Cognitive Endophenotypes of ADHD

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“ADHD-related chaos in the frontal parts of the brain”

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Cognitieve Endofenotypen van ADHD

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Chapter 1

ADHD, Genetics, and Neuropsychology: Introduction

ADHD

Clinical description

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most impairing, commonly diagnosed, and widely researched childhood-onset neuropsychiatric disorders. Children with ADHD place heavy demands on clinical, educational, and social services, and often develop chronic problems (Hechtman and Weiss, 1983). The disorder is characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity that is inappropriate for the developmental level of the child. Three subtypes defined in DSM-IV, the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association (APA), 1994, 1998) are the inattentive subtype (I), the hyperactive-impulsive subtype (HI), and the combined subtype (C). Subtype classification is based on the presence of 6 or more symptoms of hyperactive-impulsive behaviors (HI) or inattentive behaviors (I), or both dimensions (C). There must be clear evidence of clinically significant social or academic dysfunctioning, in at least two settings (e.g. at home and at school). Some symptoms that caused impairment should have been present before the age of 7. See table 1 for an overview of the diagnostic criteria according to DSM-IV.

Table 1. DSM-IV Diagnostic criteria for Attention-Deficit Hyperactivity Disorder

A. Either (1) or (2):

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

Inattention

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

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

Hyperactivity

(a) often fidgets with hands or feet or squirms in seat
(b) often leaves seat in classroom or in other situation in which remaining seated is expected
(c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
(d) often has difficulty playing or engaging in leisure activities quietly
(e) is often "on the go" or often acts as if "driven by a motor"
(f) often talks excessively

Impulsivity

(g) often blurt out answers before questions have been completed
(h) often has difficulty awaiting turn
(i) often interrupts or intrudes on others (eg. butts into conversation or games)

B. Some hyperactive-impulsive or inattentive symptoms that causes impairment were present before age 7 years.
C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).
D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.
E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder)

Code based on type:

314.01 Attention-Deficit/Hyperactivity Disorder, Combined Type:
If both Criteria A1 and A2 are met for the past 6 months
314.02 Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type:
If Criterion A1 is met but Criterion A2 is not met for the past 6 months
314.01 Attention-Deficit/Hyperactivity Disorder, Predominantly Hyperactive-Impulsive Type:
If Criterion A2 is met but Criterion A1 is not met for the past 6 months
Coding note: For individuals (especially adolescents and adults) who currently have symptoms that no longer meet full criteria, "In partial remission" should be specified (APA, 1994, 1998).

Prevalence

ADHD has been found to affect 4 to 5% of all school-aged children in western countries, and may persist into adulthood in one third of the cases or more (Spencer et al., 1998). The prevalence rates vary considerably, depending on the definition of ADHD, the population studied (clinical or community-based sample), the diagnostic measures, the geographical locale of the survey, and the degree of agreement between parents, teachers, and clinicians (Barkley, 1998; Swanson et al., 1998b; Buitelaar, 2002). The ratio between boys and girls with ADHD ranges between 3:1 and 9:1, for clinic-referred children the ratio is about 6:1. A large part of the difference between the sexes in clinic-referred samples is due to referral bias in that girls are more likely to suffer from the inattentive subtype of ADHD, resulting in less disturbing behavior. Furthermore, boys have a 2 fold increase in risk for comorbid oppositional defiant disorder and conduct disorder relative to girls, and due to these additional externalizing psychopathology they are more behaviorally disturbed. Therefore, boys are more frequently referred to psychiatric services (Jensen et al., 1997). An alternative explanation for the reported difference in sex ratio could be a difference in the etiology of ADHD for boys and girls. This issue has been examined by testing the assumptions of two models: the polygenic multiple threshold model (Cloninger et al., 1978), and the constitutional variability model (Taylor & Ounsted, 1972). The first model assumes that boys and girls differ in the prevalence of ADHD because girls require a higher liability than boys (i.e. a greater amount of the *same* causal factors that affect boys) to manifest the disorder. In contrast, the constitutional variability model posits that boys and girls differ in the prevalence of ADHD because *different* causal factors are important for each sex. Recent analyses pertinent to the comparison of the two models found evidence in support of the polygenic multiple threshold model, but further research is needed to clarify the sex ratio difference in ADHD (Rhee et al., 1999).

The proportion of children diagnosed with ADHD has risen steadily over the past 15 years, but researchers argue over whether this represents a real increase, an overdiagnosis or a better recognition of ADHD by parents, teachers and clinicians (Brown, 2003). Some investigators believe that it may be as a result of a change in culture, i.e. the high burden of the modern society (Block, 1977; Ross & Ross, 1982; Barkley, 1998; Buitelaar, 2001).

Comorbidity

As noted above, comorbidity plays an important role in ADHD. Up to 44% of the ADHD- affected children may have at least one comorbid psychiatric disorder, 32% have two others, and 11% have at least three other disorders (Szatmari et al., 1989). The most common comorbid psychiatric disorders are conduct disorder (CD) and oppositional defiant disorder (ODD) affecting 40% to 60% of children and adolescents

with ADHD (Angold et al., 1999; Wolraich et al., 1996). These children are more likely to develop antisocial activities, school disciplinary problems, greater substance use and abuse, and a generally worse overall outcome compared to ADHD children without these comorbid disorders (Barkley et al., 1990; Jensen et al., 1997; Moffitt, 1990). Mood- and anxiety disorders occur in approximately 20-30% of the ADHD children. The comorbidity of these disorders along with ADHD is often associated with a history of family stress, greater parental symptoms of anxiety and mood problems, and reduced responsiveness to stimulant medication. See for a review Jensen et al. (1997). Other comorbid conditions and disturbances associated with ADHD, are learning disorder, tic disorders (Tourette syndrome), language disorders, autism spectrum disorders, obsessive-compulsive disorder, bipolar disorder, developmental coordination disorder, and substance abuse (Biederman et al., 1993; Flory and Lynam, 2003; Jensen et al., 1997; Kadesjo and Gillberg, 2001)

Brain dysfunction

Brain damage was initially proposed as a main cause of ADHD symptoms. Brain infections (Stewart, 1970; Cantwell, 1981), trauma (Blau, 1936; Werner & Strauss, 1941), epilepsy (Holdsworth & Whitmore, 1974), and complications during pregnancy and delivery (Shirley, 1939) were associated with impaired attention, regulation of activity, and impulsivity. However, most ADHD children have no history of such damage and thus, brain injuries are unlikely to account for the majority of children with this disorder (Rutter, 1977). Throughout the century, different researchers have noted similarities between symptoms of ADHD and those following lesions or injuries to the frontal lobes (Mattes, 1980; Benton, 1991). Children and adults suffering from damage to the prefrontal region experienced deficits in sustained attention, inhibition, regulation of emotion, and organization of behavior (Stuss & Benson, 1986; Fuster, 1989). In the 1970s, Satterfield and Dawson were among the first to propose that ADHD symptoms were caused by frontolimbic dysfunction (Satterfield and Dawson, 1971). They suggested that weak frontal cortical inhibitory control over limbic functions might lead to ADHD. To examine the frontal regions and other neuroanatomical correlates of ADHD, investigators turned to brain imaging studies. One of the most important current developments in ADHD has been the convergence of findings from magnetic resonance imaging studies that show abnormalities in cerebral volume and function (Swanson et al., 1998a). Several research groups using anatomical MRI have reported reductions in prefrontal volume, predominantly in the right hemisphere (Castellanos et al., 1996; Filipek et al., 1997; Durston et al., submitted). Reductions in the caudate volume are also found, both in the right (Castellanos et al., 1994) and in the left caudate (Filipek et al., 1997; Semrud-Clikeman et al., 2000). Some structural imaging studies have also looked at other cortical areas in ADHD. They reported a total brain size reduction of up to 5%, and also volumetric re-

ductions in the posterior portion of the corpus callosum (Baumgardner et al., 1996; Giedd et al., 1994; Lyoo et al., 1996), and in the cerebellar regions (Castellanos et al., 1996; Castellanos et al., 2001; Mostofsky et al., 1998 ; Durston, et al., submitted). Recently, a study examining growth trajectories of brain volume abnormalities in ADHD patients revealed that the longitudinal growth curves of all structures, except the caudate nucleus, paralleled those of the controls during childhood and adolescence. The differences between patients and controls for the caudate disappeared by midadolescence. These results suggest that the genetic and/or environmental influences on ADHD-related brain abnormalities are nonprogressive (Castellanos et al., 2002).

The results of functional imaging studies (fMRI) are consistent with those of the structural studies in implicating a frontosubcortical system in the pathophysiology of ADHD (Casey et al., 1997; Vaidya et al., 1998). One of these studies showed reduced activation of the frontal circuitry in adolescents with ADHD during the performance of a response inhibition task (Rubia et al., 1999). The results of more recent functional imaging studies showed involvement of widespread cerebral areas in ADHD (Schweitzer et al., 2000; Teicher et al., 2000).

Genetics

Family,- twin-, and adoption studies

It is widely accepted that ADHD is influenced by genetic factors. Family studies report that siblings of children with ADHD have a 2- to 3-fold higher risk of ADHD than do children of families without a positive family history of ADHD (Biederman et al., 1992; Faraone et al., 1993; Faraone and Biederman, 1994). Furthermore, several adoption studies have provided evidence for genetic transmission by demonstrating that the adoptive relatives of children with ADHD were less likely to have ADHD than the biological relatives of children with ADHD (Cantwell, 1975; Morrison and Stewart, 1973; Van Den Oord et al., 1994). Additional data from twin and adoption studies indicate that the familial aggregation of ADHD has a substantial genetic component, with heritability ranging from 0.6 to 0.9 (Faraone et al., 1996; Gjone et al., 1996; Goodman and Stevenson, 1989; Levy et al., 1997; Nadder et al., 1998; Silberg et al., 1996; Todd, 2000a; Todd, 2000b).

Molecular studies of candidate genes and genomewide scans for loci involved in ADHD indicate a multiple-gene effect with minor-to-moderate effect sizes rather than a major gene effect (Faraone et al., 2001; Fisher et al., 2002; Bakker et al., 2003).

Candidate genes

Candidate gene studies have focused mainly on the implication of dopamine-related genes in ADHD, since methylphenidate, amphetamine and other psychostimulant drugs that control effectively the ADHD symptoms inhibit the activity of the dopamine transporter (Bakker et al., 2003; DiMaio et al., 2003). In addition, neu-

roimaging and neuropsychological studies have reported disturbances in dopamine-innervated brain regions (frontal cortex and fronto-striatal networks) and related cognitive deficits in ADHD children (Barkley, 1997a; Ernst et al., 1999; Yamasaki et al., 2002). The findings from more than 50 candidate gene studies are equivocal and the estimated effect sizes of supposed susceptibility alleles are quite small. Nevertheless, in recent meta-analyses association has been found for three candidate genes of dopaminergic neurotransmission: the dopamine D4 receptor (DRD4) gene (Faraone et al., 2001), DRD5 gene (Maher et al., 2002), and the dopamine transporter (DAT-1) gene (Cook, Jr. et al., 1995; Barr et al., 2001; Daly et al., 1999; Waldman et al., 1998). However, the effects of the genes were small, with relative risks ranging from 1.3 to 1.6, and other studies failed to replicate these associations (Holmes et al., 2000; Palmer et al., 1999).

Genomewide linkage studies

Genomewide linkage analysis enables detection of susceptibility loci without any a priori knowledge regarding the specific genes involved (Ogdie et al., 2003). So far, two genome-wide scan studies have been performed among ADHD affected siblings pairs, reporting suggestive evidence for linkage on chromosomes 16p13 (Smalley et al., 2002), 17p11(Ogdie et al., 2003), and 7p and 15q (Bakker et al., 2003). The multipoint maximum likelihood scores (MLSs) ranged from 2.98 to 3.54 in these studies. Interestingly, the chromosome regions 16p13, 17p11 and 15q are also associated with autism, which suggest that variations in genes on these chromosomes may contribute to impairments related to both ADHD and autism (Smalley et al., 2002). This is in line with the notion that susceptibility genes cut across psychiatric disorders (Castellanos and Tannock, 2002). The chromosome 15 region has also been implicated in reading disability (Grigorenko et al., 1997; Nothen et al., 1999). This is an important finding, since ADHD is frequently associated with reading disabilities (August and Garfinkel, 1990; Raberger and Wimmer, 2003; Willcutt et al., 2002).

Neuropsychology

Associated cognitive deficits

It is well established that deficits in attention and executive functioning should be viewed as the core cognitive impairments in ADHD (Barkley, 1997b; Douglas, 1972; Pennington and Ozonoff, 1996). As already noted in the brain dysfunction section, ADHD is associated with dysfunction in prefrontal-striatal neural circuits, and these brain dysfunctions are considered to contribute to the attention and executive function deficits observed in individuals with the disorder (Pennington and Ozonoff, 1996; Tannock, 1998). Welsh and Pennington (1988, pp. 201-202) defined executive functioning as the ability to maintain an appropriate problemsolving set for the attainment of a future goal (Bianchi, 1922: Luria, 1966). This problemsolving set can in-

volve one or more of the following: a) an intention to inhibit a response or to defer it to a later more appropriate time, b) a strategic plan of action sequences, and c) a mental representation of the task, including the relevant stimulus information encoded into memory and the desired future goal-state. The term executive function may refer to many behaviors and cognitive processes such as response inhibition, self-regulation, sequencing of behavior, flexibility, and planning and organization of behavior (National Institute of Child Health and Human Development, January 1994, informal survey), and is considered to overlap noticeably with the domain of attention. There are many models and theories of executive functioning, differing in the way the concept is defined and elaborated. In cognitive psychology, the concept of executive function is closely related to the notion of a limited-capacity central information processing system (Pennington and Ozonoff, 1996). According to Lezak (1983) the executive functions can be conceptualized as having four components: 1) goal formulation, 2) planning, 3) carrying out goal-directed plans, and 4) effective performance. These components could be viewed as subsequent stages. Other prominent models of executive functioning are those of Sohlberg and Mateer (1989), Stuss and Benson (1986), and Norman and Shallice (1986).

Research on attention and executive functioning in ADHD has revealed weak performance on various tasks of sustained attention, working memory, response inhibition, set shifting, complex problem solving, and motor control (Doyle et al., 2000; Grodzinsky and Barkley, 2001; Grodzinsky and Diamond, 1992; Pennington and Ozonoff, 1996; Seidman et al., 1997; Seidman et al., 1995). After Quay had stated that impulsiveness characterizing ADHD arises from diminished activity in the brain's behavioral inhibition system (BIS, for a description of the model see Quay, 1988a, 1988b), Barkley formulated a new paradigm describing deficient response inhibition as the central deficiency in ADHD (Barkley, 1990). Barkley's unifying model was based on earlier theories of cognitive functioning mediated by the prefrontal lobes, and referred to the combined type and hyperactive-impulsive type of ADHD (Barkley, 1997b). The model presumed that deficient inhibition leads to secondary impairments in four neuropsychological abilities (working memory, self-regulation, internalization of speech, and reconstitution) that are partially dependent on inhibition for their effective execution. According to Barkley, behavioral inhibition is related to three processes: a) inhibition of a prepotent response, i.e. a response that is or has been previously reinforced; b) inhibition of an ongoing response; and c) interference control, i.e. protection of a response from disruption by competing responses. According to the model, children with ADHD have poor behavioral inhibition, which causes deficiencies in four related executive functions. Together, these dysfunctions lead to problems in the motor control system that is responsible for the execution of goal-directed behavior. ADHD-related difficulties with sustained attention can be explained by disturbances in the working of interference control functions; the individual is not able to resist responding to competing responses that may arise both internally and externally during task performance, resulting in distractibility. Thus,

inattention in ADHD should be viewed as a secondary symptom rather than a primary one, since it is due to impairments in the executive control (self-regulation) consequent on poor behavioral inhibition and interference control.

Barkley's model offered a promising and testable theory of primary dysfunction in ADHD, and therefore it has drawn considerable research interest. Numerous authors have examined the putative role of behavioral disinhibition in ADHD using different measures of response inhibition like the Stroop, Go Nogo-, and Stop task. There is substantial evidence for an inhibitory deficit in ADHD, in that children with the disorder make significantly more impulsive errors and are slower to stop an ongoing action. However, poor inhibitory control seems not to be specific for ADHD since poor response inhibition is also found in other psychiatric disorders like oppositional defiant disorder (ODD) and conduct disorder (Nigg, 2001; Schachar et al., 2000). See for a review Sergeant et al. (2002).

Besides Barkley, other investigators have also attempted to formulate a single theory of ADHD that would facilitate the development of objective psychological-diagnostic tests. Theories like the state-regulation theory (core problem is nonoptimal activation/effort state, Van der Meere, 1996) and the delay aversion theory (core problem is avoidance of delay resulting in choosing an earlier, smaller reward, Sonuga-Barke, 2002) have advanced our understanding of ADHD by conducting new research. However, much research on cognitive/ psychological mechanisms associated with ADHD remains to be done.

Cognitive endophenotypes

Despite promising results from molecular genetic studies, research has had little success in definitely identifying gene regions contributing to the development of psychiatric disorders like ADHD. The majority of genetic studies remained grounded on a clinical symptom-based phenotype defined by the current diagnostic criteria of the disorder, and this appeared not to be optimal for detecting the complex genetic underpinnings of ADHD. Therefore, the concept of endophenotypes has been introduced in psychiatric genetics. Other terms like biological markers, intermediate- or latent phenotypes are synonyms that are used interchangeable. Gottesman and Shields described endophenotypes as "internal phenotypes discoverable by a biochemical test or microscopic examination" (Gottesman and Shields, 1972, 1973; Gottesman and Gould, 2003). Skuse formulated the following working definition, which will be used in this thesis: endophenotypes are latent traits that carry genetic loading and which are related indirectly to the classic behavioral symptoms as defined in DSM-IV or ICD-10 (Leboyer et al., 1998; Skuse, 2001). In line with this definition, Almasy and Blangero described three requirements for an appropriate endophenotype: 1) it should be continuously quantifiable, 2) it should be correlated with the disease by way of the underlying liability, and 3) any variation in the endophenotype should be heritable (Almasy and Blangero, 2001). A fourth criterion, added by Castellanos and Tannock (2000), was that the endophenotype should be anchored in neu-

roscience. The requirements imply that an endophenotype, which can be measured at a physiological, neurobiological, or cognitive level, may be more closely linked to the underlying genetic factors than the behavioral phenotype.

There are different strategies to study endophenotypes that moderate/mediate genetic effects of ADHD. Within the quantitative mediation/moderation framework outlined in Kraemer et al. (2001) the "candidate gene-endophenotype association approach" can be chosen to examine whether a selected candidate gene is associated with ADHD and with the candidate endophenotype. Or, one could adopt the "endophenotype-ADHD susceptibility association approach" and focus on the association between candidate endophenotypes and the genetic or familial susceptibility to ADHD by studying cognitive endophenotypes in families with affected siblings and a non-affected sibling. In this thesis, the last approach is used.

Endophenotypes composed of cognitive ability profiles are valuable in our search for the genetic correlates of ADHD, because cognitive functioning as measured by response time tasks for example, is an objective measure of the functioning of underlying mechanisms rather than of overall behavioral outcome. Furthermore, cognitive tasks are easy to administer to individuals of different ages, are cheap and harmless compared with endophenotypic measures that are physiological, structural or functional in nature. So far, only a few researchers have studied cognitive endophenotyping in ADHD. Most of them have focused on aspects of executive functioning as markers for familial ADHD, like Seidman and colleagues for example. They found that subjects with ADHD who had a family history of ADHD performed significantly worse on measures of executive functioning than subjects with ADHD without such a family history (Seidman et al., 1995). In addition, Crosbie and Schachar (Crosbie and Schachar, 2001) have shown that a familial subtype of ADHD could be delineated in terms of response inhibition. The children who exhibited poor inhibition (on the stop signal task) were significantly more likely to have a first-degree relative with ADHD than were the children with ADHD who exhibited good behavioral inhibition. To date, the results of only one study focusing on the non-referred siblings of ADHD probands, i.e. those who have the genetic liability to the disorder but not the clinical symptom-based phenotype, is published by Seidman and colleagues (2000). They examined executive functioning in non-referred siblings (of ADHD probands) without ADHD and found that they performed similar to normal controls.

Recently, Castellanos and Tannock reviewed five candidate endophenotypes and proposed that three of those: shortened delay gradient (Sonuga-Barke, 2002), working memory (Mattay et al., 2000), and temporal processing that results in high variability on reaction-time tasks (Kuntsi and Stevenson, 2001) are most suitable for further research on the etiology of ADHD (Castellanos and Tannock, 2002). Surprisingly, response inhibition was not among these candidate endophenotypes. According to the authors, this cognitive function is not well grounded in neuroscience. Furthermore, they believed that the paradigms taxing response inhibition (like the stop task) are too complex and use derived estimates of the latency of the postulated

inhibitory process. However, emerging research on different measures of response inhibition, also in combination with event-related fMRI and other brain imaging techniques (Durston et al., 2002), promises new insights. So, it may be a little too premature to conclude that response inhibition is a less valuable endophenotype of ADHD.

The overall aim of the thesis

Previous studies have provided evidence that endophenotypes composed of cognitive ability profiles may be crucial for understanding the pathway from genes to ADHD-related brain dysfunction. As discussed above, much work needs to be done before clearly defined cognitive endophenotypes can be used for molecular genetic analyses. Therefore, the overall aim of this thesis was to uncover candidate cognitive endophenotypes of ADHD. We aimed to explore which aspects of executive functioning would qualify as endophenotypes, with the ultimate goal to apply those in future genetic studies.

Outline of the thesis

In order to investigate cognitive endophenotyping in ADHD, different study-designs were used. We took much effort to include families with at least two children with diagnosed ADHD and one non-affected sibling (i.e. without clinical symptoms). If executive dysfunctioning may reflect a genetic factor that confers a biological vulnerability to ADHD (Seidman et al., 2000), we would expect that family members of ADHD probands would display (some degree of) impaired executive functioning, but only if the endophenotype and the resulting phenotype are distributed along a continuum, as suggested by different authors (Barkley, 1998; Levy et al., 1997). To investigate cognitive differences between a "familial" versus "non-familial" form of ADHD, a sample of clinically referred ADHD children and adolescents was carefully screened on the presence of a family history of ADHD.

A selection of widely used tasks measuring different aspects of executive functioning, i.e. response inhibition, attentional control, higher-order controlled motor functioning, and mental flexibility was administered to the subjects. The age of the subjects ranged from 6 to 18 in the total sample.

In **chapter 2**, response inhibition is studied in a family-genetic study design with ADHD probands, non-affected siblings of these ADHD probands, and normal controls of the same age and IQ. We examined whether non-affected siblings of ADHD probands have a response inhibition between that of ADHD probands and normal controls, although they resembled the controls at a behavioral level. Three different measures of response inhibition were used.

Chapter 3 presents the results of a study on fine motor fluency and flexibility in ADHD, using the same study-design as in chapter 2. Motor fluency was defined as the ability to execute an automatized movement fluently, and motor flexibility as the ability to execute non-automatized movements that require continuous adaptation to novel situations. It was hypothesized that ADHD probands would perform significantly worse on tasks measuring motor fluency and flexibility than controls. Further, we expected that if motor problems may be a familial marker for susceptibility to ADHD, non-affected siblings would experience motor problems similar to those of their ADHD siblings.

Chapter 4 investigates whether executive function deficits identify a meaningful familial subtype of ADHD. Previous studies have found evidence that executive dysfunction could differentiate between a familial and a nonfamilial form of ADHD. If measures of executive functioning might delineate a familial subtype of ADHD, such measures could serve as markers for molecular genetic studies. This would mean that executive dysfunctioning is likely to be a valuable endophenotype. The present study aimed to replicate previous findings and examined the hypothesis that familial ADHD may represent a distinct and meaningful subtype of ADHD characterized by measures of executive dysfunction, i.e. response inhibition, higher-order controlled motor functioning and attentional control. Referring to the results, it is discussed whether it is justifiable to differentiate between familial- and nonfamilial ADHD based on cognitive measures, and whether a non-genetic form of ADHD does exist at all.

Chapter 5 deals with familial clustering of ADHD-related executive functioning (i.e. response inhibition, motor functioning and attentional control) in affected sibling pairs. If deficient executive functioning would reflect genetic underpinnings, then ADHD affected siblings were expected to show significant correlation for measures of executive functioning.

The results of the studies described in the previous chapters have led to the examination of attentional control and mental flexibility in non-affected siblings of ADHD probands (**chapter 6**). Response inhibition and motor functioning have already been studied in family-genetic perspective (chapters 2 and 3 respectively), but attentional control and mental flexibility (other important aspects of executive functioning) have not. Our hypothesis was that siblings of ADHD probands, while not behaviorally expressing the disorder, have ADHD-associated deficits in attentional control and mental flexibility. If so, we hypothesized that the performances of the ADHD probands, non-affected siblings and the controls could be arranged on a continuum, which would be in line with the notion that ADHD should be viewed as a dimensional trait rather than a pathological category.

The aspects of executive functioning described in this thesis (response inhibition, attentional control, higher-order controlled motor functioning, and mental flexibility) and the fourteen task variables that are supposed to reflect these aspects were chosen on the basis of a review of the literature. In **chapter 7**, we report the results of an exploratory factor analysis to investigate whether these four theoretically formed con-

structs of executive functioning summarizes best the fourteen task variables used in the previous experimental studies (chapters 2 to 6). To investigate whether distinct interpretable constructs reflecting different aspects of executive functioning can be defined in a sample of ADHD siblings, a posthoc principal component analysis was performed in which a model of inter-relations between the fourteen measures of response inhibition, attentional control, higher-order controlled motor functioning, and mental flexibility was studied.

Finally, in **chapter 8** the findings of the experimental studies and the implications for clinical practice and further research are discussed.

References

Almasy L, Blangero J (2001), Endophenotypes as quantitative risk factors for psychiatric disease: rationale and study design. *Am J Med Genet* 105:42-44

American Psychiatric Association (1994), *Diagnostic and Statistical Manual for Mental Disorders.* (4th edition).Washington, DC: American Psychiatric Press

American Psychiatric Association (APA). (1998), *Diagnostic and statistical manual for mental disorders.* Washington, DC: Author

Angold A, Costello EJ, Erkanli A (1999), Comorbidity. *J Child Psychol Psychiatry* 40:57-87

August GJ, Garfinkel BD (1990), Comorbidity of ADHD and reading disability among clinic-referred children. *J Abnorm Child Psychol* 18:29-45

Bakker SC, Meulen EM, Buitelaar JK, Sandkuijl LA, Pauls DL, Monsuur AJ, Slot RR, Minderaa RB, Gunning WB, Pearson PL, Sinke RJ (2003), A whole-genome scan in 164 dutch sib pairs with attention- deficit/hyperactivity disorder: suggestive evidence for linkage on chromosomes 7p and 15q. *Am J Hum Genet* 72:1251-1260

Barkley RA (1990), *Attention Deficit Hyperactivity Disorder: A Handbook for Diagnosis and Treatment.* New York/London: The Guilford Press

Barkley RA (1997a), Attention-deficit/hyperactivity disorder, self-regulation, and time: toward a more comprehensive theory. *J Dev Behav Pediatr* 18:271-279

Barkley RA (1997b), Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychol Bull* 121:65-94

Barkley, R.A. (1998). Attention Deficit Hyperactivity Disorder. A handbook for Diagnosis and Treatment (2nd edition). New York: Guilford Press.

Barkley RA, DuPaul GJ, Mcmurray MB (1990), Comprehensive evaluation of attention deficit disorder with and without hyperactivity as defined by research criteria. *J Consult Clin Psychol* 58:775-789

Barr CL, Xu C, Kroft J, Feng Y, Wigg K, Zai G, Tannock R, Schachar R, Malone M, Roberts W, Nothen MM, Grunhage F, Vandenbergh DJ, Uhl G, Sunohara G, King N, Kennedy JL (2001), Haplotype study of three polymorphisms at the dopamine transporter locus confirm linkage to attention-deficit/hyperactivity disorder. *Biol Psychiatry* 49:333-339

Baumgardner TL, Singer HS, Denckla MB, Rubin MA, Abrams MT, Colli MJ, Reiss AL (1996), Corpus callosum morphology in children with Tourette syndrome and attention deficit hyperactivity disorder. *Neurology* 47:477-482

Benton, A. (1991). Prefrontal injury and behavior in children. *Developmental Neuropsychology,* 7: 275-282

Bianchi L (1922), *The mechanisms of the brain and the function of the frontal lobes.* Edinburgh: Livingstone

Biederman J, Faraone SV, Keenan K, Benjamin J, Krifcher B, Moore C, Sprich-Buckminster S, Ugaglia K, Jellinek MS, Steingard R, . (1992), Further evidence for family-genetic risk factors in attention deficit hyperactivity disorder. Patterns of comorbidity in probands and relatives psychiatrically and pediatrically referred samples. *Arch Gen Psychiatry* 49:728-738

Biederman J, Faraone SV, Spencer T, Wilens T, Norman D, Lapey KA, Mick E, Lehman BK, Doyle A (1993), Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. *Am J Psychiatry* 150:1792-1798

Blau, A. (1936). Mental changes following head trauma in children. *Archives of Neurology and Psychiatry,* 35: 722-769

Block, G.H. (1977). Hyperactivity: a cultural perspective. *Journal of learning disabilities*, 110: 236-240

Brown K. (2003). New Attention to ADHD Genes Kathryn Brown. *Science*, 301: 160-161

Buitelaar JK (2002), Epidemiology of Attention-deficit/Hyperactivity Disorder: what have we learned over the last decade? In S. Sandberg (Ed.), *Hyperactivity Disorders.* (pp. 30-63) Cambridge: Cambridge University Press

Buitelaar JK (2001), Discussies over ADHD. Feiten, meningen en emoties. *Ned Tijdschr Geneeskd*, 145, 1485-1489.

Cantwell DP (1975), A model for the investigation of psychiatric disorders in childhood: Its application in genetic studies of the hyperkinetic syndrome. In: *Explorations in Child Psychiatry*, Anthony EJ, ed. NY: Plenum Press, pp 57-77

Cantwell, D. (1981). Foreword. In R.A. Barkley, *Hyperactive children: A handbook for diagnosis and treatment.* New York: Guilford Press.

Casey BJ, Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Schubert AB, Vauss YC, Vaituzis AC, Dickstein DP, Sarfatti SE, Rapoport JL (1997), Implication of right frontostriatal circuitry in response inhibition and attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 36:374-383

Castellanos FX, Giedd JN, Berquin PC, Walter JM, Sharp W, Tran T, Vaituzis AC, Blumenthal JD, Nelson J, Bastain TM, Zijdenbos A, Evans AC, Rapoport JL (2001), Quantitative brain magnetic resonance imaging in girls with attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 58:289-295

Castellanos FX, Giedd JN, Eckburg P, Marsh WL, Vaituzis AC, Kaysen D, Hamburger SD, Rapoport JL (1994), Quantitative morphology of the caudate nucleus in Attention Deficit Hyperactivity Disorder. *Am J Psychiatry* 151:1791-1796

Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Vaituzis AC, Dickstein DP, Sarfatti SE, Vauss YC, Snell JW, Lange N, Kaysen D, Krain AL, Ritchie GF, Rajapakse JC, Rapoport JL (1996), Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. *Arch Gen Psychiatry* 53:607-616

Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS, Blumenthal JD, James RS, Ebens CL, Walter JM, Zijdenbos A, Evans AC, Giedd JN, Rapoport JL (2002), Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *JAMA* 288:1740-1748

Castellanos FX, Tannock R (2002), Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. *Nat Rev Neurosci* 3:617-628

Cloninger CR, Christiansen KO, Reich T, & Gottesman II (1978), Implications of sex differences in the prevalences of antisocial personality, alcoholism, and criminality for familial transmission. *Arch Gen Psychiatry* 35:941-951

Cook EH, Jr., Stein MA, Krasowski MD, Cox NJ, Olkon DM, Kieffer JE, Leventhal BL (1995), Association of attention-deficit disorder and the dopamine transporter gene. *Am J Hum Genet* 56:993-998

Crosbie J, Schachar R (2001), Deficient inhibition as a marker for familial ADHD. *Am J Psychiatry* 158:1884-1890

Daly G, Hawi Z, Fitzgerald M, Gill M (1999), Mapping susceptibility loci in attention deficit hyperactivity disorder: preferential transmission of parental alleles at DAT1, DBH and DRD5 to affected children. *Mol Psychiatry* 4:192-196

DiMaio S, Grizenko N, Joober R (2003), Dopamine genes and attention-deficit hyperactivity disorder: a review. *J Psychiatry Neurosci* 28:27-38

Douglas VI (1972), Stop, look and listen: the problem of sustained attention and impulse control in hyperactive and normal children. *Can J Behav Sci* 4:259-282

Doyle A, Seidman LJ, Weber W, Faraone SV (2000), Diagnostic efficiency of neuropsychological test scores for discriminating boys with and without attention deficit-hyperactivity disorder. *J Consult Clin Psychol* 68:477-488

Durston S, Thomas KM, Worden MS, Yang Y, Casey BJ (2002), The effect of preceding context on inhibition: an event-related fMRI study. *Neuroimage* 16:449-453

Ernst M, Zametkin AJ, Matochik JA, Pascualvaca D, Jons PH, Cohen RM (1999), High midbrain [18F] DOPA accumulation in children with attention deficit hyperactivity disorder. *Am J Psychiatry* 156:1209-1215

Faraone SV, Biederman J (1994), Genetics of attention deficit hyperactivity disorder. *Child Adolesc Psychiatr Clin N Am* 3:285-301

Faraone SV, Biederman J, Lehman BK, Keenan K, Norman D, Seidman LJ, Kolodny R, Kraus I, Perrin J, Chen WJ (1993), Evidence for the independent familial transmission of Attention Deficit Hyperactivity Disorder and Learning Disabilities - results from a family genetic study. *Am J Psychiatry* 150:891-895

Faraone SV, Biederman J, Mick E, Wozniak J, Kiely K, Guite J, Ablon JS, Warburton R, Reed E (1996), Attention deficit hyperactivity disorder in a multigenerational pedigree. *Biol Psychiatry* 39:906-908

Faraone SV, Doyle AE, Mick E, Biederman J (2001), Meta-analysis of the association between the 7-repeat allele of the dopamine D(4) receptor gene and attention deficit hyperactivity disorder. *Am J Psychiatry* 158:1052-1057

Filipek PA, Semrud-Clikeman M, Steingard RJ, Renshaw PF, Kennedy DN, Biederman J (1997), Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. *Neurology* 48:589-601

Fisher SE, Francks C, McCracken JT, McGough JJ, Marlow AJ, Macphie IL, Newbury DF, Crawford LR, Palmer CG, Woodward JA, Del'Homme M, Cantwell DP, Nelson SF, Monaco AP, Smalley SL (2002), A genomewide scan for loci involved in attention-deficit/hyperactivity disorder. *Am J Hum Genet* 70:1183-1196

Flory K, Lynam DR (2003), The relation between attention deficit hyperactivity disorder and substance abuse: what role does conduct disorder play? *Clin Child Fam Psychol Rev* 6:1-16

Fuster, J.M. (1989). *The prefrontal cortex*. New York: Raven

Giedd JN, Castellanos FX, Casey BJ, Kozuch P, King AC, Hamburger SD, Rapoport JL (1994), Quantitative morphology of the corpus callosum in Attention Deficit Hyperactivity Disorder. *Am J Psychiatry* 151:665-669

Gjone H, Stevenson J, Sundet JM (1996), Genetic influence on parent-reported attention-related problems in a Norwegian general population twin sample. *J Am Acad Child Adolesc Psychiatry* 35:588-596

Goodman R, Stevenson J (1989), A twin study of hyperactivity–II. The aetiological role of genes, family relationships and perinatal adversity. *J Child Psychol Psychiatry* 30:691-709

Gottesman II and Shields J (1972), *Schizophrenia and Genetics: A Twin Study Vantage Point*. New York, Academic Press

Gottesman II and Shields J (1973), Genetic theorizing and schizophrenia. *Br J Psychiatry* 122:15-30

Gottesman II, Gould TD (2003), The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry* 160:636-645

Grigorenko EL, Wood FB, Meyer MS, Hart LA, Speed WC, Shuster A, Pauls DL (1997), Susceptibility loci for distinct components of developmental dyslexia on chromosomes 6 and 15. *Am J Hum Genet* 60:27-39

Grodzinsky G, Barkley RA (2001), Predictive power of frontal lobe tests in the diagnosis of Attention Deficit Hyperactivity Disorder. *The clinical neuropsychologist* 13:12-21

Grodzinsky G, Diamond R (1992), Frontal lobe functioning in boys with attention deficit hyperactivity disorder. *Develop Neuropsychol* 8:427-445

Hechtman L, Weiss G (1983), Long-term outcome of hyperactive children. *Am J Orthopsychiatry* 53:532-541

Holdsworth, L., & Whitmore, K. (1974). A study of children with epilepsy attending ordinary schools: I. Their seizure patterns, progress, and behaviour in school. *Developmental Medicine and Child Neurology*, 16: 746-758

Holmes J, Payton A, Barrett JH, Hever T, Fitzpatrick H, Trumper AL, Harrington R, McGuffin P, Owen M, Ollier W, Worthington J, Thapar A (2000), A family-based and case-control association study of the dopamine D4 receptor gene and dopamine transporter gene in attention deficit hyperactivity disorder. *Mol Psychiatry* 5:523-530

Jensen PS, Martin D, Cantwell DP (1997), Comorbidity in ADHD: implications for research, practice, and DSM-V. *J Am Acad Child Adolesc Psychiatry* 36:1065-1079

Kadesjo B, Gillberg C (2001), The comorbidity of ADHD in the general population of Swedish school-age children. *J Child Psychol Psychiatry* 42:487-492

Kraemer HC, Stice E, Kazdin A, Offord D, Kupfer D (2001), How do risk factors work together? Mediators, moderators, and independent, overlapping, and proxy risk factors. *Am J Psychiatry* 158:848-856

Kuntsi J, Stevenson J (2001), Psychological mechanisms in hyperactivity: II. The role of genetic factors. *J Child Psychol Psychiatry* 42:211-219

Leboyer M, Bellivier F, Nosten-Bertrand M, Jouvent R, Pauls D, Mallet J (1998), Psychiatric genetics: search for phenotypes. *Trends Neurosci* 21:102-105

Levy F, Hay DA, McStephen M, Wood C, Waldman I (1997), Attention-deficit hyperactivity disorder: a category or a continuum? Genetic analysis of a large-scale twin study. *J Am Acad Child Adolesc Psychiatry* 36:737-744

