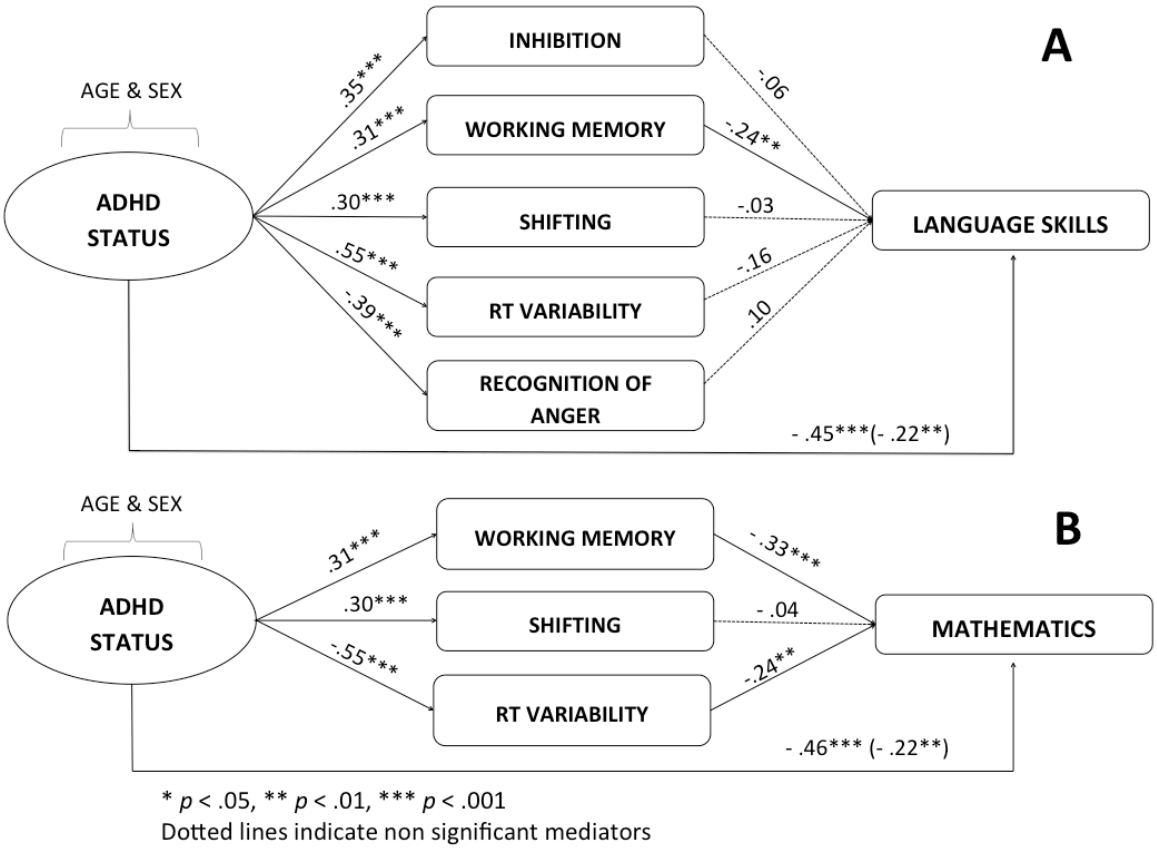


Figure 2 Multiple mediation models for the association between attention deficit hyperactivity disorder (ADHD) and academic achievement. Values on paths are standardized path coefficients (β). For the direct relation between ADHD and academic achievement, the value outside parentheses indicates the zero-order correlation, whereas the value inside parentheses indicates the partial correlation (i.e., the size of the direct effect when taking the effect of all mediators into account).

2.3.3.2 Gender Effects and Effects of Comorbid ODD/CD

Finally, two possible moderators were examined: gender and comorbid ODD/CD. With regard to gender, no significant main effects of gender and no significant interaction effects of ADHD status and gender were found for any of the neuropsychological variables. For the functional impairments, two significant main effects of gender were found. Girls had significantly lower scores than boys did in mathematics, and they were rated as having higher levels of peer problems, but no main effects of gender were found for language skills. No significant interaction effects of ADHD status and gender were found for any of the functional impairments, which indicates that the obtained gender differences were equally large among children with and without ADHD.

In order to determine whether the relation between the mediators and the outcomes were equally strong for boys and girls, we also examined interaction effects of gender and each one of the mediators (i.e., altogether 45 interaction effects, as the study involved 15 mediators and 3 outcomes). The results showed that only three interaction effects were significant (see numbers in italics in Table 3). When conducting separate mediation analyses for boys and

girls for these three relations, the results for both genders were similar to the results reported above for the whole sample. Thus, gender was not found to be a significant moderator in our mediation models.

Finally, we investigated ODD/CD as a potential moderator in the relation between emotional functioning and peer problems. The results showed that both ADHD subgroups (ADHD without ODD/CD and ADHD with ODD/CD) differed significantly from the control group with regard to peer problems and all measures of emotional functioning (all *f*s > 4.66, and *p*s < .05), except for recognition of disgust, for which none of the subgroups differed significantly from the controls (both *f*s < .74, ns). Second, no interaction effects of ODD/CD and emotional functioning on peer problems were noted (all *β*s < .14, ns). In conclusion, the relations between the different measures of emotional functioning and peer problems were equally strong in the two ADHD subgroups.

2.3.4 Conclusions

The overall aim of the present study was to investigate the role of neuropsychological functioning in explaining the link between ADHD and functional impairments associated with the disorder. The main findings were that it was primarily deficits in working memory and reaction time variability that mediated the relation between ADHD and academic achievement and that regulation of anger mediated the relation between ADHD and peer problems. The extent to which these variables acted as mediators between ADHD and the functional impairments was just over 50% for the academic measures and just over 20% for peer problems. These effects could be considered to be quite large and they should arguably be taken into both theoretical and clinical consideration. However, even though a large range of neuropsychological deficits was investigated as mediators, there is still a rather substantial amount of the relation between ADHD and the functional impairments that is still unaccounted for. Hence, targeting the neuropsychological deficits in ADHD is important, but it is likely that other factors need to be taken into consideration as well. Gender did not moderate these findings. Consequently, this means that the results of the present study are valid for both boys and girls with ADHD. Moreover, the fact that symptoms of ODD/CD did not moderate the results indicates that dysregulation of anger acts as a mediator, not just in the subgroup of children who have co-occurring ODD/CD, but also in ADHD more generally.

