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Specifying the Heterogeneity in Children with ADHD

*Symptom Domains, Neuropsychological Processes,
and Comorbidity*

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Abstract

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Heterogeneity in children with Attention Deficit Hyperactivity Disorder (ADHD) symptoms is a well-known phenomenon. Empirically, this heterogeneity is evident in at least three different respects: expression of the two ADHD symptom domains (hyperactivity/impulsivity and inattention), neuropsychological impairments, and comorbid behavior problems. The major aim of the present thesis was to examine the heterogeneity characterizing children with ADHD symptoms to enhance our understanding by examining neuropsychological factors with regard to common and independent contributions, and specificity of the two ADHD symptom domains in relation to neuropsychological factors and comorbid behavioral problems. Particular emphasis is placed on prominent neuropsychological processes such as executive functions, state regulation and delay aversion. The present thesis is based on findings from four studies on community-based samples of children – studies involving concurrent and longitudinal designs as well as both categorical and dimensional approaches.

Results provide support for the notion that executive function and state regulation, but not delay aversion, constitute independent pathways to ADHD, primarily to symptoms of inattention. However, delay aversion was shown to have an effect in combination with state regulation on both hyperactivity/impulsivity and inattention. Additionally, symptoms of hyperactivity/impulsivity and inattention have different primary correlates concerning neuropsychological factors and comorbidity. More specifically, executive function, state regulation, internalizing problems and academic achievement were specifically related to inattention but not to hyperactivity/impulsivity. Oppositional Defiant Disorder (ODD) was specifically related to hyperactivity/impulsivity, but not to inattention.

The present thesis has contributed with important and new knowledge about the heterogeneity of children with ADHD symptoms concerning neuropsychological pathways, and specificity of the two ADHD symptom domains in relation to neuropsychological factors and comorbid behavioral problems. Knowledge such as this can help us understand how to identify more homogeneous ADHD subgroups, and contribute to the further development of multiple pathway models within this area of research.

Keywords: ADHD, Heterogeneity, Hyperactivity/Impulsivity, Inattention, Neuropsychological Pathways, Comorbidity

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List of Papers

The present thesis is based on the following four studies, which will be referred to in the text by their Roman numerals.

- I** Wåhlstedt, C., Thorell, L. B., & Bohlin, G. (2008). ADHD Symptoms and Executive Function Impairment: Early Predictors of Later Behavioral Problems. *Developmental Neuropsychology*, 33, 160-178.
- II** Wåhlstedt, C., Thorell, L. B., & Bohlin, G. (in press). Heterogeneity in ADHD: Neuropsychological Pathways, Comorbidity and Symptom Domains. *Journal of Abnormal Child Psychology*.
- III** Wåhlstedt, C. (in press). Neuropsychological Deficits in Relation to Symptoms of ADHD: Independent Contributions and Interactions. *Child Neuropsychology*.
- IV** Wåhlstedt, C. & Bohlin, G. (2008). DSM-IV-Defined Inattention and Sluggish Cognitive Tempo: Independent and Interactive Relations to Neuropsychological Factors and Comorbidity. Manuscript submitted for publication.

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Introduction

Hyperactivity/impulsivity and inattention are common behaviors among young children. Developmentally inappropriate levels of these behaviors may lead to diagnosis of attention deficit hyperactivity disorder (ADHD). ADHD is one of the most prevalent psychiatric disorders in childhood and is estimated to affect 5-10% of children worldwide (Faraone, Sergeant, Gillberg, & Biederman, 2003). Thereby, the social and economic costs of childhood ADHD are considerable (Leibson, Katusic, Barbaresi, Ransom, & O'Brian, 2001).

Heterogeneity in children with ADHD symptoms is a well-known phenomenon. Empirically, this heterogeneity is evident in at least three different respects: expression of the two ADHD symptom domains (hyperactivity/impulsivity and inattention), neuropsychological impairments, and comorbid behavior problems. However, few studies have clarified more exactly how this heterogeneity is expressed in children with ADHD symptoms. One way to approach this problem is to investigate if neuropsychological impairments and comorbid behavioral problems is associated more strongly with either hyperactivity/impulsivity or inattention by controlling for hyperactivity/impulsivity when analyzing relations to inattention and vice versa. In addition, as evidence points to multiple neuropsychological factors as major contributors to ADHD symptoms (see Nigg, 2006, for a review), a better understanding of heterogeneity with regard to neuropsychological deficits should be achieved by including neuropsychological measures based on different theories in the same sample.

It should be noted that although many children do not meet the full criteria for an ADHD diagnosis they may still experience negative consequences similar to those experienced by children diagnosed with ADHD (Bauermeister et al., 2007). Yet, most studies in this area of research have been on clinical samples. Indeed, clinically based samples are generally more impaired and usually present with a variety of comorbid difficulties, which may confound actual findings. Thus, results from community-based samples can provide valuable information about ADHD symptoms in children and should be seen as a complement to more clinically oriented research.

Under the past two decades, a large number of studies have been carried out in this area, and although a great deal of new knowledge has been generated, unanswered questions remain. The present thesis aims at furthering our knowledge about the heterogeneity characterizing children with ADHD symptoms as regards neuropsychological pathways, and specificity of the two ADHD symptom domains in relation to neuropsychological factors and comorbid behavioral problems. Particular emphasis is placed on prominent neuropsychological processes such as executive functions, state regulation and delay aversion. The present thesis is based on findings from four studies on community-based samples of children – studies involving concurrent and longitudinal designs as well as both categorical and dimensional approaches. Before proceeding to the empirical studies, a background to this research area is provided, including definitions of the different constructs, current neuropsychological theories, related comorbidity and previous research.

Defining ADHD symptoms in children

Diagnostic criteria and subtypes

Historically, there have been changes in the ADHD diagnostic criteria, largely owing to the problem of appropriately defining ADHD. Attention-deficit disorder (ADD) was first introduced in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III; American Psychiatric Association, 1980) and included two subtypes: ADD with hyperactivity (inattention, hyperactivity/impulsivity) and ADD without hyperactivity (inattention and impulsivity). DSM-III-R subsequently dropped the subtype approach and introduced the general disorder of attention-deficit/hyperactivity disorder (ADHD; inattention, hyperactivity and impulsivity; APA, 1987). Finally, DSM-IV returned to the subtype approach and included three subtypes of the disorder (APA, 1994), which will be described below.

The diagnostic criteria for ADHD according to DSM-IV (1994) consist of two separate, although highly correlated, dimensions including nine symptoms of inattention and nine symptoms of hyperactivity/impulsivity. Symptoms of inattention are characterized by behaviors such as making careless mistakes and not paying close attention to details, forgetfulness, difficulty organizing tasks and activities, and failure to begin or complete tasks that require attention. Concerning symptoms of hyperactivity/impulsivity, these behaviors are characterized by fidgeting with hands or feet, running around or climbing excessively in situations in

which it is inappropriate, often talking excessively, having difficulty awaiting one's turn, and interrupting or intruding on others.

DSM-IV (1994) defines three diagnostic subtypes based on differential elevations of these two symptom dimensions: the predominantly inattentive type, the predominantly hyperactive/impulsive type and the combined type, which is characterized by high levels of both symptom domains. The primarily inattentive and hyperactive subtypes only require six symptoms from one of the two separate symptom dimensions, while the combined subtype requires the presence of six or more symptoms of hyperactive/impulsive as well as six or more inattentive symptoms. Five additional requirements for the diagnosis include: First, that the symptoms must cause a clinically significant impairment in adaptive functioning. Second, levels of hyperactivity/impulsivity and/or inattention must be inconsistent with the child's developmental level. Third, ADHD symptoms should have been present for at least six months with an onset of some symptoms before age 7. Fourth, ADHD symptoms should have been present in two or more settings (e.g., school and home). Finally, the child's behavioral symptoms should not be better accounted for by another mental disorder such as pervasive developmental disorder, psychosis, or internalizing disorder.

Concerning the requirement that ADHD symptoms should have been present in two or more settings, it is commonly known that parents and teachers usually only partially agree on their ratings of a particular child's behavior (Achenbach, McConaughy, & Howell, 1987). Results from earlier studies have shown that correlations between parent and teacher ratings of ADHD symptoms commonly range from .37 to .49 (DuPaul, Power, Anastopoulos, & Reid, 1998; Sprafkin, Volpe, Gadow, Nolan, & Kelly, 2002; Willcutt, Hartung, Lahey, Loney, & Pelham, 1999). Disagreement in ratings between parents and teachers is primarily based on the fact that they observe different ADHD behaviors (Hartman, Rhee, Willcutt, & Pennington, 2007). For example, parents seem to be more biased than teachers in their ratings of ADHD symptoms. Possible strengths of teacher ratings of ADHD symptoms, compared to parents, include a better awareness of population norms, observing children in situations that are challenging for children with ADHD symptomatology and greater objectivity (Gomez, Harvey, Quick, Scharer, & Harris, 1999; Nadder, Silberg, Rutter, Maes, & Eaves, 2001).

The DSM-IV subtypes of ADHD have not been free from debate. It has been suggested, for example, that the combined and primarily inattentive type should be considered as distinct and unrelated disorders rather than subtypes of the same disorder (Barkley, 2006; Milich, Balentine, & Lynam, 2001). Further, individuals with primarily inattentive symptoms with no or

subthreshold hyperactivity/impulsivity are assumed to be a heterogeneous group. However, the symptom dimension of DSM-IV-defined inattention remains surprisingly understudied (Diamond, 2005; Milich et al., 2001; Nigg, 2006). Concerning the primarily hyperactive/impulsive subtype, many studies have ignored this subgroup in part due to its rarity in school-age populations (Hart, Lahey, Loeber, Applegate, & Frick, 1995).

The prevalence of ADHD symptoms has been shown to vary significantly as a function of sex differences. Indeed, ADHD symptoms have been shown to occur in boys approximately three times as often as in girls in community-based samples, and five to nine times as often in clinical samples (Gaub & Carlson, 1997). Gaub and Carlson (1997) conducted the first meta-analysis on sex differences in children with ADHD. They found that in comparison to boys, girls had greater intellectual impairments, lower ratings on hyperactivity, and lower ratings of externalizing and internalizing problems.

Stability of ADHD symptoms

It is estimated that up to 30-60% of children with ADHD continue to manifest symptoms into adolescence and adulthood (Bagwell, Molina, Pelham, & Hoza, 2001; Mannuzza & Klein, 2000; Manuzza, Klein, & Moulton, 2003). It has also been demonstrated that behavioral problems at a young age that are below the clinical cutoff can persist and even meet the criteria for an ADHD diagnosis at a later age (Campbell & Ewing, 1990; McGee, Patridge, Williams, & Silva, 1991; Pierce, Ewing, & Campbell, 1999).

Several studies have shown that the symptoms of ADHD change during the developmental process. Preschoolers show more symptoms of hyperactivity/impulsivity than inattention (e.g., Gomez et al., 1999; Rohde et al., 2001). Further, research (e.g., Biederman, Mick, & Faraone, 2000; Hart et al., 1995) has shown that symptoms of hyperactivity/impulsivity decline over time, while symptoms of inattention remain relatively stable. In line with these findings, Lahey and colleagues (Lahey, Pelham, Loney, Lee, & Willcutt, 2005) found that there is instability in the ADHD subtypes from preschool to elementary school. They pointed to the fact that fluctuations above and below the boundaries of the three ADHD subtypes over time may be the rule rather than the exception.

Thus, over time, more children in the combined subtype are expected to meet the criteria for the primarily inattentive subtype as hyperactive/impulsive symptoms decline throughout adolescence. Concerning the developmental trajectories for children in the primarily hyperactive/impulsive subtype, these seem more uncertain. However, some

of these children seem less likely to meet the criteria for ADHD over time and some shift to the combined subtype. Lahey et al. (2005) considered that the primarily hyperactive/impulsive subtype may be a special case, because this subtype is so unstable over time. This instability in the expression of ADHD symptoms over time also contributes to the heterogeneity of the two ADHD symptom domains.

ADHD symptoms: As a continuum or a category?

There is an ongoing debate as to whether the ADHD diagnosis should be categorical, i.e., making a firm distinction between those children who meet the criteria for a specific number of symptoms, and those who do not, versus dimensional, i.e., viewing ADHD symptoms as falling on a continuum. In the categorical view, with regard to the DSM-IV approach, a child who meets the criteria for six of nine symptoms would be classified as having the disorder, but would not be so classified if he or she had only five of nine symptoms. On the other hand, a dimensional view of psychopathology proposes that common mental disorders, such as ADHD, can be conceptualized as extreme manifestations of normal dimensions i.e., a difference in degree along a continuum.

Nevertheless, and in line with a dimensional view, many children who do not meet the full criteria for an ADHD diagnosis may also experience problems with hyperactivity/impulsivity and inattention. As mentioned above, these children may experience negative consequences similar to those experienced by children diagnosed with ADHD (Bauermeister et al., 2007). Twin studies have shown that the heritability of high levels of ADHD symptoms is no different than the heritability for scores across the normal range (e.g., Levy, Hay, McStephen, Wood, & Waldman, 1997). Moreover, these genetic findings have been complemented by behavioral results showing a linear relation between inhibitory function and ADHD symptom severity in children (e.g., Sonuga-Barke, Dalen, Daley, & Remington, 2002; Sonuga-Barke, Dalen, & Remington, 2003).

An additional argument in line with a dimensional view is the growing consensus that ADHD is best viewed as a developmental delay rather than as a categorical disorder (e.g., Brown et al., 2001; Levy et al., 1997). Such a view emphasizes the importance of knowledge of normal developmental processes to our understanding of the nature of childhood behavioral disorders such as ADHD.

The etiology of ADHD

The exact etiology of ADHD is still unknown. However, over the past 15 years, considerable progress has been made in understanding the etiology of ADHD in childhood. Findings suggest that multiple etiologies may lead to ADHD, yet evidence points to genetic and neurological factors as the greatest contributors to this condition (e.g., Barkley, 2006; Faraone & Doyle, 2001; Faraone et al., 2005; Willcutt & Carlson, 2005). In support of genetic underpinnings, evidence from a large number of twin, family and adoption studies has shown a strong heredity component in ADHD symptoms (Faraone & Doyle, 2001; Faraone et al., 2005; Wallis, Russell, & Muenko, 2008). Based on numerous studies of twins, the mean heritability for ADHD was shown to be .77 (Biederman, 2005).

Although twin studies demonstrate that ADHD is a highly heritable condition, molecular genetic studies suggest that the genetic architecture of ADHD is complex. Candidate gene studies of ADHD have produced substantial evidence implicating several genes in the etiology of the disorder. However, as the implicated genes have shown small effects, it is assumed that genetic vulnerability to ADHD is mediated by many genes (Faraone et al., 2005). Interestingly, concerning the two ADHD symptom dimensions, recent research has shown both common and symptom-specific genetic effects (Larsson, Lichtenstein, & Larsson, 2006; McLoughlin, Ronald, Kuntsi, Asherson, & Plomin, 2007). These results highlight the importance of studying the two ADHD symptom domains separately, which would make it possible to identify three sets of neuropsychological impairments and related comorbidity, those that are: (1) specific to symptoms of hyperactivity/impulsivity, (2) specific to symptoms of inattention, and (3) common to the two ADHD symptom domains.

While genetics have a strong contribution to ADHD symptoms in children, environmental factors and potential genetic-environmental interactions also influence the susceptibility to the condition (Larsson, Larsson, & Lichtenstein, 2004; see Nigg, 2006; Swanson et al., 2007 for reviews). For example, exposure to nicotine in the prenatal period, low birth weight, psychosocial adversity in the home environment, and low social class appear to play a role in the etiology of ADHD (see Banerjee, Middleton, & Faraone, 2007, for a review). It is important to note that there is no evidence that the social environment, such as parenting practices, can directly cause ADHD in children. However, it is likely that the social environment influences the course of ADHD symptoms, particularly whether ADHD is comorbid with another disruptive behavioral disorder such as oppositional defiant disorder (ODD) or conduct disorder (CD; e.g., Burke, Pardini, & Loeber, 2008).

Neuropsychological factors and theories of ADHD

There is robust evidence of structural, functional and neurochemical differences in children with ADHD, in brain regions that support vital cognitive functions (see Biederman, 2005; Nigg, 2006, for reviews). Concerning neurological deviations, neuroimaging studies indicate that, as a group, children with ADHD have about 5% reduction in total brain volume and 10-12% reduction in the size of key brain regions. The four main regions implicated in ADHD symptoms (see Figure 1) are: (1) prefrontal cortex; (2) basal ganglia; (3) cerebellum; and (4) corpus callosum. It is important to note that these regions are heavily interconnected (see Nigg, 2006, for a review). Further, neurochemical pathways that seem to be implicated in ADHD symptoms are dopamine, noradrenaline and serotonin (see Barkley, 2006, for a review).

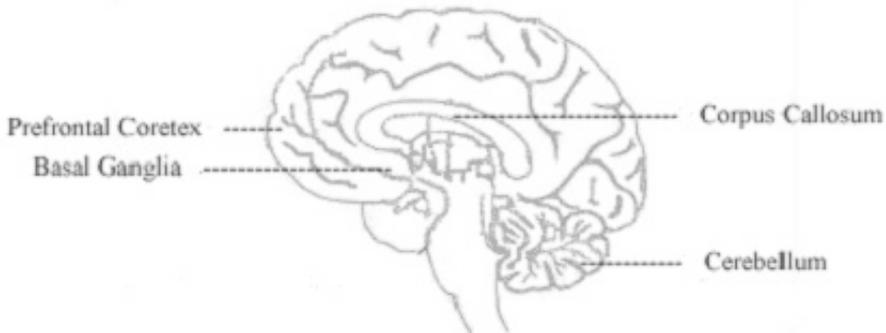


Figure 1. Implicated brain regions in children with ADHD symptoms.

Examining the neuropsychology of children with ADHD symptoms provides an opportunity to understand the relationship between underlying biological processes and symptoms of hyperactivity/impulsivity and inattention. Neuropsychological impairments refer to mental functions that are mediated by brain processes; these mental functions are not directly observable, but may be manipulated and measured using neuropsychological tasks. Considerable research has been conducted during the past decades to try to understand the neuropsychology behind ADHD symptoms. Important neuropsychological processes that have been implicated in ADHD, both theoretically and empirically, are executive functions (EFs; Barkley, 1997a, b; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005a), motivational factors (Sonuga-Barke, 2003; 2005) and state factors such as activation and effort (Lijffijt, Kenemans, Verbaten, & Van Engeland, 2005; Sergeant, 2000, 2005). However, neuropsychological studies of ADHD have mainly focused on EF impairments, mainly mediated by the frontal lobes (see Jurado & Rosselli, 2007, for a review). The reason for this concentration is based on

the observation that frontal lesions in both experimental animals and human patients sometimes produce hyperactivity, distractibility, or impulsivity, separately or in combination, similar to the behavioral symptoms seen in children with ADHD (Fuster, 1989). Importantly, abnormalities in other parts of the brain can also produce ADHD symptoms. Below I will present the most prominent neuropsychological factors studied in relation to ADHD symptoms in children.