Lezak MD (1983), *Neuropsychological assessment* (2nd ed.). New York: Oxford University Press

Luria A (1966), *Higher cortical functions in man.* New York: Basic Books

Lyoo IK, Noam GG, Lee CK, Lee HK, Kennedy BP, Renshaw PF (1996), The corpus callosum and lateral ventricles in children with attention-deficit hyperactivity disorder: a brain magnetic resonance imaging study. *Biol Psychiatry* 40:1060-1063

Maher BS, Marazita ML, Ferrell RE, Vanyukov MM (2002), Dopamine system genes and attention deficit hyperactivity disorder: a meta-analysis. *Psychiatr Genet* 12:207-215

Mattay VS, Callicott JH, Bertolino A, Heaton I, Frank JA, Coppola R, Berman KF, Goldberg TE, Weinberger DR (2000), Effects of dextroamphetamine on cognitive performance and cortical activation. *Neuroimage* 12:268-275

Mattes JA (1980), The role of frontal lobe dysfunction in childhood hyperkinesis. *Compr Psychiatry* 21:358-369

Moffitt TE (1990), Juvenile delinquency and attention deficit disorder: boys' developmental trajectories from age 3 to age 15. *Child Developm* 61:893-910

Morrison JR, Stewart MA (1973), The psychiatric status of the legal families of adopted hyperactive children. *Arch Gen Psychiatry* 28:888-891

Mostofsky SH, Reiss AL, Lockhart P, Denckla MB (1998), Evaluation of cerebellar size in attention-deficit hyperactivity disorder. *J Child Neurol* 13:434-439

Nadder TS, Silberg JL, Eaves LJ, Maes HH, Meyer JM (1998), Genetic effects on ADHD symptomatology. *Behav Genet* 28:83-99

Nigg JT (2001), Is ADHD a disinhibitory disorder? *Psychol Bull* 127:571-598

Norman D, & Shallice T (1986), Attention to action: Willed and automatic control of behaviour. Center for human information processing. In: R.J Davidson, G.E. Schwartz & D. Shapiro (Eds.), *Consciousness and self-regulation* (Vol. 4). New York: Plenum Press

Nothen MM, Schulte-Korne G, Grimm T, Cichon S, Vogt IR, Muller-Myhsok B, Propping P, Remschmidt H (1999), Genetic linkage analysis with dyslexia: evidence for linkage of spelling disability to chromosome 15. *Eur Child Adolesc Psychiatry* 8 Suppl 3:56-59

Ogdie MN, Macphie IL, Minassian SL, Yang M, Fisher SE, Francks C, Cantor RM, McCracken JT, McGough JJ, Nelson SF, Monaco AP, Smalley SL (2003), A Genomewide Scan for Attention-Deficit/Hyperactivity Disorder in an Extended Sample: Suggestive Linkage on 17p11. *Am J Hum Genet* 72:

Palmer CG, Bailey JN, Ramsey C, Cantwell D, Sinsheimer JS, Del'Homme M, McGough J, Woodward JA, Asarnow R, Asarnow J, Nelson S, Smalley SL (1999), No evidence of linkage or linkage disequilibrium between DAT1 and attention deficit hyperactivity disorder in a large sample. *Psychiatr Genet* 9:157-160

Pennington BF, Ozonoff S (1996), Executive functions and developmental psychopathology. *J Child Psychol Psychiatry* 37:51-87

Quay HC (1988a), The behavioral reward and inhibition systems in childhood behavior disorder. In LM Bloomingdale (Ed.), *Attention deficit disorder: III. New research in treatment, psychopharmacology, and attention* (pp. 176-186). New York: Pergamon Press

Quay HC (1988b), Attention Deficit Disorder and the behavioral inhibition system: The relevance of the neuropsychological theory of Jeffrey A. Gray. In: *Attention deficit disorder: Criteria, cognition, intervention*, L.M. Bloomingdale and J. Sergeant (Eds.), p. 117-126. New York: Pergamon

Raberger T, Wimmer H (2003), On the automaticity/cerebellar deficit hypothesis of dyslexia: balancing and continuous rapid naming in dyslexic and ADHD children. *Neuropsychologia* 41:1493-1497

Rhee SH, Waldman ID, Hay DA, Levy F (1999), Sex differences in genetic and environmental influences on DSM-III-R attention-deficit/hyperactivity disorder. *J Abnorm Psychol* 108:24-41

Ross, D.M., & Ross, S.A. (1982). *Hyperactivity: Research, theory, and action.* New York: Wiley

Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SC, Simmons A, Bullmore ET (1999), Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. *Am J Psychiatry* 156:891-896

Rutter, M. (1977). Brain damage syndromes in childhood: Concepts and findings. *Journal of Child Psychology and Psychiatry,* 18: 1-21

Satterfield JH, Dawson ME (1971), Electrodermal correlates of hyperactivity in children. *Psychophysiology* 8:191-197

Schachar R, mota VL, Logan G, Tannock R, klim p (2000), Confirmation of an inhibitory control deficit in ADHD. *J Abn Child Psychol* 28:227-235

Schweitzer JB, Faber TL, Grafton ST, Tune LE, Hoffman JM, Kilts CD (2000), Alterations in the functional anatomy of working memory in adult attention deficit hyperactivity disorder. *Am J Psychiatry* 157:278-280

Seidman L, Biederman J, Faraone SV, Weber W, Ouellette C (1997), Toward defining a neuropsychology of attention deficit-hyperactivity disorder: performance of children and adolescents from a large clinically referred sample. *J Consult Clin Psychol* 65:150-160

Seidman LJ, Biederman J, Faraone SV, Milberger S, Norman D, Seiverd K, Benedict K, Guite J, Mick E, Kiely K (1995), Effects of family history and comorbidity on the neuropsychological performance of children with ADHD: preliminary findings. *J Am Acad Child Adolesc Psychiatry* 34:1015-1024

Seidman LJ, Biederman J, Monuteaux MC, Weber W (2000), Neuropsychological functioning in nonreferred siblings of children with Attention deficit Hyperactivity Disorder. *J Abn Child Psychol* 109:252-265

Semrud-Clikeman M, Steingard RJ, Filipek P, Biederman J, Bekken K, Renshaw PF (2000), Using MRI to examine brain-behavior relationships in males with attention deficit disorder with hyperactivity. *J Am Acad Child Adolesc Psychiatry* 39:477-484

Sergeant JA, Geurts H, Oosterlaan J (2002), How specific is a deficit of executive functioning for attention- deficit/hyperactivity disorder? *Behav Brain Res* 130:3-28

Shirley, M. (1939). A behavior syndrome characterizing prematurely born children. *Child development,* 10: 115-128

Silberg J, Rutter M, Meyer J, Maes H, Hewitt J, Simonoff E, Pickles A, Loeber R, Eaves L (1996), Genetic and environmental influences on the covariation between hyperactivity and conduct disturbance in juvenile twins. *J Child Psychol Psychiatry* 37:803-816

Skuse DH (2001), Endophenotypes and child psychiatry. *Br J Psychiatry* 178:395-396

Smalley SL, Kustanovich V, Minassian SL, Stone JL, Ogdie MN, McGough JJ, McCracken JT, Macphie IL, Francks C, Fisher SE, Cantor RM, Monaco AP, Nelson SF (2002), Genetic linkage of attention-deficit/hyperactivity disorder on chromosome 16p13, in a region implicated in autism. *Am J Hum Genet* 71:959-963

Sohlberg MM, Mateer CA (1989), *Introduction to cognitive rehabilitation.* New York: Guilford Press

Sonuga-Barke EJ (2002), Psychological heterogeneity in AD/HD–a dual pathway model of behaviour and cognition. *Behav Brain Res* 130:29-36

Spencer T, Biederman J, Wilens TE, Faraone SV (1998), Adults with attention-deficit/hyperactivity disorder: a controversial diagnosis. *J Clin Psychiatry* 59 Suppl 7:59-68

Stewart MA (1970), Hyperactive children. *Sci Am* 222:94-98

Stuss, DT, & Benson, DF (1986). *The frontal lobes*. New York: Raven

Swanson J, Castellanos FX, Murias M, LaHoste G, Kennedy J (1998a), Cognitive neuroscience of attention deficit hyperactivity disorder and hyperkinetic disorder. *Curr Opin Neurobiol* 8:263-271

Swanson JM, Sergeant JA, Taylor E, Sonuga-Barke EJ, Jensen PS, Cantwell DP (1998b), Attention-deficit hyperactivity disorder and hyperkinetic disorder. *Lancet* 351:429-433

Szatmari P, Offord DR, Boyle MH (1989), Ontario Child Health Study: prevalence of attention deficit disorder with hyperactivity. *J Child Psychol Psychiatry* 30:219-230

Tannock R (1998), Attention deficit hyperactivity disorder: advances in cognitive, neurobiologic, and genetic research. *J Child Psychol Psychiatry* 39:65-100

Taylor D, & Ounsted C (1972), The nature of gender differences explored through ontogenetic analyses of sex ratios in disease. In C. Ounsted & D. Taylor (Eds.), *Gender differences: Their ontogeny and significance* (pp. 215-240). London: Churchill Livingstone

Teicher MH, Anderson CM, Polcari A, Glod CA, Maas LC, Renshaw PF (2000), Functional deficits in basal ganglia of children with attention-deficit/hyperactivity disorder shown with functional magnetic resonance imaging relaxometry. *Nat Med* 6:470-473

Todd RD (2000a), Genetics of attention deficit/hyperactivity disorder: are we ready for molecular genetic studies? *Am J Med Genet* 96:241-243

Todd RD (2000b), Genetics of childhood disorders: XXI. ADHD, Part 5: A behavioral genetic perspective. *J Am Acad Child Adolesc Psychiatry* 39:1571-1573

Vaidya CJ, Austin G, Kirkorian G, Ridlehuber HW, Desmond JE, Glover GH, Gabrieli JD (1998), Selective effects of methylphenidate in attention deficit hyperactivity disorder: a functional magnetic resonance study. *Proc Natl Acad Sci U S A* 95:14494-14499

Van Den Oord EJ, Boomsma DI, Verhulst FC (1994), A study of problem behaviors in 10- to 15-year-old biologically related and unrelated international adoptees. *Behav Genet* 24:193-205

Van der Meere J (1996), The role of attention. In Sandberg S (Ed.), *Hyperactivity disorders of childhood* (pp. 111-148). Cambridge University Press

Waldman ID, Rowe DC, Abramowitz A, Kozel ST, Mohr JH, Sherman SL, Cleveland HH, Sanders ML, Gard JM, Stever C (1998), Association and linkage of the dopamine transporter gene and attention- deficit hyperactivity disorder in children: heterogeneity owing to diagnostic subtype and severity. *Am J Hum Genet* 63:1767-1776

Welsh MC, Pennington BF (1988), Assessing frontal lobe functioning in children: views form developmental psychology. *Dev Neuropsychol* 4: 199-230

Werner H, & Strauss AA (1941), Pathology of figure-ground relation in the child. *Journal of Abnormal and Social Psychology*, 36: 236-248

Willcutt EG, Pennington BF, Smith SD, Cardon LR, Gayan J, Knopik VS, Olson RK, DeFries JC (2002), Quantitative trait locus for reading disability on chromosome 6p is pleiotropic for attention-deficit/hyperactivity disorder. *Am J Med Genet* 114:260-268

Wolraich ML, Hannah JN, Pinnock TY, Baumgaertel A, Brown J (1996), Comparison of diagnostic criteria for attention-deficit hyperactivity disorder in a county-wide sample. *J Am Acad Child Adolesc Psychiatry* 35: 319-324

Yamasaki H, LaBar KS, McCarthy 6 (2002), Dissociable prefrontal brain systems for attention and emotion. *Proc Natl Acad Sci USA* 99: 11447-11451

Chapter 2

Deficient Response Inhibition as a Cognitive Endophenotype of ADHD

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Abstract

Objective: To investigate whether a deficient response inhibition is a cognitive endophenotype of ADHD. We hypothesized that non-affected siblings of ADHD probands would have a response inhibition between that of ADHD probands and normal controls, although they resembled the controls at a behavioral level. Method: Participants were 25 ADHD probands with a family history of ADHD, their non-affected siblings (n=25), and 48 normal controls matched for age and IQ. All participants were between 6 and 17 years of age. The non-affected siblings were compared with their ADHD siblings and with controls on measures reflecting different types of response inhibition. Results: The non-affected siblings had results similar to those of the ADHD probands, who differed from the controls on all inhibition measures ($p < .05$). Conclusion: Siblings of ADHD probands, while not behaviorally expressing the disorder, have ADHD-associated deficits in response inhibition. This suggests that subtyping based on measures of response inhibition can help identify genetic susceptibility to ADHD. Children with a genetic vulnerability to ADHD may have hidden cognitive deficits in the absence of manifest behavioral symptoms. Therefore, they should be monitored to detect possible learning problems.

Introduction

Although the precise etiology of ADHD is still unknown, considerable evidence suggests that ADHD is influenced by genetic factors. Siblings of children with ADHD have a 2- to 3-fold higher risk of ADHD than do children of families without a positive family history of ADHD (Faraone and Biederman, 1994). In the 1970s, researchers provided evidence for genetic transmission by demonstrating that the adoptive relatives of children with ADHD were less likely to have ADHD than the biological relatives of children with ADHD (Cantwell, 1975; Morrison and Stewart, 1973). More recently, Van den Oord et al. (1994) found comparable results in their adoption studies. Additional data from twin and adoption studies indicate that the familial aggregation of ADHD has a substantial genetic component, with heritability ranging from 0.6 to 0.9 (Faraone, 1996a; Faraone et al., 1996b; Gjone et al., 1996; Goodman and Stevenson, 1989; Levy et al., 1997; Nadder et al., 1998; Silberg et al., 1996; Todd, 2000).

One of the greatest challenges in studying the genetic basis of psychiatric disorders is to find appropriate ways to define the relevant phenotype. It is increasingly recognized that the traditional nosological categories described in the DSM-IV (APA, 1994) and ICD-10 (WHO, 1994) are suboptimal when it comes to describing who is affected and carrying susceptibility genes and who is not. To unravel the genetic constellation of ADHD, emphasis should be on the description of endophenotypes. These are latent traits that carry genetic loading and which are related indirectly to the classic behavioral symptoms as defined in DSM-IV or ICD-10 (Leboyer et al., 1998; Skuse, 2001). These latent traits, which can be measured at a physiological, neurobiological, or cognitive level, may be more closely linked to the underlying genetic factors than the behavioral phenotype.

Endophenotypes composed of cognitive ability profiles are valuable in our search for the genetic correlates of ADHD. Cognitive functioning, as measured by response time tasks, is an objective measure of the functioning of underlying mechanisms rather than of overall behavioral outcome. Many researchers have studied deficits in cognitive function in ADHD. Emphasis was primarily on attention deficits, until Quay (1988) and Barkley (1990) described response inhibition deficits as being the central impairment of this disorder. In 1997, Barkley provided a unifying model of these core deficits in ADHD. The model was based on earlier theories of cognitive functioning mediated by the prefrontal lobes, and referred to the combined type and hyperactive-impulsive type of ADHD (Barkley, 1997). The model presumed that deficient inhibition leads to secondary impairments in four neuropsychological abilities that are partially dependent on inhibition for their effective execution. According to Barkley, behavioral inhibition is related to three processes: a) inhibition of a prepotent response, i.e. a response that is or has been previously reinforced; b) inhibition of an ongoing response; and c) interference control, i.e. protection of a response from disruption by competing responses.

Many researchers have studied response inhibition in individuals with ADHD, but only a few have focused on the identification of a familial form of this disorder based on inhibition or related deficits. Seidman et al. (1995) found that subjects with ADHD who had a family history of ADHD performed significantly worse on measures of response inhibition than subjects with ADHD without such a family history. In addition, Crosbie and Schachar (2001) concluded that a familial subtype of ADHD could be delineated in terms of response inhibition. The children who exhibited poor inhibition (on the stop signal task) were significantly more likely to have a first-degree relative with ADHD than were the children with ADHD who exhibited good behavioral inhibition. These findings suggest that familial ADHD may represent a form of ADHD characterized by a deficient response inhibition.

This implies that genetic factors contribute to inhibition problems in ADHD. Thus a response inhibition deficit may reflect a genetic factor that confers a biological vulnerability to ADHD (Seidman et al., 2000). If this is true, we would expect that family members of ADHD probands would display (some degree of) impaired response inhibition, only if the endophenotype and the resulting phenotype are distributed along a continuum, as suggested by different authors (Barkley, 1998; Levy et al., 1997). Seidman et al. (2000) compared the performance of non-ADHD siblings of ADHD probands and normal controls, but did not find significant differences. However, they used only one measure of response inhibition and about half of the subjects were on medication during testing, and psychotropic medication is known to affect cognitive functioning.

The aim of our study was to investigate a cognitive endophenotype of ADHD, using multiple sensitive measures of response inhibition. All participants stopped psychotropic medication at least 48 hours before testing. To be certain that the subjects had a familial form of ADHD, we selected only those families with at least two children (or one child and a parent) with a diagnosis of ADHD. Another inclusion criterion was that the ADHD siblings had a non-affected sibling who participated in the study. Our hypothesis was that the non-affected siblings of ADHD probands would exhibit a deficit in response inhibition, intermediate between that of the controls and the ADHD probands, even though at a behavioral level they resembled the normal controls.

Method

Subjects

Ninety-eight children participated in the study. The first group consisted of 25 carefully phenotyped ADHD probands with a family history of ADHD, i.e. those with at least one sibling or parent with a diagnosis of ADHD as did Seidman et al.(1995). The parents were diagnosed according to DSM-IV: at least 5 of 9 criteria of inattention and/or at least 5 of 9 criteria of hyperactivity/impulsivity (Murphy & Barkley, 1996). The diagnostic procedure for the siblings is described below. The second group con-

sisted of non-affected siblings of the ADHD probands (n = 25). Forty-eight normal controls, matched with the non-affected sibling group for age, IQ, and sex formed the third group. In all three groups age ranged from 6 to 17 years. The 25 ADHD probands were a subset of a larger population of ADHD-affected sibling pairs (n = 130) from 104 families who participated in a genome scan study (Bakker et al., 2003). In this study, we selected the affected sibling pairs that had a non-affected sibling (n = 25). Of these affected sibling pairs, the sibling who best matched the non-affected sibling in terms of age, sex and IQ was termed the proband.

The ADHD probands and their siblings were recruited from families that were referred to one of the three participating academic child psychiatric outpatient clinics, or from members of the Dutch Parents' Association. Only children that lived with their biological parent(s) of Dutch descent were included. The children were screened by experienced clinicians according to DSM-IV criteria (American Psychiatric Association, 1994). The clinical diagnoses of the affected sibling pairs were verified in structured interviews with the parents and the children. The DSM-IV version of the Diagnostic Interview Schedule for Children, DISC-P (Shaffer et al., 2000), was administered to the mother or both parents by trained graduate students in medicine or child psychology. The final diagnosis of ADHD, which served as the basis for inclusion of the family in the study, was determined using a "best-estimate procedure". To this end, the results of the medical history, clinical interview, DISC-P interview, and scores of the parent-t and teacher-rated Conners Questionnaire (Goyette et al., 1978) and Child Behaviour Checklist (CBCL, Achenbach et al., 1987; Verhulst et al., 1996), and Teacher Report Form (TRF, Achenbach, 1986; Achenbach, 1991) were summarized in a patient report. This report resulted in a final diagnosis verified by a senior child psychiatrist. Comorbidity was distributed as follows: 48% of the ADHD probands had anxiety disorders, 24% oppositional defiant disorder, 16% mood disorders, and 16% tic disorders. The non-affected siblings were non-referred siblings who did not meet the criteria for ADHD or subthreshold ADHD (5 out of 9 criteria for inattention and/ or 5 out of 9 for hyperactivity- impulsivity), according to the DISC-P. Their T-scores on the CBCL and TRF Attention Problems, Delinquent Behavior, and Aggressive Behavior subscales were not in the clinical or subclinical range (above the 95th percentile). The non-affected siblings differed significantly from the ADHD probands on number of ADHD symptoms according to DISC-P, and on CBCL and TRF scores of the subscales named above (except for TRF delinquency: p = .05, Table 1). Seventeen (68 %) of the 25 ADHD probands were taking medication (one child took risperidone; the others took methylphenidate). These medications are known to affect cognitive function, including reaction time measures (Berman et al., 1999; De Sonneville et al., 1994; Tannock et al., 1989), and therefore medication was stopped at least two days before neuropsychological assessment.

The control group consisted of 48 children. Twenty-three controls (11 twins from 11 pairs, and 12 additional siblings) were tested at the Free University of Amsterdam, where they participated in a longitudinal research project aimed at disentangling the

genetics of externalizing disorders in children. The other 25 control children were recruited from regular schools and tested in Utrecht. The controls had Total Problem scores below 67 on the CBCL, indicating that they were not likely to suffer from behavioral or emotional problems within the subclinical or clinical range. Full-Scale IQ was estimated from the Similarities, Vocabulary, Block Design, and Object Assembly subtests of the WISC-R (Sattler, 1992; Vandersteene et al., 1986). Demographic and descriptive data for the subjects are presented in Table 1. All parents signed a written consent form before participation in the study. The Medical Ethical Review Committee of the University Medical Center Utrecht approved the study.

Procedure

All children underwent a standardized neuropsychological examination including tests of response inhibition. The examination was carried out by experienced child and adolescent psychologists and trained undergraduate psychologists. To prevent distraction from external sources, the assessment was done in a quiet test room. All children were tested in the morning. Siblings of the same family were tested at the

Table 1. Demographics

	ADHD N= 25		Non-affected N= 25		Control N= 48		Significance (*p*)
Dependent measure	M or %	SD	M or %	SD	M or %	SD	
Age (months)	147.5	27.6	145.2	34.6	145.0	30.4	Ns
Estimated IQ	101.2	13.7	100.4	11.8	101.7	14.2	Ns
% Male	92		28		29		<.001[1 2]
DISC inattention	6.7	1.9	0.7	1.0	–		<.001[2]
DISC hyp/imp	7.5	1.7	0.9	1.2	–		<.001[2]
CBCL attention	69.2	9.4	54.1	5.3	52.0	3.5	<.001[1 2]
CBCL delinquency	58.2	7.2	52.5	5.0	51.5	3.1	<.001[1 2]
CBCL aggression	67.4	10.2	52.4	4.3	50.6	1.7	<.001[1 2]
TRF attention	57.6	5.4	52.7	4.5			<.05[2]
TRF delinquency	54.0	5.6	51.4	2.8			=.05[2]
TRF aggression	60.6	10.9	54.2	5.1			<.05[2]
Anxiety disorders (%)	48		12		–		
ODD (%)	24		0		–		
Mood disorders (%)	16		0		–		
Tic disorders (%)	16		0		–		

Note: ns = non significant. DISC inattention = number of symptoms of inattention scored on DISC-IV, DISC hyp/imp = number of symptoms of hyperactivity -impulsivity scored on DISC-IV. CBCL/ TRF attention = T-score on Child Behaviour Checklist/ Teacher Report Form, Attention problems subscale, CBCL/ TRF delinquency = T-score on CBCL Delinquent behavior subscale, CBCL/ TRF aggression = T-score on CBCL Aggressive behavior subscale. Anxiety disorders, ODD, Mood disorders, Tic disorders = percentage of (comorbid) disorders, based on DISC-IV.
Superscript letters indicate different significant pairwise differences: [1] = ADHD probands vs. normal controls, and [2] = ADHD probands vs. non-affected siblings.

same time. The children received verbal instructions and were allowed to practice to make sure that they understood the task instructions.

Instruments and measures

Response inhibition was operationalized by measures of response inhibition of the Go NoGo task and the Sustained Attention Task of the Amsterdam Neuropsychological Tasks (ANT, de Sonneville, 1999), and the Stroop Color Word Test.

In the Go NoGo task 24 Go signals were presented, randomly mixed with 24 NoGo signals (see Figure 1, upper left). Subjects had to press a key if a Go signal appeared on the screen and had to withhold a response if they saw a NoGo signal. In each trial, the signal was preceded by a warning tone lasting 500 ms. Signals were presented every 3000 ms. Stimulus duration was 800 ms, but the signal disappeared when a response was given within this period. Deficient inhibition was reflected by the percentage false alarms.

In the Sustained Attention task, a visual continuous performance task, 50 series x 12 patterns (600 signals) were presented in a continuous fashion, with 250 ms between the response and next stimulus onset (see Figure 1, upper right). Each series contained an equal number of signals consisting of three, four, or five dots presented

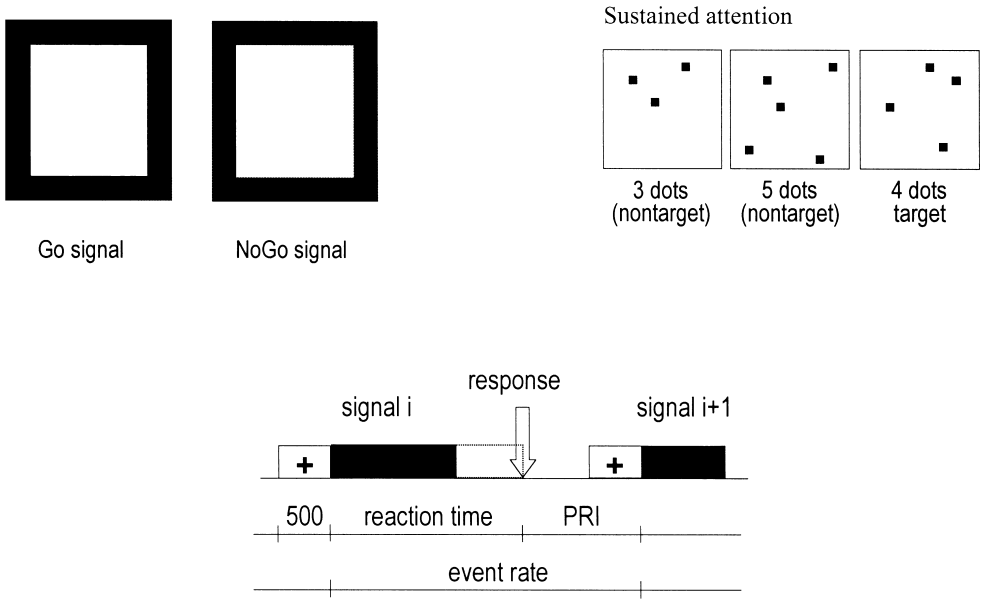

Fig. 1 Go NoGo task (upper left) and sustained attention task (upper right).
The lower middle diagram depicts the timing between signals. In the Go NoGo task a 500 ms warning signal (+) was used. Signals were presented every 3000 ms. Signal duration was 800 ms. The Sustained Attention task used a post-response interval (PRI); stimuli remained on the screen until a response was given. A warning signal was not used in this task.

in random order. With signals consisting of four dots (target signal), subjects had to press the "yes" key; with signals consisting of three and five dots (non-targets), they had to press the "no" key. During the task, subjects were informed about errors by a beep. Responses had to be generated between 200 and 8000 ms after a signal. Responses made before 200 ms were not expected to be the result of a cognitive evaluation process and were considered as undirected, impulsive hits on the mouse button, i.e. accidental responses. The number of accidental responses was used as a measure of deficient inhibition. This measure reflects basic inhibition problems, independent of task manipulation.

The Stroop test contained three parts, each having a separate card containing ten columns of ten items (Stroop, 1935). First, subjects were asked to read a list of color names as quickly as possible. Then, subjects were required to name colored patches of ink. Finally, they were required to name the dissonant color of ink in which a word was printed. Time needed to finish the Color-naming subtest was subtracted from the time needed to complete the Color-Word subtest (i.e. naming the color of the ink without paying attention to the word itself). This interference score reflects inhibition of a prepotent response (Bamford et al., 1989; Laplante et al., 1992).

Statistical Analyses

For the Go NoGo and Stroop task, univariate analyses of variance (ANOVA) with group as fixed factor were conducted to examine group differences. Age was used as a covariate whenever this parameter correlated significantly with the dependent variable. This is expected to be the case for reaction time measures (de Sonneville et al., 2002; Levy, 1980). Simple contrasts were used to examine differences between the ADHD probands and the normal controls, and between the non-affected siblings and controls. Data for the ADHD probands and non-affected siblings were compared (as within-family matched pairs) in a paired T-test, because the ADHD and the non-affected children were family members. Polynomial contrasts were used to examine whether there was a linear effect across the diagnostic categories, which would imply that cognitive performance was on a continuum, with the ADHD group at one extreme and the controls at the other. The contrast analyses were not corrected for multiple comparisons. Differences in number of accidental responses on the Sustained Attention task between the ADHD, non-affected and control group were tested using a Chi-square test. All analyses of the dependent variables were two-tailed and used the 0.05 level of statistical significance. Trend levels of significance with $p < 0.1$ are also reported. Eta square (η^2) is reported as an index of effect size, with $\eta^2 = 0.01$ denoting a weak effect, $\eta^2 = 0.06$ a moderate effect, and $\eta^2 > 0.13$ a large effect. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 9.0).

Results

In each task, the data for one normal control had to be excluded from data analysis (error score > 50% or a reaction time score more than three times the interquartile range above the median). The Stroop test data of two participants were excluded because the young children had reading problems.

Percentage false alarms Go NoGo task

The univariate analysis indicated a significant effect of group on percentage of false alarms in the Go NoGo task ($F(2,96) = 3.343$, $p = .040$, $\eta^2 = .066$). Age was not used as a covariate because it did not correlate significantly with the dependent variable. Means (SD) of task performance for the ADHD, non-affected and control group were 6.5 ± 5.9, 5.8 ± 6.3, and 3.5 ± 4.0, respectively. Simple contrast analyses showed significant differences in performance between the ADHD probands and the controls (Contrast Estimate (CE) = 3.045, p=. 021). The performance of the non-affected siblings did not differ significantly from that of the ADHD probands. The non-affected group tended to make more false alarms than did the control group: CE = 2.379, p= .070 (Figure 2, left panel). The paired t-test revealed non-significant differences in the percentage of false alarms between ADHD probands and non-affected siblings. The polynomial contrast revealed a linear effect across the diagnostic categories (CE= -2.153, p= .021).

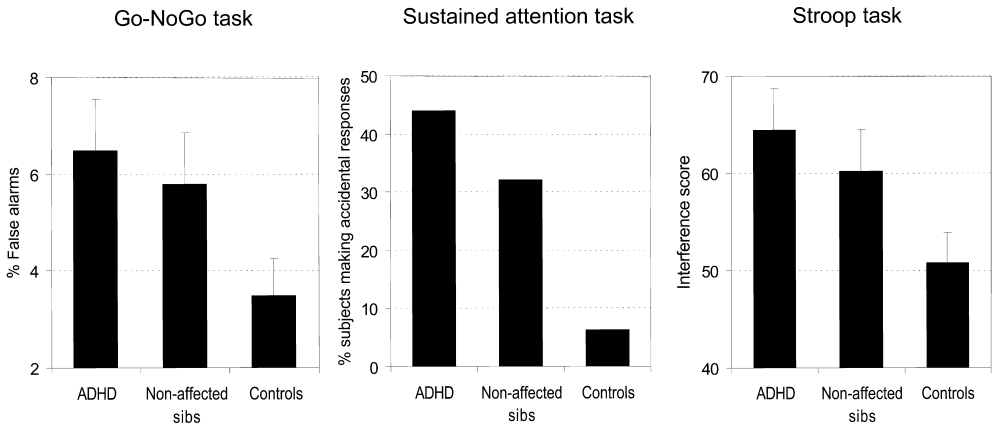

Fig. 2 Task performance as a function of group classification. The error bars denote the standard error of measurement. *Left panel*: Percentage of False alarms in the Go NoGo task. *Center panel*: Percentage of subjects making accidental responses in the Sustained attention task. *Right panel*: Stroop Interference score.
ADHD = ADHD probands; Non-affected = siblings without ADHD; Controls = normal controls

Number of Accidental responses Sustained Attention task

The number of accidental responses differed significantly across the three diagnostic groups ($\chi^2 = 14.84$, $p = 0.001$); 44% of the ADHD probands, 32% of the non-affected, and 6.4% of the controls made one or more errors (Figure 2, center panel).

Stroop interference score

The univariate analysis with age as a covariate revealed a significant effect of group on the Stroop interference score ($F(2,94) = 3.775$, $p = .027$, $\eta^2 = .077$), whereas the group effect on the time needed to complete card I (word) and card II (color) was not significant. Means (SD) of the ADHD probands, non-affected siblings and controls on card I: 56 ± 1.6; 52 ± 1.6; 52 ± 1.1, on card II: 74 ± 2.4; 71 ± 2.4; 72 ± 1.7, and on the interference score: 64 ± 4.3; 60 ± 4.3; 51 ± 3.1. Simple contrast analyses showed significant differences between the ADHD probands and the controls with respect to the Stroop interference score (CE =13.5581, p= .012). The non-affected siblings tended to have more interference problems than did the control group: CE = 9.476, p= .076 (Figure 2, right panel). The paired t-test revealed non-significant differences in Stroop interference score between ADHD and non-affected siblings. The polynomial contrast revealed a linear effect across the diagnostic categories (CE= -9.587, p=. 012).

Discussion

We tested the hypothesis that the non-affected siblings of ADHD probands exhibit deficits in response inhibition, even though they show no behavioral symptoms of ADHD. Their cognitive performance was expected to be between that of the controls and the ADHD probands. We found that the non-affected siblings of ADHD probands had response inhibition deficits, with their performance on the inhibition measures not differing significantly from that of their siblings with ADHD.

The performance of the non-affected siblings did not differ significantly from that of either the ADHD probands or the normal controls, which is considered to reflect their intermediate position between the ADHD probands and controls (see figure 2). The linear changes in response inhibition across the groups support these findings. The results are in line with Barkley´s notion that ADHD should be viewed as a dimensional trait rather than a pathological category (Barkley, 1998, p.73; Levy and Hay 2001). Furthermore, our findings are consistent with the notion of Levy et al. (1997) that ADHD should be considered as the extreme of a behavior with genetic liability and expression throughout the population.

Crosbie and Schachar (2001) also investigated deficient response inhibition as a marker of familial ADHD. Although they used a different study design and a different inhibition measure, our results are consistent with theirs. This strengthens the evidence that a defective response inhibition is a cognitive endophenotype of ADHD. In their report, Crosbie and Schachar discussed the effect of comorbidity, since oppositional defiant disorder and conduct disorder are also characterized by response inhi-

bition deficits (Barkley et al., 1992; Nigg, 1999; Sergeant et al., 2002). Although they investigated only informally whether the differences between the groups could be accounted for by comorbid disorders, they concluded that comorbidity could not have influenced their findings since "either with or without a comorbid diagnosis, those with poor inhibition had an equally high familial risk of ADHD". In our study, the ADHD probands had comorbid disorders such as ODD, anxiety, mood, or tic disorders. In the sibling group, only a few children had anxiety disorders. Thus it is unlikely that the deficient response inhibition in the siblings was due to the effect of comorbidity. The difference in comorbidity between the groups even strengthens our findings. If the siblings would have comorbid ODD and other comorbid disorders (like the ADHD probands), we would expect them to perform even worse on these cognitive measures.

A related issue concerns the specificity of a response inhibition deficit for ADHD. There is evidence that a response inhibition deficit is common to children with ADHD or ODD/CD, although it is unclear whether the same brain networks, and therefore the same genes, are involved in these two disorders (Sergeant et al., 2002). More studies are needed to investigate whether response inhibition is a cognitive endophenotype of externalizing disorders in general.

Furthermore, from a genetic perspective, it is important to study the response inhibition performance of the parents of children with externalizing behavior. Our results suggest that deficient response inhibition, as a cognitive endophenotype, is a relevant indicator of an underlying genetic susceptibility to ADHD in addition to the behavioral phenotype. Evidence from functional imaging studies suggests the involvement of frontostriatal circuits in deficient response inhibition (Casey, 2000; Cohen and Servan-Schreiber, 1992). Recently, Durston et al. (submitted) found diminished gray matter in frontostriatal circuits and related areas in children with ADHD and in their non-affected siblings. If the genes that may code specifically for these brain areas will be found in the future, some of those genes may well turn out to be interesting candidate genes for ADHD.

A strength of this study is that only carefully phenotyped ADHD probands with a family history of ADHD were included. We are certain that these children had a familial or genetic form of ADHD. Moreover, we ruled out the effect of medication by withdrawing medication two days before the tasks were performed. We also used three measures of response inhibition, all of which yielded similar results.

Limitations

Although this study provided an excellent opportunity to investigate response inhibition as a cognitive endophenotype of ADHD, the study has several potential limitations. First, sample sizes were relatively small because families with two ADHD siblings and one non-affected child are scarce. International cooperation is needed for the recruitment of such families. Secondly, the groups differed in sex ratio. Existing research on this topic, however, indicates no marked sex differences in response

inhibition in both normal children and ADHD samples (Bjorklund and Kipp, 1996; Schachar et al., 2000; Swerdlow et al., 1995). In our normal control group, boys and girls differed only on the Stroop interference score, but Stroop norm tables do not distinguish between boys and girls (Stroop, 1935). In addition, significant sex differences on Stroop interference have not been found (Jensen, 1965). Therefore, it is unlikely that our results were biased by group differences in sex ratio. However, future research should use only sex-independent cognitive measures.

Clinical implications

Identification of core cognitive deficits in a familial or genetic subform of ADHD is helpful for research into the genetics of ADHD, but is also important for clinical purposes. Children with a genetic vulnerability to ADHD may have hidden cognitive deficits in the absence of manifest behavioral symptoms and should be monitored to detect possible learning problems.