2.4 STUDY IV

Neuropsychological deficits in preschool as predictors of ADHD symptoms and academic achievement in late adolescence

2.4.1 Introduction/aims

The severe negative impact of ADHD, both in childhood and in adulthood (e.g., Barkley, 2006 for a review), underscores the importance of identifying early markers of the disorder. As interventions are more likely to be successful if implemented early (cf. Sonuga-Barke & Halperin, 2010), these predictors should be identified as early as possible. The major aim of the present study was therefore to investigate whether neuropsychological deficits in preschool are related to later ADHD symptoms, over and above the influence of preschool ADHD symptom levels. We also posed this question in relation to academic achievement, as we argue that it is important to study predictors not only of ADHD, but also of the functional impairments associated with the disorder. The present study included a broader range of predictors compared to previous studies, and the participants were followed for as long as 13 years (from preschool to 18 years of age).

2.4.2 Method

2.4.2.1 Participants

The present study included 128 children (49% boys) who were part of a longitudinal study investigating neuropsychological functioning in children from preschool until late adolescence. A national population-based register was used to recruit a random sample of 1000 children. From this sample, 705 parents filled out and returned a questionnaire, and a sub-sample of 151 children was selected to take part in the study (see Berlin & Bohlin, 2002, for detailed information on how this selection was made).

At the age of 5 and 6½ years, the sub-sample of 151 children were administered a number of different tasks (see detailed descriptions below), and ratings of emotional functioning were collected at the laboratory visit at age 6½. Teacher ratings of ADHD symptoms were collected at age 6. Finally, parent ratings of ADHD symptoms and academic achievement and self-ratings of academic achievement were collected at the age of 18. Only the 128 children (85% of the original sample) who participated at all three data collection points (i.e., at age 5, 6½ and 18 years) are included in the present study. No significant differences in neuropsychological functioning or ADHD symptoms at age 5-6 years were found between the 128 children who were included in the study and the 23 children who did not have complete data; all *t*s < .81.

2.4.2.2 Predictors

The neuropsychological measures were made at either age 5 (response inhibition and reaction time variability) or 6½ years (interference control, working memory and emotional functioning). For all neuropsychological measures, high values indicated poor functioning.

Response inhibition was measured using a go/no-go task developed by Berlin and Bohlin (2002). Altogether the task included 60 stimuli with a "go-rate" of 77%. Number of commission errors (i.e., responding to a "no-go stimulus") was used as a measure of poor inhibition. *Interference control* was measured using a Stroop-like task developed by Berlin and Bohlin (2002). Participants were presented with four pairs of pictures, where the pictures in each pair were each other's opposites (day–night, large–small, boy–girl, and up–down). After ensuring that the child understood what each picture represented, the child was instructed to say the opposite as fast as possible every time he or she saw a picture on the computer screen (e.g., to say "boy" every time a girl was presented). Each stimulus was presented during a time interval of 1500 ms (1000 ms for the second part of the task), followed by a response time of 1500 ms and a waiting period of 1500 ms before the next stimulus was presented. Number of errors on this task was used as a measure of interference control. *Working memory* was measured using the Kaufman Hand Movements Test (Kaufman & Kaufman, 1983), in which the child is presented with a sequence of hand movements and then asked to repeat the sequence. Altogether the child was presented with 17 different sequences of hand movements, ranging in length from 2 to 6 movements per sequence using 'fist,' 'palm,' and 'side.' The result was registered as number of errors, that is, how many times the child was unable to reproduce the sequence of hand movements correctly. *Reaction time variability* was measured using the standard deviations in reaction time on correct trials from the go/no-go task (see description above).

Emotional functioning was measured through parental ratings (95% mothers, 5% fathers) using the Emotion Questionnaire (see Rydell et al., 2003 for a complete version of the questionnaire). Most studies of emotion regulation have used ratings that include questions both on how often and intensely the child displays different emotions (i.e., emotional reactivity) and on how well he/she can regulate different emotions (i.e., emotion regulation). However, reactivity and regulation have been suggested to be two different aspects of temperament (see Cole et al., 2004 for a review). In support of this distinction, regulation and reactivity have been shown to be differentially related to behavioral and functional outcomes (e.g., Eisenberg et al., 1995; Melnick & Hinshaw, 2000; Thorell, Sjöwall, Diamantopoulou, Rydell, & Bohlin, 2014). In the present study, we therefore aimed to generate more in-depth knowledge in this area by using a rating instrument that allowed us to separate emotion regulation from emotional reactivity with regard to both anger and happiness/exuberance. The questionnaire also includes sadness and fear, although these two emotions were not included in the present study, as previous research has shown that it is primarily anger and happiness/exuberance that are related to ADHD symptoms (Sjöwall et al., 2013; Sjöwall, Backman & Thorell, in press). The items measuring emotional reactivity ask how often and intensely the child displays two different emotions (i.e., anger and happiness/exuberance).

For a more detailed description of emotion regulation, see the method section for Study I above (page 19).

ADHD symptoms during the preschool years were measured by teacher ratings using the abbreviated, 10-item version of the Conners Rating Scale (ATRS, Conners, 1990), sometimes referred to as the Conners ADHD Index. Factor analysis (Parker, Sitarenios, & Conners, 1999) has shown that the first 6 items of the scale tap hyperactivity/impulsivity and inattention (e.g., restless, impulsive, constantly moving around, failing to concentrate), whereas the last four items of the scale measure emotional lability (e.g., temper tantrums, cries easily). As it was important to not use a measure of ADHD symptoms that also included emotional functioning, the last four items were excluded from the scale. This resulted in a 6-item scale with an internal consistency, expressed as Cronbach's alpha, of .89. This scale has been shown to correspond very well with the symptom criteria for ADHD as they are presented in DSM-IV (APA, 1994) using teacher ratings from 135 8-year-old children (unpublished data).