Executive functions (EFs)

EFs are critically important to the overall neuropsychological functioning of the developing child and play a fundamental role in the child's cognitive, behavioral, and social development (Diamond, 2006; Pennington & Ozonoff, 1996). Moreover, EFs play a particularly central role in novel situations in which there are no established routines for behavior (Stuss & Knight, 2002). Prominent EF impairments in children with ADHD symptoms seem to be in inhibitory control and working memory (Barkley, 1997a, b; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Willcutt et al., 2005a).

Concerning the organization of EF, Miyake and coworkers (2000) suggested that EF is organized hierarchically and should be conceptualized as consisting of both a unitary construct and dissociable components. Thus, the EF construct is an umbrella term comprising a wide range of cognitive processes. As commonly found with these kinds of broad constructs (see, e.g., intelligence), there is no universal definition of EF and at least 33 definitions have been suggested (Eslinger, 1996). However, most researchers in this area agree that the term executive function refers to higher-order cognitive processes that underlie self-regulation and goal-directed behavior, including inhibitory control, working memory, set shifting, abstraction, planning, organization, and verbal fluency (Pennington & Ozonoff, 1996; Welsh, 2002).

The development of EFs has been associated with the maturation of the frontal lobe as well as its connections with other brain areas (Anderson, 2002). Different executive abilities have been shown to have different developmental trajectories, with certain executive components not reaching complete competency until late in adolescence or early adulthood (e.g., Diamond, 2006). The first executive function to emerge in children is the capacity for inhibitory control, and among the last to appear is verbal fluency (see Jurado & Rosselli, 2007, for a review). Concerning the relation between impaired EF and ADHD symptoms in children, one of the most influential neuropsychological theories is Barkley's hybrid model of ADHD (Barkley, 1997a, b), which I will explain below.

Barkley's hybrid model of ADHD

According to Barkley's model (1997a, b), the behavioral manifestations of ADHD symptoms are proposed to derive from poor EFs, with poor inhibitory control as a core deficit. Barkley divided inhibitory control into three different inhibitory functions: inhibition of prepotent responses (i.e., responses that have been reinforced in the past), stopping of ongoing responses (i.e., permitting a delay in the decision to respond), and interference control (i.e., resistance to distracters). This model calls attention to four EFs that are dependent on well-functioning inhibitory control if they are to run effectively: (1) Working memory (WM; verbal and spatial WM) refers to the capacity to maintain information in mind and use that information to guide immediate behavior in the absence of informative external cues (Goldman-Rakic, 1995); (2) Self-regulation of affect, motivation and arousal; (3) Internalization of speech; and (4) Reconstitution. It is important to bear in mind what Barkley (1997b) emphasized, namely that "behavioral inhibition, does not directly cause the four intermediate executive functions to occur but merely sets the occasion for their performance"(p 72).

In line with Barkley's theoretical prediction, several previous studies have found relations between poor EF and ADHD symptoms in both clinical and community-based samples (see, Martinussen et al., 2005; Willcutt et al., 2005a, for reviews). However, empirical evidence has not convincingly supported the primacy of impaired inhibitory control in children with ADHD symptoms (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Willcutt et al., 2005a; Zeeuw et al., 2008).

Concerning the three ADHD subtypes (i.e., the primarily inattentive, primarily hyperactive/impulsive and combined subtypes), they have generally not been found to have different EF profiles (e.g., Geurts, Verté, Oosterlaan, Roeyers, & Sergeant, 2005; Faraone, Biederman, Weber, & Russel, 1998; Huang-Pollock, Mikami, Pfiffner, & McBurnett, 2007). However, studies of specific relations to the two ADHD symptom domains (hyperactivity/impulsivity and inattention) using dimensional analyses, controlling for the overlap, i.e., the high correlation between the two ADHD symptom domains, have indicated that EFs are specifically related to symptoms of inattention (Chhabildas, Pennington, & Willcutt, 2001; Martel, Nikolas, & Nigg, 2007).

More recently, the prominence of impairments in inhibitory control and other aspects of executive functioning in theories of ADHD symptoms have been called into question. Important reasons for this are that impairments in EFs are not specific to ADHD and can be seen in other childhood disorders

as well, such as autism (e.g., Geurts, Verté, Oosterlaan, Roeyers, & Sergeant, 2004). Further, not all children with ADHD have dysfunctional EF (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Willcutt et al., 2005a) and converging evidence shows other neuropsychological impairments in children with ADHD, such as poor state regulation and delay aversion.

State Regulation

State regulation is a factor of great interest in research on the neuropsychology in children with ADHD symptoms. The concept of *state* refers to the overall level of alertness of an individual (see Van der Meere, 2005, for a review). State regulation, refers to energy mobilization, which is necessary to change the state of the organism in the direction that is optimal for a task or situation, referred to as the “required or target state” (Hockey, 1979). Further, this adaptive function has a strong resemblance to concepts such as mental effort and motivation and may be considered an important aspect of frontal lobe functioning and its rich connections with additional systems, such as the limbic structures (e.g., Eslinger, 1996). The state regulation hypothesis, which is part of the Cognitive Energetic Model (Sergeant, 2000; 2005), agrees with ideas suggesting that ADHD symptoms reflect dysfunctional EF. However, instead of a primary deficit in inhibitory control, it proposes that poor state regulation, such as regulation of effort and activation, underpins dysfunctional EF.

Poor state regulation in children with ADHD symptoms is thought to give rise to slower and more variable reaction times (RT variability). Sanders (1983) suggested that the presentation rate of stimuli during reaction time tests, such as go/no-go tasks, may affect the state of the individual. A fast presentation rate may induce over-activation, resulting in fast, inaccurate responding. On the other hand, a slow presentation rate of stimuli may induce under-activation, resulting in slow and variable responding. Consequently, poor state regulation in children with ADHD symptoms implies that they are not able to allocate extra energy in order to adjust their underactive state during reaction time tasks, such as go/no-go, especially with a slow stimulus presentation rate.

Relations between ADHD symptoms and RT variability have consistently been demonstrated in studies using both clinical (e.g., Johnson et al., 2007; Klein, Wendling, Huettner, Ruder, & Peper, 2006; Lijffijt et al., 2005) and non-clinical samples (e.g., Berwid, et al., 2005; Kuntsi, Andreou, Ma, Börger, & van der Meere, 2005). With regard to how RT variability is related to the two symptom domains of ADHD, this issue has mainly been investigated by studying differences between ADHD subtypes, and in these studies, few significant differences have been found (e.g., Martel et al.,

2007; Tucha et al., 2008). However, it is important to note that RT variability has been shown to be one of the most consistent characteristics of ADHD symptoms across a variety of tasks, cultures, and laboratories (see Castellanos & Tannock, 2000; Castellanos et al., 2006, for reviews).

In dimensional analyses, Epstein and colleagues (2003) found that RT variability was related to both symptoms of hyperactivity/impulsivity and symptoms of inattention, but this study failed to control for the overlap, i.e. the high correlation, between the two ADHD symptom domains. Clarke and colleagues (2007) employed such a control in analyses investigating independent as well as interaction effects in the two symptom domains. They found a significant interaction effect for RT variability, suggesting that it was the combination of high levels of hyperactivity/impulsivity and inattention that was associated with high RT variability. However, the authors did not specify what the interactive relation implied.

Delay Aversion

In contrast to the predominant view of ADHD as an EF disorder, Sonuga-Barke and colleagues (Sonuga-Barke, 1994; Sonuga-Barke, Taylor, Sembi, & Smith, 1992) offered an alternative perspective of ADHD as a motivational style, which characterized children with ADHD as delay averse. The delay aversion hypothesis states that children with ADHD symptoms more often choose a small, immediate reward over a larger, delayed reward than do control children, especially when this option reduces the overall delay period (Sonuga-Barke et al., 1992). When children with ADHD symptoms are in control of their environment, they can choose to minimize delay by acting impulsively. When children with ADHD symptoms are not in control of their environment, or at least when they are expected to behave in certain ways, they often choose to distract themselves from the passing of time.

Recent research supports a relation between delay aversion and ADHD symptoms in both clinical (e.g., Dalen, Sonuga-Barke, Hall, & Remington, 2004; Solanto et al., 2001) and non-clinical samples (e.g., Sonuga-Barke et al., 2003; Thorell, 2007). However, it should be noted that the relation between delay aversion and ADHD has not at all been as extensively studied as that between EF and ADHD, and some studies have failed to find a relation between delay aversion and ADHD (e.g. Scheres et al., 2006; Solanto et al., 2007; Van der Meere, Marzocchi, & Meo, 2005).

Concerning the specificity of delay aversion in relation to the two ADHD symptom domains, few studies have investigated this issue. However, at the theoretical level, it has been argued that delay aversion should be more

strongly related to hyperactivity compared to inattention (Castellanos et al., 2006), and support for this claim has been found in two studies of community-based samples (Scheres & Sumiya, 2008; Thorell, 2007).

Sustained Attention

Although recent theories emphasize a range of processes other than attention as being involved in ADHD symptoms, attentional functioning remains an area in need of further clarification, especially sustained attention (Diamond, 2005; Nigg, 2006). Sustained attention is related to vigilance and refers to the ability to maintain a state of alertness and wakefulness over time during prolonged mental activity (Weinberg & Harper, 1993). Therefore, sustained attention deficit should be operationalized as performance deteriorations over the time course of a particular task (Nigg, 2006; Van der Meere & Sergeant, 1988).

The relation between sustained attention and ADHD symptoms is under debate (Nigg, 2006), and conflicting results have been found. Although several studies have demonstrated that children with ADHD have poor sustained attention (e.g., Börger et al., 1999; Epstein et al., 2003; Hooks, Milich, & Lorch, 1994), a recent meta-analysis (Huang-Pollock & Nigg, 2003) failed to discover impaired sustained attention in children with ADHD symptoms. Concerning the specificity of the two ADHD symptom domains in relation to sustained attention, few studies have investigated this issue. One study by Epstein et al. (2003) revealed that sustained attention did not demonstrate symptom specificity in a large epidemiological sample. However, due to contradictory results, some researchers recommend a closer investigation of DSM-IV-defined inattention, as the relation to sustained attention is less clear for this ADHD symptom domain (Diamond, 2005; Nigg, 2006).

It is important to mention that all of the neuropsychological processes I have described above – EF, state regulation, and delay aversion – have been put forward as candidate endophenotypes (Castellanos & Tannock, 2002; Kuntsi et al., 2006). Endophenotypes refer to phenotypes that are more proximal to the genetic etiology of the disorder than its behavioral symptoms and are influenced by at least one of the genes that increase susceptibility to the disorder (see Gottesman & Gould, 2003, for a review). Therefore, it has been proposed that endophenotypes may be more suitable for detecting risk genes related to ADHD symptoms than phenotypes (i.e., ADHD symptoms), and their use would result, theoretically, in greater statistical power. More specifically, endophenotypes are genetically less complex than phenotypes, i.e., related to fewer genes than the phenotypes (Doyle et al., 2005). Hence,

interest has grown in using neuropsychological endophenotypes to acquire knowledge about the etiology of complex disorders, such as ADHD.

A crucial advance in this area of research would involve being able to clarify to what subgroups of children with ADHD symptoms the above-mentioned single process models apply. Below, I will give some background to the notion that multiple neuropsychological pathways, compared to single process theories, may be a better option when explaining ADHD symptoms in children. Additionally, I will describe some of the few elaborated multiple neuropsychological pathway models as well as related research.

Multiple Neuropsychological Pathways to ADHD Symptoms

As mentioned above, recent research has found effects of several neuropsychological processes in children with ADHD symptoms (e.g., Kuntsi, Oosterlaan, Stevenson, 2001; Solanto et al., 2001), which implies that it is unlikely that researchers will find a single core deficit. Therefore, single-process models are not sufficient if we are to understand the neuropsychological impairments related to ADHD symptoms. In line with this reasoning is the fact that the group effects on different neuropsychological measures for children with ADHD symptoms compared with children without ADHD symptoms are generally modest in size, ranging from $d=.60$ to $.90$. This fact, suggests a substantial distributional overlap between ADHD symptoms and normal score distributions on most neuropsychological tasks (Nigg, 2005; Nigg et al., 2005). Moreover, the modest effect sizes also imply that some children with ADHD symptoms perform in the normal range on neuropsychological measures. Indeed, Willcutt and colleagues (2005a) concluded that “EF weaknesses are neither necessary nor sufficient to cause all cases of ADHD” (p. 1343). This conclusion was confirmed by Nigg and colleagues (2005), who found that only approximately 35% to 50% of children with ADHD symptoms showed impairments in EF.

Thus, several recent theoretical propositions have emphasized the need to regard ADHD as a heterogeneous disorder with multiple neuropsychological pathways (e.g., Castellanos et al., 2006; Sonuga-Barke, 2003, 2005; Willcutt et al., 2005b). Some multiple-deficit models have proposed independent or additive effects of separate neuropsychological deficits that characterize subgroups of children with ADHD symptoms (e.g., Sonuga-Barke, 2003, 2005). Other models suggest that ADHD symptoms also could be explained by the interactive effects of several cognitive deficits (Castellanos et al., 2006; Willcutt et al., 2005b). Sonuga-Barke’s dual pathway model (2003, 2005), which I will describe below, is one of the first formal theories of multiple pathways to ADHD.

The Dual Pathway Model

To deal with the problem of the neuropsychological heterogeneity seen in children with ADHD symptoms, Sonuga-Barke's (2002, 2003, and 2005) developed the dual pathway model. He highlighted the need to end the search for a single core dysfunction, and to instead try to identify multiple developmental pathways in which different neuropsychological impairments might be considered complementary rather than competitive (Sonuga-Barke, 2005, p. 1235). The dual pathway model states that EF and delay aversion constitute independent pathways to ADHD and support for this view has been found in both clinical (Dalen et al., 2004; Solanto et al., 2001) and non-clinical samples (Sonuga-Barke et al., 2003; Thorell, 2007; see Castellanos et al., 2006; Sonuga-Barke, Sergeant, Nigg, Willcutt, 2008, for reviews).

This model further implies that EF and delay aversion are independent but related processes that may act additively to produce ADHD symptoms in children. Solanto and colleagues (2001) addressed this issue in a clinical sample of children with ADHD, and in line with the dual pathway model, they found that inhibitory control and delay aversion were largely uncorrelated, but that both phenomena were associated with ADHD. Nonetheless, it is important to note that Nigg and colleagues (2005) reanalyzed Solanto et al.'s (2001) data and found that as many as 39% of the children with ADHD had neither problems with delay aversion nor problems with inhibitory control. This in turn implies that far from all cases of high ADHD symptom levels can be explained by these two neuropsychological deficits. Consequently, the dual pathway model seems inadequate as regards fully accounting for the neuropsychological heterogeneity of ADHD symptoms. One way to handle this problem could be to include additional neuropsychological processes. For example state regulation could be a good candidate as this neuropsychological factor, measured as RT variability, is a common impairment found in children with ADHD symptoms (e.g., Castellanos et al., 2006). Moreover, as will be described below an additional complement could be to include interactive neuropsychological pathways in the model.

Multiple Interactive Pathways

Besides including several neuropsychological factors that may act independently in the development of ADHD symptoms, more recent accounts have recognized the likelihood of interaction effects between neuropsychological processes (Castellanos et al., 2006; Willcutt et al., 2005b). To my knowledge, however, few previous studies have investigated possible interaction effects of neuropsychological processes in relation to ADHD symptoms in children.

Multiple Pathway Models and empirical findings

Concerning the possibility of multiple neuropsychological pathways being part of the explanation for ADHD symptoms, few studies have examined several neuropsychological processes, such as EF, delay aversion and state regulation in the same sample. This is rather remarkable, considering that multiple neuropsychological pathway models are consistent with the multifactorial etiology of ADHD, as described above. However, Kuntsi and colleagues (Kuntsi et al., 2001) did include measures of EF (inhibition and working memory), state regulation (i.e., RT variability) and delay aversion. They found that RT variability and delay aversion, but not inhibition, contributed to discriminating between children with ADHD symptoms and controls. However, only the effect of state regulation remained when controlling for comorbid ODD/CD and intelligence. In parity with this result, findings from a community-based sample (Van der Meere et al., 2005) showed that only RT variability, but not inhibition or delay aversion, was significantly associated with ADHD symptoms.

These findings could be interpreted as being in line with the idea that poor state regulation, measured as RT variability, constitutes a more generalized cognitive deficit, which underpins other neuropsychological impairments in children with ADHD (e.g., Sergeant, 2000, 2005). On the other hand, independent effects of inhibition, when controlling for RT variability, have been found in some previous studies (Bitsakou, Psychogiou, Thompson, Sonuga-Barke, 2008; Klein et al., 2006). Thus, the exact nature of the relation between state regulation and other neuropsychological processes in the prediction of ADHD symptoms is far from clear. These contradicting results imply that more research is needed to investigate the characteristics of EF, state regulation and delay aversion in relation to ADHD symptoms. This is an important issue, in that few earlier studies have investigated different neuropsychological theories in the same sample, and it is therefore not known whether these factors constitute independent and/or interactive pathways to ADHD symptoms.

The three ADHD subtypes (i.e., the primarily inattentive, primarily hyperactive/impulsive and combined subtypes) have generally not been found to have different neuropsychological profiles (e.g., Geurts et al., 2005; Faraone et al., 1998; Huang-Pollock et al., 2007). These findings may be related to the fact that studies using categorical analyses usually exclude the hyperactive/impulsive subtype and most often fail to control for the overlap, i.e., high correlation, between hyperactivity/impulsivity and inattention. However, besides knowledge of independent and/or interactive neuropsychological pathways it is important to gain knowledge about the relevance of separating the two ADHD symptom domains in relation to

neuropsychological impairments. Such knowledge can improve our theoretical understanding of neuropsychological impairments in children with ADHD symptoms. Thereby, promoting the progress of multiple neuropsychological pathway models, additionally, such information can facilitate the progress of interventions for children with ADHD symptoms.

In this context, it is important to note the issue of the sensitivity and specificity of neuropsychological measures. More specifically, performance differences within ADHD samples have been documented in studies examining whether various neuropsychological measures could be used as diagnostic tools for ADHD in children (e.g., see Nigg et al., 2005; Sonuga-Barke et al., 2008, for reviews). These studies found that most neuropsychological measures, such as EF, RT variability and delay aversion, have good positive predictive power for ADHD, characterized by adequate sensitivity, but poor negative predictive power, i.e., poor specificity. That is, abnormal scores on neuropsychological measures are generally predictive of the diagnosis, however, normal scores cannot rule out the diagnosis. This pattern is due to the fact that not every child is impaired on every test and that some children with ADHD symptoms perform within the normal range on all or most measures.