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References

Achenbach TM (1986), *Manual for the Teacher Report Form and the Child Behavior Profile. Burlington*. University of Vermont Department of Psychiatry

Achenbach TM (1991), *Integrative Guide for the 1991 CBCL, YSR, and TRF Profiles. Burlington*. University of Vermont Department of Psychiatry

Achenbach TM, Verhulst FC, Baron GD, Althaus M (1987), A comparison of syndromes derived from the Child Behavior Checklist for American and Dutch boys aged 6-11 and 12-16. *J Child Psychol Psychiatry* 28: 437-453

American Psychiatric Association (1994), *Diagnostic and Statistical Manual for Mental Disorders*. (4th edition).Washington, DC: American Psychiatric Press

Bakker SC, van der Meulen EM, Buitelaar JK, Sandkuijl LA, Pauls DL, Monsuur AJ, van 't Slot R, Minderaa RB, Gunning WB, Pearson PL, Sinke R (2003), A whole genome scan in 164 Dutch sib pairs with Attention-Deficit Hyperactivity Disorder: suggestive evidence for linkage on chromosomes 7p and 15q. *Am J Hum Genet* 72:1251-1260

Bamford KA, Caine ED, Kido DK, Plassche WM, Shoulson I (1989), Clinical-pathologic correlation in Huntington's disease: a neuropsychological and computed tomography study. *Neurology* 39:796-801

Barkley RA (1990), *Attention Deficit Hyperactivity Disorder. A handbook for Diagnosis and Treatment*. New York: Guilford Press

Barkley RA (1997), Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. *Psychol Bulletin* 121: 65-94

Barkley RA (1998*), Attention Deficit Hyperactivity Disorder. A handbook for Diagnosis and Treatment* (2nd edition). New York: Guilford Press

Barkley RA, Grodzinsky G, DuPaul GJ (1992), Frontal lobe functions in attention deficit disorder with and without hyperactivity: a review and research report. *J Abnorm Child Psychol* 20:163-188

Berman T, Douglas VI, Barr RG (1999), Effects of methylphenidate on complex cognitive processing in attention- deficit hyperactivity disorder. *J Abnorm Psychol* 108:90-105

Bjorklund DF, Kipp K (1996), Parental investment theory and gender differences in the evolution of inhibition mechanisms. *Psychol Bull* 120:163-188

Cantwell DP (1975), A model for the investigation of psychiatric disorders in childhood: Its application in genetic studies of the hyperkinetic syndrome. In*: Explorations in Child Psychiatry*, Anthony EJ, ed. NY: Plenum Press, pp 57-77

Casey BJ (2000), Disruption of inhibitory control in developmental disorders: A mechanistic model of implicated frontostriatal circuitry. In: *Mechanisms of cognitive development: the Carnegie symposium on cognition*, Vol 28. Siegler RS and McClelland J.L. (eds.). Hillsdale NJ, Erlbaum

Cohen JD, Servan-Schreiber D (1992), Context, cortex, and dopamine: a connectionist approach to behavior and biology in schizophrenia. *Psychol Rev* 99:45-77

Crosbie J, Schachar R (2001), Deficient inhibition as a marker for familial ADHD. *Am J Psychiatry* 158:1884-1890

de Sonneville LMJ (1999), Amsterdam Neuropsychological tasks: a computer-aided assessment program. In: *Computers in Psychology, Vol. 6: Cognitive ergonomics, clinical assessment and computer-assisted learning*, B.P.L.M. Den Brinker, P.J. Beek, A.N. Brand, S.J. Maarse, and L.J.M. Mulder (Eds.), pp. 187-203. Lisse: Swets and Zeitlinger

de Sonneville LM, Njiokiktjien C, Bos H (1994), Methylphenidate and information processing. Part 1: Differentiation between responders and nonresponders; Part 2: Efficacy in responders. *J Clin Exp Neuropsychol* 16:877-897

de Sonneville LM, Verschoor CA, Njiokiktjien C, Op 't Veld V, Toorenaar N, Vranken M (2002), Facial identity and facial emotions: speed, accuracy, and processing strategies in children and adults. *J Clin Exp Neuropsychol* 24:200-213

Faraone SV (1996a), Discussion of "Genetic influence on parent-reported attention-related problems in a Norwegian general population twin sample". *J Am Acad Child Adolesc Psychiatry* 35: 596-598

Faraone SV, Biederman J (1994), Genetics of attention deficit hyperactivity disorder. *Child and Adolescent Psychiatry Clinics of North America* 3:285-301

Faraone SV, Biederman J, Mick E, Wozniak J, Kiely K, Guite J, Ablon JS, Warburton R, Reed E (1996b), Attention deficit hyperactivity disorder in a multigenerational pedigree. *Biol Psychiatry* 39:906-908

Gjone H, Stevenson J, Sundet JM (1996), Genetic influence on parent-reported attention-related problems in a Norwegian general population twin sample. *J Am Acad Child Adolesc Psychiatry* 35:588-596

Goodman R, Stevenson J (1989), A twin study of hyperactivity–II. The aetiological role of genes, family relationships and perinatal adversity. *J Child Psychol Psychiatry* 30:691-709

Goyette CH, Conners CK, Ulrich RF (1978), Normative data on revised Conners Parent and Teacher Rating Scales. *J Abnorm Child Psychol* 6:221-236

Jensen AR (1965), Scoring the Stroop test. *Acta Psychol (Amst)* 24:398-408

Laplante L, Everett J, Thomas J (1992), Inhibition through negative priming with Stroop stimuli in schizophrenia. *Br J Clin Psychol* 31 (Pt 3):307-326

Leboyer M, Bellivier F, Nosten-Bertrand M, Jouvent R, Pauls D, Mallet J (1998), Psychiatric genetics: search for phenotypes. *Trends Neurosci* 21:102-105

Levy F (1980), The development of sustained attention (vigilance) and inhibition in children: some normative data. *J Child Psychol Psychiatry* 21:77-84

Levy F, Hay DA, McStephen M, Wood C, Waldman I (1997), Attention-deficit hyperactivity disorder: a category or a continuum? Genetic analysis of a large-scale twin study. *J Am Acad Child Adolesc Psychiatry* 36:737-744

Levy F, Hay D (2001), *Attention, genes, and ADHD*. Philadelphia, P.A.: Brunner-Routledge

Morrison JR, Stewart MA (1973), The psychiatric status of the legal families of adopted hyperactive children. *Arch Gen Psychiatry* 28:888-891

Murphy KR, Barkley RA (1996), Parents of children with attention-deficit/hyperactivity disorder: psychological and attentional impairment. *Am J Orthopsychiatry* 66 (1): 93-102

Nadder TS, Silberg JL, Eaves LJ, Maes HH, Meyer JM (1998), Genetic effects on ADHD symptomatology. *Behav Genet* 28:83-99

Nigg JT (1999), The ADHD Response-Inhibition Deficit as Measured by the Stop Task: Replication with DSM-IV Combined Type, Extension, and Qualification. *J Abnorm Child Psychol* 27:393-402

Quay HC (1988), Attention Deficit Disorder and the behavioral inhibition system: The relevance of the neuropsychological theory of Jeffrey A. Gray. In: *Attention deficit disorder: Criteria, cognition, intervention*, L.M. Bloomingdale and J. Sergeant (Eds.), p. 117-126. New York: Pergamon

Sattler JM (1992), *Assessment of children: WISC-III and WPPSI-R supplement*. San Diego, SA, England

Schachar R, Mota VL, Logan G, Tannock R, Klim P (2000), Confirmation of an inhibitory control deficit in ADHD. *J Abn Child Psychol* 28:227-235

Seidman LJ, Biederman J, Faraone SV, Milberger S, Norman D, Seiverd K, Benedict K, Guite J, Mick E, Kiely K (1995), Effects of family history and comorbidity on the neuropsychological performance of children with ADHD: preliminary findings. *J Am Acad Child Adolesc Psychiatry* 34:1015-1024

Seidman LJ, Biederman J, Monuteaux MC, Weber W (2000), Neuropsychological functioning in nonreferred siblings of children with Attention deficit Hyperactivity Disorder. *J Abn Child Psychol* 109:252-265

Sergeant JA, Geurts H, Oosterlaan J (2002), How specific is a deficit of executive functioning for attention- deficit/hyperactivity disorder? *Behav Brain Res* 130:3-28

Shaffer D, Fisher P, Lucas CP, Dulcan MK, Schwab-Stone ME (2000), NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC- IV): description, differences from previous versions, and reliability of some common diagnoses. *J Am Acad Child Adolesc Psychiatry* 39:28-38

Silberg J, Rutter M, Meyer J, Maes H, Hewitt J, Simonoff E, Pickles A, Loeber R, Eaves L (1996), Genetic and environmental influences on the covariation between hyperactivity and conduct disturbance in juvenile twins. *J Child Psychol Psychiatry* 37:803-816

Skuse DH (2001), Endophenotypes and child psychiatry. *Br J Psychiatry* 178:395-396

Stroop JR (1935), Studies of interference in serial verbal reactions. *Journal of Experimental Psychology* 18: 643-662

Swerdlow NR, Filion D, Geyer MA, Braff DL (1995), "Normal" personality correlates of sensorimotor, cognitive, and visuospatial gating. *Biol Psychiatry* 37:286-299

Tannock R, Schachar RJ, Carr RP, Chajczyk D, Logan GD (1989), Effects of methylphenidate on inhibitory control in hyperactive children. *J Abnorm Child Psychol* 17:473-491

Todd RD (2000), Genetics of childhood disorders: XXI. ADHD, Part 5: A behavioral genetic perspective. *J Am Acad Child Adolesc Psychiatry* 39:1571-1573

Van Den Oord EJ, Boomsma DI, Verhulst FC (1994), A study of problem behaviors in 10- to 15-year-old biologically related and unrelated international adoptees. *Behav Genet* 24:193-205

Vandersteene G, Van Haassen PP, De Bruyn EEJ, Coetsier P, Pijl YL, Poortinga YH, Lutje Spelberg HC, Spoelders-Claes R, Stinissen J (1986), *WISC-R, Wechsler Intelligence Scale for Children-Revised*, Nederlandstalige uitgave. Lisse: Swets and Zeitlinger

Verhulst FC, Koot JM, Van der Ende J (1996), *Handleiding voor de CBCL (Child Behavior Checklist) [Manual for the CBCL]*. Afdeling Kinder- en Jeugdpsychiatry, Sophia Kinderziekenhuis/ Academisch Ziekenhuis Rotterdam/ Erasmus Universiteit Rotterdam, the Netherlands

World Health Organization (1994), *International classification of diseases* (10th ed.). Geneva, Switzerland: Author

Chapter 3

Motor Flexibility Problems as a Marker for Genetic Susceptibility to ADHD

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Abstract

Objective: Fine motor flexibility and fluency were investigated in a family-genetic study of ADHD. We hypothesized that ADHD probands would perform significantly worse on tasks measuring motor fluency and flexibility than controls of the same age and IQ. Further, we expected that if motor problems are a familial marker for susceptibility to ADHD, non-affected siblings would experience motor problems similar to those of their ADHD siblings. Method: Ninety-eight children aged 6 to 17 years participated in the study: 25 carefully phenotyped ADHD probands with a family history of ADHD, 25 non-affected siblings of the ADHD probands, and 48 normal controls. A motor fluency task and a motor flexibility task were administered. The motor fluency task measures the planning and execution of an automatized movement, whereas the motor flexibility task measures the execution of non-automatized movements that require continuous adaptation to novel situations. Results: The ADHD children performed significantly worse than the controls on both tasks. Strikingly, the performance of the non-affected siblings did not differ from that of the ADHD probands on the motor flexibility task; however, on the motor fluency task the non-affected children had results similar to those of the controls. Conclusions: Children with ADHD display poor fluency and flexibility of motor movements. However, non-affected siblings of ADHD probands also experience complex motor problems, but only in movements that require higher-order cognitive processing, as measured in a motor flexibility task. The results suggest that higher-order controlled motor deficits in ADHD may be influenced by genetic factors.

Introduction

In addition to core problems such as inattention, impulsivity, and hyperactivity, about 50% of children with Attention Deficit Hyperactivity Disorder experience motor problems (Denckla & Rudel, 1978; Barkley, 1990,1998). Research has shown that ADHD children are more likely to experience difficulties with fine motor movements than with gross motor movements (Lerer & Lerer, 1976; Stewart et al., 1966; McMahon & Greenberg, 1977; Gadow, 1983; Shaywitz & Shaywitz, 1984; Szatmari et al., 1989; Serfontein, 1991) and in particular with fine motor tasks that require complex movements, as reflected by the poor performance on tests of copying, maze-tracking, and pursuit tracking (Shaywitz & Shaywitz, 1984; Korkman & Pesonen, 1994; Moffitt, 1990; Mariani & Barkley, 1997). These tasks involve both quantitative and qualitative aspects of movements. Quantitative aspects are reflected by the speed of motor responding, whereas qualitative aspects are measured by the fluency and flexibility of the movements. Processes such as perceptual analysis, visuomotor integration, motor preparedness, and sensitivity to feedback are thought to interact in the control of motor flexibility and fluency. Here, we investigated the qualitative aspects of complex motor output, because these aspects are considered to reflect the maturity and integrity of the brain (Gabbard, 1996; Hempel, 1993), and thus are reliable predictors of the quality of cognitive functioning in adolescence and adulthood (Aylaian & Meltzer, 1962; Bender, 1938; Koppitz, 1975).

Motor fluency and flexibility deficits are already found in young children with ADHD. For example, movement patterns in complex motor control tasks are inaccurate and unstable in 5/6-year-old children later diagnosed with ADHD (Kalff et al., 2003). These authors showed that motor fluency and flexibility are disturbed early in the development of ADHD, which indicates that these disturbances could be considered a basic impairment in ADHD. Since ADHD is known to be highly influenced by genetic factors, with heritability ranging from 0.6 to 0.9 (Gjone et al., 1996; Goodman & Stevenson, 1989; Silberg et al., 1996; Levy et al., 1997; Nadder et al., 1998; Todd, 2000), it is important to determine whether motor fluency and flexibility deficits in ADHD are influenced by genetic factors.

If so, subtyping based on measures of motor fluency and flexibility may be helpful in identifying (genetic) susceptibility to ADHD. To date, few data have been published in this area. A family-genetic study comparing the performance of ADHD probands and non-affected siblings on some motor tasks failed to find significant differences; however, only tests of simple motor speed and copying were used (Seidman et al., 2000). Specific aspects of the fluency and flexibility of complex movements have not yet been studied from a genetic perspective.

In the present study, we studied motor fluency and flexibility in familial ADHD. Qualitative aspects were assessed separately in two tasks: a tracking and a pursuit task. The tracking task measures the planning and execution of an automatized movement (circle drawing; fluency of movement), whereas the Pursuit task evaluates the execu-

tion of non-automatized movements that require continuous adaptation to novel situations in order to follow a randomly moving target (flexibility of movement). We investigated these aspects of movement in carefully phenotyped ADHD probands, in (behaviorally) non-affected siblings of the ADHD probands, and in normal controls. We expected the ADHD probands to perform significantly worse on tasks measuring motor fluency and flexibility than normal control children of the same age and IQ. Furthermore, if motor problems are a familial marker for susceptibility to ADHD, we expected that the non-affected siblings would experience motor problems similar to those of the ADHD probands.

Method

Participants

Ninety-eight children aged 6 to 17 years (mean = 12.16 years) participated in the study. The first group consisted of 25 carefully phenotyped ADHD probands with a family history of ADHD, defined as "those with at least one sibling or parent with a diagnosis of ADHD" (Seidman et al., 1995). The second group consisted of non-affected siblings of the ADHD probands (n = 25). Forty-eight normal controls, matched with the non-affected sibling group for age, IQ, and sex, formed the third group. The 25 ADHD probands were a subset of a larger population of ADHD-affected sibling pairs (n = 130) from 104 families who participated in a genome scan study (Bakker et al., 2003). In the present study, we selected the affected sibling pairs that had a non-affected sibling (n = 25). Of these affected sibling pairs, the sibling that best matched the non-affected sibling in terms of age, sex, and IQ was termed the proband. The second affected sibling did not participate in the present study.

The ADHD probands and their siblings were recruited from families that were referred to one of the three participating academic child psychiatric outpatient clinics or were recruited from members of the Dutch Parents' Association. Only children that lived with their biological parent(s) of Dutch descent were included. The children were screened by experienced clinicians according to DSM-IV criteria. The clinical diagnoses of the affected sibling pairs were verified in structured interviews with the parents and the children. The DSM-IV version of the Diagnostic Interview Schedule for Children, DISC-P (Shaffer et al., 2000), was administered to the mother or both parents. The final diagnosis of ADHD, which served as the basis for inclusion of the family in the study, was determined using a "best-estimate procedure". To this end, the results of the medical history, clinical interview, DISC-P interview, and scores of the parent- and teacher-rated Conners Questionnaire (Goyette et al., 1978), the Child Behaviour Checklist (CBCL) (Verhulst et al., 1996; Achenbach et al., 1987), and the Teacher Report Form (TRF) (Achenbach, 1986, 1991) were summarized in a patient report. This report resulted in a final diagnosis verified by a senior child psychiatrist. Comorbidity was distributed as follows: 48% of the ADHD probands had anxiety dis-

orders, 24% oppositional defiant disorder, 16% mood disorders, and 16% tic disorders. The non-affected siblings did not meet the criteria for ADHD or subthreshold ADHD (5 out of 9 criteria for inattention and/ or 5 out of 9 for hyperactivity- impulsivity). Their T-scores on the CBCL and TRF Attention Problems, Delinquent Behavior, and Aggressive Behavior subscales were not in the clinical or subclinical range (above the 95 percentile). The non-affected siblings differed significantly from the ADHD probands in number of ADHD symptoms according to DISC-P, and in CBCL and TRF T-scores of the subscales mentioned above (except for TRF delinquency: p = 0.05, Table 1). Seventeen (68 %) of the 25 ADHD probands were on medication (one child used risperidone; the others were on methylphenidate). These medications are known to have a positive effect on cognitive functioning (Berman et al., 1999; Tannock et al., 1989), and therefore medication was stopped at least 2 days before neuropsychological assessment.

The control group consisted of 48 children. Twenty-three controls (11 twins from 11 pairs, and 12 additional siblings) were tested at the Free University of Amsterdam, where they participated in a longitudinal research project aimed at disentangling the genetics of externalizing disorders in children. The other 25 control children were recruited from regular schools in Utrecht. The controls had Total Problem scores below 67 on the CBCL, indicating that they were not likely to suffer from behavioral or emotional problems within the subclinical or clinical range. Full-Scale IQ was estimated

Table 1. Group characteristics

Characteristics	ADHD N= 25		Non-affected N= 25		Control N= 48		Significance (*p*)
	N	%	*N*	%	*N*	%	
Male	23	92	7	28	14	29	<.001[1 2]
Female	2	8	18	72	34	71	<.001[1 2]
	M	*SD*	*M*	*SD*	*M*	*SD*	
Age (months)	147.5	27.6	145.2	34.6	145.0	30.4	Ns
Estimated IQ	101.2	13.7	100.4	11.8	101.7	14.2	Ns
DISC inattention	6.7	1.9	0.7	1.0	–		<.001[2]
DISC hyp/ imp	7.5	1.7	0.9	1.2	–		<.001[2]
CBCL attention	69.2	9.4	54.1	5.3	52.0	3.5	<.001[1 2]
CBCL delinquency	58.2	7.2	52.5	5.0	51.5	3.1	<.001[1 2]
CBCL aggression	67.4	10.2	52.4	4.3	50.6	1.7	<.001[1 2]
TRF attention	57.6	5.4	52.7	4.5			<.05[2]
TRF delinquency	54.0	5.6	51.4	2.8			=.05[2]
TRF aggression	60.6	10.9	54.2	5.1			<.05[2]

Note: ns = non significant. DISC inattention (hyp/imp) = number of symptoms of inattention (hyperactivity-impulsivity) scored on DISC-IV. CBCL/ TRF attention (delinquency, aggression) = T-score on the Attention (Delinquency, Aggression) problems subscale of the Child Behaviour Checklist/ Teacher Report Form.
Superscript letters indicate different significant pairwise differences: [1] = ADHD probands vs. normal controls, and [2] = ADHD probands vs. non-affected siblings.

from the Similarities, Vocabulary, Block Design, and Object Assembly subtests of the WISC-R (Sattler, 1992; Vandersteene et al., 1986). Descriptive data for the subjects are presented in Table 1. All subjects older than 12 gave written informed consent for participation. Parents gave written informed consent for participation of children under 12, and these children participated only if they assented to the study procedures. The Medical Ethical Review Committee of the University Medical Center Utrecht approved the study.

Materials

The neuropsychological test battery included two motor control tasks of the Amsterdam Neuropsychological Tasks (ANT): the Tracking Task and the Pursuit Task (de Sonneville, 1999).

The Tracking Task is a motor fluency task that requires subjects to trace a mouse cursor in-between an outer (radius 8.5 cm) and inner circle (radius 7.5 cm) presented on a computer display. The ANT program computes the mean distance between the cursor trajectory and the midline. The dependent measures are completion time, mean deviation (accuracy of movement), and standard deviation of the trajectory that was followed (SD: stability of movement).

The Pursuit Task requires subjects to follow a target. They have to continuously adjust the movements of the mouse in order to position the cursor as closely as possible to a moving asterisk, which requires a high level of flexibility. The task has to be executed over 60 seconds. The ANT program computes the distance between the mouse cursor and the moving target per second. Mean deviation of the moving target (accuracy of movement) and standard deviation of the distance of the mouse cursor from the moving target (SD: stability of movement) were used as dependent variables in the analyses.

Statistical analysis

Results were analyzed using the Statistical Package for the Social Sciences-Windows version 9 (SPSS). Univariate analyses of variance with age as a covariate (ANCOVA) were used to examine group differences with respect to completion time on the Tracking Task. Mean deviation and stability of movement were analyzed by general linear model multivariate analyses of variance, with group as between-subjects factor and age as a covariate. These analyses were run separately for the Pursuit and Tracking tasks. Although the sex ratio differed between the groups, sex was not used as a covariate because there were no sex differences with respect to task performance on the Tracking and the Pursuit Tasks. Simple contrasts were used to examine differences between the ADHD probands and normal controls. Repeated contrasts were used to determine whether the non-affected siblings differed from the ADHD probands (1st contrast), and whether the non-affected siblings differed from the controls (2nd contrast). All analyses of the dependent variables were two-tailed and used the 0.05 level of statistical significance. Trend levels of significance with $p < 0.1$ are also reported.

As index of effect size partial eta squared (η_p^2) is reported and Cohen's d (for the results of the contrast analyses). Effect sizes can be interpreted as being small: $\eta_p^2 = 0.01$ or d = 0.2; medium: $\eta_p^2 = 0.06$ or d = 0.5; or large: $\eta_p^2 > 0.13$ or d > 0.8 (Cohen, 1988).

Results

Since 23 normal controls were tested at the Free University, where they participated in a research project that did not include the Tracking Task, these data are missing in the analyses of this task. The results of the Pursuit Task were analyzed for both the total control group and the limited group. The data of one subject (per task) were missing due to technical problems.

Tracking Task

No significant differences in completion time were found between the groups (F = 1.22, df = 2, 73, p = 0.30). Multivariate analysis with age as a covariate indicated a significant effect of group on accuracy and stability of movement (F = 2.44, df = 2, 73, p < 0.05, $\eta_p^2 = 0.07$). Simple contrast analyses showed that the ADHD probands had a significantly worse performance than the controls in terms of both accuracy and stability of movement (Contrast Estimate (CE): 1.38, p < 0.05, d = 0.68, and CE: 2.04, p < 0.01, d = 0.78, respectively). Repeated contrasts revealed that the ADHD probands

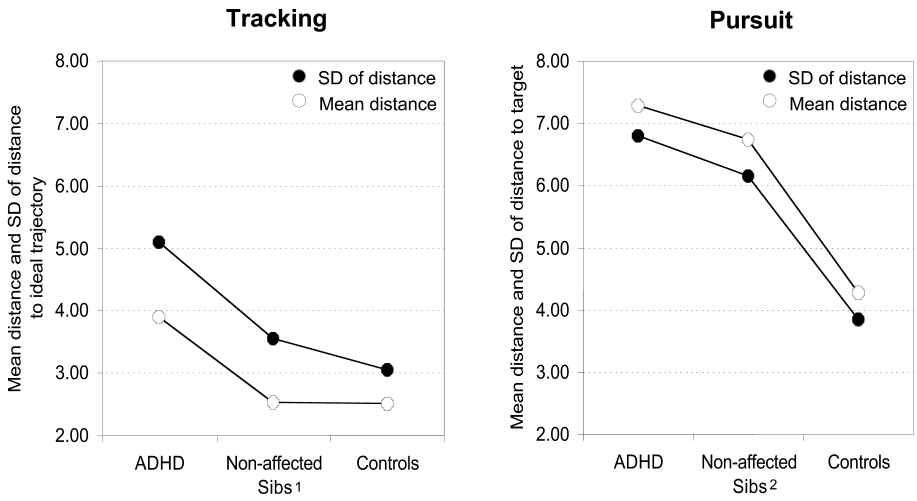

Fig.1 Task performance on Tracking (left panel) and Pursuit (right panel) of ADHD probands (N = 25), non-affected siblings (N = 25), and normal controls (N = 48).

[1] Significant differences between non-affected and ADHD group on both measures of the Tracking task (see Results).

[2] Non-significant differences between non-affected and ADHD group on both measures of the Pursuit task.

and the non-affected siblings differed significantly in terms of both accuracy and stability of movement (CE: 1.36, $p < 0.05$, $d = 0.58$, and CE: 1.53, $p < 0.05$, $d = 0.48$, respectively). The non-affected siblings did not differ significantly from the controls on these measures ($p=0.97$ and $p=0.49$ respectively). See figure 1, left panel.

Pursuit Task

Multivariate analysis with age as a covariate indicated a significant effect of group on accuracy and stability of movement ($F= 6.00$, $df = 2, 96$, $p < 0.001$, $\eta_p^2 = 0.11$). Simple contrast analyses showed that the ADHD probands performed significantly worse than the controls in terms of both accuracy and stability of movement (Contrast Estimate (CE): 3.00, $p < 0.001$, $d = 1.07$ and CE: 2.95, $p < 0.001$, $d = 0.93$, respectively). Repeated contrasts revealed that the non-affected siblings did not differ from the ADHD probands in terms of accuracy and stability of movement, whereas they differed significantly from the normal controls on these measures (CE: 2.47, $p < 0.001$, $d = 0.71$, and CE: 2.31, $p < 0.01$, $d = 0.64$, respectively). See figure 1, right panel. The analyses of the Pursuit Task repeated with the same control group as in the Tracking Task (25 instead of 48 normal controls) revealed similar results.

Discussion

In the present study, ADHD children displayed significantly more motor fluency and flexibility problems than normally developing children did. This is in line with the generally accepted view that children with ADHD are likely to suffer from motor problems (Barkley, 1990; Gillberg & Rasmussen, 1982; Gillberg et al., 1982). Further, our findings suggest that motor fluency and flexibility deficits can be viewed as cognitive correlates of a familial or genetic form of ADHD, because the ADHD children had a family history of this disorder.

Interestingly, the non-affected siblings had a performance similar to that of the ADHD probands in terms of accuracy and stability of movement in the Pursuit Task, while it differed significantly from that of the normal controls. On the Tracking Task, however, the non-affected siblings performed similarly to normal controls. This suggests that deficient motor flexibility may be a marker for genetic susceptibility to ADHD, whereas fluency seems not to be genetically affected. The discrepancy between the results of the Pursuit and Tracking Tasks probably reflects differences in the complexity of the tasks. The Tracking Task is easier to perform because drawing a circle becomes automatized during development. As a result of practice, an increasing number of segments can be organized and executed as a single motor program, which enables a child to draw a circle fluently (Van Mier et al., 1993; Huijbregts et al., in press). In contrast, the Pursuit task requires higher levels of flexibility and permanent controlled processing, since the movements of the target are unpredictable. The child has to continuously adapt to novel situations. The different findings for motor

fluency and motor flexibility suggest that only motor skills that make high demands on higher-order cognitive processing (i.e. high executive function demands) are associated with genetic susceptibility for ADHD.

This finding provides support for recent theories of ADHD that focus on poor inhibition and deficient executive functioning (self regulation) as being central to the disorder (Barkley, 2001,2003). According to Barkley, complex goal-directed motor responding is under the control of four executive function domains (domains of higher-order cognitive processing) that are closely linked to behavioral inhibition (Barkley, 1997). Thus problems with complex motor movements should be considered indicative of delayed development of motor inhibition, as Denckla proposed in 1985 (Denckla, 1985). Waber & Bernstein (1994) also provided evidence for a link between complex motor skills and inhibition. They developed the repeated Patterns Test, in which one of the parameters of graphomotor output was the ability to successfully inhibit one motor movement in order to begin another. Our results are also in line with the results of family-genetic studies of ADHD, which suggest that familial ADHD may represent a form of ADHD characterized by a deficient response inhibition (Seidman et al., 1995; Crosbie & Schachar, 2001). Thus it can be concluded that there is considerable evidence for a causal link between deficient executive functioning (response inhibition) and motor flexibility problems.

In a neuroimaging study, Rubia et al. (Rubia et al., 1999) found subnormal activation of prefrontal systems in ADHD adolescents as they performed two different motor control tasks. The authors suggested that this was due to a task-unspecific deficit in higher-order attentional regulation of motor output. The structural development of this frontal area has already been related to selective attention in ADHD (Casey et al., 1997). Thus neuroimaging studies also appear to provide evidence for the reported causal link between deficient executive functioning and motor flexibility problems, although these studies focused on attentional control rather than on response inhibition.

The question arises how inhibition and attentional control are interrelated. One could hypothesize that attentional control is needed to control responding and nonresponding (inhibition). According to Barkley, response inhibition is the basic impairment, and therefore a prerequisite for self-regulation (Barkley, 2003). Little is known about the interaction between higher-order cognitive processes which underlies the deficient motor flexibility in ADHD. More needs to be known about the interaction between attentional control and inhibition with respect to motor control and about the brain circuits involved. In the past, cognitive functions such as planning, learning, attention, and motor control were attributed solely to the prefrontal cortex, but more recently it has been discovered that cerebellar loops are also involved (Diamond, 2000; Dagher et al., 1999; Doya, 2000; Allen et al., 1997). The cerebellum may send preparatory signals to the cortex and thus may have a role in modulating the activity of the striatal-frontal loops (Giedd et al., 2001).

Overall, our findings show that children with ADHD display poor fluency and flexi-

bility of motor movements. Interestingly, the non-affected siblings of ADHD probands also experience complex motor problems, but only if controlled processing is required. In other words, they only have problems with motor movements that require higher-order cognitive processing. The results suggest that higher-order controlled motor deficits in ADHD may be influenced by genetic factors. So, deficient higher-order controlled motor performance may provide a candidate endophenotype (Gottesman & Gould, 2003) of ADHD. One of the strengths of the study is that only carefully phenotyped ADHD probands with a family history of ADHD were included. We are certain that these children had a familial or genetic form of ADHD. Moreover, we ruled out the effect of medication by withdrawing medication two days before the tasks were performed. Although this study provided an excellent opportunity to investigate whether complex fine motor deficits are associated with a genetic liability to ADHD, the findings should be interpreted with caution since sample sizes were relatively small. Families with two ADHD siblings and one non-affected child are scarce. Therefore, international cooperation is needed to replicate this study with larger samples. For future research, we recommend to investigate the motor performances of all family members (including the parents) of children with ADHD or externalizing disorders in general.

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References

Achenbach TM, Verhulst FC, Baron GD, Althaus M (1987), A comparison of syndromes derived from the Child Behavior Checklist for American and Dutch boys aged 6-11 and 12-16. *J Child Psychol Psychiatry* 28:437-453

Achenbach TM (1991), *Integrative Guide for the CBCL, YSR, and TRF Profiles*. Burlington. University of Vermont Department of Psychiatry

Achenbach TM (1986), *Manual for the Teacher Report Form and the Child Behavior Profile*. Burlington. University of Vermont Department of Psychiatry

Allen G, Buxton RB, Wong EC, Courchesne E (1997), Attentional activation of the cerebellum independent of motor control. *Science* 275:1940-1943

Aylaian A, Meltzer ML (1962), The Bender Gestalt Test and intelligence. *J Consult Clin Psychol* 26: 483

Bakker SC, van der Meulen EM, Buitelaar JK, Sandkuijl LA, Pauls DL, Monsuur AJ, van 't Slot R, Minderaa RB, Gunning WB, Pearson PL, Sinke R (2003), A whole genome scan in 164 Dutch sib pairs with Attention-Deficit Hyperactivity Disorder: suggestive evidence for linkage on chromosomes 7p and 15q. *Am J Hum Genet* 72:1251-1260

Barkley RA (1990), *Attention Deficit Hyperactivity Disorder. A handbook for Diagnosis and Treatment*. New York, Guilford Press

Barkley RA (1998), *Attention Deficit Hyperactivity Disorder. A handbook for Diagnosis and Treatment* (2nd edition). New York, Guilford Press

Barkley RA (2001), The executive functions and self-regulation: An evolutionary neuropsychological perspective. *Neuropsychol Rev* 11:1-29

Barkley RA (2003), Issues in the diagnosis of attention-deficit/hyperactivity disorder in children. *Brain Dev* 25:77-83

Barkley RA (1997), Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. *Psychol Bull* 21:65-94

Bender L (1938), A visual motor gestalt test and its clinical use. *American Orthopsychiatric Association research Monographs* 3

Berman T, Douglas VI, Barr RG (1999), Effects of methylphenidate on complex cognitive processing in attention-deficit hyperactivity disorder. *J Abnorm Psychol* 108:90-105

Casey BJ, Trainor R, Giedd J, Vauss J, Vaituzis CK, Hamburger S, Kozuch P, Rapoport J (1997), The role of the anterior cingulate in automatic and controlled processes, a developmental neuranatomical study. *Dev Psychobiol* 30:61-69

Cohen J (1988), *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Earlbaum Associates

Crosbie J, Schachar R (2001), Deficient inhibition as a marker for familial ADHD. *Am J Psychiatry* 158:1884-1890

Dagher A, Owen AM, Boecker H, Brooks DJ (1999), Mapping the network for planning: a correlational PET activation study with the Tower of London task. *Brain* 122:1973-1987

Denckla MB, Rudel RG (1978), Anomalies of motor development in hyperactive boys. *Ann Neurol* 3:231-233

Denckla MB (1985), *Motor coordination in dyslexic children: Theoretical and clinical implications, in Dyslexia: A neuroscientific approach to clinical evaluation*. Edited by Duffy FH, Geschwind N. Boston: Little. Brown, pp 187-195

de Sonneville LMJ (1999), *Amsterdam Neuropsychological tasks: a computer-aided assessment program, in Computers in Psychology*, Vol. 6: Cognitive ergonomics, clinical assessment and computer-assisted learning. Edited by Den Brinker BPLM, Beek PJ, Brand AN, Maarse SJ, Mulder LJM, Lisse, Swets & Zeitlinger, pp 187-203

Diamond A (2000), Close interrelation of motor development and cognitive development and of the cerebellum and prefrontal cortex. *Dev Psychol* 71:44-56

Doya K (2000), Complementary roles of basal ganglia and cerebellum in learning and motor control. *Curr Opin Neurobiol* 10:732-739

Gabbard CP (1996), *Livelong Motor Development*. Second edition, Boston

Gadow KD (1983), Effects of stimulant drugs on academic performance in hyperactive and learning disabled children. *J Learn Disabil* 16:290-299

Giedd JN, Blumenthal J, Molloy E, Castellanos FX (2001), Brain imaging of attention deficit/ hyperactivity disorder. *Ann N Y Acad Sci* 931:33-49

Gillberg C, Rasmussen P (1982), Perceptual, motor and attentional deficits in seven-year-old children: background factors. *Dev Med Child Neurol* 24:752-770

Gillberg C, Rasmussen P, Carlstrom G, Svenson B, Waldenstrom E (1982), Perceptual, motor and attentional deficits in six-year-old children. Epidemiological aspects. *J Child Psychol Psychiatry* 23:131-144

Gjone H, Stevenson J, Sundet JM (1996), Genetic influence on parent-reported attention-related problems in a Norwegian general population twin sample. *J Am Acad Child Adolesc Psychiatry* 35:588-596

Goodman R, Stevenson J (1989), A twin study of hyperactivity-II. The aetiological role of genes, family relationships and perinatal adversity. *J Child Psychol Psychiatry* 30:691-709

Gottesman II, Gould TD (2003), The Endophenotype Concept in Psychiatry: Etymology and Strategic Intentions. *Am J Psychiatry* 160:636-645

Goyette, CH, Conners CK, Ulrich RF (1978), Normative data on revised Conners Parent and Teacher Rating Scales. *J Abnorm Child Psychol* 6:221-236

Hempel MS (1993), *The neurological examination for toddler-age*. Groningen, The Netherlands

Huijbregts SCJ, de Sonneville LMJ, Van Spronsen FJ, Berends IE, Licht R, Verkerk PH, Sergeant JA (in press), *Executive Motor Control under Lower and Higher Controlled Processing Demands in Early- and Continuously Treated Phenylketonuria Neuropsychology*

Kalff AC, de Sonneville LMJ, Hurks P, Hendriksen JGM, Kroes M, Feron FJM, Steyaert J, van Zeben TMCB, Vles JSH, Jolles J (2003), Low- and high-level controlled processing in executive motor control tasks in 5/6-year-old children at risk of ADHD. *J Child Psychol Psychiatry* 44:1049-1057

Koppitz EM (1975), *The Bender-Gestalt test for young children*. Vol.2. New York, Grune & Stratton

Korkman M, Pesonen AE (1994), A comparison of neuropsychological test profiles of children with attention deficit-hyperactivity disorder and/or learning disorder. *J Learn Disabil* 27:383-392

Lerer RJ, Lerer MP (1976), The effects of methylphenidate on the soft neurological signs of hyperactive children. *Pediatrics* 57:521-525

Levy F, Hay DA, McStephen M, Wood C, Waldman I (1997), Attention-deficit hyperactivity disorder: a category or a continuum? Genetic analysis of a large-scale twin study. *J Am Acad Child Adolesc Psychiatry* 36:737-744

Mariani MA, Barkley RA (1997), Neuropsychological and academic functioning in preschool boys with attention deficit hyperactivity disorder. *Dev Neuropsychol* 13:111-129

McMahon SA, Greenberg LM (1977), Serial neurologic examination of hyperactive children. *Pediatrics* 59:584-587

Moffitt TE (1990), Juvenile delinquency and attention deficit disorder: boys' developmental trajectories from age 3 to age 15. *Child Dev* 61:893-910

Nadder TS, Silberg JL, Eaves LJ, Maes HH, Meyer JM (1998), Genetic effects on ADHD symptomatology. *Behav Genet* 28:83-99

Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SC, Simmons A, Bullmore ET (1999), Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. *Am J Psychiatry* 156:891-896

Sattler JM (1992), *Assessment of children: WISC-III and WPPSI-R supplement*. San Diego, SA, England

Seidman LJ, Biederman J, Monuteaux MC, Weber W (2000), Neuropsychological functioning in nonreferred siblings of children with Attention deficit Hyperactivity Disorder. *J Abnorm Child Psychol* 109:252-265

Seidman LJ, Biederman J, Faraone SV, Milberger S, Norman D, Seiverd K, Benedict K, Guite J, Mick E, Kiely K (1995), Effects of family history and comorbidity on the neuropsychological performance of children with ADHD: preliminary findings. *J Am Acad Child Adolesc Psychiatry* 34:1015-1024

Serfontein G (1991), An approach to Attention Deficit Disorder. *Modern Medicine of Australia* October:103-104

Shaffer D, Fisher P, Lucas CP, Dulcan MK, Schwab-Stone ME (2000), NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. *J Am Acad Child Adolesc Psychiatry* 39:28-38

Shaywitz SE, Shaywitz BA (1984), Diagnosis and management of attention deficit disorder: a pediatric perspective. *Pediatr Clin North Am* 31:429-457

Silberg J, Rutter M, Meyer J, Maes H, Hewitt J, Simonoff E, Pickles A, Loeber R, Eaves L (1996), Genetic and environmental influences on the covariation between hyperactivity and conduct disturbance in juvenile twins. *J Child Psychol Psychiatry* 37:803-816

Stewart MA, Pitts FN Jr., Craig AG, Dieruf W (1966), The hyperactive child syndrome. *Am J Orthopsychiat* 36:861-867

Szatmari P, Offord DR, Boyle MH (1989), Correlates, associated impairments and patterns of service utilization of children with attention deficit disorder: findings from the Ontario Child Health Study. *J Child Psychol Psychiatry* 30:205-217

Tannock R, Schachar RJ, Carr RP, Chajczyk D, Logan GD (1989), Effects of methylphenidate on inhibitory control in hyperactive children. *J Abnorm Child Psychol* 17:473-491

Todd RD (2000), Genetics of childhood disorders: XXI. ADHD, Part 5: A behavioral genetic perspective. *J Am Acad Child Adolesc Psychiatry* 39:1571-1573

Vandersteene G, Van Haassen PP, De Bruyn EEJ, Coetsier P, Pijl YL, Poortinga YH, Lutje Spelberg HC, Spoelders-Claes R, Stinissen J (1986), *WISC-R, Wechsler Intelligence Scale for Children-Revised*, Nederlandstalige uitgave. Lisse, Swets & Zeitlinger

Van Mier H, Hulstijn W, Petersen SE (1993), Changes in motor planning during the acquisition of movement patterns in a continuous task. *Acta Psychol (Amst)* 82:291-312

Verhulst FC, Koot JM, Van der Ende J (1996), *Handleiding voor de CBCL (Child Behavior Checklist) [Manual for the CBCL]*. Afdeling Kinder- en Jeugdpsychiatry, Sophia Kinderziekenhuis/ Academisch Ziekenhuis Rotterdam/ Erasmus Universiteit Rotterdam, the Netherlands

Waber DP, Bernstein JH (1994), Repetitive graphomotor output in learning-disabled and non-learning-disabled children: The Repeated Patterns Test. *Dev Neuropsychol* 10:51-65

Chapter 4

Do Executive Function Deficits Identify a Meaningful Familial Subtype of ADHD?