2.4.2.3 Outcome variables and covariates

In order to measure *ADHD symptoms* in late adolescence, we used parent ratings on the ADHD Rating Scale IV (DuPaul, et al., 1998), which contains items directly corresponding to the 18 symptom criteria as they are described in DSM-IV (APA, 1994). Items were rated on a 4-point scale: never or rarely (0), sometimes (1), often (2), or very often (3). *Academic achievement* was measured using the child's grade point average. At the time of the study, Sweden (where the study was conducted) used a grading system where each school subject was scored on a 4-point scale. *Symptoms of ODD/CD* in late adolescence were measured using the mean score of the 22 items included in the DSM-oriented subscales for CD and ODD in the Child Behavior Checklist (Achenbach, 1991). Parents completed this measure.

2.4.3 Results

2.4.3.1 Early neuropsychological functioning in relation to later ADHD symptoms

First, we examined to what extent the predictors in preschool were related to ADHD symptoms in late adolescence (see Table 5). As we expected, early ADHD symptom levels were significantly related to both symptoms of inattention and hyperactivity/impulsivity in late adolescence. Furthermore, the results showed that all measures of executive functioning (response inhibition, interference control, and spatial working memory), as well as reaction time variability, were significantly related to symptoms of inattention, whereas only response inhibition was significantly related to symptoms of hyperactivity/impulsivity at age 18. With regard to the emotional variables, both of the regulation variables and anger reactivity were significantly related to both inattention and hyperactivity/impulsivity.

Table 5 *Correlations (one-tailed) between ADHD symptoms and neuropsychological deficits in preschool (age 5-6 years) and outcomes at age 18 (n = 113-128)*

	18 years		
	Inattention	Hyperactivity/ Impulsivity	Academic achievement
ADHD symptoms	.28**	.24**	- .25**
Response inhibition	**.27****	.21**	- .25**
Interference control	.18*	.03	- .22**
Spatial working memory	**.22****	- .05	**- .32*****
Reaction time variability	**.25****	.12	**- .24****
Emotion dysregulation			
Anger	.17*	.15*	- .07
Happiness/exuberance	**.21***	**.25****	- .09
Emotional reactivity			
Anger	**.21***	**.25****	- .10
Happiness/exuberance	.07	.09	- .04

* p < .05, ** p < .01, *** p < .001

Boldfaced figures indicate significance when controlling for ADHD symptoms in preschool

2.4.3.2 Control for early ADHD symptom levels or ODD/CD

Second, we controlled for early ADHD symptom levels in the relation between neuropsychological deficits and later ADHD symptoms to ensure that the predictors were not simply a proxy of early symptom levels (cf. van Lieshout et al., 2013). The results showed that all significant predictors, except for interference control and regulation of anger, remained significant for inattention (see boldfaced figures in Table 5). For hyperactivity/impulsivity, the effects of regulation of happiness/exuberance and anger reactivity remained significant, whereas the effect of response inhibition disappeared.

Third, we controlled for symptoms of comorbid ODD/CD in adolescence because this disorder overlaps considerably with other disruptive behavior disorders (e.g., Waschbusch, 2002). The results showed that all relations for executive functioning and reaction time variability remained significant, except for the relation between response inhibition and hyperactivity/impulsivity, which just missed significance, r = .14, p = .06. For emotional functioning, the effect of regulation of happiness/exuberance remained significant in relation to hyperactivity/impulsivity, but it just missed significance in relation to inattention, r = .15, p = .052. However, for reactivity and regulation of anger, all relations to later ADHD symptoms were far from significant when controlling for ODD/CD, rs ranging between .04 - .11, all ps > .12.

2.4.3.3 Independent effects and interaction effects of gender

In the next step, we used hierarchical regression analyses to investigate the independent effects of different neuropsychological functions in relation to ADHD symptoms in late adolescence. The results (see Table 6) showed that preschool ADHD symptoms explained about 9% of the variance in inattention, with neuropsychological functioning contributing an

additional 19%. Reaction time variability as well as regulation of happiness/exuberance contributed independently to the explained variance in inattention when controlling for early ADHD symptom levels as well as for the overlap between different neuropsychological functions. With regard to symptoms of hyperactivity/impulsivity, preschool ADHD explained about 6% of the variance in hyperactivity/impulsivity in the first step, and neuropsychological functioning an additional 9% in the second step. Regarding independent effects, a trend toward a significant effect of regulation of happiness/exuberance was found. The relation between neuropsychological functioning and ADHD symptoms was found to be equally strong for boys as for girls, as none of the interaction effects of gender and neuropsychological functioning reached significance, all βs < .18, ns.

Table 6 *Regression analyses examining independent effects and overall explained variance of early predictors of ADHD symptoms and academic achievement at age 18*

	ß	R^2 change
Inattentive symptoms		
Step 1		.09**
ADHD	.30**	
Step 2		.19**
Response inhibition	.17	
Interference control	- .02	
Spatial working memory	.15	
Reaction time variability	.26**	
Dysregulation of anger	.07	
Dysregulation of happiness	.21*	
Anger reactivity	.05	
Hyperactivity/Impulsivity		
Step 1		.06*
ADHD	.24*	
Step 2		.09^{+}
Response inhibition	.11	
Dysregulation of happiness	.19^{+}	
Dysregulation of anger	- .01	
Anger reactivity	.16	
Academic achievement		
Step 1		.10**
ADHD	- .31**	
Step 2		.15**
Response inhibition	- .10	
Interference control	.07	
Spatial working memory	- .26**	
Reaction time variability	- .22*	