In this regard, it is worth noting that not all children with ADHD symptoms show impairments in neuropsychological processes, and few studies have investigated what proportion of children with ADHD symptoms show neuropsychological impairments above the 90th percentile of the comparison group (assumed to be a clinically meaningful impairment; see Nigg, 2005). Studies looking at this issue have found that only a minority of individuals in the ADHD group exhibited a deficit on any of the specific neuropsychological tasks (Nigg, 2005). Thus, more work is needed to study multiple neuropsychological theories together in the same sample; as such studies could elucidate how many children with ADHD symptoms show neuropsychological impairment in only one area, multiple areas or no impairments at all. In addition, an important issue in relation to measurement of neuropsychological processes is the choice of reliable and age appropriate measures, an issue that I will discuss below.

Measurement issues and neuropsychological factors

It is widely agreed that greater attention should be paid to the psychometric properties of neuropsychological measures (e.g., Nigg, 2001; Sergeant, Geurts, & Oosterlaan, 2002). More specifically, it is of great importance that the measure expected to tap the neuropsychological function of interest have satisfactory properties, such as adequate reliability. For a test to be useful in clinical practice, high reliability coefficients, around .80 or above, (Ryan,

Lopez, Sumerall, 2001) are commonly required. However, with neuropsychological tasks, it is uncommon to obtain reliability coefficients of such magnitude, usually, correlations of .70 or higher indicating good test-retest reliability, and correlations between .50 to .60, indicating moderate test-retest reliability (Kuntsi, Stevenson, Oosterlaan, Sonuga-Barke, 2001). It is important to note that only novel tasks can capture impairments in executive functions, and for this reason, the corresponding test-retest reliabilities are usually low (Rabbitt, 1997). Additionally, it is assumed that the reliability of summed components is better than that of single variables (Rousson, Gasser, Seifert, 2002).

Relatively few studies have examined the reliability of neuropsychological tasks in children. The studies that have been conducted have revealed low to moderate test-retest reliability (e.g., Kuntsi et al., 2001). The modest reliability of most neuropsychological measures constrains the range of effect sizes possible to obtain in group comparisons. Although measurement weaknesses are unlikely to explain the failure to find a core neuropsychological impairment in children with ADHD symptoms, these results suggest that future neuropsychological studies should carefully assess the reliability of each measure.

An additional important aspect when using neuropsychological measures is the issue of developmental changes in neuropsychological processes. For example, and consistent with Barkley's theories, components of EF, such as inhibitory control and WM, mature at different ages. More specifically, a task sensitive to a specific EF process at a young age may be too simplistic to tap the same executive process in older individuals (Denckla, 1996). Thus, when studying ADHD symptoms in children, it is important to use developmentally sensitive neuropsychological tasks in an effort to detect relations and group differences. This in turn implies that the age range of the sample cannot be too wide. We must be able to take developmental aspects into account when selecting adequate neuropsychological measures.

In addition to neuropsychological impairments in children with ADHD symptoms, problems with comorbidity are the rule, rather than the exception. I will therefore describe the most common comorbid behavioral problems associated with ADHD symptoms.

Comorbidity and ADHD symptoms

Comorbidity is defined as the co-occurrence of two (or more) independent disorders in the same individual. Comorbidity tends to be higher in clinical samples than in community-based samples (Pfflner et al., 1999; Wilens et

al., 2002), with as many as 80% of clinical samples of children with ADHD having at least one other disorder. Moreover, children with ADHD symptoms in combination with one or several comorbid conditions generally have a poorer overall outcome than do children with only ADHD symptoms (Jensen, Marin, & Cantwell, 1997).

In addition to different expressions of hyperactivity/impulsivity and/or inattention, as well as impairments in neuropsychological functioning, differences in comorbid symptom expression also contribute to the heterogeneity seen in children with ADHD symptoms. Two common behavior problems are symptoms of oppositional defiant disorder (ODD) and internalizing problems such as anxiety/mood disorders (e.g., Biederman, 2005; Schatz & Rostain, 2006). In addition, children with ADHD symptoms often show sluggish cognitive tempo (SCT), poor academic performance (e.g., Barkley, 1998; Massetti et al., 2008), poor emotional regulation (Jensen & Rosén, 2004; Maedgen & Carlson, 2000; Norvilitis, Casey, Brooklier, & Bonello, 2000), and low social competence (Bagwell, Molina, Pelham, & Hoza, 2001). Below I will give a short review of these common comorbid and socioemotional behavioral problems.

Oppositional Defiant and Conduct Disorder (ODD/CD)

Oppositional Defiant Disorder (ODD) is characterized by a pattern of negativistic, hostile, and defiant behavior. In contrast, Conduct Disorder (CD) is a more severe disorder of habitual rule breaking defined by a pattern of aggression, destruction, lying, stealing, or truancy (DSM-IV, 1994). ADHD and ODD/CD have been found to co-occur in 40% to 90% of cases in both clinical and community-based samples (see Biederman, 2005 for a review). Symptoms of ODD may begin as early as age 3, and this is a more common condition in young children than is CD. Recent research has shown that ODD symptoms in children are associated with social adversity, family psychiatric problems, family conflict and poor parenting (e.g., Barkley, 1998, p. 142). Interestingly, ODD is not only highly comorbid with ADHD, but is also a predictor of two different developmental trajectories ending in either CD or anxiety. The path that the ODD phenotype selects is influenced by complex interactions between genetics and environment (Burke, Loeber, Lahey, & Rathouz, 2005; Lavigne et al., 2001). Thus, symptoms of ODD are an important aspect to take into account when investigating disruptive behavioral problems in children.

There is a controversy regarding whether neuropsychological impairments are unique correlates to ADHD symptoms or also associated with ODD (e.g., Kuntsi et al., 2001; Oosterlaan, Logan, & Sergeant, 1998; Schacher, Mota, Logan, Tannock, & Klim, 2000; Séguin, Boulerice, Harden,

Tremblay, & Phil, 1999; Sergeant et al., 2002). However, few studies have taken into consideration symptoms of ODD when investigating the relations between neuropsychological factors and ADHD symptoms. Therefore, it is important to take into account the overlap between ADHD and ODD symptoms when investigating the relations to neuropsychological factors to discover whether neuropsychological impairments also are specifically related to ODD. Concerning the specificity of the two ADHD symptom domains, ODD symptoms are assumed to be more strongly related to hyperactivity/impulsivity than to inattention (e.g., Eiraldi et al., 1997; Gaub & Carlson, 1997).

Internalizing Problems

Internalizing problems are intrapersonal problems such as depression, anxiety and fearfulness (Achenbach & Edelbrock, 1984). Major depression in a child may be apparent from a sad or irritable mood or a persistent loss of interest or pleasure in the child's favorite activities. Also common are physiological disturbances, such as in changes in appetite and weight, abnormal sleep patterns, fatigue and diminished ability to think. Anxiety, on the other hand, is characterized by, for example, rumination, and catastrophic thinking such as the anticipation of great embarrassment. Internalizing problems are often not suspected in an overactive child. However, a recent longitudinal study (Leech, Larkby, Day, & Day, 2006) has shown that symptoms of inattention early in childhood predicted internalizing problems at the age of 10 years. In line with this finding, studies have shown that internalizing problems seem to be more strongly related to symptoms of inattention than to hyperactivity/impulsivity (e.g., Eiraldi et al., 1997; Gaub & Carlson, 1997). On the other hand, Power and colleagues (Power, Costigan, Eiraldi, & Leff, 2004) used dimensional analyses and found that internalizing problems were more consistently related to hyperactivity than to inattention. Moreover, it is important to note that internalizing problems in children with ADHD symptoms are less common than in children with ODD, occurring in approximately 15%-35% of cases (e.g., Biederman, 2005; Schatz & Rostain, 2006).

Sluggish Cognitive Tempo (SCT)

Behaviors of SCT encompass inconsistent alertness and slow processing such as sluggishness, drowsiness and apparent daydreaming (Lahey et al., 1998; McBurnett, Pfiffner, & Frick, 2001). Previous findings (Barkley, 2006) have shown that approximately 30-50% of children diagnosed as primarily inattentive have problems with SCT. Although SCT and DSM-IV-defined inattention seem to be highly correlated (Hartman, Willcutt, Rhee, & Pennington, 2004; McBurnett et al., 2001; Todd, Rasmussen, Wood, Levy,

& Hay, 2004), research has shown that SCT behaviors load on a factor separate from both DSM-IV inattention and hyperactivity/impulsivity (the latent factors were allowed to correlate with one another; Hartman et al., 2004). It is assumed that children with high levels of DSM-IV-defined symptoms of inattention in combination with SCT may have different profiles concerning neuropsychological impairments and comorbidity compared to those with only DSM-IV-defined inattention. (e.g., internalizing problems, poor academic achievement; Carlson & Mann, 2000; Mc Burnett et al., 2001; Milich et al., 2001; Mikami, Huang-Pollock, Piffner, McBurnett, & Hangai, 2007). However, few empirical studies have taken into account behaviors of SCT when investigating DSM-IV-defined inattention in relation to neuropsychological factors and comorbidity.

The few studies that have compared children who have a primarily inattentive diagnosis with and without SCT have found that these two groups do not differ in terms of poor academic achievement (Carlson & Mann, 2002), nor do they show qualitatively different performance on EF tests, such as inhibitory control, working memory and planning (Hinshaw, Carte, Fan, Jassy, & Owens, 2007; Hinshaw, Carte, Sami, Treuting, & Zupan, 2002). One explanation for the absence of the differences just defined is that most studies have used clinical samples, and no earlier studies have controlled for the overlap, i.e., high correlation, between DSM-IV-defined inattention and SCT by using a dimensional approach. The fact that DSM-IV-defined symptoms of inattention and SCT are highly correlated and that both constructs involve attention-related symptoms implies that these two symptom dimensions may have some neuropsychological impairments and comorbidity in common. They may, however, also have different correlates. For example, research has indicated that the presence of SCT may contribute to lower levels of ODD (Barkley, 2006; Carlson & Mann, 2002; Eiraldi, Power, & Nezu, 1997; Mikami et al., 2007). Thus, more research is needed that looks at population-based samples of children, with a focus on independent and interactive relations of DSM-IV-defined inattention and SCT to neuropsychological factors and comorbidity. Knowledge from such studies can further our understanding of the heterogeneity in children with ADHD symptoms, which in turn can improve intervention programs for affected children.

Emotion Regulation and Social Competence

Problems with emotional regulation are common in children with ADHD symptoms and can often lead to significantly poorer social competence (Eisenberger et al., 1994). Emotion regulation is the ongoing process of responding to one's environment with emotions that are both socially acceptable and context-appropriate for a given situation (Cole, Michel, &

Teti, 1994). Researchers have found that emotion dys-regulation is linked to disruptive behavior in general (e.g., Eisenberg et al., 1996; Keenan, 2000) as well as to ADHD symptoms (Jensen & Rosén, 2004; Maedgen & Carlson, 2000; Norvilitis, et al., 2000). According to Barkley (1997a), problems with inhibitory control are the key to understanding the myriad of social difficulties associated with ADHD symptoms. He posited that because children with ADHD have deficits in inhibition, they will also have great difficulty restricting or keeping private their emotional reactions to evocative situations. This reasoning is also supported by a recent review paper (Oscsner & Gross, 2005) suggesting that the ability to control emotion involves frontal brain regions, e.g., EF.

Social competence, such as prosocial behaviors (e.g., helping peers, reading social cues and communication skills), is characterized by children's adaptive functioning in their social environment (e.g., Elliott & Gresham, 1993). Children with ADHD symptoms have been shown to have less knowledge about social skills and appropriate behavior with others (Grenell, Glass, & Katz, 1987). Problems with social competence in children with ADHD symptoms are more common in those who are the most sensation-seeking, emotionally reactive, aggressive, and noncompliant (Hinshaw, 2003). Thus, children with ADHD symptoms in combination with poor social competence also receive the greatest disapproval from their peers (Bagwell et al., 2001; DuPaul, McGoey, Eckert, & VanBrakle, 2001; Hinshaw & Melnick, 1995).

Poor academic achievement

One common correlate of ADHD symptoms in children is academic underachievement. Thus, teachers and parents frequently report that children with ADHD symptoms underachieve academically compared to their classmates (Barkley, 1998, 2006). More specifically, up to 80% of children with this condition have been found to exhibit poor academic performance (Cantwell & Baker, 1991). Further, it is essential to determine whether each of the subtypes of ADHD is associated with academic deficits to the same extent. This is important because recent research has shown that poor academic achievement seems to be more strongly associated with symptoms of inattention than with hyperactivity/impulsivity (Masseti et al., 2008; Rabiner & Coie, 2000).

Before proceeding to the aims of this thesis I will give information about treatment of ADHD and the need for longitudinal studies as well as possible confounding factors in this area of research.

Treatment of ADHD

The most effective treatments for ADHD symptoms in children involve medication with central nervous system stimulants, such as methylphenidate and behavior therapy applied across home and school settings, as well as their combination (Pelham & Fabiano, 2008; Pelham, Wheeler, & Chronis, 1998). Stimulant medications primarily target dopaminergic and noradrenergic pathways. Recent evidence also suggests that stimulant medication improves neuropsychological impairments in children with ADHD (e.g., Bedard, Martinussen, Ickowicz, & Tannock, 2007; Riccio, Waldrop, Reynolds, & Lowe, 2001). Newer non-stimulant treatments such as atomoxetine have also shown promise in enhancing neuropsychological functioning (Spencer et al., 1998). Interestingly, Toplak and colleagues (see Toplak, Connors, Shuster, Knezevic, & Parks, 2008, for a review) showed that cognitive interventions could improve neuropsychological impairments in individuals with ADHD symptoms. For example systematic practice of computerized working memory exercises over a 5- to 6-week period, improved standard measures of working memory in children with ADHD as well as significant reduction in ADHD symptoms (Klingberg et al., 2005). Thus, by identifying different neuropsychological impairments in children with ADHD symptoms, we may have the possibility to extend these interventions, which could lead to better future outcomes for children with disruptive behavioral problems.

Longitudinal studies

To gain further knowledge about stability and how ADHD symptoms and neuropsychological processes act as predictors of behavior problems in young children, we need longitudinal studies of community-based samples. Concerning ADHD symptoms, previous research has shown that some children who display high levels of these behaviors during the preschool years not only tend to show continuing problems in this domain (e.g., Campbell, 1995, 2002; Greenfield Spira & Fichel, 2005; Jester et al., 2005), but also problems with other aspects of socioemotional development, such as poor social competence, ODD/CD, internalizing problems and dysfunctional emotion regulation (e.g., Angold, Costello, & Erkanlie, 1999a; Bagwell et al., 2001; Biederman, 2005; Norvilitis et al., 2000; Schatz & Rostain, 2006).

Concerning the stability and predictive value of impairments in neuropsychological factors in preschool children, most studies in this area have been concurrent and cross-sectional. However, cross-sectional studies can only address differences between children with ADHD symptoms and

comparison children at a particular point in time. In contrast, longitudinal studies are able to address the predictive validity of ADHD symptoms and neuropsychological factors. That is, they are able to determine, for example, whether EF predicts future ADHD symptoms and socioemotional functioning.

Regarding longitudinal relations between early impairments in EF and later behavior problems, Berlin, Bohlin and Rydell (2003) found that inhibitory control in preschool was related to both symptoms of hyperactivity and inattention at school age in a community-based sample. Further, a few additional community-based studies, investigating the broader spectrum of externalizing problems rather than ADHD symptoms specifically, have found longitudinal relations between EF and later behavior problems (Brophy, Taylor, & Hughes, 2002; Nigg et al., 1999; Riggs et al., 2003). In two of these studies (Nigg, Quamma, Greenberg, & Kusche, 1999; Riggs, Blair, & Greenberg, 2003), researchers controlled for symptom levels at baseline, enabling them to show that poor EF is a predictor of later externalizing problems, independent of the influence of early problem levels.

Moreover, poor inhibitory capacity has been shown to be associated with later non-cooperative behavior even when controlling for behavior at baseline (Ciairano, Visu-Petra, & Settanni, 2007). In addition, there are two studies demonstrating significant relations between impaired EF and internalizing problems (Nigg et al., 1999; Riggs et al., 2003). In one of these studies, relations between EF impairments and poor social competence were also found (Nigg et al., 1999). However, the effects were generally small, and for internalizing problems, Riggs and colleagues (2003) found significant effects for parental ratings of problem behavior but not for teacher ratings. Thus it would seem that the relation between early EF impairment and later socio-emotional functioning needs to be studied further, preferably including ADHD symptoms so as to clarify whether EF impairment is related to these outcomes independent of ADHD symptoms. Knowledge about early predictors of ADHD symptoms and socio-emotional functioning in children may facilitate early identification and interventions in children with disruptive behavioral problems.

Confounding Factors

There are inevitably a host of other variables correlated with ADHD symptoms and neuropsychological factors that differ between children with and without ADHD symptoms. For example, lower IQ, sex, and SES (e.g., Biederman, Faraone, & Monuteaux, 2002; Counts et al., 2005), as well as additional symptoms of externalizing behaviors, such as ODD, are

commonly found to be associated with ADHD symptoms. This is a complicated issue for the field. In particular, concerning the issue of intelligence, the field has debated about how to deal with differences in IQ, with some researchers arguing that intelligence should always be statistically controlled to ensure that neuropsychological impairments associated with ADHD cannot be explained more parsimoniously by group differences on this correlated variable (e.g., Lahey et al., 1998).

Previous research has demonstrated that lower IQ is associated with ADHD symptoms in children in both clinical and general population samples (meta-analysis by Fraizer, Demaree, & Youngstrom, 2004; Kuntsi et al., 2004). Additionally, IQ is also correlated with neuropsychological factors such as EF (Friedman et al., 2006). On the other hand, ADHD symptoms may directly cause a child to perform poorly on standardized tests of intelligence (e.g., Barkley, 1997). In this case, it would not be appropriate to control for IQ, as this would remove variance that is associated with ADHD symptoms. The issue as to whether neuropsychological impairments observed in children with ADHD symptoms are a function of IQ has not been resolved conclusively, and the optimal approach is likely to vary depending on the specific research question. However, few studies have taken into account intelligence when studying the relations between neuropsychological processes and ADHD symptoms. Therefore, I agree with Nigg (2006; p. 314) in his statement concerning intelligence: “ignoring its role entirely is simply not an option if we are to achieve a satisfactory, clinically meaningful understanding of ADHD”. Thus, we need more knowledge about the impact of intelligence on the relation between neuropsychological processes and ADHD symptoms in children.