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Abstract

Background: Previous studies have found evidence that executive dysfunction could differentiate between a familial and a nonfamilial form of ADHD. The present study aimed to replicate these findings and examined the hypothesis that familial ADHD may represent a distinct and meaningful subtype of ADHD characterised by measures of executive dysfunction. Method: The sample consisted of 29 ADHD probands with a family history of ADHD (familial ADHD), 26 ADHD probands without a family history of the disorder (nonfamilial ADHD), and 28 normal controls. Task variables of the sustained-, divided-, and focused attention tasks, the Go Nogo task, and Pursuit task of the Amsterdam Neuropsychological Tasks Program, and the Stroop test were administered to examine different aspects of executive functioning, i.e. response inhibition, higher-order controlled motor functioning, and attentional control. Results: Not response inhibition nor higher-order controlled motor functioning but only one aspect of attentional control, namely fluctuation in tempo during time-on-task, differentiated between familial and nonfamilial ADHD. Conclusions: Contrary to our hypothesis, none of the executive functions, except for one aspect of attentional control, could differentiate between a familial- and nonfamilial form of ADHD. Thus, our results barely support the idea that executive dysfunctioning might delineate a familial subtype of ADHD. Considering the strong indications that ADHD is highly hereditary in nature, the authors suggest that a non-genetic form of the disorder may not exist at all. The findings for one aspect of attentional control, fluctuation in tempo during time on task, showed significant effects, which was in line with other studies reporting that this measure is a valuable candidate endophenotype of ADHD. Therefore, it is recommended to use this aspect of executive functioning in family-genetic studies to refine the phenotype of the disorder.

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a common and impairing childhood-onset neurobehavioral disorder. It affects 3% to 5% of all school-aged children and it persists into adulthood in one third of the cases or more (Spencer et al., 1998; Buitelaar, 2002). Family and twin studies suggest that ADHD is largely a genetic condition. Siblings of children with ADHD may have a 3- to 5-fold increase in the risk for ADHD when compared with siblings of control children (Biederman et al., 1992), and twin data indicate heritability estimates of about 80% (Gillis et al., 1992; Levy et al, 1997; Thapar et al., 1999). Three candidate genes of dopaminergic neurotransmission have been associated with ADHD in recent meta-analyses: the dopamine D4 receptor (DRD4) gene (Faraone et al., 2001) DRD5 gene (Maher et al., 2002), and the dopamine transporter (DAT-1) gene (Cook, Jr. et al., 1995; Barr et al., 2001; Daly et al., 1999; Waldman et al., 1998), although the effects of the genes were small (relative risk ranging from 1.3 to 1.6). Moreover, other studies failed to replicate these associations (Holmes et al., 2000; Palmer et al., 1999). Recently, results of whole-genome screen studies have indicated suggestive linkage on chromosomes 7p and 15q (Bakker et al., 2003), 16p13 (Smalley et al., 2002), and 17p11 (Ogdie et al., 2003). Overall, the results of family-genetic, twin and molecular studies seem to be promising with respect to our search for the genetic causative factors in ADHD.

However, although these studies provide compelling evidence that genetic factors play a major role in the etiology of the disorder, findings from other studies suggest that ADHD could also result from other etiological factors, i.e. environmental factors. Different researchers have reported about a differentiation between familial and nonfamilial ADHD (Sprich-Buckminster et al., 1993; Seidman et al., 1995; Seidman et al., 1997; Crosbie and Schachar, 2001). ADHD probands were classified as having familial ADHD if they had at least one sibling or parent with diagnosed ADHD, and nonfamilial ADHD if they had no sibling or parent with diagnosed ADHD (Seidman et al., 1995). The classification suggests that familial ADHD may be a highly biologically (genetically) based type and nonfamilial ADHD a more environmentally influenced type. Potential environmental factors in nonfamilial ADHD are traumatic brain injury (Herskovits et al., 1999), psychosocial adversity (Biederman et al., 1995), and maternal smoking during pregnancy (Mick et al., 2002).

Different studies examined whether cognitive measures could differentiate between these subtypes of ADHD, and showed significant differences between the task performance of children with a familial form and those with a nonfamilial form of the disorder. For example, deficient response inhibition was found to delineate a familial subtype of ADHD: the children who exhibited poor response inhibition were more likely to have a first-degree relative with ADHD than were the children with ADHD who exhibited good response inhibition on the stop task . Furthermore, Seidman and others found that subjects with a familial form of the disorder had significantly more executive function deficits than subjects with a nonfamilial form (Seidman et al., 1995, 1997).

In conclusion, results of different neuropsychological studies demonstrate that deficient executive function may differentiate between a familial and a nonfamilial form of ADHD. These findings have important implications for the research on the etiology of ADHD. If measures of executive functioning might delineate a familial subtype of ADHD, such measures could serve as markers for molecular genetic studies (Crosbie and Schachar, 2001). This would mean that executive dysfunctioning is likely to be a valuable endophenotype, i.e. a heritable quantitative trait that index an individual's liability to develop or manifest a given disease and is thought to be more directly related than diagnostic categories to etiological factors (Morton and Frith, 1995; Almasy and Blangero, 2001; Castellanos and Tannock, 2002).

Taken together, there is substantial evidence for a differentiation between a familial and a nonfamilial form of ADHD, with familial ADHD characterised by more executive dysfunction. These findings seem encouraging for the research on the etiology of ADHD, because, etiologically homogeneous subgroups can be formed to study the genetic effects on the familial group and the environmental influences on nonfamilial ADHD group. For example, if executive function measures can discern a more biologically subtype of ADHD, this homogeneous subgroup can be used for genetic analyses. In future research, executive function measures could increase the power of the search for genetic susceptibility factors in ADHD (Crosbie and Schachar, 2001).

The present study aimed to replicate the findings of Crosbie & Schachar (2001), and Seidman and colleagues (1995, 1997). We examined the hypothesis that familial ADHD may represent a distinct and meaningful subtype of ADHD characterised by executive dysfunction. The underlying rationale is that familial ADHD is likely to be a highly genetically influenced form of the disorder characterised by a specific pattern of executive dysfunction, whereas a nonfamilial form of the disorder may have milder or different cognitive impairments. Based on a review of the literature and our previous research, a selection of well-known tasks measuring different aspects of executive function were used. We chose to assess response inhibition, motor flexibility and attentional control, measures that have proven to be valuable candidate markers for familial ADHD (Crosbie and Schachar, 2001; Slaats-Willemse et al., 2003; Slaats-Willemse et al., submitted; Kuntsi et al., 2001; Kuntsi and Stevenson, 2001).

A crucial factor in this type of research is the definition of "familial" and "nonfamilial". As long as the genetic constellation of ADHD is unknown, the term "familiality" remains controversial. One can only formulate a preliminary definition of familiality, as Seidman and colleagues, did by classifying ADHD probands as having a family status of the disorder if they had a sibling or parent with diagnosed ADHD, and a nonfamilial status if they had no sibling or parent with diagnosed ADHD (Seidman et al., 1995). In accordance with Seidman and colleagues, we included ADHD probands with at least one sibling or parent with diagnosed ADHD in the familial group. To prevent inclusion of ADHD probands with a hidden familial form of the disorder in the nonfamilial group, we refined the definition of "nonfamilial". Only

probands without a first- ór second-degree family member with the diagnosis or marked symptoms of ADHD were included in the nonfamilial group.

In this study, we intended to demonstrate that measures of 1) response inhibition, 2) higher-order controlled motor functioning and 3) attentional control could differentiate between clearly defined subgroups of familial and non-familial ADHD.

Materials and Methods

Participants

The sample consisted of 83 children aged 6-14: 29 ADHD probands with a family history of ADHD (familial ADHD), 26 ADHD probands without a family history of the disorder (nonfamilial ADHD), and 28 normal controls.

The familial ADHD probands, i.e. those with at least one sibling with diagnosed ADHD, had full ADHD according to the DSM-IV criteria (narrow phenotype). They were a subset of a larger population of ADHD-affected sibling pairs (n = 164) from 106 families who participated in a genome scan study (Bakker et al., 2003). Of these affected sibling pairs we selected the sibling that matched best the nonfamilial ADHD group in terms of age and comorbidity. The familial ADHD probands were recruited from families that were referred to one of the three participating academic child psychiatric outpatient clinics, or from members of the Dutch Parents' Association. Only children that lived with their biological parent(s) of Dutch descent were included. The children were screened by experienced clinicians according to DSM-IV criteria (American Psychiatric Association, 1994). The clinical diagnoses of the affected sibling pairs were verified in structured interviews with the parents and the children. The DSM-IV version of the Diagnostic Interview Schedule for Children, DISC-P (Shaffer et al., 2000), was administered to the mother or both parents by trained graduate students in medicine or child psychology. The final diagnosis of ADHD, which served as the basis for inclusion of the family in the study, was determined using a "best-estimate procedure". To this end, the results of the medical history, clinical interview, DISC-P interview, and scores of the parent-t and teacher-rated Conners Questionnaire (Goyette et al., 1978) and Child Behaviour Checklist (CBCL, Achenbach et al., 1987; Verhulst et al., 1996), and Teacher Report Form (TRF, Achenbach, 1986; Achenbach, 1991) were summarised in a patient report. This report resulted in a final diagnosis verified by a senior child psychiatrist.

The nonfamilial ADHD probands (i.e. those without a first or second-degree family member with diagnosed ADHD or ADHD symptoms), were children referred to the Department of Child and Adolescent Psychiatry of the University Medical Center Utrecht. The children underwent an extensive child psychiatric examination conducted by an experienced child and adolescent psychiatrist. Classification according to the DSM-IV was based on structured interviews with the parents (DSM-IV version of the Diagnostic Interview Schedule for Children, DISC-P). The final diagnosis was

based on the results of the child psychiatric examination, DISC-P, and the scores on the CBCL and TRF. Information about family status of ADHD was obtained during the interview with the psychiatrist. Absence of symptoms of ADHD in first and second-degree family members was checked in a telephone interview about lifetime ADHD symptoms.

Fifty five percent of the ADHD children were on medication (one child used risperidone and one child clonidine; the others were on methylphenidate). These medications are known to affect cognitive function, including reaction time measures (Berman et al., 1999; de Sonneville et al., 1994; Tannock et al., 1989), and therefore methylphenidate was discontinued two days before cognitive assessment, and risperidone and clonidine one week before the assessment.

The control group consisted of 28 children. Fourteen controls (6 twins from 6 pairs, and 8 additional siblings) were tested at the Free University of Amsterdam, where they participated in a longitudinal research project aimed at disentangling the genetics of externalizing disorders in children. The other 14 control children were recruited from regular schools and tested in Utrecht. The controls had Total Problem scores below 67 on the CBCL, indicating that they were not likely to suffer from behavioural or emotional problems within the subclinical or clinical range. The CBCL Total Problems, Attention, Delinquency and Aggression scores of the control group differed significantly from those of the ADHD groups. The CBCL scores of the familial ADHD group did not differ from those of the nonfamilial group, indicating similarity in severity of the disorder (see table 1). Full-Scale IQ was estimated from the Similarities, Vocabulary, Block Design, and Object Assembly subtests of the WISC-R (Sattler, 1992; Vandersteene et al., 1986). Children with a full scale IQ <70 were excluded. Demographic and descriptive data for the subjects are presented in Table 1. All parents signed a written consent form before participation in the study. The Medical Ethical Review Committee of the University Medical Center Utrecht approved the study.

Measures

Response inhibition, higher-order controlled motor functioning, and attentional control were measured by task variables of the Stroop Color-Word Interference Test (Stroop, 1935) and five tasks of the Amsterdam Neuropsychological Tasks Program (de Sonneville, 1999; de Sonneville et al., 2002).

1) Response inhibition was operationalized by the *Stroop interference score*, *percentage of misses* and *number of impulsive responses on the Sustained Attention task*, and *percentage of false alarms on the Go Nogo task*. In the Sustained Attention task, a visual continuous performance task, 50 series x 12 signals were presented consisting of three, four, or five dots presented in random order. With signals consisting of four dots (target signal), subjects had to press the "yes" key; with signals consisting of three and five dots (non-targets), they had to press the "no" key. The overall target rate was 33%, which implies that the subject had to press the "no" key twice as often as the "yes" key. This differ-

Table 1. Clinical characteristics of children with ADHD, classified by family history of disorder, and normal controls

	ADHD group (n = 55)					
	Familial ADHD (n = 29)		Nonfamilial ADHD (n = 26)		Normal Controls (n = 28)	
Characteristic	*M*	*(SD)*	*M*	*(SD)*	*M*	*(SD)*
Age (years)[1,2]	9.6	(1.8)	9.2	(1.7)	10.6	(1.8)
Estimated IQ[1,2]	94.6	(16.1)	93.6	(10.1)	102.4	(13.6)
CBCL T-score[1,2]						
Total problems	67.3	(10.8)	69.2	(8.8)	44.7	(6.5)
Attention	69.1	(9.6)	69.9	(7.7)	53.0	(4.1)
Delinquency	64.3	(8.5)	64.1	(8.9)	51.8	(3.4)
Aggression	70.3	(11.8)	69.6	(12.4)	50.8	(2.0)
	N	*(%)*	*N*	*(%)*	*N*	*(%)*
Sex[1,2]						
Male	23	(79.3)	23	(88.5)	13	(46.4)
Female	6	(20.7)	3	(11.5)	15	(53.6)
ADHD subtype (DSM-IV)[2]						
Combined	23	(79)	17	(65)		
Inattentive	5	(17)	6	(23)		
Hyperactive-impulsive	1	(4)	3	(12)		
Comorbid diagnoses (DSM-IV)[2]						
ODD	13	(45)	11	(42)		
CD	1	(4)	2	(7)		

Note: [1] Significant differences between ADHD group and controls. Age: F= 7.1, df= 1, 82, p= 0.01; Estimated IQ: F= 7.0, df= 1, 82, p= 0.01; CBCL total problems, attention, delinquency, and aggression T-scores: F= 128.5, df= 1, 81, $p < 0.0001$, F= 89.3, df= 1, 81, $p < 0.0001$, F= 53.5, df= 1, 81, $p < 0.0001$, and F= 70.7, df= 1, 81, $p < 0.0001$ respectively; sex: F= 14.4, df= 1, 82, $p < 0.001$.

[2] Non -significant differences between familial- and nonfamilial ADHD groups. χ^2 tests are used for the analyses of behavioral data.

ence in response probability is expected to invoke a response bias (de Sonneville et al., 1994; Swaab-Barneveld et al., 2000). Therefore, the percentage of misses is considered to reflect a failure to inhibit undesired responses. Responses to signals had to be generated between 200 and 8000 ms after a signal. Responses made before 200 ms were not expected to be the result of a cognitive evaluation process and were considered as premature hits on the mouse button, i.e. impulsive responses. In the Go No-Go task, 24 Go signals were presented, randomly mixed with 24 NoGo signals. Subjects had to press a key if a Go signal appeared on the screen and had to withhold a response if they saw a NoGo signal.

2) Higher-order controlled motor functioning was operationalized by the Pursuit task, a complex fine motor tracking task that requires subjects to follow a target. They have to continuously adjust the movements of the mouse in order to position the cursor as closely as possible to a moving asterisk, which requires a high level of flexibility.

Task variables were *mean and standard deviation of the distance of the mouse cursor from the moving target*, reflecting accuracy and stability of visual motor control respectively.
3) Attentional control was reflected by the *fluctuation in tempo on the Sustained Attention task* (represented by the standard deviation of the completion times of the 50 series) and the *variability (standard deviation) in response time on hits in the divided-, and focused attention task*. The Divided Attention task employs a display load of four letters and consists of three parts in which target set size (memory load) is increased from one to three target letters. Signals that contain the complete target set require a 'yes'-response. All other signals, also those containing an incomplete target set, require a 'no'-response. The Focused Attention task employs a similar four-letter display load as in the Divided Attention task, but now only two diagonal locations are relevant (known in advance to the subjects) and subjects should attend to those positions only. A target signal is defined as a signal that contains a target letter on the relevant diagonal. Upon its presentation the 'yes'-key should be pressed. Irrelevant target signals, i.e. with a target letter on the irrelevant diagonal, and non-target signals (target letter absent) require the subject to press the 'no'-key.

Statistical analyses

Multivariate analyses of variance were conducted to examine group differences for measures of response inhibition, higher-order controlled motor functioning and attentional control respectively. The task variables were analysed per domain, with exception of the Stroop interference score. Since the Stroop test was not administered to younger subjects, the data of this test were analysed separately to prevent loss of data. In all analyses age and IQ were used as covariates whenever these parameters correlated significantly with the dependent variables. Sex was not used as a covariate, since there were no sex differences with respect to task performance. Contrast analyses (reverse Helmert contrast) were used to examine differences between the total ADHD group and normal controls, and between the familial and nonfamilial ADHD group. Analysing variables per domain and not per task caused some loss of data, because the number of subjects per task differed slightly. Therefore, the analyses of the variables that showed a 0.05 or trend level of significance were repeated in a univariate design. If the contrasts between the familial and nonfamilial group reached significance or a trend level of significance for one of the measures in the three domains, post hoc multivariate analyses (familial versus nonfamilial) were conducted per domain to verify "domain-specific" differences between familial and nonfamilial ADHD. All analyses of the dependent variables were two-tailed and used the 0.05 level of statistical significance. Trend levels of significance with $p < 0.1$ are also reported. As index of effect size partial eta squared (η_p^2) is reported for the uni- and multivariate analyses and Cohen's d for the results of the contrast analyses. Effect sizes can be interpreted as being small: $\eta_p^2 = 0.01$ or $d = 0.2$; medium: $\eta_p^2 = 0.06$ or $d = 0.5$; or large: $\eta_p^2 > 0.13$ or $d > 0.8$ (Cohen, 1988). Data analysis was performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 9.0).

Results

1) Response inhibition

The data for one subject in the non-familial ADHD group was missing due to technical problems. Multivariate analysis with age and IQ as covariates indicated a significant effect of group on percentage of misses and number of impulsive responses on the sustained attention task, and percentage of false alarms on the Go Nogo task ($F = 3.73$, $df = 2, 81$, $p < 0.001$, $\eta_p^2 = 0.13$, see Table 2). Contrast analyses (level 3 versus previous) showed that the ADHD probands differed significantly from the normal controls on percentage of misses in the sustained attention task (Contrast Estimate (CE): -7.22, $p < 0.05$, $d = 0.64$), and on percentage of false alarms in the Go Nogo task: CE: -7.90, $p = 0.001$, $d = 0.94$. Number of impulsive responses in the sustained attention task showed a trend level of significance (CE: -3.63, $p = 0.066$, $d = 0.51$). The familial ADHD group did not differ significantly from the nonfamilial group (contrast level 1 versus level 2) on these measures of response inhibition.

The univariate analysis with age as a covariate revealed a significant effect of group on the Stroop interference score ($F = 5.01$, $df = 2, 69$, $p < 0.01$, $\eta_p^2 = 0.13$, see Table 2). Contrast analyses (level 3 versus previous) showed that the ADHD probands differed significantly from the normal controls on interference score (CE: -23.85, $p < 0.01$, $d = 0.68$). The contrast between the familial ADHD group and nonfamilial group (contrast level 1 versus level 2) was nonsignificant.

2) Higher-order controlled motor functioning

The data for five subjects in the non-familial ADHD group were missing, because this task was not yet in the standardised program at the time of their referral to the outpatient clinic. The data for one subject in the familial ADHD group was missing due to technical problems.

Multivariate analysis with age as a covariate indicated a significant effect of group on accuracy and stability of visual motor control in the Pursuit task ($F= 3.56$, $df = 2, 76$, $p < 0.01$, $\eta_p^2 = 0.09$, see Table 2). Contrast analyses (level 3 versus previous) showed that the ADHD probands differed significantly from the normal controls on accuracy (CE: -3.82, $p < 0.01$, $d = 0.78$) and stability of visual motor control (CE: -3.54, $p < 0.01$, $d = 0.68$). The contrasts between the familial ADHD group and nonfamilial group (contrast level 1 versus level 2) revealed a trend level of significance for stability of visual motor control (CE: -2.60, $p = 0.090$, $d = 0.38$), and a nonsignificant result for accuracy. A post hoc multivariate analysis (familial versus nonfamilial group) revealed a nonsignificant effect of group on accuracy and stability of visual motor control.

3) Attentional control

The data for three subjects in the familial group and two in the non-familial group were missing because the young subjects did not recognise the letters in the Divided- and Focused Attention task. The data for one normal control had to be excluded from the data analyses due to reaction time scores more than three times the interquartile range above the median.

Multivariate analysis with age and IQ as covariates indicated a significant effect of group on fluctuation in tempo in the Sustained Attention task and variability in response time on hits in the Divided-, and Focused Attention task (F= 5.07, df = 2, 76, p < 0.0001, $\eta_p^2 = 0.18$, see Table 2). Contrast analyses (level 3 versus previous) showed that the ADHD probands differed significantly from the normal controls on fluctuation in tempo in the Sustained Attention task and variability in response time on hits in the Divided Attention task (CE: -1.19, p < 0.0001, d = 0.91, and CE: -305.84, p < 0.0001, d = 1.05 respectively). This contrast showed a trend level of significance for variability in response time on hits in the Focused Attention task: CE: -149.59, p = 0.061, d = 0.36. The contrasts between the familial ADHD group and nonfamilial group (contrast level 1 versus level 2) revealed non-significant results for variability in response time on hits in the Divided- and Focused Attention task, and a significant result for the fluctuation in tempo in the Sustained Attention task (CE: -0.69, p ≤ 0.05, d = 0.48). A post hoc multivariate analysis (familial versus nonfamilial group) revealed a nonsignificant effect of group on the attentional control measures.

Discussion and Conclusion

The present study investigated whether familial ADHD may represent a distinct and meaningful subtype of ADHD characterised by executive dysfunction. Contrary to our

Table 2. Response inhibition, higher-order controlled motor functioning, and attentional control in ADHD probands, classified by family history of the disorder, and normal controls

Cognitive measure	ADHD group (n = 55)					
	Familial ADHD (n = 29)		Nonfamilial ADHD (n = 26)		Normal Controls (n = 28)	
	Mean	(SD)	Mean	(SD)	Mean	(SD)
Response inhibition						
Sust. att. % Misses	16.2	(12.7)	20.7	(14.4)	11.2[a]*	(7.0)
Sust. att. no. impulsive responses	6.3	(10.5)	3.9	(9.8)	1.4[a]†	(1.7)
Go Nogo % False Alarms	11.0	(11.0)	14.7	(10.4)	5.0[a]***	(29.1)
Stroop Interference	98.6	(41.1)	85.7	(43.5)	68.3[a]**	(29.1)
Higher-order controlled motor funct.						
Pursuit Movement Accuracy	10.5	(8.0)	8.8	(5.3)	5.8[a]**	(2.1)
Pursuit Stability †	10.4	(8.3)	7.8	(4.9)	5.6[a]**	(3.1)
Attentional Control						
Sust. att. fluctuation in tempo*	3.8	(1.4)	3.1	(1.5)	2.3[a]***	(1.1)
Div. att. variability time hits	758.3	(301.3)	846.2	(421.4)	496.4[a]***	(171.5)
Foc. att. variability time hits	525.2	(320.9)	577.2	(457.5)	401.6[a]†	(206.5)

Note: [a] Versus total ADHD group. † $0.05 < p < 0.10$, * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$. Boldface cognitive measures represent significant (or trend) differences between familial and nonfamilial ADHD.

hypothesis, response inhibition and higher-order controlled motor functioning did not differentiate between familial- and nonfamilial ADHD, and little evidence was found that attentional control differed significantly between these two subtypes. The lack of substantial support for the hypothesis that executive dysfunctioning would characterise a familial form of ADHD requires reconsideration of our hypothesis and close inspection of the existing research on this topic. A study cited in the introduction to lay the foundation for our hypothesis, concluded that deficient inhibition might delineate a familial subtype of ADHD (Crosbie and Schachar, 2001). The researchers found that children with ADHD who exhibited poor inhibition were significantly more likely to have a first-degree relative with ADHD than were children with ADHD who exhibited good inhibition. However, it is not said that the performance on the inhibition task of the ADHD children with a first-degree relative with ADHD would differ significantly from those of the ADHD children without a family history of the disorder. Probably, a slightly different approach to examine cognitive endophenotypes to ADHD can cause major different results. This may be due to the complex etiology of ADHD and its cognitive correlates. The study of Seidman and colleagues, comparing familial and nonfamilial ADHD, seemed to provide quite robust evidence for the idea that familial status designated a meaningful subtype of ADHD characterised by deficits in response inhibition measured by the Stroop test (Seidman et al., 1997; Seidman et al., 1995). However, statistically controlling for the influence of comorbidity reduced the effects so that the response inhibition measure did not differentiate significantly between familial and nonfamilial ADHD.

Although our results barely support the idea that executive dysfunctioning might delineate a familial subtype of ADHD, the findings for one aspect in this cognitive domain, attentional control, showed significant effects. Children with a familial form of the disorder showed more fluctuation in tempo on a sustained attention task compared with nonfamilial ADHD children. The results are consistent with the finding that response variability is highly heritable (Kuntsi and Stevenson, 2001). Furthermore, these findings are in line with the notion of Castellanos and Tannock that response variability may be a valuable candidate endophenotype for molecular genetic studies of ADHD because of the promising findings across speeded-reaction time tasks, an ocular fixation task and imaging studies (Castellanos and Tannock, 2002). The variability in response time on hits in the divided- and focused attention tasks did not show a significant difference between the familial and nonfamilial groups. These tasks have a much shorter duration and therefore they are less sensitive to variability in response time than the sustained attention task that is designed to reflect time-on-task effects. The significant effect of family status on fluctuation in tempo during time on task suggests that this measure of attentional control may be promising for research on the genetics of ADHD.

Since none of the measures of response inhibition or higher-order controlled motor functioning and only one measure in the domain of attentional control differentiated between familial and nonfamilial ADHD, we can conclude that familial and

nonfamilial ADHD are not likely to be different subtypes characterised by different patterns of executive function deficits. The nonsignificant results of the post hoc multivariate analyses (familial versus nonfamilial) per domain support this conclusion and suggest that familial ADHD may not be a meaningful subtype of the disorder with different biological roots and different related cognitive deficits. The difference between familial- and nonfamilial ADHD may be rather quantitative than qualitative. Or, possibly a non-genetic form of ADHD does not exist at all. The current view about the etiology of ADHD is that the disorder is caused by a confluence of many genes and environmental factors (Seidman et al., 2000). We suggest that ADHD children with an evident family history of the disorder may carry more genes that predispose to ADHD related cognitive deficits, and/or may be more exposed to an environment that elucidates cognitive impairments than ADHD children without such an evident family status of the disorder. This suggestion is in line with the view that ADHD is a dimensional trait (Barkley, 1998, p.73; Levy et al., 1997; Levy, 2001) characterised by executive function deficits that differ in severity according to the extent of the genetic liability and influence of a gene-environment interaction. Although our preliminary findings should be interpreted cautiously, they led us to suggest that the terms "familial" and "nonfamilial" may at least be classified as misleading. Also because of the fact that the term "familial" may be considered as being controversial, as already noted in the introduction.

In conclusion, the present study showed that none of the executive functions, except for one aspect of attentional control, could differentiate between a "familial-" and "nonfamilial" form of ADHD. The present results strongly suggest that it is not justifiable to differentiate between "familial-" and "nonfamilial" ADHD based on cognitive measures. Consistent with other studies, fluctuation in tempo during time on task, seemed to be a valuable marker for genetic analyses. Therefore, it is recommended to include this measure in future studies using a family-genetic design to refine the phenotype of ADHD.

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References

Achenbach, T.M. (1986). *Manual for the Teacher Report Form and the Child Behavior Profile.* Burlington. University of Vermont Department of Psychiatry.

Achenbach, T.M. (1991). *Integrative Guide for the 1991 CBCL, YSR, and TRF Profiles.* Burlington. University of Vermont Department of Psychiatry.

Achenbach, T.M., Verhulst, F.C., Baron, G.D., Althaus, M. (1987). A comparison of syndromes derived from the Child Behavior Checklist for American and Dutch boys aged 6-11 and 12-16. *Journal of Child Psychology and Psychiatry,* 28, 437-453.

Almasy, L., & Blangero, J. (2001). Endophenotypes as quantitative risk factors for psychiatric disease: rationale and study design. *American Journal of Medical Genetics,* 105, 42-44.

American Psychiatric Association (1994), *Diagnostic and Statistical Manual for Mental Disorders.* (4th edition).Washington, DC: American Psychiatric Press.

Bakker, S.C., Meulen, E.M., Buitelaar, J.K., Sandkuijl, L.A., Pauls, D.L., Monsuur, A.J., Slot, R.R., Minderaa, R.B., Gunning, W.B., Pearson, P.L., Sinke, R.J. (2003). A whole-genome scan in 164 dutch sib pairs with attention- deficit/hyperactivity disorder: suggestive evidence for linkage on chromosomes 7p and 15q. *American Journal of Human Genetics,* 72,1251-1260.

Barkley, R.A. (1998*). Attention Deficit Hyperactivity Disorder. A handbook for Diagnosis and Treatment* (2nd edition). New York: Guilford Press.

Barr, C.L., Xu, C., Kroft, J., Feng, Y., Wigg, K., Zai, G., Tannock, R., Schachar, R., Malone, M., Roberts, W., Nothen, M.M., Grunhage, F., Vandenbergh, D.J., Uhl, G., Sunohara, G., King, N., Kennedy, J.L. (2001). Haplotype study of three polymorphisms at the dopamine transporter locus confirm linkage to attention-deficit/hyperactivity disorder. *Biological Psychiatry,* 49, 333-339.

Berman, T., Douglas, V.I., & Barr, R.G. (1999). Effects of methylphenidate on complex cognitive processing in attention- deficit hyperactivity disorder. *Journal of Abnormal Psychol*ogy, 108, 90-105.

Biederman, J., Faraone, S.V., Keenan, K., Benjamin, J., Krifcher, B., Moore, C., Sprich-Buckminster, S., Ugaglia, K., Jellinek, M.S., Steingard, R., Spencer, T., Norman, D., Kolodny, R., Kraus, I., Perrin, J., Keller, M.B., & Tsuang, M.T. (1992). Further evidence for family-genetic risk factors in attention deficit hyperactivity disorder. Patterns of comorbidity in probands and relatives psychiatrically and pediatrically referred samples. *Archives of General Psychiatry,* 49, 728-738.

Biederman, J., Milberger, S., Faraone, S.V., Kiely, K., Guite, J., Mick, E., Ablon, S., Warburton, R., & Reed, E. (1995). Family-environment risk factors for attention-deficit hyperactivity disorder. A test of Rutter's indicators of adversity. *Archives of General psychiatry,* 52, 464-470.

Buitelaar, J.K. (2002). Epidemiology: what have we learned over the last decade? In S. Sandberg (Ed), *Hyperactivity and Attention-Deficit Disorders.* Cambridge UK, Cambridge University Press.

Castellanos, F.X. and Tannock, R. (2002). Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. *Nature Reviews Neuroscience,* 3, 617-628.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Earlbaum Associates.

Cook, E.H., Jr., Stein, M.A., Krasowski, M.D., Cox, N.J., Olkon, D.M., Kieffer, J.E., Leventhal, B.L. (1995). Association of attention-deficit disorder and the dopamine transporter gene. *American Journal of Human Genetics,* 56, 993-998.

Crosbie, J. & Schachar, R. (2001). Deficient inhibition as a marker for familial ADHD. *American Journal of Psychiatry,* 158,1884-1890.

Daly, G., Hawi, Z., Fitzgerald, M., & Gill, M. (1999). Mapping susceptibility loci in attention deficit hyperactivity disorder: preferential transmission of parental alleles at DAT1, DBH and DRD5 to affected children. *Molecular Psychiatry* ,4,192-196.

de Sonneville, L.M., Boringa, J.B., Reuling, I.E., Lazeron, R.H., Ader, H.J., & Polman, C.H. (2002). Information processing characteristics in subtypes of multiple sclerosis. *Neuropsychologia,* 40,1751-1765.

de Sonneville, L.M., Njiokiktjien, C., Bos, H. (1994). Methylphenidate and information processing. Part 1: Differentiation between responders and nonresponders; Part 2: Efficacy in responders. *Journal of Clinical and Experimental Neuropsychology,* 16, 877-897.

de Sonneville, L.M.J. (1999). Amsterdam Neuropsychological tasks: a computer-aided assessment program. In: *Computers in Psychology, Vol. 6: Cognitive ergonomics, clinical assessment and computer-assisted learning*, B.P.L.M. Den Brinker, P.J. Beek, A.N. Brand, S.J. Maarse, and L.J.M. Mulder (Eds.), pp. 187-203. Lisse: Swets and Zeitlinger.

Faraone, S.V., Doyle, A.E., Mick, E., & Biederman, J. (2001). Meta-analysis of the association between the 7-repeat allele of the dopamine D(4) receptor gene and attention deficit hyperactivity disorder. *American Journal of Psychiatry* 158,1052-1057.

Gillis, J.J., Gilger, J.W., Pennington, B.F., DeFries, J.C. (1992). Attention deficit disorder in reading-disabled twins: evidence for a genetic etiology. *Journal of Abnormal Child Psycholo*gy, 20, 303-315.

Gottesman, I.I., Gould, T.D. (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. *Amercian Journal of Psychiatry,* 160, 636-645.

Goyette, C.H., Conners, C.K., & Ulrich, R.F. (1978). Normative data on revised Conners Parent and Teacher Rating Scales. *Journal of Abnormal Child Psychology,* 6, 221-236.

Grodzinsky, G., & Barkley, R.A. (2001). Predictive power of frontal lobe tests in the diagnosis of Attention Deficit Hyperactivity Disorder. *The clinical neuropsychologist* ,13, 12-21.

Herskovits, E.H., Megalooikonomou, V., Davatzikos, C., Chen, A., Bryan, R.N., Gerring, J.P. (1999). Is the spatial distribution of brain lesions associated with closed-head injury predictive of subsequent development of attention-deficit/hyperactivity disorder? Analysis with brain-image database. *Radiology*, 213, 389-394.

Holmes, J., Payton, A., Barrett, J.H., Hever, T., Fitzpatrick, H., Trumper, A.L., Harrington, R., McGuffin, P., Owen, M., Ollier, W., Worthington, J., & Thapar, A. (2000). A family-based and case-control association study of the dopamine D4 receptor gene and dopamine transporter gene in attention deficit hyperactivity disorder. *Molecular Psychiatry,* 5, 523-530.

Kuntsi, J., Oosterlaan, J., & Stevenson, J. (2001). Psychological mechanisms in hyperactivity: I. Response inhibition deficit, working memory impairment, delay aversion, or something else? *Journal of Child Psychology and Psychiatry,* 42,199-210.

Kuntsi, J., & Stevenson, J. (2001). Psychological mechanisms in hyperactivity: II. The role of genetic factors. *Journal of Child Psychology and Psychiatry,* 42, 211-219.

Levy, F., Hay, D.A., McStephen, M., Wood, C., & Waldman, I. (1997). Attention-deficit hyperactivity disorder: a category or a continuum? Genetic analysis of a large-scale twin study. *Journal of the American Academy of Child and Adolescent Psychiatry,* 36, 737-744.

Levy, F. (2001). Introduction. In F. Levy and D.A. Hay (Eds.), *Attention, Genes, and ADHD* (pp.1-7). Philadelphia PA, Brunner-Routledge.

Maher, B.S., Marazita, M.L., Ferrell, R.E., & Vanyukov, M.M. (2002). Dopamine system genes and attention deficit hyperactivity disorder: a meta-analysis. *Psychiatric genetics,*12, 207-215.