$^{+}$ < 0.10, * p < .05; **p < .01; *** p < .001

2.4.3.4 Neuropsychological deficits in relation to academic achievement

Our next research question concerned to what extent neuropsychological functioning in preschool is related to academic achievement in late adolescence. The results (see Table 5) showed that none of the emotional variables, but all other neuropsychological variables as well as early ADHD symptoms, were significantly related to academic achievement. In the regression analyses (see Table 6), the results showed that early ADHD symptom levels explained about 10% of the variance in academic achievement, and neuropsychological functioning an additional 15%. Spatial working memory and reaction time variability contributed independently when controlling for early ADHD symptom levels as well as for the overlap between different neuropsychological functions. Finally, we investigated interaction effects of the different predictors and gender. The results showed that there was a significant interaction effect of regulation of anger and gender, β = - .19, p < .05, indicating that regulation of anger was more strongly related to academic achievement among boys (r = - .27, p < .05) than among girls (r = .10, ns). As this was an unexpected finding, we wanted to examine whether this interaction was a result of comorbid symptoms, and the findings showed that this was the case, as the significant interaction effect completely disappeared when controlling for symptoms of ODD/CD in late adolescence, β = - .14, ns. None of the other interaction effects of gender and neuropsychological functioning reached significance, all βs < .12, ns.

2.4.4 Conclusions

The main finding of Study IV was that several aspects of preschool neuropsychological functioning were significantly related to future ADHD symptoms, over and above the effect of early ADHD symptoms. Previous studies have also found a longitudinal relation between neuropsychological deficits and ADHD (see van Lieshout et al., 2013 for a review). However, the present study also extends previous findings by showing that these relations remain even when studying the predictors in preschool, conducting the follow-up in late adolescence, and controlling for early ADHD symptom levels. In contrast to previous studies, we also included a broad range of neuropsychological deficits and analyzed the symptom domains separately. Executive and attention-related functions were primarily related to symptoms of inattention, whereas emotional functioning predicted both symptom domains. Whereas previous studies investigating emotional functioning in ADHD have focused on negative emotions, the present study demonstrates the need to consider the role of positive emotions in the development of ADHD. In addition, the present study was able to show that both working memory and reaction time variability in preschool were significantly related to academic achievement in late adolescence.

3 GENERAL DISCUSSION

The following section starts with a brief summary of the respective studies before it moves on to discuss how the aims and critical issues of the thesis were addressed. Finally, the section ends with a discussion of the practical implications of the thesis as well as limitations and future directions.

3.1 SUMMARY OF MAIN FINDINGS

One of the more important findings in Study I was that ADHD is heterogeneous with regard to the underlying neuropsychological deficits seen in school-aged children. Previous research has acknowledged that children with ADHD display multiple deficits (Castellanos et al., 2006; Nigg et al., 2005), but there is a shortage of studies taking their possible overlap into consideration. We therefore analyzed this overlap both using a logistic regression analysis and by showing the overlap between the neuropsychological deficits in Venn diagrams. The results showed independent effects for executive functioning, reaction time variability as well as for both positive and negative aspects of emotional functioning. There were no effects of gender, and group differences remained significant when controlling for either IQ, conduct problems or internalizing problems (except for recognition of sadness, which did not remain significant when controlling for internalizing problems).

Similarly to Study I, Study II found support for the notion that ADHD is a disorder with multiple neuropsychological deficits, but here, in preschool children. Considering that an increasing number of children are being diagnosed already in preschool and the shortage of empirical investigations studying independent effects of neuropsychological deficits at this age, the present study provided new interesting findings on the independent effects of executive functioning, delay aversion as well as emotional functioning. The lack of significant interaction effects between different neuropsychological functions indicated that they do not combine synergistically (i.e., the combination of two deficits do not have an effect on ADHD symptoms that is larger than the sum of its parts). Moreover, the results showed that the associations with ADHD generally remained after controlling for IQ and conduct problems.

In Study III, the aim was to investigate how the multiple neuropsychological deficits included in Study I can explain secondary impairments. More specifically, Study III aimed at explaining to what extent neuropsychological deficits act as mediators in the relation between ADHD and 1) academic achievement and 2) peer relations. The results showed that working memory and reaction time variability partially mediated relations to academic achievement, whereas regulation of anger partially mediated the relation to peer problems. Neither gender nor symptoms of ODD/CD moderated these findings. These results indicate that screening for neuropsychological deficits in children with ADHD could be informative of who will be at increased risk of functional impairments and in what specific setting these impairments will occur (i.e., in school or among peers).

Finally, in Study IV, neuropsychological deficits were investigated in relation to both ADHD symptoms and functional impairments, but with a longitudinal design stretching from preschool to late adolescence. Importantly, the present study aimed at studying the role of early neuropsychological deficits in later ADHD symptoms and academic achievement while controlling for early onset ADHD symptoms (van Lieshout et al., 2013). The results showed that executive and attention-related functions were primarily related to symptoms of inattention, while emotional functioning was predictive of both symptom domains. Hence, early appearing neuropsychological deficits are predictive of the development of ADHD symptoms. With regard to the role of comorbid ODD/CD, relations to anger disappeared when controlling for symptoms of ODD/CD, but the effect of regulation of happiness/exuberance remained significant for hyperactivity/impulsivity and just missed significance for inattention. These results emphasize the need to also include positive emotions as a possible cause of ADHD symptoms.

3.2 ADHD AND NEUROPSYCHOLOGICAL FUNCTIONING

Below, the relations found between neuropsychological functioning and ADHD will be discussed. As there was no evidence to suggest that these relations differ between boys and girls, the discussion below is believed to be valid for both sexes.