Concerning age, as mentioned above, this variable has been shown to have a great impact on neuropsychological aspects and therefore could affect the relationship between the measures and ratings of disruptive behavioral problems in children (e.g., Brocki & Bohlin, 2006). Thus, it is possible that performance on the neuropsychological tasks improves with age, and that age plays an important role in the disappearance of significant group differences. Therefore, it is important to study ADHD symptoms in age-homogenous samples, as the determinants of different neuropsychological impairments and comorbidities may be different for children of different ages.

Aims of the current thesis

I have conducted four studies with the aims to improve our understanding of the heterogeneity characterizing children with ADHD symptoms as regards neuropsychological pathways, and specificity of the two ADHD symptom domains in relation to neuropsychological factors and comorbid behavioral problems. Particular emphasis is placed on prominent neuropsychological processes such as EF, state regulation and delay aversion in the explanation of ADHD symptoms in children. My studies are conducted on two community-based samples of children and involve both concurrent and longitudinal designs as well as both categorical and dimensional approaches. Using this approach, I hope to increase our knowledge about multiple neuropsychological pathways and comorbidity, in relation to the two ADHD symptom domains. More specifically, the major aims of this thesis were:

- To examine if preschool children with ADHD symptoms, but without impaired EF, tend to develop impairments in EF two years later. In addition, to investigate whether ADHD symptoms and/or impaired EF in preschool children predict continuing problem behaviors. These questions were addressed using longitudinal data (Study I).
- To study the specificity of impairments in neuropsychological factors in relation to ADHD symptoms, while at the same time taking into account symptoms of ODD (Study I, II, and III).
- To investigate whether there are independent (Study II and III) and/or interactive (Study III) neuropsychological pathways to ADHD symptoms in children.
- To examine whether different neuropsychological factors (Study II and III) and comorbid behavioral problems (Study II) are specifically related to either symptoms of hyperactivity/impulsivity or inattention, taking the overlap, i.e., high correlation between the two ADHD symptom domains, into account
- To investigate the overlap, i.e., high correlation, between sluggish cognitive tempo (SCT) and DSM-IV-defined symptoms of inattention in relation to neuropsychological factors and comorbidity (Study IV).

Empirical Studies

Participants and procedures

Study I and III are based on the same sample of children. Participants in these studies took part in a larger longitudinal study ($n = 217$; boys = 109) focused primarily on examining ADHD symptoms in relation to neuropsychological factors in a community-based sample of children. The participants, at the time of the first data collection (T_1), were between the ages of 4 years, 0 months and 6 years, 2 months ($M = 59.9$ months, $SD = 7.8$ months). The children were recruited from randomly selected preschools in Uppsala County, and the parents of all children at the selected preschools were contacted by mail. About 85% of the parents gave permission for their child to be included in the studies. From this sample, two sub-samples were selected, and the children in the sub-samples were asked to participate in a follow-up, approximately 2 years later.

Concerning the longitudinal study (Study I), the sub-sample was selected so as to include children with either good or poor performance on EF tasks and low or high levels of ADHD symptoms at T_1 . Executive functioning was measured using four different tasks that tap inhibition and working memory (Stroop-like task, verbal and spatial working memory tasks and verbal fluency; see measures below). Poor EF was defined as scoring in the lowest 30% on at least two tasks. Good EF was defined as scoring in the highest 50% on all four tasks. ADHD symptoms were assessed using teacher ratings (see measures below), and high levels of ADHD symptoms were defined as scoring in the highest 30% and low levels as scoring in the lowest 50%.

The parents of children participating at T_1 who met the criteria for one of the four groups defined above ($n = 105$) were contacted, and 83% gave permission for their child to participate in the follow-up. Study I only includes the children participating in the follow-up. This resulted in a total of 87 children in four different groups: high levels of ADHD symptoms and poor EF (ADHD+EF group), high levels of ADHD symptoms and good EF (ADHD symptom group), low levels of ADHD symptoms and poor EF (EF group), and low levels of ADHD symptoms and good EF (comparison group). The ADHD+EF group included 16 children (boys = 12, $M = 75.1$ months, $SD = 6.8$), the ADHD group 19 children (boys = 13, $M = 82.7$

months, SD = 9.4), the EF group 17 children (boys = 6, M = 72.5 months, SD = 8.8), and the comparison group 35 children (boys = 11, M = 84.9 months, SD = 7.9). In the following, the first three groups will be labeled the problem groups.

Concerning Study III, a sub-sample representing 60% of the original sample (see Study I) was selected. We used teacher ratings of ADHD symptoms from the first time point. As Study III used a dimensional approach it was important that the whole range of symptom severity should be represented in the sub-sample. To assure inclusion of high scores in the sub-sample, we oversampled for high levels of ADHD symptoms by random selection of 51 children from those with the 30% highest ratings of ADHD symptoms. Additionally, seventy-nine children were randomly selected from the group with the 70 % lowest ADHD ratings. The parents of the selected children were contacted by mail and asked to give written consent for their child to participate in the actual study. The parents of 81% of the children high in ADHD symptoms and 89% of the children in the lowest 70% gave permission for their child to take part in the study.

The sample in Study III thus comprised a total of 111 children (57 boys; M = 6 years, 7 months; SD = 10 months). The ADHD symptom scores in the original sample (T_1) ranged between 0 - 44 and the same range were obtained in the sub-sample. However, in Study III, new ratings were collected from parents and teachers. The aggregated parent and teacher ratings, of ADHD symptom scores, ranged between 0-42. Concerning clinical levels of ADHD symptoms, based on the aggregated parent and teacher ratings, approximately 13.5% of the children fulfilled the symptom criteria for ADHD according to DSM-IV (APA, 1994), 38.7% had subclinical levels, and 47.8% of the children had no ADHD symptoms. Study III took place when the children were between 5 years, 4 months and 8 years, 1 month.

In Study I and III, information on parental educational status (on a 5-step scale) was collected. Parental education was high. Only 6% of the mothers and 7% of the fathers had 9 years of compulsory schooling as their highest level of education, whereas 44% of the mothers and 47% of the fathers had completed secondary school (12 year), and 50% of the mothers and 46% of the fathers had a university degree. A minority of the children (7%) did not have any siblings, 51% had one sibling, and the remaining children had two or more siblings. Moreover, all children were tested individually in a separate room at their school. Each session took about 60 min and included tests of inhibitory control, delay aversion and RT variability. The tests were conducted in random order.

Study II and IV are based on the same sample of children. Participants in these studies were part of a larger longitudinal study ($n = 650$). The children were recruited from randomly selected childcare centers in Uppsala County, Sweden, in connection with an ordinary health control when they were 5 years of age. Informed, written consent was obtained from the parents of all children who were willing to let their child participate in the study (95%). Approximately 3 years later, the parents of all children in the sample were contacted by mail and asked to participate in a follow-up study. About 70% of the parents agreed to answer a questionnaire about their child concerning ADHD symptoms and problems with comorbidity. Furthermore, the parents also gave permission for the child's teacher to answer the same questionnaire. Based on these behavioral ratings, a sub-sample was selected and the higher end of the ADHD symptom range was oversampled (see criteria below). Study II and IV only include the children who participated in the follow-up.

In Study II, the sub-sample was selected so as to include children with either low levels of hyperactivity/impulsivity symptoms or high levels of hyperactivity/impulsivity and low or high levels of inattention symptoms. ADHD symptoms were assessed using both parent and teacher ratings (see measures below). High levels of hyperactivity/impulsivity or inattention symptoms were defined as scoring in the highest 30% on the respective symptom dimensions and low levels as scoring in the lowest 50%. The parents of the children who met the criteria for one of the four groups defined above ($n = 260$) were contacted, and 70% gave permission for their child to participate in the follow-up.

This resulted in a total of 182 children in four different groups: high levels of both symptoms of hyperactivity/impulsivity and inattention (the combined subgroup); high levels of hyperactivity/impulsivity symptoms and low levels of inattention symptoms (the hyperactive subgroup); low levels of hyperactivity/impulsivity symptoms and high levels of inattention symptoms (the inattentive subgroup); and low symptom levels of both hyperactivity/impulsivity (comparison group). The combined group included 65 children (boys = 42, $M = 8.5$ year, $SD = 2$ months), the hyperactive symptom group 29 children (boys = 18, $M = 8.5$ year, $SD = 2$ months), the inattentive symptom group 26 children (boys = 18, $M = 8.4$ year, $SD = 2$ months), and the comparison group 62 children (boys = 21, $M = 8.5$ year, $SD = 2$ months); the first three groups will be labeled the symptom groups.

Concerning the sub-sample in Study IV, to assure inclusion of high scores, we oversampled for high levels of ADHD symptoms by random selection of 90 children from those with the 30% highest ratings of ADHD symptoms. Additionally, 130 children were randomly selected from the

group with the 70% lowest ADHD ratings. The parents of the selected children were contacted by mail and asked to give written consent for their child to participate in the actual study. The parents of 88% of the children high in ADHD symptoms and 93% of the children in the lowest 70% gave permission for their child to take part in the study. The sample thus comprised a total of 209 children (111 boys; $M = 8$ years, 6 months; $SD = 2$ months).

In Study II and IV, information on parental educational status (on a 5-step scale) was collected as a measure of socioeconomic status (SES). All children were tested individually in a separate room at their school. Each session took about 60 min and included tests of inhibitory control, WM, delay aversion, state regulation and intelligence (see below). The tests were conducted in random order except for the go/go-no tasks, where the normal condition was always the first and the slow condition always the last.

Neuropsychological Measures

Executive Function

Inhibitory Control

In all the Studies inhibition was studied using two well-validated tasks based on the Stroop (Stroop, 1935) and go/no-go paradigm (e.g., Trommer, Hoepfner, Lorber, & Armstrong, 1988). Both tasks have been used extensively in previous ADHD research in both clinical and non-clinical samples. They have been used to discriminate between children with ADHD and normally developing controls and they have shown adequate (Stroop like task; $r = .62$ and go/no-go task; $r = .84$, $p < .0001$) test-retest reliability (Berlin & Bohlin, 2002; Berlin, Bohlin, Nyberg, & Janols, 2004; Brocki, Nyberg, Thorell, & Bohlin, 2007; Thorell, 2007).

Stroop-like task

Because the classic Stroop task (Stroop, 1935) requires proficient reading skills, a Stroop-like task based on the day-night Stroop task developed by Gerstadt, Hong and Diamond (1994), was used in all studies. In the current version (Berlin & Bohlin, 2002) the children were presented with four pairs of pictures, where the pictures in each pair were each other's opposite (see Figure 2; day-night, boy-girl, large-small, 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 he or she saw a girl). This test measured inhibition, as it required the participant to inhibit a prepotent response (i.e., to say what the picture normally represents), and instead say the opposite (cf. Nassauer & Halperin, 2003; Simpson & Riggs, 2005).

During the first part of the task, the child was presented with each picture three times in random order, but the pairs were not mixed (i.e., the six first pictures were either a boy or a girl, the next six pictures were either large or small, and so on). During the second part, the instructions were the same and each picture was presented three times, but the eight pictures were now presented in a fixed random order. The inter-stimulus interval differed between the four studies due to the differences in age-range between samples. Each stimulus was presented between 800-1500 ms, followed by a response time of 1200 or 1500 ms and a waiting period of 1500 ms, before the next stimulus was presented. Errors on this task were registered when the child named, or started to name, the picture instead of saying the opposite, or when no answer was given. The total number of errors for the two sessions was used as a measure of inhibition.



Figure 2. The Stroop-like task.

Go/no-go task

An additional measure was used to tap inhibition. This task was based on the go/no-go paradigm, which has been widely used in ADHD research (e.g., Trommer et al., 1988). The present task included 4 different stimuli: a blue square, a blue triangle, a red square and a red triangle. During the first part of the task, the children were instructed to press a key (“go”) when a blue figure appeared on the screen, but to make no response (“no-go”) when an infrequent stimulus (a red figure) appeared. The same stimuli were used for the second part of the task, but the children were now instructed to press a key every time they saw a square, irrespective of color. Altogether, the task included 60 stimuli with a “go-rate” of 72%. Each stimulus was presented for 800 ms, followed by a response time of 1200 ms (Study II and IV) and 1700 ms (Study I and III), and a waiting period of 1200 ms (Study II and IV) and 1700 ms (Study I and III), before the next stimulus was presented. The results were registered as commission errors (pressing the key when a “no-go” target was presented). The merged sum for commission errors in the first

and second part of this task was used as the second measure of inhibition. To form a broad measure of inhibition, the two inhibition measures were standardized and aggregated (ranging between: $r = .40$ and $r = .42$, $p < .001$).

Working Memory (WM)

The three working memory tasks used in the present thesis were well-validated tasks that have been used extensively in previous ADHD research in both clinical and non-clinical samples (Brocki & Bohlin, 2004, 2006; Thorell, 2007; Thorell & Wåhlstedt, 2006; Diamantopoulou et al., 2007). The spatial task has been shown to discriminate well between children with ADHD and normally developing controls (Brocki, Randall, Bohlin, & Kerns, 2008), and the verbal task is almost identical to the digit span task included in the Wechsler Intelligence Test for Children-3rd edition (WISC-III; Wechsler, 1991). Test-retest reliability has been shown to be adequate (the Pig House Memory Task; $r = .67$ and Backward Span; $r = .82$, $p < .0001$) for the tasks.

Verbal Working Memory

In Study I, the verbal working memory task (WISC-III; Wechsler, 1991) was used and consisted of two parts, forward and backward span, although we only included the backward part as it has been shown to be a better measure of verbal working memory (Rosenthal, Riccio, Gsanger, & Jarratt, 2006). Because of the young age of the children, words were used instead of digits. The words were simple unrelated nouns that all children knew well (e.g., cat, three, rabbit, and clown). The child was first presented with two words, and the span length thereafter increased by one word on every other trial until the child failed to repeat at least one trial correctly at that span length. After the experimenter said the words, the child had to say them in the reverse order. One point was given to the child for each correct trial, and the sum was used as a measure of verbal working memory.

In Study II and IV, the Children's Size-Ordering Task (McInerney, Hrabok, & Kerns, 2005) was used to measure verbal working memory. This is a task in which the children are presented with a list of common objects (e.g., pencil, mountain, dog), read out loud at a rate of one item per second, and are asked to repeat them back to the experimenter in order of size from smallest to largest. A minimum of two practice trials were administered first. The actual test began with two items per trial, and became progressively more difficult to a maximum of seven items per trial. All children were administered all trials, regardless of their performance. The test was not time limited. The score for this task consists of the total number of pairs of items ordered correctly across all trials. High values indicate good working memory.

Spatial Working Memory

In Study I, II, and IV, the Pig House Memory Task (see Figure 3; Thorell & Wåhlstedt, 2006) was used as a spatial working memory measure. The children were presented with a 4-by-4 matrix on the computer screen and told that this was a house with windows. Further, they were informed that pigs would look out of the windows, and that the goal of the task is to try to remember their locations in the same order as they appeared. Each pig was displayed for 1000 ms, and the time between each stimulus was 750 ms. Participants were given two trials at each span length starting with two and ending when the child failed to repeat at least one trial correctly at that span length. The child received one point for every correct answer, and the total sum was used as a measure of spatial working memory and high values indicate good working memory. Test-retest reliability for the spatial WM measure has been shown to be adequate ($r = .69, p < .001$) using 30 children tested on average two months apart (Thorell & Wåhlstedt, 2006). To form a broad measure of WM, in Study II ($r = .25, p < .001$) and IV ($r = .25, p < .001$), the Children's Size-Ordering Task and Pig House Memory Task were aggregated.

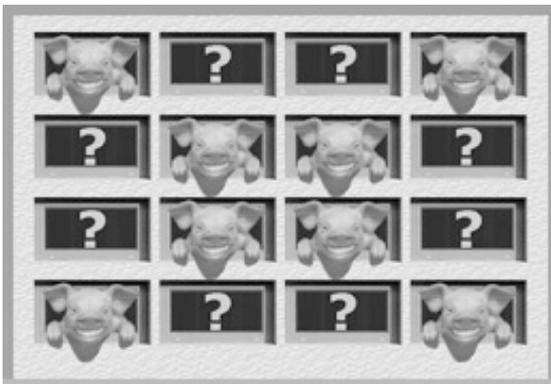


Figure 3. The Pig House Memory Task.

Verbal Fluency

In Study I, the verbal fluency task was used. The children were given two different semantic categories (animals and things to eat) and had to name as many different words as possible for each category. Each category had a time limit of one minute and the child was instructed to not repeat a word. The total number of words generated in the two categories was used as a measure of verbal fluency. This is a commonly used, well-validated measure that is included in the NEPSY test battery (Korkman, Kemp, & Kirk, 1998; Korkman, Kemp, & Kirk, 2001).

Attention

Sustained attention

In Study IV, a measure of sustained attention was used. Based on the slow go/no-go task, errors of omission, e.g., failing to respond to a “go” stimulus and reaction-times (go-trials) were calculated. Errors of omission and reaction times from the slow condition (ISI = 8000 ms) in the go/no-go task were used due to the monotonous nature of this task, which is considered to challenge the child’s ability to adjust vigilance to an optimal level for performing the task at hand. We calculated the performance differences between the first and second part of the tasks to obtain a measure of performance deteriorations over the time course, which are assumed to reflect sustained attention (e.g., Nigg, 2006; Van der Meere & Sergeant, 1988; Wilding, 2005). To form a broad measure of sustained attention, the two sustained attention measures were standardized and aggregated ($r = .43$, $p < .0001$). High values indicate poor sustained attention.

Motivational Factor: Delay Aversion

Flower-Delay Task

In Study II and III, the Flower-Delay task was used. This is a computer-based task (see Figure 4) using a design similar to the choice delay task (Sonuga-Barke et al., 1992; Solanto et al., 2001). Here, the children had to choose between a small immediate reward (one flower after 3 sec) and a larger delayed reward (two flowers after 30 sec). The experimenter explained to the children that they would play a game in which they could earn flowers and that the goal of the task was to earn as many flowers as possible. Before the game started, the children had five practice trials during which the experimenter made sure that they understood the difference in the waiting periods and that they would get more flowers if they waited for the larger, delayed reward.

Before the test trials started, the children were instructed that they would have 20 trials in which to earn flowers. Next to the computer, there was a transparent can containing 20 red balls. The children were told that after each trial, one ball would disappear and that when the can was empty, the game would be over. The percentage of times the delayed reward was chosen is used in the analyses as a measure of delay aversion, and low values indicate a problem with delay aversion. Test-retest reliability for the Flower-Delay measure has been shown to be adequate ($r = .84$, $p < .0001$) using 26 children tested on average two weeks apart (Thorell, 2007).