Mick, E., Biederman, J., Faraone,S.V., Sayer, J. & Kleinman, S. (2002). Case-control study of attention-deficit hyperactivity disorder and maternal smoking, alcohol use, and drug use during pregnancy. *Journal of the American Academy of Child and Adolescent Psychiatry,* 41, 378-385.

Morton, J., & Frith, U. (1995). In D. Cicchetti and D.J. Cohen (Eds.), *Developmental Psychopathology* (pp. 357-390). New York, John Wiley.

Ogdie, M.N., Macphie, I.L., Minassian, S.L., Yang, M., Fisher, S.E., Francks, C., Cantor, R.M., McCracken, J.T., McGough, J.J., Nelson, S.F., Monaco, A.P., & Smalley, S.L. (2003). A Genomewide Scan for Attention-Deficit/Hyperactivity Disorder in an Extended Sample: Suggestive Linkage on 17p11. *American Journal of Human Genetics* 72, 1268-1279.

Palmer, C.G., Bailey, J.N., Ramsey, C., Cantwell, D., Sinsheimer, J.S., Del'Homme, M., McGough, J., Woodward, J.A., Asarnow, R., Asarnow, J., Nelson, S., Smalley, S.L. (1999). No evidence of linkage or linkage disequilibrium between DAT1 and attention deficit hyperactivity disorder in a large sample. *Psychiatric Genetics,* 9, 157-160.

Sattler, J.M. (1992). *Assessment of children: WISC-III and WPPSI-R supplement.* San Diego, SA, England.

Seidman, L., Biederman, J., Faraone, S.V., Weber, W., & Ouellette, C. (1997). Toward defining a neuropsychology of attention deficit-hyperactivity disorder: performance of children and adolescents from a large clinically referred sample. *Journal of Consulting and Clinical Psychology,* 65,150-160.

Seidman, L.J., Biederman, J., Faraone, S.V., Milberger, S., Norman, D., Seiverd, K., Benedict, K., Guite, J., Mick, E., & Kiely, K. (1995) Effects of family history and comorbidity on the neuropsychological performance of children with ADHD: preliminary findings. *Journal of the American Academy of Child and Adolescent Psychiatry,* 34,1015-1024.

Seidman, L.J., Biederman, J., Monuteaux, M.C., Weber, W. (2000). Neuropsychological functioning in nonreferred siblings of children with Attention deficit Hyperactivity Disorder. *Journal of Abnormal Child Psychology,* 109, 252-265.

Shaffer, D., Fisher, P., Lucas, C.P., Dulcan, M.K., & Schwab-Stone, M.E. (2000). NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC- IV): description, differences from previous versions, and reliability of some common diagnoses. *Journal of the American Academy of Child and Adolescent Psychiatry,* 39, 28-38.

Slaats-Willemse, D., Swaab-Barneveld, H., de Sonneville, L, van der Meulen, E., & Buitelaar, J. (2003). Deficient response inhibition as a cognitive endophenotype of ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry,* 42, 1242-1248.

Smalley, S.L., Kustanovich, V., Minassian, S.L., Stone, J.L., Ogdie, M.N., McGough, J.J., McCracken, J.T., Macphie, I.L., Francks, C., Fisher, S.E., Cantor, R.M., Monaco, A.P., & Nelson, S.F. (2002). Genetic linkage of attention-deficit/hyperactivity disorder on chromosome 16p13, in a region implicated in autism. *American Journal of Human Genetics,* 71, 959-963.

Spencer, T., Biederman, J., Wilens, T.E., Faraone, S.V. (1998). Adults with attention-deficit/hyperactivity disorder: a controversial diagnosis. *Journal of Clinical Psychiatry*, 59 Suppl 7, 59-68.

Sprich-Buckminster, S., Biederman, J., Milberger, S., Faraone, S.V., & Lehman, B.K. (1993). Are perinatal complications relevant to the manifestation of ADD? Issues of comorbidity and familiality. *Journal of the American Academy of Child and Adolescent Psychiatry,* 32, 1032-1037.

Stroop, J.R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*,18, 643-662.

Swaab-Barneveld, H., de Sonneville, L., Cohen-Kettenis, P., Gielen, A., Buitelaar, J., & van Engeland, H. (2000). Visual sustained attention in a child psychiatric population. *Journal of the American Academy of Child and Adolescent Psychiatry,* 39, 651-659.

Tannock, R., Schachar, R.J., Carr, R.P., Chajczyk, D., Logan, G.D. (1989). Effects of methylphenidate on inhibitory control in hyperactive children. *Journal of Abnormal Child Psychology*, 17, 473-491.

Thapar, A., Holmes, J., Poulton, K., & Harrington, R. (1999). Genetic basis of attention deficit and hyperactivity. *British Journal of Psychiatry* 174,105-111.

Vandersteene, G., Van Haassen, P.P., De Bruyn, E.E.J., Coetsier, P., Pijl, Y.L., Poortinga, Y.H., Lutje Spelberg, H.C., Spoelders-Claes, R., Stinissen, J. (1986). *WISC-R, Wechsler Intelligence Scale for Children-Revised*, Nederlandstalige uitgave. Lisse: Swets and Zeitlinger.

Verhulst FC, Koot JM, Van der Ende J (1996), *Handleiding voor de CBCL (Child Behavior Checklist) [Manual for the CBCL].* Afdeling Kinder- en Jeugdpsychiatry, Sophia Kinderziekenhuis/ Academisch Ziekenhuis Rotterdam/ Erasmus Universiteit Rotterdam, the Netherlands.

Waldman, I.D., Rowe, D.C., Abramowitz, A., Kozel, S.T., Mohr, J.H., Sherman, S.L., Cleveland, H.H., Sanders, M.L., Gard, J.M., & Stever, C. (1998). Association and linkage of the dopamine transporter gene and attention- deficit hyperactivity disorder in children: heterogeneity owing to diagnostic subtype and severity. *American Journal of Human Genetics*, 63,1767-1776.

Chapter 5

Familial Clustering of Executive Functioning in Affected Sibling Pair Families with ADHD

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Abstract

Objective: To investigate familial clustering of ADHD-related executive functioning (i.e. response inhibition, fine motor functioning and attentional control) in affected sibling pairs. Method: Fifty-two affected sibling pairs ranging in age from 6 to 18 years and diagnosed with ADHD according to DSM-IV performed the Stroop test, Go Nogo task, two different fine motor tracking tasks, and a sustained-, divided-, and focused attention task. Results: Significant sibling correlations were found for response inhibition and attentional control. With respect to fine motor functioning, only motor skills that made high demands on executive functioning showed significant sibling correlations. Conclusions: Response inhibition, higher-order controlled fine motor functioning, and attentional control seem to cluster in ADHD affected siblings, which suggests that executive dysfunctioning in ADHD may reflect an endophenotype to the disorder. The results emphasize the need to assess several aspects of executive functioning extensively in children suspected of ADHD, since overall executive dysfunctioning may have more impact on daily life and academic performance than a specific, isolated deficit in one aspect of executive functioning. Furthermore, treatment programs should be specified according to the severity and nature of the executive function deficit.

Introduction

Attention Deficit Hyperactivity Disorder is a common and impairing childhood-onset psychiatric condition that may be highly influenced by (multi) genetic factors. Twin and adoption studies indicate that additive genetic effects explain up to 80% of the variance of the underlying susceptibility. Many molecular genetic studies have focused on candidate genes that are linked to dopaminergic and noradrenergic pathways, but it still remains unclear which genes cause ADHD (Swanson et al., 2000; Faraone, 2002). The search for susceptibility genes to ADHD may benefit from strategies that reflect the direct gene to symptoms pathways (Smalley et al., 2001). Examination of familial clustering of cognitive task performance may help to refine the ADHD phenotype and/or define clinical subgroups to reduce etiological heterogeneity, which would facilitate molecular genetic research. If specific cognitive deficits and ADHD share common familial or genetic susceptibility, we would expect familial clustering of those deficits. These cognitive deficits then would be a cognitive endophenotype to ADHD, i.e. a heritable quantitative trait that index an individual's liability to develop or manifest a given disease. This trait is thought to be more directly related than diagnostic categories to etiological factors (Morton and Frith, 1995; Almasy and Blangero, 2001; Castellanos and Tannock, 2002).

The search for endophenotypes presents an exciting new direction in research on the etiology of ADHD. Since executive dysfunction is supposed to be the central cognitive impairment in ADHD (Barkley, 2000; Pennington and Ozonoff, 1996), researchers have focused on impairments in this cognitive function domain as candidate endophenotypes to ADHD. Recent findings from family-genetic studies suggest that deficient inhibition, one of the core deficits in the executive function domain, may be a marker for a familial form of ADHD. The children who exhibited poor inhibition were significantly more likely to have a first-degree relative with ADHD than were the children with ADHD who exhibited good response inhibition (Crosbie and Schachar, 2001). Previous studies conducted by our research group also supported the notion that executive dysfunctioning in ADHD may be associated with genetic susceptibility for the disorder. Our results showed that the behaviorally non-affected siblings of children with a familial form of ADHD experienced response inhibition problems and higher-order controlled motor problems similar to those of their ADHD siblings (Slaats-Willemse et al., 2003; Slaats-Willemse et al, submitted). Other executive function deficits associated with ADHD have also been studied as candidate endophenotypes, under which variability in speed of responding. This variable was found to be the best discriminator between hyperactive and control children (Kuntsi et al., 2001), and on top of that twin studies showed that it shared common genetic factors with hyperactive behavior (Kuntsi and Stevenson, 2001). In a recent study, we have found that fluctuation in attentional control during time on task differentiated adequately between ADHD children with a family history of the disorder and those without (Slaats-Willemse et al., submitted). In sum, previous research strongly sug-

gests that different aspects of executive dysfunctioning may constitute potential endophenotypes to ADHD.

In the present study, we aimed to find support for this notion by examining familial clustering of ADHD-related executive functioning. If deficient executive functioning would reflect genetic underpinnings, then ADHD affected siblings were expected to show significant correlation for measures of executive functioning (Smalley et al., 2000; Kendler et al., 1997). We investigated the correlation between task performance of the eldest and second eldest sibling of affected sibling pairs with ADHD. Significant correlation for measures of a specific executive function domain would indicate that ADHD-related deficits in these aspects of executive functioning may be associated with genetic susceptibility for the disorder. This would provide evidence for a cognitive endophenotype to ADHD. On the basis of our review of the literature and our previous work, we chose to assess certain aspects of executive functioning: 1) response inhibition, 2) fine motor functioning, and 3) attentional control.

Method

Participants

The sample consisted of 104 ADHD siblings from 52 ASP (affected sibling pair) families, whose diagnoses were assigned according to DSM-IV criteria. In families with more than two affected siblings, the eldest and second eldest sibling were selected. Aged ranged from 6 to 18 years. ASPs were included in the study if both siblings met the six criteria for the diagnosis of ADHD, or if one sibling met the required criteria and the other sibling met at least five out of nine criteria for inattention and/or five criteria for hyperactive-impulsivity (subthreshold ADHD). Six of the 104 siblings were diagnosed with "subthreshold" ADHD. The 52 ASPs were a subset of a larger population of ADHD-affected sibling pairs (n= 164) from 106 families who participated in a genome scan study (Bakker et al., 2003). The ASPs were recruited from families that were referred to one of the three participating academic child psychiatric outpatient clinics, or from members of a patient organization. Only children that lived with their biological parent(s) of Dutch descent were included. The children were screened by experienced clinicians according to DSM-IV criteria (American Psychiatric Association, 1994). The clinical diagnoses were verified in structured interviews with the parents and the children. The DSM-IV version of the Diagnostic Interview Schedule for Children, DISC-P (Shaffer et al., 2000), was administered to the mother or both parents by trained graduate students in medicine or child psychology. This instrument was also used to screen for the presence of comorbid disorders. The final diagnosis of ADHD, which served as the basis for inclusion of the family in the study, was determined using a best-estimate procedure (Leckman et al., 1982). To this end, the results of the medical history, clinical interview, DISC-P interview, and scores of the parent-t and teacher-rated Conners Questionnaire (Goyette et al., 1978) and Child Behaviour

Checklist and Teacher Report Form (Achenbach and Ruffle, 2000) were summarized in a patient report. This report resulted in a final diagnosis verified by a senior child psychiatrist. Fifty six percent of the eldest siblings and sixty seven of the second eldest siblings of the ASPs were on medication. These medications are known to affect cognitive functioning (Berman et al., 1999; de Sonneville et al., 1994; Tannock et al., 1989), and therefore medication was discontinued two days (stimulants) or one week (non-stimulants) before cognitive assessment. Full-Scale IQ was estimated from the Similarities, Vocabulary, Block Design, and Object Assembly subtests of the WISC-R (Sattler, 1992; Vandersteene et al., 1986). The clinical characteristics of the siblings are shown in table 1. All parents signed a written consent form before participation in the study. The Medical Ethical Review Committee of the University Medical Center Utrecht approved the study.

Instruments and Procedure

Response inhibition, fine motor functioning, and attentional control were measured by task variables of the Stroop Color Word Interference Test (Stroop, 1935) and five tasks of the Amsterdam Neuropsychological Tasks Program (de Sonneville, 1999; de Sonneville et al., 2002).

1) Response inhibition was operationalized by the *Stroop interference score*, *percentage of misses* and *number of impulsive responses on the Sustained Attention task*, and *percentage of false alarms on the Go Nogo task*. In the Sustained Attention task, a visual continuous performance task, 50 series x 12 signals were presented consisting of three, four, or five dots presented in random order. With signals consisting of four dots (target signal),

Table 1. Characteristics

Characteristic	ADHD affected siblings pairs	
	Eldest sibling (n= 52)	Second eldest sibling (n= 52)
Mean age, in years (SD)	13.6 (2.3)	10.8 (2.1)
Mean estimated IQ (SD)	102.3 (17.0)	95.2 (15.4)
Male: *n* (%)	46 (89)	42 (81)
ADHD diagnosis: *n* (%)		
Full	49 (94)	49 (94)
Subthreshold	3 (6)	3 (6)
ADHD subtype: *n* (%)		
Combined	45 (87)	47 (90)
Inattentive	6 (12)	4 (8)
Hyperactive/impulsive	1 (2)	1 (2)
Comorbidity: *n* (%)		
ODD	18 (35)	17 (33)
CD	2 (4)	2 (4)

Note: ADHD = attention deficit hyperactivity disorder; subthreshold ADHD = five out of nine criteria for inattention and/or five criteria for hyperactive-impulsivity; ODD = oppositional defiant disorder, CD = conduct disorder.

subjects had to press the "yes" key; with signals consisting of three and five dots (non-targets), they had to press the "no" key. The overall target rate was 33%, which implies that the subject had to press the "no" key twice as often as the "yes" key. This difference in response probability is demonstrated to invoke a response bias (de Sonneville et al., 1994; Swaab-Barneveld et al., 2000). Therefore, the percentage of misses is considered to reflect a failure to inhibit undesired responses. Responses to signals had to be generated between 200 and 8000 ms following stimulus onset. Responses made before 200 ms were not expected to be the result of a cognitive evaluation process and were considered as premature hits on the mouse button, i.e. impulsive responses. In the Go NoGo task, 24 Go signals were presented, randomly mixed with 24 NoGo signals. Subjects had to press a key if a Go signal appeared on the screen and had to withhold a response if they saw a NoGo signal. A failure to withhold results in a false alarm. Extensive descriptions of the Go NoGo and the Sustained Attention task can be found elsewhere (Slaats-Willemse et al., 2003).

2) Fine motor functioning was operationalized by the Tracking task and Pursuit task. The Tracking Task is a motor fluency task that requires subjects to trace a mouse cursor in-between an outer and inner circle presented on a computer display. The ANT program computes the mean distance between the cursor trajectory and the midline per circle segment (60 radially equal segments in total) returning 60 distance values. Task variables were *mean and standard deviation of the 60 values, reflecting accuracy and stability of the visual motor control respectively*. The Pursuit task is a complex motor flexibility task that requires subjects to follow a target. They have to continuously adjust the movements of the mouse in order to position the cursor as closely as possible to a moving asterisk, which requires a high level of flexibility. The ANT program computes the mean distance between the cursor and asterisk per second time-on-task (60 s in total). Task variables were *mean and standard deviation of the 60 distance values, reflecting accuracy and stability of visual motor control respectively*. The crucial difference between these two tasks is considered to be level of complexity. The Pursuit task requires higher levels of flexibility and permanent controlled processing compared with the Tracking task, since the movements of the target in the Pursuit task are unpredictable while movement in the tracking task can be planned in advance of its execution. Extensive descriptions of the Pursuit and the Tracking task can be found elsewhere (Kalff et al., 2003).

3) Attentional control was taken to be reflected by the *variability (standard deviation) in response time of correct responses to target signals in the Divided- and Focused Attention tasks*, and the *fluctuation in tempo with time-on-task in the Sustained Attention task*. In the latter task, the completion time per series (50 series in total) is computed, and the standard deviation of the completion times of the 50 series represents the fluctuation in tempo. The Divided Attention task employs a display load of four letters and consists of three parts in which target set size (memory load) is increased from one to three target letters. Signals that contain the complete target set require a 'yes'-response. All other signals, also those containing an incomplete target set, require a 'no'-response. The

Focused Attention task employs a similar four-letter display load as in the Divided Attention task, but now only two diagonal locations are relevant (known in advance to the subjects) and subjects should attend to those positions only. A target signal is defined as a signal that contains a target letter on the relevant diagonal. Upon its presentation the 'yes'-key should be pressed. Irrelevant target signals, i.e. with a target letter on the irrelevant diagonal, and non-target signals (target letter absent) require the subject to press the 'no'-key. Extensive descriptions of the Divided Attention task and the Focused Attention task can be found elsewhere (Huijbregts et al., 2002).

The examination was carried out by experienced child and adolescent psychologists and trained undergraduate psychologists. To prevent distraction from external sources, the assessment was done in quiet test rooms. All children were tested in the morning hours. The ASP´s were tested at the same time. The children received verbal instructions and were allowed to practice to make sure that they understood the task instructions well.

Statistical analyses

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 9.0). Pearson´s partial correlation coefficients were computed to test sibling similarity for cognitive performance on the executive function measures. The cognitive measures were analyzed per domain of executive functioning, as defined in the methods section. As the two siblings differed in age, and age correlated significant with the cognitive measures, the difference in age (i.e. age of second eldest subtracted from the age of eldest sibling) was entered as a control variable. Considering the correlation between the measures of a domain, the Bonferroni correction for correlated multiple tests (Uitenbroek, 1997) was used to adjust the alpha level of the tests per domain of executive functioning downwards to ensure that the overall risk remained 0.05 (two-tailed). The correction resulted in alpha = 0.023 (Response inhibition), alpha = 0.030 (Fine motor functioning), and alpha = 0.032 (Attentional control).

Results

1) Response inhibition

The data for five ASP´s were missing because five young subjects had reading problems on the Stroop test. As shown in Table 2, the partial correlation coefficient ranged from 0.29 to 0.42, which were all significant, except for the Go NoGo % false alarms that did not meet the Bonferroni adjusted alpha criterion.

2) Fine motor functioning

The data for four ASP´s were missing due to technical problems during assessment. Only motor functioning measures that required high levels of executive functioning (Pursuit) showed significant siblings correlations. There were significant correlations

for the task variables of the Pursuit task (0.43 and 0.34 respectively), but not for those on the Tracking task (Table 2).

3) Attentional control

Since the three youngest subjects did not recognize the letters in the Divided- and Focused Attention task, the data for three ASP´s were missing. Fluctuation in tempo on the Sustained Attention task and variability in response time on the Divided Attention task showed significant sibling correlations (0.44 and 0.35 respectively), whereas the variability in response time on the Focused Attention revealed a nonsignificant sibling correlation (Table 2).

Discussion

In this study, we investigated familial clustering of executive functioning in ADHD affected sibling pairs. Sibling correlations were computed for response inhibition, fine motor functioning, and attentional control to examine whether cognitive correlates of ADHD may reflect genetic underpinnings. This would provide evidence for a cognitive endophenotype to ADHD. Consistent with our expectations, the siblings

Table 2. Sibling similarity for aspects of executive functioning in ADHD

	Siblings							
	Eldest		Second Eldest					
							95% Confidence Int.	
Cognitive measure	*Mean*	(SD)	Mean	(SD)	Partial corr.	*p* Value	Lower	Upper
Response inhibition (n = 47), α = 0.023								
Sust. att. % misses	10.9	(6.9)	15.8	(10.8)	0.42	**0.004**	0.15	0.63
Sust. att. no. impulsive resp.	1.2	(2.1)	6.0	(11.9)	0.39	**0.009**	0.12	0.61
Go Nogo % False Alarms	7.2	(11.0)	8.0	(9.6)	0.29	0.048	0.003	0.53
Stroop Interference	62.0	(35.0)	79.5	(37.9)	0.36	**0.015**	0.08	0.59
Fine motor functioning (n = 48), α = 0.030								
Tracking Accuracy	3.3	(2.4)	4.0	(2.0)	0.09	0.554	-0.20	0.37
Tracking Stability	4.5	(3.0)	5.6	(3.2)	0.19	0.197	-0.10	0.45
Pursuit Accuracy	5.8	(2.7)	9.0	(6.5)	0.43	**0.002**	0.17	0.64
Pursuit Stability	5.5	(3.7)	8.9	(6.3)	0.34	**0.019**	0.06	0.57
Attentional control (n = 49), α = 0.032								
Sust. att. tempo fluc.	2.1	(1.2)	3.4	(1.7)	0.44	**0.002**	0.18	0.64
Div. att. resp. time var.	419.3	(226.7)	661.3	(340.8)	0.35	**0.014**	0.08	0.55
Foc. att. resp. time var.	325.7	(237.9)	477.9	(281.4)	0.03	0.845	-0.25	0.31

Note: Sust. att. tempo fluc. = fluctuation in tempo in Sustained Attention task; Div. att. resp. time var. = variability in response time in Divided Attention task; Foc. att. resp. time var. = variability in response time in Focused Attention task. n = number of subjects per domain; α = Bonferroni corrected alpha. Bold face p values are significant.

proved to be highly similar with respect to response inhibition, higher-order controlled fine motor functioning and attentional control, which indicates that ADHD-related deficits in these aspects of executive functioning may be associated with genetic susceptibility for the disorder.

The findings in the present study are in line with studies on genetic influences on ADHD-related executive functioning deficits, like a twin study showing that variability in response time (attentional control) is highly heritable (Kuntsi and Stevenson, 2001), and family studies providing evidence for response inhibition and other aspects of executive functioning as biological markers for ADHD (Crosbie & Schachar, 2001; Seidman et al., 1995; Seidman et al., 1997; Slaats-Willemse et al., 2003; Slaats-Willemse et al., submitted).

With respect to fine motor functioning, the results were intriguing. The sibling correlations for flexibility in movement (Pursuit task) were significant, but those for fluency of movement (Tracking task) were nonsignificant. In the Tracking task, the trajectory can be planned in advance of its execution, whereas in the Pursuit task concurrent planning and execution of movements are required. Therefore, higher levels of flexibility and more controlled processing are needed to perform well on the Pursuit task. Thus, the discrepancy between the results on these fine motor tasks may indicate differences in the required level of executive control. Neuroimaging studies support this idea: greater involvement of the prefrontal cortex, the region that is considered to control executive functioning (Voeller, 1990) is reported during new motor learning than during automatic motor task performance (Jueptner & Weiller, 1998; Sakai et al., 1998; Seitz et al., 2000; Middleton and Strick, 2000). The different findings for motor fluency and motor flexibility suggest that only motor skills that make high demands on higher-order cognitive processing (i.e. executive functioning) show familial clustering among ASP´s. This would be in line with our hypothesis that executive function deficits in ADHD are influenced by genetic factors. The present results are consistent with those of a previous family study on ADHD, in which we found that behaviorally non-affected siblings of ADHD children experienced motor flexibility problems similar to their affected siblings, but not motor fluency problems (Slaats-Willemse et al., submitted).

In conclusion, deficits in different aspects of executive dysfunctioning, i.e. response inhibition, higher-order controlled fine motor functioning, and attentional control have been proven to be interesting candidate endophenotypes to ADHD.

Now we have stated this, it is important to unravel the nature of these executive function deficits. Kuntsi et al. (2001) suggested, in accordance with the state-regulation theory (Van der Meere, 1996) that hyperactive children have a nonoptimal activation/effort state, which means that the utilization of the cognitive capacity depends on state factors such as incentives, event rate and presence/absence of the experimenter (p. 133). This theory argues that the basic deficit underlying the core cognitive deficits in ADHD is a suboptimal psychological mechanism that controls the effort and activation state. One of the studies that supported this theory showed a re-

duction in the variability in responding in hyperactives after continuous positive verbal feedback (Douglas and Parry, 1983). This suggests that the ADHD-associated cognitive problems would reflect a state-regulation problem that can be influenced, rather than a structural cognitive deficit. Based on this, a state-regulation problem would be a link between genetic effects and ADHD (Kuntsi and Stevenson, 2001). Future research (reinforcement studies) should clarify this "state or trait issue", i.e. whether ADHD is associated with a psychological state problem or a structural cognitive deficit, or both.

Overall, response inhibition, higher-order controlled fine motor functioning, and attentional control seem to cluster in ADHD affected siblings. Our findings indicate that future studies on cognitive endophenotyping in ADHD should examine all these aspects of executive functioning, and should not be restricted to response inhibition. Furthermore, the exact nature of these problems should be investigated extensively.

Limitations

The results of this study must be interpreted in light of several limitations. First, sample sizes were small, indicating a strong need to replicate the findings in larger ASP samples. Second, executive functioning was not examined in the parents of the ASP's. In line with our hypothesis that ADHD-associated executive function deficits would have genetic underpinnings, we would expect to find similar problems in at least one of the parents. Further research on executive functioning in the parents of ADHD affected sibling-pair families is warranted to learn about the patterns of inheritance. Since we did not examine all known aspects of executive functioning, it is recommended for future research to study other aspects of executive functioning, working memory for example, in genetic perspective. The present study did not focus on the effects of medication on the different aspects of executive dysfunctioning in the ASP's. We recommend investigating a potential different effect of medication (e.g. methylphenidate) on response inhibition, higher-order controlled fine motor functioning, and attentional control in ADHD affected siblings.

Clinical implications

The conclusion that the central impairment in children with ADHD is not restricted to a deficient response inhibition but concerns different aspects of executive functioning underscores the importance of using a comprehensive test battery in the cognitive assessment of children suspected of ADHD. Based on the present results it is recommended to administer different tasks measuring higher-order controlled fine motor functioning, response inhibition, and attentional control, because an overall deficient executive functioning may have more impact on daily life and academic performance than a specific, isolated deficit in one aspect of executive functioning. Therapeutic interventions should be specified according to the severity and nature of the executive dysfunctioning. Furthermore, if ADHD-associated cognitive problems would reflect a state-regulation problem as suggested above, it seems fruitful to im-

prove the situational and motivational factors influencing the child, by positive reinforcement for example.

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References

Achenbach TM, Ruffle TM (2000), The Child Behavior Checklist and related forms for assessing behavioral/emotional problems and competencies. *Pediatr Rev* 21:265-271

Achenbach TM (1986), *Manual for the Teacher Report Form and the Child Behavior Profile. Burlington*. University of Vermont Department of Psychiatry

Achenbach TM (1991), *Integrative Guide for the 1991 CBCL, YSR, and TRF Profiles. Burlington*. University of Vermont Department of Psychiatry

Achenbach TM, Verhulst FC, Baron GD, Althaus M (1987), A comparison of syndromes derived from the Child Behavior Checklist for American and Dutch boys aged 6-11 and 12-16. *J Child Psychol Psychiatry* 28: 437-453

Almasy L, Blangero J (2001), Endophenotypes as quantitative risk factors for psychiatric disease: rationale and study design. *Am J Med Genet* 105: 42-44

American Psychiatric Association (1994), *Diagnostic and Statistical Manual for Mental Disorders*. (4th edition).Washington, DC: American Psychiatric Press

Bakker SC, Meulen EM, Buitelaar JK, Sandkuijl LA, Pauls DL, Monsuur AJ, Slot RR, Minderaa RB, Gunning WB, Pearson PL, Sinke RJ (2003), A whole-genome scan in 164 dutch sib pairs with attention- deficit/hyperactivity disorder: suggestive evidence for linkage on chromosomes 7p and 15q. *Am J Hum Genet* 72:1251-1260

Barkley RA (2000), Genetics of childhood disorders: XVII. ADHD, part 1: Executive functions and ADHD. *J Am Ac Child Adolesc Psychiat* 39:1064-1068

Berman T, Douglas VI, Barr RG (1999), Effects of methylphenidate on complex cognitive processing in attention- deficit hyperactivity disorder. *J Abnorm Psychol* 108:90-105

Castellanos FX, Tannock R (2002), Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. *Nat Rev Neurosci* 3: 617-628

Crosbie J, Schachar R (2001), Deficient inhibition as a marker for familial ADHD. *Am J Psychiatry* 158:1884-1890

de Sonneville LMJ (1999), Amsterdam Neuropsychological tasks: a computer-aided assessment program. In: *Computers in Psychology, Vol. 6: Cognitive ergonomics, clinical assessment and computer-assisted learning*, B.P.L.M. Den Brinker, P.J. Beek, A.N. Brand, S.J. Maarse, and L.J.M. Mulder (Eds.), pp. 187-203. Lisse: Swets and Zeitlinger

de Sonneville LM, Boringa JB, Reuling IE, Lazeron RH, Ader HJ, Polman CH (2002), Information processing characteristics in subtypes of multiple sclerosis. *Neuropsychologia* 40:1751-1765

de Sonneville LM, Njiokiktjien C, Bos H (1994), Methylphenidate and information processing. Part 1: Differentiation between responders and nonresponders; Part 2: Efficacy in responders. *J Clin Exp Neuropsychol* 16:877-897

Douglas VI, & Parry PA (1983), Effects of reward on delayed reaction time task performance of hyperactive children. *J Abnorm Child Psychol* 11:313-326

Faraone SV (2002), Report from the third international meeting of the Attention-Deficit Hyperactivity Disorder Molecular Genetics Network. *Am J Med Genet* 114: 272-276

Goyette CH, Conners CK, Ulrich RF (1978), Normative data on revised Conners Parent and Teacher Rating Scales. *J Abnorm Child Psychol* 6:221-236

Huijbregts SCJ, de Sonneville LMJ, van Spronsen FJ, Licht R, Sergeant JA. The Neuropsychological Profile of Early-and Continuously Treated Phenylketonuria: Selective Attention, Vigilance, and 'Maintenance' versus 'Manipulation' - functions of Working Memory. *Neuroscience & Biobehavioral Reviews, 26*: 697-712

Jueptner M, & Weiller C (1998), A review of differences between basal ganglia and cerebellar control of movements as revealed by functional imaging studies. *Brain,121,* 1437-1449

Kalff AC, de Sonneville LMJ, Hurks P, Hendriksen JG, Kroes M, Feron FJ, Steyaert J, van Zeben TM, Vles JS, Jolles J (2003). Low- and high-level controlled processing in executive motor control tasks in 5/6-year-old children at risk of ADHD. *J Child Psychol Psychiatry* 44: 1049-1057

Kendler KS, Kardowski-Shuman L, O´Neill FA, Straub RE, MacLean CJ, Walsh D (1997), Resemblance of psychotic symptoms and syndromes in affected sibling pairs from the Irish study of high-density schizophrenia families: evidence of possible etiologic heterogeneity. *Am J Psychiatry* 154: 191-198

Kuntsi J, Oosterlaan J, Stevenson J (2001), Psychological mechanisms in hyperactivity: I. Response inhibition deficit, working memory impairment, delay aversion, or something else? *J Child Psychol Psychiatry* 42:199-210

Kuntsi J, Stevenson J (2001), Psychological mechanisms in hyperactivity: II. The role of genetic factors. *J Child Psychol Psychiatry* 42:211-219

Leckman JF, Sholomskas D, Thompson WD, Belanger A, Weissman MM (1982), Best estimate of lifetime psychiatric diagnosis: a methodological study. *Arch Gen Psychiatry* 39: 879-883

Middleton FA, & Strick PL (2000), Basal ganglia and cereballar loops: motor and cognitive circuits. *Brain Res Rev* 31: 236-250

Morton J, Frith U (1995), In D. Cicchetti and D.J. Cohen (Eds.), *Developmental Psychopathology* (pp. 357-390). New York, John Wiley

Pennington BF, Ozonoff S (1996), Executive functions and developmental psychopathology. *J Child Psychol Psychiatry* 37:51-87

Sakai K, Hikosaka O, Miyauchi S, Takino R, Sasaki Y, & Pütz B (1998), Transition of brain activation from frontal to parietal areas in visuo motor sequence learning. *J Neurosci*,18:1827-1840

Sattler JM (1992), *Assessment of children: WISC-III and WPPSI-R supplement.* San Diego, SA, England

Seidman LJ, Biederman J, Faraone SV, Milberger S, Norman D, Seiverd K, Benedict K, Guite J, Mick E, Kiely K (1995), Effects of family history and comorbidity on the neuropsychological performance of children with ADHD: preliminary findings. *J Am Acad Child Adolesc Psychiatry* 34:1015-1024

Seidman L, Biederman J, Faraone SV, Weber W, Ouellette C (1997), Toward defining a neuropsychology of attention deficit-hyperactivity disorder: performance of children and adolescents from a large clinically referred sample. *J Consult Clin Psychol* 65:150-160

Seitz RJ, Stephan, KM, & Binkofski F (2000), Control of action as mediated by the *human frontal lobe. Exp Brain Res 133: 71-80*

Shaffer D, Fisher P, Lucas CP, Dulcan MK, Schwab-Stone ME (2000), NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC- IV): description, differences from previous versions, and reliability of some common diagnoses. *J Am Acad Child Adolesc Psychiatry* 39:28-38

Slaats-Willemse D, Swaab-Barneveld S, de Sonneville L, van der Meulen E, Buitelaar J (2003), Deficient repsonse inhibition as a cognitive endophenotype of ADHD. *J Am Acad Child Adolesc Psychiatry* 42: 1242-1248

Smalley SL (1997), Genetic influences in childhood-onset psychiatric disorders: autism and attention-deficit/hyperactivity disorder. *Am J Hum Genet* 60:1276-1282

Smalley SL, McCracken J, McGough J (2001), Refining the ADHD phenotype using affected sibling pair families. *Am J Med Genet* 105:31-33

Smalley SL, McGough J, Del´Homme M, NewDelman J, Gordon E, Kim T, Liu A, McCracken J T (2000), Familial clustering of symptoms and disruptive behaviors in multiplex families with attention deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 39:1135-1143

Stroop JR (1935), Studies of interference in serial verbal reactions. *Journal of Experimental Psychology* 18: 643-662

Swaab-Barneveld H, de Sonneville L, Cohen-Kettenis P, Gielen A, Buitelaar J, Van Engeland H (2000), Visual sustained attention in a child psychiatric population. *J Am Acad Child Adolesc Psychiatry* 39:651-659

Swanson JM, Flodman P, Kennedy J, Spence MA, Moyzis R, Schuck S, Murias M, Moriarity J, Barr C, Smith M, Posner M (2000), Dopamine genes and ADHD. *Neurosci Biobehav Rev* 24:21-25

Tannock R, Schachar RJ, Carr RP, Chajczyk D, Logan GD (1989), Effects of methylphenidate on inhibitory control in hyperactive children. *J Abnorm Child Psychol* 17:473-491

Thapar A, Holmes J, Poulton K, Harrington R (1999), Genetic basis of attention deficit and hyperactivity. *Br J Psychiatry* 174:105-111

Uitenbroek DG (1997), *SISA Bonferroni*. Southampton: D.G. Uitenbroek. Retrieved July 15, 2003, from the World Wide Web: http://home.clara.net/sisa/bonfer.htm

Van der Meere J (1996), The role of attention. In S. Samdberg (Ed.), Hyperactivity disorders of childhood (pp.111-148). Cambridge: Cambridge University Press

Vandersteene G, Van Haassen PP, De Bruyn EEJ, Coetsier P, Pijl YL, Poortinga YH, Lutje Spelberg HC, Spoelders-Claes R, Stinissen J (1986), *WISC-R, Wechsler Intelligence Scale for Children-Revised*, Nederlandstalige uitgave. Lisse: Swets and Zeitlinger

Voeller K (1990), The neurological basis of attention deficit hyperactivity disorder. *Int Ped* 5: 171-176

Chapter 6

A Family-genetic Study on Attentional Control and Mental Flexibility in ADHD:

Evidence for Cognitive Endophenotypes of ADHD?

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Abstract

The present study examined whether attentional control and mental flexibility, i.e. aspects of executive functioning can serve as cognitive endophenotypes of ADHD. We hypothesized that siblings of ADHD probands, while not behaviorally expressing the disorder, have ADHD-associated deficits in these executive functions. If so, we investigated whether the performances of the ADHD probands, non-affected siblings and controls could be arranged on a continuum, which would be in line with the notion that ADHD may be a dimensional trait rather than a pathological category. Participants were 25 ADHD probands with a family history of ADHD, their non-affected siblings (n=25), and 48 normal controls matched for age and IQ. All participants were between 6 and 17 years of age. Attentional control was reflected by the fluctuation in tempo on a sustained attention task, and mental flexibility by variables of the Wisconsin Card Sorting task and Shifting Attentional Set task. The performance of the non-affected siblings did not differ from that of the ADHD probands on the measure of attentional control, and some measures of mental flexibility. The linear changes of these measures across the groups reflected an intermediate position of the non-affected siblings between the ADHD probands and controls. Thus, attentional control and mental flexibility problems may be indicators of the familial predisposition to ADHD. The results indicate that what is inherited by individuals at enhanced risk of ADHD because of genetic liability is not the disorder itself but a state of vulnerability manifested by executive dysfunctioning.

Introduction

Attention Deficit Hyperactivity Disorder is a childhood-onset neuropsychiatric disorder characterized by inattention, hyperactivity and impulsivity. It is among the most commonly diagnosed and extensively studied psychiatric syndromes and affects 3 to 5% of all school-aged children (Tannock, 1998). Twin-, adoption-, and molecular genetic studies have revealed that genes may play an important role in the etiology of ADHD: association between polymorphisms in DAT1, DRD4, and DRD5 genes are found, although these findings are not replicated in multiple studies (Faraone et al., 2001; Maher et al., 2002).