3.2.1 ADHD as a neuropsychologically heterogeneous disorder

Even though research during the past decade has begun characterizing ADHD as a heterogeneous disorder with multiple underlying neuropsychological deficits (Castellanos et al., 2006; Nigg et al., 2005), very few empirical studies have taken the possible overlap between candidate predictors into account. Against this background, it was interesting to note that independent effects of different neuropsychological deficits were found in this thesis at school-age (Study I), in preschool (Study II), as well as when examining longitudinal relations (Study IV). More specifically, Study I demonstrated that executive functioning, reaction time variability and both positive and negative aspects of emotional functioning had significant independent effects in relation to ADHD. When looking at results in the first step (i.e., without emotional functioning), the number of correctly classified cases were similar to what has been found in previous studies (Nigg et al., 2005; Wåhlstedt et al., 2009). Furthermore, Study I showed that some children with ADHD were deficient with regard to only executive functioning, whereas others had high reaction time variability but well functioning executive functions. However, what was previously not known was that adding emotional functioning substantially increased the percentage of cases with ADHD that were considered impaired. Support for the notion that emotional functioning should be regarded as an important deficit in ADHD that is at least partially independent of other

neuropsychological deficits was also provided in Study II and IV. These results will be discussed in more detail below when addressing the role of neuropsychological functions in preschool and as predictors for future ADHD.

Where exactly we should draw the cut-off for impairment is a complicated issue that needs to be discussed. When the cut-off is liberal, more children with ADHD will display deficits, but too many of the controls will then also be defined as having deficits. In Study I, 39% of the controls were shown to have at least one neuropsychological deficit. Future studies need to address where cut-offs should be drawn, and it is important to emphasize that this approach will never be able to explain 100% of the ADHD cases without falsely categorizing a large number of controls as impaired. However, the role of neuropsychological functioning should be considered important not only for distinguishing between ADHD children and controls. Defining neuropsychological subtypes in ADHD could prove to be equally important for predicting what neuropsychological subgroups are at increased risk for different real-life impairments. For example, if the secondary outcomes of ADHD with underlying executive deficits are qualitatively different from ADHD with underlying emotional deficits, this could have implications for the respective treatment plan for these individuals. This will be further discussed below under the heading "ADHD, neuropsychological functioning and functional impairments."

3.2.1.1 Implications for the dual-pathway model

According to the dual pathway model, children with ADHD display executive or motivational deficits such as the tendency to choose a smaller immediate reward rather than wait for a larger delayed reward (Sonuga-Barke, 2002, 2003). However, the results from Study I did not support this model, as delay aversion failed to show significant group differences between children with ADHD and controls. This was also the case in the Venn diagrams with only 14% being defined as impaired and only 4% showing an impairment that did not overlap with either executive functioning deficits or reaction time variability. Previous research has been inconclusive regarding the role of delay aversion in ADHD, with some studies finding significant group differences (e.g., Dalen et al., 2004; Solanto et al., 2001), whereas others have failed to do so (e.g., Karalunas & Huang-Pollock, 2011; Solanto et al., 2007). One possible explanation for not finding any effect of delay aversion in our school-aged sample could be that this neuropsychological deficit is more strongly linked to ADHD in younger children (Karalunas & Huang-Pollock, 2011; Paulie-Pott & Becker, 2011). This interpretation of our results in Study I was further supported by our findings in Study II, where neuropsychological functioning was investigated in preschool children. At this age, delay aversion was shown to make independent contributions to explaining ADHD. As such, the results presented in this thesis emphasize the importance of taking age into account when evaluating the relative importance of neuropsychological deficits in relation to ADHD. However, one limitation of the present thesis was that it included only one measure of delay aversion. Future studies need to examine whether the tasks commonly used to study delay aversion are less appropriate for older children. Other measures related to motivation,

like temporal discounting tasks, may be a better option for older children and adolescents, although it should be noted that previous ADHD studies are inconsistent also with regard to this task paradigm (e.g., Barkley, Edwards, Laneri, Fletcher, & Metevia, 2001; Scheres et al., 2006).

3.2.2 Early appearing neuropsychological deficits in ADHD

As mentioned in the introduction, the notion of ADHD as a disorder with multiple deficits is largely based on school-aged samples, and it is therefore important to study whether this is true also for preschool children with the disorder. The question of whether ADHD is a neuropsychologically heterogeneous disorder in preschool could be of great importance for the development of interventions aimed at affecting the development of ADHD. Intervening early, at a stage when deficits have not yet become full-blown, could be easier than reversing the deficit (Sonuga-Barke & Halperin, 2010). The usefulness of early identification need not solely be based on the assumption that early developmental pathways can be redirected through intervention by virtue of reducing ADHD symptoms. It could also be important to identify children before the disorder has resulted in secondary impairments such as peer problems and academic underachievement. The studies in this thesis do not include any intervention. However, one aim was to help establish what functions could be targeted in such an effort.

The design of Study II was similar to that of Study I, but investigated a sample of 4-6 year olds. Overall, effect sizes for the neuropsychological functions included in this study were in line with those found in two previous meta-analyses (Pauli-Pott & Becker 2011; Schoemaker et al., 2012) and could thus be taken as an indication that our measures were well-suited to this age group. Even though the analytic approach differs between Study I and II, it can be concluded that the relative importance of these functions differs in preschool and school-age. When analyzing the combined effects of different neuropsychological deficits in relation to ADHD, the amount of variance explained was much smaller for the preschool sample compared to that found in the school-aged sample. One reason why neuropsychological deficits had a more limited impact in preschoolers compared to school-aged children could be that these functions have not yet had a chance to develop sufficiently in the preschool years, even among the controls. This would indicate that the ability to detect group differences between controls and children with ADHD (i.e., who are thought to show a developmental delay with regard to self-regulation) is more limited in preschool children (cf. Barkley, 1997).

Although it seems that the combined effect of the included functions was more limited in preschoolers, deficits in multiple neuropsychological functions were also demonstrated at this age. Independent effects were observed for executive functioning, delay aversion and emotion regulation. However, some differences with regard to what functions showed independent effects were also observed. As mentioned above and in line with previous studies (Karalunas & Huang-Pollock, 2011; Paulie-Pott & Becker, 2011), delay aversion

seems to be more important at a younger age. Moreover, there was no independent effect of reaction time variability on ADHD in preschool. However, when studying simple correlations, reaction time variability was significantly related to inattention also in preschool, and this measure was also significantly predictive of future ADHD in Study IV. Altogether, due to methodological differences such as sample characteristics (clinical and non-clinical) and that Study IV used a longitudinal design, it is difficult to come to any conclusions regarding the impact of reaction time variability on ADHD in preschool. Study II also examined whether the combination of two deficits has an effect on ADHD symptoms that is larger than the sum of its parts. However, support for interaction effects between the different neuropsychological functions was not found.