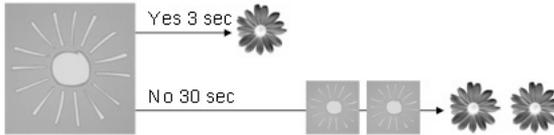
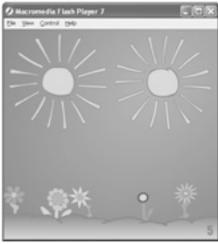


Figure 4. The Flower-Delay Task.

Star-Delay Card Game

In Study III, a second measure of delay aversion was used (see Figure 5), the Star-Delay card game also based on the choice delay task (Sonuga-Barke et al., 1992; Solanto et al., 2001). The children were presented with two decks of cards and had to choose between a card with one star and getting that star immediately (3 s) and a card with two stars and getting these stars after a delay (30 s). All other parameters (e.g., number of trials/practice trials, and the transparent can with red balls) were the same as in the Flower-Delay task. The percentage of times the delayed reward was chosen is used in the analyses as a measure of delay aversion, and low values indicate a problem with delay aversion. Test-retest reliability for the Star-Delay Card measure has been shown to be adequate ($r = .77, p < .0001$) using 26 children tested on average two weeks apart (Thorell, 2007). In Study III, the two measures of delay aversion ($r = .49, p < .0001$) were then aggregated to obtain one measure.

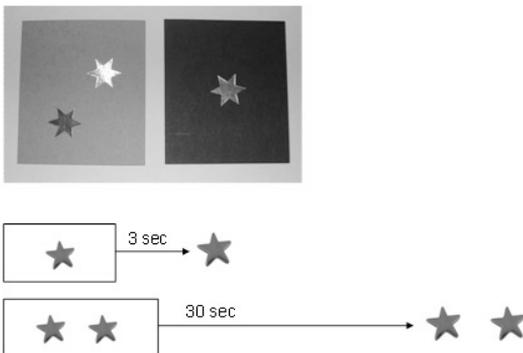


Figure 5. The Star-Delay Card Game.

State Regulation

Reaction Time Variability (RT variability)

In Study II, III, and IV, variability in reaction time was used as a measure of state regulation. Based on the go/no-go task (see description above), within subject variability in reaction times (RT variability; SDRT) was calculated and only go-trials were included. In Study II and IV, we used two conditions with different inter-stimulus intervals (ISI), normal ISI, 2000 ms and slow ISI, 8000 ms, and the mean of RT variability from these two conditions was used as a measure of state regulation. However, in Study III, due to the lower age of the sample, the ISI was 2500 ms and only this condition was used as a measure of state regulation. High values indicate poor state regulation.

Intelligence

The Information and Block Design

In all Studies, the Information and Block Design subtests of the WISC-III were used. The WISC-III (Wechsler, 1991) is a widely used measure of general intelligence for children 6-16 years of age. Both subtests are considered reliable and have been shown to correlate highly (Information: $r = .95$; Block Design: $r = .93$) with the full-scale IQ (Groth-Marnat, 1997). The child's number of points on the two subtests were converted to standard points available from norms (i.e., the raw scores corrected for the child's chronological age). An aggregated mean score of standard points was used as a measure of intelligence.

Measure of Behavioral Ratings

ADHD and ODD symptoms

In all studies, measures of ADHD and ODD symptoms were based on parent and teacher ratings. However, for all behavioral ratings, we used a composite measure of parent and teacher ratings (the inter-correlations ranging between: hyperactivity/impulsivity, $r = .41, p < .001$ to $r = .45, p < .001$; inattention, $r = .45, p < .001$ to $r = .52, p < .001$; ODD, $r = .21, p < .05$ to $r = .34, p < .05$) to obtain a measure that reflected the child's behavior across contexts.

ADHD and ODD symptoms were assessed using a well-validated rating scale containing the items for ADHD and ODD as presented in DSM-IV (APA, 1994). This measure has been well validated and is frequently used in ADHD research in both clinical and non-clinical samples (e.g., Brocki &

Bohlin, 2006; DuPaul et al., 1998). Nine items are composed to assess inattention. Nine items are composed to measure hyperactivity/impulsivity. Eight items are composed to assess ODD symptoms. Each item was rated on a 4-point scale ranging from 0 (“never or rarely”) to 3 (“very often”). Internal consistency (Cronbach’s α) scores for the aggregated teacher and parent measures were .93 for inattention, .93 for hyperactivity/impulsivity and .85 for ODD symptoms. The mean of the merged sum of parent and teacher ratings was used as a measure of symptoms of hyperactivity/impulsivity, inattention and ODD.

Sluggish Cognitive Tempo (SCT)

In Study IV, teachers rated the children on sluggish cognitive tempo, using five items from the Child Behavior Check List (CBCL; Achenbach, 1991) that, according to the research literature, are associated with this construct (Carlson & Mann, 2002). The items were: “confused or seems to be in a fog”, “daydreams or gets lost in his/her thoughts”, “stares blankly”, “underactive, slow moving or lacks energy”, and “apathetic or unmotivated”. Cronbach’s alpha was .86. High values indicate problems with symptoms of SCT.

Internalizing Problems

In Study I, II and IV, internalizing problems were rated by parents and teachers using a Swedish translation of the emotional problem subscale from the Strengths and Difficulties Questionnaire (SDQ). This instrument has been used previously on Swedish children (Malmberg, Rydell, & Smedje, 2003) and has shown good reliability and validity. Five items assessed symptoms of internalizing problems. The items were: “often complains of headaches, stomach-aches or sicknesses”; “many worries or often seems worried”; “often unhappy, depressed or tearful”; “nervous or clingy in new situations, easily loses confidence”; and “many fears, easily scared”. Ratings were made on a five-point scale ranging from 1 (“does not apply at all”) to 5 (“applies very well”). Aggregated parent and teacher ratings yielded $\alpha = .79$. High values indicate high levels of internalizing problems.

Emotion Regulation

In Study I, parents rated their children’s emotion regulation. The questionnaire used was developed by Rydell, Berlin and Bohlin (2003). This questionnaire consists of 12 items that tap four emotions (sadness, anger, fear, and positive emotions/exuberance), and the questions reflect the child’s own capacity to regulate emotions. Ratings were made on a five-point scale ranging from 1 (“does not apply at all”) to 5 (“applies very well”).

Cronbach's alpha was high, .88. High scores indicated poor emotion regulation.

Prosocial Behavior

In Study I, social competence was assessed by parents and teachers using 8 items from the Social Competence Inventory (SCI; Rydell, Hagekull, & Bohlin, 1997). The original version of the Social Competence Inventory consists of 16 items, but as these items have been shown to be highly intercorrelated, we selected 8 items shown to load highly on the prosocial orientation scale, according to a factor analysis (Rydell et al., 1997). Aggregated parent and teacher ratings yielded a cronbach's alpha of .63.

Academic Achievement

In Study II and IV, teachers rated children's academic achievement in Swedish, Mathematics, and Social Sciences, on five-point scales and five items were used. Ascending numbers indicate better performance (i.e., 1 = performance much under average, 2 = performance under average, 3 = average performance, 4 = above average performance, 5 = much above average performance). Teacher evaluations of performance in Swedish and Math have been found to correlate highly with results on national tests in a Swedish sample of 87 12-year-olds ($r = .82$, $p < .001$; Henricsson & Rydell, 2006), indicating that teachers are valid reporters of children's performance in school. Low values indicate poor academic achievement.

Study I

Title: ADHD Symptoms and Executive Function Impairment: Early Predictors of Later Behavioral Problems.

Background and aims

Earlier studies are limited in that they have mostly investigated concurrent relations between ADHD symptoms and EF and only some have used community-based samples. Furthermore, few studies have investigated longitudinal relations between poor EF and later socio-emotional functioning controlling for early ADHD symptoms. Finally, studies that investigate combined effects of ADHD symptoms and EF impairments are unusual. Therefore, little is known if ADHD symptoms and impaired EF in combination yield an effect to the same outcomes that is different than the sum of their independent effects. The aim of this study was therefore to investigate ADHD symptoms and EF impairments as predictors of

hyperactivity/impulsivity, inattention, EF functioning, and the broader scope of socio-emotional problems, such as dysfunctional emotional regulation, internalizing problems, symptoms of Oppositional Defiant Disorder (ODD), and difficulties with social competence. We selected preschool children who had high levels of ADHD symptoms with or without EF impairment, as well as children with low levels of ADHD symptoms with or without EF impairment. These children were then followed longitudinally over a two-year period. In line with recommendations made by for example Waschbusch (2002), we did not simply study additive effects as most previous studies have done, but also interactive effects of EF deficits and ADHD symptoms using a factorial ANOVA design. These analyses were complemented with group comparisons in which the group with low levels of both ADHD symptoms and EF deficits was compared with each of the three groups with either a high level of ADHD symptoms and/or EF deficits.

Results

Two-way ANOVAs with ADHD symptoms and EF impairment as independent variables were conducted, thus allowing the identification of independent, additive and interactive effects of the two predictive factors. As seen in Table 1, main effects of ADHD symptoms were found for all behavioral rating measures except internalizing problems. Effect sizes (see Table 2) were in the medium to large range for all significant effects. For inattention, but not for the other behavioral ratings, a significant main effect of EF impairment was also found, which indicated additive effects of the two predictive factors. However, the effect size of EF impairment on inattention was small, and when IQ was added as a covariate, the effect was reduced to only being marginally significant ($p = .096$). No interactive effects of ADHD symptoms and EF impairments were found for any of the variables.

As seen in Table 1, the planned comparisons of each of the problem groups with the comparison group indicated that all three groups showed significantly higher levels of both hyperactivity/impulsivity, inattention and emotion regulation than did the comparison group, whereas for social competence and ODD symptoms, only the two groups with high levels of ADHD symptoms, the ADHD+EF and the ADHD symptom group, were shown to differ significantly from the comparison group. Effect sizes were in the medium to large range for all significant effects, except when comparing the ADHD+EF group with the comparison group, where the effect size was small for ODD symptoms. When controlling for intelligence, the significant effects for emotion regulation were reduced to near significant for the EF group (.056) and the ADHD+EF group (.072).

Looking at the effects of the two predictors on EF with regard to executive functioning at T2, significant main effects of EF impairment were found for all variables, although only the effect of inhibitory control remained significant when controlling for IQ (see Table 1). For all significant results, the effect sizes were in the medium range (see Table 2). A main effect of ADHD symptoms was only found for inhibitory control with an effect size in the medium range. The results further showed that none of the interactive effects of ADHD symptoms and EF impairment on EF outcomes were significant.

Planned comparisons of the three problem groups with the comparison group indicated that the ADHD+EF group differed significantly from the comparison group on all EF measures. In addition, the EF group differed significantly from the comparison group with regard to inhibitory control and verbal fluency, although both these effects became non-significant ($p = .17$ and $.08$, respectively) when controlling for intelligence. Concerning the ADHD+EF group, the significant effects for verbal WM and verbal fluency also became non-significant ($p = .052$ and $.10$) when the effect of intelligence was taken into account. Effect sizes (before controlling for intelligence) were in the medium to large range for all significant comparisons, except for verbal fluency in the ADHD+EF group, where the effects were small. Concerning non-significant differences, there was a medium effect size for inhibition for the ADHD symptom group.

Table 1. Results of two-way ANOVAs studying main effects of EF and ADHD, as well as interactions of EF and ADHD using age, sex and SES as covariates. Planned contrasts between the three problem groups and the group with no problem ($n = 35$ for group 1, 17 for group 2, 19 for group 3, and 16 for group 4)

	Low ADHD symptoms		High ADHD symptoms		2-way ANOVAs		Planned Contrasts			
	No EF	EF deficit	No EF	EF deficit	EF	ADHD	EF*	1 vs 2	1 vs 3	1 vs 4
	(1)	(2)	(3)	(4)		ADHD	ADHD			
	M (SD)	M (SD)	M (SD)	M (SD)	F	F	F	<i>t</i>	<i>t</i>	<i>t</i>
Behavioral ratings:										
Hyperactivity	2.3 (2.2)	4.5 (4.5)	7.5 (5.4)	7.8 (5.2)	3.15	13.60***	0.71	1.95*	3.76***	3.78***
Inattention	3.1 (2.4)	5.2 (4.5)	8.0 (5.2)	9.0 (4.8)	9.60**	14.30***	0.00	2.97**	3.81***	4.80***
ODD symptoms	2.2 (1.7)	1.8 (2.2)	4.8 (3.2)	4.5 (3.0)	0.40	14.50***	0.02	0.37	3.33***	2.14*
Emotion Regulation	2.0 (0.5)	1.9 (0.6)	2.6 (0.6)	2.6 (0.6)	2.70	18.80***	0.50	1.79*	3.13**	1.17*
Social Competence	29.1 (2.9)	29.3 (2.7)	26.2 (3.8)	26.3 (3.4)	0.30	11.00**	0.05	0.28	2.97**	1.84*
Internalizing problems	8.7 (2.6)	10.2 (1.9)	9.6 (3.6)	9.8 (2.2)	0.30	0.20	0.90	1.06	0.32	0.10
Executive functions:										
Inhibitory Control	0.5 (0.5)	0.05 (0.6)	0.05 (0.5)	-0.91 (1.3)	13.70***	9.00**	2.10	1.94*	1.42	4.71***
Spatial WM	25.5 (11.6)	16.9 (7.4)	26.3 (11.8)	12.4 (7.1)	7.20**	0.80	2.00	1.17	0.32	2.55**
Verbal WM	3.7 (1.7)	2.5 (1.2)	3.4 (1.2)	1.4 (1.5)	9.30**	1.90	1.90	1.48	0.10	3.14**
Verbal Fluency	20.2 (4.1)	15.2 (3.7)	18.7 (3.8)	14.6 (6.4)	8.90**	0.90	0.04	2.21*	0.65	2.82**

* $p < .05$, ** $p < .01$, *** $p < .001$. Italic entries denote effects that were not significant ($p > .05$) when controlling for intelligence. 1 = the comparison group; 2 = the EF group; 3 = the ADHD group; 4 = the ADHD + EF group.

Table 2. *Eta-squared (η^2) effect sizes of two-way ANOVAs and planned contrasts (see Table 1) using age, sex and SES as covariates*

	2-way ANOVAs			Planned Contrasts		
	EF	ADHD	EF* ADHD	1 vs. 2	1 vs. 3	1 vs. 4
	η^2	η^2	η^2	η^2	η^2	η^2
Behavioral ratings:						
Hyperactivity/Impulsivity	.02	.14	.01	.07	.23	.12
Inattention	.05	.13	.01	.16	.22	.18
ODD symptoms	.00	.17	.00	.03	.16	.05
Emotion Regulation	.03	.18	.00	.10	.16	.07
Social Competence	.00	.12	.00	.00	.12	.06
Internalizing problems	.00	.00	.01	.02	.00	.00
Executive functions:						
Inhibitory Control	.10	.09	.02	.12	.13	.18
Spatial WM	.07	.01	.02	.03	.00	.18
Verbal WM	.07	.02	.02	.06	.00	.10
Verbal Fluency	.06	.00	.00	.13	.02	.05

Eta-squared effect size (η^2); small effect = .01 - .058;
medium effect = .059 - .137; large effect = .138 \geq .

Conclusions

In this study of a community-based sample, we have shown that early ADHD symptoms are an important predictor of a wide range of problem behaviors. From a more clinical perspective, an important question relates to the degree to which results from studies of community-based samples can be generalized to clinical populations. Our findings show that symptom levels even below the clinical cutoff are of interest in understanding childhood development. Further research is needed to address this issue, but it has been shown that ADHD-correlated comorbidity and impairments do not differ in community-based versus clinical samples (Bauermeister et al., 2007). Thus, results from community-based samples provide valuable information about ADHD symptoms in general and should therefore be seen as an important complement to more clinically oriented research. To conclude, our systematic investigation of both the additive and interactive effects of early ADHD symptoms and EF deficits on later behavioral and cognitive outcomes suggests that both ADHD symptoms and impaired EF act as early

predictors of problem behaviors, although it appears that predictions based on ADHD symptoms encompass a wider range of problems. In line with models of heterogeneity in ADHD, the present study indicates the need for theoretical development and empirical studies that will further our understanding of the relatively large group of children with high levels of ADHD symptoms, but without EF impairment.

Study II

Title: Heterogeneity in ADHD: Neuropsychological Pathways, Comorbidity and Symptom Domains

Background and aims

Recent theoretical formulations have repeatedly emphasized that Attention-deficit/Hyperactivity Disorder (ADHD) should be regarded as a heterogeneous condition (Castellanos et al., 2006; Nigg, 2006; Willcutt et al., 2005b). Empirically, this heterogeneity is evident in children with ADHD in at least three different respects: expression of the two ADHD symptom domains, neuropsychological impairments, and comorbid behavior problems. Earlier studies are limited in that few have investigated different neuropsychological theories in the same sample, and it is therefore not known whether these factors constitute independent pathways to ADHD symptoms. Additionally, research has not examined whether different neuropsychological factors and comorbid behavior problems are specifically related to either symptoms of hyperactivity/impulsivity or inattention, taking the overlap, i.e., high correlation between the two ADHD symptom domains into account. Finally, few studies have included both categorical and dimensional analyses as well as used community-based samples. In order to address the limitations of previous research, the overall aim of the present study was to investigate different neuropsychological impairments and comorbid behavioral problems in relation to ADHD symptoms, studying the independent effects of different functions as well as specific relations to symptoms of hyperactivity/impulsivity and inattention. A community-based sample was used, in which high levels of ADHD symptoms were oversampled.

Results

For the categorical analyses, analyses of variances (ANOVAs) were used to study group differences. The result of the ANOVAs, controlling for sex and SES, showed significant overall effects for all four neuropsychological measures (see Table 3). Planned comparisons revealed that when the three

ADHD symptom groups were combined, the resulting group differed significantly from the comparison group with regard to all four neuropsychological measures. The ANCOVAs showed that the effect of inhibitory control remained, $F(1, 174) = 6.2, p < .05$, when controlling for the effects of delay aversion and RT variability, as did the effect of RT variability, $F(1, 173) = 7.2, p < .01$, when controlling for inhibitory control, WM and delay aversion. However, the effects of WM, $F(1, 174) = 2.4, p > .10$, when controlling for delay aversion and RT variability, and delay aversion, $F(1, 173) = 2.0, p > .10$, when controlling for inhibitory control, WM and RT variability, did not remain significant.

Table 3. Results of ANOVA studying main effects of group differences using sex and SES as covariates and planned contrasts between the three ADHD symptom groups together and the comparison group

	<i>ANOVAs</i>	<i>Planned Contrast</i>
	<i>Subgroups</i>	1 vs. 2, 3 & 4 ¹
	<i>F</i> (η^2)	<i>t</i> (η^2)
Neuropsychological Measures:		
Inhibitory Control	6.9*** (.10)	3.8***
Working Memory	3.4* (.05)	2.2*
RT variability	7.9*** (.12)	4.1***
Delay Aversion (%)	2.9* (.05)	2.6**
Behavioral Ratings:		
ODD	22.7*** (.27)	6.0***
Internalizing	5.6** (.09)	3.1**
Academic Achievement	8.5*** (.12)	2.6**

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

Bold entries denote effects that remained significant in the planned contrasts between the three symptom groups together and the comparison group when controlling for the other neuropsychological factors.