The neuropsychological impairments associated with this disorder involve deficits in executive functioning (Pennington and Ozonoff, 1996). For a review, see Sergeant et al. (2002). The most convincing evidence is for a specific executive dysfunction, namely poor response inhibition (Barkley, 1997). Several studies using the stop task, Go Nogo task or Stroop test, reported an inhibitory dysfunction in children with ADHD (Nigg, 1999; Grodzinsky and Diamond, 1992; Seidman et al., 1997a; Seidman et al., 1995; Seidman et al., 1997b). See for a review Oosterlaan et al. (1998). Deficient response inhibition has even been suggested to be a marker for a familial form of ADHD, since it was found that ADHD children who exhibited poor inhibition were significantly more likely to have a first-degree relative with ADHD than were the children with ADHD who exhibited good behavioral inhibition (Crosbie and Schachar, 2001). In addition, Seidman and colleagues have shown that children with ADHD who had a family history of ADHD performed significantly worse on measures of response inhibition than ADHD children without such a family history (Seidman et al., 1995). Moreover, in a previous study we have found that behaviorally non-affected siblings of ADHD probands have ADHD-associated deficits in response inhibition, with their performance on the inhibition measures not differing significantly from that of their siblings with ADHD (Slaats-Willemse et al., 2003). Taken together, these results suggest that deficient response inhibition may be a core aspect of an executive function deficit in ADHD, and this cognitive dysfunction is likely to be influenced by genetic factors.

However, recent family-genetic studies on ADHD-related executive function deficits showed that several other aspects of executive dysfunctioning, like higher-order controlled motor functioning, attentional control, and mental flexibility might also be good candidate cognitive endophenotypes to ADHD. The results of our previous study on complex fine motor performance revealed that non-affected siblings of ADHD probands experienced complex visual motor problems, but only in movements that require higher-order cognitive processing, i.e. high levels of executive functioning (Slaats-Willemse et al., submitted). In a study on familial clustering of cognitive functioning in affected sibling pair families with ADHD, significant sibling correlations were found for measures of response inhibition, but also for higher-order controlled motor functioning and attentional control (Slaats-Willemse et al., submit-

ted). Moreover, we have found that attentional control, measured by fluctuation in response time in a CPT, differentiated adequately between ADHD children with a family history of ADHD and those without such a family history (Slaats-Willemse et al., submitted). These findings are in line with those of Kuntsi and others, reporting that variability in speed of responding differentiated best between hyperactives and controls (Kuntsi et al., 2001). On top of that, a twin study showed that this variable shared common genetic effects with hyperactivity (Kuntsi and Stevenson, 2001). The fourth aspect of executive functioning named above, mental flexibility, was found to be significantly affected by a familial status of ADHD (Seidman et al., 1995).

Overall, findings from previous studies suggest that not only response inhibition, but also higher-order controlled motor functioning, attentional control, and mental flexibility are likely to be important candidate endophenotypes to ADHD. So far, attentional control has not been investigated in a family-genetic study design with non-affected siblings of ADHD probands. A prior study on mental flexibility in high risk siblings without ADHD did not show significant mental flexibility problems as measured by the Wisconsin Card Sorting test (Seidman et al., 2000).

The present study aimed to examine the performance on measures of attentional control and mental flexibility in behaviorally non-affected siblings of ADHD probands, and to compare it to the performance of their ADHD siblings and to that of normal controls. Our hypothesis was that siblings of ADHD probands, while not behaviorally expressing the disorder, have ADHD-associated deficits in attentional control and mental flexibility. If so, we hypothesized that the performances of the ADHD probands, non-affected siblings and the controls could be arranged on a continuum, which would be in line with the notion that ADHD should be viewed as a dimensional trait rather than a pathological category (Barkley, 1998, p.73; Levy et al., 1997; Levy and Hay, 2001).

Methods

Subjects

Ninety-eight children participated in the study. The first group consisted of 25 carefully phenotyped ADHD probands with a family history of ADHD, i.e. those with at least one sibling or parent with a diagnosis of ADHD as did (Seidman et al., 1995). The parents were diagnosed according to DSM-IV: at least 5 of 9 criteria of inattention and/or at least 5 of 9 criteria of hyperactivity /impulsivity (Murphy and Barkley, 1996; Kooij et al., submitted). The diagnostic procedure for the siblings is described below. The second group consisted of non-affected siblings of the ADHD probands (n = 25). Forty-eight normal controls, matched with the non-affected sibling group for age, IQ, and sex formed the third group. In all three groups age ranged from 6 to 17 years. The 25 ADHD probands were a subset of a larger population of ADHD-affected sibling pairs (n = 130) from 104 families who participated in a genome scan study (Bakker et al., 2003). In this study, we selected the affected sibling pairs that had a

non-affected sibling (n = 25). Of these affected sibling pairs, the sibling that matched best the non-affected sibling in terms of age, sex and IQ was termed the proband.

The ADHD probands and their siblings were recruited from families that were referred to one of the three participating academic child psychiatric outpatient clinics, or from members of the Dutch Parents' Association. Only children that lived with their biological parent(s) of Dutch descent were included. The children were screened by experienced clinicians according to DSM-IV criteria (American Psychiatric Association (APA), 1994). The clinical diagnoses of the affected sibling pairs were verified in structured interviews with the parents and the children. The DSM-IV version of the Diagnostic Interview Schedule for Children, DISC-P (Shaffer et al., 2000), was administered to the mother or both parents by trained graduate students in medicine or child psychology. The final diagnosis of ADHD, which served as the basis for inclusion of the family in the study, was determined using a "best-estimate procedure". To this end, the results of the medical history, clinical interview, DISC-P interview, and scores of the parent-t and teacher-rated Conners Questionnaire (Goyette et al., 1978) and Child Behaviour Checklist (CBCL, Achenbach et al., 1987; Verhulst et al., 1996), and Teacher Report Form (TRF, Achenbach, 1986; Achenbach, 1991) were summarized in a patient report. This report resulted in a final diagnosis verified by a senior child psychiatrist. Comorbidity was distributed as follows: 48% of the ADHD probands had anxiety disorders, 24% oppositional defiant disorder, 16% mood disorders, and 16% tic disorders. The non-affected siblings were non-referred siblings who did not meet the criteria for ADHD or subthreshold ADHD (5 out of 9 criteria for inattention and/or 5 out of 9 for hyperactivity- impulsivity), according to the DISC-P. Their T-scores on the CBCL and TRF Attention Problems, Delinquent Behavior, and Aggressive Behavior subscales were not in the clinical or subclinical range (above the 95th percentile). The non-affected siblings differed significantly from the ADHD probands on number of ADHD symptoms according to DISC-P, and on CBCL and TRF scores of the subscales named above (except for TRF delinquency: $p = .05$, Table 1). Seventeen (68 %) of the 25 ADHD probands were on medication (one child used risperidone; the others were on methylphenidate). These medications are known to affect cognitive function, including reaction time measures (Berman et al., 1999; de Sonneville et al., 1994; Tannock et al., 1989), and therefore medication was stopped at least two days (stimulants) or one week (risperidone) before neuropsychological assessment.

The control group consisted of 48 children. Twenty-three controls (11 twins from 11 pairs, and 12 additional siblings) were tested at the Free University of Amsterdam, where they participated in a longitudinal research project aimed at disentangling the genetics of externalizing disorders in children. The other 25 control children were recruited from regular schools and tested in Utrecht. The controls had Total Problem scores below 67 on the CBCL, indicating that they were not likely to suffer from behavioral or emotional problems within the subclinical or clinical range. Full-Scale IQ was estimated from the Similarities, Vocabulary, Block Design, and Object Assembly

Table 1. Demographics

	ADHD N= 25		Non-affected N= 25		Control N= 48		Significance (*p*)
Dependent measure	M or %	SD	M or %	SD	M or %	SD	
Age (months)	147.5	27.6	145.2	34.6	145.0	30.4	Ns
Estimated IQ	101.2	13.7	100.4	11.8	101.7	14.2	Ns
% Male	92		28		29		<.001[1 2]
DISC inattention	6.7	1.9	0.7	1.0	–		<.001[2]
DISC hyp/imp	7.5	1.7	0.9	1.2	–		<.001[2]
CBCL attention	69.2	9.4	54.1	5.3	52.0	3.5	<.001[1 2]
CBCL delinquency	58.2	7.2	52.5	5.0	51.5	3.1	<.001[1 2]
CBCL aggression	67.4	10.2	52.4	4.3	50.6	1.7	<.001[1 2]
TRF attention	57.6	5.4	52.7	4.5			<.05[2]
TRF delinquency	54.0	5.6	51.4	2.8			=.05[2]
TRF aggression	60.6	10.9	54.2	5.1			<.05[2]
Anxiety disorders (%)	48		12		–		
ODD (%)	24		0		–		
Mood disorders (%)	16		0		–		
Tic disorders (%)	16		0		–		

Note: ns = non significant. DISC inattention = number of symptoms of inattention scored on DISC-IV, DISC hyp/imp = number of symptoms of hyperactivity -impulsivity scored on DISC-IV. CBCL/ TRF attention = T-score on Child Behaviour Checklist/ Teacher Report Form, Attention problems subscale, CBCL/ TRF delinquency = T-score on CBCL Delinquent behavior subscale, CBCL/ TRF aggression = T-score on CBCL Aggressive behavior subscale. Anxiety disorders, ODD, Mood disorders, Tic disorders = percentage of (comorbid) disorders, based on DISC-IV.
Superscript letters indicate different significant pairwise differences: [1] = ADHD probands vs. normal controls, and [2] = ADHD probands vs. non-affected siblings.

subtests of the WISC-R (Sattler, 1992; Vandersteene et al., 1986). Demographic and descriptive data for the subjects are presented in Table 1. All parents signed a written consent form before participation in the study. The Medical Ethical Review Committee of the University Medical Center Utrecht approved the study.

Measures

1) Attentional control was operationalized by the fluctuation in tempo with time-on-task in the Sustained Attention task of the Amsterdam Neuropsychological Tasks (ANT, de Sonneville, 1999). In the Sustained Attention task, a visual continuous performance task, 50 series x 12 signals were presented consisting of three, four, or five dots presented in random order. With signals consisting of four dots (target signal), subjects had to press the "yes" key; with signals consisting of three and five dots (non-targets), they had to press the "no" key. The completion time per series is computed, and the standard deviation of the completion times of the 50 series represents the fluctuation in tempo. Extensive descriptions of the Sustained Attention task can be found elsewhere (Slaats-Willemse et al., 2003).

2) Mental flexibility was reflected by variables of the computerized Wisconsin Card Sorting Test (WCST, Grant and Berg, 1948), and the Shifting Attentional Set task from the ANT. The most widely used scores of the WCST were analyzed: number of categories completed (number of times 10 correct responses in a row are made, reflecting overall success), total number of errors (wrong matches, documenting problems in forming concepts), and number of perseverative errors (consecutive matches according to the same wrong criterion, reflecting tendency towards perseveration) (Laurent et al., 2001; Lezak, 1983).

In the Shifting Attentional Set task, a horizontal bar consisting of ten squares was presented permanently in the centre of a standard monitor. From trial to trial a colored square moved across the bar in a random direction (either to the right or to the left). The task consisted of three parts. Subjects were instructed before each part of the task. In part one (compatible-fixed condition) spatially compatible responses were required: a green-colored square randomly moved across the bar and subjects were instructed to copy the direction of the movement (left movement- left mouse button, right movement- right mouse button). In part two (incompatible-fixed condition) spatially incompatible responses were required: a red-colored square randomly moved across the bar and subjects were instructed to respond by pressing the mouse button opposite to the direction of the movement (left movement- right mouse button, right movement- left mouse button). In part three, the color of the moving square randomly alternated between green and red. Thus, both the direction of the movement and the color of the square were unpredictable. When the color of the square was green after a movement (compatible-variable condition), a spatially compatible response was required (like in part 1). When the color of the square was red after a movement (incompatible-variable condition), a spatially incompatible response was required (like in part 2, see Figure 1). Because of the unpredictability of the direction of the movement and the color of the square, high levels of mental flexibility were required in this part of the task. The task variables were flexibility-time and flexibility-errors: reaction time on compatible responses part 3 minus reaction time on compatible responses part 1, and percentage of compatible errors part 3 minus percentage of compatible errors part 1.

Statistical Analyses

Group differences with respect to measures of attentional control and mental flexibility were analyzed by General Linear Model, multivariate analyses of variance (MANOVA), in three separate runs. In the first run, fluctuation in tempo in the Sustained Attention tasks was analyzed. The Wisconsin Card Sorting Test and the Shifting Attentional Set Task (mental flexibility) were analyzed separately, because the Wisconsin Card Sorting Test was not administered to all 48 normal controls ($n = 25$). In all analyses, age and IQ were used as a covariate whenever these parameters correlated significantly with the dependent variables. Although the sex ratio differed between the diagnostic groups, sex was not used as a covariate because there were no sex dif-

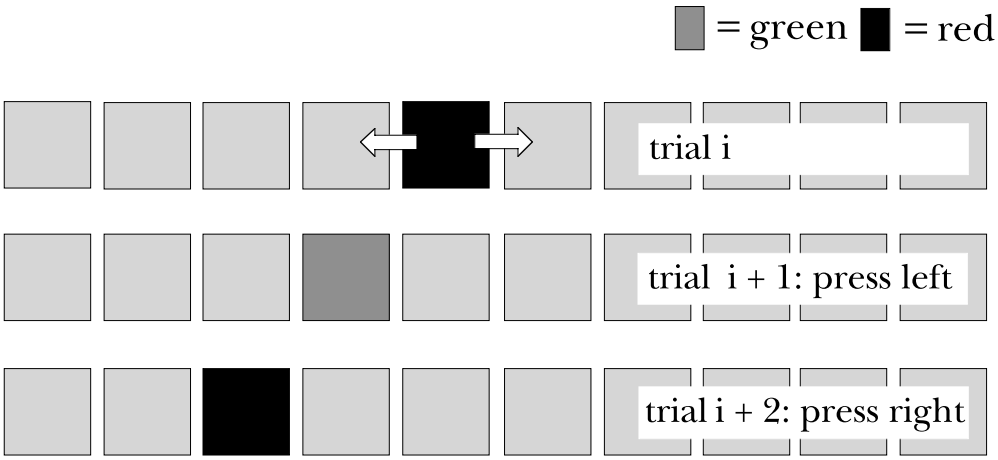

Fig. 1. Design Shifting Attentional Set-Visual, part 3

ferences with respect to task performance. Simple contrasts were used to examine differences between the ADHD probands and normal controls. Repeated contrasts were used to determine whether the non-affected siblings differed from the ADHD probands (1st contrast), and whether the non-affected siblings differed from the controls (2nd contrast). Polynomial contrasts were used to examine whether there was a linear effect across the diagnostic categories, which would imply that attentional control and mental flexibility are arranged on a continuum with the task performance of the ADHD group at one extreme and that of the controls at the other. The contrast analyses were not corrected for multiple comparisons. All analyses of the dependent variables were two-tailed and used the 0.05 level of statistical significance. As index of effect size partial eta squared (η_p^2) is reported, and Cohen's d for the results of the contrast analyses. Effect sizes can be interpreted as being small: $\eta_p^2 = 0.01$ or d = 0.2; medium: $\eta_p^2 = 0.06$ or d = 0.5; or large: $\eta_p^2 > 0.13$ or d > 0.8 (Cohen, 1988). Data analysis was performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 9.0).

Results

1) Attentional Control

The data for one normal control had to be excluded from the analysis, because of a reaction time score more than three times the interquartile range above the median. Univariate analysis with age and IQ as covariates indicated a significant effect of group on fluctuation in tempo ($F = 10.03$, $df = 2, 96$, $p < 0.0001$, $\eta_p^2 = 0.18$, see Fig. 2). Simple contrast analyses showed that the ADHD probands had a significantly worse performance than the controls (Contrast Estimate (CE): 1.12, $p < 0.0001$, $d = 0.82$).

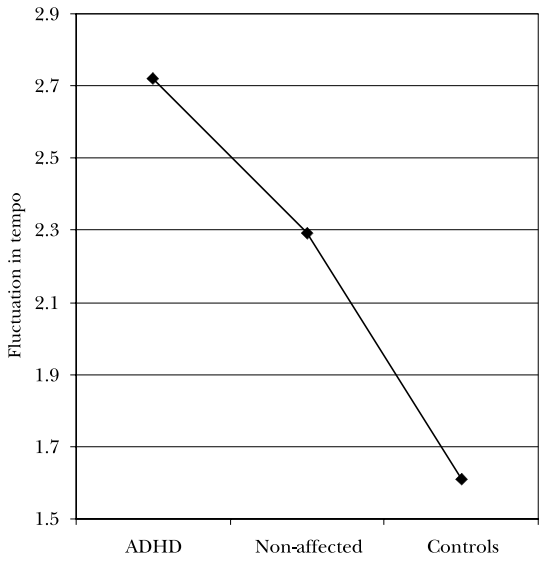

Fig. 2. Attentional control. Fluctuation in tempo on the Sustained Attention task as a function of group classification. ADHD = ADHD probands; Non-affected = siblings (of ADHD probands) without ADHD; Controls = normal controls.

Repeated contrasts revealed that the non-affected siblings differed significantly from the normal controls (CE: 0.69, $p < 0.01$, $d = 0.51$), but not from the ADHD probands. The polynomial contrast revealed a linear effect across the diagnostic categories for this measure of attentional control (CE= -0.79, $p < 0.0001$).

2) Mental Flexibility

The MANCOVA (with age as a covariate) of the WCST revealed a significant main effect of group on the three task variables ($F = 2.54$, $df = 2, 74$, $p = 0.05$, $\eta_p^2 = 0.10$, see Fig. 3.1). Simple contrast analyses showed that the ADHD probands had a significantly worse performance than the controls on number of categories completed and total number of errors (Contrast Estimate (CE): -1.06, $p < 0.05$, $d = -0.66$, and CE: 14.09, $p < 0.05$, $d = 0.64$). Repeated contrasts revealed that the performance of the non-affected siblings on the three variables did not differ significantly from that of either the ADHD probands or the normal controls. The polynomial contrast revealed a linear effect across the diagnostic categories for number of categories completed and total number of errors (CE= 0.75, $p < 0.05$, and CE: -9.96, $p < 0.05$).

In the analyses of the Shifting Attentional Set task, the data for one normal control was missing due to technical problems. Multivariate analysis with age as a covariate showed a trend level of significance for the effect of group on flexibility ($F = 2.25$, $df = 2, 96$, $p = 0.066$, $\eta_p^2 = 0.05$, see Fig. 3.2). Simple contrast analyses showed that the ADHD probands made significantly more inflexibility errors than the controls (Contrast Estimate (CE): 6.55, $p \leq 0.05$, $d = 0.46$). The ADHD probands did not differ from the normal controls with respect to the time measure of flexibility. Repeated contrasts revealed that the ADHD probands and the non-affected siblings differed significantly on flexibility-time (CE: -125.16, $p \leq 0.05$, $d = -0.24$), but not on flexibility-errors. The non-affected siblings and normal controls did not differ on any of the flexibility meas-

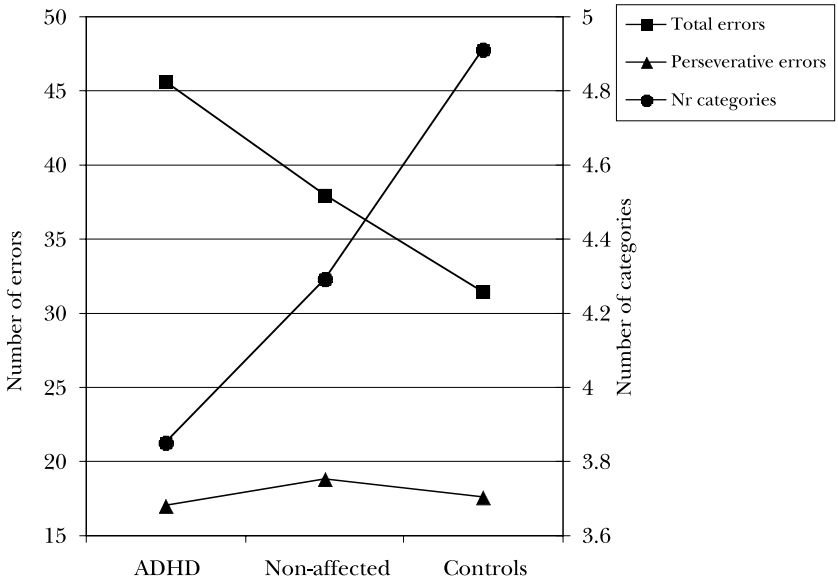

Fig. 3.1. Mental flexibility. Number of categories completed, total number of errors, and number of perseverative errors on the Wisconsin Card Sorting Test as a function of group classification. ADHD = ADHD probands; Non-affected = siblings (of ADHD probands) without ADHD; Controls = normal controls.

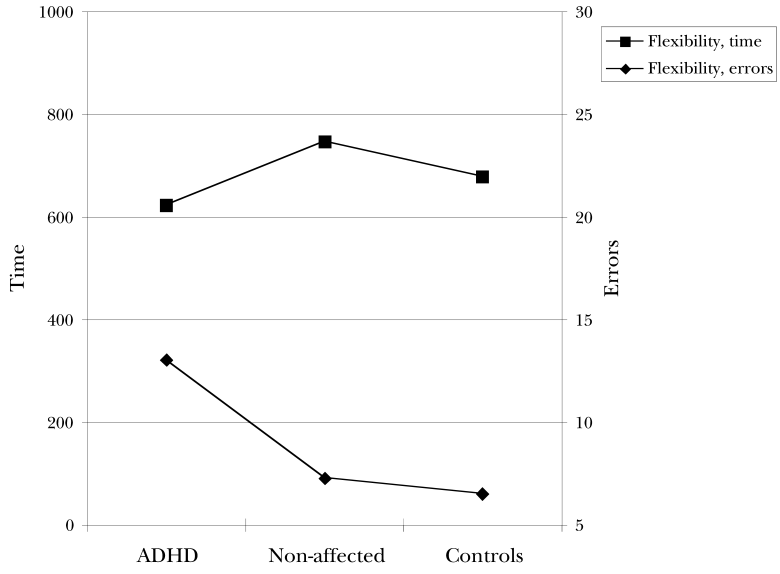

Fig. 3.2. Mental flexibility. Time-measure of flexibility and error-measure of flexibility on the Shifting Attentional Set-Visual task as a function of group classification. ADHD = ADHD probands; Non-affected = siblings (of ADHD probands) without ADHD; Controls = normal controls.

ures. The polynomial contrast revealed a linear effect across the diagnostic categories for flexibility-errors (CE= -4.63, $p \leq 0.05$), but not for flexibility-time. The results on the error-measure of flexibility were not likely an artifact of a speed accuracy trade-off, since the correlation between the time measure of flexibility and the error measure was non-significant for both the ADHD group and the non-affected siblings group (0.08 and 0.14 respectively).

Discussion

Deficient response inhibition is widely viewed as a core cognitive deficit in ADHD, it is even described as one of the most promising candidate endophenotypes of the disorder (Crosbie & Schachar, 2001; Slaats-Willemse et al., 2003). However, substantial evidence is provided that other aspects of executive functioning may also be potential endophenotypes of ADHD (Kuntsi and Stevenson, 2001; Kuntsi et al., 2001; Slaats-Willemse et al, submitted). Therefore, in this study we examined whether attentional control and mental flexibility, two important aspects of executive control, are likely to be valuable endophenotypes of ADHD as well. We hypothesized that siblings of ADHD probands, while not behaviorally expressing the disorder, have ADHD-associated deficits in attentional control and mental flexibility. We expected to see that the performances of the ADHD probands, the non-affected siblings and the controls were arranged on a continuum with those of the probands at one extreme, those of the controls at the other, and those of the non-affected siblings in between.

The results supported our hypotheses and showed that the non-affected siblings did not differ from their ADHD siblings with respect to fluctuation in tempo on a continuous performance task, while they differed significantly from the controls on this measure. The linear changes of this measure across the groups reflected an intermediate position of the non-affected siblings between the ADHD probands and controls. With respect to mental flexibility, the results were equivocal. The findings on the WCST revealed mental flexibility problems for the non-affected siblings of ADHD probands, with performances between those of the ADHD probands and normal controls. The linear changes in mental flexibility across the groups supported these findings. Such an intermediate position for the non-affected siblings was also found for the error-measure of flexibility of the Shifting Attentional Set task, but not for the time-measure of flexibility.

Overall, our findings suggest that attentional control and mental flexibility may be markers for ADHD, i.e. these aspects of executive functioning can be viewed as valuable potential endophenotypes of ADHD. Thus, not only deficient response inhibition, but also attentional control and mental flexibility problems may be indicators of the familial predisposition to ADHD, and should therefore be examined in future studies that aim to uncover the complex causal pathways of ADHD.

The results of the present study indicate that what is inherited by individuals at enhanced risk of ADHD because of genetic liability is not the disorder itself but a state of vulnerability manifested by widespread executive dysfunctioning. Our finding that the siblings of ADHD probands have ADHD-associated deficits in executive functioning, while not behaviorally expressing the disorder, suggests that the genetically acquired state of vulnerability must frequently exist without the development of symptoms of ADHD. A plausible hypothesis is that the non-affected siblings carry less risk genes coding for ADHD compared with the ADHD siblings. They "crossed the threshold for ADHD", expressed in ADHD-related cognitive impairment but not in behavioral symptoms. This would be in line with the view that ADHD represents a dimensional trait, with differences in genetic liability and expression throughout the population (Barkley, 1998; Levy et al., 1997; Buitelaar, 2002). An alternate pathway is that some other factor(s) is/are required for the development of the disorder, even in this sample where genetic influence seem obvious since the recruited families had two ADHD-affected siblings (Byrne et al., 2003). Potential factors may be environmental influences. One could hypothesize that the non-affected siblings did not develop ADHD because of the absence of risk factors, or the presence of protective factors like specific personality characteristics, positive parental attitudes, extrafamilial social support, participation in outside activities, and positive relationships with peergroups (Samudra and Cantwell, 1999; Johnston, 1996; Johnston and Mash, 2001).

If the vulnerability-hypothesis is true and the non-affected siblings have the genetic liability for the disorder reflected by cognitive impairments but not by behavioral symptoms, measures of executive functioning are less useful to differentiate between ADHD and normal controls since the clinical phenotype and objective cognitive endophenotype do not always co-occur. This complicated issue should be investigated in future research. Further research is also warranted to replicate our findings in larger samples. The sample sizes were relatively small because families with two ADHD siblings and one non-affected child are scarce.

Acknowledgements

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References

Achenbach, T.M. (1986). *Manual for the Teacher Report Form and the Child Behavior Profile. Burlington.* University of Vermont Department of Psychiatry.

Achenbach, T.M. (1991). *Integrative Guide for the 1991 CBCL, YSR, and TRF Profiles. Burlington.* University of Vermont Department of Psychiatry.

Achenbach, T.M., Verhulst, F.C., Baron, G.D., Althaus, M. (1987). A comparison of syndromes derived from the Child Behavior Checklist for American and Dutch boys aged 6-11 and 12-16. *Journal of Child Psychology and Psychiatry* ,28, 437-453.

American Psychiatric Association (APA). (1994), *Diagnostic and statistical manual for mental disorders.* Washington, DC: Author.

Bakker, S.C., Meulen, E.M., Buitelaar, J.K., Sandkuijl, L.A., Pauls, D.L., Monsuur, A.J., Slot, R.R., Minderaa, R.B., Gunning, W.B., Pearson, P.L., Sinke, R.J. (2003). A whole-genome scan in 164 dutch sib pairs with attention- deficit/hyperactivity disorder: suggestive evidence for linkage on chromosomes 7p and 15q. *American Journal of Human Genetics,* 72,1251-1260.

Barkley, R.A. (1997). Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychological Bulletin,* 121, 65-94.

Barkley, R.A. (1998). Attention Deficit Hyperactivity Disorder. A handbook for Diagnosis and Treatment (2nd edition). New York: Guilford Press.

Berman, T., Douglas, V.I., Barr, R.G. (1999). Effects of methylphenidate on complex cognitive processing in attention- deficit hyperactivity disorder. *Journal of Abnormal Psycholology,* 108, 90-105.

Buitelaar, J. K. (2002). Epidemiology of Attention-deficit/Hyperactivity Disorder: what have we learned over the last decade? In S. Sandberg (Ed.), *Hyperactivity Disorders* (pp. 30-63). Cambridge: Cambridge University Press.

Byrne, M., Clafferty, B.A., Cosway, R., Grant, E., Hodges, A., Whalley, H.C., Lawrie, S.M., Owens, D.G., Johnstone, E.C. (2003). Neuropsychology, genetic liability, and psychotic symptoms in those at high risk of schizophrenia. *Journal of Abnormal Psychology,* 112, 38-48.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Earlbaum Associates.

Crosbie, J., Schachar, R. (2001). Deficient inhibition as a marker for familial ADHD. *American Journal of Psychiatry,* 158, 1884-1890.

de Sonneville, L.M., Njiokiktjien, C., Bos, H. (1994). Methylphenidate and information processing. Part 1: Differentiation between responders and nonresponders; Part 2: Efficacy in responders. *Journal of Clinical and Experimental Neuropsychology*, 16, 877-897.

de Sonneville, L.M.J. (1999). Amsterdam Neuropsychological tasks: a computer-aided assessment program. In: *Computers in Psychology, Vol. 6: Cognitive ergonomics, clinical assessment and computer-assisted learning*, B.P.L.M. Den Brinker, P.J. Beek, A.N. Brand, S.J. Maarse, and L.J.M. Mulder (Eds.), pp. 187-203. Lisse: Swets and Zeitlinger.

Faraone, S.V., Doyle, A.E., Mick, E., Biederman, J. (2001). Meta-analysis of the association between the 7-repeat allele of the dopamine D(4) receptor gene and attention deficit hyperactivity disorder. *American Journal of Psychiatry* 158:1052-1057.

Goyette, C.H., Conners, C.K., Ulrich, R.F. (1978). Normative data on revised Conners Parent and Teacher Rating Scales. *Journal of Abnormal Child Psychology,* 6, 221-236.

Grant, D.A., Berg, E.A. (1948). *The Wisconsin Card Sorting Test.* Odessa, FL: Psychological Assessment Resources.

Grodzinsky, G., Diamond, R. (1992). Frontal lobe functioning in boys with attention deficit hyperactivity disorder. *Developmental Neuropsychology,* 8, 427-445.

Heaton, R.K., Chelune, G.I., Talley, J.L., Kay, G.G., Curtis, G. (1993). *Wisconsin Card Sorting Test Manual: Revised and Expanded.* Odessa, FL: Psychological Assessment Resources.

Johnston, C. (1996). Parent characteristics and parent-child interactions in families of nonproblem children and ADHD children with higher and lower levels of oppositional-defiant behavior. *Journal of Abnormal Child Psychology,* 24, 85-104.

Johnston, C., Mash, E.J. (2001). Families of children with attention-deficit/hyperactivity disorder: review and recommendations for future research. *Clinical Child and Family Psychology Review,* 4, 183-207.

Kuntsi, J., Oosterlaan, J., Stevenson, J. (2001). Psychological mechanisms in hyperactivity: I. Response inhibition deficit, working memory impairment, delay aversion, or something else? *Journal of Child Psychology and Psychiatry,* 42, 199-210.

Kuntsi, J., Stevenson, J. (2001). Psychological mechanisms in hyperactivity: II. The role of genetic factors. *Journal of Child Psychology and Psychiatry,* 42, 211-219.

Laurent, A., Duly, D., Murry, P., Foussard, N., Boccara, S., Mingat, F., Dalery, J., d'Amato, T. (2001). WCST performance and schizotypal features in the first-degree relatives of patients with schizophrenia. *Psychiatry Research,* 104, 133-144.

Levy, F., Hay, D.A., McStephen, M., Wood, C., Waldman, I. (1997). Attention-deficit hyperactivity disorder: a category or a continuum? Genetic analysis of a large-scale twin study. *Journal of the American Academy of Child and Adolescent Psychiatry,* 36, 737-744.

Levy, F., Hay, D. (2001). *Attention, genes, and ADHD.* Philadelphia, P.A.: Brunner-Routledge.

Lezak, M.D. (1983). *Neuropsychological assessment,* 2nd Edn. Oxford University Press, New York.

Maher, B.S., Marazita, M.L., Ferrell, R.E., Vanyukov, M.M. (2002). Dopamine system genes and attention deficit hyperactivity disorder: a meta-analysis. *Psychiatric Genetics,*12, 207-215.

Murphy, K., Barkley, R.A. (1996). Attention deficit hyperactivity disorder adults: comorbidities and adaptive impairments. *Comprehensive Psychiatry,* 37, 393-401.

Nigg, J.T. (1999). The ADHD Response-Inhibition Deficit as Measured by the Stop Task: Replication with DSM-IV Combined Type, Extension, and Qualification. *Journal of Abnormal Child Psychology,* 27, 393-402.

Oosterlaan, J., Logan, G.D., Sergeant, J.A. (1998). Response inhibition in AD/HD, CD, comorbid AD/HD + CD, anxious, and control children: a meta-analysis of studies with the stop task. *Journal of Child Psychology and Psychiatry,* 39, 411-425.

Pennington, B.F., Ozonoff, S. (1996). Executive functions and developmental psychopathology. *Journal of Child Psychology and Psychiatry,* 37,51-87.

Samudra, K., Cantwell, D.P. (1999). Risk factors for Attention-Deficit/ Hyperactivity Disorder. In: *Handbook of disruptive behavior disorders,* Quay and Hogan. Kluwer Academic/ Plenium Publishers, New York.

Sattler, J.M. (1992). *Assessment of children: WISC-III and WPPSI-R supplement.* San Diego, SA, England.

Seidman, L.J., Biederman, J., Faraone, S.V., Milberger, S., Norman, D., Seiverd, K., Benedict, K., Guite, J., Mick, E., Kiely, K. (1995). Effects of family history and comorbidity on the neuropsychological performance of children with ADHD: preliminary findings. *Journal of the American Academy of Child and Adolescent Psychiatry,* 34, 1015-1024.

Seidman, L., Biederman, J., Faraone, S.V., Weber, W., Ouellette, C. (1997a). Toward defining a neuropsychology of attention deficit-hyperactivity disorder: performance of children and adolescents from a large clinically referred sample. *Journal of Consulting and Clinical Psycholo*gy, 65,150-160.

Seidman, L.J., Biederman, J., Faraone, S.V., Weber, W., Mennin, D., Jones, J. (1997b). A pilot study of neuropsychological function in girls with ADHD, *Journal of the American Academy of Child and Adolescent Psychiatry,* 36, 366-373.

Seidman, L.J., Biederman, J., Monuteaux, M.C., Weber, W. (2000). Neuropsychological functioning in nonreferred siblings of children with Attention deficit Hyperactivity Disorder. *Journal of Abnormal Child Psychology,* 109, 252-265.

Sergeant, J.A., Geurts, H., Oosterlaan, J. (2002). How specific is a deficit of executive functioning for attention- deficit/hyperactivity disorder? *Behavioral Brain Research,* 130, 3-28.

Shaffer, D., Fisher, P., Lucas, C.P., Dulcan, M.K., Schwab-Stone, M.E. (2000). NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC- IV): description, differences from previous versions, and reliability of some common diagnoses. *Journal of the American Academy of Child and Adolescent Psychiatry,* 39, 28-38.

Slaats-Willemse, D., Swaab-Barneveld, H., de Sonneville, L., van der Meulen, E., Buitelaar, J. (2003). Deficient response inhibition as a cognitive endophenotype of ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry,* 42, 1242-1248.

Tannock, R. (1998). Attention deficit hyperactivity disorder: advances in cognitive, neurobiologic, and genetic research. *Journal of Child Psychology and Psychiatry,* 39, 65-100.

Tannock, R., Schachar, R.J., Carr,R.P., Chajczyk, D., Logan, G.D. (1989). Effects of methylphenidate on inhibitory control in hyperactive children. *Journal of Abnormal Child Psychology,* 17, 473-491.

Vandersteene, G., Van Haassen, P.P., De Bruyn, E.E.J., Coetsier, P., Pijl, Y.L., Poortinga, Y.H., Lutje Spelberg, H.C., Spoelders-Claes, R., Stinissen, J. (1986) *WISC-R, Wechsler Intelligence Scale for Children-Revised*, Nederlandstalige uitgave. Lisse: Swets and Zeitlinger.

Verhulst, F.C., Koot, J.M., Van der Ende, J. (1996). *Handleiding voor de CBCL (Child Behavior Checklist) [Manual for the CBCL].* Afdeling Kinder- en Jeugdpsychiatry, Sophia Kinderziekenhuis/ Academisch Ziekenhuis Rotterdam/ Erasmus Universiteit Rotterdam, the Netherlands.

Chapter 7

Executive Dysfunctioning as a Cognitive Endophenotype of ADHD:

Several Distinct Constructs or A Single Underlying Construct?

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Abstract

Executive dysfunctioning is viewed as the cognitive core impairment in Attention Deficit Hyperactivity Disorder (ADHD). This study investigates whether distinct interpretable constructs reflecting different aspects of executive functioning can be defined in a sample of ADHD siblings. Therefore, a posthoc principal component analysis was performed in which a model of inter-relations between fourteen measures of response inhibition, attentional control, higher-order controlled motor functioning, and mental flexibility was studied. The sample consisted of 104 carefully phenotyped ADHD siblings from 52 ASP (affected sibling pair) families (age ranged from 6 to 18 years). The factor analysis revealed that a three-factor model appeared to be the best solution to summarize the data. The first factor, attentional and motor control, consisted of cognitive task variables measuring stability of information processing and motor execution. The second factor, mental flexibility, consisted of measures reflecting the ability to adapt to a changing environment and the third factor, response inhibition, was composed of task variables measuring the ability to inhibit undesired responses. The high factor loadings and the minimal overlap between the factors provided evidence for the presence of three distinct constructs of executive functioning in ADHD.

Introduction

Deficits in executive functioning are widely viewed as the core cognitive symptoms in Attention Deficit Hyperactivity Disorder (Barkley, 1997b; Barkley, 2000; Nigg, 2001; Nigg et al., 2002; Pennington and Ozonoff, 1996). The term executive functioning refers to many cognitive processes and behaviors such as response inhibition, self-regulation, sequencing of behavior, mental flexibility, and planning and organization of behavior (National Institute of Child Health and Human Development, January 1994, informal survey), and is considered to overlap noticeably with the domain of attention.