3.2.2.1 The ability of early appearing neuropsychological deficits to predict future ADHD

Study II analyzed the relation between neuropsychological deficits and ADHD at one time point, whereas Study IV investigated these associations using a longitudinal design. A recent review aimed at evaluating the role of neuropsychological deficits in future ADHD acknowledged some of the shortcomings of existing studies (van Lieshout et al, 2013). First, there is a need for longitudinal studies that extend over longer time periods. Second, such studies should include a broad range of possible predictors. Third, such studies need to control for early ADHD symptoms. If neuropsychological deficits cannot explain some of the variance in the outcome variable, over and above ADHD severity at baseline, they may simply be a proxy of early ADHD symptom levels (cf. van Lieshout et al., 2013). Study IV addressed these limitations of previous studies, and the results showed that early appearing neuropsychological deficits are predictive of the development of ADHD, also when controlling for ADHD symptoms at baseline. Hence, adding to the results from Study II, Study IV showed that neuropsychological deficits in preschool were not only related to concurrent ADHD, but also to development of future ADHD symptoms.

The results from Study IV show that executive and attention-related functions were primarily related to development of symptoms of inattention, while emotional functioning was predictive of both symptom domains. These functions are thus also important to consider as predictors of the development of ADHD, and it is not just executive and attention-related functions but also emotional aspects that should be studied. Importantly, another limitation of this study was that it did not include any measure of delay aversion. As this measure has been shown to be predictive of later ADHD symptoms but only over a short time span (Campbell, & von Stauffenberg, 2009), it would have been interesting to study whether this is also related to development of future ADHD over a longer time span.

3.2.3 Emotional functioning in ADHD

Overall, all of the studies in this thesis show that emotional functioning is an important component of ADHD that is dissociable from deficits in other neuropsychological functions. Of the emotional functions studied, emotion regulation deficits may be of especially great

importance for ADHD. However, there has been a call for a clearer conceptualization of emotional regulation within the field of ADHD (cf. Shaw et al., 2014). As pointed out as a critical issue in the introduction, most studies of emotion regulation and ADHD encompass how often and intensely the child displays different emotions (i.e., emotional reactivity) as well as how well he/she can regulate different emotions (i.e., emotion regulation). However, temperament research has described reactivity and regulation as two different aspects of temperament (see Cole et al., 2004 for a review), and these two aspects were therefore separated in the measures used in this thesis. The need to make this distinction becomes especially apparent when studying how happiness/exuberance is related to ADHD symptoms. In Study IV, reactivity with regard to happiness/exuberance is far from significant, whereas regulation is. This means that frequent and intense displays of happiness/exuberance seem to be unproblematic, whereas as not being able to regulate your happiness is. Thus, the general assumption that having a positive and cheerful mood (i.e., high reactivity of happiness/exuberance) is associated with adaptive outcomes might be correct – at least it is not a negative factor in Study IV. However, the present study suggests that more unrestrained excitement, like being too wound up at a party or being overly excited when one wins a contest (i.e., poor regulation of happiness/exuberance), is something qualitatively different. Hence, researchers need to be clearer in how they operationalize emotion regulation, as different aspects of this construct may be differentially related to ADHD.

The issue of being more specific when defining emotion regulation is closely related to the need to also study regulation in relation to several different types of emotions. This thesis included regulation of four emotions: sadness, fear, happiness/exuberance, and anger. The ability to regulate behavior in relation to these four emotions was related to ADHD in general. However, the strongest effects were observed in relation to regulation of anger and happiness/exuberance. Critically, the majority of previous studies investigating emotion regulation in relation to ADHD have focused on more negative aspects of regulation and have, thus, failed to acknowledge one important part of regulation.

3.2.3.1 The overlap with ODD/CD

Another critical issue when studying the role of emotional functioning in relation to ADHD is to consider the co-occurrence of ODD/CD and ADHD. As stated in the introduction, there is a need to 1) measure emotion regulation with scales that are separable from ODD/CD and 2) evaluate whether possible associations between emotion regulation and ADHD can be explained by comorbid symptoms of ODD/CD. Regarding the first issue, some of the rating scales used in previous studies include items that overlap with symptoms of ODD and/ or CD (e.g., temper outburst). Thus, there is a risk of conflating emotion regulation with ODD/CD if these are not separated. We addressed this issue using a rating scale that specifically targeted the regulatory aspect of emotional functioning in Study I-III. Study IV also included a scale that measured emotion reactivity, but associations with the outcome variables were reported separately for regulation and reactivity. More specifically, the scale measuring emotion regulation included both one general statement (e.g., “When angry, he/she has difficulties

calming down on his/ her own.") and two statements regarding regulation in specific situations (e.g., "When my child is forbidden to do something that he/she wants to do, he/she has difficulties calming down on his/her own." and "When my child gets into a conflict with a peer, he/she has difficulties calming down on his/her own."). Thus, we added to previous research by showing that the association between emotion regulation and ADHD could not be explained by the use of overlapping items with ODD/CD.

Regarding the second issue raised above, the co-occurrence of ADHD and ODD/CD, this was addressed by controlling for ODD/CD when significant relations were found between emotion regulation and ADHD. Importantly, the relation between happiness/exuberance and ADHD did not disappear in any of the studies in the present thesis when controlling for comorbid ODD/CD. Results are more inconclusive when it comes to regulation of anger. In Study I and II, where clinically diagnosed children where included, the relation between regulation of anger and ADHD was still significant when controlling for ODD/CD, whereas this relation disappeared in Study IV, which included a non-clinical sample. One possible explanation for the differences between studies could therefore be that regulation of anger is more closely connected to ADHD symptoms in clinical samples. Besides the differences in sample characteristics (i.e., clinical versus non-clinical), Study IV studied the relation between emotional functioning and ADHD symptoms over a time span of 13 years, whereas Study I and II investigated concurrent relations. Finally, when considering the role of ODD/CD in the relation between emotion regulation and ADHD, it should also be acknowledged that causal processes could be shared across disorders. Therefore, disregarding shared variance could be problematic, and it might be more fruitful to consider that emotional functioning could be an important aspect of both ADHD and ODD/CD.