¹ 1 = the comparison group; low hyperactivity/impulsivity and low inattention; 2 = the hyperactive symptom group; high hyperactivity/impulsivity and low inattention; 3 = the inattentive symptom group; low hyperactivity/impulsivity and high inattention; 4 = the combined symptom group; high hyperactivity/impulsivity and high inattention.

Thereafter, post hoc analyses comparing each of the three ADHD symptom groups with the comparison group were conducted (see Table 4). The results showed that the combined symptom group differed from the comparison group with regard to inhibitory control, WM and RT variability. The inattentive symptom group differed from the comparison group only with regard to inhibitory control and RT variability. Finally, the hyperactive symptom group differed from the comparison only with regard to inhibitory

control and delay aversion. When controlling for intelligence, the effect of WM was no longer significant in the combined symptom group.

Table 4. *Planned contrasts between the three ADHD subgroups separately and the comparison group using sex and SES as covariates*

	<i>Planned Contrasts</i>		
	<i>1 vs. 2</i>	<i>1 vs. 3</i>	<i>1 vs. 4</i>
	<i>t</i> (η^2)	<i>t</i> (η^2)	<i>t</i> (η^2)
Neuropsychological Measures:			
Inhibitory Control	2.2* (.08)	2.4* (.09)	4.5*** (.13)
Working Memory	0.6 (.01)	1.7 (.03)	3.0** (.06)
RT variability	1.6 (.08)	3.7*** (.20)	4.3*** (.11)
Delay Aversion (%)	2.8** (.08)	1.8 (.04)	1.4 (.01)
Behavioral Ratings:			
ODD	3.5*** (.25)	2.9** (.14)	8.2*** (.33)
Internalizing	0.8 (.01)	3.4*** (.13)	3.2** (.10)
Academic Achiev.	0.0 (.00)	2.1* (.07)	4.5*** (.13)

* $p < .05$, ** $p < .01$, *** $p < .00$

Italic entries denote effects that were not significant ($p > .05$) when controlling for intelligence and ODD.

As part of the group analyses, we also analyzed how many children in the three symptom groups had a clinically significant impairment on each of the neuropsychological measures (i.e., they had poorer scores than 90% of the comparison group on a certain task; Nigg et al., 2005). The results showed (see Table 5) that when the three ADHD symptom groups were combined, 26% of the children did not show impairments on any of the neuropsychological measures, 40% had a single impairment and 34% had multiple impairments. Looking at the three ADHD symptom groups separately, the results showed that between 21-27% of the children did not show impairments on any of the neuropsychological measures, single impairments varied between 32-55% and multiple impairments varied between 24-46%.

In the dimensional analyses, symptoms of both inattention and hyperactivity/impulsivity were significantly associated with all neuropsychological factors. Further, regression analyses (see Table 6) were used to control for symptoms of hyperactivity/impulsivity when studying relations to inattention and vice versa. The results of these analyses showed that inhibitory control, WM and variability in RT were related to symptoms of inattention, but not to symptoms of hyperactivity/impulsivity, whereas delay aversion was not related to either of the two ADHD symptom domains. Among the variables shown to be associated with inattention, inhibitory control, and RT variability, but not WM, showed independent

relations. It is important to note that when using symptoms of ODD as a control variable, in both the categorical and dimensional analyses, all significant results remained.

Concerning comorbidity, the results from the categorical analyses showed that when all three ADHD symptom groups were combined, the resulting group differed significantly from the comparison group concerning symptoms of ODD, internalizing problems and poor academic achievement (see Table 3). The planned comparisons revealed that all three symptom groups showed significantly higher levels of ODD symptoms than did the comparison group, but only the combined and the inattentive symptom groups differed significantly from the comparison group with regard to internalizing problems and academic achievement. When controlling for intelligence, the inattentive symptom group no longer differed from the comparison group with regard to academic achievement.

Table 5. Percent impaired of neuropsychological measures (ADHD subgroups beyond comparison group 90th percentile) as single and multiple impairments comparing ADHD subgroups and ADHD total (including all three ADHD subgroups) to comparison group

		% Impairments		
		Single	Multiple	None
Subgroups:				
Comparison	(n = 62)	27	9	64
Combined	(n = 65)	32	46	22
Inattentive	(n = 26)	42	31	27
Hyperactive	(n = 29)	55	24	21
ADHD subgroups total:				
ADHD	(n=120)	40	34	26

In the dimensional analyses, significant correlations were obtained between both symptoms of inattention and hyperactivity/impulsivity on all aspects of comorbidity except for hyperactivity/impulsivity and internalizing problems. When controlling for the overlap between the two ADHD symptom domains (see Table 6), ODD symptoms were related to hyperactivity/impulsivity, but not to inattention, and internalizing problems, as well as academic achievement, were related to symptoms of inattention, but not to hyperactivity/impulsivity.

Table 6. Results of regression analyses studying specificity of neuropsychological factors and comorbidity in relation to the two ADHD domains adjusting for SES and sex

	ADHD Symptoms	
	Hyperactivity/Impulsivity	Inattention
	β	β
ADHD domain	.67	.67
Neuropsychological Measures:		
Inhibitory Control	.10	.20*** (.15*)
Working Memory	-.01	-.13* (-.09)
RT variability	.03	.19** (.14*)
Delay Aversion	-.09	-.03 (-.02)
Behavioral Ratings:		
ODD	.35***	.11
Internalizing problems	.02	.12*
Academic Achievement	.02	-.31***.

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

The alternate symptom domain is entered in a first step with each separate neuropsychological factor in a second step. Numbers in parentheses are values for independent contributions of neuropsychological factors when they are all entered together in a second step after the respective ADHD domain.

Conclusions

Our results suggest that inhibition and RT variability constitute independent pathways to high levels of ADHD symptoms, primarily to inattention. The relevance of separating the two symptom domains is also justified by the finding on comorbidity, showing differential relations for inattention and hyperactivity. These are new and important findings, as very few previous studies have addressed the issue of independent effects of different neuropsychological functions. Additionally, few studies have used the full range of symptom severity and controlled for the overlap of inattention and hyperactivity/impulsivity. By using this approach in the present study, we have gained new knowledge of neuropsychological functioning and comorbidity in relation to the two ADHD symptom domains. Conclusively, the present study lends empirical support to the notion that ADHD is a heterogeneous disorder (e.g., Castellanos et al., 2006; Willcutt et al., 2005b) and indicates that the neuropsychological functions underlying RT variability are worthy of further theoretical and empirical attention in analyses of the multiple neuropsychological pathways to ADHD.

Study III

Title: Neuropsychological Deficits in Relation to Symptoms of ADHD: Independent Contribution and Interactions.

Background and aims

Evidence points to neuropsychological factors as major contributors to ADHD symptoms (see Nigg, 2006, for a review). Prominent theoretical explanations in this research area focus on deficits in executive functions (EF; Barkley, 1997), problems with delay aversion (Sonuga-Barke et al., 1992) and poor state regulation (Sergeant, 2000; 2005), and these neuropsychological factors have also been put forward as candidate endophenotypes (Castellanos & Tannock, 2002; Kuntsi et al., 2006). Multiple deficit models have recently been put forward to account for the neuropsychological heterogeneity of ADHD (e.g., Castellanos et al., 2006; Sonuga-Barke, 2003, 2005; Willcutt et al., 2005b). Some multiple-deficit models have emphasized the independent or additive effects of separate neuropsychological deficits that characterize subgroups of children with ADHD symptoms (e.g., Sonuga-Barke, 2003; 2005). Other models suggest that ADHD symptoms can also be explained by the interactive effects of several cognitive deficits (Castellanos et al., 2006; Willcutt et al., 2005b).

However, few empirical studies have investigated the different neuropsychological single process theories in relation to ADHD symptoms in the same sample. Furthermore, they have not taken into account the high comorbidity between symptoms of ADHD and ODD. To our knowledge, no previous studies have investigated the possible interactive effects of problems with neuropsychological factors on hyperactivity/impulsivity and inattention in non-clinical children. The aim of the present study was therefore to examine how inhibitory control, delay aversion and RT variability act separately and together in relation to symptoms of hyperactivity/impulsivity and inattention, while at the same time controlling for ODD, in a population-based sample of school-aged children.

Results

Table 7 provides the inter-correlations for behavioral ratings and neuropsychological measures. The three neuropsychological factors were entered simultaneously into a multiple regression model to examine to what extent inhibitory control, delay aversion and RT variability are related to hyperactivity/impulsivity and inattention, respectively, when all other factors are controlled for. Results showed (see Table 8) that only inhibitory control made a significant independent contribution to the explained variance in hyperactivity/impulsivity. For symptoms of inattention, the results showed

that only inhibitory control made a significant independent contribution to the explained variance. The significant relationships remained after intelligence and ODD symptoms were controlled for.

Table 7. *Inter-correlations between all variables adjusting for age. Figures in parentheses represent the relationships adjusted for ODD symptoms*

	2	3	4	5
1. Hyperactivity/Impulsivity	.77*** (.72***)	-.31*** (-.34***)	-.12 (-.07)	.20* (.22*)
2. Inattention		-.48*** (-.49***)	-.11 (-.07)	.30** (.31***)
3. Inhibitory Control			.18 (.18)	-.52***(-.54***)
4. Delay Aversion				-.06 (-.05)
5. RT Variability				

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

Entries in italics denote effects that were not significant ($p > .05$) when controlling for intelligence.

To study the specificity of the significant neuropsychological factors in relation to the two ADHD symptom domains, we performed regression analyses separately for inhibitory control, delay aversion and RT variability and let the respective symptom domains control for each other in the analysis. The results showed (see Table 8) that the effect of inhibitory control on symptoms of hyperactivity/impulsivity disappeared when controlling for inattention and the same result was found for RT variability. However, the effect of inhibitory control on symptoms of inattention remained significant when controlling for symptoms of hyperactivity/impulsivity and the same was found for RT variability.

The results concerning the interaction effects are presented in Table 8. No significant interaction effect of inhibitory control and delay aversion or of inhibitory control and RT variability on symptoms of hyperactivity/impulsivity or inattention was evident. However, a significant interaction effect of delay aversion and increased RT variability was found both for symptoms of hyperactivity/impulsivity and for inattention. As can be seen in Figure 6, children who had both delay aversion problems and increased RT variability had higher ratings on symptoms of hyperactivity/impulsivity and inattention than did children who had either impairment alone. When controlling for intelligence and ODD symptoms, the significant interaction effects remained. Finally, besides controlling for age, parental education, ODD symptoms and intelligence, we also added inhibitory control as a control variable in the regression analyses. The results showed that the significant interaction effects of delay aversion and increased RT variability on both hyperactivity/impulsivity and inattention remained.

Table 8. Results of regression analyses studying independent contributions, specificity and interaction effects of neuropsychological factors on symptoms of hyperactivity/impulsivity and inattention, controlling for age and SES

	ADHD Symptoms	
	Hyperactivity/Impulsivity	Inattention
	β	β
Independent Contribution:		
Inhibitory Control	.27*	.43***
Delay Aversion	.08	.02
RT variability	.07	.08
Specificity ¹ :		
Inhibitory Control	.07	.26***
Delay Aversion	.05	.01.
RT variability	.04	.16*.
Interaction Effects:		
Inhibition * Delay Aversion	.08	.09
Inhibition * RT variability	.06	.15
Delay Aversion * RT variability	.32***	.33***

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

¹ Controlling for the overlap, i.e., the high correlation, between the two ADHD symptom domains in the analyses.

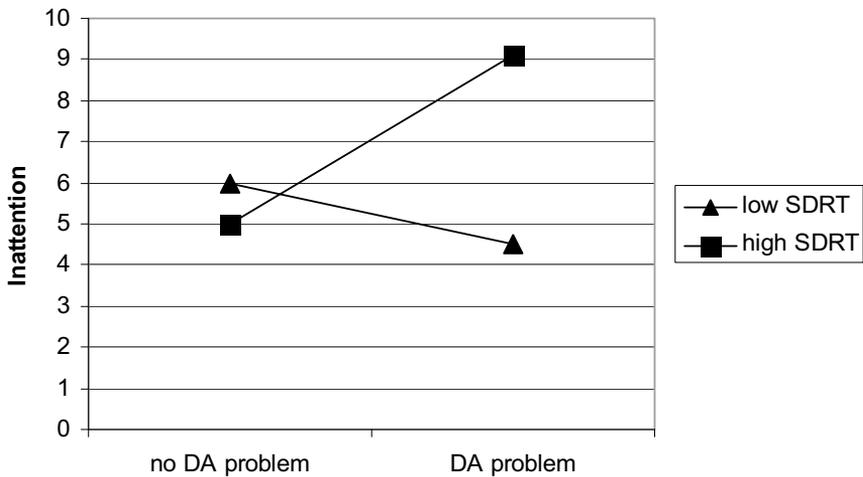
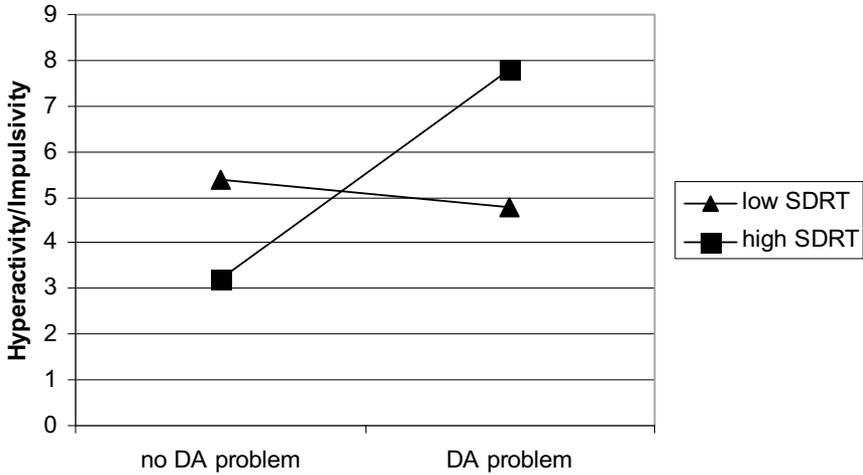


Figure 6. Interaction effects of delay aversion (DA) and RT variability (SDRT) on symptoms of hyperactivity/impulsivity (A) and inattention (B).

Conclusions

In accordance with multiple pathway models (Castellanos et al., 2006; Willcutt et al., 2005b), the present results showed that neuropsychological deficits that are related to symptoms of hyperactivity/impulsivity and inattention are not mutually exclusive; they can, independently or in combination, exert influences that may result in ADHD symptoms. As few studies have investigated several neuropsychological processes in the same

sample, the empirical findings from this study are new and important and could result in considerable theoretical advances in our understanding of neuropsychological pathways contributing to ADHD symptoms. Moreover, knowledge from this study may facilitate the progress of effective interventions for children with disruptive behavioral problems. For example, it has been shown that cognitive-based interventions ameliorate cognitive processes in children with ADHD and reduce ADHD symptoms (see Toplak, Connors, Shuster, Knezevic, & Parks, 2008, for a review). However, further studies about possible neuropsychological pathways are needed, to learn more about strengths and weaknesses as well as changes in neuropsychological impairments over time in children with ADHD symptoms.

Study IV

Title: DSM-IV-defined Inattention and Sluggish Cognitive Tempo: Independent and Interactive Relations to Neuropsychological Factors and Comorbidity

Background and aims

Symptoms of hyperactivity/impulsivity and inattention are the two major symptom domains in Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV). Additionally, research has clearly shown that symptoms belonging to a different dimension of inattention, compared with DSM-IV-defined symptoms of inattention, described as sluggish cognitive tempo (SCT), frequently exist among children with ADHD symptoms. SCT is characterized by inconsistent alertness and slow processing, such as sluggishness, drowsiness and apparent daydreaming (Lahey et al., 1998; McBurnett et al., 2001). Although SCT and DSM-IV-defined inattention seem to be highly correlated (Hartman, Willcutt, Rhee, & Pennington, 2004; McBurnett et al., 2001; Todd, Rasmussen, Wood, Levy, & Hay, 2004), Hartman et al. (2004) showed that SCT behaviors loaded on a factor separate from – but correlated with – DSM-IV-defined inattention. Few studies have taken into account the overlap, i.e., the high correlation, between DSM-IV-defined symptoms of inattention and SCT in relation to neuropsychological factors and comorbidity. Therefore, we have no knowledge about common and independent relations of DSM-IV-defined inattention and SCT to neuropsychological factors and comorbidity. Moreover, previous studies within this area of research have mostly been conducted using clinical samples, which mean that the full range of symptom severity has not been taken into account. In order to address the limitations of previous research, the aim of the study was to investigate

independent relations of DSM-IV-defined inattention and behaviors of SCT to neuropsychological factors (inhibitory control, working memory, sustained attention, and state regulation) and associated problems (internalizing problems, academic achievement, and ODD), in a community based sample of school children. Additionally, we intended to study possible interactive relations of DSM-IV-defined inattention and SCT to the same outcomes to clarify if these two inattentive domains in combination yield an effect that is different than the sum of their independent effects.

Results

Table 9 provides the correlations for behavioral ratings and neuropsychological measures. Symptoms of inattention and SCT were entered simultaneously into a multiple regression model to examine to what extent they are independently related to neuropsychological measures, letting the respective symptom dimensions control for each other in the analyses. Results showed (see Table 10) that only symptoms of inattention were independently related to inhibitory control, WM, and RT variability. However, only symptoms of SCT were independently related to sustained attention. When we added symptoms of hyperactivity/impulsivity, intelligence and ODD as covariates, all significant independent relations remained.

Table 9. *Inter-correlations between hyperactivity/impulsivity, inattention and SCT as well as correlations with all variables adjusting for age and SES, n = 209*

	Inattention	SCT
1. Inattention		
2. SCT	.65***	
3. Inhibitory Control	.33***	.19**
4. Working Memory	-.20**	-.07
5. Sustained Attention	.15*	.24***
6. RT Variability	.32***	.20**
7. ODD	.43***	.16*
8. Internalizing Problems	.22**	.16*
9. Academic Achievement	.48***	-.33***

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

Entries in italics denote effects that were not significant ($p > .05$) when controlling for intelligence.

The results showed (see Table 10) that both symptoms of inattention and SCT were independently related to ODD. However, it is important to note that the significant independent relation between SCT and ODD was negative, which implies that high levels of SCT were associated with low levels of ODD, when inattention is controlled for. However, when we added hyperactivity/impulsivity as a control variable, the independent effects of inattention and SCT on ODD did not remain significant. Further, only symptoms of inattention were independently related to internalizing problems and academic achievement. When we added intelligence as a covariate, all significant independent relations remained.