Neuropsychological paradigms and theories focusing on executive functioning are valuable for the research on the etiology of ADHD by linking cognitive deficits, brain abnormalities, and genetic-/environmental causative factors (Zametkin and Rapoport, 1987). An elaborate theory concerning executive functioning in children with ADHD has been presented by Barkley, who described a unifying model based on earlier theories of cognitive functioning mediated by the prefrontal lobes (Barkley, 1997a; Barkley, 1997b). The model presumed that deficient response inhibition leads to secondary impairments in four neuropsychological abilities (working memory, self-regulation, internalization of speech, and reconstitution) that are partially dependent on inhibition for their effective execution. According to the model, children with ADHD have poor behavioral inhibition, which causes deficiencies in four related executive functions. Numerous studies based on this model have found evidence for an inhibitory control deficit in ADHD (Grodzinsky and Diamond, 1992; Nigg, 2001; Schachar et al., 2000). For a meta-analysis, see Oosterlaan et al. (1998). Deficient response inhibition is even found to be a marker for a familial form of ADHD: Children with ADHD who exhibit poor inhibition are more likely to have a first-degree relative with ADHD than are children with ADHD who exhibit good response inhibition (Crosbie and Schachar, 2001). Furthermore, children with ADHD who have a family history of ADHD are found to perform significantly worse on measures of response inhibition than ADHD children without such a family history (Seidman et al., 1995). A previous study conducted by our research group also supported the notion that response inhibition deficits in ADHD may be associated with familial/genetic susceptibility for the disorder (Slaats-Willemse et al., 2003). However, other aspects of executive functioning, attentional control, mental flexibility, higher-order controlled motor functioning have also proven to be valuable potential indicators of the familial predisposition to ADHD (Kuntsi et al., 2001; Kuntsi and Stevenson, 2001; Slaats-Willemse et al., submitted). In other words, these aspects may also be potential endophenotypes of ADHD, i.e. latent traits that carry genetic loading and which are related indirectly to the classic behavioral symptoms as defined in DSM-IV or ICD-10 (Leboyer et al., 1998; Skuse, 2001). This suggests that deficits in *other* aspects of executive functioning may also be important in ADHD, rather than one single aspect, i.e. response inhibition. If this is true, it is important to know whether these aspects of ex-

ecutive functioning may overlap. If so, do these measures then reflect the same underlying construct or several distinct constructs?

In the present study, we investigated whether distinct interpretable constructs reflecting different aspects of executive functioning can be defined in a sample of ADHD siblings. Therefore, we performed a posthoc principal component analysis in which a model of inter-relations between measures of response inhibition, attentional control, higher-order controlled motor functioning, and mental flexibility was studied. We analyzed task variables that have proven to be valuable measures in the cognitive research on ADHD, namely the 1) Stroop interference score, 2) percentage of misses and 3) number of impulsive responses on a Sustained Attention task, 4) percentage of false alarms on a Go Nogo task, variability in response time of correct responses to target signals in a Divided- and a Focused Attention task (5 and 6), 7) fluctuation in tempo with time-on-task in a Sustained Attention task, accuracy and stability of visual motor control (Pursuit task, 8 and 9), 10) WCST number of categories completed, 11) WCST total number of errors and 12) WCST number of perseverative errors, and flexibility-time and flexibility-errors in the shifting attentional set task (13, 14) (Crosbie and Schachar, 2001; Seidman et al., 1995; Kuntsi and Stevenson, 2001; Kuntsi et al., 2001; Slaats-Willemse et al., 2003; Slaats-Willemse et al., submitted).

Method

Subjects

The sample consisted of 104 ADHD siblings from 52 ASP (affected sibling pair) families, who were a subset of a larger population of ADHD-affected sibling pairs (n = 164) from 106 families that participated in a genome scan study (Bakker et al., 2003). ASPs were included in the genome scan study if both siblings met the six criteria for the diagnosis of ADHD, or if one sibling met the required criteria and the other sibling met at least five out of nine criteria for inattention and/ or five criteria for hyperactivity-impulsivity (subthreshold). Six of them were diagnosed with "subthreshold" ADHD. Aged ranged from 6 to 18 years. The ASPs were recruited from families that were referred to one of the three participating academic child psychiatric outpatient clinics, or from members of a patient organization. Only children that lived with their biological parent(s) of Dutch descent were included. The children were screened by experienced clinicians according to DSM-IV criteria (American Psychiatric Association (APA), 1994). The clinical diagnoses were verified in structured interviews with the parents and the children. The DSM-IV version of the Diagnostic Interview Schedule for Children, DISC-P (Shaffer et al., 2000), was administered to the mother or both parents by trained graduate students in medicine or child psychology. This instrument was also used to screen for the presence of comorbid disorders. The final diagnosis of ADHD, which served as the basis for inclusion of the family in the study, was

determined using a "best-estimate procedure" (Leckman et al., 1982). To this end, the results of the medical history, clinical interview, DISC-P interview, and scores of the parent-t and teacher-rated Conners Questionnaire (Goyette et al., 1978) and Child Behaviour Checklist (CBCL, Achenbach et al., 1987; Verhulst et al., 1996) and Teacher Report Form (TRF, Achenbach, 1986; Achenbach, 1991; Achenbach and Ruffle, 2000) were summarized in a patient report. This report resulted in a final diagnosis verified by a senior child psychiatrist. Sixty-two percent of the ADHD siblings were on medication. These medications are known to affect cognitive functioning (Berman et al., 1999; de Sonneville et al., 1994; Tannock et al., 1989), and therefore medication was discontinued two days (stimulants) or one week (non-stimulants) before cognitive assessment. Full-Scale IQ was estimated from the Similarities, Vocabulary, Block Design, and Object Assembly subtests of the WISC-R (Sattler, 1992; Vandersteene et al., 1986). The clinical characteristics of the ADHD siblings are shown in table 1. The Medical Ethical Review Committee of the University Medical Center Utrecht approved the study. All patients or the parents of the younger patients filled out an informed consent.

Cognitive assessment

Based on a review of literature and our previous work, we selected fourteen cognitive task variables from the Stroop Color Word Interference Test (Stroop, 1935), the computerized Wisconsin Card Sorting Test (WCST, Grant and Berg, 1948) and four tasks of the Amsterdam Neuropsychological Tasks Program (de Sonneville, 1999; de Sonneville et al., 2002). These variables are considered to reflect different aspects of ex-

Table 1. Clinical Characteristics of the sample

	Number	Percentage	Mean (SD)
Gender			
Boys	46	89	
Girls	6	11	
Mean age, in years			13.6 (2.3)
Mean estimated IQ			102.3 (17.0)
ADHD diagnosis			
Full	49	94	
Subthreshold	3	6	
ADHD subtype			
Combined	45	87	
Inattentive	6	12	
Hyperactive/impulsive	1	2	
Comorbidity			
ODD	18	35	
CD	2	4	

Note: ADHD = attention deficit hyperactivity disorder; subthreshold ADHD = five out of nine criteria for inattention and/or five criteria for hyperactive-impulsivity; ODD = oppositional defiant disorder, CD = conduct disorder.

ecutive functioning, i.e. response inhibition, attentional control, higher-order controlled motor functioning, and mental flexibility:
1) Response inhibition was operationalized by the *Stroop interference score*, *percentage of misses* and *number of impulsive responses on the Sustained Attention task*, and *percentage of false alarms on the Go Nogo task*. In the Sustained Attention task, a visual continuous performance task, 50 series x 12 signals were presented consisting of three, four, or five dots presented in random order. With signals consisting of four dots (target signal), subjects had to press the "yes" key; with signals consisting of three and five dots (non-targets), they had to press the "no" key. The overall target rate was 33%, which implies that the subject had to press the "no" key twice as often as the "yes" key. This difference in response probability is demonstrated to invoke a response bias (de Sonneville et al., 1994; Swaab-Barneveld et al., 2000). Therefore, the percentage of misses is considered to reflect a failure to inhibit undesired responses. Responses to signals had to be generated between 200 and 8000 ms following stimulus onset. Responses made before 200 ms were not expected to be the result of a cognitive evaluation process and were considered as premature hits on the mouse button, i.e. impulsive responses. In the Go NoGo task, 24 Go signals were presented, randomly mixed with 24 NoGo signals. Subjects had to press a key if a Go signal appeared on the screen and had to withhold a response if they saw a NoGo signal. A failure to withhold results in a false alarm. Extensive descriptions of the Go NoGo and the Sustained Attention task can be found elsewhere (Slaats-Willemse et al., 2003).
2) Attentional control was taken to be reflected by the *variability (standard deviation) in response time of correct responses to target signals in the Divided- and Focused Attention tasks*, and the *fluctuation in tempo with time-on-task in the Sustained Attention task*. In the latter task, the completion time per series (50 series in total) is computed, and the standard deviation of the completion times of the 50 series represents the fluctuation in tempo. The Divided Attention task employs a display load of four letters and consists of three parts in which target set size (memory load) is increased from one to three target letters. Signals that contain the complete target set require a 'yes'-response. All other signals, also those containing an incomplete target set, require a 'no'-response. The Focused Attention task employs a similar four-letter display load as in the Divided Attention task, but now only two diagonal locations are relevant (known in advance to the subjects) and subjects should attend to those positions only. A target signal is defined as a signal that contains a target letter on the relevant diagonal. Upon its presentation the 'yes'-key should be pressed. Irrelevant target signals, i.e. with a target letter on the irrelevant diagonal, and non-target signals (target letter absent) require the subject to press the 'no'-key. Extensive descriptions of the Divided Attention task and the Focused Attention task can be found elsewhere (Huijbregts et al., 2002).
3) Higher-order controlled motor functioning was operationalized by two variables of the Pursuit task. The Pursuit task is a complex motor flexibility task that requires subjects to follow a target. They have to continuously adjust the movements of the mouse in order to position the cursor as closely as possible to a moving asterisk, which re-

quires a high level of flexibility. The ANT program computes the mean distance between the cursor and asterisk per second time-on-task (60 s in total). Task variables were *mean and standard deviation of the 60 values, reflecting accuracy and stability of the visual motor control respectively.* The Pursuit task requires high levels of flexibility and permanent controlled processing, since the movements of the target are unpredictable. Extensive descriptions of the Pursuit can be found elsewhere (Kalff et al., 2003).
4) Mental flexibility was reflected by variables of the WCST, and the Shifting Attentional Set task from the ANT. The most widely used scores of the WCST were analyzed: *number of categories completed* (number of times 10 correct responses in a row are made, reflecting overall success), *total number of errors* (wrong matches, documenting problems in forming concepts), *and number of perseverative errors* (consecutive matches according to the same wrong criterion, reflecting tendency towards perseveration) (Laurent et al., 2001; Lezak, 1983). In the Shifting Attentional Set task, a horizontal bar consisting of ten squares was presented permanently in the center of a standard monitor. From trial to trial a colored square moved across the bar in a random direction (either to the right or to the left). The task consisted of three parts. Subjects were instructed before each part of the task. In part one (compatible-fixed condition) spatially compatible responses were required: a green-colored square randomly moved across the bar and subjects were instructed to copy the direction of the movement (left movement- left mouse button, right movement-right mouse button). In part two (incompatible-fixed condition) spatially incompatible responses were required: a red-colored square randomly moved across the bar and subjects were instructed to respond by pressing the mouse button opposite to the direction of the movement (left movement-right mouse button, right movement-left mouse button). In part three, the color of the moving square randomly alternated between green and red. Thus, both the direction of the movement and the color of the square were unpredictable. When the color of the square was green after a movement (compatible-variable condition), a spatially compatible response was required (like in part 1). When the color of the square was red after a movement (incompatible-variable condition), a spatially incompatible response was required (like in part 2). Because of the unpredictability of the direction of the movement and the color of the square, high levels of mental flexibility were required in this part of the task. The task variables were *flexibility-time and flexibility-errors: reaction time on compatible responses part 3 minus reaction time on compatible responses part 1, and percentage of compatible errors part 3 minus percentage of compatible errors part 1.*

Statistical analyses

First, the data were screened in scatterplots to indicate whether there was evidence of linear relationships between the fourteen variables. Next, Pearson´s correlation coefficients were computed to test how the measures were interrelated. The analyses were two-tailed and used the 0.05 level of statistical significance. Finally, all task variables were entered in a principal component analysis (PCA) with varimax rotation. With

this rotation, each component or factor tends to load high on a smaller number of variables and low or very low on the other variables, which makes interpretation of the resulting factors easier (Stevens, 2002). Three, four, and five component solutions were examined to decide which solution best summarized the data. Following the Kaiser criterion (1960) those components with eigenvalues greater than 1 were retained. In a graphical method called the screetest, the magnitude of the eigenvalues was plotted against their ordinal number (De Heus, et al., 1995). This method was used to decide how many components to retain: the components with eigenvalues before the breaking point, the point where the eigenvalues start to drop should be retained. A rough check as to whether a loading was statistically significant was obtained by doubling the standard error, that is, doubling the critical value required for significance for a correlation between the variable and the factor/component (at $\alpha = 0.01$). For an overview of critical values see table 11.1, Stevens (2002). Since the PCA has been run with 92 subjects (12 cases were excluded due to missing data), only loadings $> 2 \times 0.27 = 0.54$ were declared statistically significant. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 9.0).

Results

The principal component analysis with three extracted components/ factors was chosen to summarize the data, because the eigenvalues of the three components were higher than 1. This choice was also supported by the scree plot, that showed three eigenvalues (associated with the first three components) before the breaking point, the point where the eigenvalues start to drop. The percentage explained variance for the three-component solution was 54.1%. In determining the final composition of the factors, the variables with loadings > 0.54 were chosen. However, since the rough check as to whether the loadings are statistically significant seemed to be quite conservative (see section statistical analysis), the cognitive variable with a factor loading of 0.52 was also declared statistically significant. Variables with factor loadings < 0.52 were discarded. The rotated component matrix indicated only a few cross loadings (see table 2). The first factor "attentional and motor control" (eigenvalue 3.6; explained variance 25.9) comprised variables that reflected fluctuation in response time on different attention tasks, accuracy and stability of visual motor control, and sensitivity to interference of competing responses. The second factor (eigenvalue 2.1; explained variance 14.8%) was termed "mental flexibility" and was composed of the variables of the Wisconsin Card Sorting Test. This factor reflects the (in)ability to adapt to a changing environment. The third factor "response inhibition" (eigenvalue 1.9; explained variance 13.4) reflects the (in)ability to inhibit undesired responses. The factor was composed of task variables measuring impulsive misses and impulsive hits in the sustained attention task, and flexibility-time on the shifting attentional set task.

Table 2. Rotated component matrix with factor loadings (principal component analysis)

	Factor		
Cognitive variables	1	2	3
Sust. att. tempo fluctuation	**0.826**		
Pursuit stability	**0.745**		0.307
Pursuit accuracy	**0.743**		
Foc. att. response time variability	**0.709**		
Stroop interference	**0.642**		
Div. att. response time variability	**0.579**		
Shift. att. set flexibility-errors	0.467		
Go Nogo % false Alarms			
WCST total errors		**0.893**	
WCST no. categories		**-0.805**	
WCST perseverative errors		**0.678**	
Sust. att. % misses			**0.834**
Sust. att. no. impulsive responses			**0.793**
Shift. att. set flexibility-time	0.395	0.340	**-0.519**

Note: ADHD = attention deficit hyperactivity disorder
Bold face factor loadings indicate selected variables.

Discussion

This study presents the results of a principal component analysis on fourteen cognitive task variables in a sample of ADHD siblings, to investigate whether distinct interpretable constructs can be defined reflecting different aspects of executive functioning. The results of the principal component analysis revealed that these variables could be better summarized in three clusters or constructs of executive functioning than in the four clusters (response inhibition, higher-order controlled motor functioning, attentional control and mental flexibility) we defined according to the literature.

The first factor, *attentional and motor control* reflected continuous attention capacity/stability of information processing and execution. The factor included different measures of variability in speed of responding and motor control. Surprisingly, the Stroop interference score also loaded high on this factor, although the interference score is considered to be an estimate of response inhibition (Nigg, 2001; Pennington and Ozonoff, 1996). However, complex neuropsychological tasks like the Stroop tend to assess different aspects of cognitive functioning. The data suggests that the Stroop interference factor is more likely to reflect a general failure to control information processing, rather than a specific failure to inhibit undesired responses.

The second factor, *mental flexibility* revealed high loadings on all measures of the Wisconsin Card Sorting Test (WCST). The positive factor loadings of the variables "total errors" and "perseverative errors" and the negative loading of "number of cate-

gories completed" showed that mental flexibility problems in ADHD may be reflected by a large number of errors and a small number of categories completed on the WCST.

The third factor, *response inhibition* was composed of variables measuring impulsive hits (premature hits on the mouse button) and impulsive misses (failure to inhibit undesired responses) on the Sustained Attention task. The third cognitive variable with high loadings on this factor, "flexibility-time" measures response time. The negative factor loading indicated a quick, impulsive response pattern. Surprisingly, the variable "percentage of false alarms on the Go NoGo task" did not have a significant loading on this factor, although this measure is widely viewed as a measure of response inhibition. A possible explanation is the heterogeneity of the concept of response inhibition, which is consistent with the present view that behavioral inhibition is related to different processes (Barkley, 1997a, 1997b). Probably, the Go NoGo task may reflect a different process of response inhibition and may be related to different brain structures than the inhibition measures that showed a significant loading on the third factor. Furthermore, this version of the Go NoGo task is originally designed for young children (age range 4 to 6), and may therefore show a ceiling-effect in this older sample (age range 6 to 18).

Although the ratio of variables to cases was marginal, the high factor loadings and the minimal overlap between the factors provided evidence for the presence of three distinct constructs of executive functioning in ADHD. Based on this, it is unlikely that a *general* executive function deficit is central in ADHD. The first factor, attentional and motor control had the highest explained variance, suggesting that the underlying measures cover an important part of the cognitive functions in the domain of executive functioning. This is in line with the finding that variability in speed of responding (measure of attentional and motor control) differentiates best between hyperactives and controls (Kuntsi et al., 2001). Furthermore, this measure is reported to share common genetic effects with hyperactivity (Kuntsi and Stevenson, 2001). In addition, Castellanos and Tannock reported in a review on endophenotypes of ADHD that response variability may be a valuable candidate endophenotype for molecular genetic studies of ADHD because of the promising findings in neuroscience- and imaging studies (Castellanos and Tannock, 2002).

The present findings and those of other studies reported above seem not to be consistent with Barkley´s view that deficient response inhibition is the central impairment in ADHD. The factor analysis revealed that response inhibition is one of the three aspects of executive functioning that may be important in ADHD, but it is not likely to be the underlying factor that causes problems in different domains of executive functioning as suggested by Barkley. However, the number of cases in the factor analysis was rather small to draw firm conclusions. It is recommended for future research to replicate this study in an independent, larger database. Furthermore, a confirmative factor analysis should be conducted to verify the hypothesis that three distinct aspects of executive functioning may be central in ADHD.

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References

Achenbach TM (1986), *Manual for the Teacher Report Form and the Child Behavior Profile. Burlington*. University of Vermont Department of Psychiatry

Achenbach TM (1991), *Integrative Guide for the 1991 CBCL, YSR, and TRF Profiles. Burlington*. University of Vermont Department of Psychiatry

Achenbach TM, Verhulst FC, Baron GD, Althaus M (1987), A comparison of syndromes derived from the Child Behavior Checklist for American and Dutch boys aged 6-11 and 12-16. *J Child Psychol Psychiatry* 28: 437-453

Achenbach TM, Ruffle TM (2000), The Child Behavior Checklist and related forms for assessing behavioral/emotional problems and competencies. *Pediatr Rev* 21:265-271

American Psychiatric Association (APA) (1994), *Diagnostic and statistical manual for mental disorders*. Washington, DC: Author

Bakker SC, Meulen EM, Buitelaar JK, Sandkuijl LA, Pauls DL, Monsuur AJ, Slot RR, Minderaa RB, Gunning WB, Pearson PL, Sinke RJ (2003), A whole-genome scan in 164 dutch sib pairs with attention- deficit/hyperactivity disorder: suggestive evidence for linkage on chromosomes 7p and 15q. *Am J Hum Genet* 72:1251-1260

Barkley RA (1997a), Attention-deficit/hyperactivity disorder, self-regulation, and time: toward a more comprehensive theory. *J Dev Behav Pediatr* 18:271-279

Barkley RA (1997b), Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychol Bull* 121:65-94

Barkley RA (2000), Genetics of childhood disorders: XVII. ADHD, part 1: Executive functions and ADHD. *J Am Ac Child Adolesc Psychiat* 39:1064-1068

Berman T, Douglas VI, Barr RG (1999), Effects of methylphenidate on complex cognitive processing in attention- deficit hyperactivity disorder. *J Abnorm Psychol* 108:90-105

Castellanos FX, Tannock R (2002), Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. *Nat Rev Neurosci* 3:617-628

Crosbie J, Schachar R (2001), Deficient inhibition as a marker for familial ADHD. *Am J Psychiatry* 158:1884-1890

De Heus P, Van der Leeden R, & Gazendam B (1995), *Toegepaste Data-analyse: technieken voor niet-experimenteel onderzoek in de sociale wetenschappen*. Utrecht: Uitgeverij Lemma

de Sonneville LMJ (1999), Amsterdam Neuropsychological tasks: a computer-aided assessment program. In: *Computers in Psychology, Vol. 6: Cognitive ergonomics, clinical assessment and computer-assisted learning*, B.P.L.M. Den Brinker, P.J. Beek, A.N. Brand, S.J. Maarse, and L.J.M. Mulder (Eds.), pp. 187-203. Lisse: Swets and Zeitlinger

de Sonneville LM, Boringa JB, Reuling IE, Lazeron RH, Ader HJ, Polman CH (2002), Information processing characteristics in subtypes of multiple sclerosis. *Neuropsychologia* 40:1751-1765

de Sonneville LM, Njiokiktjien C, Bos H (1994), Methylphenidate and information processing. Part 1: Differentiation between responders and nonresponders; Part 2: Efficacy in responders. *J Clin Exp Neuropsychol* 16:877-897

Goyette CH, Conners CK, Ulrich RF (1978), Normative data on revised Conners Parent and Teacher Rating Scales. *J Abnorm Child Psychol* 6:221-236

Grant D, Berg E (1948), *The Wisconsin Card Sorting Test. Directions for Administration and Scoring*. Odessa, Florida: Pschological Assessment Resources

Grodzinsky G, Diamond R (1992), Frontal lobe functioning in boys with attention deficit hyperactivity disorder. *Develop Neuropsychol* 8:427-445

Huijbregts SCJ, de Sonneville LMJ, van Spronsen FJ, Licht R, Sergeant JA (2002). The Neuropsychological Profile of Early-and Continuously Treated Phenylketonuria: Selective Attention, Vigilance, and 'Maintenance' versus 'Manipulation' - functions of Working Memory. *Neuroscience & Biobehavioral Reviews, 26*: 697-712

Kalff AC, de Sonneville LMJ, Hurks P, Hendriksen JG, Kroes M, Feron FJ, Steyaert J, van Zeben TM, Vles JS, Jolles J (2003). Low- and high-level controlled processing in executive motor control tasks in 5/6-year-old children at risk of ADHD. *J Child Psychol Psychiatry* 44: 1049-1057

Kuntsi J, Oosterlaan J, Stevenson J (2001), Psychological mechanisms in hyperactivity: I. Response inhibition deficit, working memory impairment, delay aversion, or something else? *J Child Psychol Psychiatry* 42:199-210

Kuntsi J, Stevenson J (2001), Psychological mechanisms in hyperactivity: II. The role of genetic factors. *J Child Psychol Psychiatry* 42:211-219

Laurent, A., Duly, D., Murry, P., Foussard, N., Boccara, S., Mingat, F., Dalery, J., d'Amato, T. (2001). WCST performance and schizotypal features in the first-degree relatives of patients with schizophrenia. *Psychiatry Research* 104:133-144

Leboyer M, Bellivier F, Nosten-Bertrand M, Jouvent R, Pauls D, Mallet J (1998), Psychiatric genetics: search for phenotypes. *Trends Neurosci* 21:102-105

Leckman JF, Sholomskas D, Thompson WD, Belanger A, Weissman MM (1982), Best estimate of lifetime psychiatric diagnosis: a methodological study. *Arch Gen Psychiatry* 39: 879-883

Lezak, M.D. (1983). *Neuropsychological assessment*, 2nd Edn. Oxford University Press, New York

Mirsky AF, Anthony BJ, Duncan CC, Ahearn MB, Kellam SG (1991), Analysis of the elements of attention: a neuropsychological approach. *Neuropsychol Rev* 2:109-145

Nigg JT (2001), Is ADHD a disinhibitory disorder? *Psychol Bull* 127:571-598

Nigg JT, Blaskey LG, Huang-Pollock CL, Rappley MD (2002), Neuropsychological executive functions and DSM-IV ADHD subtypes. *J Am Acad Child Adolesc Psychiatry* 41:59-66

Oosterlaan J, Logan GD, Sergeant JA (1998), Response inhibition in AD/HD, CD, comorbid AD/HD + CD, anxious, and control children: a meta-analysis of studies with the stop task. *J Child Psychol Psychiatry* 39:411-425

Pennington BF, Ozonoff S (1996), Executive functions and developmental psychopathology. *J Child Psychol Psychiatry* 37:51-87

Sattler JM (1992), *Assessment of children: WISC-III and WPPSI-R supplement*. San Diego, SA, England

Schachar R, Mota VL, Logan G, Tannock R, Klim P (2000), Confirmation of an inhibitory control deficit in ADHD. *J Abn Child Psychol* 28:227-235

Seidman LJ, Biederman J, Faraone SV, Milberger S, Norman D, Seiverd K, Benedict K, Guite J, Mick E, Kiely K (1995), Effects of family history and comorbidity on the neuropsychological performance of children with ADHD: preliminary findings. *J Am Acad Child Adolesc Psychiatry* 34:1015-1024

Seidman LJ, Biederman J, Monuteaux MC, Weber W (2000), Neuropsychological functioning in nonreferred siblings of children with Attention deficit Hyperactivity Disorder. *J Abn Child Psychol* 109:252-265

Sergeant JA, Geurts H, Oosterlaan J (2002), How specific is a deficit of executive functioning for attention- deficit/hyperactivity disorder? *Behav Brain Res* 130:3-28

Shaffer D, Fisher P, Lucas CP, Dulcan MK, Schwab-Stone ME (2000), NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC- IV): description, differences from previous versions, and reliability of some common diagnoses. *J Am Acad Child Adolesc Psychiatry* 39:28-38

Skuse DH (2001), Endophenotypes and child psychiatry. *Br J Psychiatry* 178:395-396

Slaats-Willemse D, Swaab-Barneveld S, de Sonneville L, van der Meulen E, Buitelaar J (2003), Deficient repsonse inhibition as a cognitive endophenotype of ADHD. *J Am Acad Child Adolesc Psychiatry* 42:1242-1248

Stevens JP (2002), Exploratory and confirmative factor analysis. In: *Applied multivariate statistics for the social sciences*. London, Lawrence Erlbaum Assicates, Publishers, pp. 385-471

Swaab-Barneveld H, de Sonneville L, Cohen-Kettenis P, Gielen A, Buitelaar J, Van Engeland H (2000), Visual sustained attention in a child psychiatric population. *J Am Acad Child Adolesc Psychiatry* 39:651-659

Tannock R, Schachar RJ, Carr RP, Chajczyk D, Logan GD (1989), Effects of methylphenidate on inhibitory control in hyperactive children. *J Abnorm Child Psychol* 17:473-491

Vandersteene G, Van Haassen PP, De Bruyn EEJ, Coetsier P, Pijl YL, Poortinga YH, Lutje Spelberg HC, Spoelders-Claes R, Stinissen J (1986), *WISC-R, Wechsler Intelligence Scale for Children-Revised*, Nederlandstalige uitgave. Lisse: Swets and Zeitlinger

Verhulst, F.C., Koot, J.M., Van der Ende, J. (1996). *Handleiding voor de CBCL (Child Behavior Checklist) [Manual for the CBCL]*. Afdeling Kinder- en Jeugdpsychiatry, Sophia Kinderziekenhuis/ Academisch Ziekenhuis Rotterdam/ Erasmus Universiteit Rotterdam, the Netherlands

Zametkin AJ, Rapoport JL (1987), Neurobiology of attention-deficit disorder with hyper-activity: where have we come in 50 years? *J Am Acad Child Adolesc Psychiatry* 26:676-686

Chapter 8

General Discussion, clinical implications, and future research

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a common genetic neuropsychiatric disorder that has a great impact on affected families and society in terms of academic and behavioral dysfunctioning, and financial costs (Mannuzza et al., 1989). Although candidate gene studies have found association for candidate genes of dopaminergic neurotransmission and whole genome scan studies have identified chromosomal regions that show linkage with the syndrome, the precise etiology of ADHD still remains unknown. The majority of genetic studies are grounded on a clinical symptom-based phenotype derived from reports of parents, teachers, and clinicians, and this appears not to be optimal for detecting the complex genetic underpinnings of ADHD. Therefore, research on the etiology of ADHD is increasingly focusing on the development of heritable quantitative traits that index an individual's liability to manifest ADHD, i.e. endophenotypes[1] (Almasy and Blangero, 2001).

Cognitive endophenotypes of ADHD

The studies presented in this thesis investigated potential cognitive endophenotypes of ADHD in the domain of executive functions, since it is generally accepted that deficits in these cognitive functions are central to ADHD (Pennington and Ozonoff, 1996). To study candidate endophenotypes, a selection of well-known tasks measuring different aspects of executive functioning, i.e. response inhibition, fine motor functioning, attentional control, and mental flexibility was tested in different study-designs. These aspects of executive functioning were examined in a family-genetic study design with carefully phenotyped ADHD probands with a family history of ADHD, their non-affected siblings, and 48 normal controls. Furthermore, familial clustering of those executive functions was examined in affected siblings from ADHD affected sibling pair families. It was also investigated whether executive function deficits could identify a meaningful familial subtype of ADHD.

The results strongly suggest that different aspects of executive dysfunctioning may be endophenotypes of particular promise for use in molecular studies of ADHD: deficient response inhibition, higher-order controlled motor dysfunctioning, deficient

[1] endophenotypes are latent traits that carry genetic loading and which are related indirectly to the classic behavioral symptoms as defined in DSM-IV or ICD-10 (Leboyer et al., 1998; Skuse, 2001).

attentional control, and mental inflexibility are found to reflect a genetic susceptibility to the disorder. This conclusion is based on findings indicating that behaviorally nonaffected siblings of ADHD probands experience executive function problems similar to their affected siblings (chapters 2, 3, and 6). In addition, ADHD affected siblings (from affected sibling pairs) are found to be highly similar with respect to response inhibition, higher-order controlled motor functioning and attentional control (chapter 5).

A familial- and a nonfamilial form of ADHD?

The study described in chapter 4 examines the question whether cognitive measures could differentiate between a familial and a nonfamilial subtype of ADHD. This study is conducted to replicate earlier findings from researchers who found evidence for a differentiation between those two subtypes based on cognitive dysfunctioning. The binary classification suggests that familial ADHD may be a highly biologically (genetically) based type and nonfamilial ADHD a more environmentally influenced type. A differentiation between these two subtypes would have important implications for the research on the etiology of ADHD. If measures of executive functioning might delineate a genetic subtype of ADHD, such measures could serve as markers for molecular genetic studies. However, our results did not lend substantial support to the hypothesis that executive dysfunctioning would characterise a distinct, genetic form of ADHD. According to the current view about the etiology of ADHD, it seems more likely that a non-familial form of ADHD does not exist at all, and that ADHD should be considered as the extreme of a behavior with variable genetic liability and expression throughout the population (Levy et al., 1997). In line with this view, ADHD children with an evident family history of the disorder may carry more risk genes, and/ or may be more exposed to an environment that elucidates ADHD and the related cognitive impairments than ADHD children without such an evident family status of the disorder. If this is true, we would expect that the disorder-related executive function deficits differ in severity according to the extent of the genetic liability and influence of a gene-environment interaction. However, in the present study, the performances of the familial ADHD group were not significantly worse than those of the non-familial group, except for the performance on a measure of attentional control. Should we conclude then that attentional control can reflect the extent of liability (genetic and environmental) to ADHD? Results of previous studies described in this thesis are in line with this sugestion and showed that attentional control seems to be a core deficit in ADHD.

Anyhow, the studies presented in this thesis should be viewed as preliminary research, providing the basis for new integrative and multidisciplinary approaches in the process of unravelling the causes of ADHD. Therefore, it is too early to conclude that attentional control can differentiate between ADHD children with -, and without a family history of the disorder, in other words, between children that have a high- or a low liability to ADHD.

No evidence for a general executive dysfunctioning as an endophenotype of ADHD

So far, neuropsychological studies on ADHD concentrated mainly on response inhibition, following Barkley´s notion that deficient response inhibition should be viewed as the central impairment in ADHD. In Barkley's model, a primary deficit in response inhibition leads to secondary impairments in executive functions that are partially dependent on inhibition for their effective execution. See for an overview Barkley (1997). Based on our findings, we suggest that it seems to be more complex than Barkley suggests. In our view, deficits in other aspects of executive functioning may also be central in ADHD. The findings presented in chapter 7 support this suggestion. In this chapter, we describe the results of a factor analysis providing evidence that three factors can summarize the executive functions that are central in ADHD, namely attentional and motor control, mental flexibility, and response inhibition. The first factor, attentional and motor control, showed the highest explained variance, indicating that the underlying measures cover an important part of the cognitive functions in the domain of executive functioning. So, these findings are not in line with Barkley's view that deficient response inhibition is central in ADHD. The findings suggest that inhibition may be one of the executive functions that should be investigated in further research on the etiology of ADHD. Based on the present findings, we are even inclined to suggest that attentional and motor control may be the core cognitive deficits in ADHD and a valuable candidate endophenotype of the disorder. This assumption is consistent with results from other studies reporting that measures of attentional control differentiate best between hyperactives and controls (Kuntsi et al., 2001), and that they share common genetic effects with hyperactivity (Kuntsi and Stevenson, 2001). Furthermore, since the three extracted factors did show minimal overlap, we may conclude that a *general* executive function deficit is unlikely to constitute an endophenotype of ADHD.

This conclusion may also have implications for clinical practice with respect to the assessment of cognitive strengths and weaknesses, and treatment programs. Assessment of the inability to inhibit undesired responses appeared not to be conclusive. In line with our findings, the cognitive assessment should include tasks measuring the three different aspects of executive functioning reported above. Furthermore, it is recommended to focus on attentional and motor control, i.e. the variability in response time during time on task and the flexibility in motor output. A detailed profile of strengths and weaknesses with respect to the different aspects of executive functioning may provide a basis for the development of specific treatment programs, the evaluation of treatment, and the development of the individual from childhood to adulthood. For example, if a child diagnosed with ADHD or with the genetic liability to this disorder experiences problems in attentional control, medical treatment (methylphenidate) and therapeutic interventions could be specified to tackle this particular problem.

Having the endophenotype but not the phenotype: genetic- and environmental influences

Our finding that siblings of ADHD probands experience executive function problems similar to their affected siblings, although they do not display the behavioral symptoms is remarkable. This may indicate that what is inherited by individuals at enhanced risk of ADHD because of genetic liability is not the disorder itself but a state of vulnerability manifested by executive dysfunctioning (vulnerability hypothesis). Thus, the genetically acquired state of liability to ADHD can exist without the expression of the behavioral symptoms of the disorder. In chapter 6, two plausible hypotheses are discussed, the "risk-gene threshold hypothesis", and the "environmental influence hypothesis". The first hypothesis proposes that the non-affected siblings carry sufficient risk genes to develop ADHD-related deficits in executive functioning, but not enough to show the behavioral symptoms. The "environmental influence hypothesis" states that the affected and non-affected siblings have the same genetic liability, but a different expression of the disorder due to other influences, i.e. environmental or genetic factors. One could hypothesize that the non-affected siblings did not develop the behavioral symptoms of ADHD because of the absence of risk factors, or the presence of protective factors. Those factors can be divided roughly in three categories: 1) characteristics of the individual, and 2) characteristics of the environment. Characteristics of the individual include psychological factors such as the (in)ability to adapt to change, to cope with stress, and to express feelings easily (Grizenko and Pawliuk, 1994). The extent of social support from peer groups or family members, parental warmth, and family adversity in general are potential environmental factors (Coie et al., 1993). Characteristics of the environment also include the presence or absence of complications during pregnancy, delivery, and early infancy (Samudra and Cantwell, 1999). Individual and environmental factors may even interact: Responsive, sensitive parenting behaviors (environment) can serve as protective factors that facilitate the development of self-regulation (individual) and may attenuate ADHD symptoms in biologically predisposed children (Johnston and Mash, 2001).

In addition, protective and risk factors may interact in complex ways to prevent the development of ADHD symptoms: the protective factors may modify the effects of risk factors, or even prevent the occurrence of risk factors. Also the timing of these interactions in an individual's development matters. Risk- and protective factors and even the basic genetic influences may act differentially at varying points in the development (Samudra and Cantwell, 1999). The brain changes constantly throughout lifespan due to changes of gene functions and environmental changes, and the interactions between them (Plomin et al., 1997). The results of a recent study emphasizes the importance of incorporating environmental cofactors in genetic studies on ADHD after demonstrating that ADHD was associated with DAT polymorphism but only when the child also had exposure to maternal prenatal smoking (Kahn et al., 2003). Future research should move away from studies of single causative factors, and

should concentrate on the complex interaction of risk and protective factors, both genetic and environmental in nature.

If the vulnerability-hypothesis stated above is true and the genetic liability for the disorder of non-affected siblings results in cognitive impairments but not in behavioral symptoms, measures of executive functioning are less useful to differentiate between ADHD and normal controls since the clinical phenotype and objective cognitive endophenotype do not always co-occur. However, cognitive assessment in clinical practice should not be used as a diagnostic instrument, but as an examination of disorder-related strengths and weaknesses. Cognitive assessment can help estimate the impact of the executive functioning deficits on academic performances and development. Furthermore, it can be used to formulate and evaluate treatment- and monitoring programs.