3.3 ADHD, NEUROPSYCHOLOGICAL DEFICITS AND FUNCTIONAL IMPAIRMENTS

More than the actual ADHD symptom levels, impairments in everyday functioning, is perhaps a more clinically relevant motive to why it is important to find out more about the underlying neuropsychological deficits of this disorder. It is not known why some children with ADHD go on to develop problems whereas other does not. To address this issue, Study III and IV investigated the role of neuropsychological functioning in academic achievement and peer problems. In Study III, this was done in a school-aged sample with both clinically diagnosed children with ADHD and typically developing controls. In Study IV, this was investigated in a community sample that was followed from preschool to late adolescence. Overall, the relations discussed below apply to both boys and girls, as the results from Study III and IV do not suggest otherwise.

3.3.1 Academic achievement

In line with previous research, Study III and IV both found support for the involvement of executive deficits in academic achievement (Barry et al., 2002; Biederman et al, 2004; Diamantopoulou et al., 2007; Miller & Hinshaw, 2010; Miller et al., 2012; Rogers et al., 2011). More specifically and adding to previous research, working memory was shown to be the executive function that was most strongly associated with academic achievement both concurrently and longitudinally. This is in line with a longitudinal study that stretched into early adulthood, much like in Study IV, but that sample consisted only of girls (Miller et al., 2012). In addition, the results in the present thesis added to previous research by showing that it is not just executive functioning that is related to academic achievement. Both Study III and IV showed that reaction time variability also has an independent effect in relation to academic achievement. Thus, high reaction time variability appears to reflect a central deficit in ADHD that is comparable to working memory deficits in its relevance to later academic achievement.

Study III used an analytic approach that allowed us to evaluate to what extent neuropsychological deficits could explain the relation between ADHD and academic achievement. Together, they accounted for just over 50% of this relation, which should be considered substantial given that the effect size of the association between ADHD and academic achievement was large. However, it should also be acknowledged that the deficits included in Study III cannot fully explain the relation between ADHD and academic achievement (i.e., only partial mediation was demonstrated). It is possible that other neuropsychological deficits could be included to explain additional variance, but we must also consider that neuropsychological deficits may only partially account for this association. The results from Study III and IV suggest that both neuropsychological functions and ADHD symptoms make independent contributions to academic achievement. From a clinical perspective, if both ADHD symptoms and neuropsychological deficits contribute to the overall impairment, then they should both be the target of interventions and treatment efforts (cf. Coghill, Hayward, Rhodes, Grimmer, & Matthews, 2014).

Finally, it is worth noting that while emotional functioning deficits (especially dysregulation of happiness/exuberance) were strongly related to ADHD symptoms, no such effects were seen in relation to academic achievement. This indicates that, unlike working memory deficits or high reaction time variability, emotional deficits do not pose an additional risk for poor academic achievement in children with ADHD.

3.3.2 Peer relations

In line with previous research (e.g., Hoza, 2007; McQuade & Hoza, 2008), the present study showed that the children with ADHD were rated as having much more peer problems compared to the controls. Previous research has largely focused on the role of executive functioning in accounting for the relation between ADHD and peer problems. With the

exception of a few studies (Miller & Hinshaw, 2010; Rinsky & Hinshaw, 2011), the bulk of the results suggest that it is not primarily executive functions that mediate this association (Biederman et al., 2004; Diamantopoulou et al., 2007; Huang-Pollock et al., 2009; Scholtens et al., 2012). The results of Study III also suggest that other deficits need to be taken into account (even though several aspects of executive functioning were included) if we are to better understand why children and adolescents with ADHD have troublesome peer relations. Interestingly, the results of Study III showed that regulation of anger was a significant mediator in the relation between ADHD and peer problems. This finding is in line with one of the few previous studies that included emotional functioning and that was able to show that a measure of emotional lability mediated the relation between ADHD and social skills (Anastopoulos et al., 2011). However, this thesis contributes new information. First, it showed that the mediating effect of regulation of anger could not be accounted for by other neuropsychological deficits. Second, the focus was on emotion regulation specifically, rather than using a measure that includes both reactivity and regulation of emotions. Third, the effects of different emotions were investigated, and it was shown that regulation of anger in particular, and not regulation of other emotions, was related to peer problems. Fourth, comorbid ODD/CD did not moderate the relation between ADHD and peer problems (i.e., the relation between emotional functioning and peer problems was equally strong for ADHD children with or without ODD/CD). As Study III was the only study in this thesis that investigated peer problems and as few previous studies have addressed this issue, there is a need to conduct further studies before we can draw any solid conclusions about the involvement of emotion regulation deficits in relation to peer problems.

3.4 PRACTICAL IMPLICATIONS

It is important to consider the possible implications of the present results for clinical practice. Regarding the diagnostic procedure, the classification rate was too low to regard deficits in neuropsychological functions as a viable replacement for behavioral symptoms. Even though emotional functioning substantially improved the classification rate, future studies need to address possible shared variance with other clinical groups. Importantly, although ADHD was shown to be heterogeneous with regard to the neuropsychological deficits in both preschool and school-aged children, the impact of these deficits varied with age. For example, early screening for ADHD should consider motivational aspects such as delay aversion, whereas including this measure in older children appears to be less important.