The results showed (see Table 10) that no significant interaction effect of inattention and SCT on measures of neuropsychological factors was evident. Concerning comorbidity, a significant interaction effect of inattention and SCT was found for symptoms of ODD. As can be seen in Figure 7, children who had high levels of inattention in combination with high levels of SCT had lower ratings on symptoms of ODD than did children who had only high levels of inattention with low levels of SCT. Symptoms of hyperactivity/impulsivity did not affect the significant interaction effect of inattention and SCT on symptoms of ODD.

Table 10. *Results from regression analyses studying independent and interactive relations of DSM-IV-defined inattention and SCT to neuropsychological factors and comorbidity*

	DSM-IV-defined inattention and SCT		
	Independent Relations		Interactive Relations
	Inattention	SCT	Inattention*SCT
	β	β	β
Executive Function:			
Inhibitory Control	.37***	-.06	-.15
WM	-.25**	.09	.15
Sustained Attention:			
Omission + RT	.02	.26**	.02
State Regulation:			
RT variability	.34***	-.03	-.06
Comorbidity:			
Internalizing problems	.19*	.03	-.11
Academic Ach.	-.45***	-.03	.04
ODD	.56***	-.20*	-.22**

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

Italic entries denote relations that were not significant ($p > .05$) when controlling for hyperactivity/impulsivity.

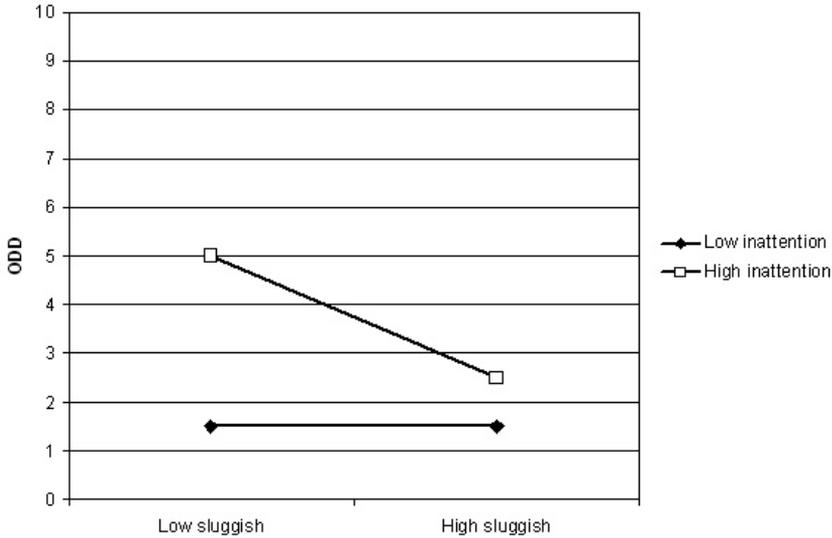


Figure 7. Interactive relation of DSM-IV-defined symptoms of inattention and SCT to symptoms of ODD.

Conclusions

Only symptoms of DSM-IV-defined inattention, and not SCT, were independently related to measures of EFs and state regulation. Interestingly, symptoms of SCT, but not DSM-IV-defined inattention, were independently related to sustained attention. This finding can explain some of the contradicting results concerning a related impairment in sustained attention in children with ADHD symptoms. Thus, children with primarily high levels of DSM-IV-defined inattention in combination with SCT appear to be a meaningful subgroup of children with ADHD symptoms, and at least behaviorally, such children seem to be the best candidates for poor sustained attention, while they tend to be protected against symptoms of ODD. Therefore, the findings from this study are new and important, as to our knowledge no earlier studies have addressed the issue of independent and interactive relations of DSM-IV-defined inattention and SCT to neuropsychological factors and comorbidity. This kind of knowledge improves our theoretical understanding of the heterogeneity seen in children with ADHD symptoms and may show us how to identify more homogeneous ADHD subgroups, which in turn may facilitate the improvement in interventions for affected children.

General Discussion

The overarching aim of the present thesis was to clarify the heterogeneity surrounding children with ADHD symptoms concerning neuropsychological pathways, and specificity of the two ADHD symptom domains in relation to neuropsychological factors and comorbid behavioral problems. Particular emphasis is placed on prominent neuropsychological processes such as executive function (EF), state regulation and delay aversion in the explanation of ADHD symptoms in children. The main results will be discussed in relation to the aims presented in the introduction. Proposals for future research will conclude the discussion.

Do ADHD symptoms and/or EF impairments in preschool children predict later behavioral problems?

As a starting point of my research about the heterogeneity seen in children with ADHD symptoms, I wished to investigate if preschool children with ADHD symptoms but without impaired EF had developed impairments in EF two years later. In Study I, a predictive cross-domain effect was found between ADHD symptoms and inhibition, which implies that these two phenomena tended to correlate over time. However, the group analyses revealed that the preschool children with only high ADHD symptoms had not developed problems with EF two years later. Yet, this group had continued behavioral symptoms. This result is important and corroborates a meta-analysis by Nigg and colleagues (2005), who found that merely 50% of children with ADHD symptoms showed impaired EF. Thus, our finding provides further support for models of neuropsychological heterogeneity in ADHD (Castellanos et al., 2006; Nigg, 2006).

Concerning the issue whether ADHD symptoms and/or impaired EF in preschool children act as early predictors of continuing problem behaviors, in line with previous research (e.g., Campbell, 1995, 2005; Nigg et al., 1999), the results from Study I showed that preschool children with high levels of ADHD symptoms and/or EF impairments continued to show these behavioral problems two years later. Interestingly, the result showed that preschool children with poor EF, but without ADHD symptoms, may be at

risk for developing ADHD symptoms two years later. Thus, our results are in accordance with the few earlier longitudinal studies of community samples, which have found that early EF impairments are related to ADHD symptoms (Berlin et al., 2003; Brophy et al., 2002; Nigg et al., 1999; Riggs et al., 2003). However, these previous longitudinal studies investigated externalizing problems in general, rather than separating ADHD symptoms and conduct problems, or failed to control for early levels of ADHD symptoms. Study I adds to the literature by showing that EF impairments are specifically related to ADHD symptoms and that these relations exist even when controlling for problem levels at baseline.

Overall, the findings from Study I emphasize the need to investigate multiple neuropsychological processes in the same sample, as this approach can help us explain why some children with ADHD symptoms do not show EF impairments. Study I also highlights the importance of early identification of EF impairments and/or ADHD symptoms in children.

Are impairments in neuropsychological factors specifically related to ADHD symptoms when taking ODD into account?

An additional major aim of the present thesis was to gain knowledge about the specificity of neuropsychological impairments in relation to symptoms of ADHD versus ODD. Indeed, there are controversies about this issue in the literature. For example, Séguin and coworkers (1999) found in a community based sample that impaired EF is connected to ODD even after controlling for ADHD symptoms. Others, however, have maintained that impaired EF is specifically related to ADHD symptoms and not to ODD in both clinical and non-clinical samples (Berlin & Bohlin, 2002; Brocki & Bohlin, 2006; Brocki et al., 2007; Oosterlaan, Scheres, & Sergeant, 2005; Thorell & Wåhlstedt, 2006; Waschbusch, 2002). Our results from Study I, II and III are in line with the latter of the reported findings, in that we found neither concurrent nor predictive effects of EF impairment on symptoms of ODD.

Interestingly, the results from Study II and III point to the fact that the relations between ADHD symptoms and delay aversion as well as RT variability remained when controlling for ODD. Together, Study I, II and III suggest that impairments in EF, state regulation and delay aversion play an important role in the neuropsychology of ADHD symptoms rather than ODD. These findings are important, as few earlier studies have investigated these issues using dimensional analyses and controlling for the large overlap between ADHD and ODD symptoms. Future studies should further

investigate potential neuropsychological processes other than those included here before any firm conclusion can be drawn concerning the relation between neuropsychological impairments and ODD symptoms.

Explanation of ADHD symptoms in children: single process theories or multiple pathway models?

In line with previous findings (Biederman et al., 2004; Nigg et al., 2005), the results from Study I emphasize that not all children with high levels of ADHD symptoms also suffer from EF impairments. Given earlier findings, it is worth noting that the majority of studies in this area of research have examined only one neuropsychological theory at a time and most of them have found modest effect sizes. In other words, the ability of any single neuropsychological theory to fully account for ADHD symptoms in children is limited (see Nigg, 2005, for a review). Thus, to gain more knowledge about possible neuropsychological pathways to ADHD symptoms in children, Study II and III were designed to investigate the independent contributions as well as interactive effects of EF, state regulation and delay aversion by using both categorical (Study II) and dimensional approaches (Study II and III).

Independent neuropsychological pathways

One conclusion that can be drawn from Study II and III – showing independent contributions of inhibitory control (Study II and III) and RT variability (Study II) as well as interactive relations of delay aversion and RT variability (Study III) to ADHD symptoms – is that these findings are not in accordance with the view of a single core deficit as an explanation for ADHD symptoms in children. Rather, the findings from Study II and III confirm the need for multiple neuropsychological pathway models in our attempts to explain ADHD symptoms.

Theoretically, Study II and III showed that problems with state regulation, measured as RT variability, do not seem to constitute a more generalized cognitive deficit proposed to underpin impairments in EF, such as inhibitory control (e.g., Sergeant, 2000, 2005). Similarly, the results are not in line with Barkley's (1997a, b) notion that inhibitory control is a superordinate process that controls regulation of arousal and motivation. Further, these findings are not in accordance with the delay aversion hypothesis, which states that ADHD symptoms are characterized by an underlying motivational style rather than by dysfunctional EF (Sonuga-Barke, 1994; Sonuga-Barke et al., 1992).

There were some differences between the findings of Study II and III that are important to discuss. First, in Study II, both inhibitory control and RT variability made independent contributions to the explained variance of ADHD symptoms. In Study III, however, only inhibitory control explained unique variance in ADHD symptoms. The finding from Study III corroborates the theoretical propositions made by Barkley (1997a, b) as well as empirical findings (e.g., Sonuga-Barke et al., 2002; Wodka et al., 2007) suggesting that poor inhibitory control is one of the key neuropsychological impairments in ADHD symptoms. One possible explanation for why only inhibitory control made a significant independent contribution to ADHD symptoms in Study III could be the lower age of the sample ($M = 6.5$ year), compared with that in Study II ($M = 8.5$ year). This interpretation is in line with findings showing that inhibitory control has a greater impact on ADHD symptoms in young children compared to older children (Brocki & Bohlin, 2004; Sonuga-Barke et al., 2002). This reasoning is also useful in explaining the finding from Study II concerning the prominence of inhibitory control over WM in terms of contributing independently to the variance in ADHD symptoms. Thus, and as mentioned in the introduction, child age may be important when comparing the contribution of various neuropsychological factors, especially EF. Slower maturation of more complex EF components, such as WM, may mean that they become more important in later developmental phases (cf. Bitsakou et al., 2008; Brocki & Bohlin, 2006). Hence, the relationship between different neuropsychological markers and ADHD symptoms may depend on where in the developmental process the sample of children is assessed.

In contrast to earlier studies (e.g., Solanto et al., 2001; see Sonuga-Barke et al., 2008, for a review), neither Study II nor Study III found independent contributions of delay aversion to ADHD symptoms. Although delay aversion was related to ADHD symptoms in Study II, the findings do not support the idea that delay aversion constitutes a pathway to ADHD symptoms that is independent of both EF and state regulation. It is important to note that some previous studies have also failed to show that children with ADHD are more delay averse than are controls in both clinical (Scheres et al., 2006; Solanto et al., 2007) and community-based samples (Van der Meere et al., 2005), which indicates that the use of community-based samples cannot explain the lack of significant effects.

Further, my intention with Study II and III was not to investigate the more specific dual-pathway model by Sonuga-Barke (2003, 2005), in which delay aversion is supposed to contribute independently when controlling for the effects of EF. One reason for this choice is that the dual-pathway model is clearly inadequate as regards fully accounting for the heterogeneity and complexity of ADHD. For example, this model does not take into account

the possibility of interactive effects between motivational and neuropsychological factors, which was the main investigative aim of Study III. Moreover, the dual-pathway model also does not take into account poor state regulation (measured as RT variability), which has been shown to be one of the most consistent impairments in children with ADHD symptoms (e.g., Castellanos et al., 2006).

Interactive neuropsychological pathways

To go one step further in the search for neuropsychological pathways (i.e., beyond independent effects), Study III investigated the possibility of interactive relations between neuropsychological processes. No significant interactive relation of inhibitory control and delay aversion or of inhibitory control and RT variability to symptoms of hyperactivity/impulsivity or inattention was evident. As mentioned above, no significant independent relation of delay aversion was found to symptoms of ADHD (Study II and III). However, delay aversion was shown to have an effect in combination with RT variability on both hyperactivity/impulsivity and inattention (Study III). These interactive relations imply that level of delay aversion played almost no role for children with low RT variability, whereas for children with high RT variability, being delay averse was associated with higher levels of ADHD symptoms. Thus, the presence of an interactive relation between delay aversion and RT variability implies that these two neuropsychological impairments in combination yield an effect that is greater than the sum of their independent relations to symptoms of hyperactivity/impulsivity and inattention.

A comparison with previous studies is difficult, as interactive relations of different neuropsychological factors on hyperactivity and inattention have not been examined previously. However, it has been suggested that motivation and cognition are integrated via connections between ventral frontal brain regions involved in the processing of reward-related stimuli and dorsolateral prefrontal brain regions associated with cognitive processes (Gilbert & Fiez, 2004; Haber et al., 2000), which in turn supports the view that there may be interactive effects of neuropsychological factors in the development of ADHD symptoms. Further, a tentative interpretation could be made in terms of the cognitive-energetic model (Sergeant 2000, 2005), in which effort is closely linked to motivation and controls arousal and activation. Thus, for children characterized by increased RT variability, being delay averse may mean that their motivational resources are more often challenged, which in turn may lead to hyperactive or inattentive behavior.

Further research is needed to examine whether the interactive relations of delay aversion and RT variability to ADHD symptoms can be replicated using clinical samples of children. Nevertheless, findings from Study II and III support multiple neuropsychological pathway models that emphasize both independent and interactive effects (Castellanos et al., 2006; Willcutt et al., 2005b) in explaining ADHD symptoms in children. Importantly, multiple pathway models allow us to differentiate between groups of children with ADHD based on different neuropsychological impairment profiles.

Proportion of children with neuropsychological impairments

To gain deeper knowledge of neuropsychological heterogeneity, Study II investigated the proportion of children with ADHD symptoms that showed single, multiple or no neuropsychological impairments (i.e., performance above the 90th percentile cutoff for the comparison group). The results showed that 40% of the children had only a single impairment and 34% had multiple impairments. Note that as many as 26% did not show impairments on any of the neuropsychological measures. These results are in line with those of Nigg et al. (2005), who investigated EF and delay aversion in a clinical sample of children with ADHD. They found that 23% of the children had multiple deficits, e.g., both impairments in inhibitory control and delay aversion, 15% had only delay aversion, 23% had only impaired inhibitory control and 39% did not show neuropsychological impairments.

Compared to the findings by Nigg et al. (2005) Study II showed a higher proportion of children that suffered from neuropsychological impairment. This inconsistency can be explained by the fact that Study II included four neuropsychological factors, while two were used in the study by Nigg et al. (2005). Even when adding measures of WM and state regulation, a substantial number of children with high levels of ADHD symptoms do not show impairment, which suggests that other potential cognitive and psychological factors have to be included in order to more fully explain the different pathways to ADHD. As Nigg (2006) suggested, associations to psychosocial factors such as psychological trauma, early deprivation and attachment problems can be expected as possible pathways. These suggestions are in line with the findings that in addition to genetics, environmental factors and potential gene-environmental interactions can also contribute to ADHD symptoms in children (Larsson et al., 200; see Nigg, 2006; Swanson et al., 2007 for reviews).

Summarizing remarks about neuropsychological heterogeneity

There may be neuropsychological factors other than those addressed in the three neuropsychological theories used in Study II and III. However, EF,

state regulation and delay aversion are the most frequently discussed and well-studied factors in relation to ADHD symptoms (e.g., Castellanos et al., 2006; Sonuga-Barke et al., 2008; Willcutt et al., 2005a). As such, they seem to be the most critical to examine when trying to identify multiple neuropsychological pathways to ADHD symptoms in children.

The findings from Study II and III add new valuable theoretical information about the independent and interactive relations of inhibitory control, delay aversion as well as RT variability to ADHD symptoms. Thus, these findings imply that neuropsychological deficits that are related to ADHD symptoms are not mutually exclusive: They can, alone or in combination, exert influences that result in ADHD symptoms in children. However, dysfunctional EF, state regulation and delay aversion are not necessary or sufficient to cause all cases of ADHD symptoms. Nonetheless, EF and state regulation play important roles in the complex multifactorial neuropsychology of ADHD symptoms in children. It is important to note, that in the studies of this thesis delay aversion did not show independent effects in relation to ADHD symptoms.

The fact that the results just presented were obtained from normal population samples with rather low levels of ADHD symptoms, indicates that individual differences in neuropsychological abilities are important for understanding normal variation in ADHD symptoms, not just clinical extremes. Note that the modest effect sizes on different neuropsychological measures in Study I and II are in line with those found in clinical samples (e.g., Willcutt et al., 2005a). Therefore, these results are consistent with the characterization of variation in ADHD symptoms as an underlying continuum of risk for psychopathology (e.g., Levy et al., 1997).

Are the two ADHD symptom domains specifically related to different neuropsychological factors?

Besides the issue of multiple neuropsychological pathways to ADHD symptoms, the specificity of the two ADHD symptom domains in relation to neuropsychological factors was one of the main issues studied here. In our analyses of group differences in Study II, each of the three ADHD symptom groups had significantly poorer inhibitory control compared to the comparison group, which is in line with earlier categorical findings. However, when we controlled for the overlap between the two ADHD symptom domains using a dimensional approach, the results from both Study II and III showed that inhibitory control and RT variability were specifically related to symptoms of inattention, rather than to hyperactivity/impulsivity.

The fact that inhibition was only related to symptoms of inattention when controlling for hyperactivity/impulsivity is in line with the findings of Chhabildas et al. (2001). However, all three ADHD symptom groups in Study II showed impaired inhibition in the categorical analyses, which implies that children in the hyperactive subgroup had higher levels of inattention compared to the comparison group. However, problems with RT variability do not seem to be as sensitive to sub-threshold levels of inattention as poor inhibitory control is. More specifically, children in the hyperactive symptom group in Study II did not show significant problems with RT variability compared with the comparison group. As few previous studies have investigated RT variability in relation to the two ADHD symptom dimensions while controlling for the overlap in the analyses, the results of Study II and III add new valuable information to this field of research.