Further research

Quantitative determination of cognitive deficits that can serve as endophenotypes seems to be a valuable approach to uncover the causal pathways of ADHD. Despite the promising unequivocal results of the present studies, it is too early to draw firm conclusions. Since the present sample sizes were relatively small, replication of the findings in larger samples is essential. Families with two ADHD siblings and one non-affected child (chapters 2, 3, and 6) are scarce and ADHD children without a family history of the disorder (chapter 4) are hard to find. National and even international cooperation is needed for the recruitment of subjects. For future research, it is recommended to repeat the study described in chapter 7 in a new, independent and larger database. Subsequent to an explorative factor analysis, the cognitive measures described in this thesis should be entered in a confirmative factor analysis to specify which measures will load on which factors, i.e. aspects of executive functioning. Confirmative factor analysis can verify our hypothesis that three distinct aspects of executive functioning are central in ADHD: attentional and motor control, mental flexibility, and response inhibition. Next, the three factors should be examined in a large sample of ADHD probands, their non-affected siblings, and normal controls to examine whether they differentiate significantly between ADHD probands and normal controls. Furthermore, the presumed intermediate position of the non-affected siblings between the ADHD probands and controls should be verified.
In this thesis, two of the three main clinical characteristics of ADHD according to DSM-IV are investigated, i.e. attention and impulsivity (disinhibition). We did not report on hyperactivity. In the near future, we will start analysing data from an objective measure of hyperactivity during time on task (Optical tracking and attention test, OPTAX). This program measures the child's ability to sit still during cognitive testing. Previous research indicates that locomotor hyperactivity may be a primary symptom

of ADHD. Children with ADHD are found to move their head about two times more often, and about three times as far as control children (Teicher et al., 1996). Furthermore, locomotor hyperactivity has been associated with dopaminergic dysfunction in animal models (Cardinal et al., 2001; Giros et al., 1996). It is even suggested to be a candidate endophenotype of ADHD (Castellanos and Tannock, 2002).

An important issue that needs further consideration is the relation between the clinical behavioral symptoms and cognitive functions. It has been hypothesised that inattention and hyperactivity/ impulsivity may be caused by different sets of genes (Rohde et al., 2001). Based on our finding that cognitive dysfunctioning may reflect a genetic liability to ADHD, we would suggest that a child with clinical inattention might be characterised by cognitive deficits different from those in a child with predominantly hyperactive/ impulsive problems. If so, cognitive assessment can help to define homogeneous subgroups for molecular genetic studies. With respect to those molecular genetic studies, clearly defined cognitive endophenotypes can be used in linkage analyses of candidate regions for ADHD. The use of cognitive measures can help stratify the genetic vulnerability to ADHD across all members of ADHD families prior to linkage.

Conclusion

The studies described in this thesis provide substantial evidence for three distinct cognitive endophenotypes of ADHD in the domain of executive functioning: 1) attentional and motor control, 2) mental flexibility, and 3) response inhibition. See figure 1 for a neurodevelopmental model of ADHD to illustrate the role of these endophenotypes in the etiology of ADHD. The studies presented in this thesis demonstrate that both clinicians and researchers are recommended to concentrate on these dif-

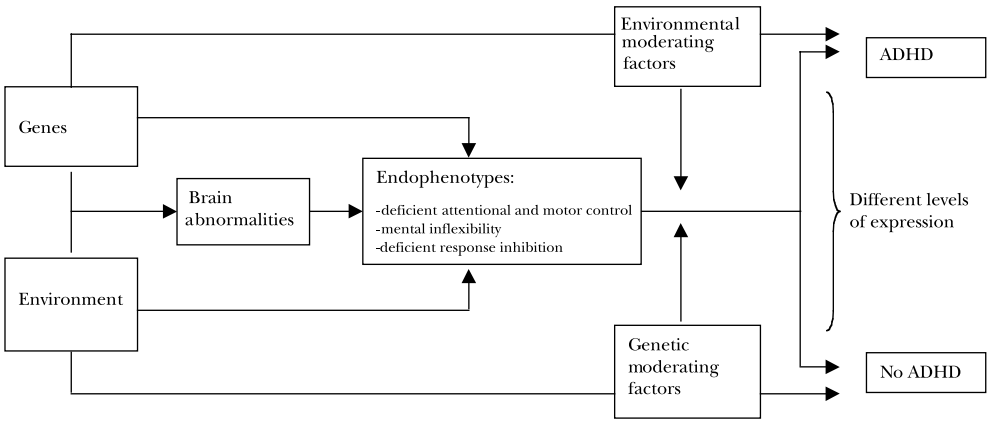

Figure 1. Neurodevelopmental model of ADHD, derived from Cornblatt and Malhotra's model of schizophrenia (2001)

ferent aspects of executive functioning as central deficits in ADHD. Since sample sizes were relatively small, the studies should be replicated in larger, independent samples. Nevertheless, the present studies can be viewed as the basis for new integrative research on cognitive endophenotypes of ADHD that aims to unravel the complex etiology of ADHD.

References

Almasy L, Blangero J (2001), Endophenotypes as quantitative risk factors for psychiatric disease: rationale and study design. *Am J Med Genet* 105:42-44

Barkley RA (1997), Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychol Bull* 121:65-94

Buitelaar, J. K. (2002), Epidemiology of Attention-deficit/Hyperactivity Disorder: what have we learned over the last decade? In: *Hyperactivity Disorders*, Sandberg S, ed. Cambridge: Cambridge University Press, pp 30-63

Cardinal RN, Pennicott DR, Sugathapala CL, Robbins TW, Everitt BJ (2001), Impulsive choice induced in rats by lesions of the nucleus accumbens core. *Science* 292:2499-2501

Castellanos FX, Tannock R (2002), Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. *Nat Rev Neurosci* 3:617-628

Coie JD, Watt NF, West SG, Hawkins JD, Asarnow JR, Markman HJ, Ramey SL, Shure MB, Long B (1993), The science of prevention. A conceptual framework and some directions for a national research program. *Am Psychol* 48:1013-1022

Cornblatt BA, Malhotra AK (2001), Impaired attention as an endophenotype for molecular genetic studies of schizophrenia. *Am J Med Genet* 105:11-15

Giros B, Jaber M, Jones SR, Wightman RM, Caron MG (1996), Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. *Nature* 379:606-612

Grizenko N, Pawliuk N (1994), Risk and protective factors for disruptive behavior disorders in children. *Am J Orthopsychiatry* 64:534-544

Johnston C, Mash EJ (2001), Families of children with attention-deficit/hyperactivity disorder: review and recommendations for future research. *Clin Child Fam Psychol Rev* 4:183-207

Kahn RS, Khoury J, Nichols WC, Lanphear BP (2003), Role of dopamine transporter genotype and maternal prenatal smoking in childhood hyperactive-impulsive, inattentive, and oppositional behaviors. *J Pediatr* 143:104-110

Kuntsi J, Oosterlaan J, Stevenson J (2001), Psychological mechanisms in hyperactivity: I. Response inhibition deficit, working memory impairment, delay aversion, or something else? *J Child Psychol Psychiatry* 42:199-210

Kuntsi J, Stevenson J (2001), Psychological mechanisms in hyperactivity: II. The role of genetic factors. *J Child Psychol Psychiatry* 42:211-219

Leboyer M, Bellivier F, Nosten-Bertrand M, Jouvent R, Pauls D, Mallet J (1998), Psychiatric genetics: search for phenotypes. *Trends Neurosci* 21:102-105

Levy F, Hay DA, McStephen M, Wood C, Waldman I (1997), Attention-deficit hyperactivity disorder: a category or a continuum? Genetic analysis of a large-scale twin study. *J Am Acad Child Adolesc Psychiatry* 36:737-744

Mannuzza S, Klein RG, Konig PH, Giampino TL (1989), Hyperactive boys almost grown up. IV. Criminality and its relationship to psychiatric status. *Arch Gen Psychiatry* 46:1073-1079

Pennington BF, Ozonoff S (1996), Executive functions and developmental psychopathology. *J Child Psychol Psychiatry* 37:51-87

Plomin R, DeFries J, et al. (1997), General cognitive ability. In: *Behavioral Genetics* (pp.148-149). W.H. Freeman and company. New York

Rohde LA, Barbosa G, Polanczyk G, Eizirik M, Rasmussen ER, Neuman RJ, Todd RD (2001), Factor and latent class analysis of DSM-IVADHD symptoms in a school sample of Brazilian adolescents. *J Am Acad Child Adolesc Psychiatry* 40:711-718

Samudra K, Cantwell DP (1999), Risk factors for Attention-Deficit/ Hyperactivity Disorder. In: *Handbook of disruptive behavior disorders,* Quay and Hogan. Kluwer Academic/ Plenium Publishers, New York

Skuse DH (2001), Endophenotypes and child psychiatry. *Br J Psychiatry* 178:395-396

Teicher MH, Ito Y, Glod CA, Barber NI (1996), Objective measurement of hyperactivity and attentional problems in ADHD. *J Am Acad Child Adolesc Psychiatry* 35:334-342

Summary

Attention Deficit Hyperactivity Disorder (ADHD) is an impairing childhood-onset neuropsychiatric disorder characterized by inattention, hyperactivity and impulsivity. It is among the most commonly diagnosed and extensively studied psychiatric syndromes and affects 3 to 5% of all school-aged children. Family and twin studies indicate that ADHD is highly influenced by (multi) genetic factors, with heritability ranging from 0.6 to 0.9. Although association has been found for three candidate genes of dopaminergic neurotransmission (DRD4, DRD5, DAT-1) and suggestive evidence has been reported for linkage on chromosomes 16p13, 17p11, 7p and 15q, the precise genetic constellation of ADHD is still unknown.

One of the greatest challenges in studying the genetic basis of psychiatric disorders is to find appropriate ways to define the relevant phenotype. It is increasingly recognized that the traditional nosological categories described in the DSM-IV (APA, 1994) and ICD-10 (WHO, 1994) are suboptimal when it comes to describing who is affected and carrying susceptibility genes and who is not. In order to unravel the genetic constellation of ADHD, emphasis should be on the description of endophenotypes. Endophenotypes are latent traits that carry genetic loading and which are related indirectly to the classic behavioral symptoms as defined in DSM-IV or ICD-10. Endophenotypes composed of cognitive ability profiles are valuable in our search for the genetic correlates of ADHD, because cognitive functioning as measured by response time tasks for example, is an objective measure of the functioning of underlying mechanisms rather than of overall behavioral outcome. Furthermore, cognitive tasks are easy to administer to individuals of different ages, and are cheap and harmless compared with endophenotypic measures that are physiological, structural or functional in nature. Cognitive measures in the domain of executive functioning are most amenable in our search for endophenotypes of ADHD, since deficits in these cognitive functions are viewed as the central impairments in this disorder.

The main aim of this thesis was to uncover candidate endophenotypes of ADHD. The underlying rationale was that genetic factors might contribute to executive function problems in ADHD. Thus executive function deficits may reflect a genetic factor that confers a biological vulnerability to ADHD. If this is true, ADHD affected sibling pairs are expected to show familial clustering (i.e. significant association) of executive functions. Furthermore, if the endophenotype and the resulting phenotype are distributed along a continuum as suggested by different researchers, family members of ADHD probands are expected to display some degree of impaired executive functioning. To study candidate endophenotypes of ADHD, a selection of well-known tasks measuring different aspects of executive functioning, i.e. response inhibition, fine motor functioning, attentional control, and mental flexibility, was tested in different study-designs.

The **chapters 2 and 3** focused respectively on response inhibition and fine motor functioning as candidate endophenotypes of ADHD. These aspects of executive functioning were examined in a family-genetic study design with 25 carefully phenotyped ADHD probands with a family history of ADHD, their non-affected siblings ($n = 25$),

and 48 normal controls. The controls were matched with the non-affected sibling group for age, IQ, and sex (age ranged from 6 to 17 years in all groups). The non-affected siblings were compared with the ADHD probands and with the controls on three measures of response inhibition (**chapter 2**), and on two measures of fine motor functioning that differed significantly in complexity (**chapter 3**). It was hypothesized that the non-affected siblings of ADHD probands would exhibit deficits in response inhibition and fine motor functioning intermediate between that of the controls and the ADHD probands. The results revealed significant differences in cognitive performance between the ADHD probands and normal controls (chapter 2 and 3). The most striking finding from the study on response inhibition (chapter 2) was that the non-affected siblings had results similar to those of the ADHD probands, which demonstrated that deficient response inhibition might constitute a cognitive endophenotype of ADHD. The results of the study on motor functioning (chapter 3) revealed that the non-affected siblings experienced fine motor problems similar to those of their affected siblings, but only in the more complex movements that required higher-order cognitive processing (i.e. high levels of executive functioning). In conclusion, the findings from both studies suggest that deficient response inhibition and higher-order controlled motor deficits in ADHD may be influenced by genetic factors, and may therefore be valuable candidate endophenotypes of ADHD. Support was also found for the notion that ADHD should be viewed as a dimensional trait, or even as the extreme of a behavior with genetic liability and expression throughout the population. At the end of the chapters 2 and 3 important issues like the specificity of the reported cognitive deficits for ADHD, and potential related brain circuits are discussed.

The study described in **chapter 4** investigated whether executive function deficits could identify a meaningful familial subtype of ADHD. This hypothesis was based on previous reports about differences between familial ADHD (i.e. with a family history of the disorder) and nonfamilial ADHD (i.e. without a family history of the disorder): Children with a familial form of the disorder have been found to display more executive function deficits than children with a nonfamilial form. If measures of executive functioning might indeed delineate a familial subtype of ADHD, such measures could serve as markers for molecular genetic studies. To examine the hypothesis that familial ADHD may represent a distinct and meaningful subtype of ADHD characterised by executive dysfunctioning, the cognitive performance of 29 ADHD probands with a family history of ADHD was compared with the performance of 26 ADHD probands without a family history of the disorder, and with that of 28 controls. Different measures of response inhibition, higher-order controlled motor functioning and attentional control were used. Contrary to the hypothesis, none of the executive functions, except for one aspect of attentional control, could differentiate between the familial- and nonfamilial ADHD groups. Thus, the results barely supported the idea that executive dysfunctioning might delineate a familial subtype of ADHD. Considering the strong indications that ADHD is highly hereditary in nature, the authors suggested

that a non-genetic form of the disorder might not exist at all. The findings for one aspect of attentional control, fluctuation in tempo during time on task, showed significant effects, which was in line with other studies reporting that this measure is a valuable candidate endophenotype of ADHD. Therefore, it was argued that this aspect of executive functioning should be used in future family-genetic studies to refine the phenotype of the disorder.

The study in **chapter 5** examined familial clustering of executive functioning to provide support for the notion that different aspects of executive dysfunctioning might constitute potential endophenotypes to ADHD. The underlying rationale was: if deficient executive functioning would reflect genetic underpinnings, then ADHD affected siblings were expected to show significant association for measures of executive functioning. Tasks measuring response inhibition, fine motor functioning, and attentional control were administered to 52 ADHD affected sibling pairs ranging in age from 6 to 18 years. Significant sibling correlations were found for measures of these aspects of executive functioning. With respect to fine motor functioning, only motor skills that made high demands on executive functioning (i.e. higher-order controlled motor functioning) showed significant sibling correlations. It was concluded that response inhibition, higher-order controlled motor functioning and attentional control seemed to cluster in ADHD affected siblings. These findings were in line with those from our previous studies in that it provided evidence for the hypothesis that deficits in response inhibition, higher-order controlled motor functioning, and attentional control might reflect endophenotypes of ADHD.

The findings reported in the chapters 2 up to 5 motivated the authors to examine attentional control, and mental flexibility (another important aspect executive functioning) in the family-genetic study design that is used in the first two studies (chapter 2 and 3). Attentional control was not yet investigated in a study-design with ADHD probands, non-affected siblings and normal controls. Although other research groups studied mental flexibility in family-genetic perspective before, significant mental flexibility problems have not been found in non-affected siblings of ADHD probands. Therefore, the performance on measures of attentional control and mental flexibility were examined in behaviorally non-affected siblings of ADHD probands ($n = 25$), and compared to the performance of their ADHD siblings ($n = 25$), and to that of normal controls ($n = 48$) (**chapter 6**). It was hypothesized that the cognitive performance of the ADHD probands, non-affected siblings and normal controls could be arranged on a continuum, which would be in line with the notion that ADHD should be viewed as a dimensional trait rather than a pathological category. The results revealed that the performance of the non-affected siblings did not differ from that of the ADHD probands on attentional control, nor on most measures of mental flexibility. The linear changes of these measures across the groups reflected an intermediate position of the non-affected siblings between the ADHD probands and controls. It was concluded that attentional control and mental flexibility problems might be indicators of the familial predisposition to ADHD. The finding that behaviorally non-affected siblings

of ADHD probands displayed ADHD-related executive function deficits suggests that what is inherited by individuals at enhanced risk of ADHD because of genetic liability is not the disorder itself but a state of vulnerability manifested by executive dysfunction. This notion is discussed thoroughly at the end of the chapter.

Chapter 7 presented the results of a post hoc principal component analysis in which the cognitive measures that are used in the experimental studies (chapter 2 up to 6) were included to identify interpretable underlying constructs of executive functioning. The hypothesis was that distinct interpretable constructs reflecting different aspects of executive functioning could be defined in a sample of ADHD siblings. The PCA revealed that a three-factor model was the best solution to summarize the data. The first factor, *attentional and motor control* reflected stability of information processing and motor execution. The second factor, *mental flexibility* revealed high loadings on all measures of the Wisconsin Card Sorting Test (WCST). The third factor, *response inhibition* reflected the ability to inhibit undesired responses. Although the ratio of variables to cases was marginal, the high factor loadings and the minimal overlap between the factors provided evidence for the presence of three distinct constructs of executive functioning in ADHD. The first factor, attentional and motor control had the highest explained variance, indicating that the underlying measures cover an important part of the cognitive functions in the domain of executive functioning. Since the number of cases in the factor analysis was rather small to draw firm conclusions, it was recommended for future research to conduct a confirmative factor analysis in an independent, larger database.

Finally, **chapter 8** provided a discussion of the overall findings, and implications for future research and clinical practice. In short, substantial evidence is found for three distinct cognitive endophenotypes of ADHD in the domain of executive functioning: attentional and motor control, mental flexibility, and response inhibition. One of the most important recommendations is that both clinicians and researchers should concentrate on these different aspects of executive functioning as central deficits in ADHD. The present studies provide a basis for new multidisciplinary research on the etiology of this complex, but fascinating disorder.

Samenvatting

Kinderen met ADHD (Attention Deficit Hyperactivity Disorder) worden gekenmerkt door een verhoogde mate van hyperactiviteit, impulsiviteit en inattentie. ADHD komt bij ongeveer 3-5% van de schoolgaande kinderen voor en leidt vaak tot problemen in het dagelijks functioneren zoals leerproblemen, voortijdig schoolverlaten, middelenmisbruik (alcohol, drugs), en antisociaal gedrag. ADHD en de genoemde problemen blijven in veel gevallen bestaan tot in de volwassenheid. Het is dus van groot belang de oorzaak en pathofysiologie van deze stoornis te onderzoeken. Uit onderzoek is reeds bekend dat genetische invloeden een belangrijke rol spelen in de etiologie van ADHD; deze stoornis zou voor zo'n 60-80% bepaald worden door genetische factoren. Verder weten we dat de kans op ADHD bij broertjes en zusjes van een kind met ADHD ongeveer 3 maal zo groot blijkt te zijn als in de gewone populatie.

Ondanks het feit dat er duidelijke aanwijzingen bestaan voor de betrokkenheid van dopaminerge genen bij het ontstaan van ADHD (DRD4, DRD5, DAT-1), is nog niet bekend welke genen precies een rol spelen en hoe deze interacteren met de omgeving. Wanneer wij onze kennis over het samenspel van genetische invloeden en omgevingsinvloeden kunnen vergroten, kan dit leiden tot meer geschikte mogelijkheden voor nauwkeuriger fenotypering, diagnostiek, behandeling en preventie van ADHD. Om de genetische basis van ADHD te kunnen ontrafelen is het van groot belang het fenotype van de stoornis helder te definiëren. Het huidige classificatiesysteem voor psychiatrische stoornissen, de DSM-IV is niet ontworpen om te bepalen wie ADHD óf de genetische kwetsbaarheid voor deze stoornis heeft en wie niet. Bovendien zijn de gedragsrapportages van behandelaren, ouders en leerkrachten op basis van de DSM-IV criteria subjectief, d.w.z. gekleurd door hun persoonlijke invalshoek. Om die reden is het van belang om op zoek te gaan naar endofenotypen: kenmerken ("traits") die door genen worden beïnvloed en alleen indirect gerelateerd zijn aan de klassieke ADHD-symptomen volgens DSM-IV. Stoornissen in het cognitief functioneren zijn uitermate geschikt als endofenotypen, omdat ze de werking van hersenfuncties objectief in kaart brengen en niet gerelateerd zijn aan de gedragssymptomen. Cognitieve taken zijn bovendien makkelijk af te nemen, goedkoop en minder belastend in vergelijking met fysiologische- en imaging (beeldvormende) technieken. In het onderzoek naar endofenotypren van ADHD richt men zich met name op de executieve functies, d.w.z. uitvoerende controle functies, ofwel cognitieve functies die het gedrag sturen, omdat stoornissen in het executief functioneren gezien worden als de kernproblemen in ADHD.

De studies die beschreven worden in dit proefschrift hebben tot doel potentiële cognitieve endofenotypen in kaart te brengen. De onderliggende gedachte is dat stoornissen in het executief functioneren een genetische kwetsbaarheid voor ADHD weerspiegelen. Als dit zo is, verwachten we een "familiaire clustering" van executief functioneren in sibparen[1] met ADHD, d.w.z. een significante correlatie tussen twee broertjes of zusjes (of tussen een broertje en een zusje) met ADHD. En, wanneer het

[1] twee kinderen met een bepaalde stoornis in één gezin vormen een sibpaar. Afzonderlijk worden zij siblings genoemd.

endofenotype en het fenotype op een continuüm liggen zoals door diverse onderzoekers wordt gesuggereerd, verwachten we dat familieleden van de ADHD siblings in enige mate defecten in het executief functioneren zullen vertonen. Om deze verwachtingen te toetsen, zijn diverse cognitieve taken geselecteerd die respons inhibitie[2], fijnmotorische vaardigheden, stabiliteit van de aandacht, en mentale flexibiliteit[3] meten. Er zijn verschillende onderzoeksontwerpen gebruikt om kandidaat endofenotypen te kunnen ontdekken in gezinnen met meerdere ADHD kinderen.

De **hoofdstukken 2 en 3** richten zich op respectievelijk respons inhibitie en fijnmotorische vaardigheden als kandidaat endofenotypen van ADHD. Deze aspecten van het executief functioneren zijn onderzocht in een familiegenetisch studiedesign met 25 zorgvuldig gefenotypeerde ADHD kinderen met een familiaire geschiedenis van de stoornis, hun niet-aangedane siblings (zonder gedragssymptomen, $n = 25$), en 48 controle kinderen. De controles zijn met de niet-aangedane siblings gematched op leeftijd, geslacht en IQ. De leeftijd van de kinderen in de drie groepen varieerde van 6 tot 17 jaar. De niet-aangedane siblings, de ADHD kinderen en de controles zijn vergeleken op drie respons inhibitie-maten (**hoofdstuk 2**) en op twee maten voor fijnmotorische vaardigheden (**hoofdstuk 3**). De hypothese was dat de niet-aangedane siblings stoornissen in de respons inhibitie en in de fijnmotorische vaardigheden vertonen, maar in mindere mate dan hun aangedane siblings. Verwacht werd dat hun prestaties temidden van die van de ADHD siblings en de controle kinderen zouden liggen. De resultaten lieten significante verschillen zien in cognitieve prestaties tussen de ADHD siblings en de controles (hoofdstukken 2 en 3). De belangrijkste en meest opvallende bevinding van de studie in hoofdstuk 2 was dat de niet-aangedane siblings even slecht presteerden als hun aangedane siblings. Deze bevinding geeft duidelijke aanwijzingen voor het bestaan van een cognitief endofenotype in de vorm van respons inhibitie stoornissen. De resultaten van de studie in hoofdstuk 3 toonden aan dat niet alleen de aangedane siblings maar ook de niet-aangedane siblings fijnmotorische problemen ondervonden, maar dan alleen in de motorische vaardigheden die sterk beroep doen op het executief functioneren. Concluderend kan gesteld worden dat ADHD-gerelateerde stoornissen in respons inhibitie en in fijnmotorische vaardigheden worden beïnvloed door genetische factoren, hetgeen betekent dat deze vormen van cognitief disfunctioneren gezien kunnen worden als geschikte kandidaat endofenotypen van ADHD. De bevindingen ondersteunen tevens het idee dat ADHD gezien moet worden als een dimensionele “trait”, of zelfs als een extreme vorm van gedrag dat gekenmerkt wordt door verschillende niveaus van genetische kwetsbaarheid en ernst van symptomen verspreid over de bevolking. Aan het einde van de hoofdstukken 2 en 3 worden hersengebieden besproken die mogelijk verantwoordelijk zijn voor de gevonden cognitieve problemen in ADHD. Verder worden de specificiteit van de gevonden cognitieve stoornissen voor ADHD, en de onderlinge relatie tussen de gevonden stoornissen in executief functioneren bediscussieerd.

[2] vermogen om ongewenst gedrag te stoppen.
[3] vermogen om gedrag aan te passen aan een veranderende omgeving.

In de studie die beschreven wordt in **hoofdstuk 4** staat de vraag centraal of stoornissen in het executief functioneren een relevant familiair subtype van ADHD kunnen onderscheiden. Deze hypothese was gebaseerd op eerder onderzoek naar de verschillen tussen een veronderstelde familiaire vorm (met aangedane familieleden) en een veronderstelde non-familiaire vorm van ADHD (zonder aangedane familieleden). Diverse onderzoekers hebben in het verleden aanwijzingen gevonden dat kinderen met een familiaire vorm van de stoornis meer problemen in het executief functioneren ondervinden dan kinderen met een non-familiaire vorm. Als executieve functiematen inderdaad een familiair subtype van ADHD kan onderscheiden, kunnen dergelijke maten gebruikt worden als markers voor moleculair-genetische studies. Om de hypothese te toetsen dat familiaire ADHD een duidelijk omlijnd apart subtype is dat gekarakteriseerd wordt door stoornissen in het executief functioneren, zijn de cognitieve prestaties van 26 ADHD kinderen met een familiaire geschiedenis van de stoornis vergeleken met die van 26 ADHD kinderen zonder een dergelijke familiaire geschiedenis, en met de prestaties van 28 controlekinderen. Diverse respons inhibitiematen, en tests voor motorische vaardigheden die sterk beroep doen op de executieve functies en taken die de stabiliteit in de aandacht meten, zijn afgenomen bij deze groepen kinderen. In tegenstelling tot de hypothese was geen enkele maat, behalve een maat voor stabiliteit van de aandacht, in staat om te differentiëren tussen de familiaire- en non-familiaire ADHD groepen. Deze resultaten steunen dus nauwelijks de hypothese dat executieve functies een familiair subtype van ADHD onderscheiden dat afwijkt van een non-familiair subtype. Gezien de sterke aanwijzingen voor genetische invloeden op het ontstaan van ADHD, wordt gesuggereerd dat een non-familiare/ niet-genetische vorm van ADHD wellicht niet eens bestaat. Op deze suggestie wordt in de discussie van dit hoofdstuk nader ingegaan. De bevinding dat één maat voor stabiliteit van de aandacht, namelijk fluctuatie in tempo tijdens een volgehouden aandachttaak, een significant effect liet zien, is in overeenstemming met de resultaten van andere studies die aangeven dat dit aspect van executief functioneren mogelijk een geschikt endofenotype is. Om die reden wordt aan het einde van hoofdstuk 4 geadviseerd deze cognitieve maat te gebruiken in toekomstige studies die tot doel hebben het ADHD fenotype te verfijnen.

De studie in **hoofdstuk 5** richt zich op familiaire clustering van executieve functies in een sample met 104 ADHD siblings uit 52 aangedane sibpaar-families. Uitgaande van de aanname dat stoornissen in het executief functioneren een genetische kwetsbaarheid voor ADHD weerspiegelen (zie eerdere resultaten), verwachtten we significante sibling-correlaties te zien voor de diverse executieve functiematen. Bij deze siblings (variërend in leeftijd van 6 tot 18 jaar) zijn respons inhibitiematen en taken voor fijnmotorische vaardigheden en stabiliteit in de aandacht afgenomen. In overeenstemming met de hypothese werden significante sibling correlaties gevonden voor deze maten van executief functioneren. De bevindingen voor de fijnmotorische vaardigheden lieten alleen significante associatie tussen de siblings zien voor motorische vaardigheden die een sterk beroep doen op het executief functioneren. Op

basis van de resultaten werd geconcludeerd dat respons inhibitie, fijnmotorische vaardigheden die sterk beroep doen op het executief functioneren, en stabiliteit in de aandacht, familiaire clustering laten zien in ADHD siblings. Deze conclusie is in overeenstemming met eerdere bevindingen in dit proefschrift die aantonen dat stoornissen in deze aspecten van het executief functioneren geschikte kandidaat-endofenotypen van ADHD zijn.

De bevindingen zoals beschreven in de hoofdstukken 2 tot en met 5 vormden de aanzet tot het uitvoeren van een familie-genetische studie waarin stabiliteit in de aandacht en mentale flexibiliteit (een ander belangrijk aspect van het executief functioneren) werden onderzocht (**hoofdstuk 6**). Stabiliteit in de aandacht was nog nooit onderzocht in een dergelijk studie-design met ADHD siblings, hun niet-aangedane siblings en controle kinderen. Ondanks het feit dat mentale flexibiliteit reeds in familie-genetisch perspectief is bestudeerd door andere onderzoeksgroepen, is nog niemand erin geslaagd significante mentale flexibiliteitproblemen aan te tonen in de niet-aangedane siblings van ADHD kinderen. Om die reden zijn de prestaties op maten voor de stabiliteit in de aandacht en mentale flexibiliteit bekeken in niet-aangedane siblings van ADHD kinderen (n = 25), en vergeleken met die van de aangedane kinderen (n = 25) en controle kinderen (n = 48). De hypothese was dat de cognitieve prestaties van de ADHD kinderen, de niet-aangedane siblings en de controles op een continuüm liggen, met de ADHD kinderen aan het ene uiterste en de controlekinderen aan het andere uiterste. Dit zou in overeenstemming zijn met het idee dat ADHD gezien moet worden als een dimensionele "trait" in plaats van een pathologische categorie. Uit de resultaten bleek dat de niet-aangedane siblings niet verschilden van de aangedane siblings op de maten voor stabiliteit van de aandacht, en op de meeste mentale flexibiliteitmaten. Een lineair verband toonde aan dat de niet-aangedane siblings een middenpositie innamen temidden van de ADHD siblings en de controle kinderen. Op basis van de resultaten werd geconcludeerd dat stabiliteit in de aandacht en mentale flexibiliteit geschikte indicatoren zouden zijn voor een familiaire of genetische kwetsbaarheid voor ADHD. De bevinding dat niet-aangedane siblings van ADHD kinderen ADHD-gerelateerde stoornissen in het executief functioneren lieten zien terwijl zij geen klinische symptomen hebben, suggereert dat wat aangeboren is bij mensen met een verhoogd risico op ADHD vanwege een genetische kwetsbaarheid niet de stoornis zelf is, maar een bepaalde vorm van kwetsbaarheid die gekenmerkt wordt door stoornissen in het executief functioneren. Deze suggestie wordt uitgebreid besproken in de discussie van hoofdstuk 6.

In **hoofdstuk 7** wordt verslag gedaan van een principale componenten analyse (PCA) in een groep ADHD siblings. In deze analyse zijn alle cognitieve maten onderzocht die in voorgaande experimentele studies zijn gebruikt (zie de hoofdstukken 2 tot en met 6). Het doel van deze analyse was om één of meerdere constructen te definiëren die de diverse executieve functiematen weerspiegelden. Uit de PCA kwam naar voren dat de cognitieve maten het best werden samengevat in een drie-factor model. De eerste factor, *controle over de aandacht en motorische output ("attentional and*

motor control") reflecteert stabiliteit in de informatieverwerking en motorische output. De tweede factor, *mentale flexibiliteit,* weerspiegelt het vermogen om het gedrag aan te passen aan een veranderende omgeving, en de derde factor, *respons inhibitie*, reflecteert het vermogen om ongewenste reacties te onderdrukken. Ondanks de marginale verhouding tussen het aantal variabelen en het aantal proefpersonen, gaven de hoge factorladingen en de minimale overlap tussen de factoren aanleiding om aan te nemen dat er drie verschillende constructen van executief functioneren onderscheiden kunnen worden. De eerste factor, controle over de aandacht en motorische output, had de hoogste verklaarde variantie, hetgeen suggereert dat de onderliggende maten een belangrijk deel van de cognitieve functies in het domein van het executief functioneren beslaan. Echter, het aantal proefpersonen was relatief te klein om sterke conclusies te verbinden aan de resultaten. Om die reden wordt aangeraden dit type onderzoek te herhalen in een grotere, onafhankelijke database. Geadviseerd wordt om dan een confirmatieve factor analyse uit te voeren, zodat de hypothesen uit het huidige onderzoek statistisch getoetst kunnen worden.

In **hoofdstuk 8** worden de resultaten van de zes studies besproken en wordt ingegaan op de betekenis ervan voor toekomstig onderzoek en voor de klinische praktijk. Kort samengevat: Er is aanzienlijk bewijs gevonden voor drie cognitieve endofenotypen van ADHD in het domein van de executieve functies: 1) stoornissen in de controle over de aandacht en motorische output, 2) mentale flexibiliteit, en 3) repons inhibitie. Eén van de belangrijkste aandachtspunten voor de toekomst is dat zowel clinici als onderzoekers zich bewust worden van het feit dat deze drie aspecten van executief functioneren zeer waarschijnlijk een centrale rol spelen in het disfunctioneren van kinderen met ADHD en kinderen met de genetische kwetsbaarheid voor ADHD. Tot slot, de onderzoeken die in dit proefschrift zijn beschreven kunnen een basis vormen voor nieuw multidisciplinair onderzoek naar de etiologie van deze complexe, maar zeer boeiende stoornis.

Publications, journal articles, abstracts and presentations

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Publications and journal articles

Slaats-Willemse D, Swaab-Barneveld H, de Sonneville L, van der Meulen E, & Buitelaar J (2003). Deficient Response Inhibition as a Cognitive Endophenotype of ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry*, 42: 1242-1248.

Slaats-Willemse D, de Sonneville L, Swaab-Barneveld H, & Buitelaar J, Motor Flexibility Problems as a Marker for Genetic Susceptibility to ADHD.
Submitted.

Slaats-Willemse D, Swaab-Barneveld H, de Sonneville L, & Buitelaar J, Do Executive Function Deficits Identify a Meaningful Familial Subtype of ADHD?
Submitted.

Slaats-Willemse D, Swaab-Barneveld H, de Sonneville L, & Buitelaar J, Familial Clustering of Executive Functioning in Affected Sibling Pair Families with ADHD.
Submitted.

Slaats-Willemse D, Swaab-Barneveld H, & Buitelaar J, A Family-genetic Study on Attentional Control and Mental Flexibility in ADHD: Evidence for Cognitive Endophenotypes of ADHD.
Submitted.

Abstracts and oral presentations

Slaats-Willemse D, Swaab-Barneveld H, De Sonneville L, van der Meulen E, Buitelaar J. Evidence for a familial subtype of ADHD based on cognitive deficits [oral presentation]. Thirty-first Annual International Neuropsychological Society Conference, February 2003, Honolulu, Hawaii.

Slaats-Willemse D, Swaab-Barneveld H, De Sonneville L, van der Meulen E, Buitelaar J. Cognitive endophenotyping in ADHD: Executive functioning as a marker for genetic susceptibility to ADHD [oral presentation]. 2nd Dutch Endo-Neuro-Psycho Meeting, June 2003, Doorwerth, the Netherlands.

Slaats-Willemse D, de Sonneville L, Swaab-Barneveld H, Buitelaar J. Higher-order controlled motor performance as a maker for genetic susceptibility to ADHD [abstract]. 12th International Congress of the European Society for Child and Adolescent Psychiatry (ESCAP), September 2003, Paris, France.

Endophenotypes for ADHD [oral communication]. Fifth annual ADHD molecular genetics network meeting, May 2003, Boston, USA

Dankwoord

Dankwoord

Het dankwoord: waarschijnlijk het meest gelezen deel van een proefschrift. Eigenlijk vreemd dat dit niet kan worden aangeboden voor publicatie in een tijdschrift!
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Curriculum Vitae

Curriculum Vitae

Dorine Willemse werd geboren op 31 augustus 1972 te Utrecht. In 1990 behaalde zij haar VWO diploma aan het Christelijk Lyceum te Zeist. In datzelfde jaar ging zij Psychologie studeren aan de Universiteit Utrecht. Zij koos voor de afstudeerrichtingen Cognitieve Functiestoornissen, en Klinische- en Gezondheidspsychologie. Tijdens de studie Psychologie volgde zij extra keuzevakken Neurologie aan de faculteit Geneeskunde. Na een klinische stage op de afdeling Neuropsychologie van het Leids Universitair Medisch Centrum (LUMC), en een afstudeeronderzoek naar cognitieve veroudering i.s.m. het RIVM studeerde zij in maart 1997 af. Per 1 april van datzelfde jaar vertrok zij naar Maastricht om als onderzoeksassistent bij de vakgroep Psychiatrie en Neuropsychologie van de Universiteit Maastricht te gaan werken aan het onderzoek van Dr. A.C. Tjeenk-Kalff naar de 'Neurocognitive performance and demographic variables in children at risk of Attention-Deficit/Hyperactivity Disorder'. Gedurende deze periode werkte zij ook mee aan de Nederlandse vertaling van een neuropsychologische testbatterij voor kinderen (NEPSY, prof. Dr. M. Korkman). In januari 1998 is zij gestart met de postdoctorale opleiding tot Gezondheidszorgpsycholoog. In het kader van deze opleiding werkte zij als psycholoog binnen de afdeling Psychiatrie en Neuropsychologie van het Academisch Ziekenhuis Maastricht ten behoeve van het neuropsychiatrisch kinderspreekuur, het Dyslexiecentrum Limburg, en de geheugenpolikliniek voor volwassenen. In januari 2000 werd zij als Gezondheidszorgpsycholoog ingeschreven in het BIG-register. Sinds februari 2000 is zij tevens geregistreerd als Kinder- en Jeugdpsycholoog bij het Nederlands Instituut van Psychologen (NIP). Februari 2000 begon zij als assistent in opleiding bij de afdeling Kinder- en Jeugdpsychiatrie van het Universitair Medisch Centrum Utrecht (UMCU) aan het onderzoek dat leidde tot dit proefschrift. Daarnaast werkte zij een aantal maanden als Gezondheidszorgpsycholoog (0.2 fte) bij het Pedologisch Instituut, behorende bij het Centrum Educatieve Diensten te Rotterdam, en vervolgens enkele maanden op de afdeling Jeugdpsychiatrie van het UMC Utrecht. Sinds 2000 is zij docent bij de jaarlijkse nascholingscursus "Neuropsychologisch onderzoek bij kinderen en jeugdigen" van RINO Zuid-Nederland.