Regarding interventions for ADHD, a relatively large number of previous studies have tried to improve working memory through computerized training in preschool (e.g., Thorell, Lindqvist, Bergman, Bohlin & Klingberg, 2009) and school-age (e.g., Klingberg et al., 2005) children. However, neuropsychological heterogeneity should also be considered when developing intervention and prevention programs. It may therefore be more fruitful to

identify subgroups of ADHD children with different neuropsychological deficits and then develop individualized intervention programs that target the specific function that is most impaired. Another alternative would be to use programs that target a broader range of regulatory functions, such as the New Forest Parenting Program (e.g., Thompson et al. 2009). Because the present results emphasize the need to target different forms of emotion regulation, it is important to acknowledge interventions that include these functions, such as The Parenting Your Hyperactive Preschooler Program. This intervention has an especially strong emphasis on strengthening emotion regulation, and it has been shown to reduce ADHD symptoms and associated behavior in preschool-aged children (Herbert, Harvey, Roberts, Wichowski, & Lugo-Vandelas, 2013). Importantly, any program that targets emotion regulation should focus not only on negative emotions, but also on enhancing regulatory skills in situations where extreme levels of happiness/exuberance are inappropriate.

Arguably, it should be important to address situations in which children and adolescents with ADHD encounter real-life problems, such as poor academic achievement and difficult peer relations. It has recently been suggested that if both ADHD symptoms and neuropsychological deficits contribute to the overall impairment, they should both be addressed in interventions and treatment efforts (Coghill et al., 2014). Regarding academic achievement, there is some evidence that computerized working memory training programs can enhance mathematics ability (Holmes, Gathercole, & Dunning, 2009). Furthermore, teaching strategies should be adapted to suit the needs of children with ADHD (e.g., giving one instruction at a time and repeating the important parts of longer instructions; Raggi & Chronis, 2006). Our findings also suggest that it is important to identify children with ADHD who have high reaction time variability. Because the finding that reaction time variability has implications for academic achievement is new, making specific adjustments to academic settings for children with variable reaction time has not yet been suggested. However, two aspects thought to be of importance are rewards and the speed/intensity of presentation (cf. Tamm et al., 2012).

Regarding peer relations, the results of Study III suggest that dysregulation of anger offers a partial explanation for why children with ADHD encounter problems in this domain. The use of intervention programs targeting emotion dysregulation (see Eisenberg, Spinrad, & Eggum, 2010 for a review) at an early age may be especially important, as ADHD children who are rejected by their peers (e.g., Mikami & Hinshaw, 2006) often go on to develop secondary problems (e.g., internalizing behavior problems). Such problems could eventually maintain problematic peer relations even after the children have become better at regulating their emotions.

3.5 LIMITATIONS AND FUTURE DIRECTIONS

The findings and limitations of the present thesis have led to new scientific questions that are both specific and general in nature. The results of the studies included in the thesis suggest that emotional functioning, particularly the regulatory aspects, should be included in future research. However, when using ratings, it is important to consider that such methods risk being more inclusive than laboratory measures are. Even when specific questions are asked, the answer could be affected by the rater's view of the child as generally problematic. Thus, when evaluating the impact of emotion regulation found in this thesis, one should consider the risk that the relation between ADHD and emotion regulation has been overestimated due to the use of questionnaires for measuring both emotion regulation and ADHD symptoms. As the impact of emotion regulation is one of the major findings of this thesis, it is important to replicate these findings using laboratory measures. Based on the present findings, it will be important to consider the following aspects and challenges: 1) that the measures specifically encompass regulation of emotion rather than emotional functioning in general and 2) that regulation is studied in relation to different types of emotions.

Another important finding of this thesis concerned reaction time variability. The present results show that reaction time variability is not only independently related to ADHD symptoms, but also to secondary impairments of the disorder, such as academic achievement. However, there is need to learn more about the exact nature of reaction time variability. Given the large impact that this deficit has, future studies need to investigate how it can best be targeted by interventions. Although reaction time variability was measured in the same way as in the bulk of previous studies, it should be considered that recent review articles have discussed the need to consider alternative ways of measuring this deficit (Tamm et al., 2012, Karalunas et al., 2014).

The present thesis stressed the need for theoretical models of ADHD to also take into consideration the functional impairments of the disorder. Measures of academic achievement and peer relations were therefore included in the thesis, but the list of functional consequences of ADHD is much longer. Hence, future studies also need to study the role of neuropsychological deficits in relation to, for example, substance use, unemployment, traffic accidents, health, depression, etc. Importantly, it would be of interest to try to replicate findings related to peer problems using sociometric peer nominations, as this method has been argued to be the most valid measure of children's social functioning (e.g., McQuade & Hoza, 2008). Furthermore, as mentioned above, there is a risk that the relation between emotion regulation and peer problems is overestimated when using questionnaires that measure both emotion regulation and peer problems.

The effect of comorbid ODD/CD was investigated in the present study, but it would have been interesting to include other comorbidities as well. When this is not done, there is always a risk that relations would have been better explained by a comorbid disorder. However, it should also be acknowledged that causal processes could be shared across disorders. Therefore, and as mentioned above, disregarding shared variance could be problematic, and it

might be more fruitful to consider neuropsychological deficits as possible important aspects in relation to both ADHD and other disorders.

Studying neuropsychological functioning in ADHD using a non-clinical sample, as done in Study IV, has both its advantages and its limitations. Studies of clinical samples need to be complemented with studies examining the predictive power of hypothetical markers of ADHD in community samples to avoid the referral bias associated with clinic samples (e.g., Goodman, Lahey, Fielding, & Dulcan, 1997). However, it is also important that samples encompass a wide range of behaviors concerning the key variables in order to increase the statistical power to detect associations. Thus, the relatively small and homogeneous sample included in Study IV could have limited our ability to detect significant associations.

Finally, in the future, it will be important to study large samples of preschool children and conduct person-oriented analyses to identify neuropsychological subgroups. These children should thereafter be followed over time to investigate possible functional impairments at follow-ups at different points during childhood, adolescence and even adulthood. Such samples should preferably include children who are at risk of developing ADHD and other disorders, as well as children with low levels of ADHD symptoms at preschool age.

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