Unexpectedly, in Study II and III, delay aversion was not specifically related to either symptoms of hyperactivity/impulsivity or inattention. However, in the categorical analyses in Study II, the hyperactive symptom group differed from the comparison group with regard to delay aversion. This finding is to some extent in line with the notion that delay aversion should be related primarily to symptoms of hyperactivity/impulsivity. However, it is not in line with the ensuing assumption that delay aversion should also be characteristic of the combined symptom group in Study II. The somewhat inconsistent findings in Study II and III with regard to delay aversion cannot be easily explained. One could speculate that hyperactivity is not a unitary phenomenon, implying that some aspects of the broad phenomenon of hyperactivity are indeed characterized by delay aversion, whereas others are not. In this context, the literature on Type A behavior (i.e., restlessness, impatience, difficulty waiting) could be brought to mind. In child studies, for example, it has been found that ratings of hyperactivity correlate highly with ratings of Type A behavior, although the two phenomena could be differentiated in their relations to outcomes, with Type A children being superior to children diagnosed with ADHD with regard to several measures of executive functioning (Nyberg, Bohlin, Berlin & Janols, 2003; Nyberg, Bohlin, & Hagekull, 2004).

Findings from Study II and III support the utility of using a dimensional approach when studying specificity by controlling for the overlap between the two ADHD symptom domains in relation to different neuropsychological factors (Sonuga-Barke et al., 2008). More specifically, findings from Study II and III confirm the importance of separating the two ADHD symptom domains in relation to neuropsychological impairments.

Are DSM-IV-defined inattention and SCT associated with different neuropsychological impairments?

Regarding differences and similarities between DSM-IV-defined symptoms of inattention and SCT in relation to neuropsychological factors, Study IV revealed exciting findings. In line with our expectation, both DSM-IV-defined inattention and SCT were related to inhibitory control, sustained attention and RT variability. However, when taking into account the overlap between the two inattentive symptom domains, by using a dimensional approach, their relations to neuropsychological factors changed. More specifically, DSM-IV-defined inattention, but not SCT, was independently related to inhibitory control, WM and RT variability. Interestingly, SCT, but not DSM-IV-defined inattention, was independently related to sustained attention. The finding that DSM-IV-defined inattention was independently related to inhibitory control, WM, and RT variability is in accordance with results from Study II and III. However, the finding that SCT was independently related to sustained attention, but not inhibitory control, WM and RT variability is new and interesting, as no previous study has investigate this issue.

As mentioned in the introduction, poor sustained attention is related to vigilance and refers to the ability to maintain a state of alertness and wakefulness over time during prolonged mental activity (Weinberg & Harper, 1993). Thus per definition, sustained attention should be operationalized as a decline in performance over time (Nigg, 2006; Van der Meere & Sergeant, 1988; Wilding, 2005). Importantly, some studies revealing impaired sustained attention in children with ADHD symptoms have only reported mean levels (e.g., Manly et al., 2001) instead of decline in test performance over time. Conclusions based on these studies may therefore be questioned. However, some studies investigating sustained attention as a decline in performance over time have failed to find significant relations to ADHD symptoms (see Huang-Pollock & Nigg, 2003, for a review; Stins et al., 2005). Our result implies that poor sustained attention in children with ADHD symptoms is not due to DSM-IV-defined inattention per se, but instead that high levels of SCT may contribute to sustained attention. Thus, this finding may help to bring some clarity to the ongoing debate on whether or not children with ADHD symptoms have impaired sustained attention (e.g., Huang-Pollock & Nigg, 2003; Manly et al., 2001; Wilding, 2005).

Comorbidity

Do ADHD symptoms and EFs act as predictors?

Study I revealed that ADHD symptoms, but not EF, act as an early predictor of comorbidity in preschool children. The finding that ADHD symptoms predict later problems with social competence, emotion regulation and ODD is in line with previous empirical findings (e.g., Angold et al., 1999a; Bagwell et al., 2001; Biederman, 2005; Norvilitis et al., 2000; Rasmussen & Gillberg, 2000). The results also showed that ADHD symptoms did not predict internalizing problems. One possible explanation for this finding could be that internalizing problems are more common in older children with high levels of ADHD symptoms. In other words, the children in Study I may have been too young to have developed internalizing problems as a possible consequence of several years of externalizing behaviors (cf. Mesman, Bongers, & Koot, 2001). Another possible explanation is that internalizing problems in a child are harder to detect for parents and teachers compared with externalizing problems. Internalizing problems may be better operationalized through self-ratings, but in Study I this would not have been a good alternative as the children were too young.

The findings from Study I showing that EF impairments in preschool children did not predict socio-emotional problems (concerning the relation between EF and ODD, see discussion above) are important to notice with regard to the theoretical importance of EF in relation to social functioning (Jurado & Rosselli, 2007; Pennington & Ozonoff, 1996). Additionally, previous research findings has also revealed relations between poor EF and socio-emotional problems (Brocki & Bohlin, 2006; Ciairano et al., 2007; NICHD, 2003; Nigg et al., 1999; Riggs et al., 2003). Nevertheless, Biederman and colleagues (2004) also failed to find relations between impaired EF and socio-emotional problems. One possible explanation for our finding is related to the fact that EF is not fully developed until late adolescence/early adulthood and that socio-emotional problems associated with EF impairments may therefore become evident first late in adolescence. Thus, further research is needed, to further our understanding of the relation between impaired EF and socio-emotional functioning of different age groups using both concurrent and longitudinal designs.

Specificity of the two ADHD symptom domains

In line with previous research (e.g., Eiraldi et al., 1997; Gaub & Carlsson, 1997), the dimensional analyses in Study II and IV showed that hyperactivity/impulsivity was specifically associated with symptoms of ODD. As expected, symptoms of inattention were specifically related to internalizing problems and academic achievement (e.g., Masetti et al.,

2008). The finding that symptoms of inattention are primarily related to poor academic achievements and poor EF show that the presence of neuropsychological (e.g., EF) impairments may exacerbate or modify the comorbid profile of children with ADHD symptoms. This reasoning is in line with results from Biederman et al. (2004), who found that it was only children with ADHD symptoms in combination with impaired EF who showed poor academic achievement.

Differences and similarities between DSM-IV-defined inattention and SCT

In line with recent findings, both symptoms of inattention and SCT were significantly related to internalizing problems and academic achievement (Hartman et al., 2004; Carroll, Maughan, Goodman, & Meltzer, 2005). However when we controlled for the overlap between DSM-IV-defined inattention and SCT, only DSM-IV-defined inattention, and not SCT, was independently related to internalizing problems and poor academic achievement. Thus, the claim that high levels of SCT are primarily related to internalizing problems (Barkley, 2006; Carlson & Mann, 2000; Milich et al., 2001) would seem to be incorrect. As no earlier studies have controlled for the overlap between DSM-IV-defined inattention and SCT when investigating the relations to comorbidity, the findings from the present study add new valuable information to this field of research.

Contrary to our expectations, both symptoms of inattention and SCT were independently related to ODD. However, when controlling for hyperactivity/impulsivity, the independent effects did not remain significant, which is in line with findings from Study II and earlier research. These findings indicate that hyperactivity/impulsivity is primarily related to ODD, rather than inattention or SCT (Eiraldi et al., 1997; Gaub and Carlson, 1997; Mikami et al., 1997). Study II further revealed that the inattentive symptom group showed high levels of ODD symptoms. In addition to this finding, Study IV showed an interaction effect of inattention and SCT on ODD symptoms. The interaction effect showed that symptom levels of SCT played almost no role in children with low levels of inattention, whereas in children with high levels of inattention, high levels of SCT was associated with lower levels of ODD compared to those children with low levels of SCT. Interestingly, the finding of an interaction effect implies that high levels of SCT in children with ADHD symptoms, primarily inattention, protect children against symptoms of ODD.

Methodological issues

Measures

A possible explanation for the generally poor sensitivity of neuropsychological tests is that these measures do not always capture neuropsychological impairments. Therefore, it should be acknowledged that the neuropsychological measures used in the present thesis may not fully capture the phenomena of interest. It has been argued, for example, that a latent variable approach to studying EF yields more reliable measures and valid results (e.g., Friedman et al., 2007). Similarly, it should be fruitful to use a latent variable approach in studies of delay aversion and state regulation. In this thesis the measure of state regulation rests on the idea that RT variability fully represents this phenomenon. Although this operationalization is a common practice, it may only capture a narrow aspect of state regulation.

The theoretical underpinnings of RT variability in individuals with ADHD symptoms are a subject of ongoing debates. RT variability has been attributed, for example, to slower cognitive processing and deviant time perception (Kalff et al., 2005), deficient attentional processes (Lijffijt et al., 2005; Castellanos et al., 2005) and sustained attention (Alderson, Rapport, & Kofler, 2007), as well as problems with state regulation, which is in line with Sergeant's (2000, 2005) interpretation of the regulation of energetic state. Interestingly, results from Study IV indicated that RT variability is a different construct than sustained attention, measured as performance decrement over time, as the correlation between these two measures was rather low ($r = .24$). In addition, these two phenomena were independently related to different behavioral symptoms, in that RT variability was primarily related to inattention (Study II, III and IV) and sustained attention was primarily related to SCT (Study IV), which also confirms the notion that they are separable constructs. This in turn, strengthens the use of RT variability as a measure of state regulation in Study II and III.

It is also important to mention that there is no gold standard for assessment of neuropsychological processes. Many tests that have been designed to capture specific components of these complex constructs are now available. However, as partly shown in the moderate effect sizes commonly found for most measures in this research area, it is necessary to further improve the reliability and validity of these neuropsychological tests. These types of improvements can facilitate more accurate, sensitive and specific assessment of neuropsychological factors. Moreover, with the advancement of theories and models of neuropsychological heterogeneity in children with ADHD symptoms, the second-generation of

neuropsychological tests should focus more on theoretical accounts of the underlying deficits of specific components.

It is important to note that neuropsychological tests cannot be used for diagnosis of ADHD. Instead, neuropsychological testing may be useful for purposes other than diagnosis, such as identification of neuropsychological impairments, clarification of strengths and weaknesses as a guide for treatment and information about changes in neuropsychological processes over time. Thus, neuropsychological assessment may help the child with ADHD symptoms, as well as his/her parents and teachers, achieve a better understanding of the child's individual strengths and weaknesses.

Confounding variables

Together, the findings from the present four studies revealed that neuropsychological impairments were primarily related to ADHD symptoms, rather than to IQ. Thus, the link between ADHD symptoms and neuropsychological impairments is not simply due to lower levels of general cognitive ability. Still, it should be mentioned that the categorical analyses that were used to control for intelligence in Study I, showed reduced levels of significance, when comparing the group with EF deficits only to the comparison group with regard to EF outcomes. These results are of interest in the debate among researchers regarding the relevance of controlling for intelligence when studying the relation between ADHD symptoms and neuropsychological factors (e.g., Barkley, 1997a; Nigg, 2006; Sergeant et al., 2002), and they indicate the need to report results both with and without using intelligence as a covariate.

Generalizability

From a more clinical perspective, an important question relates to how well results from studies of community-based samples can be generalized to clinical populations. Studies examining ADHD symptoms and neuropsychological factors in population-based samples of children have usually found results (low correlations and low to moderate effect sizes) similar to those found in clinical samples. The present findings confirm earlier community-based research showing that the relation between ADHD symptoms and neuropsychological factors is not confined to clinical populations. Thus, results from community-based samples provide valuable information about ADHD symptoms in general and should therefore be seen as an important complement to more clinically oriented research. Although the use of clinically referred samples may have increased the likelihood of finding significant ADHD-related differences on neuropsychological tasks, clinically referred samples are generally more impaired and usually present

with a variety of comorbid difficulties that may confound results. Consequently, some caution is advisable in generalizing results from community-based samples to clinical samples, as impairments are likely to be more severe in these groups and they may also have additional impairments.

Summary and directions for future research

The findings from the present thesis have shown that:

- Both ADHD symptoms and impaired EF in preschool children act as early predictors of later behavioral problems. However, it is clear that predictions based on ADHD symptoms encompass a wider range of problems including social competence, emotion regulation and ODD, in early school-age children.
- Impairments in EF, delay aversion and state regulation, play an important role in the neuropsychology of ADHD symptoms, rather than ODD.
- Rather than a single neuropsychological deficit, multiple neuropsychological pathways, such as inhibitory control, RT variability and delay aversion, act both separately and in combination in explaining ADHD symptoms in children. This is an important conclusion given the fact that RT variability has not been systematically examined or integrated into multiple neuropsychological pathway models, and thereby its role and function together with EF and delay aversion in relation to ADHD symptoms have not been understood. Thus, findings from Study II and III contribute to advancing the theoretical multiple pathway models of ADHD.
- Not all children with high levels of ADHD symptoms seem to have impairments in neuropsychological processes.
- Symptoms of hyperactivity/impulsivity and inattention have different primary correlates. These findings point to the importance to separate the two ADHD symptom domains and control for the large overlap, i.e., the high correlation, between hyperactivity/impulsivity and inattention when investigating relations to neuropsychological factors and comorbidity. This conclusion corroborates previous research showing both common and symptom-specific genetic effects in relation to the two ADHD symptom domains (Larsson et al., 2006; McLoughlin et al., 2007).

- DSM-IV-defined inattention constitutes a somewhat heterogeneous condition, in that only children with high levels of SCT seem to be candidates for poor sustained attention. However, children with SCT behaviors seem to be protected against symptoms of ODD. Thus, instead of maintaining that DSM-IV-defined inattention in combination with SCT is a separate disorder from ADHD, a better approach would be to see problems with SCT as comorbid with ADHD symptoms, primarily inattention. More specifically, SCT symptoms should be seen as comorbid behaviors that modifies the developmental course and outcomes of children with ADHD symptoms.

Thus, findings from the present thesis have contributed with important and new knowledge about the heterogeneity of children with ADHD symptoms concerning neuropsychological pathways, and specificity of the two ADHD symptom domains in relation to neuropsychological factors and comorbid behavioral problems. Knowledge such as this can help us understand how to identify more homogeneous ADHD subgroups. Moreover, the present findings contribute to the further development of multiple neuropsychological pathway models. Therefore, to summarize my findings on neuropsychological heterogeneity, I will present a simplified schematic illustration (see Figure 8) of possible multiple neuropsychological pathways to ADHD symptoms in children.

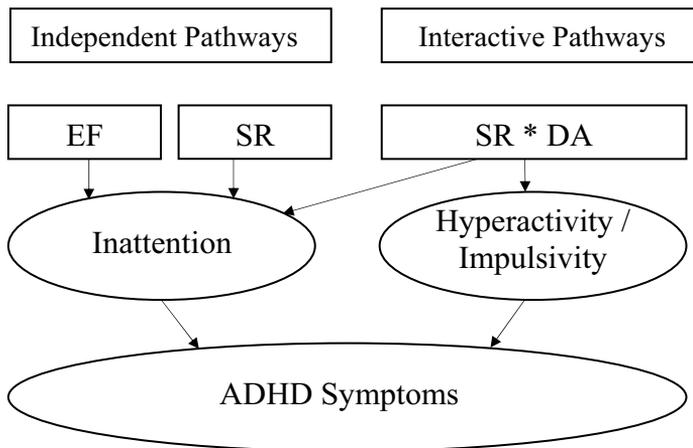


Figure 8. Schematic illustration of possible neuropsychological pathways to ADHD symptoms. EF = executive functions; SR = state regulation; DA = delay aversion. Lines indicate independent and interactive effects/relations.

The present results have also contributed with information for, and ideas about, future research. Therefore, some research issues will now be presented, which I think needs to be investigated in the near future:

- Despite relatively intact neuropsychological test performances in some children with ADHD symptoms, as revealed in Study I and II, these children seem to have marked difficulties in everyday functioning caused by the effects of hyperactivity/impulsivity and inattention on participation in daily activities. These findings further underscore the importance of continuing to study children with ADHD symptoms without neuropsychological impairments to help us discover the mechanisms underlying ADHD symptoms in these children. More specifically, an important goal for future research is to identify other potential factors that mediate the underlying cause of ADHD symptoms in children unimpaired by EF, state regulation and delay aversion. Besides other potential neuropsychological processes, psychosocial factors would be interesting to investigate.
- As RT variability has been shown to be one of the most consistent characteristics of ADHD symptoms (e.g., Castellanos et al., 2006), it is important to continue investigating the theoretical underpinnings of this measure.
- Based on the present findings, it is not clear how the neuropsychological impairments specifically related to inattention and hyperactivity/impulsivity will change with development. Because most of the available data are cross-sectional, longitudinal studies are needed to better understand the course of neuropsychological impairments in individuals with ADHD symptoms across the life span. Therefore, further investigations must be undertaken so that developmental perspectives can be considered more fully. As there is considerable variation in the course of ADHD symptoms over time, identifying risk factors that influence the developmental course of ADHD is an important aim. More specifically, the neuropsychological factors that influence ADHD symptoms may differ across developmental stages, e.g., neuropsychological impairments that contribute to ADHD symptoms in early school age children may not be the same as neuropsychological impairments contributing to ADHD symptoms in adolescents. In this context, it would also be interesting to investigate possible sex differences.

- An interesting approach to use would be person-oriented analyses, such as cluster analyses, designed to group types of individuals rather than to group variables. For example, comparing children with different neuropsychological impairments in relation to ADHD symptoms and comorbidity.
- Multiple comparisons with other clinical groups are required to understand how neuropsychological impairments could be related to ADHD symptoms in children in a way that differentiates ADHD from other childhood disorders, such as autism. Thus, it is important that we discover whether overall neuropsychological functioning in children with ADHD symptoms is distinct from that in children with other disorders.

Concluding remarks

The four studies in the present thesis have revealed a number of important findings that will hopefully provide a foundation and inspiration for future work in this area of research. More specifically, the findings highlight the need to integrate competing single-process theories and to elaborate on a neuropsychological multi-process model that can explain at least a relatively large group of children with ADHD symptoms. Moreover, efforts are needed to classify and subdivide children with ADHD symptoms not only with regard to the two ADHD symptom domains, but also putative neuropsychological impairments, comorbidity and sluggish cognitive tempo. Another relevant distinction appears to be whether or not a child with ADHD symptoms has neuropsychological impairments. However, continued research is needed to improve our understanding of the diverse nature and complexity of ADHD symptoms in children. Importantly, if we are to gain deeper knowledge of the multifaceted nature of ADHD symptoms, increasing collaboration between research groups within psychology/psychiatry, such as developmental neuropsychology, behavioral genetics and brain imaging, is necessary. Knowledge from such collaborations will provide a greater opportunity for early detection as well as improved and more integrated intervention approaches for children with disruptive behavioral problems, thereby making it possible to reduce the social and economic costs associated with ADHD symptoms in childhood.

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